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

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Highlight

- Meta-analysis of social cognition in epilepsy and relatives of people with autism.
- People with epilepsy (TLE and other epilepsies) have a social cognition deficit.
- The social cognition deficit is less severe in relatives of people with autism.
- Reduced social cognition is associated with an earlier age at epilepsy onset.
- The findings suggest shared neurobiological mechanisms between epilepsy and autism.

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.

Keywords: Epilepsy, Autism Spectrum Disorder, Broader Autism Phenotype, Facial Emotion Recognition, Theory of Mind, Meta-analysis

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 epilepsy (Mouridsen et al., 2013). These rates reflect those of the Finnish nationwide register (5% rate of epilepsy in the population with ASD without ID) (Jokiranta et al., 2014). The reported rates of epilepsy in all of these studies are greater than general population prevalence estimates and raise the possibility of a direct association between epilepsy and ASD.

1.2 *Shared mechanisms between epilepsy and ASD*

Genetic disorders in which both epilepsy and ASD commonly occur, such as Fragile X, Rett and Angelman syndrome, and tuberous sclerosis, offer valuable models for identifying shared mechanisms between epilepsy and ASD (Brooks-Kayal, 2011; Trillingsgaard and Østergaard, 2004). Abnormalities in synaptic plasticity, neuronal morphology, proliferation and migration are thought to cause the epilepsy-ASD comorbidity in these genetic disorders, leading researchers to suggest that an abnormal balance of excitation and inhibition underpins the comorbidity (Bourgeron, 2009). A number of models in which epilepsy and ASD are considered to be different manifestations of the same underlying pathology have been proposed and are reviewed below (Table 1).

1.2.1 *Enhanced protein synthesis in the mTOR pathway*

Kelleher and Bear (2008) put forward a neurobiological model based on our understanding of mutations in the mTOR pathway genes *TSC1/TSC2* (tuberous sclerosis), *FMR1* (Fragile X syndrome), and *PTEN* (a tumour suppressor gene). Additional mTOR pathway genes associated with epilepsy and ASD include *DEPDC5*, *NPRL3*, and *MTOR* (Dibbens et al., 2013; Kuwano et al., 2011; Moller et al., 2016; Ricos et al., 2016). This model proposes that defects in translational regulation in the mTOR pathway contribute to expression of the epilepsy-ASD comorbidity through enhanced protein synthesis and consequent hyperplasticity (Ehninger et al., 2008; Huber et al., 2002; Kwon et al., 2006). This may cause excess synaptic consolidation and enhanced connectivity (Kelleher and Bear, 2008). Hyperconnectivity across certain regions, including the mesial temporal lobe has also been reported in temporal lobe epilepsy (TLE) (Bernhardt et al., 2015; Bonilha et al., 2013; Bonilha et al., 2012; DeSalvo et al., 2014; Dinkelacker et al., 2015) and may underlie hyperexcitable, epileptogenic cortex (Morgan and Soltesz, 2008). Moreover, increased connectivity has been reported in individuals with ASD. For example, Keown et al. (2013) reported enhanced local connectivity in primary visual and extrastriate cortices, extending into the temporal lobe and suggested that this may relate to enhanced local visual processing in individuals with ASD.

1.2.2 *Disrupted neurotransmission: Channelopathies, neurotransmitter and protein dysfunction*

Channelopathies are disorders of ion channels. Mutations of sodium channel subunit genes are a common cause of genetic epilepsies, such as mutation of the alpha 1 subunit of the sodium channel gene, *SCN1A*, in Dravet syndrome and GEFS+ (Marini and Mantegazza, 2010; Mullen and Scheffer, 2009). Likewise, in ASD family studies, missense mutations in *SCN1A* and *SCN2A*, and nonsense mutations in *SCN2A*, confer risk for ASD (Sanders et al.,

2012; Weiss et al., 2003). This implies that sodium channel abnormalities constitute a possible shared mechanism of the epilepsy-ASD comorbidity.

There is also mounting evidence for a role for GABAergic system disruption in expression of an epilepsy-ASD comorbidity. GABA is the brain's principal inhibitory neurotransmitter and disrupted GABAergic system functioning may cause increased cortical excitability (Fedi et al., 2008). Reduced GABA receptor binding has been found in the brains of individuals with epilepsy with a mutation of the GABA_A receptor subunit gene *GABRG2* (Fatemi et al., 2009; Fedi et al., 2006; Guptill et al., 2007). In ASD, post-mortem studies have found reduced GABA_A binding sites in the brain (Guptill et al., 2007) as well as decreased expression of GABA_A receptor subunits associated with epilepsy (*GABRA1*, *GABRB3*, *GABRD*, and *GABRG2*) (Fatemi et al., 2014; Fatemi et al., 2009; Macdonald et al., 2010). Moreover, single nucleotide polymorphisms (SNPs) in *GABRG2* and *GABRA4* may interact to increase risk for ASD (Sesarini et al., 2015). SNPs across *GABRB3* have been associated with ASD independently and through their interaction with *GABRD* (McCauley et al., 2004; Sesarini et al., 2014). Notably, rare mutations of *GABRB3* have been identified in childhood absence epilepsy (Tanaka et al., 2008) and also in ASD (Delahanty et al., 2011).

GABRB3 is located in the 15q11-q13 region of chromosome 15 and duplication of this region is the most common copy number variant (CNV) in ASD, with an estimated prevalence of 0.5-3% (Hogart et al., 2010). Disruption of the 15q11-q13 region is also relevant to epilepsy. Maternally derived deletion of 15q11-q13 is the most common cause of Angelman syndrome, in which 90% of individuals have epilepsy (Saitoh, 2015). Notably, this deletion is associated with more severe epilepsy than other causes of Angelman syndrome. Furthermore, maternally derived isodicentric and interstitial duplication of chromosome 15, affecting the 15q11-q13 region, are often associated with the co-occurrence of ASD and epilepsy (Hogart et al., 2010).

Proteins that are involved in GABA neurotransmission have also been implicated. For example, mutation of *ARX*, which is integral to the development and migration of GABA interneurons (Kato and Dobyns, 2005), is found in genetic epilepsies often associated with ASD (e.g. X-linked myoclonic epilepsy with spasticity and intellectual disability) (Scheffer et al., 2002; Shoubridge et al., 2010; Stromme et al., 2002). Also, *FMRI* knockout mice display downregulation of GABA receptor subunits, a reduction in cortical interneurons, and impaired functioning of interneurons, all of which may lead to increased seizure susceptibility (El Idrissi et al., 2005; Paluszkiwicz et al., 2011; Selby et al., 2007). Treatment of *FMRI* knockout mice with GABA_A and GABA_B agonists reduces ASD-associated behaviours and seizures (Henderson et al., 2012; Heulens et al., 2012). Interestingly, in humans with Fragile X syndrome, a GABA_B agonist alleviates social deficits (Berry-Kravis et al., 2012).

Neurexin dysfunction may also be implicated in the comorbidity of epilepsy and ASD, since mutation in the neurexin 1 gene *NRXN1*, has been associated with both conditions. Neurexins are neuronal adhesion proteins involved in forming trans-synaptic complexes required for synaptic contact and neurotransmission, and are thus relevant to synaptic plasticity (Thalhammer and Cingolani, 2014). CNVs causing exon-disrupting deletions of *NRXN1* increase risk for generalised genetic epilepsy (GGE) (Moller et al., 2013). Similarly, CNVs causing deletions of *NRXN1* have been linked with ASD (Girirajan et al., 2013; Glessner et al., 2009; Matsunami et al., 2013) as have SNPs (Feng et al., 2006; Griswold et al., 2015). In the Feng et al. (2006) study, one of the missense variants was associated with a co-occurrence of ASD, epilepsy and ID. Moreover, SNPs affecting *CNTNAP2*, which encodes Caspr2, a member of the neurexin superfamily, cause Cortical Dysplasia-Focal Epilepsy syndrome that involves regression of language and social skills, and ASD (Strauss et al., 2006). Linkage and association analyses have suggested that SNPs

affecting *CNTNAP2* increase susceptibility for ASD independent of epilepsy (Alarcon et al., 2008). Knock out of *CNTNAP2* in mice causes spontaneous seizures, perseveration, motor stereotypies, and communication and social behaviour abnormalities (Penagarikano et al., 2011). These likely relate to aberrant neuronal migration, reduced number of GABAergic interneurons, and reduced cortical neuronal synchrony observed in these mice.

Additionally, mutations in *SYN1* and *SYN2*, genes coding for synapsins, have been associated with increased risk for epilepsy and ASD. Synapsins are phosphoproteins implicated in synaptic vesicle trafficking and neurotransmitter release in neurons (Cesca et al., 2010). They play a role in neuron development, synaptogenesis, and maintenance of mature synapses (Fornasiero et al., 2010). Nonsense and missense mutations in *SYN1* have been linked to the epilepsy-ASD comorbidity (Fassio et al., 2011). In a large study of 2717 adults with epilepsy and 1118 controls that investigated the potential contribution of common variants across 279 candidate genes, SNPs of *SYN2* were associated with epilepsy with a history of febrile seizures (Cavalleri et al., 2007). Prasad et al. (2014) also reported differences in the genotypic distribution of *SYN2* A>G polymorphisms between individuals with GGE and controls. Mutations of *SYN2* (one nonsense and two missense) have been associated with increased risk of ASD (Corradi et al., 2014).

Mouse models have demonstrated that knock out of *SYN1* and *SYN2* may lead to hyperexcitable cortex, reduced inhibitory neurotransmission, and increased susceptibility to seizures, as well as impaired social behaviour, with *SYN2* knock out mice also displaying repetitive grooming (Farisello et al., 2013; Greco et al., 2013; Li et al., 1995). Interestingly, impaired social behaviour in these mice is apparent prior to the onset of seizures (Greco et al., 2013). This suggests that autism behavioural traits are not merely a consequence of an epileptic encephalopathy, since the seizures and interictal epileptiform discharges post-date the appearance of autistic features (Berg et al., 2010).

These findings illustrate that the bulk of our understanding of the shared neurobiological and genetic mechanisms between the epilepsies and ASD has relied on drawing parallels between the two disorders, rather than studying populations with both. This limits our potential for discovery of shared mechanisms, as it is not clear to what extent mechanisms that occur in each disorder independently account for symptom expression in the comorbid population. As noted by Tuchman et al. (2010), a more rigorous approach is to carefully phenotype the epilepsy-ASD comorbidity and then identify similarities and differences with the ASD-only and epilepsy-only populations to elucidate the neurobiological and genetic mechanisms that are core to joint expression of these disorders.

1.3 Comparing patients with epilepsy and ASD to those with epilepsy or ASD

Few investigators have conducted such phenotype-comparison studies. Turk et al. (2009) reported that compared to children with ASD-only, those with the epilepsy-ASD comorbidity had more gross and fine motor difficulties (e.g. clumsiness, poor writing), reduced daily living skills (e.g. greater dislike for being washed), and reduced non-verbal communication and social interactions (e.g. atypical eye gaze, poor peer interactions). However, interpretation of these findings is limited by poor matching of the groups on IQ, with a larger proportion of individuals with ID in the comorbidity group (98% versus 88% in the ASD-only group). The potential influence of the IQ discrepancy is highlighted by the null-findings of Smith and Matson (2010a, 2010b, 2010c) who employed a similar study design, but matched groups on severity of ID. They found no differences in behaviour problems (e.g. stereotypy and aggression, social skills, repetitive behaviours, hyperactivity, anxiety and depressive symptoms) in individuals with the comorbidity compared to individuals with ASD-only. Their studies however, had relatively small numbers, with groups of 25, and a higher than normal proportion of severely intellectually impaired participants

(48-96% with severe to profound ID compared to ASD population estimates of ID of 13-31%) (Baio, 2014; Jokiranta et al., 2014) such that the results may not generalize to the wider comorbidity population.

The relevance of severity of ID to the interpretation of phenotype-comparison studies was further demonstrated by a large study of 2645 ASD patients with a broad range of intellectual abilities (30% with ID, Mean IQ = 81.17 [SD = 27.88]). An association was observed in which individuals with epilepsy had more severe ASD; however, when controlled for IQ, the association was no longer evident and a comorbid diagnosis of epilepsy now only predicted hyperactivity (Viscidi et al., 2014). Separately examining participants with and without ID, suggested that IQ moderates the epilepsy-ASD phenotype, with different mechanisms potentially underpinning the comorbidity in these subgroups. In those with ID more significant autistic mannerisms were seen, and in the subgroup without ID, a comorbid diagnosis of epilepsy predicted hyperactivity and irritability. The intellectual ability of participants is therefore important to consider in studies examining the behavioural phenotype of the epilepsy-ASD comorbidity.

The focus on severely impaired individuals limits our understanding of the comorbidity by restricting the generalizability of findings and the subtlety of traits that may be examined. An alternative study design that circumvents these challenges involves the characterisation and genetic dissection of endophenotypes in individuals without ID. Endophenotypes are heritable, circumscribed elements of a phenotype, hypothetically subserved by fewer genes with less complex genetics than the phenotype they represent (Gottesman and Gould, 2003). They are believed to increase the chances of detecting the genetic variants contributing to disease susceptibility, with linkage analyses incorporating endophenotypes in complex diseases such as schizophrenia (Freedman et al., 1997), cardiac arrhythmia (Keating et al., 1991), and ASD (Bradford et al., 2001) yielding successful results.

For example, by including information on proband language deficits (i.e. age of onset of phrase speech) as well as parental language development and skills, Bradford et al. (2001) achieved increased power to detect susceptibility loci for ASD.

1.4 *The Broader Autism Phenotype*

The Broader Autism Phenotype (BAP) refers to mild autism traits such as subtle difficulties in language and communication, reciprocal social interactions, visual attention and sensory integration, and obsessional behaviours (Sucksmith et al., 2011). Such traits were first noted by Kanner and Asperger in their original reports of ASD and Asperger's syndrome in which some of their patients' parents were described as emotionally unresponsive, withdrawn, pedantic, late speakers, obsessional, and eccentric (Asperger, 1944; Kanner, 1943). Features of the BAP span behavioural, cognitive, and personality domains (Sucksmith et al., 2011).

In normal individuals, expression of the BAP may reflect the presence of susceptibility gene(s) for ASD. This concept is drawn from the observation that approximately 20% of first-degree relatives of individuals with ASD have the BAP compared to 3-9% in the general population (Bolton et al., 1994; Sasson et al., 2013). BAP trait expression is also more prominent in multiplex families, defined by the presence of at least two members with ASD, compared to simplex families with a single affected individual (Gerds et al., 2013). This may result from a greater frequency of ASD susceptibility alleles in multiplex families (Risch, 2001). In simplex families, on the other hand, ASD expression may be more heavily influenced by *de novo* mutations (Sebat et al., 2007). BAP traits are also reportedly more common in male than female relatives of individuals with ASD (Piven et al., 1997), paralleling the sex ratio in ASD (Schendel et al., 2013).

The current meta-analysis will examine BAP feature expression in people with

epilepsy (PWE) and in relatives of individuals with ASD. In particular, we will consider two components of social cognition, namely facial emotion recognition (FER) and theory of mind (ToM). Broadly, social cognition relates to the role that cognitive processes play in social interactions, including how we process, encode and apply information about other people and our interactions with them in social situations (Green et al., 2015). Emotion recognition and ToM are two principal social cognitive domains that have received considerable attention in social neuroscience research (Frith and Frith, 2008), with impaired ToM reflecting an inability to infer another person's state of mind and thus, a hallmark feature of ASD (Premack and Woodruff, 1978). Emotion recognition and ToM also constitute social cognitive components of the BAP that have been studied in PWE to examine the extent to which social cognition is disrupted by epilepsy-related neural changes. The impact of epilepsy on social cognition has typically been studied in terms of the site and laterality of the seizure focus in the brain, the age at habitual seizure onset (epilepsy onset), the duration of epilepsy, and the frequency of seizures, all of which will be considered in this meta-analysis.

1.4.1 Facial emotion recognition (FER) and theory of mind (ToM)

Abnormalities in facial emotion processing and ToM are usual in ASD (Harms et al., 2010; Senju et al., 2009) and correlate with their reduced social skills (Assaf et al., 2013; Humphreys et al., 2007). Similar abnormalities have also been detected in relatives of individuals with ASD perhaps reflecting BAP features (Baron-Cohen and Hammer, 1997; Bolte and Poustka, 2003).

It is likely that FER underpins the development of ToM. Typically developing infants as young as four months of age can discriminate between facial expressions of emotion (Montague and Walker-Andrews, 2001); this ability continues to develop into adolescence (Tonks et al., 2007). ToM develops after FER (Chakrabarti and Baron-Cohen, 2006), with

infants as young as nine months using awareness of others' emotions to predict their actions (Barna and Legerstee, 2005). It is only by the age of three to four years that children begin to attribute representational epistemic mental states (e.g. thoughts, beliefs, and knowledge) to themselves and others (Saxe et al., 2004). ToM continues to develop until early adulthood (Dumontheil et al., 2010).

Arguably, the developmental association between FER and ToM implies that early deficits in FER may contribute to delayed ToM development. This is consistent with longitudinal data demonstrating that emotional understanding at three to four years old predicts later performance on ToM tasks (Hughes and Dunn, 1998) and suggests that early onset of epilepsy-related neural disruption may contribute to FER and ToM difficulties.

A close association between the development of facial emotional processing and ToM is also proposed by the social motivation theory, which postulates that deficits in FER and ToM are both a consequence of reduced social motivation (Chevallier et al., 2012). A leading theory about the core deficit in ASD, the social motivation theory refers to the psychological disposition and biological mechanisms that bias individuals to preferentially orient to the social world, to seek and take pleasure in social interactions, and to dispense effort toward maintaining social bonds. Social motivation is subserved by a brain network including the amygdala, ventral striatum, and orbital and ventro-medial prefrontal cortices (Chevallier et al., 2012). In ASD, reduced interest in social stimuli deprives the developing child of social inputs and learning opportunities. In support of this model, reduced social orienting and joint attention have been identified as early risk markers for ASD (Zwaigenbaum et al., 2013). The social motivation theory may have wider repercussions and relate to those with mild autism traits as well. This is supported by an association of reduced social motivation and abnormalities in FER and ToM in the general population (Germine et al., 2011; Wellman et al., 2004).

In addition to being linked through their developmental trajectory, emotion perception and ToM are hierarchically linked in cognitive processing, where emotion perception and evaluation is a precursor to ToM reasoning (Spunt and Lieberman, 2012). This hierarchical relationship is incorporated in the Empathising System model (Chakrabarti and Baron-Cohen, 2006), which describes the neurocognitive mechanisms underpinning empathy and sympathy. It is one of the leading models linking emotional perception and ToM and has been largely derived from ASD research (Mitchell and Phillips, 2015).

1.4.2 The overlapping brain networks of FER and ToM

The brain regions primarily involved in facial emotion processing overlap with those involved in ToM reasoning such that neural changes that affect one function are likely to impact the other (Fig .1). Processing of emotional faces engages a broad, bilateral brain network including visual areas (e.g. fusiform gyrus, lingual gyrus), limbic areas (amygdala, parahippocampal gyrus, posterior cingulate cortex), temporo-parietal areas (parietal lobule, middle temporal gyrus, superior temporal sulcus [STS], insula), prefrontal areas (dorso-medial prefrontal cortex [PFC], lateral PFC), and the putamen and cerebellum (Fusar-Poli et al., 2009; Lee and Siegle, 2012). A meta-analysis found that the amygdala, lateral PFC, and dorso-medial PFC were activated across different forms of explicit FER tasks (Lee and Siegle, 2012). Moreover, the STS/temporo-parietal junction (TPJ) was commonly activated in tasks requiring the recognition of emotions in others. Such FER tasks are frequently used in studies of PWE and individuals with ASD and their relatives.

The amygdala is involved in rapid automatic evaluation and orientation to biologically relevant stimuli, such as the reward value of social orienting (Adolphs and Spezio, 2006; Klein et al., 2009). The lateral and medial PFC modulate the automatic amygdala-based response to expressions of emotion (Lieberman et al., 2007) while the STS is

implicated in analysing changeable aspects of faces including expressions (Haxby et al., 2000). Anterior mesial temporal regions, including the amygdala, modulate activity in the STS during face processing (Ahs et al., 2014).

While there is a broad network engaged in ToM, specific regions are involved in its different facets. The network of brain regions activated by ToM tasks comprises the medial PFC, precuneus, temporal pole, inferior frontal gyrus, fusiform gyrus, and STS/TPJ (Mar, 2011; Schurz et al., 2014). A meta-analysis found that the right TPJ and the medial PFC were activated during performance of various types of ToM tasks (e.g. false belief task, strategic games, Reading the Mind in the Eyes task) (Schurz et al., 2014). In ToM processing, the TPJ is involved in inferring and predicting mental states based on available information about a person (Schurz et al., 2014), while the medial PFC is more broadly involved in processing socially or emotionally relevant information about others (Saxe and Powell, 2006). Another meta-analysis found substantial overlap in regions of activation during the performance of heavily language-based and less language-based ToM tasks (Mar, 2011). This suggests that a shared network implicated in ToM is involved in performing these tasks. This is despite evidence that individuals with high functioning ASD may perform normally on heavily language-based ToM tasks in contrast to less language-based tasks (Schuwerk et al., 2015). Their strong performance may reflect the use of verbal reasoning and learned scripts as compensatory mechanisms (Frith, 2004).

Although involvement of the amygdala in ToM reasoning has not been consistently demonstrated (Mar, 2011; Schurz et al., 2014), a recent large-scale fMRI study (N = 462) found that healthy controls activated the amygdala bilaterally during a false-belief task. The inconsistent identification of amygdala involvement may have been limited by many neuroimaging studies only having 12-16% power to detect activation (Spunt et al., 2015). Moreover, this study found that amygdala activation correlated with activation in the

STS/TPJ bilaterally, adding further support to the involvement of the amygdala in ToM processing. Also, reduced amygdala volume and activation in people with ASD has been associated with poor performance on the Reading the Mind in the Eyes task (Baron-Cohen et al., 1999; Radeloff et al., 2014).

Overall, the literature suggests a close association between FER and ToM, as the development of ToM partly depends upon that of emotion processing abilities or may result from the same underlying social motivation deficit that underpins reduced FER. Moreover, emotion processing is a precursor to ToM during ToM reasoning and there is substantial overlap in the brain regions subserving FER and ToM.

1.4.3 FER and ToM in people with epilepsy

Seizure focus and laterality

Patients with TLE show structural and functional changes in regions involved in the FER and ToM brain networks, thus most studies of FER and ToM in epilepsy have focused on individuals with TLE (Fig. 1). Individuals with TLE show reduced activation in the amygdala, STS, fusiform gyrus, occipital face area, and PFC when engaging in facial emotion processing (Riley et al., 2015). Reduced structural connectivity of the inferior longitudinal fasciculus, which links the occipital face area to the anterior temporal lobe, was also noted. Moreover, mesial TLE (mTLE) is associated with decreased cortical surface area and cortical thinning in the superior temporal gyrus, altered cortical surface morphology and folding in the medial orbitofrontal cortex, and decreased functional connectivity between temporal lobe regions and the medial PFC (Alhusaini et al., 2012; Pittau et al., 2012). These findings raise the possibility that disruption of a network extending beyond the temporal lobe seizure focus may be responsible for FER and ToM deficits (Riley et al., 2015).

Multiple studies have reported reduced FER and ToM in TLE compared to non-

epilepsy controls. A recent systematic review of emotion recognition (Monti and Meletti, 2015) and a meta-analysis of ToM (Stewart et al., 2016) strongly supported deficits in these abilities in patients with TLE. In contrast, few studies have compared individuals with TLE to other forms of epilepsy (i.e. other focal epilepsies or GGE). The few studies that exist tend to report poorer FER and ToM in TLE than in patients with other forms of epilepsy (e.g. Broicher et al., 2012b; Reynders et al., 2005). However, in studies comparing patients with TLE to those with frontal lobe epilepsy (FLE), results are more variable; some studies find no differences, while those that do, show inconsistency in the direction of their effects (Giovagnoli et al., 2011; Giovagnoli et al., 2013; Golouboff et al., 2008). This may reflect the involvement of frontal lobe regions in the FER and ToM brain networks, which is supported by findings of reduced social cognition in FLE (e.g. Farrant et al., 2005; Giovagnoli et al., 2013; Stewart et al., 2016).

A number of studies have also compared FER and ToM in patients with left and right TLE. Despite some evidence suggesting a greater right- than left-hemisphere contribution to social cognition (Mazza et al., 2007; Ortigue et al., 2009), most studies in TLE fail to find an effect (e.g. Benuzzi et al., 2004; Reynders et al., 2005). Moreover, Golouboff et al. (2008) reported greater left-hemisphere involvement. Reasons underlying inconsistent findings may include low statistical power due to small sample sizes, a lack of support for greater right-hemisphere involvement (Bzdok et al., 2012), or the use of tasks that are differentially weighted towards left- or right-hemisphere processes (e.g. language-based ToM measures, such as the Faux Pas task).

Age at epilepsy onset, epilepsy duration and seizure frequency

With respect to age at epilepsy onset, a number of studies have reported that earlier seizure onset is associated with more marked FER and ToM deficits (e.g. Meletti et al., 2003;

Tanaka et al., 2013). The early-onset hypothesis postulates poorer emotion recognition in individuals with early epilepsy onset (< 6 years) (McClelland et al., 2006). An association between early age at epilepsy onset and FER deficits is consistent with studies examining the impact of amygdala lesions on FER, which demonstrate that adult-acquired lesions are associated with more subtle deficits than those acquired in childhood (Calabrese et al., 2014). This may be partly explained by the more prominent role of the amygdala earlier in development during the acquisition of FER skills, compared to greater reliance on later developing regions of the FER network in adulthood (e.g. PFC) (Vink et al., 2014). The increased functional connectivity between the amygdala and other core FER regions that develops from childhood to adulthood may permit greater reliance on these other regions (Gabard-Durnam et al., 2014; Gee et al., 2013; Vink et al., 2014). It is noteworthy however, that few studies have controlled for the duration of epilepsy when reporting an association of age at epilepsy onset with FER and ToM (Cohn et al., 2015; Giovagnoli et al., 2013; Meletti et al., 2009). This is problematic because ongoing seizures may lead to a subtle progressive decline in cognition (Bernhardt et al., 2009; Hermann et al., 2006). Whilst a relationship between epilepsy duration and FER has not been demonstrated independent of age at epilepsy onset (Cohn et al., 2015; Meletti et al., 2009), such a relationship has been reported in ToM studies (Amlerova et al., 2014; Giovagnoli et al., 2011). In addition, most studies fail to find an association between seizure frequency and social cognition (e.g. Giovagnoli et al., 2013; Li et al., 2013).

Overall, there is substantial variability in the reported associations between social cognition and epilepsy-related variables (i.e. seizure focus and laterality, age at epilepsy onset, epilepsy duration, and seizure frequency). This makes it challenging to understand how these variables contribute to expression of mild autistic traits. Conflicting findings may be due to differences in the characteristics of the cohort, such as the age of participants, the age

at epilepsy onset and its duration, the epilepsy syndrome, and intellectual abilities. Moreover, methods of assessing social cognition vary widely between studies. For example, whilst some FER measures require participants to identify an intensely expressed emotion, others include facial stimuli with more subtle expressions or require participants to identify a non-matching emotion, constituting more challenging tasks. Furthermore the findings of individual studies may be biased due to small sample sizes, reducing statistical power to detect significant effects. This latter issue can be overcome by performing meta-analyses.

Two recent reviews have examined some of these associations but with a narrower remit. Monti and Meletti (2015) focused their narrative review of FER studies on patients with mTLE, compared with non-TLE patients and controls, rather than performing a meta-analysis. In contrast, Stewart et al. (2016) performed a meta-analysis of ToM in PWE, but their method of analysis precluded direct comparison of patients with TLE to those with other forms of epilepsy, and of patients with right and left TLE. As acknowledged by Stewart et al. (2016), their meta-regressions examining the association of demographic and epilepsy related variables with ToM had low sensitivity and may partly explain the lack of significant associations. Their findings could be expanded by directly comparing patients with different forms of epilepsy, and extending the analysis to other measures of social cognition.

1.5 Models of co-morbid epilepsy and ASD independent of ID

BAP trait expression in neurologically healthy individuals is common and is seen in the general population, where it is not pathological. In healthy individuals, we conjecture it may be due to the presence of ASD susceptibility genes. In PWE who have BAP features, these may be the consequence of ASD susceptibility genes or epilepsy-specific mechanisms, or a combination of these.

The cognitive and behavioural symptoms associated with epilepsy may reflect not

only the secondary effects of epilepsy, but may be a direct consequence of the network disease causing seizures (Wilson and Baxendale, 2014). BAP traits in PWE may represent, therefore, an essential or secondary comorbidity. An essential comorbidity means that the underlying genetic or neurobiological cause of an individual's epilepsy also causes their cognitive and behavioural comorbidities. Conversely, a secondary comorbidity arises due to the effects of seizures or a lesion affecting neural functioning and development (Berg, 2011; Wilson and Baxendale, 2014). Epilepsies are diseases of brain networks and therefore the networks causing seizures are also responsible for associated cognitive and behavioural symptoms (Wilson and Baxendale, 2014).

In the past, there has been debate as to whether secondary effects of epilepsy are solely responsible for ASD in people with both disorders. This is unlikely as epilepsy often begins after ASD diagnosis, suggesting that the neurobiological features that give rise to ASD also underpin epilepsy. In ASD, in addition to the epilepsy onset peak in childhood, there is a well-recognised peak in adolescence (>10 years) (Bolton et al., 2011; Deykin and MacMahon, 1979). This second epilepsy onset peak is noteworthy because such a peak is not seen in the general population or in individuals with ID without ASD (Branford et al., 1998; Forsgren et al., 2005). The latter is particularly important as it supports an association of epilepsy and ASD independent of ID. Similarly, in individuals with a neurobiological predisposition to the comorbidity, expression of BAP features prior to epilepsy onset would support a contribution of ASD susceptibility mechanisms to epilepsy. Thus far, this possibility has not been directly examined, although it is supported by findings of reduced social competence in children with new-onset epilepsy compared to controls (Almane et al., 2014). Interestingly, murine studies also show impaired social behaviour prior to seizure onset in *SYN1* and *SYN2* knock out mice (Greco et al., 2013).

The essential comorbidity and secondary effects models are not mutually exclusive

and the extent to which each contributes to the co-occurrence of epilepsy and ASD is as yet undetermined. Examining the relationship of epilepsy-related variables with expression of the BAP offers a new way of shedding light on the extent to which secondary effects of epilepsy may contribute to the epilepsy-ASD comorbidity.

1.6 *Aims and Hypotheses*

This series of meta-analyses examines the relationship between social cognition deficits and epilepsy-related and demographic variables in PWE. We compare findings from studies of social cognition in PWE versus controls to the findings of studies of ASD-relatives versus controls, to examine whether social cognition difficulties are more prominent in PWE than ASD-relatives. Our study is the first meta-analysis to compare FER and ToM in PWE and ASD-relatives.

We hypothesise that FER and ToM will be poorer in PWE than in controls. We further suggest that these difficulties will be greater in people with TLE compared to other forms of epilepsy (excluding FLE). We will analyse whether age at epilepsy onset, epilepsy duration, and laterality are associated with the presence of BAP features. By directly comparing patient groups with different forms of epilepsy and employing a more statistically powerful approach to examining the correlation of BAP traits with age at epilepsy onset and duration than previous research, we can draw strong conclusions regarding the association of social cognition with epilepsy-related variables.

We also hypothesise that ASD-relatives, particularly males, will show poorer FER and ToM compared to female relatives and controls. We will examine the relationships of age, IQ and sex with the expression of ASD features in PWE and ASD-relatives.

2 Methods

2.1 *Literature search*

We conducted a systematic search of the published literature available through the PubMed, PsycINFO, and Current Contents Connect databases. The key words entered to retrieve relevant reports are listed in Table 2. We evaluated the titles and abstracts of the retrieved reports to find those that examined FER or ToM in our target groups of PWE and ASD-relatives. The literature search was completed in August 2014 and included peer-reviewed journal articles, article abstracts, conference and meeting proceedings, presentation abstracts, and theses and dissertations. Since a report could contain more than one study, our unit of analysis was an empirical study, defined as data collected under a single research plan from a specified sample of respondents. Inclusion criteria for the empirical studies were as follows:

- A. Study published in English or French, in which objective measures of FER or ToM were employed with at least five participants in each group.
- B. The target group's performance on the task was compared to that of a non-epilepsy or non-ASD control group or to population norms.
- C. The data reported in the study enabled the ascertainment of mean test scores and standard deviations for the target and control groups, or exact t -, F -, or p -values were available. When these values were unavailable, authors were contacted. For the study by Shaw et al. (2004), we estimated effect size based on the proportion of participants succeeding on a ToM task (p. 200; Lipsey and Wilson, 2001).
- D. The target sample principally comprised individuals without ID. We accepted studies (1) that excluded individuals with ID ($IQ < 70$), or developmental disorders, (2) whose target group had mean $IQ \geq 80$, or a mean score within two standard deviations from the normative mean on measures considered to reflect general intellect (e.g. Raven's progressive matrices, K-ABC), (3) whose participants performed within normal limits on a

neuropsychological test battery or dementia screening measure, (4) that had mean years of education ≥ 9 , or where (5) over 50% of the target sample completed primary school, or (6) none required teaching aides in school.

E. The epilepsy sample did not exclusively comprise post-neurosurgery patients. In reports of PWE that provided data for non-surgical and surgical patients separately, only data for the non-surgical patients was used. When this division was not possible, data from the combined group was included in the analyses.

The literature search produced 2512 reports, of which 53 met eligibility criteria for this meta-analysis. Six of these reports included two studies (Fig. 2). When data from multiple measures of the same construct (i.e. FER or ToM) were reported in a single study, a summary effect size was calculated to combine effects across tasks such that a single FER or ToM effect size was generated from each study. We used the approach described by Borenstein et al. (2009) to calculate these summary effect sizes since it accounts for correlations between the same construct measures and gives more weight to combined effect sizes from measures that were less correlated. Moreover, including multiple effect sizes from individual studies would have resulted in an underestimation of error. Tables 3 and 4 present characteristics of included studies of PWE and ASD-relatives, respectively.

2.2 *Statistical analyses*

Data were analysed using Open Meta-Analyst (Wallace et al., 2012) and SPSS Version 22 (Lipsey and Wilson, 2001; Wilson, 2010). Four principal meta-analyses were performed on studies that examined: FER in (1) PWE and (2) ASD-relatives, and ToM in (3) PWE and (4) ASD-relatives; each target group was compared with data from controls. To assess the association between seizure focus and FER or ToM, secondary meta-analyses were conducted on studies comparing patients with TLE and non-TLE to controls, and TLE to non-TLE patients.

The non-TLE patient group was defined as any combination of participants with GGE or focal epilepsy with a seizure focus outside the temporal lobe, with the exception of groups consisting exclusively of FLE patients. Studies of only FLE patients were excluded because as for TLE, regions of structural and functional change in FLE overlap with the social cognition brain network (Xinzhi et al., 2014). Because there were only two studies providing data to examine FER in TLE compared to non-TLE patients, data relating to FER and ToM were combined for this analysis to examine a broader construct of social cognition, for which we generated a summary effect size for overall performance, using Borenstein et al.'s approach (Borenstein et al., 2009). Finally, two additional secondary meta-analyses were used to explore the laterality effect, one each comparing FER and ToM in right TLE (RTLE) and left TLE (LTLE) patients.

To examine the relationship of FER and ToM with age at epilepsy onset and epilepsy duration, secondary meta-analyses were conducted on the reported correlations of FER and ToM with these variables. Given that epilepsy is a developmental disorder, we also used ANOVA to examine the impact of age at epilepsy onset, by comparing studies with a mean age at epilepsy onset ≤ 12 years (childhood onset) to those with mean age at onset > 12 years (adolescent/adult onset). Studies of FER and ToM were combined for this analysis due to the small number of available studies (Borenstein et al., 2009). Because only two studies reported correlations of FER or ToM with seizure frequency and only nine studies provided data on the mean seizure frequency of epilepsy patients, we could not explore the association of FER and ToM with seizure frequency. To examine the relationship of social cognition with demographic variables, including IQ, age, and sex (male to female ratio), we conducted meta-regressions combining FER and ToM studies of PWE. In studies of ASD-relatives, similar meta-regressions examined the relationship of IQ and age with FER and ToM and finally, meta-analyses of FER and ToM task performance in male versus female ASD-relatives were performed.

To ascertain the potential effect of publication bias, we used Orwin's failsafe N method

(Orwin, 1983). This determines the number of studies with an effect size of zero required to reduce the overall effect size to a specified level of 0.2 for meta-analyses of group comparisons and 0.1 for meta-analyses of correlations, which constitute small effects (Cohen, 1992). Cumulative meta-analyses were also performed to assess the possible influence of the small study effect since small studies may have systematically different effects than larger studies. In particular, small studies that are published may tend to have effects of larger magnitude than larger studies (Borenstein, 2005). Moreover, because studies of PWE tended to employ heavily language-based ToM tasks, whilst those of ASD-relatives tended to employ less language-based tasks and since it has been suggested that the latter may be more sensitive to ASD-related ToM deficits (Schuwerk et al., 2015), the potential moderating effect of task type was examined using subset meta-analyses. These separately examined studies employing heavily language-based tasks and those using less language-based tasks. The tasks included under each category are noted in Tables 3 and 4.

2.2.1 *Meta-analysis indices*

We used the random-effects model, which assumes that the true effect size estimated across studies varies due to the impact of study characteristics. Therefore, in contrast to the fixed-effects model, variability in effect size estimates is not only a function of within-study error but also of between-studies variability (Raudenbush, 2009). In this approach, the weights assigned to each study are more balanced than those of the fixed-effects model because larger studies are less likely to dominate the analysis and smaller studies have more weight (Borenstein et al., 2010). Heterogeneity across studies was examined using the Chi-square test, tau-square statistic, and I-square statistic.

For meta-analyses that involved comparison of FER and ToM task performance between groups, the standardized mean difference, otherwise known as Cohen's d was calculated (with a 95% confidence interval [CI]) as the effect size measure for each study. Cohen's d is the ratio of

the difference between the target group's mean score on the FER or ToM measures and that of the control group to their pooled standard deviation. We applied a correction to Cohen's d to compensate for its upward bias, particularly in small samples (Cooper et al., 2009), generating the corrected estimate known as Hedges' g . This can be interpreted in the same manner as Cohen's d (Hedges and Hunter, 1981). For the secondary meta-analyses of correlations, Fisher Z_r -transformed correlations were meta-analysed rather than Pearson correlations because the former's variance is less heavily dependent on the correlation value and has been found to be more stable (Borenstein, 2009; Hotelling, 1953). The inverse variance method, which weighs each study by its inverse variance, was used to compute overall mean effect sizes (Cooper et al., 2009).

3 Results

Table 5 provides an overview of the demographic and clinical characteristics of the participants from the meta-analysed studies. Individuals with epilepsy were older and had lower IQ than relatives of individuals with ASD across studies of FER and of ToM (t-test P -values < 0.001). In FER studies, PWE had a greater ratio of males to females than was observed in ASD-relatives (Chi-square test P -value < 0.001). There was no difference in the sex ratio of patients with epilepsy and ASD-relatives from ToM studies.

3.1 *Principal meta-analyses: FER and ToM in PWE and ASD-relatives versus controls*

3.1.1 *FER in PWE versus controls*

Figure 3a presents the results of the principal meta-analysis of studies of FER in PWE versus controls. There was a significant medium effect of poorer FER in PWE than controls (Hedges' $g = -0.73$, 95% CI: $-0.88, -0.58$, $P < 0.001$). A significant Chi-square test ($P < 0.001$) revealed heterogeneity in the effect size estimates. When analyses were re-run excluding the study by Farrant et al. (2005) which had an outlying effect size of -1.78 (95% CI: $-2.65, -0.90$), a

significant medium effect remained (Hedges' $g = -0.70$, 95% CI: $-0.85, -0.55$, $P < 0.001$) with a significant heterogeneity value (Chi-square test P -value = 0.004).

Orwin's failsafe N estimate suggested that 58 studies with an effect size of zero were required to reduce the mean effect size to -0.2 . This is over twice the number of published studies included in this meta-analysis ($N = 22$), suggesting that publication bias is unlikely to have unduly influenced the findings of reduced FER in PWE compared to controls.

The cumulative meta-analysis shown in Figure 3b suggests that small studies did not have a systematic effect on the mean effect size. As seen in Figure 3c, the exclusion of the outlying study by Farrant et al. (2005) did not alter the pattern of the cumulative meta-analysis.

3.1.2 FER in ASD-relatives versus controls

Figure 4a presents the results of the principal meta-analysis of studies of FER in ASD-relatives compared to controls. There was a medium effect of poorer FER in ASD-relatives than controls; however, the test of overall effect was not significant (Hedges' $g = -0.60$, 95% CI: $-1.31, 0.12$, $P = 0.10$). The Chi-square test value was significant and substantially larger than its degrees of freedom ($\chi^2 = 261.59$, $df = 9$, $P < 0.001$), suggesting variation of effect beyond sampling error. The very large I-square value ($I^2 = 97.65$) indicated that variation in the true effect size, rather than sampling error, made a major contribution to the variability. When analyses were re-run excluding the study by Oerlemans et al. (2014) which had an outlying effect size of -3.78 (95% CI: $-4.23, -3.33$), the mean effect size was now small, but significant (Hedges' $g = -0.22$, 95% CI: $-0.42, -0.02$, $P = 0.03$) and although the heterogeneity value remained significant (Chi-square test P -value = 0.009), there was a substantial drop in the Chi-square and I-square values ($\chi^2 = 20.52$, $df = 8$; $I^2 = 63.71$). These results highlight a substantial contribution of the overall effect size estimate from Oerlemans et al.'s (2014) outlying study. This is supported by the cumulative meta-analysis displayed in Figure 4b, demonstrating that this study, which included a relatively large number of participants (79 ASD siblings, 139 controls),

importantly shifted the mean effect size downward. When excluding this outlying study, the cumulative meta-analysis displayed in Figure 4c suggests that smaller studies systematically increased the effect size magnitude. This is suggestive of potential bias in the available studies of FER in ASD-relatives where small studies of large effect may be unduly enhancing the effect size estimate. Overall, the available studies support reduced FER in PWE, but offer only weak support for a FER deficit in ASD-relatives, potentially influenced by publication bias.

3.1.3 *ToM in PWE versus controls*

Figure 5a presents the results of the principal meta-analysis of studies of ToM in PWE compared to controls. There was a significant large effect of poorer ToM in PWE than controls (Hedges' $g = -0.81$, 95% CI: $-1.00, -0.62$, $P < 0.001$). Heterogeneity of effect sizes was significant (Chi-square test P -value < 0.001). When analyses were re-run with exclusion of the study by Broicher et al. (2012a), which had an outlying effect size of -1.92 (95% CI: $-2.64, -1.21$), a medium effect remained (Hedges' $g = -0.76$, 95% CI: $-0.93, -0.59$, $P < 0.001$) with a significant heterogeneity value (Chi-square test P -value < 0.001).

Orwin's failsafe N estimate suggested that 43 studies with an effect size of zero were required to reduce the mean effect size to -0.2 . This is three times the number of published studies included in this meta-analysis ($N = 14$), suggesting that publication bias is unlikely to have substantially influenced the findings of reduced ToM in PWE compared to controls.

The cumulative meta-analysis displayed in Figure 5b shows no evidence of a systematic effect of small studies on the mean effect size estimate. As seen in Figure 5c, exclusion of the outlying study by Broicher et al. (2012a) did not alter this finding.

3.1.4 *ToM in ASD-relatives versus controls*

Figure 6a presents the results of the principal meta-analysis of studies of ToM in ASD-relatives versus controls. The mean Hedges' g indicated a small significant effect of poorer ToM

in ASD-relatives than controls (Hedges's $g = -0.27$, 95% CI: -0.39, -0.15, $P < 0.001$). Heterogeneity of effect sizes was not significant (Chi-square P-value = 0.26) and removal of the outlying study by Baron-Cohen and Hammer (1997) (Hedges' $g = -1.13$, 95% CI: -1.91, -0.36) did not alter these findings (Hedges' $g = -0.25$, 95% CI: -0.37, -0.13, $P < 0.001$; Chi-square test P-value = 0.55). Orwin's failsafe N estimate suggested that only 5 studies with an effect size of zero were required to reduce the mean effect size from -0.27 to -0.2.

Since the studies included in this meta-analysis were all relatively small (largest sample size $N = 117$), cumulative meta-analysis is of reduced value. Nonetheless Figure 6b indicates that smaller studies did not systematically increase the magnitude of the mean effect size estimate. Figure 6c shows that the outlying study by Baron-Cohen and Hammer (1997) did not substantially alter this finding.

The magnitude of mean effect size generated from studies of ToM in PWE compared to controls was greater than that from studies of ASD-relatives compared to controls and there was no overlap in the 95% confidence intervals for the mean effect size estimates (95% CI for the meta-analysis of studies of PWE: -1.00, -0.62; ASD-relatives: -0.39, -0.15). This suggests that available studies support poorer ToM in PWE than ASD-relatives.

Moderator analysis

As shown in Table 6, subset meta-analyses revealed that PWE and ASD-relatives had deficits on both heavily language-based and less language-based ToM tasks compared to controls. In PWE and ASD-relatives, there was substantial overlap in the 95% confidence intervals of effect sizes from heavily and less language-based tasks. This suggests that task type did not have a differential impact on the results of reduced ToM in PWE and ASD-relatives and that it was appropriate to combine studies employing such tasks for our main analyses. Also, the trend of poorer ToM in PWE than ASD-relatives was maintained across task types, although, there was now overlap in the 95% confidence intervals for the mean effect size estimates from

studies using less language-based tasks in PWE and ASD-relatives.

3.2 *Sub-group meta-analyses: The relationship of seizure focus and laterality with social cognition*

3.2.1 *Social cognition in patients with TLE versus controls*

A large proportion of the studies of PWE have focused on patients with TLE, including 19 of the 22 studies examining FER in PWE (78% of participants) and 11 of the 14 studies examining ToM (72% of participants). As a result, compared to controls, the mean effect sizes of FER and ToM in individuals with TLE (FER: Hedges' $g = -0.73$, 95% CI: -0.88, -0.57, $P < 0.001$; ToM: Hedges' $g = -0.85$, 95% CI: -1.10, -0.60, $P < 0.001$) were nearly identical to those obtained from the principal meta-analyses described above. Of note, the effect size generated from the ToM studies is also similar to that reported by Stewart et al. (2016). Heterogeneity values were significant across both meta-analyses (FER: Chi-square test P -value = 0.01; ToM: Chi-square test P -value < 0.001).

Orwin's failsafe N estimate suggested that 51 FER studies and 36 ToM studies with an effect size of zero were required to reduce the mean effect sizes to -0.2. This suggests that publication bias is unlikely to influence the outcome of these meta-analyses.

3.2.2 *Social cognition in non-TLE patients versus controls*

Four studies provided data on FER performance in non-TLE patients compared to controls. Combined these included 99 participants (14 described as having seizures originating outside the temporal and frontal lobes from Broicher et al. (2012b); 52 with GGE from Reynders et al. (2005) and Jiang et al. (2014); 18 with frontal lobe, 4 with occipital lobe, 5 with parietal lobe, and 6 with a sensorimotor cortex seizure focus from Meletti et al. (2003)) and 138 controls. There was a medium significant effect of poorer FER in non-TLE patients than controls (Hedges' $g = -0.67$, 95% CI: -1.13, -0.21, $P = 0.004$). There was significant heterogeneity of effect sizes (Chi-square test P -value = 0.024). Orwin's failsafe N estimate suggested that 10

studies with an effect size of zero were required to reduce the mean effect size to -0.2. Relative to the small number of studies that have been performed (N=4), this means that a moderate number of further studies with null results would need to be conducted to negate the significant findings.

Although one study contributing data to this analysis included a subset of FLE patients, these comprised only 18% of the non-TLE patients and the effect size estimate from this study (Meletti 2003) did not differ substantially from the other studies included in this analysis. It is thus considered unlikely that these patients unduly influenced our findings of reduced FER in individuals with seizures originating outside the temporal lobe.

Across the five studies examining ToM in non-TLE patients and controls, 119 non-TLE patients (41 described as having seizures originating outside the temporal and frontal lobes (Broicher et al., 2012b; Schacher et al., 2006), 21 with Unverricht-Lundborg Disease (Giovagnoli et al., 2009); 15 with childhood epilepsy with centrotemporal spikes (Genizi et al., 2012); 42 with GGE (Jiang et al., 2014)) and 124 control participants were included. ToM was significantly poorer in non-TLE patients than controls with a medium effect size (Hedges' $g = -0.56$, 95% CI: -0.94, -0.19, $P = 0.003$). The heterogeneity value was significant (Chi-square test P -value = 0.009). Orwin's failsafe N estimate suggested that nine studies with an effect size of zero were required to reduce the mean effect size to -0.2. Relative to the small number of studies that have been performed (N=5), this represents a moderate number of further studies, suggesting that the results may be robust to publication bias.

3.2.3 *Social cognition in TLE versus non-TLE patients*

To further explore the association between seizure focus and social cognition, a meta-analysis of studies examining FER and ToM in patients with TLE versus patients with seizures originating outside the temporal lobe was conducted. Overall, 103 patients with TLE and 72 non-TLE patients (41 described as having seizures originating outside the temporal and frontal lobes

(Broicher et al., 2012b; Schacher et al., 2006); 21 patients with Unverricht-Lundborg Disease (Giovagnoli et al., 2009); 10 with GGE (Reynders et al., 2005)) were included in these analyses. The mean Hedges' g was -0.40 (95% CI: $-1.21, 0.42$), but the test of overall effect was not significant ($P = 0.34$). There was significant heterogeneity between studies (Chi-square test P -value < 0.001).

3.2.4 *Social cognition in RTLE versus LTLE patients*

There were 13 studies reporting data on FER in a total of 272 participants with RTLE and 268 participants with LTLE. Across these studies, the mean effect size was not significant (Hedges' $g = -0.27$, 95% CI: $-0.61, 0.07$, $P = 0.12$). The heterogeneity value was significant (Chi-square test P -value < 0.001). Similarly, across the five studies reporting data on ToM in a total of 120 participants with RTLE and 137 participants with LTLE, the mean effect size was not significant (Hedges' $g = -0.25$, 95% CI: $-0.57, 0.08$, $P = 0.14$), but heterogeneity across studies was significant (Chi-square test P -value = 0.01).

3.3 *The relationship of epilepsy variables to social cognition*

3.3.1 *Age at epilepsy onset*

Nine studies of FER reporting on a total of 567 patients with epilepsy and six of ToM including 357 patients reported correlations of FER or ToM with age at epilepsy onset. The meta-analysis of correlations of FER with age at epilepsy onset revealed a significant positive effect of small magnitude (Pearson $r = 0.17$, 95% CI: $0.05, 0.29$, $P = 0.007$), indicating that earlier age at onset was associated with poorer FER. The heterogeneity value was significant (Chi-square test P -value = 0.03). A similar small effect was found across studies of ToM (Pearson $r = 0.28$, 95% CI: $0.18, 0.37$, $P < 0.001$), but without significant heterogeneity (Chi-square test P -value = 0.35). Orwin's failsafe N estimate suggested that seven studies of FER and 11 of ToM with an effect size of zero were required to reduce the mean effect size to 0.1 , a small

Pearson correlation. Relative to the small number of studies that have been performed, this suggests that a moderate number of further studies with null results would be required to negate the findings. However, the ANOVA comparing effect sizes from six studies with mean age at epilepsy onset in childhood (≤ 12 years old) to 18 studies with mean age at epilepsy onset in adolescence/adulthood (> 12 years old) was not significant ($Q_B = 0.01$, $df = 1$, $P = 0.91$).

3.3.2 *Epilepsy duration*

Six studies of FER including 381 patients with epilepsy and six of ToM with 381 patients reported correlations of FER or ToM with epilepsy duration. The meta-analyses of correlations of FER and ToM with epilepsy duration each revealed moderate significant negative effects (FER: Pearson $r = -0.35$, 95% CI: -0.53, -0.14, $P = 0.001$; ToM: Pearson $r = -0.33$, 95% CI: -0.40, -0.26, $P < 0.001$), with longer epilepsy duration associated with poorer social cognition. The heterogeneity value was only significant in the FER studies (FER: Chi-square test P -value = 0.003; ToM: Chi-square test P -value = 0.47). Orwin's failsafe N estimate suggested that 15 studies of FER and 14 of ToM with an effect size of zero were required to reduce the overall effect size to -0.1, suggesting that these effects may be robust to publication bias.

3.4 *The relationship of demographic variables to social cognition in PWE and ASD-relatives*

Regression analyses suggested that neither age nor IQ was correlated with FER and ToM in PWE or ASD-relatives (PWE: Age: $\beta = -0.007$, $P = 0.43$; IQ: $\beta = 0.03$, $P = 0.10$; ASD-relatives: Age: $\beta = 0.009$, $P = 0.48$; IQ: $\beta = -0.002$, $P = 0.96$). Sex ratio was not correlated to FER and ToM in PWE ($\beta = -0.19$, $P = 0.36$), whereas across the three studies comparing FER in a total of 110 male and 335 female ASD-relatives, a small positive relationship was found (Hedges' $g = 0.32$, 95% CI: 0.10, 0.53, $P = 0.004$), suggesting poorer FER in males. The heterogeneity value was not significant (Chi-square test P -value = 0.79). It should be noted, however that Orwin's failsafe N estimate suggested that only two studies with an effect size of

zero were needed to lower the effect size to 0.2. In light of the low number of available studies, it is difficult to interpret whether the effect is robust to publication bias. Across the four studies providing data on ToM in a total of 70 male and 70 female ASD-relatives, meta-analysis did not reveal a significant difference between the sexes (Hedges' $g = 0.04$, 95% CI: -0.46, 0.53, $P = 0.89$). The heterogeneity value was not significant (Chi-square test P -value = 0.16).

4 Discussion

In this meta-analysis, we assessed the evidence for expression of BAP features, specifically deficits in FER and ToM in the absence of ID, in PWE and ASD-relatives compared to controls. We included 31 reports of PWE and 22 of ASD-relatives, providing data on 1449 PWE and 1295 ASD-relatives. As hypothesised, we found that FER and ToM were reduced in PWE compared to controls. These findings were robust to the exclusion of outlying studies of large effect and to publication bias. FER and ToM deficits were found in individuals with TLE as well as those with other forms of epilepsy. Earlier age at epilepsy onset and longer disease duration were associated with poorer FER and ToM in PWE.

Interestingly however, the hypothesis of reduced social cognition in ASD-relatives was only partially supported with a significant but small effect for ToM and a non-significant effect for FER. Moreover, ToM was poorer in PWE than ASD-relatives. Age and IQ were not associated with social cognition deficits in PWE or ASD-relatives. Poorer FER, but not ToM, in male than female ASD-relatives offered partial support for the hypothesis of greater BAP trait expression in males than females.

4.1 *Expression of BAP traits in PWE may reflect shared mechanisms of epilepsy and ASD*

The expression of BAP traits in PWE is consistent with the hypothesis that epilepsy and ASD share causal neurobiological and possibly genetic mechanisms. However, it does not refute the possibility that reduced social cognition in PWE arises from mechanisms distinct from those

involved in ASD. This possibility appears less likely, however, in light of findings from this meta-analysis combined with findings from genetic and family studies suggesting a genetic association between these conditions and evidence for similar neurobiological features in epilepsy and ASD (Brooks-Kayal, 2011).

In particular, the findings of this meta-analysis, including the presence of FER and ToM deficits in people with non-TLE compared to controls and the lack of a significant difference in FER and ToM in TLE versus non-TLE patients, challenge the prediction of the secondary effects model that a seizure focus in areas implicated in FER and ToM are more strongly associated with social cognition deficits. Furthermore, FER and ToM deficits were found in studies of patients with GGE and thus were not unique to individuals with focal epilepsy (Jiang et al., 2014; Reynders et al., 2005). This observation is important because whilst individuals with focal epilepsy other than TLE may show structural and functional abnormalities in non-temporal regions implicated in FER and ToM (e.g. frontal, parietal lobule, lingual gyrus), this is less likely to be the case for patients with GGE, particularly in relation to FER (Fusar-Poli et al., 2009; Lee and Siegle, 2012). Our findings therefore suggest that epilepsy-related network disruption in brain regions central to social cognition is not necessary for expression of FER and ToM deficits. This raises the possibility that these deficits in PWE reflect shared susceptibility mechanisms between epilepsy and ASD, which supports a role for the essential comorbidity model. These findings extend those of the recently published reviews by Monti and Meletti (2015) and Stewart et al. (2016), and are consistent with the observation that individuals with ASD may have GGE or focal epilepsy originating outside the temporal (or frontal) lobes (Jokiranta et al., 2014).

That social cognition was not poorer in RTLE than LTLE is less surprising since fMRI studies of individuals with ASD and their relatives have revealed reduced activation across bilateral brain regions when processing facial expressions of emotion or performing ToM tasks (Baron-Cohen et al., 2006; Greimel et al., 2010; Spencer et al., 2011). Moreover, functional

imaging studies in healthy controls report activation of a bilateral brain network during performance of FER and ToM tasks (Fusar-Poli et al., 2009; Schurz et al., 2014).

Our findings suggest that secondary effects of epilepsy also play a role in reduced FER and ToM. Namely, the correlation of earlier age at epilepsy onset and longer epilepsy duration with more severe FER and ToM deficits implies a contribution from secondary effects. These associations are consistent with the early-onset hypothesis (McClelland et al., 2006) and with neuroimaging studies demonstrating more widespread connectivity abnormalities in individuals with greater seizure frequency and epilepsy duration (Englot et al., 2015). However, the correlations we derived through meta-analysis were relatively weak. This suggests that the impact of secondary effects of seizures to FER and ToM deficits are limited. A restricted impact of early age at onset is also supported by similar FER and ToM deficits in participants with mean age at epilepsy onset in childhood compared to a mean age at epilepsy onset in adolescence/adulthood.

Overall, the findings of this meta-analysis demonstrate that social cognition deficits in PWE (1) may be present in patients whose epilepsy is not directly linked to the networks implicated in FER and ToM, (2) are not heavily determined by secondary effects of epilepsy, and (3) exist in non-lesional epilepsy with high heritability, such as GGE (Vadlamudi et al., 2014). These point to a role of shared susceptibility mechanisms, possibly genetic, in expression of BAP traits in PWE as predicted by the essential comorbidity model.

4.1.1 Evidence from genetic and family studies for shared mechanisms between epilepsy and ASD

The high heritability of ASD and epilepsy individually (Colvert et al., 2015; Thomas and Berkovic, 2014), in conjunction with evidence for shared genetic pathways between epilepsy and ASD (reviewed in section 1.2), support likely shared genetic mechanisms between these conditions. Compelling evidence for shared genetic pathways is also offered by family studies.

Specifically, a higher rate of epilepsy was observed in individuals with ASD from multiplex than simplex families with ASD (13% versus 2%) (Amiet et al., 2013b). Individuals with ASD from multiplex families are more likely to be carriers of inherited autism susceptibility genes relevant to the expression of BAP traits (Risch, 2001; Virkud et al., 2009). These findings suggest an association of epilepsy with inherited autism susceptibility genes and support the relevance of examining BAP trait expression in PWE. Although less conclusive, certain findings in ASD-relatives are also consistent with this association. Namely, a 2% rate of epilepsy in siblings without ASD drawn from multiplex families with ASD was found compared to 1% in the general population (Amiet et al., 2013a; Bell et al., 2014). In contrast, Bolton et al. (2011) failed to find an elevated rate of epilepsy in non-affected ASD-relatives; however, they did not appear to investigate multiplex ASD families. Interestingly they found that relatives of individuals with an epilepsy-ASD comorbidity were more likely to express the BAP than relatives of individuals with ASD-only, suggesting that individuals with the comorbidity are more likely to be carriers of more penetrant autism susceptibility genes than individuals with ASD alone.

4.1.2 Evidence from neuroimaging studies for shared mechanisms between epilepsy and ASD

Similarities in the aberrant connectivity of the default mode network in individuals with epilepsy and those with ASD support a role of shared neurobiological pathways in these conditions. It is noteworthy that many of the shared genetic mechanisms between epilepsy and ASD impact neural circuit formation by affecting axonal and dendritic growth, synaptogenesis, and synaptic homeostasis (Nair et al., 2013). These shared genetic pathways may contribute to similar alterations in connectivity observed in epilepsy and ASD (Clemm von Hohenberg et al., 2013). In particular, reduced resting-state functional connectivity of the default mode network is common in PWE (focal and generalized epilepsy) (Englot et al., 2015; McGill et al., 2012; Wei et al., 2015) and individuals with ASD (Di Martino et al., 2014; Washington et al., 2014). Such abnormalities have been linked to altered structural connectivity (Greicius et al., 2009; Mueller

et al., 2013; Voets et al., 2012).

The default mode network may be implicated in BAP trait expression. Reduced connectivity in the default mode network has been associated with social deficits in individuals with ASD and in ASD-relatives (Barnea-Goraly et al., 2010; Monk et al., 2009). This network may be of particular relevance to social cognition because it overlaps substantially with the FER and ToM networks. The core regions of the default mode network include the medial PFC, precuneus/posterior cingulate cortex, and inferior parietal and posterior temporal areas around the TPJ (Mars et al., 2012). Other regions often activated together with these are the mesial temporal lobe and lateral temporal areas extending into the temporal pole. Interestingly, structural connectivity abnormalities in the default mode network have also been detected in children with recent onset non-lesional epilepsy (Widjaja et al., 2013). This is consistent with a role of epilepsy susceptibility mechanisms in causing the connectivity abnormalities of PWE, which may contribute to the cognitive deficits and reduced social skills present at onset in some first seizure patients (Almane et al., 2014; Commission on Classification and Terminology of the International League Against Epilepsy, 1989; Ostrom et al., 2003).

4.2 *The relevance of epilepsy-specific mechanisms to expression of social cognition deficits in PWE*

A contribution from epilepsy-specific mechanisms to social cognition deficits is supported by evidence for a role of secondary effects of epilepsy in these deficits, as well as the greater severity of these deficits in PWE than ASD-relatives. Epilepsy-specific mechanisms may be particularly relevant to FER deficits since, counter to expectations and in contrast to PWE, our meta-analysis did not support FER deficits in ASD-relatives. That FER deficits are not a reliable marker of the BAP is less surprising when considering that, at a behavioural level, FER deficits are not consistently detected in individuals with ASD and their relatives (e.g. Bolte and Poustka, 2003; Ogai et al., 2003). This is despite neuroimaging studies offering compelling

evidence for functional abnormalities in facial emotion processing in both groups (Harms et al., 2010; Spencer et al., 2011). Harms et al. (2010) reviewed the evidence for deficient FER in ASD and concluded that mixed findings in behavioural studies may be due to poor sensitivity of certain FER measures and the use of compensatory strategies by individuals with ASD. Selection of measures that are sensitive to the nature of the social cognition deficit in ASD may be required to capture this endophenotype, such as emotion matching rather than labelling tasks (Bolte et al., 2015; Harms et al., 2010; Senju et al., 2009).

4.3 *The dual-strike model of social cognition deficits in PWE*

Overall, our findings and the literature suggest that shared susceptibility mechanisms of epilepsy and ASD as well as epilepsy-specific mechanisms, including secondary effects of seizures, contribute to FER and ToM deficits in PWE. Based on this, we propose a ‘dual-strike’ model of social cognition deficits in PWE. This model proposes that both shared mechanisms and epilepsy-specific effects may influence an individual’s expression of BAP traits (Figure 7). When these mechanisms act together, this results in a dual-strike, providing a possible explanation for more pronounced BAP trait expression in PWE.

In Figure 7, the impact of shared mechanisms is represented as the ‘Shared Epilepsy-ASD Pathway’ (green arrows). This pathway specifies that BAP trait expression reflects neurobiological features common to epilepsy and ASD, which are underpinned by shared susceptibility mechanisms, such as genetic factors (Fassio et al., 2011). The impact of epilepsy-specific mechanisms is represented by the ‘Epilepsy-Dependent Pathway’. This pathway encompasses two routes (blue and orange arrows) by which epilepsy-specific mechanisms are associated with BAP trait expression. First, susceptibility mechanisms of epilepsy not shared with those of ASD, as well as the secondary effects of seizures (e.g. neuronal reorganization associated with the effect of repeated seizures on the brain) may cause neurobiological features that are causal to core ASD symptoms (blue arrows). These neurobiological features then

contribute to the expression of BAP traits through a neurobiological pathway that is involved in ASD (Englot et al., 2015). Second, epilepsy-specific mechanisms that affect general cognitive abilities (Berg, 2011) may contribute to the expression of BAP traits (orange arrows). In individuals with ASD, cognitive abilities such as general intellectual level and executive functions influence the manifestation of core ASD symptoms, but do not wholly account for these symptoms (American Psychiatric Association, 2013; Bartak and Rutter, 1976; Pellicano, 2013). Similarly, in PWE executive dysfunction has been associated with reduced ToM task performance, but this did not wholly account for ToM difficulties (Shaw et al., 2004).

This meta-analysis supports the dual-strike model and suggests a potentially limited role of secondary effects of epilepsy to expression of the BAP. Assessing the dual-strike model through the direct comparison of BAP trait expression in PWE and ASD-relatives will be crucial to further investigating this model. This would address the indirect comparison of social cognition in PWE and ASD-relatives that was performed in this meta-analysis. Differences in demographic characteristics and in methodology between studies of PWE and ASD-relatives may have influenced our indirect comparison of these groups. PWE had older age and lower IQ than ASD-relatives. Although our meta-regressions did not support an association of age or IQ with social cognition in either PWE or ASD-relatives, these analyses had low power such that these null findings must be interpreted with caution. In individuals without ID, positive correlations of IQ with FER and ToM task performance have previously been reported (Cohn et al., 2015; de Achaval et al., 2010). This raises the possibility that the lower IQ in PWE compared to ASD-relatives contributed to the poorer social cognition in the former group. With respect to the older age of epilepsy patients compared to ASD-relatives, this is not likely to have had substantial impact because in the general population, notable decline in FER and ToM is typically observed only in older adults. None of the studies of PWE included in our analyses had a mean age of participants beyond middle age (Duval et al., 2011; Sasson et al., 2010). An

increased rate of cognitive decline in PWE could mean that the older age of PWE compared to ASD-relatives may nonetheless contribute to poorer social cognition in the former group. However, this possibility is less likely, given that epilepsy-related cognitive decline is only mild and has not been demonstrated for social cognition (Hermann et al., 2006).

Studies of PWE had a greater proportion of males than studies of ASD-relatives. The influence of this discrepancy on our results is unclear because of inconsistent findings regarding an association of male sex with more pronounced BAP trait expression. Greater penetrance of ASD susceptibility genes in males than females is thought to contribute to the greater proportion of males with ASD (Werling and Geschwind, 2015) and may contribute to the more pronounced expression of BAP traits in male ASD-relatives (Piven et al., 1997) and in neurotypical males (Ruzich et al., 2015). However, some studies in ASD-relatives and in the general population fail to find an association of sex with BAP trait expression and may even report an opposite direction of effect (Sasson et al., 2013; Seidman et al., 2012). Variability in results has been linked to the use of different BAP assessment methods and to the assessment of different BAP traits (Davidson et al., 2014; Sasson et al., 2013). This may explain our finding of equivalent ToM ability in male and female ASD-relatives in contrast to poorer FER in male relatives. Although an impact of sex was not revealed in our analyses of PWE, the meta-regression performed had low power and low sensitivity. Further research is required to ascertain how expression of different BAP traits differs between the sexes (e.g. Levin-Decanini et al., 2013).

With respect to methodological differences between studies of PWE and ASD-relatives, the most commonly used measures of FER and ToM differed. Whilst 71% of studies examining FER in PWE employed the Ekman and Friesen stimuli (Ekman and Friesen, 1976), only 40% of studies of ASD-relatives employed these, with the other studies using stimuli unique to that study. The greater variability in FER measures used in studies of ASD-relatives may have contributed to the elevated heterogeneity in effect size estimates compared to studies of PWE. In

support of this, in studies of ASD-relatives, heterogeneity across studies that did not employ Ekman and Friesen stimuli (excluding Oerleman's outlying study) was significant whereas studies employing these stimuli were more homogeneous. With respect to ToM measures, 85% of studies of PWE administered a heavily language-based measure, with the Faux Pas task being most common (71% of studies). In studies of ASD-relatives, only 46% of studies administered a heavily language-based measure, with the Reading the Mind in the Eyes task being most common (54% of studies). It may be speculated that greater reliance on less language-based measures in ASD-relatives would be appropriate because performance on such tasks may be less affected by compensatory strategies employed by this group (Schuwerk et al., 2015). We explored a contribution of this factor to ToM-task performance in ASD-relatives and PWE by conducting a moderator analysis. This did not support an effect of task type in either group because the effect sizes obtained from meta-analysing the subset of studies employing heavily language-based ToM tasks were similar to the effect sizes of the subset using less language-based measures. Also, these analyses suggest that PWE may be more likely to show a ToM deficit compared to ASD-relatives in heavily language-based tasks. Since these results are largely carried by patients with TLE, this may reflect a greater influence of epilepsy-specific effects on performance of language-based tasks. This is consistent with reduced language skills in individuals with TLE and associated abnormalities in the connectivity of their language network (Bartha-Doering and Trinkka, 2014; McDonald et al., 2008).

A limitation of our analyses is that there was not sufficient data to appropriately examine the impact of certain potentially relevant variables. Importantly, the influence of multiplex versus simplex family status of ASD-relatives could not be examined. The single study retrieved from our systematic search and comparing social cognition in these groups, reported poorer social cognition in relatives from multiplex families (Bolte and Poustka, 2003). This means that the degree of disparity in social cognition between PWE and ASD-relatives may have been

amplified by inclusion of relatives from simplex families in the latter group.

Also due to the unavailability of data, the impact of an epileptogenic lesion to expression of BAP traits was not assessed. Furthermore, our examination of the association between demographic variables and social cognition was limited by the low number of studies providing data for subgroup comparisons (e.g. male versus female epilepsy patients) or for meta-analysis of correlations (i.e. IQ and age with social cognition). Moreover, these correlations were performed in different samples across studies (e.g. epilepsy patients only or epilepsy patients and controls together) and a number of studies provided data only for significant and not for non-significant correlations of social cognition with demographic or epilepsy-related variables. This likely introduced bias in our analysis of the correlations between age at epilepsy onset and epilepsy duration with FER and ToM. Orwin's failsafe N analyses however, suggested that the significant association between these variables may be relatively robust to such bias. When the available data was insufficient for a meta-analysis of correlations, we performed meta-regressions. These have less power than meta-analyses of correlations because they rely on group means rather than individual participant scores. Even for these, insufficient data were available to examine the influence of seizure frequency on FER and ToM.

Although there was significant heterogeneity across most of the meta-analyses performed, for most analyses outliers were not important contributors to this heterogeneity as their removal did not significantly alter the I-square values and resulted in effect size estimates with substantial overlap of confidence intervals to those of the original estimates (Figures 3 to 6). Differences in sample characteristics and methodological factors (e.g. tests administered) likely contributed to the heterogeneity between studies. In the meta-analysis of FER in ASD-relatives however, the outlying study by Oerlemans et al. (2014) was responsible for introducing substantial heterogeneity between studies. The effect size magnitude of this study was greater than that of other studies of FER in ASD-relatives. It is unclear why this study's effect was so

much larger, but one potential contributor is that it was one of two studies conducted in children in whom it may be easier to detect FER deficits. This is because children may be less likely to have developed effective compensatory strategies for FER difficulties. Moreover, a short, three-second time limit for responding to the FER task was imposed, potentially rendering the task more sensitive. A similarly short time limit was only employed in three other studies included in this analysis. None of these reported a significant effect, but all were conducted with adolescents or adults (Greimel et al., 2010; Wallace et al., 2010; Yucel et al., 2015) and imposing a time limit may have greater impact on children than adults.

This systematic review and meta-analysis highlights areas in which our knowledge remains limited. Analyses that allow one to disentangle the impact of different patient variables are sorely lacking as are studies examining the relationship of FER and ToM with other cognitive abilities, such as executive functions, in PWE and ASD-relatives. Overall, both sides of the equation remain to be elucidated: that is, how epilepsy impacts on social and non-social cognitive abilities, and how non-social cognition impacts on social cognition (FER and ToM), and equally, the impact of both social and non-social cognition on epilepsy (Wang et al., 2015).

5 Conclusion

Our results, based on data from over 1000 epilepsy patients and ASD-relatives, show that PWE, including those with non-TLE, have reduced FER and ToM compared to controls and that the social cognition deficit in PWE is more severe than that in ASD-relatives. Moreover, earlier age at epilepsy onset and longer epilepsy duration are associated with poorer FER and ToM. Based on these patterns of FER and ToM deficits in PWE, we have presented a dual-strike model. It suggests that social cognition deficits in PWE likely reflect the impact of (1) shared mechanisms, which are independent of ID and potentially genetic, between individuals with epilepsy and ASD, as well as (2) epilepsy-specific mechanisms. A more careful characterisation and differentiation of BAP traits and their neurobiological underpinnings in PWE and ASD-

relatives will be important for the identification of the nature of those shared mechanisms between epilepsy and ASD and for the elucidation of the extent of the contribution from shared mechanisms versus epilepsy-specific mechanisms. Finally, in addition to having implications for our understanding of the epilepsy-ASD comorbidity, our finding of poorer social cognition in PWE than ASD-relatives, highlights the importance of clinicians being alert to these deficits in patients with epilepsy, particularly as they may have significant psychosocial sequelae for patients and families and impact their care and management (Wang et al., 2015).

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Figure captions

Figure 1. The overlap between regions of seizure propagation in TLE and GGE and regions activated during FER and ToM tasks.

Regions implicated in FER are in blue and those involved in ToM are in red. Regions involved in both are in purple. These regions were identified through meta-analyses of fMRI studies of emotion recognition and ToM (Fusar-Poli et al., 2009; Lee and Siegle, 2012; Mar, 2011; Schurz et al., 2014).

The more consistently activated regions in fMRI studies of emotion recognition include the amygdala, fusiform gyrus, and lateral and medial PFC (Fusar-Poli et al., 2009; Lee and Siegle, 2012). For ToM, the most consistently activated regions include the medial PFC, STS/TPJ and IPL. Primary areas of seizure propagation in TLE overlap with FER and ToM regions and include the medial temporal lobe, temporal pole, fusiform gyrus, medial PFC, STS/TPJ, and precuneus (Dupont et al., 2009; Nelissen et al., 2006). Seizure generation and propagation in GGE principally involves thalamo-cortical networks. Some regions within these networks overlap with those activated by FER and ToM tasks: medial PFC, lateral PFC, IPL, precuneus and PCC (Benuzzi et al., 2012; Ji et al., 2015). Notably, certain primary regions of the FER and ToM networks, such as the amygdala and STS/TPJ, are not principally involved in GGE, in contrast to TLE.

FER: facial emotion recognition; GGE: generalised genetic epilepsy; IFG: inferior

frontal gyrus, IPL: inferior parietal lobule; PCC: posterior cingulate cortex; PFC: prefrontal

cortex; STS: superior temporal sulcus; TLE: temporal lobe epilepsy; ToM: theory of mind;

TPJ: temporo-parietal junction.

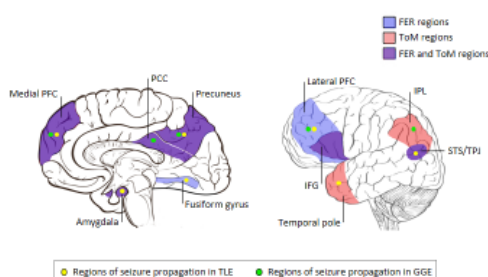


Figure 2. Flowchart of reports retrieved through the systematic database search.

193 full-text reports assessed for eligibility were excluded because: there was no control or target group, all patients with epilepsy were post-surgical, there were fewer than five participants per group, the report was a review or commentary, FER or ToM was not measured, or insufficient data was reported.

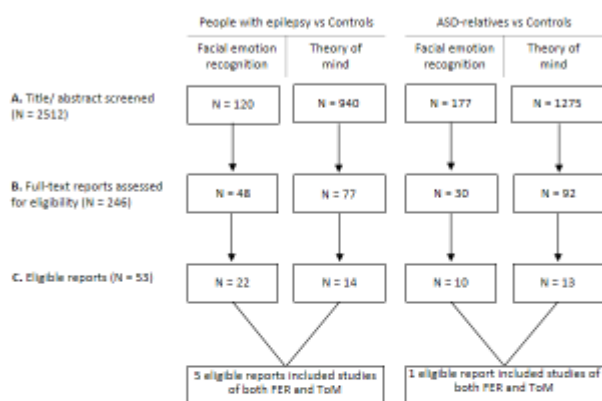
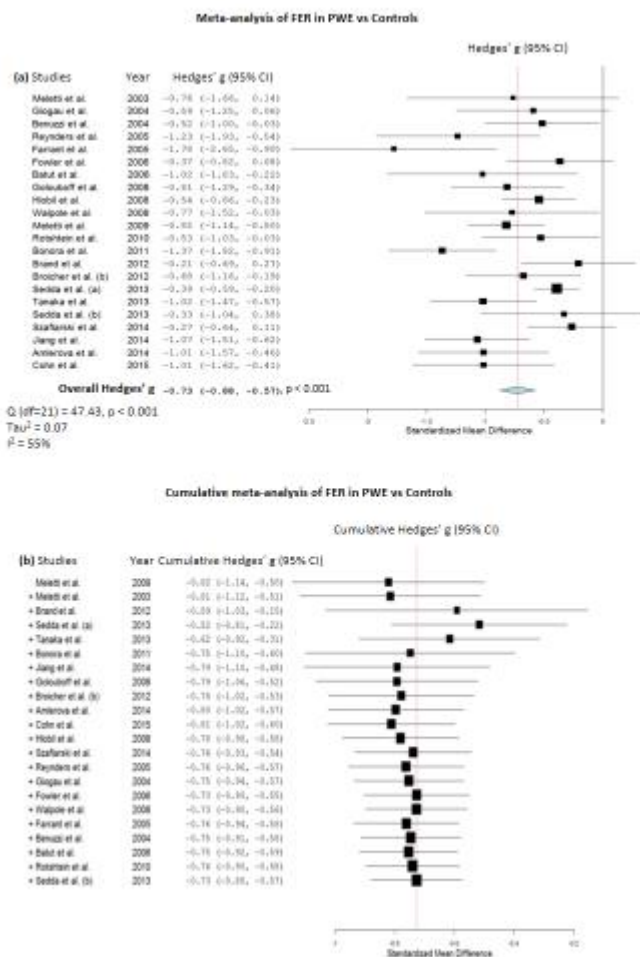


Figure 3. Overview of (a) the meta-analysis of studies of FER in PWE compared to controls, (b) the cumulative meta-analysis of studies of FER in PWE compared to controls, and (c) the cumulative meta-analysis of studies of FER in PWE compared to controls excluding the outlying study by Farrant et al. (2005)



Cumulative meta-analysis of FER in PWE vs Controls excluding study by Farrant et al. (2005)

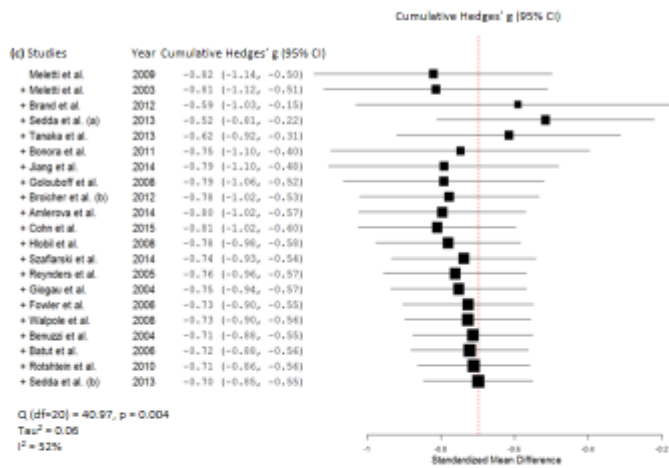
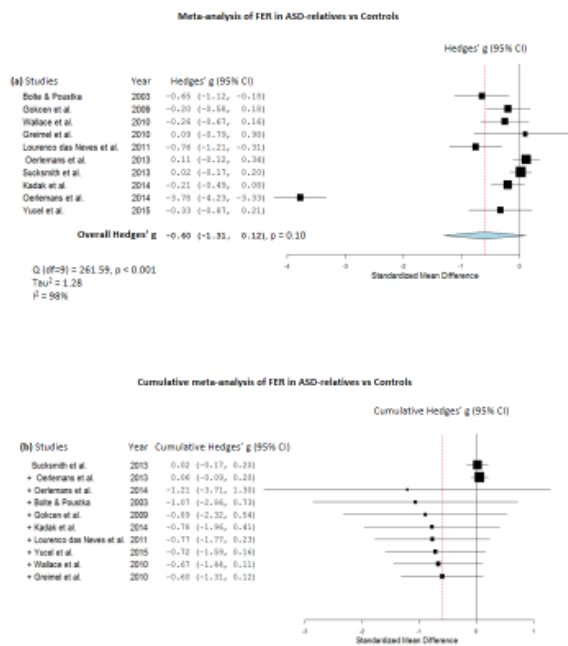


Figure 4. Overview of (a) the meta-analysis of studies of FER in ASD-relatives compared to controls, (b) the cumulative meta-analysis of studies of FER in ASD-relatives compared to controls, and (c) the cumulative meta-analysis of studies of FER in ASD-relatives compared to controls with exclusion of the outlying study by Oerlemans et al. (2014)



Cumulative meta-analysis of FER in ASD-relatives vs Controls excluding study by Oerlemans et al. (2014)

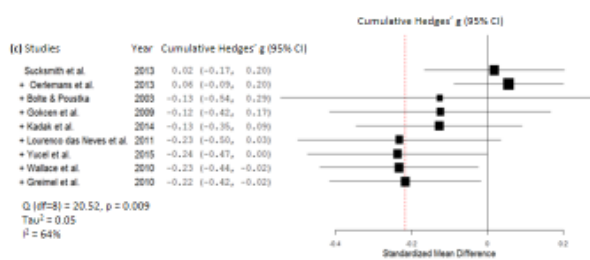
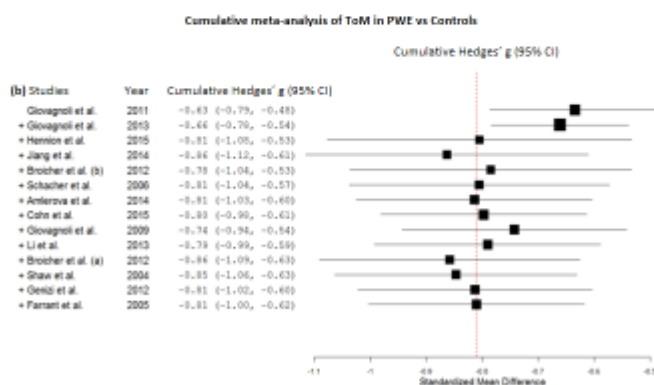
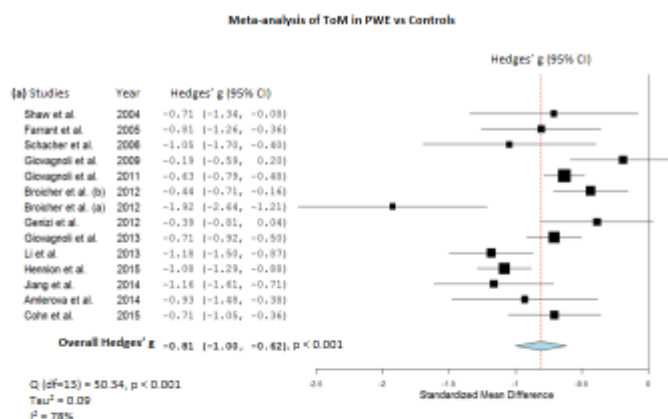


Figure 5. Overview of (a) the meta-analysis of studies of ToM in PWE compared to controls, (b) the cumulative meta-analysis of studies of ToM in PWE compared to controls, and (c) the cumulative meta-analysis of studies of ToM in PWE compared to controls with exclusion of the outlying study by Broicher et al. (2012a)



Cumulative meta-analysis of ToM in PWE vs Controls excluding study by Broicher et al. (2012a)

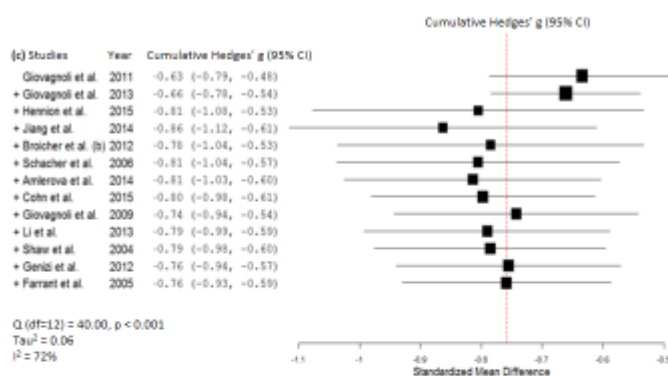
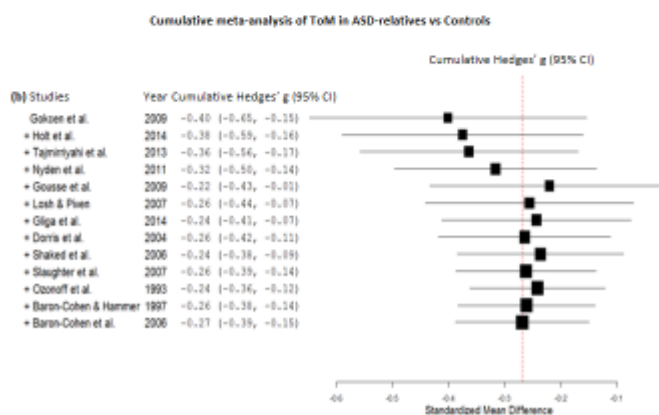
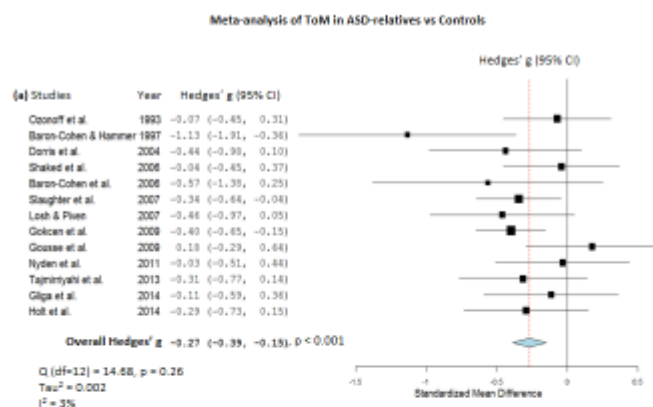


Figure 6. Overview of (a) the meta-analysis of studies of ToM in ASD-relatives compared to controls, (b) the cumulative meta-analysis of studies of ToM in ASD-relatives compared to controls, and (c) the cumulative meta-analysis of studies of ToM in ASD-relatives compared to controls with exclusion of the outlying study by Baron-Cohen & Hammer (1997)



Cumulative meta-analysis of ToM in ASD-relatives vs Controls excluding study by Baron-Cohen & Hammer (1997)

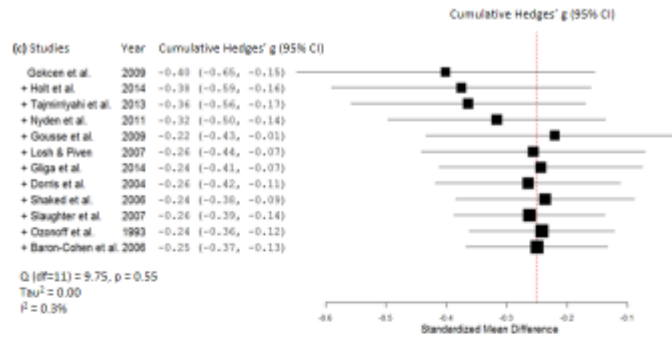


Figure 7. The dual-strike model of BAP trait expression in PWE proposes that both shared mechanisms and epilepsy-specific effects contribute to expression of the BAP. Shared mechanisms have their effect via the first (top) pathway. (I) The Shared Epilepsy-ASD Pathway (green arrow): shared susceptibility mechanisms between epilepsy and ASD lead to neurobiological abnormalities that increase both seizure and ASD susceptibility. Epilepsy-specific effects may amplify BAP trait expression via the Epilepsy-Dependent Pathway (blue arrows), causing a ‘dual-strike’. (II) The Epilepsy-Dependent Pathway: epilepsy-specific susceptibility mechanisms distinct from those of ASD, and secondary effects of epilepsy amplify the expression of BAP traits by causing neurobiological abnormalities that underpin ASD (blue arrows) or by causing neurobiological abnormalities that increase seizure susceptibility, but are not causal to expression of ASD symptoms (orange arrows). Note the dotted line for secondary effects represents the finding of their more limited impact in this meta-analysis.

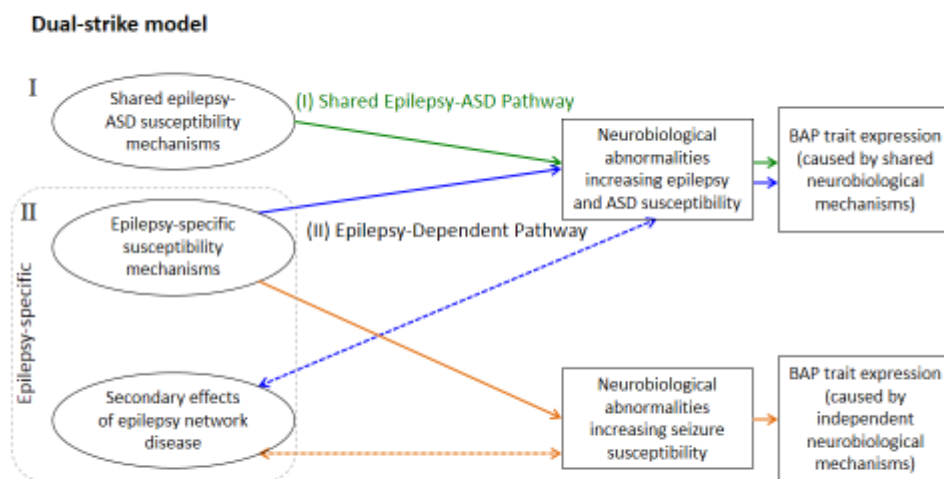


Table 1 Shared mechanisms between epilepsy and ASD

Proposed shared mechanisms	Implicated genes	References
1. Enhanced protein synthesis in mTOR pathway	<i>TSC1/TSC2, FMR1, PTEN, DEPDC5, MTOR, NPRL3</i>	e.g. Dibbens et al. (2013); Kelleher and Bear (2008); Moller et al. (2016); Ricos et al. (2016)
2. Sodium channelopathy	<i>SCN1A, SCN2A</i>	e.g. Mullen & Scheffer (2009); Weiss et al. (2003); Howell et al. (2015)
3. Disruption of GABA receptor binding sites	<i>GABRG2, GABRA1, GABRB3, GABRD, GABRA4</i>	e.g. Fatemi et al. (2009); Fatemi et al. (2014); Macdonald et al. 2010
4. Protein disruption:		
<ul style="list-style-type: none"> • ARX and FMRP Development, migration and function of interneurons 	<i>ARX, FMR1</i>	e.g. Heulens et al. (2009); Stromme et al. (2002)
<ul style="list-style-type: none"> • Neurexins Neuronal development and migration, and forming trans-synaptic complexes required for neurotransmission 	<i>NRXN1, CNTNAP2</i>	e.g. Moller et al. (2013); Glessner et al. (2009); Strauss et al. (2006); Alarcon et al. (2008)
<ul style="list-style-type: none"> • Synapsins Synaptic vesicle trafficking and neurotransmitter release 	<i>SYN1, SYN2</i>	e.g. Fassio et al. (2011); Cavalleri et al. (2007); Corradi et al. (2014)

Table 2 Search terms employed for systematic search

Target population terms			
PWE	ASD-relatives	FER terms	ToM terms
epilepsy/seizure	broad(er)		theory of mind/ mindreading/
	autism	face/ facial AND (emotion	mentalising/ mental
	phenotype/	recognition/ processing/	representation/ mental state/
	autism/	perception/ identification OR	belief-desire reasoning/ social
	Asperger/	affect recognition/ processing/	intelligence/ social cognition/
	pervasive	perception/identification OR	meta-cognition/ faux pas/
	developmental	expression recognition)	strange stories/ false-belief/
	disorder		mind in the eyes

Table 3

Included studies: Facial emotion recognition (FER) and theory of mind (ToM) in people with epilepsy

Report	Number epilepsy patients	Epilepsy patients subgroups	Number controls	Percent TLE patients	FER task (stimuli-emotions)	ToM task	Mean age (SD), years	Sex ratio (m:f)	Mean IQ (SD)	Mean epilepsy onset age (SD), years	Mean epilepsy duration (SD), years	Mean seizure frequency (SD), seizures/month
Meletti et al (2003)	96	63 TLE 33 extraTLE	50	66	Multiple choice labelling task (Ekman & Friesen (1976)- Anger, Disgust, Fear, Happiness, Sadness)	-	35.1 (10.6)	40:56	-	16.1 (11.3)	18.9 (11.9)	-
Shaw et al (2004)	29	15 with amygdala damage 14 without amygdala damage	14	83	-	False Belief ^L Happe Stories ^L	31.1 (11.1)	13:16	101.5 (15.8) (PIQ)	14.4 (9.7)	-	-
Glogau et al (2004)	33	18 RTLE 15 LTLE	13	100	Indication of whether two faces express the same emotion (Ekman & Friesen (1976)- Anger, Fear, Happiness, Sadness)	-	37.1 (12.5)	18:15	-	-	21.7 (13.1)	8.6 (7.9)

Benuzzi et al (2004)	13	8 RmTLE 5 LmTLE	14	100	Emotion Recognition Battery (Ekman & Friesen (1976)- Anger, Disgust, Fear, Happiness, Sadness, Neutral)	-	33.7 (7.4)	7:6	-	-	-	-
Reynders et al (2005)	37	27 mTLE 10 GGE	12	73	Multiple choice labelling task (Ekman & Friesen (1976)- Anger, Disgust, Fear, Happiness, Sadness, Surprise)	-	37.7 (13.7)	15:22	101 (12.2)	11.8 (9.8)	25.8 (15.8)	-
Farrant et al (2005)	14	14 FLE	14	0	Multiple choice labelling task (Ekman & Friesen (1976)- Anger, Disgust, Fear, Happiness, Sadness, Surprise)	Faux Pas ^L Happe Stories ^L Happe Cartoons ^M Reading the Mind in the Eyes ^{LL}	34.4 (12.1)	6:08	96.6 (11.9)	11.8 (8.6)	-	-
Schacher et al (2006)	54	27 mTLE 27 extra-mTLE (excluding FLE)	12	50	-	Faux Pas ^L	36.2 (11.7)	26:28	108.4 (16.5)	14.5 (13.0)	21.3 (14.4)	-

Batut et al (2006)	12	12 mTLE	15	100	Unspecified task (Karolinska's facial affect pictures- Fear, Happiness, Sadness, Neutral)	-	35.5 (11.1)	6:6	85.5 (14.1)	16.5 (8.6)	-	-
Fowler et al (2006)	28	13 RmTLE 15 LmTLE	18	100	Multiple choice labelling task (Ekman & Friesen (1976) -Anger, Disgust, Fear, Happiness, Sadness)	-	38.0	-	-	10.0	28.0	-
Hlobil et al (2008)	36	24 RmTLE 12 LmTLE	28	100	Identification of the unique facial expression of emotion amongst distractor faces (Ekman & Friesen (1976); Lyons et al (1998); PICS Image Data Base (2007)- Anger, Fear, Happiness)	-	29.0 (10.1)	13:23	95.7 (15.1)	-	20.6 (10.9)	5.0 (4.8)

Golouboff et al (2008)	37	13 RmTLE 16 LmTLE 8 extra-temporal FCE	37	78	Test de Reconnaissance des Emotions Faciales pour Enfants (TREFE) (TREFE stimuli- Anger, Disgust, Fear, Happiness, Sadness, Neutral)	-	13.2 (2.8)	16:21	97.1 (13.2)	5.5 (3.6)	6.1 (3.7)	-
Walpole et al (2008)	16	9 RTLE 7 LTLE	14	100	Multiple choice labelling task (Ekman & Friesen (1976)- Anger, Disgust, Fear, Happiness, Sadness, Surprise)	-	45.3 (11.8)	9:7	107.3 (9.1)	-	32.4 (17.2)	3.6 (3.3)
Giovagnoli et al (2009)	42	21 TLE 21 ULD	21	50	-	Faux Pas ^L	39.5 (14.9)	19:23	-	14.9 (7.9)	24.8 (13.6)	-
Meletti et al (2009)	176	68 RmTLE 59 LmTLE 13 BmTLE 36 lateral TLE	50	100	Multiple choice labelling task (Ekman & Friesen (1976)-Anger, Disgust, Fear,	-	38.3 (10.3)	79:97	-	14.4 (11.2)	23.9 (12.2)	-

					Happiness, Sadness)								
Rotshtein et al (2010)	14	14 LmTLE	10	100	Multiple choice labelling task (Ekman & Friesen (1976); Calder et al (1996)- Anger, Disgust, Fear, Happiness, Sadness, Surprise)	-	-	-	-	-	-	-	-
Brand et al (2012)	101	101 Epilepsy (any type)	20	-	CATS- Abbreviated (Ekman & Friesen (1976)- Anger,Disgust, Fear, Happiness, Sadness, Surprise)	-	35.9 (12.8)	40:61	103.8 (13.4)	20.7 (15.1)	-	-	-
Bonora et al (2011)	41	20 RmTLE 17 LmTLE 4 BmTLE	51	100	Multiple choice labelling task (Ekman & Friesen (1976)-Anger, Disgust, Fear Happiness, Sadness)	-	48.1 (11.5)	17:24	92.2 (18.6)	20.7 (15.9)	27.7 (18.7)	-	-
Giovagnol i et al (2011)	138	47 RTLE 62 LTLE 29 FLE	69	79	-	Faux Pas ^L	36.6 (11.5)	55:83	-	22.3 (14.5)	14.0 (13.0)	9.1 (9.6)	

Broicher et al (2012 a)	28	12 RmTLE 16 LmTLE	18	100	-	Faux Pas ^L	37.4 (12.6)	11:17	94.2 (12.8)	16.6 (12.5)	20.8 (12.5)	-
Broicher et al (2012 b)	42	28 mTLE 14 extra- mTLE (excluding FLE)	29	67	CATS (Ekman & Friesen (1976)- Anger, Disgust, Fear, Happiness, Sadness, Surprise, Neutral)	Moving Triangles ^{LL} Reading the Mind in the Eyes ^{LL} Faux Pas ^L	34.1 (12.6)	22:20	102.5	19.7 (10.9)	14.4 (12.0)	-
Genizi et al (2012)	15	Childhood Epilepsy with Centrotemp oral Spikes	15	0	-	Yoni task ^{LL}	10.5 (2.2)	-	-	7.6	-	-
Giovagnoli et al (2013)	66	54 TLE 12 FLE	42	82	-	Faux Pas ^L	37.7 (10.0)	32:34	-	19.9 (14.1)	17.6 (12.8)	10.3 (16.2)
Li et al (2013)	31	13 RTLE 11 LTLE 7 BTLE	24	100	-	False belief ^L Faux Pas ^L Happe Stories ^L Happe Cartoons ^M	41.9 (13.2)	18:13	99.3 (13.8)	24.5 (13.5)	18.6 (13.2)	1.3 (1.2)

Sedda et al (2013 a)	56	24 RTLE 32 LTLE	54	100	The Animated Full Facial Expression Test (Ekman & Friesen (1976)- Anger, Disgust, Fear, Happiness, Sadness)	-	37.0 (11.7)	32:24	-	-	-	-
Tanaka et al (2013)	63	17 RmTLE 26 LmTLE 20 BmTLE	32	100	Multiple choice labelling task (Group generated stimuli- Anger, Disgust, Fear, Happiness, Sadness, Surprise)	-	41.5	32:31	-	30.8 (21.9)	13.0 (13.6)	-
Sedda et al (2013 b)	9	TLE	10	100	Multiple choice labelling task (Ekman & Friesen (1976)- Anger, Disgust, Fear, Happiness, Sadness, Surprise)	-	-	-	-	-	-	-

Szaflarski et al (2014)	34	34 LmTLE	30	100	Multiple choice labelling task (NimStim stimuli- Fear, Happiness, Sadness, Neutral)	-	41.0 (12.0)	7:27	-	27.0 (14.0)	-	2.0 (4.0)
Amlerova et al (2014)	46	22 RTLE 24 LTLE	20	100	Multiple choice labelling task (Unspecified- Anger, Disgust, Fear, Happiness, Sadness)	Faux Pas ^L	36.8 (11.1)	26:20	97 (14.8)	20.4 (12.9)	-	-
Jiang et al (2014)	42	42 GGE	47	0	Eye Basic Emotion Discrimination Task (Adolphs et al (2002)- Anger, Disgust, Fear, Happiness, Surprise)	Eye Complex Emotion Discrimination task ^{LL}	16.5	27:15	-	12.0	4.0	0.1
Hennion et al (2015)	50	50 TLE	50	100	-	Faux Pas ^L Comprehension of Sarcasm Task ^L Comprehension of Action Task ^L	42.4 (11.8)	23:27	-	21.06 (15.27)	21.3 (14.6)	13.2 (63.6)

Cohn et al (2015)	50	26 RTLE 24 LTLE	15	100	Part 1 of TASIT: Emotion Evaluation Test (TASIT stimuli- Anger, Anxiety, Disgust, Happiness, Sadness, Surprise, Neutral)	Part 2 of TASIT: Sarcastic Exchanges ^M Part 3 of TASIT: Sarcastic and Deceitful Interactions ^M	38.4 (12.8)	27:23	105.2 (12.2)	20.3 (13.2)	18.1 (14.6)	-
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TLE: temporal lobe epilepsy; LTLE: left TLE; RTLE: right TLE; mTLE: mesial TLE; BTLE: bilateral TLE; GGE: generalized genetic epilepsy; FLE: frontal lobe epilepsy; FCE: fronto-central epilepsy; PIQ: performance IQ. This was used to estimate IQ when a total IQ score was not reported; CATS: Comprehensive Affect Testing System; TASIT: The Awareness of Social Inference Test

^L: Heavily language-based ToM task, principally involves interpretation of written or orally presented text; ^{LL}: Less language-based ToM task, principally involves interpretation of visually-presented non-textual information; ^M: Mixed ToM task, involves interpretation of verbal and non-verbal information. Mixed ToM tasks were not included in task-based moderator analyses.

Table 4

Included studies: Facial emotion recognition (FER) and theory of mind (ToM) in relatives of individuals with ASD (ASD-relatives)

Report	Number ASD-relatives	ASD-relatives subgroups	Number controls	FER task (stimuli-emotions)	ToM task	Mean age (SD), years	Sex ratio (m:f)	Mean IQ (SD)
Ozonoff et al (1993)	18	18 ASD siblings	18	-	Second-Order Belief Attribution Task ^{LL} Fox and Grapes Task ^L Apple-Dog Task ^{LL}	11.8 (4.1)	10:8	107.4 (14.8)
Baron-Cohen & Hammer (1997)	30	15 ASD mothers 15 ASD fathers	30	-	Reading the Mind in the Eyes ^{LL}	44.4 (10.6)	15:15	120.3 (10.6)

Bolte & Poustka (2003)	102	36 ASD multiplex parents and siblings 66 ASD simplex parents and siblings	22	-	Multiple choice labelling task (Ekman & Friesen (1971); Bullock & Russell (1984); Group generated photographs- Anger, Disgust, Fear, Happiness, Sadness, Surprise, Neutral, Happiness/Surprise, Happiness/Neutral, Sadness/Neutral)	33.5 (12.6)	49:53	106.8 (13.5) (PIQ)
Dorris et al (2004)	27	27 ASD siblings	27	-	Reading the Mind in the Eyes ^{LL}	11.1 (2.8)	18:9	-
Shaked et al (2006)	24	24 ASD siblings	24	-	False belief ^L Happe stories ^L	4.6 (0.1)	16:8	109.3 (15.0) (PIQ)
Baron-Cohen et al (2006)	12	6 ASD mothers 6 ASD fathers	12	-	Reading the Mind in the Eyes ^{LL}	38.2 (5.6)	6:6	115.1 (4.6)

Slaughter et al (2007)	24	24 ASD mothers	24	-	Coding mothers' narratives for use of mental state utterances ^{LL}	35.7 (6.3)	0:24	-
Losh & Piven (2007)	48	13 aloof ASD parents 11 rigid ASD parents 24 BAP negative parents	22	-	Reading the Mind in the Eyes ^{LL}	46.5 (6.7)	23:25	117.2 (11.0)
Gokcen et al (2009)	76	38 ASD mothers 38 ASD fathers	41	Multiple choice labelling task (Adolphs et al (2002)- Anger, Disgust, Distress, Fear, Happiness, Sadness, Surprise)	Reading the Mind in the Eyes ^{LL} Hinting task ^L Unexpected Outcome Test ^L	36.9 (6.5)	38:38	97.8 (9.1)
Gousse et al (2009)	39	39 ASD parents	32	-	Happe Cartoons ^M	38.7 (17.8)	18:21	-

Wallace et al (2010)	22	22 parents and adult siblings of children with ASD from multiplex families	26	Multiple choice labelling task (Ekman & Friesen (1976); Matsumoto & Ekman (1988)- Anger, Disgust, Fear, Happiness, Sadness, Surprise, Neutral)	-	35.0 (13.0)	16:6	93.5 (15.0) (PIQ)
Greimel et al (2010)	11	11 ASD fathers	9	Multiple choice labelling task (Group generated photographs- Happiness, Sadness)	-	47.7 (5.3)	11:0	117.7 (15.3)
Lourenco das Neves et al (2011)	40	30 ASD mothers 10 ASD fathers	41	Multiple choice labelling task (Penn Emotion Recognition Test- Anger, Fear, Happiness, Sadness, Neutral)	-	41.5 (10.0)	10:30	-
Nyden et al (2011)	44	18 ASD mothers 18 ASD	28	-	Happe Cartoon ^M	-	-	-

fathers
8 ASD
siblings

Oerlemans et al (2013)	172	172 ASD siblings	127	Indicate whether the emotion expressed in a face matches the emotion label (Identification of Facial Emotions task from the Amsterdam Neuropsychological Tasks program- Anger, Fear, Happiness, Sadness)	-	12.2 (3.9)	82:90	105.5 (12.9)
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Sucksmith et al (2013)	297	261 ASD mothers 36 ASD fathers	184	Multiple choice labelling task (modified Karolinska Directed Emotional Faces task- Anger, Disgust, Fear, Happiness, Sadness, Surprise, Neutral)	-	41.0 (6.3)	36:261	-
Tajmirriyahi et al (2013)	48	48 ASD parents	31	-	Reading the mind in the Eyes ^{LL} Reading the Mind in the Voice ^{LL}	36.7 (7.6)	10:38	-
Kadak et al (2014)	72	36 ASD mothers 36 ASD fathers	38	Emotion Recognition Test (Ekman & Friesen (1976)- Anger, Disgust, Fear, Happiness, Sadness, Surprise, Neutral)	-	33.6 (5.3)	36:36	-

Gliga et al (2014)	30	18 ASD siblings with typical development 12 ASD siblings with atypical development	39	-	False belief ^L	3.2 (0.13)	21:9	109.3 (17.1)
Oerlemans et al. (2014)	79	79 ASD siblings	139	Indicate whether the emotion expressed in a face matches the emotion label (De Sonnevile et al (2002)-Anger, Fear, Happiness, Sadness)	-	9.7 (2.0)	34:45	106.4 (12.5)
Yucel et al (2014)	40	15 aloof ASD parents 25 non-alloof ASD parents	20	Identification of the face matching a target face (Ekman & Friesen (1976)-Anger, Fear)	-	41.5 (6.1)	20:20	108.1 (8.2)
Holt et al (2014)	40	28 ASD female siblings 12 ASD male siblings	40	-	Reading the Mind in the Eyes ^{LL}	14.9 (2.2)	12:28	113.2 (10.1)

PIQ: performance IQ

^L: Heavily language-based ToM task, principally involves interpretation of written or orally presented text; ^{LL}: Less language-based ToM task, principally involves interpretation of visually-presented non-textual information; ^M: Mixed ToM task, involves interpretation of verbal and non-verbal information. Mixed ToM tasks were not included in task-based moderator analyses.

Table 5

Characteristics of people with epilepsy (PWE) and relatives of individuals with ASD (ASD-relatives)

Studies	N	Percent males	Mean (SD) age, years	Mean (SD) IQ	Mean (SD) epilepsy onset age, years	Mean (SD) epilepsy duration, years	Mean (SD) seizure frequency, seizures/month
FER in PWE vs controls	996 (78% TLE)	48	35.8 (11.3)	99.9 (13.9)	17.6 (13.3)	19.5 (13.0)	3.7 (5.5)
FER in ASD-relatives vs controls	911	36	31.1 (7.1)	104.7 (12.3)	-	-	-
ToM in PWE vs controls	647 (75% TLE)	49	35.40 (11.82)	101.7 (14.4)	18.6 (13.1)	16.9 (13.4)	8.1 (28.5)
ToM in ASD-relatives vs controls	460	45	29.48 (7.91)	109.4 (11.7)	-	-	-

Table 6

Results of subset meta-analyses of theory of mind (ToM) in people with epilepsy (PWE) and relatives of individuals with ASD (ASD-relatives) compared to controls

Group comparison	ToM task type	Effect size estimate (Hedges' g [95% CI]; P-Value)	Test of homogeneity of effect size (Chi-square test P-value)
PWE vs Controls	Heavily language-based tasks	-0.84 (-1.06, -0.63); < 0.001	< 0.001
	Less heavily language-based tasks	-0.67 (-1.09, -0.24); 0.002	0.01
ASD-relatives vs Controls	Heavily language-based tasks	-0.26 (-0.50, 0.00); 0.05	0.37
	Less heavily language-based tasks	-0.36 (-0.53, -0.19); < 0.001	0.55



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