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Epilepsy and Autism

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Epilepsy and autistic spectrum disorder frequently coexist in the same individual. Electroencephalogram (EEG) epileptiform activity is also present at a substantially higher rate in children with autism than normally developing children. As with epilepsy, there are a multitude of genetic and environmental factors that can result in autistic spectrum disorder. There is growing consensus from both animal and clinical studies that autism is a disorder of aberrant connectivity. As measured with functional magnetic resonance imaging (MRI) and EEG, the brain in autistic spectrum disorder may be under- or overconnected or have a mixture of over- and underconnectivity. In the case of comorbid epilepsy and autism, an imbalance of the excitatory/inhibitory (E/I) ratio in selected regions of the brain may drive overconnectivity. Understanding the mechanism by which altered connectivity in individuals with comorbid epilepsy and autistic spectrum disorder results in the behaviors specific to the autistic spectrum disorder remains a challenge.

Autism spectrum disorder (ASD) refers to a group of complex neurodevelopmental disorders, characterized by deficits in social communication and interaction and demonstrating restricted, repetitive, and stereotyped patterns of behavior. The symptoms are present from early childhood and are impairing to everyday functioning. People with ASD have co-occurring intellectual disability (ID), language disorder, and epilepsy at higher rates than the general population. The exact prevalence of ASD is difficult to ascertain, but the rate of diagnosis is rising and best estimates put the prevalence between 1 in 88 and 1 in 100 individuals (Buescher et al. 2014). Estimates from the Centers for Disease Control and Prevention (CDC) (Baio et al. 2014) predict that, soon, 1 in 68 will be diagnosed with ASD. The rate of increase in diagnosis, coupled with the limited effectiveness of treatments and the costs of care for these patients makes autism a growing public health concern.

There is substantial evidence that genetics plays an important role in ASD (Risch et al. 1999; Anney et al. 2010; Gaugler et al. 2014; Pinto et al. 2014). However, delineating the exact contribution of genes to the eventual behavioral expression of ASD in any given individual is complicated. For example, we currently recognize >50 genes or genomic variants, as well as numerous copy number variations (CNVs), that either cause or predispose individuals to ASD (Zoghbi 2003; Abrahams and Geschwind 2008; Geschwind 2008; Sudhof 2008; Sanders et al. 2011). In addition to the number of poten-

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tial causative genes, the known ASD-related proteins (including those mapping within CNVs) span diverse categories, from transcription factors (Amir et al. 1999; Voineagu et al. 2011) to RNA-binding proteins (Bassell and Warren 2008) and cell-adhesion molecules (Wang et al. 2009), to enzymes involved in protein modification (Geschwind 2008; Walsh et al. 2008) and degradation (Beaudet 2007). Further complicating efforts to trace the pathogenesis of the disorder, it is also known that environmental factors may play an important role in the development of ASD (Hallmayer et al. 2011).

Since the earliest writings about ASD, there has been a known association with epilepsy (Kanner 1968) and a tacit recognition that both conditions often exist in the same individual at a much higher rate than would be expected by chance alone (Tuchman and Rapin 2002; Matsuo et al. 2010; Tuchman and Cuccaro 2011; Tuchman et al. 2013). This association between epilepsy and ASD has challenged researchers to find the pathophysiological link between the two conditions. Because of the myriad of genetic and nongenetic causes resulting in both epilepsy and ASD, a singular pathophysiological mechanism responsible for the seizures and autistic phenotype is unlikely. However, the high rate of co-occurrence of epilepsy and ASD has led many to search for common pathological links between the two conditions that could provide a final pathway to either seizures or ASD. Precisely because any number of deviations from normal development could potentially alter brain function, there is great utility in trying to identify the shared "end products" of such alterations that result in seizures, ASD, or both. In this article, we explore common threads that may account for this high comorbidity rate.

PREVALENCE OF COMORBID AUTISM AND EPILEPSY

Estimates of the prevalence of epilepsy in ASD vary widely, with some studies reporting almost 50% (Spence and Schneider 2009). The variation in prevalence appears to directly relate to the differences in sample characteristics between studies, such as cohort size, ascertainment factors, age, inclusion or exclusion of patients with conditions known to have a high rate of epilepsy, such as tuberous sclerosis complex (TSC), and the presence or absence of ID (Spence and Schneider 2009). Clinic-based samples report the highest rates, as patients with epilepsy are often overrepresented in these settings (Hughes and Melyn 2005). Population-based studies avoid this bias and provide the best estimate of true prevalence of epilepsy in autism, but even in these reports, rates have been variable (Danielsson et al. 2005; Saemundsen et al. 2013). In a meta-analysis of studies conducted from 1963 to 2006, the pooled prevalence of epilepsy was 21.5% in individuals with ASD with ID compared with 8% in ASD without ID (Amiet et al. 2008). In a more recent meta-analysis of 16 studies, the rate of epilepsy was 8.9% in individuals without an ID but 23.7% in those with an ID (Woolfenden et al. 2012). In addition to ID, the age of the participants influences the prevalence rates. In a large cross-sectional study evaluating 5815 people with ASD, the average prevalence of epilepsy differed by age of the cohort examined, with a prevalence rate of 12.5% in children between 2 and 17 yr but 26% in those 13 yr or older (Viscidi et al. 2013). In children with ASD, having co-occurring epilepsy has been associated with a higher rate of cognitive deficits, and frontal lobe epileptiform activity (Matsuo et al. 2011) when compared with children with ASD alone. Although there is a strong association between co-occurring ID and ASD in populations of people with epilepsy (Viscidi et al. 2013), studies have indicated that even in cases with a normal IQ there is evidence that autism itself is associated with an increased risk of epilepsy (Olsson et al. 1988; Elia et al. 1995; Amiet et al. 2008).

Not only does having ASD increase the risk of developing epilepsy, but the prevalence of ASD in individuals with epilepsy is substantially higher than the prevalence of ASD in the general population (Tuchman and Cuccaro 2011; Woolfenden et al. 2012). In a large population-based cohort of 64,188 people with epilepsy, the odds ratio of having ASD was 22.2 (95% CI; 16.8–29.3) (Selassie et al. 2014). Two large prospective studies have looked at

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rates of ASD within an epilepsy population and found that ~4%–5% of children with epilepsy had ASD (Berg et al. 2011; Geerts et al. 2011). In studies of children with epilepsy in an English school system, ~21% had ASD (Reilly et al. 2014, 2015). The developmental sequelae of seizures early in life includes a particularly high risk for developing autism (Saemundsen et al. 2007, 2008, 2013).

PREVALENCE OF EEG ABNORMALITIES IN AUTISM

In addition to an increased prevalence of epilepsy in individuals with ASD, there is also a marked increased incidence of epileptiform activity on the EEGs of people with ASD (Giovanardi et al. 2000; Hrdlicka et al. 2004; Canitano et al. 2005; Gabis et al. 2005; Hughes and Melyn 2005; Baird et al. 2006; Chez et al. 2006; Kim et al. 2006; Akshoomoff et al. 2007; Hara 2007; Parmeggiani et al. 2007; Giannotti et al. 2008; Spence and Schneider 2009). Whereas interictal spikes occur in >5% of normally developing children without a history of epilepsy (Eeg-Olofsson et al. 1971), more recent studies have shown that up to 60% of EEG records from children with ASD have interictal spikes (Hughes and Melyn 2005) and many of the children with abnormal EEGs do not have a history of epilepsy (Hughes et al. 2015). The location of spikes in children with ASD also differs from their typical peers with a higher percentage of interictal spikes in the frontal lobe in children with ASD than in those without ASD (Fig. 1) (Hashimoto et al. 2001; Matsuo et al. 2010).

GENETICS OF EPILEPSY AND AUTISM

Although there is a high comorbidity rate between ASD and epilepsy and between ASD and EEG epileptiform activity, this relationship is not necessarily a causal one. It is far more likely that epilepsy and ASD have a complex interaction and possibly share common pathophysiological properties.

One way to approach these shared interactions is to study genetic syndromes in which epilepsy and ASD frequently coexist (Table 1).

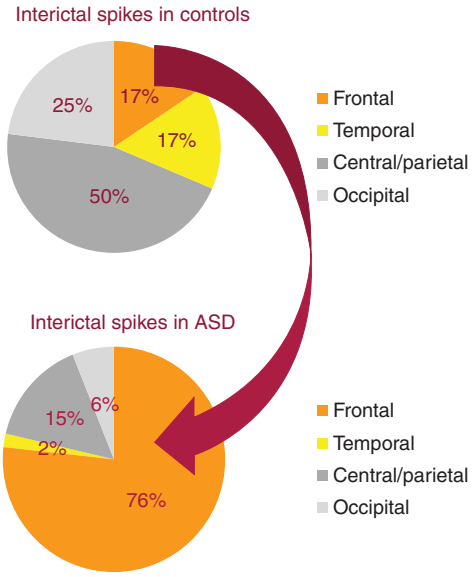

Figure 1. Interictal spikes in normal children without seizures and children with ASD. Note that frontal lobe spikes are more common in children with ASD than controls (based on data in Hashimoto et al. 2001 and Eeg-Olofsson et al. 1971, respectively).

In these syndromes, there is a disproportionately increased risk of developing both/either ASD and epilepsy compared with the general population. A large proportion of the genes associated with ASD in humans or with autistic-like behaviors (ALBs) in mice, are also associated with epilepsy.

TSC offers a natural paradigm through which we can begin to understand the relationship between epilepsy and ASD in neurodevelopmental disorders. TSC is an autosomal dominant inherited disorder of high penetrance, characterized pathologically by the presence of hamartomas (tumor-like lesions) in multiple organ systems (Holmes and Stafstrom 2007). Many patients also have renal lesions; usually angiomyolipomas and cysts, polycystic renal disease, and renal carcinoma can also occur. The neurological manifestations of TSC are particularly challenging and include infantile spasms, intractable epilepsy, cognitive disabilities that vary from mild learning disabilities to severe intellectual impairment, ASD, and behavioral disturbances.

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Table 1. Genetic syndromes with ASD and epilepsy coexisting

Syndrome	Percent with ASD	Percent with seizures	Co-occurrence
Angelman syndrome	1.9% (Veltman et al. 2005) 42% (Peters et al. 2004)	85% (Fiumara et al. 2010) 100% (Valente et al. 2006)	Case study ($n = 4$) with ASD reports all had seizure disorders (Steffenburg et al. 1996)
Cornelia de Lange syndrome	32% (Oliver et al. 2008) 39% (Moss et al. 2008) 65% (Moss et al. 2012)	23%–26% (Pavlidis et al. 2014)	
Down syndrome	3.1% (Kohane et al. 2012) 5.8% (Lowenthal et al. 2007) 18.2% (DiGuiseppi et al. 2010)	1%–13% (Verrotti et al. 2013) 8% (Goldberg-Stern et al. 2001)	Seizures occur significantly more often in ASD + Down than in Down only control (Molloy et al. 2009)
Dravet syndrome	24.3% (Li et al. 2011) 61.5% (Berkvens et al. 2015)	100% (Wolff et al. 2006) 100% (Berkvens et al. 2015)	
Duchenne muscular dystrophy	15% (Banihani et al. 2015)	6.3% (Pane et al. 2013)	
Fragile X syndrome	21% (Kohane et al. 2012) 30% (Miles 2011)	11.8%–18% (Berry-Kravis 2002)	Case study ($n = 57$) with ASD found 28.1% had seizures (Garcia-Nonell et al. 2008)
Hypomelanosis of Ito syndrome	10% of patients with ID (Pascual-Castroviejo et al. 1998) 64% (Zappella 1993)	11.5%–50% (Ruggieri and Pavone 2000) 37%–53% (Assogba et al. 2010) 49% (Pascual-Castroviejo et al. 1998)	Most children with ID and autism had infantile spasms or severe drug-resistant seizures (Ruggieri and Pavone 2000)
Mowat–Wilson syndrome	40% (Evans et al. 2012)	70%–75% (Cordelli et al. 2013)	
Rett syndrome	Transient autism features (Chahrour 2007; Percy 2011)	61% (Bao 2013)	
Phelan–McDermid syndrome	0%–94% (Kolevzon 2014) 26% (Sarasua et al. 2014) 31% (Sarasua et al. 2014)	0%–40% (Kolevzon 2014) 27% (Sarasua et al. 2014)	
Pitt–Hopkins syndrome	100% (Sweatt 2013)	50% (Sweatt 2013)	
Prader–Willi syndome	25.3% (Veltman et al. 2005)	13.5% (Gilboa 2013) 26% (Vendrame 2010)	
Sotos syndrome	Rare (Mouridsen 2002; Buxbaum 2007)	41% (Tatton-Brown 2004)	
Smith–Lemli–Opitz syndrome	53% (Tierney 2001)	Epileptiform discharges are common but low prevalence of epilepsy (Schreiber 2014)	Autism symptoms more prevalent in group with interictal epileptiform discharges (Schreiber 2014)
Smith–Magenis syndrome	90% (Laje 2010)	45% (Goldman 2005)	

Continued

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Table 1. *Continued*

Syndrome	Percent with ASD	Percent with seizures	Co-occurrence
Tuberous sclerosis complex	10.8% (Kohane et al. 2012) 25%–50% (Wiznitzer 2004)	70%–80% (Crino 2006)	75%–100% of patients with ASD will also have seizures (Wiznitzer 2004)

ASD, Autism spectrum disorder; ID, intellectual disability.

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The majority of individuals with TSCs have mutations of *Tsc1* (encoding for the protein hamartin) or *Tsc2* (encoding for the protein tuberin). Hamartin and tuberin proteins form a functional complex, which inhibits the serine/threonine protein kinase mammalian target of rapamycin (mTOR) (Curatolo et al. 2015). The mTOR kinase complex is the central component of a cell-growth pathway that responds to changes in nutrients, energy balance, and extracellular signals to control cellular processes including protein synthesis, energy metabolism, and autophagy (Laplante and Sabatini 2012). Loss-of-function of the *Tsc1* and *Tsc2* protein complex results in deregulated and constitutively active mTOR complex 1, which promotes cell growth and contributes to tumor formation in dividing cells including the hamartomas and giant cells that are characteristic of TSC.

In TSC, early seizure onset is associated with a high risk for ASD (Numis et al. 2011; van Eeghen et al. 2013). In a retrospective review of 103 patients with TSC, 40% were diagnosed with an ASD (Numis et al. 2011). Patients with ASD also had an earlier age-at-seizure onset, more frequent seizures, and their EEG recordings had a significantly greater amount of interictal epileptiform features in the left temporal lobe when compared with those patients who did not develop ASD. These investigators concluded that ASD may be associated with persistent seizure activity early in development, particularly when it occurs in brain regions integral to the proper development of social perception and communication. Supporting this hypothesis is the fact that the risk of ASD in TSC can be reduced by early treatment of the epilepsy. In a long-term study of children with TSC identified as infants and followed for 3.5 yr, the difference in the proportion of who developed a co-occurring epilepsy between children treated early with vigabatrin (9%) and children treated later (52%) was quite stark (Cusmai et al. 2011). Thus, early treatment of seizures in TSC seems to clearly reduce but not eliminate the risk of ASD in this disorder (Bombardieri et al. 2010; Cusmai et al. 2011).

Although these studies implicate seizures in the development of ASD in children with TSC, especially when they are medically intractable and occur early in the course of neurodevelopment, these findings still do not prove causation. The children with more severe TSC who will eventually develop ASD may be a distinct group from those children with TSC who remain socially and intellectually intact. It is entirely possible that whatever sets this group apart is also responsible for the "nonresponse" to antiepileptic intervention, and that the link between autism and epilepsy lies within a common pathophysiologic substrate responsible for the child's vulnerability to both conditions.

Mouse models of TSC show behavioral changes paralleling human disease phenotypes, including seizures, deficits in learning and memory, and ALB (Ehninger et al. 2008; Meikle et al. 2008; Young et al. 2010; Tsai et al. 2012).

Functional mutations in *Tsc1* or *Tsc2* significantly alter synapse structure, function, and plasticity (Tavazoie et al. 2005; Ehninger et al. 2008; Auerbach et al. 2011; Bateup et al. 2011; Chevere-Torres et al. 2012). Protein synthesis, regulated by TSC-mTOR signaling, plays a role in learning-associated synaptic changes. In TSC, increased local availability of proteins may stabilize plasticity at synapses that would not normally undergo synaptic consolidation. The net result is to increase the signal-to-noise ratio and degrade the specificity of synaptic modifications that occur during normal learning, as evidenced

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by lower thresholds for the induction of late-phase long-term potentiation (LTP) in mouse models of TSC (Banko et al. 2005; Costa-Mattioli et al. 2005; Ehninger et al. 2008). Rapamycin, an mTOR inhibitor, not only reverses abnormal synaptic consolidation but also restores learning deficits in *Tsc2*$^{+}$ mice (Ehninger et al. 2008).

Although it is clear that perturbations of *Tsc1/2* and mTOR alter many aspects of neuronal function, it is unclear which alterations are directly causal and which are induced secondarily as a consequence of altered brain function. To address this issue, Bateup et al. (2011) knocked out *Tsc1* selectively in CA1 pyramidal neurons in P14–16 mouse pups. The loss of *Tsc1* produced hyperexcitable pyramidal cells caused by deficits in inhibitory synaptic function manifested as decreased amplitude of miniature inhibitory currents, reduced evoked inhibitory currents, and reduced synaptic inhibitory potentials. These studies suggest that *Tsc1* is critical for establishing inhibitory synapses onto CA1 pyramidal cells. The overall deficit in inhibitory drive onto pyramidal cells resulted in a disrupted E/I ratio and increased hippocampal network activity both in vivo and in vitro. The observed reduction in inhibition was reversed by blocking mTOR activity with rapamycin, suggesting that amelioration of the signaling abnormality can restore normal cell activity. Thus, disrupted development of inhibitory synaptic transmission is likely an important consequence of altering Tsc1/2-mTOR signaling and restoration of E/I balance may stabilize normal cell activity. Indeed, artificial elevation of cellular E/I ratio has also been shown to disrupt information processing and social behavior in mice, further suggesting that stabilization of the balance between excitatory and inhibitory drive is important for cognitive function (Yizhar et al. 2011). Maintenance of E/I balance has also been shown to drive normal hippocampal oscillations. In oscillating hippocampal pyramidal cells synaptic excitation is immediately followed by a proportional synaptic inhibition, and modification of the amplitude of these events directly modulates oscillation frequency (Atallah and Scanziani 2009).

Another example of a genetic syndrome with a high incidence of both ASD and epilepsy is fragile X syndrome (FXS). FXS is the most common inherited form of ID in males, occurring in ~1 in 4000 males (Turner et al. 1996). Many of the children have both autism and epilepsy (Wheeler et al. 2015). Mutations in the *FMR1* gene in FXS result in reduced production of the fragile X mental retardation 1 protein (FMRP). This protein helps regulate the production of other proteins and plays a role in the development of synapses. Nearly all cases of FXS are caused by a mutation, in which the CGG triplet repeat is expanded within the *FMR1* gene. Normally, this DNA segment is repeated from 5 to ~40 times. However, in individuals with FXS, the CGG segment is repeated >200 times. The abnormally expanded CGG segment turns off (silences) the *FMR1* gene, which prevents the gene from producing FMRP. Loss or deficiency of this protein disrupts nervous system functions and leads to the signs and symptoms of FXS.

FMRP knockout mice show ALB (Mines et al. 2010; Paz et al. 2013; Tyzio et al. 2014). The knockouts have a significant increase in global protein synthesis and in protein synthesis at the synapse (Bassell and Warren 2008). These knockouts have impaired synaptic plasticity, alterations in dendritic morphology, and neurocognitive deficits in FMRP mutants, indicating a major role for FMRP in the regulation and maintenance of synaptic function. It has been suggested that exaggerated signaling through mGluR5 can account for multiple cognitive and syndromic features of FXS (Dolen and Bear 2008). As with TSC, imbalances in E/I may contribute to both the impaired behavior and to seizures in the mouse model.

Other genetic models of epilepsy and autism have also suggested that an imbalance of the E/I ratio contributes to both the development of ALB and to seizures. SynGAP1, a synaptic Ras GTPase-activating protein is involved in NMDA receptor synaptic plasticity and in membrane insertion of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. *Syngap1* haploinsufficiency in mice can cause cognitive impairment, seizures, and ALB. Haploinsufficiency restricted to just forebrain gluta-

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matergic neurons is sufficient to disrupt cognition. Restoring mutations from this population prevents cognitive abnormalities; whereas, manipulating Syngap1 function in γ-aminobutyric acid (GABA)ergic neurons had no effect on cognition, excitability, or neurotransmission, indicating the specificity of *Syngap1* mutations within forebrain excitatory neurons. In this model, cognitive abnormalities were induced by *Syngap1* dysfunction in developing but not in mature forebrain neurons. It is likely that the isolated impairment of forebrain glutamatergic neurons in *Syngap1* mutants disrupts synaptic homeostasis and alters the balance of E/I at a critical window in development (Clement et al. 2012; Ozkan et al. 2014).

Homologous mutations of *CNTNAP2*, which encode contactin-associated protein-like 2, result in cortical dysplasia, focal epilepsy, and macrocephaly (Strauss et al. 2006). People with this mutation develop intractable focal seizures beginning in early childhood, after which language regression occurs and is often accompanied by hyperactivity, impulsive and aggressive behavior, cognitive impairment, and ASD (Strauss et al. 2006). In common with some patients with *CNTNAP2* mutations, *CNTNAP2* mutant mice have epileptic seizures and ALB. In this mouse model, migration of cortical projection neurons is impaired, as is cortical neuronal synchrony, and the number of GABAergic interneurons (Penagarikano et al. 2011). Taken together, these changes likely indicate abnormalities in E/I.

Mice with *PRICKLE1* mutations show both ALB and seizures. Endogenous Prickle1 and synapsin 1, a protein involved in synaptogenesis, synaptic vesicle formation and regulation of neurotransmitter release, colocalize in neurons and physically interact. Mutations in *PRICKLE1* disrupt its ability to increase the size of synaptic vesicles. Studies suggest that *PRICKLE1* mutations contribute to ALB and seizures by disrupting the interaction with synapsin 1 and the regulation of synaptic vesicles, thus leading to abnormalities in the E/I ratio (Paemka et al. 2013, 2015).

Although genetic mouse models of epilepsy and ALB suggest that E/I balance has a role in both the epilepsy and the aberrant behavior, it should be cautioned that the development of ALB and seizures is likely far more complex. As in the clinical situation in which most children with ASD do not have epilepsy, there are a significant number of mouse models of autism, which do not have seizures. Although a common pathway may link epilepsy and ALB in some of the genetic models, extrapolation of altered E/I to all autism models is not possible.

ALTERED E/I BALANCE AND CONNECTIVITY

The idea that altered E/I balance can play a role in ALB in rodents has been supported by studies of early-life seizures (ELS) (Holmes et al. 2015). In this model of acquired ASD, rats received 70 seizures over 10 d spanning postnatal (P) d 5–14. Seizures were induced by the convulsant inhalant, flurothyl. Previous work with this model showed that rats with ELS have persistent increased excitation (Isaeva et al. 2010) and decreased GABA currents (Isaeva et al. 2009) in the neocortex and a substantially reduced lower seizure threshold (Holmes et al. 2015). ELS also have been shown to increase short-term plasticity in the mesial prefrontal cortex (mPFC) (Hernan et al. 2013). Alterations in short-term plasticity in the mPFC have been associated with changes in hippocampal-PFC synchrony (Sigurdsson et al. 2010; Fenelon et al. 2013). Taken together, these findings suggest there is a long-standing increase in the E/I ratio in the mPFC. Similar to children with ASD, rats with ELS have impaired sociability (Lugo et al. 2014) and behavioral inflexibility (Kleen et al. 2011a).

To understand how altered E/I balance results in autistic-like behavior, multisite local field potentials (LFP) within and between brain regions that are critical for cognition, the medial prefrontal cortex (mPFC), ventral (VH), and dorsal hippocampus (DH) in the ELS model were assessed following ELS (Holmes et al. 2015). Because ASD presents in early childhood and brain connectivity changes with age (Doyle-Thomas et al. 2015), the studies were performed serially in developing rats from P18–P25. These ages would be human equivalent age of 5 to 6 yr

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(Clancy et al. 2007; Workman et al. 2013). Coherence was used as a measure of functional connectivity between brain regions during cognitive tasks. Coherence is a measure of "coupling" oscillations and, therefore, provides a functional link between brain areas required for the integration of distributed information (Varela et al. 2001; Thatcher 2012). Coherences are dynamic and, as we have shown previously in the ELS model (Kleen et al. 2011b), are related to short-term memory. Pearson product correlation coefficients were used as another assessment of brain connectivity (Bonita et al. 2014). As coherences do not take voltage into account, voltage correlations are useful to assess the degree of association between EEG amplitude from two sources over a time interval, and provide a distinctly different measure of connectivity from coherence.

In rat pups with ELS, field recordings from DH, VH, and mPFC show marked increases in coherence as well as decreases in voltage correlation at all bandwidths compared with controls, although there were minimal differences in total power and relative power spectral densities. The alterations in coherences and voltage correlation occurred within days (P18) of the last seizure and suggested that the brains of ELS are overly connected and weakly modulated by distant brain rhythms.

Rats with ELS had resulting impairment in the sociability and social novelty tests (Fig. 2) and behavioral flexibility but showed no evidence of increased motor activity or generalized anxiety as measured in the open field. For example, rats with ELS showed no differences in coherence measurements when the rat approached an object or another rat. Although

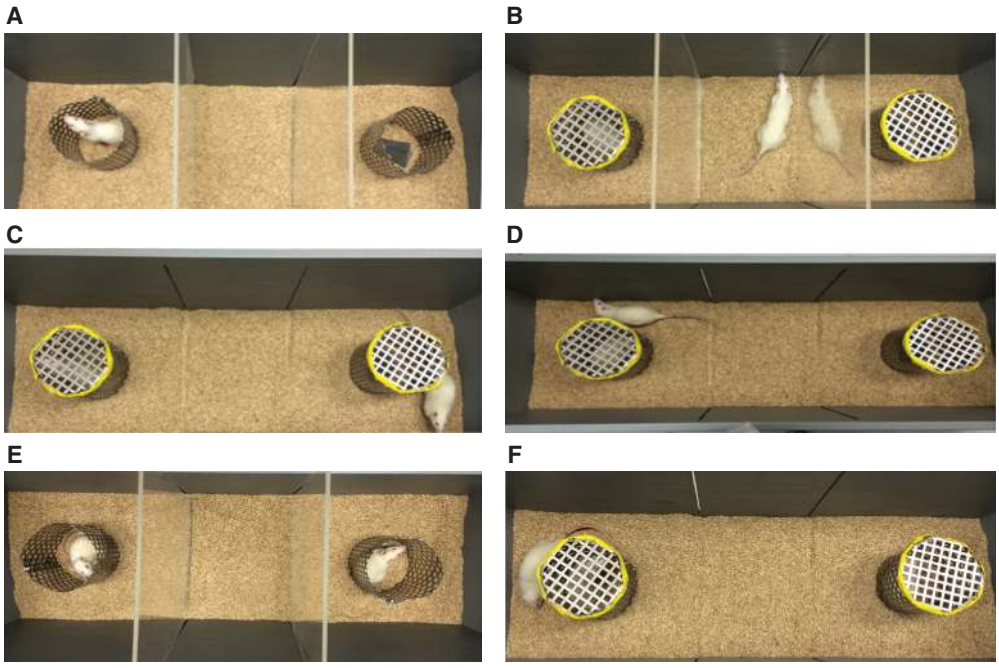

Figure 2. Sociability and social novelty test. (*A*) Rectangular wood box with opaque sides divided into three equal squares using removable plastic doors. An unfamiliar male rat is placed in one grated cylinder and an object in the other. (*B*) Starting point for test with test rat placed in the center square for 5 min. The rat and object cylinders are covered. (*C*) Once doors are removed, the animal is allowed to wander in the chamber for 10 min (sociability test). In *C*, the rat is spending time near the object. (*D*) Rat spending time near the other rat. (*E*) After 15 min, a new rat replaces the object. (*F*) The test rat was then tracked for time investigating the new and old rat (social novelty test).

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in contrast, control rats' coherences were higher when presented with another rat than with an object, suggesting limited plasticity in connectivity during this social task in those animals with ELS. This study showed that ELS in otherwise normal rodents can result in acquired deficits in social behaviors. These data suggested that one possible pathway by which ELS can result in an autistic-like phenotype is through alterations in the dynamic flexibility of brain connectivity, manifesting as enhanced coherences across a broad span of frequencies (Fig. 3).

To determine whether preventing the increased E/I ratio following ELS could prevent the alterations in coherence and behavior, bumetanide, a pharmacological agent that blocks the activity of NKCC1 and induces a significant shift of E_{Cl} toward more hyperpolarized values, was administered at the time of the ELS seizures (Holmes et al. 2015). Treatment with bumetanide at the time of the seizures totally prevented the subsequent increases in coherence and resulted in normal sociability. Similarly, Tyzio et al. (2014) reported that bumetanide restored the impaired oxytocin-mediated GABA excitatory–inhibitory shift during delivery in the valproate and fragile X rodent models of autism, ameliorating ALB characteristics in the offspring.

Aberrant Connectivity in Autism

Similar to the rodent studies, there is increasing evidence from both imaging and neurophysiologic studies pointing to altered brain connectivity as a key feature of the pathophysiology of ASD (Casanova and Trippe 2009; Dinstein et al. 2011; Kana et al. 2011; Muller et al. 2011). Additionally, there is some evidence that the changes in neuronal organization in ASD are differentially expressed with age, marked by early life brain overgrowth including increased neuron number, followed by decreases in both structural volumes and neuron number as the brain ages. Courchesne (2002, 2004) and Courchesne and colleagues (2003) identified growth abnormalities in frontal, cerebellar, and temporal structures that normally mediate the development of higher order social, emotional, speech, language, attention, and cognitive functions that are often abnormal in ASD. In other structures (e.g., occipital cortex), known to mediate functions that are either mildly or entirely unaffected in ASD patients, growth pathologies are milder or nonexistent (Courchesne et al. 2005).

In parallel with these changes in volume in both gray and white matter (Lange et al. 2015), imaging techniques have shown changes in brain connectivity as well (Chen et al. 2011; Pina-Camacho et al. 2012). Magnetic resonance imaging (MRI) studies have consistently shown differences in individuals with autism compared with normal controls. Reports have been published revealing reduced long-range, distant brain connectivity during both task-specific (Besag 2004; Koshino et al. 2005, 2008; Kana et al. 2006; Just et al. 2007) and resting-state paradigms (Cherkassky et al. 2006; Weng et al. 2010). Likewise, a number of studies have shown reduced short-range, local connectivity (Besag 2004; Koshino et al. 2005, 2008; Just et al. 2007; Kana et al. 2011). Results from yet other studies have shown increased connectivity, both long range (Ben Bashat et al. 2007; Cheng et al. 2010; Supekar et al. 2013) and short range (Weng et al. 2010; Anderson et al. 2011; Keown et al. 2013; Khan et al. 2013; Lewis et al. 2013).

Connectivity differences in ASD have also been evaluated by EEG. As in the imaging reports, the resulting evidence is conflicting and inconsistent. Twenty-one studies in the last decade have been published; 11 evaluated resting state (Murias et al. 2007; Coben et al. 2008; Barttfeld et al. 2011; Bosl et al. 2011; Duffy and Als 2012; Mathewson et al. 2012; Sheikhani et al. 2012; Leveille and Hannagan 2013; Peters et al. 2013; Machado et al. 2015), eight were task related (Isler et al. 2010; Lazarev et al. 2010; Catarino et al. 2013; Garcia Dominguez et al. 2013; Carson et al. 2014; Orekhova et al. 2014; Righi et al. 2014; Lazarev et al. 2015; Machado et al. 2015); one obtained during non-rapid eye movement (NREM) sleep (Lazar et al. 2010) and one obtained during rapid eye movement (REM) sleep (Leveille et al. 2010). It is not possible to directly compare these studies as the acquisition paradigm, the age of the subjects,

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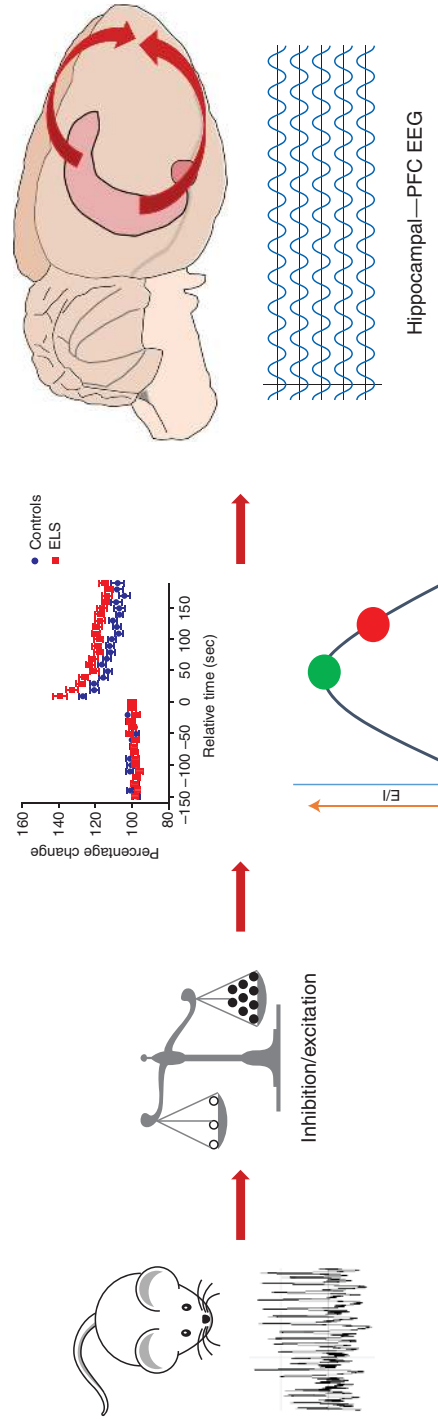

Figure 3. In the early-life seizure (ELS) model, immature rats are given a series of flurothyl seizures. This results in an imbalance of the excitatory/inhibitory (E/I) ratio, which leads to increased short-term plasticity and an increase in coherence. There is likely a "sweet spot" for coherence in which there is an optimal coherence (green ball). Increased coherence (red ball) may result in overconnectivity as shown by highly coherent wave forms in both the dorsal (DH) and ventral hippocampus (VH) and prefrontal cortex. PFC, Prefrontal cortex; EEG, electroencephalogram.

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the inclusion/exclusion criteria related to ID, the regions, and even the frequencies reported vary by publication. Overall, EEG-derived coherence literature generally mirrors that obtained using MRI, in that the results are widely varied and provide evidence for both over- and underconnectivity in ASD (Luckhardt et al. 2014; Maximo et al. 2014).

It is important to note that ASD is an evolving disorder and, like changes in regional brain volume (Courchesne et al. 2011; Lange et al. 2015), brain connectivity changes with age (Cheng et al. 2010; Doyle-Thomas et al. 2015). Therefore, it is extremely important that age and developmental stage be accounted for when evaluating functional connectivity in ASD. For example, in a recent study examining age-related changes in default mode network connectivity, children with ASD showed a mixed pattern of increased and decreased connectivity between the posterior cingulate cortex and the default mode network (Doyle-Thomas et al. 2015). Importantly, in the children with ASD, connectivity between the posterior cingulate cortex and mPFC was higher than neurotypical controls in the youngest children but then decreased with age. The default mode network is a network of brain areas mostly along the midline of the brain, which is active during rest but decreases activity during externally directed, attention-demanding, cognitive tasks (Kennedy et al. 2006). This network shares many of the same regions implicated in social emotion processing and self-awareness, which are impaired in ASD (Minshew and Keller 2010).

SUMMARY

There are multiple genetic and environmental causes for both ASD and epilepsy, and both can be conceptualized as disorders of aberrant connectivity. Evidence is accumulating that the co-occurrence may be explained by the same nascent insult. For example, early life seizures may result in the altered function of neurotransmitter systems and intrinsic neuronal properties during neurodevelopment leading directly to disrupted cortical connectivity. The clinical expression of this derailment can result in seizures or devastating impairments in social communication and behavior, or both. Further investigations in animal models with both epilepsy and ALB are needed to resolve many unanswered questions regarding this important co-occurrence.

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Epilepsy and Autism

Ashura W. Buckley and Gregory L. Holmes

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