Review article

Epilepsy and autism spectrum disorders: Are there common developmental mechanisms?

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Abstract

Autistic spectrum disorders (ASD) and epilepsies are heterogeneous disorders that have diverse etiologies and pathophysiologies. The high rate of co-occurrence of these disorders suggest potentially shared underlying mechanisms. A number of well-known genetic disorders share epilepsy and autism as prominent phenotypic features, including tuberous sclerosis, Rett syndrome, and fragile X. In addition, mutations of several genes involved in neurodevelopment, including ARX, DCX, neuroligins and neuropilin2 have been identified in children with epilepsy, ASD or often both. Finally, in animal models, early-life seizures can result in cellular and molecular changes that could contribute to learning and behavioral disabilities as seen in ASD. Increased understanding of the common genetic, molecular and cellular mechanisms of ASD and epilepsy may provide insight into their underlying pathophysiology and elucidate new therapeutic approaches of both conditions.
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1. Introduction

Epilepsy and autistic spectrum disorders (ASD) often occur together. Approximately 30% of children with autism have epilepsy and 30% of children with epilepsy have autism [1]. When epilepsy and ASD occur together

they are often associated with intellectual disabilities. Epilepsy and ASD are both heterogeneous disorders with multiple etiologies and pathophysiologies, but might there be common underlying pathophysiological mechanisms that can help us to explain the frequent co-occurrence of these two conditions?

It has been proposed that both ASD and epilepsy can be understood as disorders of synaptic plasticity that result in imbalances of excitation and inhibition in the developing brain (Fig. 1). How might this result in an increased association of ASD and epilepsy? Both ASD and epilepsy may result from the same pathophysiological mechanisms resulting in a developmental imbalance of excitation and inhibition. This may occur in genetic conditions that result in abnormal excitability and disrupted synaptic plasticity in the developing brain. This abnormal plasticity can be of genetic origin resulting in both ASD and epilepsy such as fragile X, Rett syndrome, CDKL5 mutations, tuberous sclerosis complex
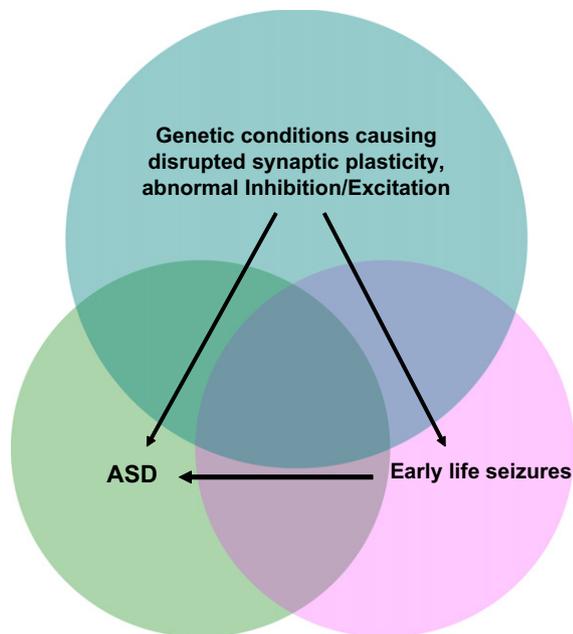
Fig. 1. There is evidence that both epilepsy and ASD arise from abnormal excitability and disrupted synaptic plasticity in the developing brain. This abnormal plasticity can result from genetic conditions. In addition, epilepsy development (epileptogenesis) and/or seizures during early post-natal development may alter synaptic plasticity and contribute to ASD. Abnormalities in synaptic plasticity can arise from alterations in receptors, signaling molecules or neurotrophins. Multiple of these molecules are known to be altered by early-life seizures and genetic conditions associated with both ASD and epilepsy.

(TSC), neuroligin mutations and "interneuronopathies" resulting from anstaless-related homeobox, X-linked (ARX) and Neuropilin 2 (NRP2) gene mutations. In addition, the process of epilepsy development (i.e., epileptogenesis) and/or spontaneous seizures themselves may result in maladaptive synaptic plasticity producing imbalances of excitation and inhibition that contribute to learning and behavioral difficulties. Abnormalities in synaptic plasticity can arise from alterations in receptors, signaling molecules or neurotropins. Alterations in multiple of these molecules are known to occur after early-life seizures and with genetic conditions known to be associated with both ASD and epilepsy (Fig. 1).

Synaptic plasticity describes the process whereby synapses, the connections between 2 neurons, get strengthened by experience or practice. When synapses are activated, depolarization mediated by AMPA receptors allows release of magnesium blockade and calcium entry through NMDA receptors. This triggers calcium dependent activation of kinases and other signaling pathways resulting in enhanced gene transcription and trafficking of receptors that result in faster and stronger synaptic connections. This is known as long-term potentiation and is thought be the cellular basis of learning. Synaptic plasticity depends on a variety of proteins whose genes are disrupted in genetic conditions associated with autism and epilepsy. These include cyclin-dependent

kinase-like 5 (CDKL5) in West syndrome, MeCP2 in Rett syndrome, FMRP in fragile X mental retardation syndrome, mTOR in tuberous sclerosis, and reelin in lissencephaly. These are discussed in more detail below.

2. Fragile X syndrome

Fragile X syndrome (FXS) is the most frequent form of inherited mental retardation and often presents with autism spectrum disorder and epilepsy. The hallmark of FXS pathology is the hyperabundance of dendritic spines with a long, thin, and otherwise immature morphology [2,3]. Fragile X results from an expanded triplet repeat in the *FMR1* gene. *Fmr1* knock-out mice (an animal model for FXS) exhibits a similar excess of long, thin spines [4] and display altered learning and behavior, greater susceptibility to seizures, and altered synaptic plasticity [5]. The *FMR1* gene is located at the cytogenetic fragile X site on the X-chromosome [6]. Expanded CGG repeats within the 5′-untranslated region of *FMR1* result in FXS (normal length of ∼30 triplets, 55–200 triplets in premutations (in FXS carriers), 200–800 triplets in affected FXS individuals). *FMR1* gene codes for the fragile X mental retardation protein (FMRP). FMRP is an mRNA-binding protein abundant in the brain, that binds to and regulates 4% of brain mRNA, including many RNAs important for synaptic plasticity. FMRP regulates mRNA transport in dendrites and is associated with polyribosomes in neuronal dendrites and spines where it regulates local protein synthesis important for spine development and synaptic plasticity. In the absence of FMRP, excess and dysregulated mRNA translation leads to altered synaptic function and loss of protein synthesis-dependent plasticity. FMRP is also involved in axonal development, synapse formation, and the development and wiring of neuronal circuits [6–14].

FMRP regulates metabotropic glutamate receptor (mGluR)-induced long-term depression (LTD), and in the absence of FMRP, there is excessive AMPA receptor (AMPAR) internalization and exaggerated LTD leading to impaired synaptic excitatory function ("The mGluR theory of fragile X"; [15]). Stimulation of group1 mGluRs activates protein phosphatase 2-A (PP2A) and dephosphorylates FMRP, allowing rapid translation of FMRP-associated mRNAs that lead to removal of AMPARs from the cell membrane (LTD). Soon after, the mammalian target of rapamycin (mTOR) is activated and inhibits PP2A and leads to FMRP phosphorylation via S6 kinase. Inhibition of FMRP phosphorylation leads to excessive AMPA receptor internalization, disrupted synaptic function and exaggerated Ltd. This is known as the "mGluR theory of fragile X", and although it adds to our understanding of intellectual impairment in fragile X syndrome, it does not seem to readily explain the CNS hyperexcitability

and resultant epilepsy associated with this disorder. Recent studies on group I mGluR-mediated epileptogenesis, however, have begun to reveal a possible connection [16]. Bianchi et al. provided compelling evidence that a voltage-gated inward current, I mGluR(V), is the cellular basis for the epileptogenic behavior induced by activation of the mGluR5 receptor [17–20]. Evidence for a connection between the absence of *Fmr1* and epileptogenesis was further supported a study of neocortical circuits in FMRP knock-out mice that found an increased intrinsic excitability in excitatory neurons from the knockout [14]. In addition, dysregulation of glutamergic neurons in fragile X syndrome can disrupt the normal actions of inhibitory GABAergic neurons, and downregulation of GABA receptor subunits [21–23] and altered expression of a number of enzymes involved in the metabolism of GABA [24] have also been identified that could contribute to hyperexcitability and epilepsy in the fragile X syndrome.

3. Tuberous sclerosis

Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome characterized by benign tumors, early-onset epilepsy, mental retardation, and autism. TSC results from mutations of hamartin or tuberin (encoded by TSC1 and TSC2 genes), which together inhibit the phosphatidyl inositol 3-kinase (PI3) signaling pathway, involving the mammalian target of rapamycin (mTOR) and a cascade of other downstream kinases and translational factors that stimulate protein translation, cell growth and proliferation (see Fig. 3). Mutations of hamartin or tuberin in TSC leads to hyperactivation of the mTOR and downstream signaling pathways result in increased cell growth, proliferation and abnormal gene expression. Exact mechanisms of epilepsy and autism in TSC are still unknown, but alterations in trafficking of AMPARs, and in expression of specific glutamate and GABA-A receptor subunits and decreases in the glutamate transporter GLT-1 may all contribute to imbalances of excitation and inhibition [25,26].

4. Rett syndrome

Rett syndrome (RTT) is a post-natal progressive neurodevelopmental disorder that manifests in girls during early childhood. Symptoms appear over stages beginning at 6–18 months and include loss of acquired speech, social skills, purposeful use of the hands and motor skills. Patients also suffer from epilepsy, anxiety, and a host of autonomic abnormalities. Girls appear normal at birth. After a period of normal development, a healthy-looking baby girl falls into developmental stagnation at 6–18 months, followed by rapid deterioration, loss of acquired speech, and the replacement of purposeful use of the hands with incessant stereotypies, a char-

acteristic of the syndrome. Patients also develop social behavior abnormalities and are often misdiagnosed as having autism. The condition worsens with loss of motor skills and profound cognitive impairment, anxiety, seizures, and a host of autonomic abnormalities [27]. RTT is caused by mutations in the gene encoding methyl-CpG binding protein 2 (MeCP2), a transcriptional regulator involved in chromatin remodeling and the modulation of RNA splicing. In resting neurons, MeCP2 regulates gene expression by binding to methylated CpG dinucleotides and recruiting histone deacetylase (HDAC) co-repressor complexes and chromatin remodeling proteins. This most commonly leads to chromatin compaction, making the promoter inaccessible to the transcriptional machinery and transcriptional repression [28], although recent evidence suggests that MeCP2 can also act as a transcriptional activator for some genes [27]. Neuronal activity induces MeCP2 phosphorylation and leads to its release from the promoter region and dissociation of the corepressor complex. The hyperacetylated chromatin allows access to transcriptional machinery and target gene expression. In RTT, the absence of MeCP2 causes a loss of activity dependent changes in gene expression that may disrupt synaptic plasticity [29]. MeCP2 loss has been shown to induce changes in expression of thousands of genes [27], although the precise mechanism by which loss of MeCP2 results in either epilepsy or ASD remains uncertain. Recent evidence suggests that alterations in cortical glutamatergic synaptic responses and excitatory connectivity resulting in a relative excess of inhibition compared to excitation may play an important role [30–32].

5. Neuroligin/neurexin mutations

Neuroligins and neurexins are proteins crucial for aligning and activating both excitatory and inhibitory synapses during development. Mutations in a number of these genes, along with the associated Shank3 scaffolding protein, have been implicated in autism. An altered balance between excitatory synapses and inhibitory synapses could affect learning and social behavior as well as contribute to epilepsy. Mutations in neuroligin-1, 3 and -4 have been identified in human patients with ASDs [33,34]. The Arg451 → Cys451 substitution in NL-3 found in ASD patients results in enhanced inhibitory transmission and impaired social behavior in knock-in mice [35]. Overexpression of the mutant NL-1 found in ASD patients depressed the number of excitatory synapses and excitatory synaptic strength and resulted in abnormal social behavior in mice [36]. These findings suggest that a decreased *E/I* ratio due to either increased inhibitory synaptic transmission or decreased excitatory transmission may contribute to human.

6. Interneuronopathies

6.1. Arx

Developmental abnormalities resulting in reduced numbers of cortical and hippocampal interneuron subtypes have been reported to cause both severe early-life epilepsies and autism. In humans, ARX mutations of the aristaless-related homeobox, X-linked (ARX) gene result in several clinical syndromes all of which are associated with intellectual disability, ASD and early-life seizures, most often infantile spasms. In animal models, ARX knockouts have reduced interneuron cell types and a variety of seizure types (absence, myoclonic, generalized tonic-clonic) beginning in early life [37].

6.2. Neuropilin 2 mutations

Neuropilin 2 (NRP2) is a receptor for the axon guidance mediator Semaphorin 3F. Polymorphisms of *NRP2* gene have been associated with autism [38]. *NRP2* deficient mice have shorter seizure latency after chemoconvulsants, develop spontaneous seizures, have reductions in specific subsets of hippocampal interneurons (parvalbumin and neuropeptide Y) and reduced dendritic length and complexity on CA1 pyramidal neurons [39].

In conclusion, a number of different genetic mutations result in both ASD and epilepsy. Many of these mutations cause abnormalities of synaptic plasticity that result in imbalances in excitation and inhibition in the developing brain. In addition to genetic abnormalities that disrupt synaptic plasticity and contribute to both epilepsy and ASD, seizures and epilepsy development (epileptogenesis) in early life may impact synaptic plasticity and potentially contribute to ASD and intellectual disability. What are the changes resulting from epileptogenesis or seizures in the developing brain that may alter synaptic plasticity and contribute to ASD?

7. Effects of seizures and epileptogenesis on the developing brain

Epileptogenesis is a process that proceeds over months to years in humans, and over days to weeks in rodent models. After an initial precipitating event such as a prolonged febrile seizure or head trauma, there are processes that occur very rapidly including ion channel activation, post-translational changes, and immediate early genes. Next, over a period of days to weeks, there are transcriptional events, neuronal death and inflammation. Over the ensuing weeks, months to years, sprouting, network reorganization, neurogenesis and gliosis occur. These processes may lead to the development of the first spontaneous seizures, and then be recapitulated with each seizure, resulting in perpetuation or progression of epilepsy. Changes associated with epileptogenesis and seizures occur simultaneously with and may disrupt normal activity dependent developmental processes in the brain including synaptic pruning, dendritic and axonal refinement and receptor and ion channel maturations (Fig. 2). These effects may occur independently of and in addition to genetic
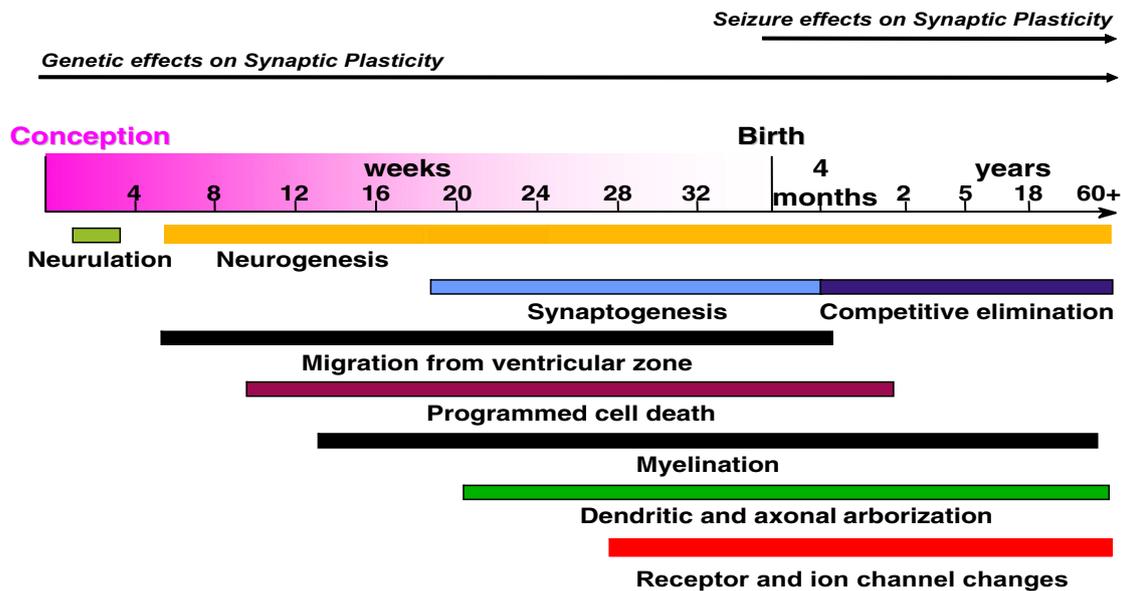

Fig. 2. Changes associated with epileptogenesis and seizures occur simultaneously with and may disrupt normal activity dependent developmental processes in the brain including synaptic pruning, dendritic and axonal refinement and receptor and ion channel maturations. These effects may occur independently of or in addition to genetic disruptions of synaptic plasticity discussed earlier that can have effects beginning very early in development and continue through later life.

disruptions of synaptic plasticity discussed earlier (Fig. 2).

There are many potential effects of seizures and epileptogenesis in the developing brain on synaptic plasticity. Emerging evidence suggests that early-life seizures can alter the function of neurotransmitter systems and intrinsic neuronal properties in the brain possibly contributing to cognitive and learning impairments. GABA is the main inhibitory neurotransmitter in the brain and GABA-A receptors mediate most fast synaptic inhibition. Changes in inhibitory neurotransmission are known to affect learning. Enhancement of GABA-A receptor function with benzodiazepines disrupts LTP and memory formation [40,41] and GABA-A receptor alpha-subunits have been shown to be key regulators of "critical periods" for cortical plasticity [42] and hippocampal dependent spatial learning [43]. Evidence exists for enhanced inhibition after early-life seizures that could impair these cognitive processes. On a circuit level, increased paired pulse inhibition in hippocampus has been seen after both hyperthermic and kainate-induced seizures in the post-natal period [44]. At the cellular/molecular level, early-life lithium–pilocarpine-induced seizures produce an increase in GABA-A receptor expression and a selective increase in the alpha1 subunit in the hippocampal dentate gyrus both immediately and when the animals reach adulthood [45,46]. These alterations are associated with functional changes including enhanced type I benzodiazepine augmentation of the receptor [45]. This is in contrast to the alpha1 subunit expression decrease seen in adult rats following pilocarpine-induced seizures [47]. These findings suggest that the effects of seizures on expression of GABA-A receptor subunits are age-dependent and that increased GABA-A receptor expression and resulting enhanced inhibition could contribute to cognitive deficits following early-life seizures.

Changes in excitatory neurotransmission may also contribute to learning and behavioral differences after early-life seizures. Glutamate is the primary excitatory neurotransmitter in brain and its activity is mediated by a variety of receptor subtypes including NMDA and non-NMDA (AMPA and kainate) ionotropic receptors and metabotropic receptors. Excitatory signaling through both the AMPA and NMDA receptors are critical for different types of LTP and hippocampal learning [48–51], and mutant mice lacking subtypes of AMPA or NMDA receptors have impaired learning [52,53]. Deficits in excitatory synaptic density and in excitatory signaling through both AMPA and NMDA receptors have been found after early-life seizures. Tetanus-toxin induced seizures in the post-natal period produce a 30% decrease in dendritic spine density on hippocampal CA3 neurons [54], and a 30–40% decrease in NMDA receptor NR1, NR2A, and NR2B subunit proteins in hippocampus [55,56]. Decreased AMPA
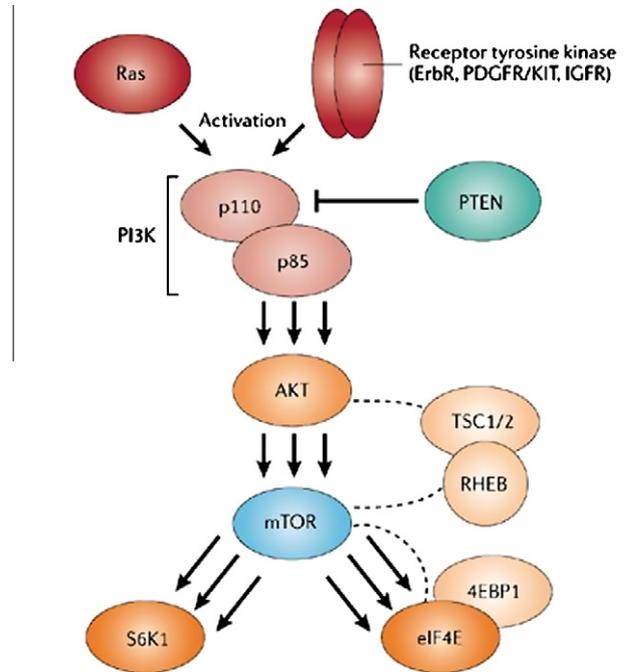
Faivre et al. Nature Reviews Drug Discovery 5, 671–688 (August 2006)

Fig. 3. PI3K/AKT/mTOR pathway. The pathway can be activarted by Ras or receptor tyrosine kinase activation. Mutations of TSC1/2 lead to hyperactivation of the mTOR and downstream signaling pathways resulting in increased cell growth, proliferation and abnormal gene expression that characterize the condition of tuberous sclerosis. eIF4E, eukaryotic initiation factor 4E; 4EBP1, eIF4E-binding protein 1; HCC, hepatocellular carcinoma; IGFR, insulin-like growth factor receptor; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homologue deleted on chromosome 10; RHEB, Ras homologue enriched in brain; TSC, tuberous sclerosis.

receptor GluR2 subunit expression has been shown after post-natal hypoxia-induced seizures [57] and lithium–pilocarpine-induced seizures [45].

In addition to early seizures effects on neurotransmitter receptor systems, they also affect a number of molecules that are essential for intrinsic neuronal function. Recent studies have demonstrated that prolonged post-natal febrile (hyperthermic) seizures produce a profound, long-lasting enhancement of intrinsic hyperpolarization activated membrane current, Ih, [58] due to a decrease in hyperpolarization activated, cyclic nucleotide-gated channel-1 (HCN1) mRNA and simultaneous enhancement of HCN2 mRNA expression in hippocampal CA1 neurons [59,60]. These changes are associated with persistent limbic hyperexcitability and a 35% incidence of spontaneous seizures in adulthood [58,61,62]. This suggests that a variety of receptors and important cell signaling proteins may be permanently altered following early-life seizures.

Changes in neuromodulatory pathways may also contribute to learning and behavioral differences after early-life seizures. cAMP response element binding

protein (CREB) is a key mediator of stimulus-induced changes in gene expression that underlie plasticity of the nervous system and phosphorylation of CREB is required for LTP, learning and memory [63]. CREB phosphorylation with learning has been shown to be diminished after repetitive febrile seizures in animals [64]. Corticotropin releasing hormone (CRH) is a neuro-modulatory peptide released from hippocampal inter-neurons in response to stress. Early-life seizures have been shown to enhance hippocampal CRH mRNA expression in adulthood [65], and excessive CRH [66] and early-life stress [67] have been shown to lead to reductions in dendritic length and arborization as well as progressive cognitive deficits.

8. Conclusion

In conclusion, early-life seizures may produce a variety of cellular and molecular changes in hippocampus including short-term enhancement of excitation and long-term enhancement of inhibitory neurotransmission and reductions in excitatory neurotransmission. These alterations may in part underlie the enhanced risk of ASD in patients with early-life seizures and epilepsy. Abnormalities of synaptic plasticity resulting in imbalances of excitatory and inhibitory neurotransmission resulting either from genetic mutations or effects of early-life seizures may provide a common mechanism for both ASD and epilepsy and provide a basis for understanding of the frequent co-occurrence of these disorders. Although this concept can provide a broad framework in which to begin to understand the frequent association of epilepsy and autism, many questions remain unanswered. Why are ASD and epilepsy sometimes comorbid, but not always? How can alterations that increase inhibition (i.e., loss of NL-3) as well as those than decrease inhibition (i.e., interneuronopathies such as ARX and NRP2 mutations) both cause ASD and epilepsy phenotypes? In what specific brain regions, pathways and cell types do excitatory–inhibitory imbalances occur in ASD and epilepsy, and does the spatial and developmental profile in part determine the specific pheontype? Do identified changes in the excitatory–inhibitory balance and the cellular and molecular mechanisms that produce them represent new therapeutic targets for treatment of these conditions, and if so what is the developmental window in which these treatments might be effective? Continued research is essential to begin to address these and other gaps in our understanding of the neurobiological basis of the complex association between ASD and epilepsy.

Acknowledgements

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