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What is More Harmful, Seizures or Epileptic EEG Abnormalities: Is There any Clinical Data?

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Abstract

Cognitive impairment is a common and often devastating co-morbidity of childhood epilepsy. While the etiology of the epilepsy is critical determinant of cognitive outcome, there is considerable evidence from both rodent and human studies that indicate that seizures and interictal epileptiform abnormalities can contribute to cognitive impairment. A critical feature of childhood epilepsy is that the seizures and epileptiform activity are occurring in a brain with developing, plastic neuronal circuits. The consequences of seizures and interictal epileptiform activity in the developing brain differ from similar paroxysmal events occurring in the relatively fixed circuitry of the mature brain. In animals it is possible to study interictal spikes independently from seizures and it has been demonstrated that interictal spikes are as detrimental as seizures during brain development. In the clinic distinguishing the differences between interictal spikes and seizures is more difficult, since both typically occur together. However, both seizures and interictal spikes result in transient cognitive impairment. Recurrent seizures, particularly when frequent, can lead to cognitive regression. While the clinical data linking interictal spikes to persistent cognitive impairment is limited, interictal spikes occurring during the formation and stabilization of neuronal circuits likely contributes to aberrant connectivity. There is insufficient clinical literature to indicate whether interictal spikes are worse than seizures during brain development.

Keywords

Interictal spikes; cognition; learning; memory

Introduction

Cognitive impairment is a devastating co-morbidity of childhood epilepsy. Many parents and clinicians consider the cognitive impairment associated with childhood epilepsy to be far more impairing than the seizures. While the primary determinant of cognitive outcome in childhood epilepsy is etiology, there is increasing evidence that seizures and interictal EEG abnormalities contribute to cognitive impairment. A critical question is which is more detrimental, the seizures or the interictal abnormalities? Answering this question is fundamental to our therapeutic approach to children with epilepsy.

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In children it is often difficult to differentiate the adverse cognitive effects of interical spikes (IIS) from seizures since typically they occur together. In addition, teasing out the effects of the seizures and IIS from the etiology can be difficult. In animal studies one can induce seizures, IIS, or both, in the normal brain allowing investigation into the biological mechanisms underpinning cognitive impairment due to seizures or IIS. In this review pertinent animal data will first be briefly discussed laying the groundwork for the human studies.

Animal Data

Recurrent Seizures

There is now a substantial literature showing that recurrent seizures in the developing brain can result in long-term adverse consequences. Rat pups subjected to a series of recurrent seizures during the first weeks of life have considerable cognitive impairment including deficits of spatial cognition in the Morris water maze {Holmes, 1998 8430 /id;Huang, 1999 8412 /id;Liu, 1999 8414 /id;Karnam, 2009 11908 /id;Karnam, 2009 11909 /id} and delayed non-match to sample task {Kleen, 2011 13211 /id}, impairment of auditory discrimination {Neill, 1996 8451 /id}, altered activity level {Karnam, 2009 11908 /id} and reduced behavioral flexibility {Kleen, 2011 12674 /id}. Recurrent early-life seizures also result in a number of physiological changes including a persistent decrease in GABA currents in the hippocampus {Isaeva, 2006 9420 /id} and neocortex {Isaeva, 2009 11924 /id;Isaeva, 2009 11924 /id}, enhanced excitation in the neocortex {Isaeva, 2010 12190 /id}, impairment in spike frequency adaptation {Villeneuve, 2000 8409 /id}, marked reductions in afterhyperpolarizing potentials following spike trains {Villeneuve, 2000 8409 /id}, impaired long-term potentiation (LTP) {Karnam, 2009 11908 /id}, enhanced short-term plasticity {Hernan, 2013 13406 /id}, alterations in theta power {Karnam, 2009 11909 /id} and impaired place cell coherence and stability {Karnam, 2009 11909 /id}.

Despite the detrimental effects of early-life seizures on cognitive function, recurrent seizures during the first two weeks of life do not result in cell loss {Holmes, 1998 8430 /id;Liu, 1999 8414 /id;Riviello, 2002 8383 /id}. However, seizures in immature rats can result in synaptic reorganization as evidenced by CA3 sprouting {Holmes, 1998 8430 /id;Huang, 1999 8412 /id;Huang, 2002 8615 /id;Sogawa, 2001 8390 /id} and decreased neurogenesis {McCabe, 2001 8398 /id}.

To determine the relationship between age of seizure onset and cognitive outcome Karnam et al. {Karnam, 2009 11908 /id}, induced 50 seizures using flurothyl, an inhaled convulsant in rat pups between postnatal day (P) P0–10 or P15–P25. Rats were studied as adults in the Morris water maze, radial-arm water maze, open field, and active avoidance test. To assess synaptic strength and network excitatory and inhibitory function animals were evaluated with long-term potentiation (LTP) and paired-pulse facilitation/inhibition. Compared to controls, both groups of rats with recurrent seizures were impaired in spatial memory in both water maze tests and had altered activity in the open field. Rats with recurrent seizures had impaired LTP but showed no deficits in paired-pulse facilitation or inhibition. The cognitive deficits did not vary as a function of age during which the seizures occurred.

Whereas recurrent seizures in immature rats result in cognitive impairment, recurrent seizures in adult animals, in which the neuronal circuitry is relatively fixed, appears to result in fewer deficits. Investigators have examined the effect of kindling on spatial memory with the animal being studied after or during kindling using both the radial arm maze and water maze. The timing of the kindling stimulations determines type of deficit. If the kindling stimulation is given prior to the learning trial there is impaired performance {Robinson, 1993 10034 /id}{McNamara, 1992 1167 /id}{Gilbert, 2000 7058 /id} whereas kindling immediately after the learning trial impaired retention {Gilbert, 1996 9903 /id}. Whether kindling has long-term effects on learning is not clear, with some authors finding impairment following hippocampal kindling {Leung, 1990 335 /id;Leung, 1991 334 /id} while other authors have found no long-standing effects {McNamara, 1992 1167 /id}. While Lin et al. {Lin, 2009 11539 /id} found that recurrent flurothyl-induced seizures over 11 days in adult rats lead to progressive impairment in a spatial hidden goal task, full recovery did occur.

In the majority of studies, recurrent seizures have been induced in normal rats. However in children seizures do not occur in the “normal brain.” The assumption that seizures induced in the normal brain versus the pathological have similar effects may be erroneous. Lucas et al. {Lucas, 2011 12463 /id} found that seizures induced in rat pups with malformations of cortical development but without seizures had severe spatial cognitive deficits in the water maze. When the rat pups were subjected to recurrent flurothyl-induced seizures and tested at 25 days of age (immediate post-weaning) there was a worsening of performance. In contrast, in animals tested during adolescence, there was no longer an additional adverse effect of seizures. The authors also investigated whether the severity of the structural abnormality and seizures impacted brain weight, cortical thickness, hippocampal area and cell dispersion area. Early-life seizures did not have a significant impact on any of these parameters. These observations indicate that the major factor responsible for the cognitive impairment in the rats with cortical dysplasia was the underlying brain substrate, not the seizures.

Interictal spikes

In adult rats, IIS have been shown to result in task specific cognitive impairment in adult rodents. Using a within-subject analysis to analyze how IIS might independently memory processing in the hippocampus, Kleen et al. {Kleen, 2010 12185 /id} studied rats that developed chronic IIS following intrahippocampal pilocarpine in a hippocampal-dependent operant behavior task, the delayed-match-to-sample test. Hippocampal IIS that occurred during memory retrieval strongly impaired performance. However, IIS that occurred during memory encoding or memory maintenance did not affect performance in those trials. IIS were most dysfunctional when occurring when hippocampal function was critical, during the active engagement of neurons involved in performing the task.

Single cell firing patterns have been investigated following IIS in mature rodents. There is a sustained reduction of action potentials in the hippocampus for up to two seconds following IIS. Furthermore, when occurring in flurries, IIS can reduce action potential firing for up to six seconds {Zhou, 2007 10857 /id}. The widespread inhibitory wave immediately after IIS can also reduce the power of gamma oscillations and other oscillatory signals in the hippocampus {Urrestarazu, 2006 11616 /id}. Since oscillations are closely coupled with

ongoing learning and memory function {Halasz, 2005 12171 /id}, this disruption in oscillations likely contributes to cognitive deficits.

In addition to causing transitory cognitive impairment, IIS during early brain development may have long-term adverse effects on the developing neural circuits. In studies of the effects of IIS on network development IIS were elicited by either penicillin {Baumbach, 1981 11994 /id;Crabtree, 1981 12010 /id} or bicuculline {Ostrach, 1984 12009 /id;Campbell, 1984 12008 /id} through focal application on the striate cortex of rabbits. IIS were elicited for 6–12 hours following each drug application which were given daily from P8–9 to P24–30. Despite frequent IIS, none of the rabbits had behavioral seizures. In single-unit recordings from the lateral geniculate nucleus, superior colliculus and occipital cortex ipsilateral to the hemisphere with IIS, there was an abnormal distribution of receptive field types, whereas normal recording were found from the contralateral hemisphere. Remarkably, this finding was age-dependent. Adult rabbits with similarly induced IIS during adulthood had normal disruption of receptive field types, highlighting an additional vulnerability of critical developmental periods to cumulative IIS effects over time.

To determine the long-term effects of IIS on executive function, Hernan et al. {Hernan, 2013 13517 /id} studied the effects of IIS in the prefrontal cortex. P21 rat pups received intracortical injections of bicuculline into the prefrontal cortex while the EEG was continuously recorded and the animals were tested as adults for short-term plasticity. At the time the adults were tested IIS were no longer present. IIS resulted in a significant increase in STP bilaterally in the prefrontal cortex. In a delayed non-match-to-sample task IIS rats showed marked inattentiveness without deficits in working memory. Rats also demonstrated deficits in sociability, showing autism-like behavior. The study showed that early-life focal IIS in the PFC have long-term consequences for cognition and behavior at a time when IIS are no longer present. This study also showed that focal IIS during development can disrupt neural networks, leading to long-term deficits and thus may have important implications in attention deficit disorder and autism.

Generalized and multifocal IIS have also been elicited in young rats with flurothyl {Khan, 2010 13396 /id}. Rat pups were given a low dose of flurothyl for four hours for a period of ten days during continuous EEG monitoring. Rats developed IIS without seizures while age-matched controls under similar testing conditions showed few IIS. When rats were tested as adults, there was impairment in reference memory in the probe test of the Morris water maze, reference memory impairment in the four-trial radial-arm water maze and impaired LTP. Early-life IIS also resulted in impaired new cell formation and decreased cell counts in the hippocampus, indicating a potential mechanism in which IIS during development can produce cumulative lasting effects in addition to any dynamic disruptions.

Lessons from the animal data

Animal data indicates that recurrent seizures and IIS can result in adverse effects on cognition. Both seizures and IIS can result in transient cognitive impairment. In the case of seizures the transient cognitive impairment occurs during the seizure and post-ictal period whereas IIS specifically alters the neural circuits involved in that process, stressing the importance of matching the affected neural substrate with a cognitive test that assesses its

intrinsic function. The IIS must occur at a particular moment in cognitive processing such that the process is vulnerable to disruption.

Both seizures and IIS in the immature brain can have permanent adverse effects on cognition that extend well beyond the time when the seizures and IIS have stopped. Both seizures and IIS appear to be deleterious when occurring in the developing brain than in the fully mature neural network. While the animal data on IIS remains limited, it appears that IIS are as harmful as seizures in the developing brain.

Human data

Seizures

Animal data would predict that recurrent seizures in the immature brain, particularly if very frequent, would result in cognitive impairment. This appears to be the case in children. In general, childhood epilepsy carries a significant risk for a variety of problems involving cognition. The distribution of IQ scores of children with epilepsy is skewed toward lower values {Farwell, 1985 51 /id;Neyens, 1999 6375 /id} and the number of children experiencing difficulties in school because of learning disabilities or behavioral problems is greater than in the normal population {Wakamoto, 2000 6372 /id;Bailet, 2000 6373 /id;Williams, 1998 6376 /id;Sillanpaa, 1998 6383 /id}. Predictors of poor cognitive outcome include a high seizure frequency {Hermann, 2008 11488 /id} and long duration of the epilepsy {Farwell, 1985 51 /id;Seidenberg, 1986 9076 /id}.

However, many children that develop epilepsy appear to have cognitive deficits that precede the onset of the seizures, suggesting that etiology of the seizures, not the seizures themselves are responsible for the impaired cognition {Jackson, 2013 13507 /id}{Fastenau, 2009 12774 /id}. Most children with epilepsy maintain stable IQ scores. However, there is evidence that some children with epilepsy slow in their mental development {Neyens, 1999 6375 /id} or even have progressive declines of IQ on serial intelligence tests over time {Bourgeois, 1983 179 /id}. In the case of temporal lobe epilepsy in children, increasing duration of epilepsy is associated with declining performance across both intellectual and memory measures {Hermann, 2002 7176 /id}

Animal data would also suggest that epilepsy onset in early childhood would be detrimental. Indeed predictors of cognitive impairment in children with epilepsy include early onset of seizures {Huttenlocher, 1990 11115 /id;Glosser, 1997 11116 /id;Bulteau, 2000 11117 /id;Cormack, 2007 10188 /id;Hermann, 2002 7176 /id;Bjornaes, 2001 11121 /id}, particularly during the neonatal period {Glass, 2009 12031 /id}. The epileptic syndromes in which psychomotor deterioration occurs have an early age of onset. Such syndromes include early infantile epileptic encephalopathy with suppression-burst (Ohtahara syndrome), early myoclonic encephalopathy, migrating partial epilepsy in infancy, infantile spasms (West syndrome), severe myoclonic epilepsy of infancy (Dravet syndrome), Lennox-Gastaut syndrome, myoclonic-astatic epilepsy, continuous spike-wave discharges of sleep (CSWDS), and Landau-Kleffner syndrome {Nabbout, 2003 7961 /id;Panayiotopoulos, 2002 7624 /id;Genton, 1997 6016 /id}.

While etiology of the epilepsy undoubtedly plays a major role in cognitive development, there are indications that early-life seizures independent of etiology can lead to cognitive impairment {Glass, 2009 12031 /id}{Korman, 2013 13506 /id}. In a study of neuropsychological function in children with focal cortical dysplasia Korman et al. {Korman, 2013 13506 /id} found that age of onset of epilepsy and extent of the dysplasia each contributed independently to cognitive dysfunction. The authors suggested that early onset of epilepsy disrupted critical periods of development and lead to poor cognitive outcomes. Furthermore, it was concluded that a later age of onset of epilepsy would not be expected to mitigate deficits because of widespread pathology, nor would a localized lesion be likely to mollify the developmental deficits resulting from an early age of epilepsy onset.

Interictal spikes

Animal studies would predict that IIS will result in transitory cognitive impairment. IIS in humans can produce brief disturbances in neural processing, resulting in a phenomenon called transitory cognitive impairment {Binnie, 2003 7831 /id}. Aarts et al. {Aarts, 1984 6586 /id} noted that IIS can briefly disrupt neural processes affecting function within the brain region where they occur. The authors analyzed the effect of IIS on verbal or non-verbal short-term memory in patients with epilepsy but without overt clinical manifestations during these discharges, thus targeting the so-called “subclinical” manifestations of IIS. In right-handed individuals the authors reported that right-hemisphere IIS were associated with errors in a non-verbal task whereas left-hemisphere IIS resulted mainly in errors in verbal tasks. EEG discharges interfered mainly when they occurred simultaneously with the presentation of the stimulus, corresponding with the encoding phase of the task. Shewmon and Erwin in a series of elegantly performed studies {Shewmon, 1989 7827 /id;Shewmon, 1988 7828 /id;Shewmon, 1988 7829 /id;Shewmon, 1988 7830 /id} further localized the effect, noting that occipital IIS could disrupt visual perception. IIS in the occipital region caused transitory deficits with stimuli presented in the contralateral visual field. Deficits were most pronounced when the stimulus was presented during the slow wave following the IIS.

In a study of 10 adult patients with depth electrodes implanted into their hippocampi for preoperative seizure localization, Kleen et al. {Kleen, 2013 13395 /id} recorded EEG during 2,070 total trials of a short-term memory task, with memory processing categorized into encoding, maintenance, and retrieval. The influence of hippocampal IIS on these processes was analyzed and adjusted to account for individual differences between patients. Hippocampal IIS occurring in the memory retrieval period decreased the likelihood of a correct response when they were contralateral to the seizure focus ($p < 0.05$) or bilateral ($p < 0.001$). Bilateral IIS during the memory maintenance period had a similar effect ($p < 0.01$), particularly with spike-wave complexes of longer duration ($p < 0.01$). The results strengthen the view that IIS contribute to cognitive impairment in epilepsy depending upon when and where they occur. The results of this study confirmed an earlier study by Krauss et al. {Krauss, 1997 11988 /id} who found declines in working memory due to IIS.

Because of their frequent nature, IIS in Benign Epilepsy with Centro-Temporal Spikes (BECTS) has generated considerable interest. The vast majority of studies have found that

children with BECTS have a variety of cognitive impairments {Danielsson, 2009 13504 /id} {Fonseca, 2007 13494 /id}. Children with BECTS have been reported to have mild language defects, revealed by tests measuring phonemic fluency, verbal re-elaboration of semantic knowledge, and lexical comprehension {Verrotti, 2011 13503 /id}{Riva, 2007 13486 /id} as well as impairment in non-verbal functions {Metz-Lutz, 1999 13121 /id;Metz-Lutz, 2006 13492 /id}. The cognitive profile of the deficits is related to the side of focus with non-verbal deficits significantly correlated with the lateralization of the epileptic focus in the right hemisphere with verbal deficits seen with left hemisphere discharges. Frontal functions like attention control, response organization and fine motor speed, were impaired in the presence of active discharges independently of the lateralization of the epileptic focus {Metz-Lutz, 1999 13121 /id;Metz-Lutz, 2006 13492 /id}. However, not all studies have shown consistent neuropyshological profiles in children with BECTS. Some of the variability in function may be explained by fluctuations in IIS frequency and cognitive performance. In a study of six children with BECTS month-to-month marked fluctuations in cognitive abilities and frequency and location of IIS have been noted {Ewen, 2011 13502 /id}.

Transitory cognitive impairment has been studied during IIS in children with BECTS using EEG and computerized neuropsychological testing in a visual discrimination between words and pseudowords task {Fonseca, 2007 13505 /id}. A small percentage of children (15.4%) made a significantly greater proportion of errors during IIS than during IIS-free periods. Of interest, in this study the IIS were inhibited by the task, likely due to increased alertness, in 20 of the 33 children.

Whether there is a relationship between the frequency of IIS and cognition is unclear with some authors showing a relationship between number of spikes {Filippini, 2013 13510 /id} and others finding no such relationship {Fonseca, 2007 13494 /id;Tedrus, 2010 13512 /id} {Goldberg-Stern, 2010 13513 /id}. In a study of IIS in 182 children with a variety of epilepsy syndromes, including BECTS, Ebus et al. {Ebus, 2012 13484 /id} calculated the IIS index using a 24 hour ambulatory EEG and compared the findings to neuropsychological tests. The IIS index was calculated in wakefulness and in sleep, as percentage of time in five categories (0%, <1%, 1–10%, ≥10–50% and ≥50%). The group of patients with diurnal IIS in ≥10% of the EEG record showed impaired central information processing speed, short-term verbal memory and visual-motor integration. This effect was seen independently from other EEG-related and epilepsy-related characteristics, and independently from epilepsy syndrome diagnosis.

If IIS can cause cognitive impairment it would be reasonable to consider suprressing the IIS with antiepileptic drugs. In a double-blinded, placebo-controlled, crossover study, 61 children with well-controlled or mild epilepsy were randomly assigned to add-on therapy with either lamotrigine followed by placebo or placebo followed by lamotrigine {Pressler, 2005 10280 /id}. Global rating of behavior significantly improved only in patients who showed a significant reduction in either frequency or duration of discharges during active treatment, but not in patients with without a significant change in discharge rate. However, in a small study using sulthiame to treat the IIS in BECTS, it was found that children had a significant deterioration in their reading ability, despite a reduction in IIS frequency

{Wirrell, 2008 13516 /id}. A major obstacle to designing studies to treat IIS is the lack of well tolerated drugs that effectively suppress IIS.

Despite the impairment seen while there are active IIS, children with BECTS have no permanent effects of the IIS with the vast majority of children having no residual cognitive impairment {Callenbach, 2010 13501 /id}. However, two related conditions which appear to be a continuum of BECTS, Landau-Kleffner syndrome (LKS) and and Continuous Spike-Wave of Sleep (CSWS), have a substantially worse prognosis {Metz-Lutz, 2006 13492 /id} {Halasz, 2005 12171 /id}{Seegmuller, 2012 13519 /id}{Mikati, 2005 13520 /id}{Margari, 2012 13524 /id}.

LKS is a rare childhood disorder characterized by a loss or regression of previously acquired language and epileptiform discharges involving the temporal or parietal regions of the brain {Beaumanoir, 1992 2006 /id;Cooper, 1978 4311 /id;Hirsch, 1990 4680 /id;Landau, 1957 4891 /id}. Although a considerable amount of variation exists in the disorder, the typical history is of a child developing an abrupt or gradual loss of language ability and inattentiveness to sound, with onset during the first decade of life. This interruption in communication skills is generally closely preceded, accompanied, or followed by the onset of seizures or an abnormal EEG, or both {Deonna, 1991 3351 /id;Sawhney, 1988 5325 /id}. Receptive dysfunction, often referred to as auditory agnosia, may be the dominant feature early in the course of the disorder. In some children, the disorder progresses to a point at which the child cannot even recognize sounds. In addition to the aphasia, many of the children have behavioral and psychomotor disturbances, often appearing autistic.

The EEG in LKS typically shows repetitive spikes, sharp waves, and spike-and-wave activity are seen in the temporal region or parietal-occipital regions bilaterally. Sleep usually activates the record, and, in some cases, the abnormality is seen only in sleep recordings. Speech deficits in the syndrome may be explained by either disruption of normal connections or an excessive inhibitory reaction to epileptiform discharges. However, the severity of the aphasia does not always have a close correlation with degree of EEG abnormality {Foerster, 1977 4533 /id;Holmes, 1981 4699 /id} or clinical seizures {Landau, 1957 4891 /id}. It has been suggested that the epileptiform activity is an epiphenomenon and simply is reflective of an underlying cortical abnormality {Holmes, 1981 4699 /id;Kellermann, 1978 4836 /id;Lou, 1977 4971 /id}. Even if the EEG parallels speech recovery, this does not prove that epileptiform activity causes aphasia. It is also possible that the decreased epileptiform activity during speech recovery simply reflects resolving injury to the speech areas.

While steroid treatment and IVIG has been somewhat effective in treating LKS {Mikati, 2005 13520 /id}, this treatment could treat the underlying cause of LKS, such as inflammation. However, there is limited data indicating that there is a direct relationship between IIS and language impairment. Subpial resection, which eliminates epileptiform activity in the receptive language cortex, has been shown to reduce IIS and resolve linguistic function in LKS {Castillo, 2008 13518 /id}{Grote, 1999 6331 /id}. Since subpial resection would not be expected to alter the underlying etiology of LKS, the fact that the patients

improve with a destructive surgical procedure would indicate that the epileptiform discharges contribute LKS.

A condition related to LKS is epilepsy with continuous spike- wave discharges during sleep (CSWS){Tassinari, 1992 2007 /id}. The disorder has also been called *electrical status epilepticus during sleep* (ESES){Tassinari, 2000 7308 /id}. The distinguishing feature of CSWDS is the continuous bilateral and diffuse slow spike-wave activity persisting through all of the slow wave sleep stages. The spike-wave index (total minutes of all spike-waves multiplied by 100 and divided by the total minutes of non-REM sleep without spike-wave activity) ranges from 85% to 100%. The cause of CSWS is unknown, but early developmental lesions play a major role in approximately half of the patients, and genetic associations have recently been described. Clinical, neurophysiological, and cerebral glucose metabolism data support the hypothesis that IED play a prominent role in the cognitive deficits by interfering with the neuronal networks at the site of the epileptic foci but also at distant connected areas {Van, 2013 13523 /id}. High-dose benzodiazepines and corticosteroids have been successfully used to treat clinical and electroencephalographic features {Sanchez, 2013 13521 /id;Sanchez, 2013 13522 /id}. As with LKS there is no definitive data that indicates that the EEG abnormalities are responsible for the cognitive impairment. However, as with LKS, children with CSWS typically does not improve unless there is a reduction of spike-wave discharges during sleep {Scholtes, 2005 9064 /id} {Brazzo, 2012 13525 /id}.

There also appears to be a link between IIS and autism. Studies examining the EEG of individuals with autistic spectrum disorder show a very high rate of IIS {Kim, 2006 6 /id} {Parmeggiani, 2007 13419 /id}{Hashimoto, 2001 13418 /id}. For example, Hughes and Melyn {Hughes, 2005 12157 /id} found abnormal EEGs with IIS in 75% of 59 children with childhood autism. Many children with ASD with have IIS on their EEG but do not experience seizures {Kim, 2006 13514 /id}. In children with ASD the most common location of IIS are in the frontal region, suggesting that frontal dysfunctions are important in the mechanism of symptoms in autism {Hashimoto, 2001 13418 /id}, The location of IIS in the frontal regions is of interest since one of the major abnormalities in children with ASD is a disturbance in executive control {Hughes, 1997 12155 /id;Hughes, 1999 12156 /id;Hughes, 1994 12154 /id}. The prefrontal cortex is a critical structure likely to be involved in executive control {Shalom, 2009 12149 /id;Dumontheil, 2008 12150 /id;Bachevalier, 2006 12151 /id}.

In children with ASD it is not clear whether epileptiform discharges contribute or cause ASD or whether ASD is a disturbance of brain function and epileptiform discharges are a reflection of a dysfunctional brain. In this regard the rodent data is of interest in view of the finding that IIS in the prefrontal cortex of rats results in ASD-like behavior {Hernan, 2013 13406 /id}.

Which is Worse: IIS or Seizures

There is now clear evidence that both seizures and IIS in immature rodents and children can result in cognitive impairment. The effects of both IIS and spikes in the immature brain are dependent upon brain maturation. In the fully developed brain seizures and IIS result in

temporary impairment and appear to have few long term effects whereas in the developing brain both IIS and seizures have more profound effects.

Determining which is worse, seizures or IIS is difficult to determine clinically since it is difficult to separate out the two. However considering that IIS occur 24 hours/day 7 days a week, it may be that IIS are more detrimental. It is widely believed that frequent epileptiform events seen in children with epilepsy are capable of causing deleterious alterations in developing brain networks and are therefore associated with the high incidence of cognitive deficits and psychiatric comorbidities in these patients

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