Current Topics in Behavioral Neurosciences 55

Nigel C. Jones
Andres M. Kanner *Editors*

Psychiatric and Behavioral Aspects of Epilepsy

Current Perspectives and Mechanisms

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Preface

The bi-directional relationship between depression and epilepsy has been appreciated for millennia. In 400 B.C., Hippocrates coined the famous phrase:

> Melancholics ordinarily become epileptics, and epileptics, melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy. (Lewis 1934)

In more recent times, it has become apparent that, in addition to mood disorders, other psychiatric and neurocognitive disorders are also highly prevalent in people with epilepsy, and these are the greatest predictors of the quality of life of patients. Furthermore, in many cases, these conditions predate the onset of spontaneous seizures and epilepsy and predict the response to anti-seizure medications, suggesting bidirectional associations. Ever since these famous words were spoken, philosophers, physicians, scientists, psychiatrists, and neurologists have been studying these interactions, characterising phenomena and working to identify the underlying biological or psychological mechanisms which link these conditions. Such identification would provide numerous benefits, including from clinical management and treatment perspectives.

In some ways, it is easy to consider that features of epilepsy may cause or contribute to psychiatric conditions: the repeated effects of seizures, constant exposure to anti-seizure medications, or the psychosocial stressors of living with an unpredictable neurological condition such as epilepsy may result in cellular brain damage or distort neural circuitry associated with mood regulation and various cognitive domains. But what of the reverse direction? Why would a person suffering from depression be more vulnerable to develop epilepsy? Neurotransmitter or hormonal alterations associated with mood and anxiety disorders may interact with pathobiological alterations associated with development of epilepsy, but it is likely that a secondary insult may be required to set into motion 'epileptogenesis', the processes underlying epilepsy development. This robust field is constantly investigating these mechanisms, and the wealth of research done in this field is testament to the desire – both from a clinical and experimental perspective – to understand these interactions.

When I was invited to produce this volume, I immediately realised the book would benefit greatly from clinical insights to complement my own discovery science

perspectives. I could think of no better co-editor than Prof Andres Kanner, eminent clinician researcher and esteemed world leader in the field of psychiatric comorbidity in epilepsy. Together, we recruited specialists from around the world to contribute to the final product. The primary goal of our book is to summarise the state-of-the-art thinking about age-old problems such as the mechanisms underpinning the interrelationships between epilepsy and melancholia, as well as more recently identified interactions between epileptic phenomena and psychiatric/neurocognitive features, which have important impacts on clinical management and diagnosis.

Utilisation of animal models lends itself perfectly for the study of psychiatric and cognitive disorders in epilepsy, since most, if not all, animal models of epilepsy exhibit abnormalities in behavioural domains which align well with those observed in patients with epilepsy. As such, 'Part 1 – Discovery Science Chapters' features reviews compiled by experts in the field which focus on knowledge gained from the study of animal models relevant to mechanisms and inter-relationships of behavioural disorders in epilepsy. Katerina Lin and Carl Stafstrom rigorously explore the consequences of early life seizures on the developing brain. Febrile seizures often experienced by children are estimated to afflict 3% of the population, and so understanding the cognitive, behavioural, and psychosocial consequences of these seizures has far-reaching impact. This is followed by commentary from Avery Liening and Alisha Epps who also focus on early brain development, here detailing the extensive experimental literature which describes the vulnerability to seizures and epilepsy brought about by stress and adversity experienced in early life. It is widely considered, especially by patients, that stressful events can trigger seizures, and the works from Samba Reddy, Wesley Thompson, and Gianmarco Calderara describe this literature. The primary focus of this chapter is to describe the mechanisms by which stress can influence seizure threshold and touches on how this information may be valuable from a treatment perspective. Next, we explore abnormalities in neuronal dynamics as a consequence of epilepsy, which could explain deficits in cognitive processing in these patients. Pierre-Pascal Lenck-Santini and Sophie Sakkaki produce a detailed evidence-based description of neuronal network alterations in epilepsy models and summarise how these contribute to learning and memory deficits. The focus of Jamie Maguire's contribution targets the biological mechanisms which have been posited to contribute to psychiatric comorbidities in epilepsy. This piece draws from extensive literature from both clinical and discovery science research. Finally, we then delve into the holy grail of epilepsy research – disease modification. To conclude Part 1, Emilio Russo and Rita Citraro summarise the state of play regarding disease modification in epilepsy. They provide extensive evidence from models of genetic generalised epilepsy that prolonged treatment with anti-seizure medications results in prolonged improvements both in epilepsy severity and behavioural comorbidities.

'Part 2 – Clinical Chapters' focuses on clinical research which addresses different aspects of the very close relation between psychiatric disorders and epilepsy and highlights the clinical implications of such relations. Thus, Antonio Teixeira reviews the peri-ictal and para-ictal phenomena that result from a complex temporal relation

between ictal activity and psychiatric phenomena. These phenomena are relatively frequent in patients with treatment-resistant epilepsy and yet, they usually go unrecognised by clinicians, leading to erroneous diagnoses and treatment strategies. The complex relation between epilepsy and psychiatric comorbidities is explored in the chapter on Psychotic Disorders in Epilepsy by Kousuke Kanemoto, in which he illustrates their various clinical expressions, which may often differ clinically from those of primary psychotic disorders and which can be closely associated with the occurrence of ictal activity. The common pathogenic mechanisms operant in psychiatric disorders and epilepsy are demonstrated in two chapters. In the first one, Hrvoje Hećimović, Zvonimir Popović, and Frank Gilliam review the neurobiologic pathogenic mechanisms operant in suicidality and epilepsy. In the other chapter, I review the reasons for the higher comorbid occurrence among depression, epilepsy, and migraine, which can be explained by the bidirectional relation that exists among the three conditions, and their common pathogenic mechanisms. The therapeutic and iatrogenic effects of psychotropic drugs on epilepsy and the effects of anti-seizure medications and epilepsy surgery on comorbid psychiatric disorders are another expression of the complex relation between epilepsy and psychiatric disorders with important clinical implications. First, Kamil Detyniecki reviews the available evidence on the 'reported proconvulsant properties' of psychotropic drugs and debunks the misunderstandings surrounding those unfounded concerns. He identifies the few psychotropic drugs that can increase the risk of seizures and reviews the experimental and clinical data that appear to suggest a possible antiepileptic effect of certain families of antidepressant drugs. Having a clear understanding of these data and unmasking these misconceptions is of the essence as they have become an unnecessary obstacle in the pharmacologic treatment of psychiatric comorbidities in people with epilepsy. In a second article Gerardo Maria de Araujo discusses how the psychiatric history of patients with epilepsy can allow clinicians to identify patients at risk of iatrogenic psychiatric effects caused by anti-seizure medication and epilepsy surgery. In his chapter, Luis Pintor reviews the iatrogenic and therapeutic effects of temporal lobectomies. Finally, Petr Sojka, Sara Paredes-Echeverri, and David L. Perez close this section with a review of the multifaceted aspects of psychogenic non-epileptic events.

We thoroughly hope our readers find this book informative and provocative, and enjoy reading the contents as much as we enjoyed developing the final product for you.

Melbourne, VIC, Australia — Nigel C. Jones
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Part I
Discovery Science

Cognition, Behavior, and Psychosocial Effects of Seizures in the Developing Brain

Katerina Lin and Carl E. Stafstrom

Contents

Abstract Epilepsy, a complex neurological disorder of recurrent seizures, is associated with significant impacts on the developing brain. Patients commonly face multiple comorbidities, including debilitating effects on cognition, behavior, and psychiatric outcomes. These conditions can be a source of great distress for patients that may even be greater than the burden of epilepsy itself. Here we investigate the relationship between seizures and the development of these comorbidities, specifically cognition, memory, learning, behavior, and psychiatric disorders. We first delineate the current research methodology in clinical and basic science that is employed to study the impact of epilepsy and seizures. We then explore neurobiological mechanisms underlying the development of seizures and cognitive and behavioral outcomes. Potential avenues of intervention to best support individuals and optimize their neurodevelopmental progress are also highlighted.

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1 Introduction

Seizures, characterized by paroxysmal, hypersynchronous electrical neuronal activity within the brain, can engender profound impacts on the developing brain. Epilepsy, the fourth most common neurological disorder in the USA (Institute of Medicine Committee on the Public Health Dimensions of the Epilepsies et al. 2012), is often a debilitating condition that is defined by recurrence of unprovoked seizures. Individuals with epilepsy often face a myriad of chronic conditions, including cognitive dysfunction, depression, and anxiety. Scientific evidence supports the model that brief and prolonged seizures can inflict lasting disruptions to brain development. The goal of this review is to investigate how seizures alter brain development and generate lasting changes in multiple neurobehavioral domains, including cognition, memory, learning, and psychiatric outcomes.

We delineate current clinical and scientific methodology for studying seizures and comorbidities in patients and animal models. We then examine current medical and neurobiological research on mechanisms underlying these changes. Of note, the relationship between epilepsy and associated comorbidities is not unidirectional; rather, each may contribute to each other, and they may also have shared pathologies. There are likely also dynamic interactions between genetic predisposition, environmental influences, and baseline abnormalities in the brain that contribute to the complex disorder of epilepsy and its associated cognitive and psychiatric impairments.

The neurobehavioral clinical phenotype seen in patients with epilepsy also has significant contributions from psychosocial and environmental influences. We conclude with potential interventions to support individuals through their neurodevelopment. We discuss how future avenues of therapy should support family and social networks, which can play a critical role in helping to alleviate symptoms and provide much needed support for young patients with epilepsy through their development.

2 Laboratory Assessment of Seizure-Induced Cognitive and Behavioral Changes

Clinical research provides important insights into the medical condition of epilepsy and its comorbidities. It can provide information regarding epilepsy and associated illnesses, including cognitive deficits, memory impairment, and psychological

disturbances throughout development. Studies of adults and children with epilepsy can also explore associations and the qualitative impacts of the disease, imparting critical understanding of patients' personal experiences with epilepsy, such as emotional effects and impairment on quality of life. Clinical studies, however, can have potential difficulty with establishing causative effect between seizures and cognitive and behavioral changes, particularly when invasive studies are impractical or ethically prohibitive. There are also effects due to potential confounders, such as usage of antiseizure medicine (ASMs), baseline brain structural abnormalities, and underlying comorbidities.

Laboratory investigation utilizing animal models provides a powerful method to help elucidate the pathophysiology of epilepsy and comorbidities in a relatively controlled setting. Animal models of acquired epilepsy allow for experimental control over potentially confounding factors, including the cause of seizures and their duration, frequency, and severity, which are more difficult to modify in clinical studies. Prolonged seizures in animals can be induced through administration of substances such as kainic acid (KA), pilocarpine, and pentylenetetrazole, and can be performed at varying times throughout an animal's lifespan. Each of these chemoconvulsants has a different mechanism of action and mimics a different seizure type.

There are a multitude of methods and tests to study seizure-induced changes in the brain of animal models. These tests evaluate a wide range of functions and characteristics, such as sensorimotor function, locomotor activity, visuospatial learning and memory, anxiety, and depression (Table 1). Assessment of preserved sensorimotor function is a common and critical behavioral test. Studies demonstrating normal sensorimotor and reflexive function are necessary to establish that these variables are not causing behavioral or cognitive differences. One of the more commonly used sensorimotor tests is the rotarod test, which implements a rod rotating at different speeds and requires the animal to balance and keep pace with

Table 1 Key behavioral and cognitive tests in animal models

Test	Purpose	Characteristics
Open field test Curzon et al. (1976, 2009)	Exploratory and locomotor activity	Exploration of novel environment, namely newly introduced objects or recently poked holes in an open field
Morris water maze Morris et al. (1982, 1984)	Visual spatial learning and memory	Utilizing visual cues to locate platform under water; requires intact function of hippocampus
Rotarod Curzon et al. (2009)	Sensorimotor function	Balancing and keeping pace with rod rotating at different speeds
Elevated plus-maze Lister (1987), File (1993)	Anxiety	Placement in enclosed space consisting of two elevated, brightly lit arms juxtaposed perpendicularly with two darkly lit arms
Forced swimming test Porsolt et al. (1977a, b)	Depression	Identifying behavioral immobility through cessation of vigorous activity when swimming in a container filled with water

the changing rotation rates (Curzon et al. 2009). Other tests are used to compare activity and function in animals with epilepsy compared to those without epilepsy. Testing exploration and locomotor activity can be completed through the open field test (Curzon et al. 2009; Walsh and Cummins 1976). The Morris water maze assesses visual spatial learning and memory (Morris et al. 1982; Morris 1984). The wide variety of methods allows for comprehensive study of seizure-induced changes.

Psychiatric comorbidities are often a key component of the epilepsy phenotype. Many studies can assess these outcomes, including anxiety and depression, in animal models. The elevated maze-plus is a common method to examine behavior related to anxiety (Lister 1987; File 1993). The forced swimming test is a popular method to evaluate depressive behavior in animals (Porsolt et al. 1977a, b). It induces a depression-like state in rodents that is amenable to antidepressant therapy. Analyzing psychiatric outcomes in mice, however, has limitations. While diagnosing psychiatric conditions in humans relies on physicians' clinical acumen and communication with patients to understand their unique perceptions and individual experiences, this type of interaction is not feasible with a non-human subject. Therefore, animal studies must rely on behaviors associated with psychiatric states, like anxiety or depression-related behaviors, as a correlate to the human condition. This is a practical, yet inherently imperfect, approach. These shortcomings must be taken into consideration prior to implementing such a study and in the analysis of the outcomes if such a study is performed.

When laboratory behavioral and cognitive tests are used, there are specific practices that should be implemented. Tests should be selected based on carefully constructed a priori hypotheses and with an understanding of the functions of the specific tests under consideration. When tests are performed in the same animal, they should be completed in order of increasing aversiveness. There must also be appropriate respite between tests to prevent emergence of habituation. Adherence to best practices in using animal models allows for a rigorous, thorough study design.

3 Changes in Cognitive and Behavioral Development

3.1 Cognition, Learning, and Memory

Cognitive challenges are common and can be greatly debilitating for patients with epilepsy (Powell et al. 2015). A population-based study of school-aged children with epilepsy found that 80% had cognitive impairment and/or a behavioral disorder, with 40% having intellectual disability, as determined by an intelligence quotient less than 70 (Reilly et al. 2014). Earlier exposure to seizures in the first 2 years of life was independently associated with intellectual disability compared to later presentation of seizures (Reilly et al. 2014). Cognitive impairment encompasses a wide spectrum, ranging from intellectual disability and global cognitive dysfunction, which is

present in 26% of children with epilepsy (Berg et al. 2008a), to attention deficit–hyperactivity disorder (ADHD) (Nickels et al. 2016). These impairments increase risks of academic underachievement, learning disabilities (Fastenau et al. 2008), and decreased performance in reading, spelling, and writing (Berg et al. 2008b; Dunn et al. 2010). Children with epilepsy have high rates of special education services and grade retention (Bailet and Turk 2000).

Cognitive effects are related to seizure-related factors. Earlier age of onset, longer history of epilepsy, and increased seizure frequency have a higher risk of cognitive impairment (Wang et al. 2018). Furthermore, cognitive effects often vary based on the type of epilepsy. Epileptic encephalopathy is characterized by severe epilepsy and intellectual disability (Howell et al. 2016) and is an independent risk factor for cognitive outcome (Berg et al. 2008a). Severe epilepsies, such as drug-resistant epilepsy, are associated with increased frequency and more severe cognitive impairment compared to drug-sensitive epilepsy (Gavrilovic et al. 2019). On the other hand, benign focal epilepsies of childhood, such as benign epilepsy with centrotemporal spikes, are associated with relatively favorable long-term cognitive outcomes (Ross et al. 2020).

The pathophysiology of seizure-induced deficits in cognition is an area of active research. Extensive behavioral studies in rodent models have demonstrated that seizures differentially affect adult animals compared to younger animals. For instance, an early study of KA-induced seizures in rats found behavioral and cognitive deficits that occurred in an age-dependent manner (Stafstrom et al. 1993). Adults and older animals had deficits in exploration, learning, and memory and increased aggression during handling. Conversely, younger rats did not display behavioral or cognitive changes. Further studies on long-term effects of recurrent seizures on spatial learning and memory using a similar rodent model discovered loss of hippocampal cells and profound impairment in spatial learning retention in adults but not immature rats (Sarkisian et al. 1997). Younger age appeared to be protective of macroscopic structural alterations in the brain compared to the much more severe changes seen in adults. Thus, there is a spectrum of age-specific influences on brain structure and function.

There is also evidence that seizure exposure at a young age can lead to persistent changes in cognition and behavior. Notably, there may be a critical period of neuronal plasticity in hippocampal development that influences the brain's ability to permanently modify circuitry resulting from seizure activity (Sayin et al. 2015). Many studies have elucidated cellular changes and potential biological mechanisms that may underlie these alterations in learning and memory as a result of early exposure to seizures. In rat models, early seizures induce longstanding alterations in hippocampal firing, specifically of place cells, and thus impair spatial learning (Karnam et al. 2009). The mechanism of seizure-induced hippocampal impairment involves changes in synaptic plasticity and long-term potentiation (Zhou et al. 2007).

There are multiple potential relationships between seizures and cognitive comorbidities. A causal relationship is one possibility, with seizures contributing to biological changes that lead to impaired cognition. Basic scientific research as described above provides a controlled manner with which to investigate this

relationship. However, there is mounting evidence that suggests other associations may also exist; for instance, there may be a common pathophysiology of epilepsy and cognitive changes. A prospective study of children with newly diagnosed epilepsy found significant differences in baseline cognitive status at or near the time of diagnosis. These differences were sustained over 5–6 years with neither improvement nor decline (Rathouz et al. 2014). Similarly, symptoms of ADHD can present before or at the time of seizure onset (Williams et al. 2016) and even in patients who are not on antiepileptic medications (Kwong et al. 2016a). This indicates that cognitive symptoms are not caused solely by medication effects or seizure activity. Furthermore, recent neuroimaging research has demonstrated that individuals with new-onset epilepsy already had brain abnormalities at the time of diagnosis. There was significant disruption within structural brain networks, and this was associated with lower IQ and poorer executive function (Bonilha et al. 2014). Moreover, there may also be a genetic contribution, as specific gene mutations have been identified that lead to both epilepsy and cognitive impairment (Dibbens et al. 2008; Damaj et al. 2015). The occurrence of cognitive and structural baseline abnormalities in children newly diagnosed with epilepsy suggests a common pathophysiology related to underlying brain dysfunction.

3.2 Psychiatric Outcomes

Co-existing psychiatric conditions are common among patients with epilepsy. Patients demonstrate high prevalence of depression (Kwong et al. 2016b), anxiety (Pham et al. 2017), and suicide attempts (Hesdorffer et al. 2016). Children in particular are at risk for psychiatric and neurodevelopmental disorders (Berg et al. 2011), with rates estimated as high as 37% (Davies et al. 2003). They have significantly more behavioral problems compared to unaffected siblings at baseline that persist over time (Austin et al. 2011). Childhood epilepsy is also associated with adverse long-term mental health outcomes, with worse mental health in those with poor cognitive development (Chin et al. 2011). Even for individuals without cognitive impairment, childhood epilepsy is associated with difficulties maintaining personal relationships (Chin et al. 2011). There is increased risk of emotional hardships, difficulties maintaining connections with others, and challenges interacting with peers (Davies et al. 2003).

The relationship between epilepsy and development of concurrent psychiatric conditions is complex. There is likely a bidirectional relationship between psychiatric disorders and seizures, meaning that seizures may contribute to the generation of psychiatric differences, but psychiatric disorders may not always arise directly from seizure activity. We first review evidence for seizure-induced changes in psychiatric outcomes. For example, early seizure exposure can lead to alterations in psychiatric outcomes. In rodent models, early seizures result in deficits in social behavior and interactions (Lugo et al. 2014) and induce anxiety and autistic-like behaviors (Waltereit et al. 2011). Even a single exposure to status epilepticus in the

neonate induces lasting deficits in anxiety (Smith et al. 2017). Following epilepsy surgery, levels of depression and anxiety can be significantly reduced, supporting the concept that epileptogenesis may engender neurobiological alterations that predispose individuals to developing psychiatric comorbidities (Smith et al. 2017). Potential mechanisms include seizure-induced hyperactivity of the hypothalamic-pituitary-adrenal axis, which correlates with severity of depressive behavior, and subsequent decrease in serotonergic raphe-hippocampal transmission (Mazarati et al. 2009; Pineda et al. 2010).

Baseline psychiatric differences, however, may also influence an individual's susceptibility to seizures. For instance, a history of major depression or attempted suicide independently increases risk of unprovoked seizures (Hesdorffer et al. 2006, 2007). Mood disorders and generalized anxiety disorder are associated with increased risk of seizure recurrence (Baldin et al. 2017). Furthermore, suicide attempts are associated with epilepsy before the time of diagnosis, even in those without use of ASMs (Hesdorffer et al. 2016). Thus, preexisting psychiatric disorders increase the predisposition to seizures. Interestingly, the neurobiological underpinnings of psychiatric disorders may also interact and even exacerbate the pathogenesis of epilepsy. Depression is associated with worse prognosis in epilepsy and increases the risk of pharmacoresistant epilepsy (Hitiris et al. 2007). Although baseline differences in psychiatric condition may increase risk of epilepsy, evidence also supports that psychiatric disorders can also occur independently from epilepsy and do not necessarily lead to seizure activity. For example, de novo psychopathology, including depression and anxiety, can arise in patients after temporal lobe epilepsy surgery (Cleary et al. 2012).

Psychiatric comorbidities and epilepsy may also share a common pathological basis. There are many potential biological mechanisms and neurological structural changes underlying both psychiatric comorbidities and epilepsy. Alterations in the balance of neurotransmitters in the brain may predispose individuals to both seizures and psychiatric dysfunction. Research has suggested the involvement of monoaminergic systems such as dopamine, serotonin, and norepinephrine in epileptogenesis and seizure susceptibility (Giorgi et al. 2004; Guiard and Giovanni 2015; Svob Strac et al. 2016). The monoamine system is also crucially involved in the genesis of neuropsychiatric disorders. Other neurotransmitter systems, specifically GABAergic signaling, have been implicated as a common mechanism for the pathogenesis of autism and epilepsy (Kang and Barnes 2013).

Neuroimaging has also provided important insights into possible neuroanatomical pathologies. Among patients with temporal lobe epilepsy, decreased cortical thickness of the orbitofrontal cortex is associated with depressive symptoms (Butler et al. 2012; Nogueira et al. 2019). Dysfunction within frontolimbic structural and functional networks predicts depressive symptoms in patients with temporal lobe epilepsy (Kemmotsu et al. 2014). Structural brain abnormalities may additionally contribute to psychiatric pathophysiology independent of seizure activity. Reductions in gray matter in the orbitofrontal cortex and cingulate gyrus are associated with de novo depression after temporal lobe epilepsy surgery (Pope et al. 2014). Overall, numerous neurobiological mechanisms are likely at play in the development

of psychiatric comorbidities and epilepsy. Further investigation of these processes may provide further insight into possible therapeutic options and improve treatment for patients.

4 Supporting Neuropsychiatric Development

Patients with epilepsy must be provided with ample comprehensive medical, psychological, and social support in order to optimize their neuropsychiatric development. Comprehensive medical care is essential to helping patients, as they face increased mortality compared to the general population (Chin et al. 2011) as well as cognitive and behavioral difficulties associated with seizures. Childhood epilepsy can lead to devastating long-term consequences on employment, education, and adulthood throughout an individual's lifetime. It can impact an individual's ability to integrate into society and is an independent risk factor for having single marital status and lack of parenthood (Chin et al. 2011). Improved seizure control is associated with reduction in behavioral difficulties, suggesting that early intervention through adequate medication that reduces seizure frequency may help alleviate behavioral and social challenges (Powell et al. 2015).

In addition to standard medical care, interventions to support the neurodevelopment of children with epilepsy should target psychosocial influences, such as family environment. A variety of seizure-independent factors impact patients' cognitive and behavioral phenotype. For instance, parental intelligence and features of the home and family environment are associated with cognitive impairment in patients with childhood epilepsy (Hermann et al. 2016). Specific family-related variables associated with behavioral problems include less education of caregivers, decreased child satisfaction with family relationships, ability of the family to problem solve and support one another, and familial support of children's autonomy (Austin et al. 2011). Social adversity relating to family problems is associated with poor cognitive and behavioral performance in children with epilepsy (Oostrom et al. 2003). Other environmental influences impact psychological outcomes among individuals with epilepsy; marital status, alcohol misuse, nicotine dependence, and nonadherence to medications are associated with worse mental health outcomes (Wubie et al. 2019). Thus, to promote patients' neurobehavioral progress, it is essential to address psychosocial determinants of their development and ensure that social and environmental support is provided for patients and their families managing complex medical illnesses.

A crucial psychosocial intervention to promote development of children with epilepsy is providing support for caregivers. Parents and family play a critical role in the emotional and psychiatric growth of their children. They provide psychological support, helping their children understand the reality of their illness and cultivate acceptance of their differences from their peers; however, parents can be negatively affected by the stress and social stigma associated with the diagnosis of epilepsy, which can hinder their ability to optimally support their children. In a study of

60 parents of children with epilepsy, parents expressed emotional, financial, and social stress associated with caring for their child with epilepsy as measured by the Childhood Illness-related Parenting Stress Inventory (Rani and Thomas 2019). Most parents felt confused about their child's condition and expressed difficulty discussing the matter with their physicians. Other studies have similarly demonstrated that most caregivers of children with epilepsy have limited understanding of the term epilepsy (Nagan et al. 2017). Furthermore, parents also worry about their children's integration with society and marital prospects due to cultural misconceptions surrounding the epilepsy diagnosis (Rani and Thomas 2019). These observations warrant interventions that provide emotional and psychological support for caregivers. It is also necessary to improve communication between caregivers and health care providers surrounding the terms and definition of epilepsy. This will help parents achieve greater understanding of their children's diagnoses. The goal is to help parents gain greater empowerment in asking health care providers further questions and clarification so they are best equipped when taking care of their children with epilepsy.

It is necessary to target societal influences, such as stigma, which directly impact patients' psychological wellbeing and development. Patients often face immense pressure from social stigma associated with epilepsy. This exacerbates behavioral outcomes, increasing rates of aggression in the setting of anxiety and depression (Seo et al. 2015). Stigma is worsened by psychiatric comorbidities including anxiety and depression (Shi et al. 2017; Suljic et al. 2018). Thus, individuals with epilepsy often face the unique challenges of dual social stigma, one associated with epilepsy and another associated with mental health disorders. Therefore, to promote the best medical and developmental outcomes, it is necessary to target social influences of stigma on health. This includes raising awareness and promoting education to dismantle misperceptions, discrimination, and mistreatment within communities and society (Paschal et al. 2007). In addition, providing information about their condition and psychoeducational programs should be provided to patients and families to help them confront, overcome, and dispel perceived stigma (Snead et al. 2004; Austin et al. 2014).

5 Conclusions

Epilepsy carries tremendous morbidity and mortality and generates immense medical, emotional, and financial consequences for patients and their families. It is associated with multiple neurological, cognitive, and psychiatric comorbidities. For many patients, these comorbidities can have greater burden than that of epilepsy (Institute of Medicine Committee on the Public Health Dimensions of the Epilepsies et al. 2012). Furthermore, societal factors, including perceived social stigma, compound the suffering of patients and contribute to negative quality of life (Abadiga et al. 2019). Neuroscientists and clinicians have focused research on investigating the impact of seizures on development and how the neuropsychiatric phenotype arises.

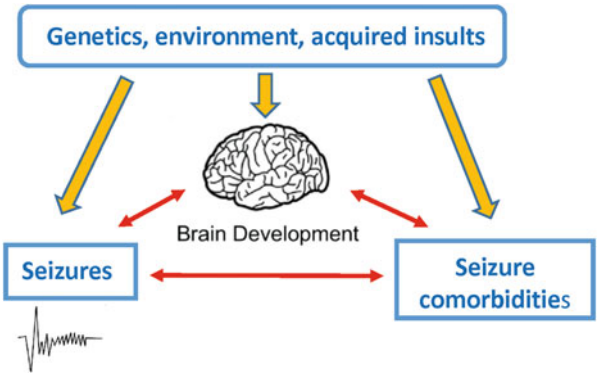

Fig. 1 Schematic illustrating the complex relationship between brain development, seizures, and seizure comorbidities. Etiologies such as genetic mutations, environmental factors, and acquired insults can case seizures or their comorbidities, and also affect brain development, as depicted by the thick arrows. Likewise, seizures and their comorbidities themselves influence ongoing neuronal development as illustrated by thin double-headed arrows. See text for details

The relationship between epilepsy and neuropsychiatric comorbidities is multifactorial (Fig. 1). Both basic science and clinical research provide useful modes to study these relationships. The evidence supports complex interactions between seizures and cognition, memory, behavior, and psychiatric disorders. Early seizures increase risk of cognitive deficits, but there is also evidence for a common pathophysiology underlying cognitive impairment and epilepsy. Likewise, early exposure to seizures increases risk of psychiatric outcomes like anxiety, but there is also likely shared pathology that gives rise to both conditions. Importantly, environmental and familial influences also contribute.

The collection of complex conditions presenting in an individual with epilepsy likely arises from a confluence of many risk factors, with vital public health implications. Interventions are needed to support patients suffering from serious comorbidities and must address these medical, emotional, and psychosocial aspects. Ultimately, the scientific community must spearhead continued investigations to provide further insight into the neurobiology of seizures and development and to guide future therapies. Overall, future research elucidating the mechanisms underlying seizures and neurobehavioral comorbidities will help to delineate pathophysiology, identify treatment targets, and optimize quality of life for patients with epilepsy.

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In Up to My Ears and Temporal Lobes: Effects of Early Life Stress on Epilepsy Development

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Contents

Abstract Epilepsy and stress are each significant concerns in today's society, bearing heavy impacts on mental and physical health and overall quality of life. Unfortunately, the intersection between these is potentially even more concerning, as stress is a frequent trigger of seizures and may contribute to neural hyperexcitability. A growing body of research suggests a connection between early life stress (occurring in the prenatal or postnatal stage) and later development of epilepsy. While the larger part of this literature suggests that early life stress increases vulnerability for epilepsy development, there are a number of interacting factors influencing this relationship. These factors include developmental stage at which both stressor and seizure assessment occur, type of stressor, sex effects, and type of seizure (convulsive or non-convulsive). Additionally, a number of potential mechanisms have been

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identified, including activation of the hypothalamic-pituitary-adrenal axis, neuroinflammation, altered inhibitory/excitatory balance, and temporal lobe structures. Developing a clearer understanding of this relationship between early life stress and epilepsy, the factors that influence it, and underlying mechanisms that may serve as targets for intervention is crucial to improving quality of life for persons with epilepsy.

Keywords Development · Early life stress · Epilepsy · HPA axis · Neuroinflammation · Seizure · Temporal lobe

1 Introduction

According to the CDC, approximately 3.4 million people in the USA suffered from epilepsy in 2015. Of these, nearly 470,000 were children under the age of 18 (Zack and Kobau 2017). Globally, more than 65 million people were affected by epilepsy in 2015 (Moshé et al. 2015), with approximately 8.5 million of these cases attributed to children (Kassebaum et al. 2017). Regardless of age, epilepsy poses a number of physical and psychological challenges. Persons with epilepsy (PWE) often contend with the unpredictability of seizure timing and severity, a heightened likelihood of comorbidities, side effects of pharmaceutical treatments, stigma and discrimination, financial cost of care, limitations on independence, and, in some forms of epilepsy, increased risk of mortality from sudden unexpected death in epilepsy (SUDEP) (Covanis et al. 2015). Notably, many of these challenges are associated with decreases in quality of life (Conway et al. 2016; Ridsdale et al. 2017). Reflecting the scale and scope of these concerns, the World Health Assembly passed a 2015 Resolution on the "Global Burden of Epilepsy and the Need for Coordinated Action at the Country Level to Address its Health, Social and Public Knowledge Implications" (Covanis et al. 2015). Supported by leaders from 42 different nations, the Resolution called for greater recognition of the burden of epilepsy and outlined specific actions for leaders of these countries to promote educational platforms and healthcare plans including prevention, diagnosis, treatment, and research development (Covanis et al. 2015).

In addition to being associated with decreased quality of life, many of the challenges faced by PWE are also significant stressors. In 2015, the American Psychological Association's *Stress in America* survey found that more people were living under "extreme stress" than in 2014, with females and younger adults experiencing heightened levels of stress (American Psychological Association 2016). Worldwide, the 2019 *Gallup Global Emotions* report found that more than one-third of people in 142 nations experienced stress on the day prior to the survey. Countries reporting the highest levels of stress included Chad, Greece, and the USA, with approximately 50–59% of survey responses in those countries indicating

prior-day stress (Gallup Inc 2019). This is concerning for a number of reasons, including the intersecting relationship between stress and epilepsy. Studies have shown that stress may increase the severity and frequency of seizures in those who already suffer from epilepsy (Sawyer and Escayg 2010). Indeed, stress has been repeatedly identified as the most common trigger experienced prior to seizure initiation (Galtrey et al. 2016; McKee and Privitera 2017). However, much remains to be learned about the timing, duration, and nature of stress and its effects on epilepsy.

Researchers have begun to investigate if early life stress can be a factor in the development of epilepsy. Studies have shown that prenatal stress can be dangerous for the mother and the infant (Coussons-Read 2013). Infants exposed to prenatal stress can suffer from health and developmental issues, with potential implications for long-term functioning. When infants are exposed to stress-related glucocorticoids in utero, it can alter their own developing stress responses. More traumatic stressors, like death of a loved one or divorce around the time of conception, can lead to heart complications for the fetus or loss of pregnancy. Meanwhile, less acute stressors like anxiety, perceived stress, and pregnancy-specific distress tend to lead to low birth weight and preterm birth (Coussons-Read 2013). Pregnancy-specific distress has been linked to increased risk of epilepsy, with both preterm delivery (Hirvonen et al. 2017) and postterm delivery (Ehrenstein et al. 2007) being associated with elevated incidence of seizures during childhood. Additionally, maternal emotional state is linked to earlier age of first febrile seizure (Thébault-Dagher et al. 2017), supporting a role of prenatal stress in childhood epileptogenesis.

Postnatal stress also has negative consequences on child development. Adverse childhood experiences (ACEs) categorize stressors that involve forms of abuse or trauma within the home related to incarceration, poor mental health, domestic violence, or strained parental relationships (Merrick et al. 2018). Long-term ACEs are associated with excessive activation of the stress-response system and increased risk of physical and psychological morbidity, with long-term developmental consequences (Deighton et al. 2018). Indeed, PWE report higher levels of childhood emotional and sexual trauma (Labudda et al. 2017); these rates are further increased in patients with stress-sensitive epilepsy (Lee et al. 2015) and those with psychiatric comorbidities (Labudda et al. 2017). Socioeconomic status (SES) can also play a role in the creation of stress and its impacts on development. Low SES is linked to decreased performance in almost every area of functioning (Bradley and Corwyn 2002). Access to resources is a majority of this problem. Nutrition, access to health care, cognitively stimulating materials and experiences, parenting styles, and teacher attitudes and expectations are all affected by a lower SES (Bradley and Corwyn 2002). For PWE, low SES is often intertwined with epilepsy-related stigma, further exacerbating the impact on well-being (Chomba et al. 2008). This lack of resources changes the experience of the child and can drastically increase the level of stress starting at an early age.

A better understanding, then, of the relationship between stress and its role in the development and propagation of epilepsy is essential for improving patient care and quality of life. Animal models have been crucial for the insights gained to date, as

prenatal and early postnatal stress can affect the likelihood of epilepsy later in life in rat and mouse models (Koe et al. 2009). A review of these studies suggests common themes that may link risk of epilepsy following early life stress, including seizure type, age, and sex, as well as underlying mechanisms that may contribute. While the majority of evidence suggests early life stress is pro-convulsant, early life stress may have different effects on epileptogenesis under a number of factors.

2 Convulsive Seizures, Early Life Stress, and the Effects of Age

A majority of studies on this topic have assessed the role of early life stress in convulsive seizure susceptibility during that same life stage. Whether the stress was applied prenatally or postnatally, early life stress generally increases convulsive seizure susceptibility in animal models assessed before adulthood. Although there are exceptions, this finding was consistent across both partial (kindling, pilocarpine, and kainic acid) and generalized (pentylenetetrazol and flurothyl) convulsions.

2.1 Prenatal Stress and Early Life Seizure Susceptibility

Prenatal stress is most frequently studied by exposing the pregnant dam to a stressor, as stress-induced hormones will cross the placenta to affect the pup embryos as well. For example, application of restraint stress to pregnant dams decreased latency to first tonic-clonic seizure of offspring at postnatal day (PND) 14 and 21 in a pilocarpine model (Nejatbakhsh et al. 2018). Similarly, multiple studies have shown increases in seizure susceptibility using pentylenetetrazol (PTZ)-induced seizures following maternal restraint stress. This was measured by increased severity (Lopim et al. 2020), shortened time to seizure with greater number of tonic-clonic attacks (Hashemi et al. 2013), and increased frequency of focal and tonic-clonic seizure (Hashemi et al. 2016), at both PND 15 and 25. Maternal restraint stress also increased seizure susceptibility to lipopolysaccharide (LPS) and kainic acid-induced seizures at PND 14 (Qulu et al. 2012) and to NMDA-induced infantile spasms (Baek et al. 2016; Yum et al. 2012). Similar findings of increased seizure susceptibility in neonatal offspring were also identified using other maternal stressors, including maternal exposure to predator odor (Ahmadzadeh et al. 2011), water stress (Ebrahimi et al. 2014; Saboory et al. 2015), and fetal hypoxia through maternal nitrogen exposure (De Riu et al. 1995). Other forms of prenatal stressors, like dietary protein deficiency, also showed increased seizure susceptibility in offspring at PND 44. Offspring born to a dam fed a malnourished casein diet during gestation and lactation showed lower afterdischarge threshold and longer afterdischarges when hippocampally kindled (Bronzino et al. 1986).

In contrast, there were maternal stressors that did not appear to result in enhanced seizure susceptibility in offspring, or which had varying results. Velisek injected pregnant dams with one of two different corticosteroids. Offspring of dams injected with hydrocortisone showed no differences in susceptibility to either kainic acid- or flurothyl-induced seizures at PND 15 (Velisek 2011). Those who experienced elevated betamethasone in utero showed an increased threshold to flurothyl-induced clonus, suggesting that this prenatal exposure actually *decreased* their seizure susceptibility in this particular model (Velisek 2011). Similarly, prenatal injection with betamethasone on gestation days 15–19 led to an increased threshold for both maximal electroshock-induced seizures and hippocampal kindling, although rate of seizure progression was unaffected (Young et al. 2006). However, other studies of prenatal betamethasone injection have supported the idea of maternal stress increasing later seizure susceptibility of offspring. Hippocampal slices from offspring of dams injected with betamethasone revealed an early latency to interictal discharge and seizure-like events when kainic acid was bath applied, suggesting increased hippocampal excitability in these offspring (Benson et al. 2020). Similarly, other studies using prenatal maternal injection of betamethasone showed increased susceptibility to NMDA-induced infantile spasms on PND 15 (Baek et al. 2016), suggesting that different seizure paradigms may yield differing results.

While some maternal dietary deprivation studies did show increases in seizure susceptibility of offspring, as discussed above, this seemed dependent on the particular element that was deficient in the diet. Iron deficiency during gestation served to *decrease* overall seizure frequency and number of severe Class V seizures induced by PTZ on PND 44 (Rudy and Mayer-Proschel 2017). This decreased susceptibility following prenatal iron deficiency was seen in the same study through an increased seizure threshold for hypoxia testing on PND 9. Others, like prenatal choline deprivation, showed no difference in severity of kainic acid-induced seizures on PND 42 (Holmes et al. 2002), suggesting that malnutrition may have varying effects depending on the particular nutrient being deprived.

Yet, other studies have suggested that timing of maternal stress during pregnancy may play a critical role in seizure outcome for offspring. Moriyama et al. revealed an effect of transport stress (shipping via air travel during pregnancy) at gestation day (G) 9, but not G16. Pups born to a dam transported at G9 showed longer and more severe febrile convulsions at PND 14. This was not seen in pups born to dams transported at G16 (Moriyama et al. 2013), suggesting that timing of the maternal stressor may also play a role in later seizure susceptibility.

2.2 Postnatal Stress and Early Life Seizure Susceptibility

As with prenatal stress, postnatal early life stress also generally increases susceptibility to convulsive seizure during the first 2 months of life. This has been demonstrated consistently with a number of stressors, including isolation and malnutrition.

Maternal separation during the early postnatal period involves separating the pups from their dam, most commonly for 180 min per day from PND 2 through 14. Neonatal isolation paradigms separate the pups from each other as well as from their dam, often for a shorter time (i.e., 60 min). These studies predominantly support increased seizure susceptibility in early life following these stressors. Isolation from PND 2 through PND 9 or 12 has been associated with decreased seizure threshold to pilocarpine at PND 10 (Lai et al. 2006) and longer seizure duration at PND 12 (Lai et al. 2009). Male mice who were singly housed for 28 days post-weaning required a lower dose of PTZ to induce seizure at PND 50 (Amiri et al. 2014). Other studies have demonstrated increased burst firing in the hippocampus during the interictal period (Ali et al. 2013) and longer PTZ-induced seizures in PND 10 to 14 pups who experienced maternal separation from PND 2 to 9 (Huang et al. 2002). Although these studies would both suggest increased susceptibility in males following maternal separation, it is important to note that other studies have shown a decreased susceptibility, as with *increased* seizure threshold with PTZ at PND 50 (Amini-Khoei et al. 2015)

The effects of maternal separation and neonatal isolation may be influenced by sex differences. Despite an overall lack of effect of maternal separation on pilocarpine-induced seizure susceptibility, Akman et al. (2015) noted that outcomes were worse in female rats compared to males. In addition to sex, there are also suggestions that duration of maternal separation could be a factor in this outcome as well. Edwards et al. saw no effect of maternal separation on either sex when tested with hippocampal kindling on PND 14; however, their maternal separation paradigm occurred only on PND 4 and 5 (Edwards et al. 2002). Similarly, Akman et al. (2015) reported no effect of maternal separation on pilocarpine- or flurothyl-induced seizures at PND 19 or PND 32, respectively, using a three-day maternal separation paradigm. When taken together, these studies may suggest that there is a certain threshold duration of maternal separation required for an effect on later seizure susceptibility, and that perhaps this threshold is lower in females than in males.

Other forms of early postnatal stress also mirrored these findings, including early life handling. Early life handling before weaning or between PND 30 to 37 increased seizure susceptibility in a genetic mouse model, the EL mouse, when tested at PND 67 (Todorova et al. 1999). Similar findings showed reduced latency to pilocarpine-induced seizures following early life handling of rats (Persinger et al. 2002). This increased susceptibility only happened when the handling occurred during early life, suggestive of a critical window in which this stressor could increase susceptibility. Chronic early life stress induced by limited quantities of bedding, causing disruptions in maternal care, has been shown to increase the presence of spontaneous EEG seizures in the amygdala and limbic system, paired with flexion behaviors at PND 15 (Dube et al. 2015). Neonatal injections of inflammatory agents like lipopolysaccharide on PND 10 decreased latency to both hyperthermia-induced seizures on PND 18–19 and PTZ-induced seizures on PND 25–26 (Saboory et al. 2019). Collectively, these studies suggest a facilitating role of postnatal stress on development of seizure activity during early life.