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► To cite this version:

Jana Velíšková, Jill L Silverman, Melissa Benson, Pierre-Pascal Lenck-Santini. Autistic traits in epilepsy models: Why, when and how?. *Epilepsy Research*, 2018, 144, pp.62-70. 10.1016/j.epilepsyres.2018.05.009 . hal-01963593

HAL Id: hal-01963593

<https://amu.hal.science/hal-01963593>

Submitted on 21 Dec 2018

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Review article

Autistic traits in epilepsy models: Why, when and how?

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ARTICLE INFO

Keywords:

Autism spectrum disorder
Epilepsy comorbidity
Seizures
Translation
Novel mechanisms
Behavioral assays
Neuroinflammation
Network coordination
Excitation-inhibition balance

ABSTRACT

Autism spectrum disorder (ASD) is a common comorbidity of epilepsy and seizures and/or epileptiform activity are observed in a significant proportion of ASD patients. Current research also implies that autistic traits can be observed to a various degree in mice and rats with seizures. This suggests that there are shared mechanisms in both ASD and epilepsy syndromes. Here, we first review the standard, validated methods used to assess autistic traits in animal models as well as their limitations with regards to epilepsy models. We then discuss two of the potential pathological processes that could be shared between ASD and epilepsy. We first focus on functional implications of neuroinflammation including changes to excitable networks mediated by inflammatory regulators. Finally we examine mechanisms at the cellular and network level involved in neuronal excitability, timing and network coordination that may directly lead to behavioral disturbances present in both epilepsy and ASD. This mini-review summarizes the work first presented at an Investigators Workshop at the 2016 American Epilepsy Society meeting.

1. Introduction

Autism spectrum disorder (ASD) and epilepsy are prevalent and pervasive lifelong disorders for which medicinal interventions are either not readily available or need drastic improvements. ASD represents a common co-morbidity in patients with epilepsy and vice versa, evidenced by the prevalence statistics that show that epileptic disorders are 10 times more likely to be diagnosed with ASD (Sundelin et al., 2016). According to prevailing estimates, ~30% of patients with ASD develop epilepsy at some point of their lives, and at the same time ~30% of patients with epilepsy as a primary diagnosis fit the criteria of being diagnosed with ASD (Clarke et al., 2005; Seidenberg et al., 2009; Tuchman and Rapin, 2002).

ASD prevalence is higher in boys compared to girls (Baron-Cohen et al., 2011). However in the past two years, research suggests that the ASD sex-bias toward boys may be the result of cases of under- or misdiagnosis in girls, who present with distinct, subtler behavioral profiles than boys due to a variety of compensatory behaviors and camouflaging the symptoms (Lai et al., 2015; Park et al., 2016; Rynkiewicz et al., 2016). Interestingly, association of epilepsy and ASD has been diagnosed more often in girls than in boys (for review see (Tuchman et al.,

2010b)).

Most significant indicators that predict whether patients with epilepsy will also have ASD are an early onset of epilepsy together with low cognitive functioning and intellectual disability. Thus, the highest incidence of ASD is in those patients with epilepsy suffering from severe epileptic encephalopathies of infancy and childhood, i.e., Ohtahara, West (infantile spasms) and Lennox-Gastaut syndromes, and in those children with identifiable severe structural damage (symptomatic epilepsies). In these patients, a large number of uncontrolled seizures together with the structural abnormalities also likely contribute to ASD.

Stratifying patient subgroups and focusing on genetically identifiable ASD populations with co-morbid epilepsy is a main focus in autism research (i.e. genetic disorders); therefore, use of similar tools would be advantageous to both research focus groups. In fact, several neurodevelopmental syndromes with causal genetic etiology show co-existence of epilepsy and ASD as parallel syndromes, such as Rett, Dravet, Angelman, Dup15q and/or Landau Kleffner syndromes. In these syndromes, seizures and epilepsy often occur as a sign of general hyperexcitability with EEG epileptiform abnormalities, which is also common in some children with ASD (Tuchman et al., 2010b). Besides seizures, associated symptoms often found in ASD patients can include lack of

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Table 1
Summarizes representative behavioral assays and examples in the genetic models of ASD literature that were used to identify phenotypes using the two core ASD-relevant behavioral domains and possible confounding behaviors relevant in epileptic animal models.

Behavioral Domain	Assay	ASD-relevant core symptoms	References for detailed description of the test	Common seizure behaviors that can mimic ASD traits
Reciprocal social communication	Three-chambered task	Equal or less time spent with the novel mouse and the novel object	Dhamne et al. (2017), Ey et al. (2012), Moy et al. (2007), Silverman et al. (2012), Wöhr et al. (2013) and Yang et al. (2011)	Increased/decreased anxiety
	Reciprocal dyad interactions	Lack of interest in the partner	Bozdagi et al. (2010), Dhamne et al. (2017) and Silverman et al. (2015)	Depression-like behavior
	Social recognition	Lack in: 1) two-exposure recognition, 2) habituation-dishabituation, and 3) social discrimination	Ferguson et al. (2001), Ferguson et al. (2000), Lee et al. (2008a), Lee et al. (2008b) and Macbeth et al. (2009)	Aggressive behavior Hypo-/hyper-activity Olfactory damage Learning and memory deficits due to neurodegeneration
Repetitive behaviors, with restricted interests and behavioral inflexibility	Partition test	Lack of interest in the partner	Hamilton et al. (2014), Spencer et al. (2005), Spencer et al. (2008) and Veeragavan et al. (2016)	
	Social transmission of food preference	Missing	Wrenn et al. (2003)	
	Ultrasonic vocalization	Reduction in ultrasonic emissions	Scattoni et al. (2009), Scattoni et al. (2008), Wöhr et al. (2013) and Yang et al. (2012)	
Hypo-/hyper-activity following seizures Deficits in spatial discrimination learning due to neurodegeneration	Stereotypies	Repetitive self-grooming; circling; jumping; back flipping; perseverative wood block chewing	Bechara et al. (2017), Blumdel et al. (2010), Copping et al. (2017), Dhamne et al. (2017), Etherton et al. (2009), Hamilton et al. (2014), Lewis et al. (2007), Muehlmann et al. (2012), Portmann et al. (2014), Silverman et al. (2015), Silverman et al. (2012) and Yang et al. (2012)	Often a part of seizure behavior
	Marble burying	> 50% covered marbles	Thomas et al. (2009)	
	Insistence on sameness and lack of cognitive flexibility	Impaired reversal learning in the Morris water maze or T maze	Moy et al. (2007)	

achievement of neurodevelopmental milestones, learning and memory deficits, poor motor skills, hyperactivity, hyperexcitability, changes in responsiveness, aggression, anxiety, fear, sensory processing, altered sleep patterns and gastrointestinal distress.

Assessing social abilities in children is based on standardized interviews and observations using Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview (ADI). The latest Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) recognizes two main behavioral domains for diagnostic criteria of ASD in humans: 1) impairments in reciprocal social communication (verbal and non-verbal) and 2) repetitive behaviors, with restricted interests and behavioral inflexibility. New diagnostic criteria include a broader definition of the ASD phenotype and reflect the current consensus that the causes and clinical presentations of ASD are highly heterogeneous (Association, 2013; Lai et al., 2014). To diagnose ASD clinically, at least six symptoms have to be present with a minimum two abnormal measures in social interaction, and at least one measure of disturbed social communication with some type of repetitive behavior. The new criteria in the DSM-5 manual help more specifically diagnose the patients with ASD (Kulage et al., 2014) and assure better tailored treatments for distinct social behavior disorders (Halls et al., 2015). The new clinical benchmarks for ASD also lead to re-evaluation of the criteria for animal models of ASD and pose more strict rules for the ASD relevant behavioral phenotypes, especially to identify and study ASD as co-morbidity in animal models of epilepsy.

ASD as well as epilepsy have multifactorial etiology and the high prevalence of co-existence of ASD and epilepsy suggests some shared underlying neurological abnormalities. New research suggests that a combination of heritable and environmental factors have a strong influence on both ASD and epilepsy (Meltzer and Van de Water, 2017; Ornoy et al., 2016; Sandin et al., 2017; Shorvon, 2014; Wipfler et al., 2018). Yet etiology in the overwhelming majority of cases is still unknown. Animal models have become important tools for studying the roles of genetic and environmental factors, and their reciprocal influence on the onset and severity of disorders, including ASD and epilepsies. Here, we would like to first review standard, validated methods used to assess autistic traits in animal models consistent with the human DSM-5 criteria recommendations as well as review their limitations with regards to epilepsy models. Then we want to focus on two newly implicated mechanisms contributing to neurodevelopmental dysfunction and etiology in both ASD and epilepsy: the immune dysfunction associated with chronic neuroinflammation and the changes in network synchrony. While other mechanisms have been proposed and discussed in recent excellent reviews and meta-analysis studies (Besag, 2015; Jeste and Tuchman, 2015; Lee et al., 2015; Spence and Schneider, 2009; Strasser et al., 2018), neuroinflammation and network coordination hypothesis recently gained attraction of the research community. We believe they may also form common substrates for epilepsy and ASD and contribute to the disturbances in the excitatory-inhibitory (E-I) balance characteristic for both diseases. This mini-review summarizes the work presented at an Investigators Workshop at the 2016 American Epilepsy Society Annual Meeting held in Houston, Texas. Both clinicians and basic scientists have participated to discuss the new directions in epilepsy and ASD research.

2. Modeling the social brain: preclinical assays for behavioral outcomes relevant to ASD and epilepsy. A cautionary tale for epilepsy models

The criteria for ASD diagnosis are purely behavioral and in vivo assessments in preclinical rodent models are important tools to determine the presence of autism-relevant phenotypes (Crawley, 2012; Silverman et al., 2010). Whether or not ASD-relevant behavioral phenotypes are present in an animal model of epilepsy, it is imperative that the criteria established for the endophenotypes of the human syndrome correspond to the behavioral phenotypes of the animals without

confounding effects. Such strategies will ensure not collecting false positive or false negative data (Sukoff Rizzo and Silverman, 2016).

Standard, validated methods for quantifying behavior relevant to social communication and repetitive behaviors with restricted interests are available in the rodent model behavioral neuroscience literature (Kazdoba et al., 2016; Silverman et al., 2010; Sukoff Rizzo and Silverman, 2016) and summarized in Table 1.

The methods employed for behavioral phenotyping for ASD-relevant traits are complex and warrant caution with regards to confounding factors. Some behaviors seen in animal models of ASD can overlap with seizure behavior. Therefore, cautious interpretations are necessary to determine whether the behavior of the animal is the result of ASD traits or seizures (see Table 1). The ultimate goal is to identify disease-relevant and translational behavioral endpoints that are robust, reliable, and reproducible, and that can be employed to evaluate potential of novel therapeutic agents to treat disease. The impact of a competing or confounding behavior on the behavioral endpoints should not be underestimated. For example, previous experience of seizures or some mutations can cause physical impairments that limit a subject's ability to perform a task. Genetic mutations relevant to ASD that caused physical defects, including smaller body weights include the most common copy number variant in ASD, 16p11.2 deletions (Portmann et al., 2014). Motor defects in ASD models including hypo- (Copping et al., 2017; Dhamne et al., 2017) and hyper- locomotion (Kazdoba et al., 2014; Penagarikano et al., 2011; Pietropaolo et al., 2011; Spencer et al., 2011; Spencer et al., 2006; Uutela et al., 2012) can also have consequences on the behavioral outcome of interest by competing or preventing the subject from engaging in the tasks of core symptomology testing. Another example is that strains of mice with visual impairments (FVB or CE3H) may not be useful for cognitive tests that employ visual cues as reference stimuli, and, further, it is well documented that blind mice tend to be hyperactive (Dyer and Weldon, 1975). Olfactory impairments that can occur following seizures (Tiedeken et al., 2013) may abolish sociability in mice and rats. Animals with history of seizures may exhibit long-term changes in locomotor activity (Samotaeva et al., 2012). Most importantly, seizures may lead to other co-morbidities, i.e., depression-like behavior, changes in anxiety or developing aggressive behavior (Castelano et al., 2015; Kalynchuk, 2000; Medel-Matus et al., 2017; Szyndler et al., 2002; Tiedeken and Ramsdell, 2013) and all of those may interfere with proper evaluation in complex social communication behavior. Repetitive behavior and automatisms in rodents such as wet dog shakes, excessive grooming, scratching, jumping or circling could be part of seizure behavior (Velišková and Velišek, 2017) and not necessarily a sign of autistic-like behavior. EEG recordings can provide the information regarding ongoing ictal activity to distinguish ASD and ongoing seizure activity.

Just as it is important to understand the limitations of a behavioral task itself, it is important to investigate, acknowledge, and report the limitations of the rodent model being tested so as not to be shortsighted in the interpretations of the data.

3. A common thread: neuroinflammation in epilepsy and ASD

Neuroinflammation is a pathological process actively present in both epilepsy and ASD, further linking the two diseases. The causes of neuroinflammation in both cases are poorly understood, however recent studies have begun to shine a light on how inflammation in the brain is contributing to these diseases' pathologies. In this mini review, we will focus mainly on commonalities between epilepsy and ASD in terms of neuroinflammation and functional implications of neuroinflammation, including changes to excitable networks mediated by inflammatory regulators.

3.1. Inflammation in ASD

In ASD, the presence of neuroinflammation has been reported in

both clinical and preclinical studies. Post-mortem brain tissue from ASD patients, ranging in age from 3 years to adult, was shown to have Allograft Inflammatory Factor 1 (Iba1) –positive microglia with an activated morphology, defined by truncated processes and an enlarged cell soma volume, compared to age matched controls (Morgan et al., 2010). However in this study, microglial activation was not specific to ASD patients with seizure presence, as data from these patients showed “normal” ramified microglial morphology. This highlights that microglial activation is not always dependent on seizure presence, nor is it a consistent marker of seizures in ASD patients.

Astrocytes, another inflammation-associated cell type in the brain, are also activated in ASD patients (Vargas et al., 2005). Increased Glial fibrillary acidic protein (GFAP; astrocytic marker) expression is observed in cerebellum and cortex and accompanied by localized expression of pro-inflammatory cytokine interleukin-6 (IL-6), and chemokine MCP-1. IL-6 drives microglial activation and promotes astrogliosis, whilst MCP-1 is a chemoattractant driving macrophage migration, both contributing to the neuro-inflammatory cycle.

A recent study found that increased serum levels of high mobility group box protein 1 (HMGB1) significantly correlated to impaired social interaction in ASD patients (Emanuele et al., 2010). This protein is a key inflammatory molecule, which can activate interleukin-1 (IL-1) mediated signaling (including IL-1 β) leading to activation of toll-like receptor 4 (TLR4) through NF κ B-mediated processes.

Besides the changes in neuroinflammatory markers, the brain's immune response, in general, is compromised in ASD patients, namely the imbalance in pro-inflammatory/anti-inflammatory signaling (Ashwood et al., 2011). Adaptive immune response, primarily coordinated by T helper cells, differs in ASD patient frontal cerebral cortex compared to healthy controls (Li et al., 2009). Increased Th1 type cytokines, which are typically pro-inflammatory and pro-injury inducing (e.g. IL-6, TNF α and IFN γ), are increased, whilst Th2, reparative/counteracting inflammation cytokines (e.g. IL-4, IL-10 and IL-5) are unchanged resulting in an increased Th1/Th2 ratio in ASD patients. Another study showed an exacerbated immune response in ASD patients (Jyonouchi et al., 2001); peripheral blood mononuclear cells (PBMCs) taken from ASD patients displayed two-fold higher cytokine expression basally compared to controls, and this difference was further increased after LPS stimulation, a classical immune trigger. TNF α was the primary cytokine found to be increased at baseline conditions in ASD samples compared to controls, and increased further after LPS stimulation. Interestingly, when the TNF α levels were compared to unaffected siblings, the difference was still significant yet not so prominent as the comparison to unrelated individuals, suggesting some genetic contribution. In conclusion, the data illustrate that heightened response of immune cells determines the ASD pathology.

Finally, mast cell (MC) activation is a key process found present in ASD patients contributing to neuroinflammation. It is proposed that MC located in the hypothalamus can be activated via triggers such as stress, which is strongly associated with ASD, and lead to changes in blood-brain barrier (BBB) integrity (Theoharides and Zhang, 2011). The hormone neurotensin, which activates MCs, is increased in ASD patients. Activation of MCs then leads to pre-formed TNF α and other MC mediators (e.g. IL-6, vascular endothelial growth factor and mitochondrial DNA) being carried to target endothelial cells and comprising the BBB tight junctions along with other cytokines to exert pro-inflammatory effects driving BBB breakdown. Additional cross-talk between glia and MCs can lead to further immune activation, such as activation of the complement pathway, further promoting neuroinflammation.

3.2. Inflammatory processes in epilepsy

Like ASD, neuroinflammation is also present in epilepsy as shown by several key studies (reviewed by (Vezzani et al., 2011; Vezzani et al., 2016)). Significant increases in pro-inflammatory cytokines, including

TNF α , IL-1 β and IL-6, have been found in human temporal lobe epilepsy (TLE) brain samples (Vezzani and Granata, 2005). These cytokines are known to be proconvulsant in vivo (Kalueff et al., 2004) and in vitro (Chiavegato et al., 2014). IL-1 β expression was also ectopically localized to astrocytes in TLE patients with hippocampal sclerosis (HS), which is not observed in patients without HS suggesting relation to the neurodegeneration (Ravizza et al., 2008). Astrocytic end-feet projecting around endothelial cells expressing IL-1 β provide the potential for neuroinflammation to affect BBB integrity.

Furthermore, it has been shown in several experimental models, that antagonizing the pro-inflammatory cytokines can be anticonvulsant. Similarly to ASD brains, increased HMBG1 expression is present in the hippocampus of TLE patients (Maroso et al., 2010) and children with febrile seizures (Choi et al., 2011), triggering IL-1/TLR4 signaling cascades driving inflammation and resultant increased excitability. Accordingly, when the endogenous antagonist, IL-1 receptor antagonist (IL-1ra), is applied to the brain or expressed selectively in astrocytes (Vezzani et al., 2000), seizures are inhibited. Antagonists of TLR4 and HMGB1 are also effective at controlling seizures in preclinical models (Maroso et al., 2010).

Further examples of inhibiting cytokine signaling have also proved to be anticonvulsant including modulation of the complement activation pathway. Inhibition of a key pro-inflammatory complement factor, C5a, was shown to be anticonvulsant in several acute and chronic models of epilepsy potentially due to inhibition of downstream cytokine upregulation and signaling (i.e. TNF α , IL-1 β) (Benson et al., 2015). Neuroprotective outcomes following status epilepticus were observed following inhibition of C5a signaling, an effect attributed to reduction of TNF α production (Benson et al., 2015) and increases in IL-4 (Benson et al., 2017). Finally, the BBB integrity is compromised following complement activation resulting in increases in peripheral inflammatory immune cell migration (Benson et al., 2017).

3.3. Common inflammatory pathologies in ASD and epilepsy

Approximately in 30% of childhood ASD patients with epilepsy, the seizures are typically difficult to control adequately with current anticonvulsant drugs (Tuchman et al., 2010a). Shared inflammatory pathologies occurring in both ASD and epilepsy are numerous. More specifically, increased HMBG1, compromised BBB integrity, microglial activation and stress-induced inflammation are key players in both pathologies. The neuroinflammation in both diseases significantly contributes to brain excitability and to the severity or progression of both syndromes, as well as more obviously increase seizure incidence/occurrence. A delicate equilibrium between excitatory and inhibitory neurotransmitters, glutamate and GABA respectively, is key to maintaining homeostasis by maintaining the E-I balance and preventing unwanted and uncontrollable neuronal firing manifesting in seizures, which are observed in both conditions and discussed in details below. Regarding the neuroinflammation, it is known to affect the E-I balance in multiple ways. Astrogliosis, detected in samples from both epilepsy and ASD postmortem brain tissue, leads to impairments in glutamate uptake by astrocytes resulting in excessive extracellular glutamate stores, which drives the glutamate receptor activation (Tian et al., 2005). Further contributing to this rise in extracellular glutamate are the microglial cells, which when activated also expel glutamate (Hu et al., 2000). Increased levels of pro-inflammatory cytokine IL-6, measured in both conditions, worsens this state of heightened excitability as it stimulates excitatory synapse formation in conjunction with impairing inhibitory synapse formation (Nelson and Valakh, 2015; Nelson et al., 2012). The pro-inflammatory cytokine TNF α also increased in both ASD and epilepsy brains works via an NF κ B mediated mechanism to repress expression of excitatory amino acid transporter 2 (EAAT2) reducing the glutamate uptake (Sitcheran et al., 2005) and reduces the strength of inhibitory signaling between neurons (Pribiag and Stellwagen, 2013).

4. Neuronal coordination hypothesis: between etiology and phenotype

The common presence of epileptiform activity and ASD symptoms in various syndromes can be interpreted in two ways: 1) epileptiform activity causes ASD symptoms and/or 2) both are manifestations of a similar underlying cause. In the following section, we will discuss both possibilities separately. However, it is highly probable that they are non-exclusive. Although, epileptiform events may originate from the same etiological origin as the autistic symptoms, they may aggravate the behavioral phenotype.

4.1. Is epileptiform activity responsible for ASD symptoms?

The co-existence of seizures and interictal discharges in ASD patients is well documented (Spence and Schneider, 2009). It has been proposed that the EEG abnormalities may pose a causal role in the behavioral disturbances observed in ASD patients. In syndromes such as Rett, Fragile X, Angelman or Prader-Willi and other childhood epileptic encephalopathies, both epileptiform manifestations and ASD phenotypes are commonly observed together. In these syndromes, the onset of behavioral deficits often coincides with the apparition of the first epileptiform manifestations, leading to the hypothesis that seizures and/or epileptiform discharges during critical periods of development contribute, at least in part, to the behavioral deficits.

This hypothesis is indeed supported by animal model studies. When epilepsy is induced by prolonged status epilepticus, be it via chemical, hyperthermia or hypoxia/ischemia, a wide range of modifications is observed at different levels of organization. Specifically, prolonged SE has been shown to induce inflammation, epigenetic changes, cell metabolism, ion channels and receptors, rewiring or aberrant wiring, cell death, apoptosis and neurogenesis. In turn, affected networks become prone to seizures and, less able to sustain normal cognitive function (Lenck-Santini and Scott, 2015). It is important to note that induction protocols in animal models are extremely severe compared to what happens in real life. When prolonged SE occurs it is because of pre-existing conditions, trauma or brain infection that can also directly affect brain function, making it difficult to disentangle the role of etiology versus SE. In addition, the correlation between seizure frequency or severity and the extent of cognitive or behavioral impairment is not always straightforward, particularly in the context of epileptic encephalopathies (Nabbout et al., 2013). Finally, seizure suppression, particularly in epileptic encephalopathies, is associated with little to no improvement of the functional aspects. Therefore, it is likely that etiology, i.e. the underlying cause of epilepsy, may also contribute directly to cognitive/behavioral impairment in syndromes with epilepsy.

Apart from seizures, interictal EEG abnormalities are also believed to play an important role in behavioral comorbidities. Indeed, data show that both in humans and animal models (Holmes and Lenck-Santini, 2006; Kleen et al., 2010; Kleen et al., 2013) interictal abnormalities (IAs) can alter sensory, memory and higher cognitive functions such as verbal recognition. IAs interference with cognitive processes is transient, in the sense that the impact is limited to the ongoing process supported by the structure where IAs occur or propagate. However, IAs impact could be dramatic in situations where attention is critical such as when operating machines, driving or while at school. In addition, there are conditions where IAs are particularly frequent during sleep, a process known to play a fundamental role in learning and memory. This is the case of conditions such as continuous spike and wave discharges during slow wave sleep or Landau-Kleffner syndrome where during sleep a large majority of the patient EEG is occupied by IAs. These patients suffer from severe cognitive impairment and commonly have ASD. To help patients with large number of IAs and cognitive impairment although no or only few seizures, attempts have been made to suppress IAs by administration of anticonvulsant drugs with the hope to restore cognitive function.

Unfortunately, although few cases have been successful, the efficacy of such approach has not been confirmed and some treatments have actually a negative effect on cognition (Wirrell et al., 2008). Although it is recognized that IAs have a significant impact on cognitive/behavioral function, the limited and inconclusive efficacy of different anticonvulsant drugs in restoring cognitive/behavioral function (see (Frye et al., 2013) for review) suggests that another mechanism is at play. The following section will aim at identifying such mechanism.

4.2. Is there a common mechanism?

4.2.1. E-I balance hypothesis

A hallmark of epilepsy research is the concept of E-I balance. This term is based on the assumption that normal brain function depends on the perfect balance between excitatory and inhibitory inputs to principal cells. Too much excitation or too little inhibition leads to hyperexcitability of the network, in turn leading to seizures. So far, this notion has been critical to further our understanding of epileptogenesis, ictogenesis and treatment design. Indeed, in a large number of epilepsy syndromes, the apparition of seizures can be explained either by a loss of inhibition, for instance by alterations of GABAergic receptors or interneuron function, or by excessive excitation when there is gain of function of excitatory receptors or increase in excitatory pathways. In accordance with the E-I balance hypothesis, drugs that increase inhibition, such as GABAergic agonists, or decrease excitation, such as sodium or calcium channels blockers are highly efficient in regulating seizures. In this regard, the E-I balance concept is critical as it provides a functional framework with clearly identified benefits, namely suppression of seizures.

In the mindset that seizures result from an alteration of E-I balance, we could logically propose that the mere presence of seizures in ASD is an indication of E-I imbalance in ASD. This hypothesis has been proposed for a more than a decade (Brooks-Kayal, 2011; Nelson and Valakh, 2015; Rubenstein and Merzenich, 2003). Loss of inhibition (via alteration of GABAergic synaptic transmission, interneuron dysfunction and abnormal migration) has been documented in ASD patients. Particularly, there is a decrease of GABA levels in various cortical regions of ASD patients, including the frontal cortex (Puts et al., 2017) where reduced GABA_A receptor binding has been observed (Zurcher et al., 2015). Furthermore, recent post-mortem studies in patients show a reduction of parvalbumin interneurons in the medial prefrontal cortex (Ariza et al., 2018). On the top of loss of inhibition, gain of excitation (via an increased principal cell excitability of glutamatergic transmission) has also been identified in ASD (Nelson and Valakh, 2015). Characteristic findings in ASD syndromes, such as abnormal microcolumn organization (Casanova, 2006; Frye et al., 2016), changes in metabolic pathways (Huber et al., 2015; Kwon et al., 2006), homeostatic plasticity (Nelson and Valakh, 2015) or alterations of glial function (Lioy et al., 2011) are also known to affect E-I balance. Finally, various genetic abnormalities, known to alter E-I balance have been identified in both syndrome families (Lee et al., 2017). These include SCN1A (Weiss et al., 2003) GRIN2A mutations (Lesca et al., 2012), PTEN (Elia et al., 2012; Orrico et al., 2009) and others.

A logical consequence of the role of E-I imbalance hypothesis in ASD and epilepsy is that anticonvulsant drugs should restore cognitive/behavioral comorbidities in such syndromes. This strategy has indeed proven successful in animal models. For instance *Scn1a*^{+/-} mice show improvement of social and memory deficits after clonazepam treatment (Han et al., 2012) and juvenile diazepam treatment of the BTBR mouse model of autism prevented the emergence sensory integration deficits in this model. Unfortunately, in humans, anticonvulsant drugs have a limited to no efficacy in restoring cognitive and behavioral function in ASD (Belsito et al., 2001; Frye et al., 2013; Hellings et al., 2005). This is also the case for epilepsy syndromes. For instance, although clonazepam, a common Dravet syndrome treatment (Shi et al., 2016) restores cognitive function in mouse models (Han

et al., 2012), it fails to do so in humans. Therefore, targeting E-I balance, at least using traditional anticonvulsant drugs, fails to treat cognitive disturbances (see (Frye et al., 2013) for review). This suggests that the mechanisms involved in cognitive dysfunction observed in ASD and epilepsy may be more complex than the seizures or E-I balance alteration. To help identify potential mechanisms let us reconsider the E-I balance hypothesis in light of recent theories.

4.2.2. Role of etiology: interneurons and information processing

One important caveat with the E-I balance concept is that the term “balance” does not necessary mean static equilibrium. In the eye of early neuroscientists, brain systems were considered as systems prone to remain in an equilibrium state that only fluctuates when disturbed by external or internal (excitatory) inputs and quickly return back to a quiescent state. However, recent advances in fundamental research demonstrate that this is not the case and that, even in the resting state, brain structures are constantly active and that information in the brain is being processed via specific rhythms. Brain rhythms, by coordinating the firing of neurons, enable the transmission of information across and within structures (Fries, 2015). In addition, they are believed to allow the segregation of pyramidal cells into functional groups, called cell assemblies that convey meaningful information (Buzsaki, 2010). Importantly, GABAergic innervation plays a fundamental role in these processes. GABAergic inhibition provides, via perisomatic inhibition, a pace making activity for the oscillations (Bartos et al., 2007). It has been also proposed that such rhythmical silencing of neurons during oscillations creates short time windows, in which information is being segmented in “chunks” that can be transmitted and interpreted efficiently (Buzsaki, 2010). On the other hand, GABA inhibition is also critical for driving the flow of information within the dendritic microcircuits. In the hippocampus for example, each interneuron subtype projects to a specific part of the pyramidal cell dendritic arborization and is active at specific phase of ongoing oscillations, hereby routing and filtering excitatory flow to the cell (Klausberger and Somogyi, 2008; Kullmann and Lamsa, 2011; Leao et al., 2012; Varga et al., 2012).

The GABAergic innervation is altered in ASD. In addition, brain rhythms and coordination of oscillations across structures are also affected (reviewed by (Kessler et al., 2016; Simon and Wallace, 2016)). Indeed, there is now accumulating evidence that ASD patients show reduced gamma (30–80 Hz) and alpha (8–14 Hz) power and phase synchrony when presented with visual or auditory stimuli (Buard et al., 2013; Edgar et al., 2015; Grice et al., 2001; Milne et al., 2009; Rojas et al., 2008; Stroganova et al., 2012; Sun et al., 2012). Recent work from Vakorin and colleagues (Vakorin et al., 2017) shows that the maturation profile of oscillatory power and network synchrony during resting state are abnormal in children and adolescent with ASD. Although the link between GABAergic alterations, altered rhythms and behavioral deficits in ASD has not yet been completely established, it is likely that, the E-I imbalance observed in ASD induces alterations of brain rhythms, and a poor coordination within and across networks. The resulting deficits in functional connectivity may be responsible for the sensory, perceptual, attention and social disturbances, the characteristics of ASD (Simon and Wallace, 2016).

Similarly to what has been documented in ASD, a significant number of epilepsy syndromes are caused by alterations of GABAergic function. It is highly plausible that the information processes mediated by GABA activity are also directly affected in these syndromes. A classic illustration of this idea is provided by SCN1A mutations in the context of Dravet syndrome: The SCN1A gene codes for the voltage gated sodium channel Nav1.1, that is involved in the generation and propagation of action potentials in the axonal initial segment and along the axon. While SCN1A mutations are observed in various epilepsy syndromes such as generalized epilepsy with febrile seizures plus (GEFS+), it is only when mutations cause a loss of function of the protein that epileptic encephalopathy is observed. Loss of function of Nav1.1 prevents neurons to fire at high frequencies, yet such mutations

paradoxically cause epilepsy. This phenomenon is explained by the fact that Nav1.1 is preferentially highly expressed in GABAergic interneurons expressing parvalbumin (Ogiwara et al., 2007; Yu et al., 2006). Therefore, Nav1.1 down regulation preferentially alters inhibitory function, explaining the seizure phenotype. As for other epileptic encephalopathies, cognitive impairment in Dravet syndrome was for a long time thought to be caused by seizures and ongoing epileptiform activity during infancy. However, there is no correlation between seizure frequency or severity and the extent of cognitive impairment in this syndrome. Moreover, the antiseizure treatments such as clobazam fail to improve cognitive function. Note finally that SCN1A mutations have been observed in ASD patients, suggesting that etiology could directly, in addition to seizures, cause behavioral and cognitive impairment.

The main difficulty in understanding the mechanisms of cognitive impairment in epilepsy is to dissociate the impact of etiology from the impact of seizures. To overcome this difficulty, we developed a targeted approach, in which the etiological alteration is restricted to a specific portion of the brain. This can be readily achieved using RNA interference, a technique enabling to down regulate the expression of a specific gene in vivo. Using either lipofectamine or viral vectors injected into the target structure, we managed to down-regulate the expression of *scn1a* in adult rats.

To determine the impact of Nav1.1 deficit on neuronal function independently of seizures, we (Bender et al., 2013, 2016) conducted two sets of experiments. In both experiments, *scn1a* expression was down regulated in a restricted brain region to avoid seizures and in adult rats to prevent developmental disruptions. Our goal was to identify the direct physiological and behavioral consequences of *scn1a* down regulation and avoid the confounding effect of seizures. In the first series of experiments (Bender et al., 2013), we targeted Nav1.1 expression in the medial septum/diagonal band of Broca (MSDB), a structure controlling theta oscillations in the hippocampal formation. Theta oscillations have been shown to play a critical role in learning and memory as well as in organizing cell activity into cell assemblies that represent ongoing trajectories of rodents. We found that reduction of Nav1.1 expression in the MSDB induced a significant decrease of both amplitude and frequency of hippocampal oscillations. Theta frequency decrease was associated with spatial memory deficit in a reaction to spatial change task. Importantly, Nav1.1 down regulation in the MSDB did not cause seizures, therefore demonstrating that cognitive impairment in Dravet syndrome could directly be the result of etiology.

In the second set of experiments using single unit recordings (Bender et al., 2016) we showed that the decrease in hippocampal theta oscillation following MSDB Nav1.1 knock down was likely caused by a selective loss of fast spiking activity, a characteristic of GABAergic neurons in this structure. In addition, the induced decrease in hippocampal theta frequency was correlated with decreased performance in T-maze alternation task. Here again, no seizure was observed.

Finally, there is now accumulating evidence that effective GABA signaling, which is the first one to emerge during development, plays a critical role in orchestrating the maturation of cortical function (see (Le Magueresse and Monyer, 2013) for review). For example, in the primary visual cortex, the initiation of the critical period during which neural circuits are shaped with experience is strongly influenced by the maturation of fast-spiking parvalbumin interneurons (Takesian and Hensch, 2013). It is therefore extremely likely that alterations of GABA signaling during such critical periods of development would have devastating impacts on the establishment and future maturation of cognitive/behavioral processes.

5. Conclusions

In conclusion, this paper highlights the most important autistic traits commonly tested in models of ASD. These traits should be considered when modeling ASD as a co-morbid functional outcome in

models of seizures and epilepsy.

Recent studies implicate novel mechanisms involved in neurodevelopmental diseases such as ASD and epilepsy including the neuroinflammation and deficits in immune system and mechanisms involved in neuronal excitability, timing and network coordination that may directly lead to behavioral disturbances and thus, form a common substrate for epilepsy and ASD.

The clinical impact of neuroinflammation is difficult to interpret and put into action given the diverse types of inflammation observed in both disorders including severity and location within the brain. As discussed above, ASD patients even with severe microglia activation may not present with seizures and vice versa (Morgan et al., 2010), similarly not all patients with epilepsy (even the same type, i.e., TLE) may have ongoing neuro-inflammatory processes associated with seizures (Ravizza et al., 2008). Thus, the choice of patients eligible for adjunct anti-inflammatory treatment in both diseases has to be carefully made. Yet, a clear biomarker of neuroinflammation presence in these syndromes still awaits to be established especially given the diverse number of cellular activators and signaling molecules involved in these processes. Nevertheless, clinical trials show promise of adjunct anti-inflammatory and immune system modulating therapies in alleviating of some key symptoms in ASD patients (Chez et al., 2012) as well as in patients with epilepsy targeting the neuroinflammatory signaling seems to show promising directions as a disease modifying therapy (Terrone et al., 2017). Yet, further research has to be done to identify the sub-population of patients most benefitting by targeting the inflammatory signaling.

Finally, taken together, preclinical studies show that altering interneuron function in the context of an epilepsy syndrome or ASD can also have direct effects on brain rhythms, cognitive function, maturation and ultimately cognitive and behavioral performance. Therefore, designing new treatments targeting these functions, including the anti-inflammatory therapies, and not exclusively seizures will certainly benefit the patients.

Acknowledgements

The work was supported by the UC Davis MIND Institute; NIH grants R21NS084900 (JLS); R01NS092786 (JV), R01NS076763 (PPLS); R01 NS097808 (JLS).

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