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Review article

Features of the broader autism phenotype in people with epilepsy support shared mechanisms between epilepsy and autism spectrum disorder

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ABSTRACT

Richard, A.E., I.E. Scheffer and S.J. Wilson. Features of the broader autism phenotype in people with epilepsy support shared mechanisms between epilepsy and autism spectrum disorder. NEUROSCI BIOBEHAV REV 21(1) XXX–XXX, 2016. To inform on mechanisms underlying the comorbidity of epilepsy and autism spectrum disorder (ASD), we conducted meta-analyses to test whether impaired facial emotion recognition (FER) and theory of mind (ToM), key phenotypic traits of ASD, are more common in people with epilepsy (PWE) than controls. We contrasted these findings with those of relatives of individuals with ASD (ASD-relatives) compared to controls. Furthermore, we examined the relationship of demographic (age, IQ, sex) and epilepsy-related factors (epilepsy onset age, duration, seizure laterality and origin) to FER and ToM. Thirty-one eligible studies of PWE (including 1449 individuals: 77% with temporal lobe epilepsy), and 22 of ASD-relatives (N = 1295) were identified by a systematic database search. Analyses revealed reduced FER and ToM in PWE compared to controls ($p < 0.001$), but only reduced ToM in ASD-relatives ($p < 0.001$). ToM was poorer in PWE than ASD-relatives. Only weak associations were found between FER and ToM and epilepsy-related factors. These findings suggest shared mechanisms between epilepsy and ASD, independent of intellectual disability.

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1. The association between epilepsy and autism spectrum disorder

Epilepsy is a disorder characterised by unprovoked seizures, with diagnosis requiring at least one unprovoked seizure and high risk for another (Fisher et al., 2014). The reported prevalence of epilepsy ranges from 0.2–2% (M = 1%; Bell et al., 2014). Age at onset is typically in childhood or late adulthood, but first seizures can occur at any age (Cockerell et al., 1995).

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by persistent impairment in reciprocal social communication and interaction, and restricted, repetitive patterns of behaviour, interests, or activities (American Psychiatric Association, 2013). The prevalence of ASD is approximately 1% (Elsabbagh et al., 2012). An association between epilepsy and ASD was noted in Kanner's original description of ASD in 1943 (Kanner, 1943). Of 11 children with autism described in his report, at least two (18%) had epilepsy (Kanner, 1971). More recent estimates suggest that the rate of epilepsy in adolescents and adults with ASD is 20%, while for those with epilepsy, 8% have ASD (Kohane et al., 2012; Rai et al., 2012). These are far greater than the prevalence of epilepsy or ASD in the general population.

1.1. Epilepsy-ASD comorbidity and intellectual disability

A notable feature of the epilepsy-ASD comorbidity is its association with lowered cognitive functioning. Epilepsy and ASD are more likely to co-occur in individuals with, than without, intellectual disability (ID). In a Finnish population-based study, the rate of epilepsy in children and adolescents with a comorbidity of ASD and ID was 19% compared to 5% in individuals without ID (Jokiranta et al., 2014). This increased rate in individuals with ID is unsurprising because ID is a risk factor for both epilepsy and ASD. A systematic review of 31 studies examining the prevalence of chronic health conditions in children with ID, reported a 22% rate of epilepsy and 10% rate of ASD; however, it is worth noting that estimates vary greatly across studies (6–35% epilepsy; 5–25% autistic disorder) (Oeseburg et al., 2011).

In a sample of 4509 individuals with ASD, a multivariate model including age, IQ, sex, adaptive functioning, language skills, and a history of developmental regression, revealed that only IQ and age were significant predictors of epilepsy (Viscidi et al., 2013). Controlling for all other variables in the model, a one standard deviation increase in IQ was associated with a 47% decrease in the odds of having epilepsy. These findings compellingly demonstrate that patients with ASD and more severe ID have a greater frequency of epilepsy (Amiet et al., 2008). Similarly, Tuchman et al. (1991) reported that after controlling for mental deficiency and motor deficits, the occurrence of epilepsy in ASD was not predicted by a difficult perinatal course, the presence of other medical conditions, and a family history of epilepsy.

ID is also an important predictor of ASD symptoms in individuals with epilepsy. In conditions in which ASD, ID and epilepsy commonly co-occur such as tuberous sclerosis and neurofibromatosis type 1, a study of 180 patients (also including childhood onset epilepsy of unknown cause) found that 14% had ASD and 68% had epilepsy (van Eeghen et al., 2013). A multivariate prediction model found that ID was the largest predictor of ASD symptom severity as measured by the Social Responsiveness Scale (Constantino et al., 2003), whereas epilepsy was not predictive.

Some argue that the association of epilepsy with ASD is due to the underlying ID (Berg and Plioplys, 2012). This is difficult to disentangle because the majority of studies of individuals with an epilepsy-ASD comorbidity include an unrepresentatively large proportion of participants with ID (e.g. Danielsson et al., 2005; Hara, 2007; Parmeggiani et al., 2010; Rossi et al., 2000). Studies with such samples cannot convincingly demonstrate a relationship between epilepsy and ASD independent of ID. Without clear evidence for this relationship, one cannot be confident that a direct link exists *per se* between epilepsy and ASD.

However, studies of individuals with ASD and normal intellect show that there is a greater prevalence of epilepsy than in the general population, raising the possibility of a direct association between epilepsy and ASD. A recent systematic review of four studies found a pooled prevalence of epilepsy of 9% in ASD (Woolfenden et al., 2012), corroborating an earlier meta-analysis of 10 studies (Amiet et al., 2008). Moreover, epidemiological studies show a lower but definite increase in prevalence of epilepsy in those with ASD. Namely, a Danish nationwide register of 4180 individuals with Asperger's syndrome found that 5% of females and 4% of males had