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Review article

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

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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), Wohr et al. (2013) and Yang et al. (2011)	Increased/decreased anxiety Depression-like behavior
	Reciprocal dyad interactions	Lack of interest in the partner	Bozdagi et al. (2010), Dhamne et al. (2017) and Silverman et al. (2015)	Aggressive 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)	Hypo-/hyper-activity Olfactory damage Learning and memory deficits due to neurodegeneration
	Partition test	Lack of interest in the partner	Hamilton et al. (2014), Spencer et al. (2005), Spencer et al. (2008) and Veeraragavan 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), Wohr et al., (2013) and Yang et al. (2012)	
Repetitive behaviors, with restricted interests and behavioral inflexibility	Stereotypies	Repetitive self-grooming; circling; jumping; back flipping; perseverative wood block chewing	Bechard et al. (2017), Blundell 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)	Hypo-/hyper-activity following seizures
	Insistence on sameness and lack of cognitive flexibility	Impaired reversal learning in the Morris water maze or T maze	Moy et al. (2007)	Deficits in spatial discrimination learning due to neurodegeneration

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