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NEUROPROFILES: NEUROdevelopment in PReschool children Of FIfe and Lothian Epilepsy Study

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Abstract

Neurobehavioural problems (i.e. cognitive impairment/behaviour problems) are common in childhood epilepsy. There are very limited data in children with early-onset epilepsy (CWEOE; onset ≤4 years). This study: (1) estimated the incidence of early-onset epilepsy, (2) described the spectrum and prevalence of neurobehavioural problems in CWEOE, and their risk factors, and (3) explored eye-gaze behaviour as a marker of neurobehavioural problems.

This two year, prospective, population-based, case-controlled study identified newly diagnosed CWEOE in South East Scotland using active multi-source capture-recapture surveillance. CWEOE and controls completed detailed age-appropriate neuropsychological assessment - including Bayley III/WPPSI III, NEPSY II and social-emotional behaviour questionnaires. Children completed five eye-tracking tasks which assessed memory, attention, and social cognition.

59 CWEOE were identified (36M:23F); ascertainment-adjusted incidence 62/100,000 ≤4yrs/yr (95%CI 40-88). Asian and White-European children were at increased risk of epilepsy. 46 CWEOE (95%CI 62-84, 27M:19F) and 37 sex-age matched controls (18M:19F) underwent neuropsychological assessment. CWEOE had poorer general cognitive ability ($p<.001$, $\eta^2=.24$), and increased parent reports of abnormal behaviour – significantly so in adaptive behaviour, ASD behaviours, hyperactivity/inattention, and atypical social behaviour. Overall 63% of CWEOE met criteria for neurobehavioural problems across multiple domains, vs 27% of controls ($p<.001$). Risk factors varied by domain. Prematurity and symptomatic/cryptogenic aetiology were common risk factors but other seizure-related variables were not. CWEOE with social problems exhibited abnormal eye-gaze behaviour toward social stimuli. Subtle atypicalities in sustained attention were noted in CWEOE, and an unexpected absence of antisaccade production was seen in all children.

This is the first population-based study to describe the neurobehavioural profile, and explore eye-gaze behaviour, in CWEOE. Neurobehavioural problems are present, detectable, and highly prevalent in CWEOE, with implications for medical, psychosocial and educational resource provision, and provides an argument for early intervention. Eye-tracking may be a viable marker of neurobehavioural problems, and this study provides impetus for future eye-tracking investigations in CWEOE. Lastly, certain ethnic groups may be at increased risk of early-onset epilepsy in Scotland, providing opportunity for targeted intervention.

Lay Summary

Thinking and behaviour problems have been reported in up to 80% of school aged children with epilepsy. Much less is known about the extent and types of problems in children with early-onset epilepsy (CWEOE; epilepsy which starts in children under five years of age). This study aimed to describe the kinds of problems CWEOE might have, how often they occur, and to also explore what might increase the risk of these problems occurring. It is helpful to identify new ways that problems could be detected early in life, when children could be helped more quickly. This study used a technology that tracked children's eye movements, to see if using this method would help identify problems in CWEOE at a very early age.

To meet the aims above, this study attempted to find all children, who had recently been diagnosed with epilepsy, in an area of South-East Scotland. These CWEOE, along with healthy control children of the same age, completed some assessments that measured their thinking and reasoning, while parents answered questionnaires that evaluated the children's behaviour. The children's eye movements were tracked while watching some specially designed pictures and animations.

The number of new cases of CWEOE in South-East Scotland was determined, and meant that every year there are approximately 62 new diagnoses of epilepsy, for every 100,000 children under the age of five. Children from mainland Europe and of Asian origin were at increased risk of developing epilepsy compared to white British children. CWEOE had more problems with thinking and behaviour compared to control children. A broad spectrum of problems were identified in CWEOE, with 63% having a problem with thinking and/or behaviour, compared to 27% of controls. Those CWEOE who had epilepsy as the result of a structural brain abnormality, who were born premature, or who had a family member with a thinking or behaviour problem, were more likely to have a thinking or behaviour problem themselves. CWEOE looked less at pictures of children during eye-tracking compared to healthy control children, which may indicate a difficulty in social reasoning in CWEOE.

Given that problems are evident and detectable during infancy, toddlerhood, and preschool, there are implications for the care and management of CWEOE in Scotland. Thus, the findings may be of interest to researchers, and medical, social, and educational policy makers. It also provides argument for early intervention in CWEOE. Eye tracking has shown potential as a tool for identifying social problems, and should be explored further in CWEOE.

Declaration

This thesis has been composed entirely by the candidate, and the work is the candidate's own, except where indicated throughout the thesis. This work has not been submitted in whole, or in part, for any other degree or professional qualification. At 84,297 words, this thesis does not exceed the University of Edinburgh's word count limit.

Matthew Hunter

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Chapter I. Introduction and Study Background

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Chapter I offers an introduction to this thesis, and argues the rationale and importance of gathering data on neurobehavioural problems in children with early-onset epilepsy (i.e. CWEOE; onset ≤4 years). A systematic literature review on the subject revealed a major gap in detailed information on the prevalence and spectrum of neurobehavioural problems in CWEOE, providing justification for the current study. The chapter then describes the structure and main aims of the study, and gives a description of the general methods used.

***

1. Introduction

1.1 Neurobehavioural Comorbidities in Epilepsy: A call to Action

The importance of knowledge and understanding of epilepsy and comorbid neurobehavioural problems (i.e. cognitive impairments and behavioural problems) is of paramount importance. The International League Against Epilepsy (ILAE[1]) has recognised the presence and importance of neurobehavioural problems by incorporating this into the very definition of epilepsy itself, conceptually defining it as "a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition" (Fisher et al., 2005). Epilepsy has a substantial economic burden (Hunter et al., 2015; Strzelczyk et al., 2008), and is an important detriment to quality of life - more so than other health conditions (Moreira et al., 2013). Neurobehavioural problems add to the financial and health burden imposed by seizures, and further impair quality of life beyond that of seizures themselves (Ferro et al., 2013).

The significance of impairing comorbid conditions has been recognised by the scientific community, who have called for increased funding and research into neurobehavioural problems in childhood epilepsy (Baulac et al., 2015; England et al., 2012). In 2010 the Institute of Medicine (England et al., 2012) set out a number of recommendations to promote and improve research into epilepsy and its comorbidities, with a view to improving understanding and public health; citing the financial, social, and health-care challenges associated with epilepsy, as well as the personal consequences of the condition toward education, employment, stigma and quality of life. The World Health Organisation's Resolution on the Global Burden of Epilepsy (WHO, 2015) recognised the need to transform and implement policy change surrounding all aspects of care for people with epilepsy by 'urging' member states, including the UK, to:

Strengthen effective leadership and governance, for policies on general health, mental health and noncommunicable diseases that include consideration of the specific needs of people with epilepsy, and to make the financial, human and other resources available that have been identified, as necessary, to implement evidence-based plans and actions (p. 3)

[1] See appendix J for a full list of common abbreviations used in this thesis.

Furthermore, in 2013 the European Forum on Epilepsy Research recommended a number of research priorities, which have been summarised by the ILAE and International Bureau for Epilepsy's (IBE) joint task force (Baulac et al., 2015). The task force has recommended particular focus into childhood epilepsy populations, endorsing research that promotes understanding of comorbidities, and factors that lead to neurobehavioural problems, in the developing brain. Such research has been recommended with the aim of increasing public awareness of epilepsy and its comorbidities, and to craft local and European policy and legislation in order to improve community integration and access to health-care services.

The need to address neurobehavioural comorbidities in the first five years of life are of particular concern given the increased epileptogenic nature of the developing brain, and its vulnerability to abnormal and maladaptive development (Dennis et al., 2013). The National Scientific Council on the Developing Child (NSC, 2007) has advocated the need for early childhood policies and practices across the first five years of life, for all children, which support healthy development, and which are preventative, or intervening, in factors or processes that contribute toward maladaptive development. Therefore, data on comorbidities in children with early-onset epilepsy (CWEOE, onset ≤4 years) is of critical importance in order to meet the requirements of understanding epilepsy within the developing brain, and to understand the burden of epilepsy on the child, family and wider community.

Early childhood would be the most advantageous time to identify those with, or at risk of, neurobehavioural problems, in order to put interventional or preventative strategies into place. Despite a lack of clinical focus and neuropsychological assessment in very early childhood (Baron and Anderson, 2012), evidence suggests behavioural problems are common and detectable during the early-onset period (Bagner et al., 2012; Poulou, 2015), and are often stable, persisting into adolescence and adulthood (Asendorpf et al., 2008; Bayer et al., 2011; Bosquet and Egeland, 2006). Taken together with evidence that childhood epilepsy is associated with adverse psychosocial consequences in adulthood, even in cases with seizure remission (Camfield and Camfield, 2009; Camfield and Camfield, 2010; Chin et al., 2011; Jalava et al., 1997; Sillanpaa et al., 1998; Wakamoto et al., 2000; Wirrell et al., 1997) (c.f. Camfield and Camfield, 2014), it is imperative to intervene early to improve both current circumstances, and future psychosocial outcomes. Early interventions have been shown to be effective. In a systematic review of randomised control trials in children 0-8 years old, Bayer and colleagues (2009) concluded that early interventions have been successful in reducing internalising and externalising problems. Furthermore, early interventions can have lasting implications into

adulthood (Hawkins et al., 1999), and may be more advantageous than school-age interventions (Ramey and Ramey, 1998), and more cost effective (Chowdry and Oppenheim, 2015).

Taken together, the identification of, and knowledge surrounding, neurobehavioural comorbidities in CWEOE is extremely valuable toward the formulation of health, social, and educational policy, as well as vital toward targeted, early medical and psychosocial intervention.

1.2 Early-Onset Epilepsy: An Important but Understudied Risk Factor

Here, the argument is put forward for an increased risk of abnormal neurobehavioural development in CWEOE compared to later childhood onset epilepsies. First, the theoretical ground for an increased biological risk is stated, then some of the current evidence from the scientific literature is reported to support that assertion. It is acknowledged that this answer remains uncertain and incomplete, and that further evidence is required.

Neurogenesis is lifelong. However, at no point is it faster than during the prenatal period and early years of life. By four or five years of age the brain weighs approximately 89% of that of an adult brain (Dekaban and Sadowsky, 1978), and cerebral volume has reached 95% of its adult peak by age six (Lenroot and Giedd, 2007). The first years of life include rapid overgrowth of neurons and differentiation, neuronal maturation and elaboration, and axonal myelination (Anderson et al., 2001). Neural overgrowth and pruning occur at different locations at different times, meaning that structural and functional development in those regions may be particularly sensitive during those periods (Thompson and Nelson, 2001). Magnetic resonance imaging (MRI) studies show age-related changes in cortical area size, cortical thickness, and in functional development during infancy and the preschool years (Brown and Jernigan, 2012) - with the development of psychological skills presumably mirroring those anatomical and functional changes within the brain. To date, there is limited direct imaging evidence to corroborate this in the preschool age group (Brown and Jernigan, 2012). Nevertheless, skill development does coincide with neuroanatomical growth and differentiation (Herschkowitz et al., 1997; Paterson et al., 2006).

The brain's rapidly changing landscape during maturation makes it particularly prone to adverse events (Dennis et al., 2013), with evidence suggesting that plasticity in the developing

brain is not as advantageous as once believed (Dennis et al., 2013). Indeed, there is a higher prevalence of developmental (i.e. congenital malformations, neuronal migration abnormalities) and structural (e.g. hypoxic-ischemic, post-infection, trauma) antecedents to epilepsy during the early years than later childhood (Annegers, 2004). And as will be discussed in section 1.4, these structural aetiologies are strongly associated with cognitive impairment. This is of particular importance to CWEOE, as the developing brain is more prone to seizures than the mature brain. Indeed, febrile and neonatal seizures are common in the first year of life, and the incidence of epilepsy (Hauser et al., 1996) and single unprovoked seizures (Olafsson et al., 2005) are disproportionately higher than at any other time in childhood or adulthood.

While it is difficult to establish a cause and effect relationship between recurrent epileptic seizures and adverse cognition in the childhood brain, epilepsy and repeated seizures may have a more prominent effect in the very early brain. Rhythmic and synchronous bursts of electrical activity (i.e. seizures) in the brain can be a normal adaptive function (Avanzini et al., 2014), but activity-dependent age-related structural and functional change coupled with immature GABA-ergic excitatory/inhibitory mechanisms, and immature synaptic architecture contributes to an increased risk of non-adaptive seizures, and the likelihood of maladaptive functional and structural changes in response (Ben-Ari and Holmes, 2006; Nardou et al., 2013; Sutula, 2004).

Taken together, the immature brain is a high-risk ground for abnormal development. Indeed, early age of epilepsy onset is associated with poor developmental and cognitive outcomes (Battaglia et al., 1999b; Chevrie and Aicardi, 1978; Rantanen et al., 2011; Vendrame et al., 2009), and is the period that includes most of the epileptic encephalopathies (Neville, 1997). An increased risk of cognitive impairment is also seen in those children with refractory seizures undergoing epilepsy surgery who have earlier onsets (Cormack et al., 2007; Freitag and Tuxhorn, 2005; Lespinet et al., 2002; Vasconcellos et al., 2001). Several studies have demonstrated that early-onset epilepsy is associated with poorer cognitive outcomes than onset after five years of age (Berg et al., 2008; Dikmen et al., 1977; O'Leary et al., 1981; O'Leary et al., 1983; Reilly et al., 2014a), even when structural aetiology and encephalopathy are controlled for (Battaglia et al., 1999b; Berg et al., 2008).

Although the theoretical and scientific evidence suggests a strong relationship between CWEOE and cognitive impairment, most of the studies mentioned above are based on children assessed during the school-age or beyond, and the findings might simply reflect a longer

duration of epilepsy when compared to children whose onset began in later childhood. An effect of early age of onset does remain in some studies after controlling for epilepsy duration (Dikmen et al., 1977; Hermann et al., 2002), but not in all (Park et al., 2013). There is also emerging evidence to suggest that poorer cognition may be due to the duration of epilepsy as a function of poor seizure control, rather than because of age-of-onset, or length of epilepsy, per se (Berg et al., 2012; Park et al., 2013).

The above data suggest the relationship between early-onset epilepsy and neurobehavioural problems is unclear. Primarily, data on the prevalence and spectrum of neurobehavioural problems *during* the early-onset period itself, rather than during later childhood or adulthood, is required in order to understand if problems exist during the early stages, or if they are more likely to develop in later childhood. To address this lack of knowledge a systematic review on the topic was undertaken.

1.3 Prevalence and Spectrum of Neurobehavioural Problems in CWEOE: A Systematic Review

1.3.1 Systematic Review: Methods

Studies of early childhood often report observations from parent interview and clinic observation. While this is useful, in order to increase the empirical validity of findings, this review focused on studies reporting standardised psychometric data. The main goal of the literature review was to identify studies with psychometric data reported from standardised cognitive and behavioural assessment tools on five or more CWEOE *during* the first five years of life. This review follows the guidance set out in the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) report (Moher et al., 2009).

The electronic databases Medline (Ovid), Embase (Ovid), PsycINFO (Ovid), Web of science Core Collection (Thomson Reuters), and CINAHL were systematically searched for period 1970 to July 1 2015. Searches were performed August 8 2015 using MeSH terms, database specific subject headings, or equivalent, for terms; "children", "epilepsy", "cognition", and "behavior". Indexed searches were supplemented with free-text searches, including non-indexed searches for Medline and Embase. Database specific search protocols are documented in appendix A. In addition, articles were searched for additional references, and study authors were approached for unpublished data when appropriate.

Inclusion criteria were: (1) children with physician confirmed, or validated diagnosis of epilepsy (≥2 unprovoked seizures), with or without a comorbid condition (e.g. Autism Spectrum Disorder, ASD) as the main cohort, (2) age of children were five years or less at the time of assessment, (3) cognitive or behavioural assessment using standardised tools or diagnosis of behaviour disorder based on Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) classifications, (4) English-language based journal articles from high and low/middle income countries (World Bank, 2016), and (5) population-based, community-based, hospital-based, cohort studies, case-control studies, and case series, with the exception of studies with less than five participants meeting criteria, were included.

Exclusion criteria were: (1) children ≥6 years at time of neuropsychological assessment, (2) articles focused exclusively on non-epileptic seizure disorders, neonatal or febrile seizures, or exclusively status epilepticus, (3) <5 children with available data , and (4) data based on informal parent or clinic observation, or from unvalidated/unstandardised assessment tools.

Extracted data included assessment scores or qualitative categorisations, based on validated/standardised assessment tools. Where possible, individual and group level psychometric data were extracted, and means and standard deviations calculated. Study and participant demographics, study design, assessment tool, and presence of control group were recorded.

Study selection was carried out by consensus agreement of two reviewers (Candidate & Dr Michael Yoong). Titles and abstracts were screened for relevant articles. Full-text papers were acquired when title/abstracts did not contain enough information, or when inclusion criteria were met. Full-text reviews were carried out applying the above inclusion/exclusion criteria.

Dr Michael Yoong contributed to the written production of the systematic review, by writing an initial draft of the infantile spasms and surgical cohorts sections of the results. The remainder of the review was written by the candidate.

1.3.2 Systematic Review: Results

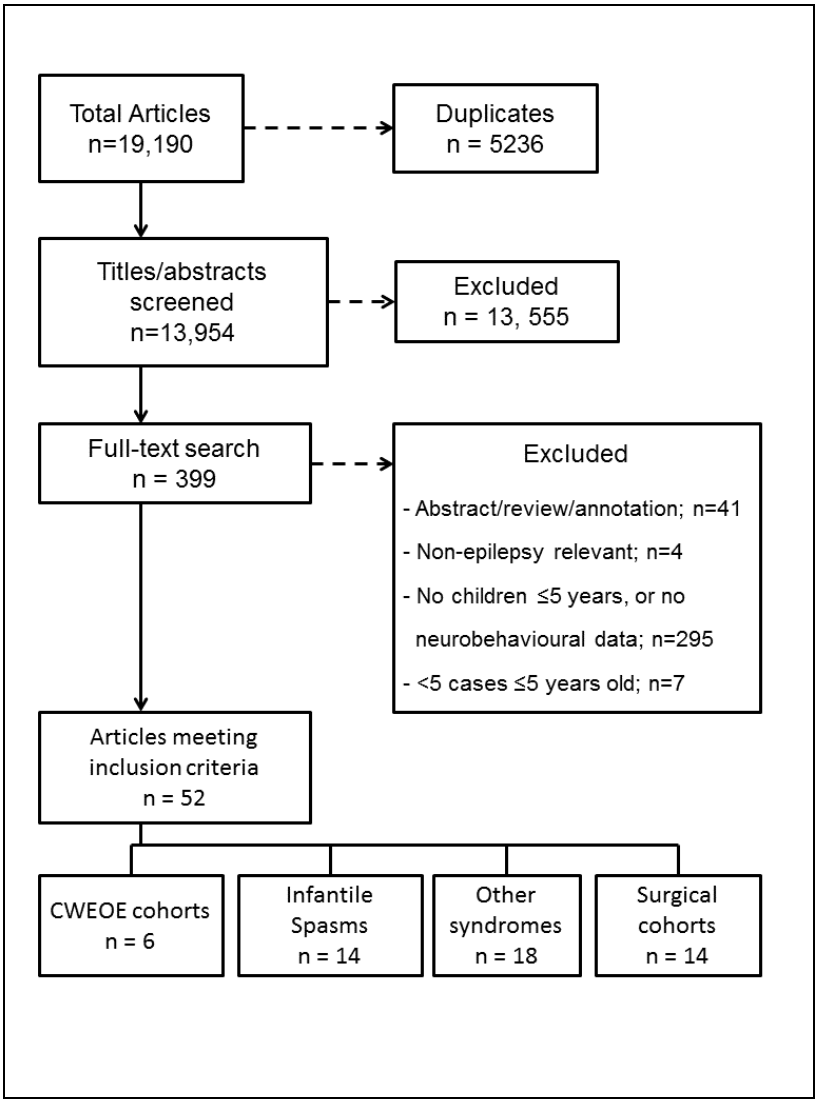
(i) Overview

13,954 articles were screened (figure 1). Fifty-two articles reported psychometric data on CWEOE, and met criteria for review. Findings were reviewed according to category: six studies

were in CWEOE of all types, 14 were in children with infantile spasms, 18 were in other epilepsy syndromes, and 14 were in epilepsy surgery cohorts. As study methods, assessment measures and populations were heterogeneous, formal meta-analysis was inappropriate.

Neuropsychological tools varied but primarily described cognitive or general development in terms of developmental quotient (DQ), general quotient (GQ), Intelligence Quotient (IQ), or adaptive behaviour. Each of these constructs are standardised to a mean of 100 with a standard deviation of 15. Cognitive or developmental impairment is widely classified as an IQ/DQ/GQ score <70 (i.e. ≥2 standard deviations, SD, below the mean), with scores in the 71-80 range considered borderline, and scores >80 normal. Behaviour scores and problems were reported less frequently, with problems typically defined according to DSM criteria.

Figure 1 Article exclusion flow chart



(ii) CWEOE Cohorts

Six articles reported psychometric data on CWEOE of all types (table 1.1). Four reported on cognitive or general development - one of which also reported on ASD features (Fisher et al., 2012b). Three of the four articles were based on single centre studies (Czochanska et al., 1994; Fisher et al., 2012a; Vendrame et al., 2009), and the fourth was a population-based study (Martinos et al., 2013, additional data obtained from author). The remaining two papers focused on adaptive behaviour from the community-based population of the Connecticut Study of Epilepsy (Berg et al., 2004; Berg et al., 2013).

Population-based studies are a preferred source of reporting, with reduced sampling bias and greater generalisability of disease characteristics within a culture. The population-based study here, however, was limited to a small sample of children (n=18) with epilepsy and an accompanying history of convulsive status epilepticus (Martinos et al., 2013, additional data obtained from author) – a seizure condition whose effect on cognitive functioning is uncertain but possibly detrimental (Novorol et al., 2007). It was, therefore, not possible to build an accurate and representative neurobehavioural profile of CWEOE. Nevertheless, it was clear that cognitive and general development in CWEOE was unfavourable in significant proportions of children represented by the studies, particularly those from at risk populations, including those with symptomatic/structural aetiologies.

Martinos et al. (2013) cohort had a mean cognitive development score, as assessed by the Bayley III, in the borderline range (Mean, M, =78.8, SD=17.64). After breaking the cohort down by aetiology, those with idiopathic epilepsy were relatively spared (M=90.60) but scores decreased markedly in those with cryptogenic (M=79.29), and symptomatic (M=68.33) aetiologies. Eight of 18 children (44%) were cognitively impaired – four children with cryptogenic aetiology, and four with symptomatic aetiology. Impaired development (DQ<70) ranged between 33-91% of children in the remaining three studies. In the first of these, one third of children with epilepsy in the first year of life, and over two thirds of children with infantile spasms had impaired development (Czochanska et al., 1994). The second found developmental impairment in all but three of 33 children (91%), and with an overall extremely low mean DQ of 37 (Vendrame et al 2009). However, the children involved in that study were either surgical candidates or had been referred for developmental evaluation – two high risk populations for cognitive impairment. The final study, from a tertiary epilepsy

Table 1.1 General CWEOE cohort studies

Author (year)	Location (design)	Cohort	N (age, m)	Outcome (tool)	Mean (SD)	Other Results	Commentary
Martinos et al (2013)*	London, UK (population-based)	Epilepsy +CSE	18 (≤61)	Cognition (Bayley III)	78.8 (17.64), vs controls 107.35 (16.87)	Mean score by aetiology: idiopathic 90.6, cryptogenic 79.29, and symptomatic 68.33. Eight (44%) impaired (cognitive score <70).	*Unpublished data.
Czochanska et al (1994)	Warsaw, Poland (single centre)	Epilepsy & IS	133 (<12)	DQ (Brunet-Lezine)	n/a	63 (69%) children with infantile spasms, and 14 (33.3%) with other epilepsies were developmentally impaired (DQ<70).	At 3-7 years follow-up, no overall change in DQ; poor seizure control associated with deterioration. No control group.
Vendrame et al (2009)	Cleveland, USA (single centre)	Epilepsy	33 (<34)	DQ (BSID III)	37 (29)	30 (91%) had DQ <70	Lower DQ associated with earlier onset, epilepsy duration, and spasms. But not seizure type, frequency, or brain pathology. No control group.
Fisher et al (2012)	Chicago, USA (hospital-based)	Epilepsy	65 (<72)	Development (ASQ) ASD (MCHAT/SCQ)	n/a	47 (72%) had abnormal development. 32 (49%) had positive screening for ASD	Abnormal development was associated with positive ASD screening. No control group.
Berg et al (2004)	Connecticut, USA (community-based)	Epilepsy	172 (<36)	Adaptive behaviour (VABS)	92 at baseline, 81.5 at three year follow-up (trend p<.001)	Poor adaptive behaviour and decline at follow-up in symptomatic aetiology or encephalopathy only. Cryptogenic/ idiopathic epilepsy preserved VABS at 98.1.	Age of onset not associated with VABS, except daily living composite. No control group.
Berg et al (2013)	Connecticut, USA (community-based)	Neuro-typical Epilepsy	108 (<72)	Adaptive behaviour (VABS)	103 (SD 17.1)*	Adaptive behaviour score predicts later achievement at school. 55% of cohort had school problems.	*Derived from supplementary material. No control group.

ASQ – Ages and Stages Questionnaire
BSID – Bayley Scales of Infant and Toddler development
CG – Control Group
CSE – Convulsive Status Epilepticus
MCHAT – Modified Checklist for Autism in Toddlers
SCQ – Social Communication Questionnaire
VABS – Vineland Adaptive Behaviour Scales

centre, found abnormal development in 72% of children, based on the Ages and Stages Questionnaire; half of whom screened positive for ASD (Fisher et al 2012). Similar to the previous study, this cohort may not have been representative of the general epilepsy population, as there was an increased risk of referral centre bias (Sackett, 1979).

Berg and colleagues (2004; 2013), in their community-based cohort, focused on adaptive behaviour, as assessed by the Vineland Adaptive Behaviour Scales (VABS). Adaptive behaviours are a set of conceptual, social and practical skills, reflective of the child's ability to develop and function in everyday life circumstances. Adaptive behaviour assessment is a necessary component in the formulation of an intellectual disability diagnosis. Berg et al found preserved adaptive functioning in children with no neurological abnormality and normal IQ (Berg et al., 2004; Berg et al., 2013). However, adaptive behaviour was significantly poorer in refractory epilepsy, symptomatic aetiology, and epileptic encephalopathy (Berg et al., 2004). Interestingly, adaptive behaviour scores for those in the former category remained stable across time, but declined for those in the latter over the three years of follow-up. Age of onset was not a significant predictor of adaptive behaviour, except for the daily-living domain, which was higher in the first year of life.

(ii) Infantile Spasms

14 papers were found describing a total of 468 patients, all of whom had met clinical criteria for a diagnosis of infantile spasms or West Syndrome, herein referred to as infantile spasms, (table 1.2). Case definitions were characterised by the electro-clinical triad of: 1) spasms 2) hypsarrhythmia on electroencephalogram (EEG) and 3) developmental regression at seizure onset. The majority of studies were small cohort studies of consecutive patients with infantile spasms from single tertiary centres (Prats et al., 1991; Koo et al., 1993; Guzzetta et al., 1993; Ouss et al., 2014) or groups of centres (Rando et al., 2005; Guzzetta et al., 2008), with two larger multi-centre randomised controlled trials also contributing cognitive data on their cohorts – the United Kingdom Infantile Spasms Study (UKISS; Lux et al., 2005; O'Callaghan et al., 2011), and a Canadian group (Bitton et al., 2012; Bitton et al., 2015). Three small studies looked specifically at subgroups: children with prominent visual impairment and infantile spasms (Jambaque et al., 1993), children with cryptogenic infantile spasms and good response to initial treatment (Gaily et al., 1999) and children with tuberous sclerosis (Humphrey et al., 2014). Four studies looking at the impact of epilepsy surgery on cognitive outcomes in children with infantile spasms are discussed with other surgical papers.

Table 1.2 Infantile spasms studies

Author (year)	N	Outcome (tool)	Age (m)	Mean DQ (SD) or equivalent	Other results	Commentary
Takahashi et al. (1990)	33	DQ (Enjoji test of development)	3-32	89 (14) in children without structural brain abnormality (n=8) 58 (32) in children with structural brain abnormality (n=25)	Follow-up 4m-19y. DQ declined in structural brain abnormality group, but not normal brain group	Method of patient selection unknown
Prats et al. (1991)	42	Intellect (Termann-Merrill & WISC-R)	8-72	n/a	12 (28%) had normal intellect, 4 (9%) mild impairment, 26 (62%) severe impairment	
Jambaque et al. (1993)	8	DQ (Gesell)	24-36	49.3 (19.1)	5 (63%) with severe impairment (DQ <60)	Method of patient selection unclear. All patients had moderate-severe visual loss
Koo et al. (1993)	57	Developmental Score (Griffiths)	12-60	Overall: 55.1 (26.4) Cryptogenic 71.2 (24.2) Symptomatic 48.3 (24.5)	41 (73%) impaired (DS <70)	Cognitive outcome better with early AED treatment. No significant difference between ACTH or nitrazepam treatment groups.
Guzzetta et al. (1993)	31	DQ (Uzgiris-Hunt)	28-60	39.9 (SD not given)	22 (71%) had moderate-severe delay (DQ < 60) at diagnosis, 16/29 (55%) at follow-up	2 patients died during study period
Gaily et al. (1999)	15	IQ (WPPSI) NEPSY	48-71	96.0 (23.2)	8 children showed specific impairments of attention and/or memory	All children had cryptogenic aetiology, and were selected from a larger cohort of 46 children with infantile spasms
Rando et al. (2005)	25	DQ (Griffiths)	4-16	60.3 (31.8) at onset 56.2 (29.4) at 2 months after onset	19 (76%) had impairment (DQ < 70)at onset, 18 (72%) at follow-up	3 of 4 children with cryptogenic WS and 3 of 4 children with TSC had normal DQ.

Table 1.2 continued

Lux et al. (2005)	107	Adaptive Behaviour (VABS)	14	Overall: 78.0 (14.9) Cryptogenic: 83.8 (16.5) Symptomatic: 73.3 (11.4)		Higher VABS scores after steroid treatment, compared to vigabatrin, in cryptogenic infantile spasms.
Guzzetta et al. (2008)	21	DQ (Griffiths)	24	53.6 (39.9)	14 (66%) had impairment (DQ < 70)	Follow-up study from Rando et al.
O'Callaghan et al. (2011)	77	Adaptive Behaviour (VABS)	48	76.2 (28.4) at shortest treatment delay (<8 days), to 55.5 (24.3) at longest delay (>2m).	Younger age of onset and longer treatments delays associated with poorer VABS scores	Steroid treatment had a positive effect on VABS in those with unknown aetiology
Bitton et al. (2012)	45	DQ (BSID) Adaptive Behaviour (VABS)	7 & 24	DQ: 38.0 (33.2) at onset, 51.8 (33.7) at 24 months VABS: 90.1 (12.7) at onset, 65.4 (16.6) at 24 months	DQ: 29 (64%) had impairment (<70) at follow-up	No significant impact of flunarizine treatment on DQ
Humphrey et al. (2014)	6	IQ (Mullen Scales of Early Learning)	<10-70	92.4 (23.2) (prior to onset) 65.9 (11.9) (after seizure onset)	IQ drop in the 6 children with TSC+IS, but none in 5 children with TSC+ other seizure types	Development of spasms in children with TSC associated with IQ decline
Ouss et al. (2014)	25	DQ (Brunet-Lezine) ASD (ADI-R, CHAT & CARS)	DQ : 24 ASD: 48	59.5 (27.6)	7 (28%) had ASD, and 2 (8%) had PDD-NOS	CHAT scores were highly predictive of eventual autism status.
Bitton et al. (2015)	69	DQ (BSID) ASD (CHAT & ADOS)	BSID & CHAT: 24 ADOS: 30 & 60	22/39 (56%) patients assessed had DQ <70	10/44* (22.7%) patients were diagnosed with ASD on ADOS	*25 patients were not assessable due to severe delay or death

ACTH - Adrenocorticotropic Hormone
ADI-R - Autism Diagnostic Interview - Revised
ADOS - Autism Diagnostic Observation Schedule
ASD - Autism Spectrum Disorder
BSID - Bayley Scales of Infant and Toddler Development
CARS - Children's Autism Rating Scale
CHAT - Checklist for Autism in Toddlers
NEPSY – Developmental Neuropsychological Assessment
TSC – Tuberous sclerosis complex
VABS - Vineland Adaptive Behaviour Scale
WISC-R – Wechsler Intelligence Scales for Children Revised
WPPSI – Wechsler Preschool and Primary Scales of Intelligence

A number of different neuropsychological tools were used, predominantly measuring DQ. Two studies reported on measures of autism, and the two larger multi-centre studies used the VABS to measure adaptive behaviour. Despite the varying methodology, all studies of an unselected cohort of children with infantile spasms found them to be highly impaired, with 60-70% of children having moderate-severe impairment, and mean reported DQ between 40 and 60, with the exception of a small group of children with normal brain imaging who had a mean DQ of 89 (Takahashi et al., 1990). Standard deviations were high, suggesting considerable heterogeneity of outcome. Children without a diagnosed aetiology for infantile spasms (i.e. cryptogenic) performed better; with significantly higher DQ (Koo et al., 1993) and lower rates of moderate-severe impairment (Rando et al., 2005). Gaily et al (1999) found that 15 patients with cryptogenic infantile spasms who became seizure-free on medication had IQs within the normal range, although over half of them showed measurable deficits of attention and/or memory suggesting the persistence of subtle deficits.

The timing of assessment was important, as two studies with longitudinal measurements reported that cognitive scores are lowest at seizure onset and improved at 1-2 year follow-up, albeit remaining in the moderate-severely impaired range (Guzzetta et al., 1993, Bitton et al., 2012). The one study that found scores to remain static (Rando et al., 2005), re-tested children 2 months after seizure onset, which may be too early to see meaningful clinical recovery and cognitive improvement.

Changes in medical practice do not appear to have made significant impacts on cognitive outcomes, with similar rates of impairment in more recent studies (Ouss et al., 2014, Bitton et al., 2015) as earlier ones (Prats et al., 1991, Koo et al., 1993), despite different treatment regimes. An interesting study by Humphrey et al (2014) that monitored 11 children with tuberous sclerosis before and after the onset of seizures and showed that, at least for this group of patients, DQ fell from the normal range prior to seizure onset, deteriorating markedly after the of spasms, but not other forms of epilepsy.

The two more recent clinical trials (Lux et al., 2005; Bitton et al., 2012) showed that children with infantile spasms also perform below population norms on measures of adaptive behaviour. Bitton et al. (2012) were also able to show an impact on cognition at baseline and at 2 years, consistent with the DQ scores reported in previous studies. Neither showed an effect of treatment on the cohort as a whole, but both found that children with cryptogenic infantile

spasms showed significant improvements in adaptive behaviour with hormonal treatment (Lux et al., 2005; O'Callaghan et al., 2011), or flunarizine (Bitton et al., 2012). Interestingly, age of seizure onset and time delay from first seizure to treatment, were independently and negatively correlated with VABS scores by four years of age (O'Callaghan et al., 2011).

Performance on autism-specific screening tools (PreAut, CHAT) was found to be strongly related to lower DQ (Ouss et al., 2014; Bitton et al., 2015). However, the general risk of Autism was much higher than the general population, regardless of DQ.

In summary, there is now good quality data from prospective multicentre infantile spasms cohorts recruited as part of randomised controlled trials that confirm the findings from earlier case series. That being, approximately 60% of children with infantile spasms have moderate-severe impairment in cognition, adaptive behaviour and/or autism. The risk of this is highest in symptomatic IS, and lower in children with cryptogenic IS. Children with cryptogenic infantile spasms may benefit from rapid treatment, but the evidence for symptomatic causes is weaker.

(iii) Other Early-Onset-Related Syndromes

Eighteen single- and multi-centre studies, describing nine early-onset syndromes, excluding infantile spasms/west syndrome, were included for review. Study details can be found in table 1.3 (several studies compared younger age groups with older onset groups. These have been referenced in the table for comparison). Dravet Syndrome, was described in seven of those studies (39%), with the eight remaining syndromes represented by only one (Benign Epilepsy with Centrotemporal spikes, PCDH19-related epilepsy, Symptomatic Focal Epilepsy, and Sturge-Weber Syndrome) or two studies (Benign Myoclonic Epilepsy of Infancy, Childhood Absence Epilepsy, and Panayiotopoulos Syndrome). Sample sizes varied between 5 and 110 children across studies, with 12 (67%) having ≤15 children. No study had a control group. 16 of 18 studies described cognitive development via DQ, IQ, or GQ. Nine studies reported behavioural data. Behaviour disorders, including ASD and ADHD, were identified using the DSM in four, whilst three studies reported behaviour outcomes using the CBCL or SDQ questionnaires.

Despite receiving limited and uneven attention, several broad conclusions can be proposed. Firstly, adverse IQ/DQ/GQ outcomes were consistently found across syndromes. The majority

Table 1.3 Studies of other early-onset-related syndromes

Author (year)	Location	Type (N)	Age	Outcome (tool)	Results	Commentary
Brunklaus et al. (2011)	Glasgow, UK	DS (62)	24-60m	Total Stress (SDQ)	2 & 3y old children scored in borderline range (16, SD 6). 4 & 5y old children scored in high risk range (18, SD 5).	Similar scores noted in children >5 years. Behaviour most important predictor of quality of life.
Nabbout et al. (2013)	Paris, France	DS (57)	9-24m	DQ (Brunet-Lezine) Behaviour (CRS)	Mean DQ 79.5 (SD 12.0) in children <2 years, and 73.7 (SD 15.0) in children <3 years of age.	Long term follow-up showed decrease in DQ/IQ after age 3. 13/15 children with DQ <60. No difference in DQ/IQ between SCN1A+ or -. Abnormal learning and hyperactivity and attention deficit noted, at 2-5y. Figures not stated by age.
Chieffo et al. (2011a)	Rome, Italy#	DS (11)	9-42m & 48-64m	GQ (Griffiths) & Various cognitive tests	GQ in normal range for 5 patients <3 years of age. Nine children had subnormal cognition by age 5. Visuomotor and perceptive skills particularly affected, even in those with normal GQ. Those with borderline DS did not have motor disorders.	After long term follow-up (≤10y), cognitive decline was found to occur between 3-5 years before stabilising.
Chieffo et al. (2011c)	Rome, Italy#	DS (5)	6-12m & 30-51m	GQ/DQ (Griffiths/Bayley) Behaviour (CBCL) Visual function	Mean GQ/DQ 100.5 (SD 9.5) at 6-12m. Cognitive decline in four children at final follow-up (30-51m); mean 94 (SD 16.5). One had IQ <70. Four patients had visual dysfunction by fourth year of age. Three had behaviour issues. Behaviour was normal in two cases. Two also had emotional problems.	Visual impairment precedes cognitive decline in the early stages of DS.

BECTS – Benign Epilepsy with Centrotemporal Spikes
BMEI – Benign Myoclonic Epilepsy of Infancy
BVMGT – Bender Visual Motor Gestalt Test
CAE – Childhood Absence Epilepsy
CBCL – Childhood Behaviour Checklist
CRS – Conners Rating Scale
DS – Dravet syndrome
PS – Panayiotopoulos Syndrome
SDQ – Strength and Difficulties Questionnaire
SFE – Symptomatic Focal Epilepsy
SWS – Sturge Weber Syndrome
TSC – Tuberous Sclerosis Complex
TVLO – Oral Language Test

Table 1.3 continued

Author (yr)	Location	Type (N)	Age	Outcome (tool)	Results	Commentary
Ragona et al. (2011)	Rome, Italy#	DS (26)	4-26m	GQ (Griffiths' Scales/Brunet-Lezine)	Mean GQ 88.46 (SD 14.56) at 12m, and 56.15 (SD 22.09) at 60m. All but two children aged 4-26m had normal GQ. At 60m 19 had GQ <70.	Absence of myoclonus and absences early in disease course may be associated with a reduction in severity of cognitive decline. SCN1A variations were not predictive of cognitive outcome.
Ricci et al. (2015)	Rome, Italy#	DS (5)	2y & 4y	GQ (Griffiths) Various visual tests	Mean GQ 88.2 (SD 16.24) at 2 years, and 75.2 (SD 14.70) by 4 years of age. Evidence of broad visuomotor/cognitive and executive difficulties.	Mean GQ/IQ 59 (SD 9.54) by age 6-8 years.
Wolff et al. (2006)	Marseille, France	DS (8)	≤65m	DQ (Brunet-Lezine)	Mean DQ 50.88	Age-related DQ decline noted, stabilising at age 4 years. Behavioural abnormalities noted, but method of classification unknown.
Jambaque et al. (1991)	Rome/ Paris	Epilepsy +TSC (8)	36-71m	DQ/IQ (Brunet-Lezine/Terman-Merrill/WPPSI) Behaviour (DSM-III-R)	Mean DQ/IQ 64.87 (SD 26.18). Six children (75%) had DQ/IQ <70. Six children had behaviour problems: most notably hyperkinesia in four.	Children aged 6-16y mean DQ/IQ 58.53 (SD 32.15). 67% had DQ <70. Abnormal behaviour in 67%, including 6 with ASD. Cognitive outcome mediated by tuber frequency and seizure history/severity.
Kotulska et al. (2014)	Warsaw, Poland	Epilepsy +TSC (18)	18-60m	IQ (Psyche-Cattell)	Eleven children (73.3%) were intellectually impaired (IQ<69), seven of those severely.	Cortical dysplasia associated with poorer cognitive outcome. Six children >5y at test, all with moderate-severe impairment.

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BMEI – Benign Myoclonic Epilepsy of Infancy
BVMGT – Bender Visual Motor Gestalt Test
CAE – Childhood Absence Epilepsy
CBCL – Childhood Behaviour Checklist
CRS – Conners Rating Scale
DS – Dravet syndrome
PS – Panayiotopoulos Syndrome
SDQ – Strength and Difficulties Questionnaire
SFE – Symptomatic Focal Epilepsy
SWS – Sturge Weber Syndrome
TSC – Tuberous Sclerosis Complex
TVLO – Oral Language Test

Table 1.3 continued

Author (yr)	Location	Type (N)	Age	Outcome (tool)	Results	Commentary
Verrotti et al. (2011)	Italy	CAE (9)	47-71m	IQ (WPPSI-R)	Eight (89%) had normal intellectual development. One had mild cognitive impairment (IQ 69).	Further 31 children 5-15y at test. Overall, 83% had normal IQ. Poor IQ associated with poor seizure control.
Masur et al. (2013)	USA	CAE (110)	30-60m	IQ/Attention/ Executive Function (including WPPSI-III and K-CPT)	Mean IQ 97.6 (SD 16.2). Normal vocabulary, verbal memory, and visuomotor ability. 17% had attention difficulties at baseline.	Children tested prior to AED treatment. Similar results found in 336 children >5 years. Attention problems, mainly inattentive, persisted at follow-up. Attention deficits related to AED type.
Auvin et al. (2006)	France	BMEI (8)	38-67m	IQ (WPPSI-R) and/or Adaptive Behaviour (VABS)	Mean IQ 79.5 (SD 10.34). Mean adaptive behaviour 85.2 (SD 16.16).	Similar results found in 12 patients 6-26y; VABS mean 83.42 (SD 20.9).
Mangano et al. (2005)	Italy	BMEI (7)	13-36m & 36-66m	DQ/IQ (Brunet Lezine/WPPSI) Visuomotor (BVMGT) Language (TVLO)	Mean DQ 91.71 (SD 15.09), and IQ 78.57 (SD 14.36) at follow-up. 2 children had language impairment and 2 had visuomotor deficits.	Final follow-up 5-10y, Mean IQ 74.0 (SD 18.43). Behaviour issues reported but method of diagnosis unclear.
Cappelletti et al. (2015)	Rome, Italy	PCDH19 gene epilepsy (5)	1y & 5y	GQ (Griffiths) Behaviour (DSM-IV)	Mean GQ 81.2 (SD 22.19) at 1y, and 78.6 (SD 24.28) at follow-up (3-5y). All had language delay. One had ASD and three had attention difficulties.	Including 6 others (n=11), long-term follow-up 3-37y: Mean GQ/IQ/AQ= 61.6 (SD 27.4). 5 had ASD, 1 had mood disorder, and 5 had an attention deficit

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Table 1.3 continued

Author (yr)	Location	Type (N)	Age	Outcome (tool)	Results	Commentary
Alkonyi et al. (2011)	Detroit, USA	Epilepsy+ SWS (5)	36-54m	IQ (WPPSI-III)	Mean IQ 101.60 (SD 20.16) Control data not reported	10 children aged 6-12y. Mean IQ 63.2 (SD 15.36). IQ associated with white matter abnormalities.
Hirano et al. (2009)	Tokyo, Japan	Atypical PS (12)	35-63m	IQ (Modified Binet/WPPSI) Behaviour (DSM-IV)	7 (66%) had neurobehavioural disorders. Two had borderline to mild retardation (i.e. 80-50 IQ), 1 had ADHD, 1 ASD, and 1 learning disability.	No difference in IQ between atypical or typical PS (n=45, 18-91m). However, incidence of neurobehavioural disorders higher in atypical PS.
Ohtsu et al. (2008)	Tokyo, Japan	Early-onset BECTS (24) PS (46)	<5y	IQ (Modified Binet/ WPPSI) Behaviour (DSM-IV)	BECTS had significantly more development and behaviour disorders (Asperger's, LD, ADHD) than PS (21% vs 8%). BECTS had significantly more children with IQ <80 (37.5% vs 15.2%).	
Gonzalez et al. (2014)	Melbourne, Australia	SFE (18)	3-5y	Adaptive behaviour (VABS) Cognitive skills (various)	Adaptive behaviour score 90.56 (SD 12.86). Auditory and visuomotor skills were impaired.	No difference in adaptive behaviour vs a late onset epilepsy group (n=8, 6-8y). Different pattern of impairment between ages suggests epilepsy onset at different periods interferes with different developing functions.

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of studies reported mean IQ/DQ/GQ scores in the borderline, or impaired ranges, or they reported moderate-high percentages of children with developmental impairment. Secondly, developmental profiles differed between syndromes in severity and extent, suggesting some syndromes are more at risk than others. Finally, behaviour problems and other developmental or cognitive skills (e.g. attention or visuomotor skills) were apparent, when investigated. Of the studies applying DSM criteria, behaviour problems were identified in 8-80% depending on syndrome studied (Cappelletti et al., 2015; Hirano et al., 2009; Jambaque et al., 1991; Ohtsu et al., 2008). Although no control groups were available for comparison, these figures are considerably higher than the estimated prevalence of 6-7% in the general preschool-age population (Niemczyk et al., 2015; Wichstrom et al., 2012). These were found to be present despite preserved IQ or adaptive functioning (e.g. Masur et al., 2013; Gonzalez et al., 2014), suggesting that difficulties in early-onset syndromes are multi-dimensional. The main outcomes of the early-onset-related syndromes are summarised below.

Dravet Syndrome is a well-documented epileptic syndrome associated with severe long-term developmental regression and intellectual impairment. Studies reviewed here showed a clear pattern of age-related developmental decline over the first five years of life, typically after age two or three years. Four of seven studies were conducted by Chieffo and colleagues (Chieffo et al., 2011b; Chieffo et al., 2011c; Ragona et al., 2011; Ricci et al., 2015), using overlapping cohorts. They showed that Dravet Syndrome presents with normal intellectual development during the first two years of life followed by progressive cognitive decline. Although this may be debatably regarded as developmental stagnation rather thean decline. Borderline cases of Dravet Syndrome (i.e. children with severe myoclonic epilepsy in infancy without myoclonic seizures or atypical absence seizures) often present with an absence of gross motor dysfunction and later cognitive stagnation compared to non-borderline cases (Chieffo et al., 2011a). Visuo-motor dysfunction may be a universal feature of the syndrome, even during late development of the syndrome (Ricci et al., 2015). The pattern of age-related cognitive stagnation was supported in two other single-centre studies (Nabbout et al., 2013; Wolff et al., 2006b). Age-related increases in behavioural difficulties, as measured by the SDQ, were also reported (Brunklaus et al., 2011), although it is unclear what the precise nature of those difficulties entailed. Hyperactivity and attention deficit was noted between ages 2 and 5 in one study (Nabbout et al., 2013).

Childhood Absence Epilepsy (CAE) peaks between the ages of 5-7 years, and is associated with normal intellectual development, although subtle neuropsychological and behavioural difficulties have been reported (Caplan et al., 2008). Two multi-centre studies with data gathered on 119 children with early-onset CAE (onset <3 years) were included for review here (Masur et al., 2013; Verrotti et al., 2011). Verrotti et al. (2011) reported normal IQ in eight of nine children. Similarly, Masur et al. (2013) found normal IQ (M=97.6, SD=16.2) in a larger sample of 110 children. However, Masur et al. also noted that 17% of children ≤5 years had attentional difficulties, as assessed by the KIDDIE Continuous Performance Test. Interestingly, poor attention was evident at study entry, prior to antiepileptic drug (AED) treatment.

Tuberous sclerosis complex (TSC) is an autosomal disorder often accompanied by epilepsy. Approximately 45% of children with TSC have intellectual impairment, which is strongly associated with the presence of epilepsy (Joinson et al., 2003). Two papers reviewed here, describing 23 children with TSC and early-onset epilepsy, support that assertion (Jambaque et al., 1991; Kotulska et al., 2014). Three quarters of the samples were found to be intellectually impaired, often severely so.

Benign Myoclonic Epilepsy of Infancy (BMEI) is a rare idiopathic generalised form of epilepsy occurring before age three. The two studies reviewed here both reported mean IQ in the borderline range, between three and five years of age (Auvin et al., 2006; Mangano et al., 2005a). There was a notable decline between DQ (1-3 years of age) and IQ at 3-5 years, in a longitudinal follow-up assessment (Mangano et al., 2005b), suggesting developmental stagnation. Additionally, two children displayed language impairment and two had visuomotor deficits in that study.

The remaining five studies had modest sample sizes and described six different syndromes with variable outcome measures. One study included both Panayiotopoulos Syndrome and Benign Epilepsy with Centrotemporal Spikes (BECTS) (Ohtsu et al., 2008). It is impossible to draw firm conclusions for each syndrome based on a very limited pool of studies. However, from the available data, it was evident that developmental and behavioural profiles differed across syndromes, and in many cases adversely so. Specifically, IQ was in the normal range in those with epilepsy and Sturge-Weber syndrome (Alkonyi et al., 2011), while GQ was in the borderline range in PCDH19-related epilepsy (Cappelletti et al., 2015). All those with PCDH19-related epilepsy (n=5) also had language delay, and ASD or attention difficulties. 8% of children with Panayiotopoulos Syndrome (Ohtsu et al., 2008), 66% with atypical Panayiotopoulos

Syndrome (Hirano et al., 2009), and 21% with early-onset BECTS (Ohtsu et al., 2008) had developmental or behavioural problems. Lastly, adaptive behaviour was in the normal range in children with symptomatic generalised epilepsy, but as a group, children had visuoperceptive and auditory deficits (Gonzalez et al., 2014).

(iv) Surgical Cohorts

Fourteen papers meeting inclusion criteria were identified that described series of patients undergoing epilepsy surgery (table 1.4). All represent case series from single centres, with the largest cohort being 55 patients by Jonas et al. (2005). The majority of papers described a mixed case load of children with any symptomatic epilepsy occurring in the first years of life who received resective surgical treatment for epilepsy. Four papers described cohorts of children with symptomatic infantile spasms, and there were single papers describing series of children with focal cortical dysplasia (Tanaka et al., 2004), and hemimegalencephaly (Battaglia et al., 1999a). No studies included a control group for comparison.

A number of tools were used for neuropsychological assessment. The most common was the Bayley series (five studies), but several studies calculated a DQ for each patient and used this to combine results from multiple different types of assessment. Many papers tried to assess improvement in cognition following surgery but varying follow-up times and general low methodological quality of the studies make comparison and drawing definitive conclusions difficult. Nevertheless, some broad conclusions can be drawn.

Children receiving neurosurgical treatment for epilepsy within the first five years of life are highly likely to be impaired. Mean cognitive scores lie over three standard deviations below population norms regardless of assessment tool, although isolated patients are reported with relatively preserved cognition. There is little evidence of improvement in DQ following surgery, regardless of seizure outcome; although several papers highlight that children subjectively improve and start learning new skills, with improvement in their raw scores; in each case this parallels their increasing chronological age.

This group of children is comprised of severe, medically refractory epilepsy, and may have considerable intellectual morbidity from ongoing seizure activity and aetiological antecedents. That they show severely impaired development is not surprising, but establishing the degree.

Table 1.4 Studies of Surgical Cohorts

Author (year)	N	Type	Outcome (tool)	Surgery age, m, Mean (SD)	Follow-up age, m, Mean (SD)	Pre-surgery findings	Post-surgery findings (≤5y)	Commentary
Caplan et al. (1992)	8	IS	Non-verbal Communication (ESCS) Language Age (REEL)	13.5 (7.7)	28.8 (12.3)	Social interaction M=0.03 (SD 0.05) Language age M=6.25m (SD 8.8)	Social interaction M=0.12 (SD 0.02) Language age M=8.53m (SD 10.16)	Significant increase in post-surgery communication scores but as expected for increasing age
Asarnow et al. (1997)	24	IS	Adaptive Behaviour (VABS)	20.0 (15.0)	46.4 (16.5)	n/a	1 child in normal range (>85), 3 borderline (68-85), and 20 with moderate-severe impairment (<67)	Significant improvement two years post-surgery
Caplan et al. (1999)	29	IS	Non-verbal Communication (ESCS) Adaptive Behaviour (VABS)	18.2 (11.5)	24.3 (17.8)	All children had below normal non-verbal communication	Social interaction improved ($p<.001$) but remained below normal. No improvement in joint attention.	Post-surgical improvement in social interaction was restricted to right-sided resection.
Iwatani et al. (2012)	6	IS	DQ (TIDS or KSPD)	15 (5.7)	31.4 (12.4)	Mean DQ=35.6 (SD 9.1)	Mean DQ=33.4 (SD 8.9)	4/5 patients diagnosed with ASD
Lee et al. (2014)	13	IS	DQ & SQ (BSID)	23.0 (10.3)	32.7 (14.4)	n/a	Mean difference in DQ= -3 (SD 6.0; $p=.055$), and SQ= 15.0 (SD 9.1; $p<.05$)	Social developmental improved post-surgery but DQ unchanged

BSID Bayley Scales of Infant Development
DQ - Developmental Quotient
ESCS: Early Social Communication Scales
FCD – Focal Cortical Dysplasia
HME – Hemimegalencephaly
KSPD - Kyoto Scale of Psychological development
REEL – Receptive Emergent Language Scale
SIE – Symptomatic Infantile Epilepsy
SQ - Social Quotient
TIDS - Tsumori-Inage Developmental Scale
VABS - Vineland Adaptive Behaviour Scale
WPPSI – Wechsler Preschool and Primary Scales of Intelligence

Table 1.4 continued

Author (year)	N	Type	Outcome (tool)	Surgery age, m, Mean (SD)	Follow-up age, m, Mean (SD)	Pre-surgery findings	Post-surgery findings (≤5y)	Commentary
Jonas et al. (2005)	55	SIE	Adaptive Behaviour (VABS)	42.1 (44.8)	36 (4.8)	Composite= 39.2 (23)	Composite: 41.2 (19). 53% of children had increase in scores.	Better VABS scores associated with earlier surgery, shorter epilepsy duration, and treated hypsarrhythmia in IS cases
Loddenkemper et al. (2007)	24	SIE	DQ (BSID/BSID-II)	Median 12 (3-33)	Median 24 (10-53)	Median 37 (0-92)	Median 49 (2-92)	Modest post-surgical improvement. Improvements associated with younger age at surgery and epileptic spasms
Lettori et al. (2008)	19	SIE	DQ (Griffiths/ Uzgiris-Hunt)	26.1 (19.8)	109 (40)	Mean DQ= 41.8 (SD 18.2)	Mean DQ= 39.7 (SD 17.8)	2 patients showed significant (>10 points) improvement in DQ at follow-up
Roulet-Perez et al. (2010)	11	SIE	DQ (BSID-II)	34.5 (19.4)	2-6y	Mean DQ= 42.8 (SD 21.4)	Mean DQ= 50 (SD 13.8)	4 children showed increase of >10 DQ points, little further gains after 2 years follow-up
van Schooneveld et al. (2011)	17	SIE	DQ (BSID/BSID-II)	17.8 (11.8)	>2 years	Mean DQ= 38.4 (SD 18.7)	Mean DQ= 37.0 (SD 26.7)	DQ extrapolated from developmental delay figures. Resumption of development post-op but no catch-up

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Table 1.4 continued

Author (year)	N	Type	Outcome (tool)	Surgery age, m, Mean (SD)	Follow-up age, m, Mean (SD)	Pre-surgery findings	Post-surgery findings (≤5y)	Commentary
Dunkley et al. (2011)	23	SIE	DQ (Griffiths/BSID/ Clinical estimate)	20 (3-36)	63.5 (27-158)	Normal DQ (>75) in 5, mild-moderate impairment (55-75) in 2, and 16 severely impaired (<55)	2 children improved, 5 declined (15 point decrease) Normal DQ in 1, mild-moderate impairment (55-75) in 3, and 19 severely impaired (<55)	No correlation between seizure freedom and improved developmental outcome
Ramantani et al. (2013)	30	SIE	Various	20 (5-33.6)		Normal (IQ ≥70): 7 Moderate (IQ 50-69): 3 Severe (IQ <50): 18		Long-term follow-up (1-9y post-surgery): Normal (IQ ≥70): 3 Moderate (IQ 50-69): 3 Severe (IQ <50): 22
Battaglia et al. (1999a)	19	HME	DQ/IQ (Uzgiris-Hunt/WPPSI)	27 (5-60)	45.8 (13.3)	Mean DQ/IQ= 41.84 (SD=17.74). 18/19 had DQ/IQ <70		At long-term follow-up (8.9 (3-15) years), mean DQ/IQ was 39.79 (SD=17.32).
Kimura et al. (2014)	11	FCD	DQ (Tanaka-Binet)	37.1 (15.3)	93.1 (29.5)	Mean DQ= 50.0 (26.3)	Mean DQ= 50.8 (28.8)	No mean change in post-surgical DQ

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of impairment in these cohorts compared to other groups of children with early onset epilepsy provides weak evidence that outcomes of symptomatic epilepsies themselves are worse

1.3.3 Systematic Review: Discussion

The aim of this review was to extract and synthesise psychometric data on the neurobehavioural characteristics of CWEOE during the first years of life. Of the 52 studies meeting criteria for review, only six described a general CWEOE cohort. The majority of the articles reviewed (32) focused on specific early-onset syndromes - most notably, infantile spasms and Dravet Syndrome. The remaining fourteen described surgical candidates. These three populations represent a minority of the early-onset epilepsy population. Infantile spasms accounts for 6-11% of cases in children ≤5 years (Dura-Trave et al., 2007; Wirrell et al., 2011), whilst Dravet Syndrome and epilepsy surgery occur in an even smaller number of patients (Neligan et al., 2013; Wu et al., 2015). Therefore, it was impossible to build a complete neurobehavioural profile of CWEOE, the benefits for which have been argued earlier.

In terms of the prevalence of cognitive impairment in general CWEOE cohorts, a wide range of 33-91% of children was reported. This data came from a limited number of studies with several stemming from potentially biased population sources; namely children <1 year of age, and children referred to tertiary centre settings. Thus, the true prevalence across the early-onset period may present a different picture. A relevant series of studies by Rantanen and colleagues (Rantanen et al., 2009; Rantanen et al., 2010b; Rantanen et al., 2011) is of notable mention. Rantanen et al. described cognitive and social-behavioural aspects in a population-based sample of children aged 3-6 years in Tampere, Finland. The authors found impaired intellectual development in 50% of children with established epilepsy, and an increased indication of subtle social-behaviour difficulties, particularly in children with 'complicated' epilepsy (i.e. symptomatic aetiology and/or neurological abnormality). Although well within the range reported in the current review, this study included children with established epilepsy, and as such, other factors such as chronic seizure and chronic AED use may have played a role.

The age at which data is collected is an important factor when considering the true prevalence of impairment. In population-based studies, cognitive impairment is estimated in 21-41% of children 0-16 years, and 31-43% in children ≥5 years (Hoie et al., 2005; Reilly et al., 2014a; Sillanpaa, 1992; Waaler et al., 2000). It is possible these figures have been diluted by children whose onset began before or after 5 years of age, thereby masking the impact of age of onset.

When age of onset is considered, the prevalence of impairment may be more age biased. In their community-based study of persons aged ≤29 years, Berg et al. (2008) found subnormal cognition in 33.4% of persons whose onset began 0-5 years, and 11.2% in those with onset 5-16 years. Taken together with the data presented above, the evidence potentially suggests a higher prevalence of cognitive impairment in CWEOE compared to later onset epilepsy. Nevertheless, a baseline estimation of cognitive impairment in approximately 1/3rd of CWEOE is not unreasonable. Further data from CWEOE cohorts are required. As yet, there is no population-based study, or otherwise, that has reported the prevalence of cognitive impairment or behaviour problems *during* the early-onset age period, and at the beginning of the disease. It is important to mention that the relationship between age of onset and cognitive impairment may vary *within* the early-onset period (Reilly et al., 2014a), and further studies are needed to establish age-specific risk in CWEOE.

Our findings in children with Dravet Syndrome echo that of earlier reviews (Ceulemans et al., 2004; Incorpora, 2009). That is, normal development before the age of two with stagnation from age three. Two of the longitudinal studies reviewed also noted stable and low DQ/IQs after the age of five (Nabbout et al., 2013; Wolff et al., 2006a), consistent with other reports. In children with CAE, earlier-onset CAE (<3 years) has been associated with less favourable cognitive and behavioural outcomes, albeit in a small sample of children, many of whom had poor seizure control (Chaix et al., 2003). Evidence from two studies of earlier-onset CAE reviewed here did not support that conclusion (Verrotti et al., 2011; Masur et al., 2013), with one consisting of a large cohort of 110 children with CAE, although a high prevalence of attention problems were noted indicating the presence of subtle deficits (Masur et al., 2013). There was little difference in performance between children below or above six years of age in the latter study, suggesting earlier-onset CAE may provide no further risk to cognitive status than typical onset.

Studies describing developmental outcome in infantile spasms are often estimated from clinical observation and/or medical review. The results from studies using standardised tools in this review were comparable. For example, a population-based study by Lúthvígsson (1994) reported the number of infantile spasms children developmentally impaired, based on medical record review, at 54%. This was similar to the figure of 40-60% found in the current review. Similarities in estimation are presumably due to the severity of psychomotor impairment apparent upon clinical presentation. A much lower figure of developmental/cognitive impairment of 24% was reported from a large multi-centre series of those with infantile spasms

by adulthood (Riikonen, 2001b). In that study, 31% of patients died over the course of follow-up, with the vast majority of those who died having previous intellectual impairment. This suggests that the difference in prevalence observed in that study may be a result of death rather than intellectual improvement in children with infantile spasms. Thus, there appears to be relative stability in impaired cognitive functioning with age. Follow-up data from the studies in this systematic review suggest that children with cryptogenic/unknown aetiologies have more favourable outcomes. A similar finding is echoed in long-term follow-up studies (Luthvigsson et al., 1994; Karvelas et al., 2009; Kivity et al., 2004; Montenegro et al., 2008; Oh et al., 2010).

It is evident from the articles reviewed here that impaired development *is* detectable in CWEOE, and is not uncommon. However, the spectrum and prevalence of neurobehavioural problems remains unclear, particularly in the general CWEOE population. There was a clear dearth of information on behavioural problems with most studies limited to cognition or adaptive behaviour, commonly used as an indicator of general development. Whilst behaviour problems are commonly recognised in school-age children with epilepsy (see Besag, 2004; Caplan and Austin, 2000; Dunn and Austin, 2004; Ekinci et al., 2009; Hamiwka et al., 2011; Otero, 2009; Plioplys et al., 2007; Rantanen et al., 2012; Reilly et al., 2013; Reilly et al., 2011; Rodenburg et al., 2005; Verrotti et al., 2014, for reviews), much less is understood about the spectrum and prevalence of behaviour in CWEOE. This is despite the fact that behavioural problems are detectable and common during the preschool period (Poulou, 2015).

The studies reviewed provided little information on the risk factors for neurobehavioural problems in CWEOE. From the available evidence, the occurrence of comorbid neurobehavioural problems seem to be related to aetiology, or epileptic syndrome. Dravet Syndrome and infantile spams were two syndromes particularly at risk, whilst those with structural causes for their epilepsy, including infantile spasms and surgical candidates, had a higher prevalence of problems than those with unknown causes. Development in idiopathic epilepsies was more favourable, although neurobehavioural problems could still present. Sociodemographic and epilepsy-related risk factors were rarely addressed in the studies reviewed. There were insufficient data on the effect of socioeconomic status, gender or geographical differences, whilst epilepsy-related variables received occasional mention. Of the six studies on general CWEOE cohorts, only two included information on epilepsy-related variables (Berg et al., 2004; Vendrame et al., 2009). When one considers reported risk factors

for neurobehavioural problems in children with epilepsy across all age groups (section 1.4), these have not been robustly examined as risk factors in CWEOE.

This review highlights the need for high-quality population-based studies investigating the neurobehavioural profile of CWEOE. That is, the need to identify the prevalence and spectrum of neurobehavioural problems, particularly including behavioural data. There is also a need to identify risk factors for neurobehavioural problems. To determine which risk factors need to be evaluated in CWEOE, the following section will briefly review the possibilities.

1.4 Neurobehavioural Problem Risk Factors in Children with Epilepsy of All Ages

Brain abnormality is a clear risk factor of neurobehavioural problems. Cognitive impairment and behaviour problems are strongly and consistently associated with neurological disorders (Camfield and Camfield, 2007; Davies et al., 2003; Ellenberg et al., 1986; Rutter et al., 1970; Steffenburg et al., 1995), complicated epilepsy (i.e. IQ<70 or 80, and a structural brain lesion or neurological problem; (Berg et al., 2008; Berg et al., 2011a; Rantanen et al., 2011; Rutter et al., 1970), and structural/symptomatic epilepsy (for an explanation of aetiological classifications see section 2.4.2), with more favourable outcome in children with idiopathic/unknown aetiology (Berg et al., 2008; Hoie et al., 2005; Park et al., 2013). In other words, impaired cognition and behaviour problems are associated with brain abnormalities as identified via clinical examination or clinical brain imaging. Research based MRI studies have found abnormalities at the macro and micro structural level, where neurobehavioural problems have been associated with brain volumes, white matter integrity, and functional differences, across epilepsy syndromes (see Addis et al., 2013; Hermann et al., 2009; Braakman et al., 2012; Yoong, 2015). Brain abnormalities are also evident in non-lesional localisation-related epilepsies (Widjaja et al., 2013), and idiopathic generalised epilepsies (Betting et al., 2006; Chan et al., 2006; Pulsipher et al., 2011), which have been associated with cognitive deficits (Lin et al., 2013; Pulsipher et al., 2009; Tosun et al., 2011) – indicating that cognitive deficits can be apparent in otherwise clinically normal brains, and non-structural-related epilepsies.

Epilepsy-related variables are inconsistently linked to neurobehavioural problems. The most robustly linked factors are having a diagnosis of an epileptic encephalopathy and seizure intractability (Smith et al., 2002), with up to 70% of surgical candidates evidencing cognitive impairment (Van Schooneveld and Braun, 2013). Epileptic encephalopathies are epileptic syndromes where the epileptic activity itself contributes to severe cognitive and behavioural

impairment above that caused by the underlying pathology alone (Berg et al., 2010). Infantile spasms, Dravet Syndrome, and Lennox-Gastaut Syndrome, for example, are all associated with poor and often severe developmental outcomes (Khan and Al Baradie, 2012; Neville, 1997; Shields, 2000). Epileptic encephalopathies are characterised by gross EEG abnormalities, reflective of underlying aberrant neuronal activity. In non-encephalopathic epilepsies, and in children without epilepsy, abnormal epileptiform and non-epileptiform (i.e. slow wave) EEG recordings have been associated with both temporary and long-term adverse cognitive and behavioural outcomes (Aldenkamp and Arends, 2004; Clarke et al., 2001; Massa et al., 2001; Mulligan and Trauner, 2014). This suggests that abnormal EEG is a potential risk factor for neurobehavioural problems.

It is unclear if seizures themselves, chronicity of seizures, or high frequency of seizures represent increased risk for cognitive impairment or behavioural problems. One would expect cognitive decline in children with chronic epilepsy if seizure activity had a cumulative and damaging effect on the brain. However, reviews of longitudinal studies in childhood epilepsy provide mixed findings (Dodrill, 2004; Seidenberg et al., 2007). Vingerhoets (2006) reviewed longitudinal and cross-sectional studies, finding that while IQ remained relatively stable across time in longitudinal studies, it was only subsets of children (11-24%) who had evidence of cognitive decline. The frequency of seizures was inconsistently associated with decline. Indeed, seizure frequency may play a less significant role once other factors such as aetiology are considered (Park et al., 2013). The case for single or repeated prolonged seizures (>30 minutes) may be stronger. Martinos et al. (2012; 2013) reported cognitive deficits in children with at least one episode of convulsive status epilepticus, but also in children with a single prolonged febrile seizure without epilepsy.

AEDs have been associated with adverse cognitive and behavioural effects, although only limited studies exist on newer generation AEDs, and studies are often fraught with methodological limitations making findings inconclusive or tentative (Caplan, 2012; Eddy et al., 2012; Ekinci et al., 2009; Lagae, 2006; Loring and Meador, 2004). There is a general consensus however, that multiple AED use, termed polytherapy, is more detrimental to cognitive functioning than monotherapy (Aldenkamp and Bodde, 2005; Hermann et al., 2010; Mula and Trimble, 2009).

Non-epilepsy related variables including gender, socioeconomic status (SES), and familial factors have been variably linked to neurobehavioural problems. Gender differences in

cognitive performance and behaviour are uncommon but have been reported (see Menlove and Reilly, 2015; Ekinci et al., 2009; Otero, 2009; Reilly et al., 2011). In the general population, behaviour and cognition are robustly associated with SES (Bradley and Corwyn, 2002), including those with intellectual disability or chronic health conditions (Emerson and Hatton, 2007; Gortmaker et al., 1990). In childhood epilepsy however, SES has not been robustly linked to behaviour problems (Ekinci et al., 2009; Plioplys et al., 2007) (c.f. Carson et al., 2015), or cognitive functioning (Hoie et al., 2005; Hoie et al., 2006). Adverse familial and child factors, however, are more consistently associated with neurobehavioural problems, particularly depression. These include maladaptive parenting styles and parent-child relationships (Carlton-Ford et al., 1997; Hoare and Kerley, 1991; Austin et al., 1992; Mitchell et al., 1994; Rodenburg et al., 2006), negative perceptions and sense of control over epilepsy and behaviour problems (Austin and Huberty, 1993; Austin et al., 2004; Dunn et al., 1999; Plioplys, 2003), family stress (Adewuya and Ola, 2005; Dunn et al., 1999; Oostrom et al., 2001; Pianta and Lothman, 1994), and the effect of stigma (Adewuya and Ola, 2005; Dunn et al., 1999; MacLeod and Austin, 2003). Psychopathology in the parent is associated with behaviour problems in the child (Hoare and Kerley, 1991; Lothman and Pianta, 1993; Shore et al., 2002; Shore et al., 2004), but this is not always supported (Baki et al., 2004).

In summary, a number of epilepsy and non-epilepsy related variables have been associated with neurobehavioural problems in children with epilepsy of all ages, with some variables more strongly associated than others. The relationship between these variables and neurobehavioural problems specifically in CWEOE remains unknown and requires direct investigation.

1.5 Biological/Cognitive Markers of Neurobehavioural Problems

In the previous section it was shown that neurobehavioural problems were variably associated with epilepsy- and non-epilepsy-related risk factors. Whilst these relationships can provide insight into neurobehavioural problems, there is a need for more robust markers of neurobehavioural problems in children with epilepsy. Recently, the ILAE-IBE joint task force (Baulac et al., 2015) have advocated the development of biomarkers that could allow the early-identification of those at risk of severe cognitive impairment. It would also be advantageous to develop markers that could detect both cognitive impairment and behavioural problems at epilepsy onset.

As reported previously, brain imaging studies have linked MRI abnormalities with cognitive impairments, suggesting that MRI might provide a readily available biomarker. Additionally, studies have reported cognitive and behavioural problems at, or before, the onset of epilepsy (Austin et al., 2001; Dunn et al., 2002; Hesdorffer et al., 2004; Hermann et al., 2006; Hermann et al., 2007b; Oostrom et al., 2003; Oostrom et al., 2005; Jones et al., 2007), with associated neuroanatomical differences (Pulsipher et al., 2011; Lin et al., 2012b; Tosun et al., 2011) - suggesting that these neuroanatomical abnormalities might underlie both epilepsy and neurobehavioural problems. To date, there are no brain imaging studies focused on neurobehavioural problems on CWEOE (Yoong, 2015), and requires attention.

MRI does, however, have its limitations in its application to the general epilepsy population, not all of whom will receive brain imaging in the course of regular care. MRI requires expensive machinery, and technical speciality in its application, maintenance, and interpretation. Alternative technologies are therefore advantageous. Eye-tracking is one possible alternative, which has the potential to provide fast and cost-effective assessment. Eye-tracking technology assesses eye-gaze behaviour through the use of visual attention paradigms. Eye-gaze behaviour itself reflects underlying neuropsychological processes, and neurological correlates of cognition. It has been widely used to aid the understanding of visual attention and neurodevelopment (Boraston and Blakemore, 2007; Duchowski, 2007; Karatekin, 2007). Eye-gaze behaviour can be indicative of cognitive impairment (Rose et al., 2005), or behaviour problems (e.g. ADHD; Tseng et al., 2013) in children, and has been extensively used in children with ASD (Ames and Fletcher-Watson, 2010; Falck-Ytter et al., 2013; Karatekin, 2007), highlighting its application in clinical populations.

A major advantage of using eye-tracking in the investigation of neurobehavioural comorbidities in CWEOE is that paradigms can be developed which are not reliant on verbal instruction. This makes the technology accessible to non-verbal populations such as infants, toddlers, and preschool children, where it has widely been employed. It may also be advantageous to children with common disorders associated with epilepsy, such as communication disorders, and developmental disabilities. As young children and developmentally delayed children may otherwise be unable to complete standardised neuropsychological assessments, it provides a promising means of identifying those with, or at risk of, neurobehavioural problems. Therefore, it may be valuable to explore eye-tracking as a marker of neurobehaviour in CWEOE.

1.6 Summary, Scope, and Aims of the Study

It was argued in this introduction that early-onset epilepsy is a risk factor for neurobehavioural problems, particularly cognitive impairment, and that the risk for neurobehavioural problems may be potentially greater than that of later onset epilepsies. However, the evidence presented in the systematic review of CWEOE identified a clear lack of representative data on the prevalence, spectrum, and risk factors of neurobehavioral problems. It was reasoned that information on neurobehavioural problems in CWEOE are of crucial importance for several reasons. Firstly, neurobehavioural problems are impairing, even beyond the impact of seizures themselves, which has prompted calls from the scientific community for further research into these epilepsy related comorbidities. Second, the immature brain is particularly vulnerable to adverse events, and the early years are a period of rapid neural and psychological development where new skills are being learned and foundations are laid for future skill acquisition. It is imperative to understand the potential impact to cognitive and behavioural functioning after disruption by epilepsy during this critical time of development. Third, should neurobehavioural problems be present and detectable, then there is the need to identify risk factors for those problems, particularly if the prevalence is high. Data on risk factors of children with epilepsy of all ages has received more attention, yet it is unknown if risk factors for problems are different in CWEOE. Fourth, accurate data is needed to better inform policy makers on the planning of early interventions, and toward the delivery of targeted health, social, and educational resources. Lastly, there is also a need to identify biological or cognitive markers which could allow rapid and early detection of neurobehavioural problems in children with epilepsy.

Thus, the research reported in this thesis was primarily concerned with determining the neurobehavioural profile of CWEOE - defined here as the quantitative representation of neurobehavioural characteristics, including distributions of assessment scores and prevalence of problems, as determined by psychometric tests. To meet this aim, the study recruited a population-based sample of CWEOE. An incidence based cohort was preferred, as this allowed a closer appraisal of the true burden of epilepsy than a prevalent sample (further explanation is described in section 2.2). Thus, a secondary main aim of the study arose, which involved the estimation of the incidence of early-onset epilepsy. The third main aim of the study was to explore eye-tracking, using selected eye-tracking tasks, as a potential cognitive marker of neurobehavioural problems. To summarise, this thesis addressed three main aims: (1) to estimate the incidence of early-onset epilepsy, (2) to determine the neurobehavioural profile

of CWEOE, and (3) to explore eye-gaze behaviour (via eye-tracking) as a marker of neurobehavioural problems in CWEOE.

The central hypothesis of this study was that CWEOE would have an abnormal neurobehavioural profile compared to the general population. That is, poorer cognitive functioning and more problematic social-emotional behaviour compared to controls, as well as having a greater prevalence of neurobehavioural problems. It was expected that the epilepsy- and non-epilepsy-related risk factors would have a similar relationship to that of older children as reported in the scientific literature. It was also expected that children with neurobehavioural problems would be identified by the selected eye-tracking tasks.

There were limitations on the scope of this study, which meant several factors alluded to in the introduction could not be directly addressed, and which deserve mention here. First, it was suggested that CWEOE may be at greater risk of neurobehavioural problems than later childhood onset epilepsy. This question requires direct focus using younger and older childhood onset epilepsies, and as the thesis was focused on determining the neurobehavioural profile of CWEOE, this could not be directly assessed. Second, brain imaging was identified as a potential biological marker of neurobehavioral problems in children with epilepsy. However, quantitative MRI was not explored by the candidate due to the additional time and expertise required. Quantitative MRI markers, including T1 and T2 weighted images, and diffusion tensor imaging, were undertaken by Dr Michael Yoong in a sibling project entitled "Biomarkers in early-onset epilepsy" using the same cohort of children as the current study. Instead, qualitative MRI classifications were included as a risk factor variable in the present study. Lastly, this study focused on quantitative epilepsy-related and sociodemographic variables in the study of risk factors. Familial risk factors, which have a robust association with behavioural problems were not studied. This particular variable requires focused attention, including assessment of parent and family relationships.

1.7 Thesis Overview

As outlined above, this study is characterised by three main aims, and this thesis is structured according to those aims. Chapter II describes the identification and recruitment of CWEOE onto the study, including descriptive statistics of the cohort, and an estimation of the incidence of early-onset epilepsy. Chapter III details the methods of neurobehavioural assessment, and presents the findings of that assessment by describing the neurobehavioural profile of CWEOE

and controls, as well as determining the risk factors for neurobehavioural problems in CWEOE. Chapter IV introduces eye-tracking and its application in the exploration of neurobehavioural problems. It details the results of selected eye-tracking tasks in exploring eye-gaze behaviour in CWEOE compared to controls, and toward identifying neurobehavioural problems in CWEOE. Chapter V concludes this thesis by summarising the findings of this study, and offering suggestions for future research. Prior to these chapters, the remainder of chapter I describes study methods common to all chapters.

1.8 Unique Contributions of the Study

This study provides a number of unique contributions to the scientific literature including;

(1) The first population-based study of the incidence, sociodemographic, and clinical features of early-onset epilepsy (onset ≤4 years of age) in the UK.

(2) The first population-based, case-control study of the prevalence, spectrum and risk factors for neurobehavioural problems in CWEOE.

(3) The first case-control study to examine eye-gaze behaviour as a marker for neurobehavioural problems in CWEOE.

2. General Methods

2.1 Overview

NEUROPROFILES is a prospective, population-based, case-controlled, observational study, primarily aimed at estimating the incidence of early-onset epilepsy, determining the neurobehavioural profile of recently diagnosed CWEOE (to remind the reader, onset ≤4 years of age), and the exploration of eye-gaze behaviour as a marker of neurobehaviour. The following subsection lists the primary aims and associated research questions for each chapter. The remainder of the general methods section describes methods relevant to all chapters of this thesis.

2.2 Chapter Aims and Primary Research Questions

Chapter II. Incidence of Early-Onset Epilepsy in Fife and Lothian

Main aims: To estimate the incidence of early-onset epilepsy, describe the clinical and sociodemographic characteristics, and in doing so, obtain a population-based CWEOE cohort.

Primary research Question: What is the incidence of, and risk factors for, early-onset epilepsy in Fife and Lothian?

Chapter III. The Neurobehavioural Profile of Children with Early-Onset Epilepsy

Main aims: To understand the neurobehavioural burden of epilepsy by determining the neurobehavioural profile (i.e. distribution of cognitive and behavioural scores, and the prevalence and spectrum of cognitive impairment and behaviour problems) of the population-based sample of CWEOE, in contrast to a control sample, and to identify the risk factors for neurobehavioural problems identified.

Primary Research Questions: What is the neurobehavioural profile of CWEOE compared to control children; and what are the risk factors associated with neurobehavioural problems identified?

Main aims: To explore differences in eye-gaze behaviour between CWEOE and controls, and to assess eye-gaze behaviour as a means of predicting neurobehavioural problems in CWEOE. The inclusion criteria for this aim was broadened to also include children outwith the defined population-based region. This aim did not require a population-based sample, as it explored the identification of neurobehavioural problems, not the distribution of problems within a population.

Primary Research Questions: Is eye-gaze behaviour different in CWEOE compared to controls; and, amongst CWEOE, does eye-gaze behaviour differentiate between those with and without neurobehavioural problems?

2.3 Project Development

2.3.1 Methodology: Development of the Study Methods

The systematic review in the introduction revealed that most studies investigating cognition and behaviour in CWEOE used hospital-based cohorts and/or specific early-onset syndromes, and thus may provide biased information. To obtain data on the general population, a population-based approach was preferred since these have greater external validity while reducing selection bias (Szklo, 1998). Applying a case-controlled element to the study allowed the findings to be contrasted against a healthy peer group, and increase the validity of those findings.

An incidence cohort was chosen for study, as opposed to, or in addition to, a prevalence cohort, based on the following theoretical and practical reasons: (1) data gathered from an incidence cohort offers a more accurate reflection of the burden of epilepsy, compared to a prevalence cohort, as the data are not influenced by epilepsy remission or death rates; (2) combined with a prospective approach, an incidence cohort allowed the assessment of the burden of epilepsy at the beginning of the disease, and which may have reduced the influence of confounding epilepsy related factors, such as the influence of chronic seizures or AEDs; (3) the resources required for both an incidence and prevalence cohort would have been potentially unmanageable based on the available resources. To explain, based on a prevalence of 0.18% (Purcell et al., 2002), and incidence rate of 57-86 per 100,000 children ≤4 years per year in the

UK (Kurtz et al., 1998; MacDonald et al., 2000; Martinez et al., 2009), it was estimated that between 136-162 cases would be identified over the study period. With approximately 6 hours assessment time, scoring, and written feedback, per child, the time demands may have been untenable given the limitations on the use of shared assessment equipment, shared assessment space, and the time available for the candidate to carry out those research activities during the recruitment and assessment phase; and (4) an incidence study allowed the creation of a cohort that could be followed up in future investigations. This is advantageous as the natural history of CWEOE is unknown.

2.3.2 Study Branding

Figure 2.1 Study Logo

In an effort to aid recognisability, communication, and awareness of the study to participants, colleagues, and the scientific community, a study name and logo was created by the candidate. Study branding has well-known influences on consumer behaviour (Girard et al., 2013). The acronym, NEUROPROFILES - **Neuro**development in **Pr**eschool children **O**f **Fi**fe and **L**othian **E**pilepsy **S**tudy – was created. A name brand and logo distinguishes this study from others in a simple and recognisable way by using a meaningful identifier, and increases memory retention for that brand (Kanungo, 1969). The title served to represent the purpose of the study, and the acronym served to make reference to the overall aim of the study, namely, neurodevelopmental 'profiling'.

The logo created is illustrated in figure 2.1. It was designed with children in mind and reflects a simple, child-like drawing of a person. The figure is of neutral-gender to encompass both male and female children, and using the entire body in the picture is meant to be representative of a holistic profile (i.e. the cognitive, social and emotional aspects of development), rather than a narrow perspective.

2.3.3 Research Team

The core research team consisted of: (1) Matthew Hunter, PhD Candidate at The University of Edinburgh, and Honorary Assistant Psychologist with NHS Lothian; (2) Dr Richard F Chin, Senior Clinical Lecturer in paediatric neurosciences, University of Edinburgh, and Consultant

Paediatric Neurologist, Royal Hospital for Sick Children, Edinburgh (RHSC). Dr Chin was the main PhD supervisor and Principal Investigator on the project; (3) Dr Kirsten Verity, Paediatric Neuropsychologist, RHSC, and (4) Dr Ruth Sumpter, Consultant Clinical Psychologist in neuropsychology, formerly of RHSC and now Head of Neuropsychology at the Institute of Neurological Sciences, Queen Elizabeth University Hospital, Glasgow, were also PhD supervisors. They supervised clinical assessment training, and advised on neuropsychological testing, assessment analysis, and aided in the interpretation of test results; (5) Dr Michael Yoong, clinical lecturer at Edinburgh University, was responsible for the analysis of quantitative magnetic resonance and diffusion tensor imaging of the CWEOE and controls.

Additionally, chief collaborators at the relevant NHS boards included: (6) Dr Ailsa McLellan, Paediatric Neurologist, RHSC, and lead clinician for the South East Scotland Epilepsy Network, was key project collaborator for NHS Lothian; and (7) Dr Christopher Steer, Paediatric Neurologist (Ret.), Victoria Hospital Kirkcaldy, Fife, was the key project collaborator for NHS Fife, prior to Dr Jamie Cruden's appointment as Consultant Paediatric Neurologist.

2.3.4 Ethical Approval

Ethics, reference number 13/SS/0031, was granted by the South East Scotland Research Ethics Committee 01 on 18th March 2013, with amendments on 21st May 2013, and 4th December 2013. The first amendment added a consent request for access to routinely stored health and social care data for participants, with a view for longer term follow-up data beyond the current study. A second amendment was added to the original study in order to include Diffusion Tensor Imaging to the protocol, a recently added standard clinical imaging procedure at RHSC, and to recruit children from outside the predefined geographical area, in order to increase the number of participants for eye-tracking. Local Research and Development ethical approval was granted by Research Governance of NHS Lothian (reference number 2013/0013) and NHS Fife (reference number 13-018 NRS13/P61 13/SS/0031). Participant information sheet and consent form can be found in appendices B and D, respectively).

2.4 Definitions

2.4.1 Epilepsy Definition

Epilepsy is conceptually defined as "a disorder characterized by an enduring predisposition to generate epileptic seizures and by neurobiologic, cognitive, psychological and social

consequences of this condition. The definition requires the occurrence of at least one epileptic seizure" (Fisher et al., 2005).

The diagnosis of children in this study was based on the ILAE 2005 (Fisher et al.), and 2014 (Fisher et al.), definitions and criteria of epilepsy. That is, the occurrence of two or more seizures more than 24 hours apart, unprovoked by acute or transient causes, or one unprovoked epileptic seizure with a ≥60% risk or recurrence, or diagnosis of an epilepsy syndrome. All diagnoses were established from clinical history, clinical examinations and investigation findings by a paediatrician/paediatric neurologist with expertise in epilepsy from RHSC, St. John's Hospital, or Victoria Hospital Kirkcaldy, and thus met criteria for "definite" epilepsy (Thurman et al., 2011). This is differentiated from "probable" epilepsy, which does not have *both* documented source evidence of epileptic seizures and a diagnosis from a specialised clinician, or "suspected" cases, which are persons with suspected epilepsy but without the evidence of either of the previously mentioned criteria (e.g. a single ICD code for unspecified seizure). These indicate a lesser degree of reliable evidence supporting the diagnosis of epilepsy (Thurman et al., 2011). Febrile seizures, neonatal seizures, acute symptomatic seizures, or single episodes of status epilepticus were not considered as epileptic seizures.

2.4.2 Epilepsy Classification

Epilepsy type, seizure, and aetiological classification was determined by members of the core research team according to the ILAE Commission on Classification and Terminology 2005-2009 (Berg et al., 2010), as well as the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE, 1989). Classification was made independently by clinicians within the research team and differences in opinion resolved by consensus opinion. At recruitment, children were classified according to the data available, with subsequent review of medical data at the end of recruitment into the study. The final classifications presented in this thesis reflect all available data at the end of the recruitment period, although some children may not have been "classifiable" based on the available data.

CWEOE were classified according to epilepsy type (i.e. syndrome/constellation/type), seizure type (i.e. mode of onset; focal or general), and aetiology. The most recent aetiological classification system was proposed in 2010 by ILAE (Berg et al., 2010), with the previous classification system published in 1989 (ILAE, 1989) (table 2.1). The two aetiological classification systems do not include like-for-like categories, and the newer proposal has

received criticism (Panayiotopoulos, 2011; Shorvon, 2011). The change in classification is likely to impact the current utility of aetiology as a prognostic factor for cognitive and behavioural problems. For example, children with cryptogenic aetiologies are at risk of lower intelligence (Park et al., 2013), yet these same children could now be classified as 'unknown' or 'genetic', which are associated with more favourable cognitive outcomes (Berg et al., 2008; Hoie et al., 2005; Park et al., 2013). Additionally, some syndromes formerly classified as symptomatic could now be classified as genetic, such as Dravet Syndrome, which is associated with unfavourable cognitive outcomes (Ceulemans et al., 2004; Incorpora, 2009). Therefore, for the purposes of this study, patients were classified according to both aetiological classification systems in order to evaluate the predictive value of one system against the other.

Table 2.1 Aetiological Classification Systems

ILAE 1989	ILAE 2010
Idiopathic – No underlying structural or neurological cause identified. Presumably genetic in nature	*Genetic* – The epilepsy is the direct result of a known or presumed genetic cause in which seizures are the core symptom of the disorder
Symptomatic – Epilepsy is the result of a structural lesion in the brain	*Structural/Metabolic* – The epilepsy is the result of a distinct structural or metabolic condition. These conditions may be of acquired or of genetic origin
Cryptogenic/Probably Symptomatic – Believed to be the result of a brain lesion, but which has not been identified	*Unknown* –The underlying cause is as yet unknown or not presumed genetic

ILAE – International League Against Epilepsy

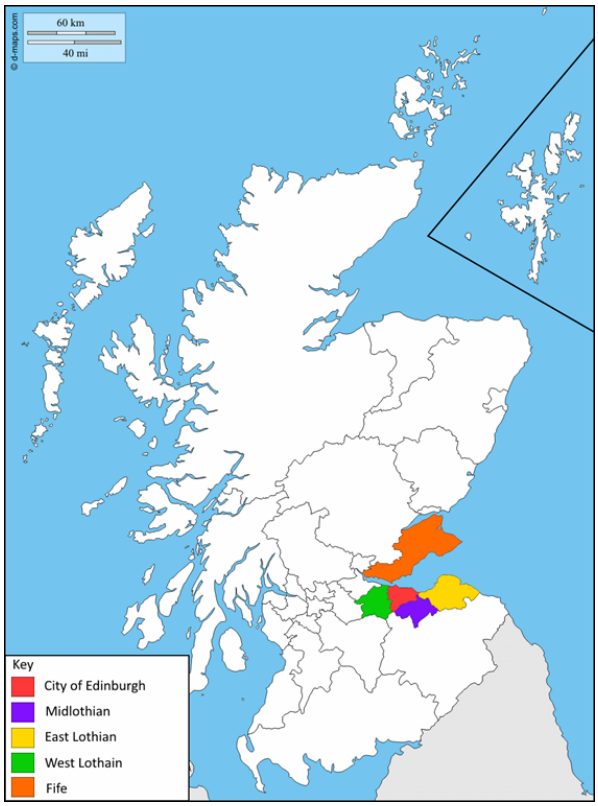
2.4.3 Socioeconomic Status (SES)

SES is the social and economic standing of an individual, group of individuals, or geographic location based on a combination of predefined contributors, such as monetary income, education level, or occupation. A higher SES is considered to be more advantageous. Power and resources available, such as money, health services, and amenities, are all potential contributors to the promotion of health, or may "buffer individuals from detrimental effects of adverse situations and events" (American Psychological Association Task Force on Socioeconomic Status, 2007, p.9). Therefore, SES is an important consideration for assessing risk of epilepsy, or as a mediator or confound of cognition and behaviour.

Social deprivation is a term used to describe the relative inequality of resource provision and access to resources within a population, and can be considered a proxy for well-being. The Scottish Index of Multiple Deprivation (SIMD) is a quantitative tool for assessing the variability in wealth, resources, and environment across geographic locations in Scotland. SIMD provides a relative measure of deprivation across Scotland by ranking predefined geographic areas, called datazones, from least to most deprived. Ranking is based on the weighted sum of seven domains of interest, namely income, employment, health, education, geographic access to services, housing and crime. SIMD allows the comparison of one area in Scotland to another based on their deprivation rank. Ranks range from one to five, where quintile one is the most deprived, and quintile five is the least deprived. SIMD provides a relative measure of deprivation, not an absolute one. SIMD is a Scottish Government initiative with the latest data published in 2012 (http://www.gov.scot/Topics/Statistics/SIMD). Quintile rank for each participant was obtained using resident postal code at time of diagnosis, or study entry if control (http://www.gov.scot/Topics/Statistics/SIMD/SIMDPostcodeLookup).

For the purposes of this study, SES was classified as 'high', reflecting SIMD quintiles 4 and 5, or 'low', reflecting quintiles 1, 2 and 3. Two categories were selected due to modest sample sizes. In the reference population of our defined geography, 37.4% reside in high SES areas, and 62.6% reside in low SES areas.

Figure 2.2 Fife and Lothian Councils



2.5 Participants and Demographics

2.5.1 Population and Geography

Scotland has a population of 5,295,403 people (2011 Scottish Census, http:// www.scotlandscensus.Gov.uk/), and land area of 77, 925 km^2. Fife and Lothian are two densely populated geographic areas of Scotland. Fife is a distinct council region while Lothian is made up of the distinct council regions of City of Edinburgh (herein, referred to as Edinburgh), Midlothian, East Lothian, and

West Lothian (figure 2.2). The regions of Lothian and Fife cover 1,724km^2 and 1,325 km^{2,} respectively, and are comprised of 22.7% of the total Scottish population. They have a similar proportion of children aged 0-4 years (5.9%) as the national structure (5.3%).

Edinburgh, West Lothian, and Fife were selected as the geographic location of our population-based samples. East Lothian and Midlothian were omitted due to logistical reasons. Specifically, a child presenting with seizures in either of these regions may be admitted or managed during the course of diagnosis, at various hospital sites including those outside of the Fife and Lothian region. The method of patient identification, described in the following sub-section, used district hospitals as a primary gateway. Accordingly, we could not be sure of capturing every child in the desired remit. Additionally, these councils have relatively lower population densities, and the addition of hospitals to the existing network, which would include another NHS Health Board, would cause disproportionate administrative and networking time.

Table 2.2 Council population size

Region	Population	% of total population
Scotland	5,295,403	
- *Edinburgh*	476,626	9.0
- *West Lothian*	175,118	3.3
- *Fife*	122,799	2.3
Councils Total	774,543	14.6

Table 2.3 Ethnicity of population-based region

White		**89.90%**
	White (British/Irish)	83.57%
	White (other)	6.33%
Non-White		**10.10%**
	Asian	5.33%
	African/Caribbean	1.56%
	Other non-white	3.18%

During the preparation stages of the study, the research team became aware that some CWEOE from Fife may be managed by hospitals and health services outside the Fife council district. We could not be certain of accurately identifying all these cases through our identification networks, which may have resulted in an underestimation of the true incidence. Fife was therefore restricted to children residing in postal codes KY1, KY2, KY5, KY6, and KY7. Children from these areas were guaranteed to be routed to, and managed by, the main district hospital as part of the diagnostic and/or management process for epilepsy, thereby increasing the likelihood of capture. For the purposes of this Thesis, the term Fife herein refers to these specific postal codes. These three well defined regions of Edinburgh, West Lothian, and Fife represent 14.6% of the Scottish population (table 2.2), and can still be considered

representative of the population as a whole. Edinburgh, West Lothian, and Fife are predominantly white but ethnically diverse regions (table 2.3).

2.5.2 Participants

NEUROPROFILES prospectively recruited children with early-onset epilepsy, and neurologically healthy controls, over a 26 month period, between the dates of May 1st 2013 and June 30th 2015.

Inclusion Criteria

CWEOE and control children were male or female Scottish residents (i.e. resided at a permanent address in Scotland), and were of any cultural or ethnic background. CWEOE and controls were included in the population-based components of the study if they resided in the City of Edinburgh, West Lothian, or Fife council districts at the time of diagnosis (CWEOE), or recruitment (controls), even if they later migrated during the study period. All children within and outwith the defined population region were included in the eye-tracking component of the NEUROPROFILES study as previously explained.

All children were aged ≤4 years at time of epilepsy diagnosis (CWEOE), or at the time of initial contact or identification (controls). CWEOE were included in neuropsychological assessment if they were five years old at the time of assessment, but had a diagnosis of epilepsy made before their fifth birthday. Likewise, controls were given neuropsychological assessment if they were five years of age at the time of assessment but were identified and recruited prior to their fifth birthday.

Exclusion Criteria

Children were excluded if they were not resident in Scotland. For population-based components, children were excluded if they resided outside the predefined geographical boundary, at the time of diagnosis (CWEOE), or recruitment (controls). CWEOE were excluded if they did not meet the criteria for epilepsy indicated in section 2.4.1, or were five years or older at the time of epilepsy diagnosis. CWEOE were withdrawn after recruitment if an initial diagnosis of epilepsy was subsequently corrected to a non-epileptic diagnosis or non-epileptic

seizure disorder upon review of medical records. Controls were excluded if they had a known neurodevelopmental disability or neurological abnormality.

2.6 Procedures

2.6.1 Participant Identification

Children with Early-Onset Epilepsy

A multi-source, multi-site active surveillance capture-recapture system utilising the usual clinical care pathway of managing children with a suspected new diagnosis of epilepsy was used to identify CWEOE.

Incidence calculations assume that all possible persons with a disease are identified and included in analysis. In practice, capturing all new cases is unlikely. Cases may be missed depending on the accuracy of the strategies and sources used for case identification. One method of estimating and adjusting for missing cases is capture-recapture. The premise of capture-recapture is that persons with a disease are captured by one source, then recaptured by a second [or third] independent source. The discrepancies between source estimates are used to estimate the number of potential missing cases, and subsequently ascertainment-adjusted incidence rates can be calculated (Brittain and Böhning, 2008; Stephen, 1996). As the identification system used in the current study used multiple sources within the natural clinical care pathway, it is first necessary to understand that pathway.

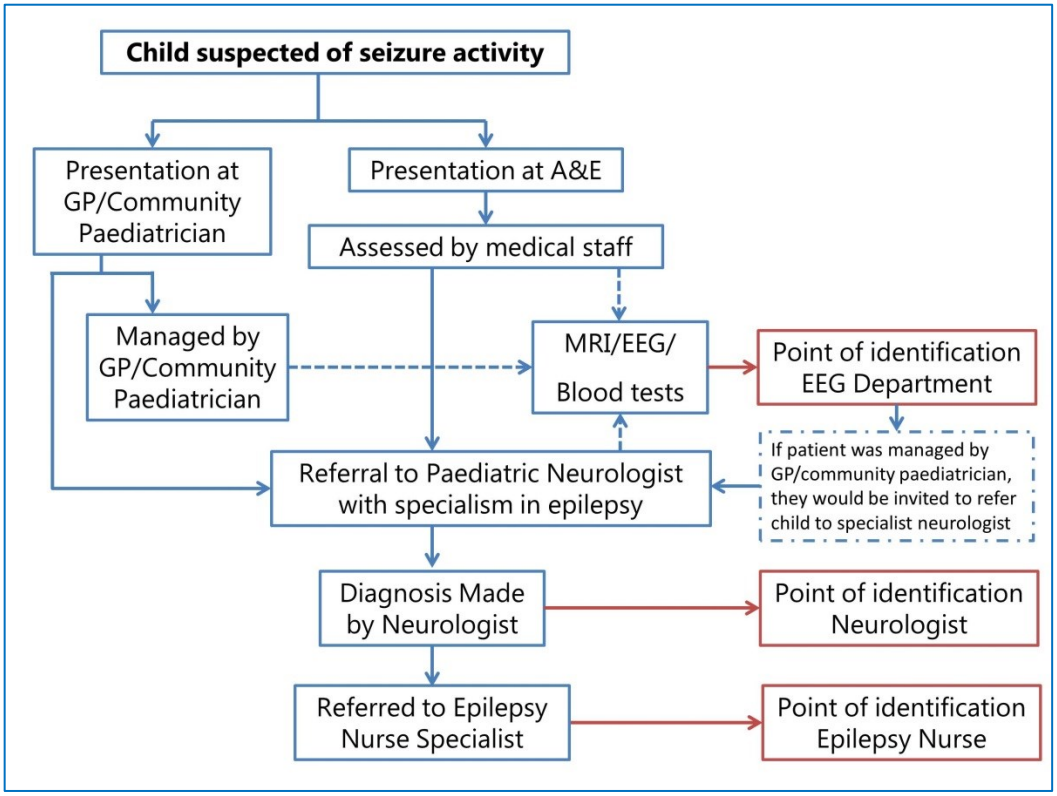
A child who is suspected of having seizures would normally seek medical advice at a General Practitioner (GP), or Hospital accident & emergency unit. After initial assessment by either route, if the child is believed to have had a seizure it is recommended that they be referred to a paediatrician with a specialism in epilepsy for further assessment and investigation (SIGN 81, 2005, Section 2.2, http://www.sign.ac.uk/pdf/sign81.pdf). Therefore, paediatricians/paediatric neurologists with expertise in epilepsy would be a primary point of identification for newly diagnosed CWEOE. However, a recent national UK wide audit examining the provision of epilepsy services to children and young people from 2010 to 2011 (RCPCH, 2012), recognised that a small number of patients in Scotland were being managed by community paediatricians without any input from experts in epilepsy, signifying that further sources of identification were needed. As part of the diagnostic procedure for epilepsy, whether by GP, neurologist, or other paediatrician, a child will routinely have an EEG test, and frequently, an MRI test and blood

tests. This means that the EEG department can act as a point of convergence for children undergoing diagnosis (irrespective of whether they were being managed by a paediatrician with expertise in epilepsy or not), and serve as another point of identification. Indeed this was the single source of identification of epilepsy subjects for the Epilepsy 12 Audit.

Once a diagnosis has been reached, a child should have access to specialist epilepsy services, including an epilepsy specialist nurse (SIGN 81, 2005). Epilepsy specialist nurses play an integral part in the management of CWEOE, acting as a point of contact for the child and family, and liaison between school and multidisciplinary services (SIGN 81, 2005). Thus, they were a third potential source of identification. Any single CWEOE on their clinical care pathway should be identified by any of those individual sources, or via a combination of those sources, thus increasing the likelihood of capture.

Therefore, three sources of case identification were used in the present study: (1) paediatricians with expertise in epilepsy, (2) epilepsy specialist nurses and, (3) EEG departments. Figure 2.3 shows a simplified pathway of natural clinical care with case identification points.

Figure 2.3 Case identification pathway



Capture-recapture assumes that all cases have an equal chance of being captured by each independent source. Lack of source independence leads to an underestimation bias (Stephen, 1996). In NHS Lothian and NHS Fife, epilepsy patients are referred to epilepsy specialist nurses directly by paediatricians. Therefore, sources 1 and 2 lacked independence, and were collapsed into a single data source – labelled here as 'neurology department'. The EEG department receives referrals investigating seizures from all hospital departments, and community physicians, and thus, has low positive dependency.

Three hospital sites acted as the primary gateway sites for case identification: RHSC, St. John's Hospital, West Lothian, and Victoria Hospital, Kirkcaldy, Fife. These are the main paediatric hospitals for Fife and Lothian. All CWEOE in the defined geographical study area are routed through these hospitals. At each of these Hospitals there was one or more consultant paediatric neurologists who collaborated on the project and acted as contact points. Two epilepsy specialist nurses, based at RHSC, covered the areas of Edinburgh and West Lothian, while a single epilepsy specialist nurse was responsible for Fife. Children from West Lothian and Edinburgh are referred to the neurophysiology department at RHSC, while children from Fife attend the neurophysiology department at Victoria Hospital. These three hospitals also manage and admit patients resident outside the study area from other areas of Scotland - due to physical location, or due to specialist paediatric services. Thus, with multiple identification sources, and by checking home postal codes, most if not all CWEOE from the study area could be confidently identified, and additional CWEOE from outwith the study region could be identified in order to address the eye-tracking component.

In order to identify new diagnoses of epilepsy at the earliest possible time, active surveillance of data sources was carried out. To do so, a network of paediatricians and epilepsy specialist nurses at the aforementioned Hospital sites was established. This network was contacted through regular emails, telephone calls, and face-to-face contact, where new cases could be referred directly to the candidate. Awareness of the study was further increased through candidate presence at weekly neurology meetings. The EEG departments were audited by clinical neurophysiologists on a fortnightly to monthly basis for cases displaying an abnormal EEG consistent with epileptiform activity. As epileptiform activity is also high in patients with neurological or medical disorders without epilepsy (Panayiotopolous, 1999, http://www.ncbi.nlm.nih.gov/books/NBK2601/), EEG testing is not a definitive diagnostic tool but an instrument used to aid diagnosis. Therefore, the referring paediatrician of the patient would be contacted for further information, no earlier than two weeks after identification. This

was to allow the diagnostic process to unfold. If no diagnostic conclusion had been drawn, the referring paediatrician would then be contacted again at regular intervals by the research team. If the child was subsequently diagnosed with epilepsy but was not identified through the neurology department source, the GP or paediatrician would be invited by the research team to refer the child to a paediatric epilepsy specialist through the normal care pathway (figure 2.3).

Control Children

Controls were identified through public advertisement. Recruitment posters were located at the main hospital sites, and flyers were placed at nursery schools and parent & toddler groups. A digital recruitment poster was posted online at http://www.mumsnet.com/ using the mumsnet "Local Talk" services for Edinburgh, Falkirk & West Lothian and Fife. A study advertisement email was drafted to all NHS Lothian staff using a global email system.

In addition to public advertisement, non-epileptic patients attending the MRI department at RHSC, for the investigation of headaches, and who had no abnormalities on their subsequent brain scan, were invited to take part as controls on the previously mentioned sibling project, entitled "Biomarkers in early-onset epilepsy", led by Dr Michael Yoong. This project investigated MRI brain markers in early-onset epilepsy using the same cohort of CWEOE recruited for the current study. Thus, control children identified for that study were invited to participate in the NEUROPROFILES study during the active recruitment phase. Control children recruited via this pathway underwent the same neuropsychological assessment and eye-tracking protocol as all other controls.

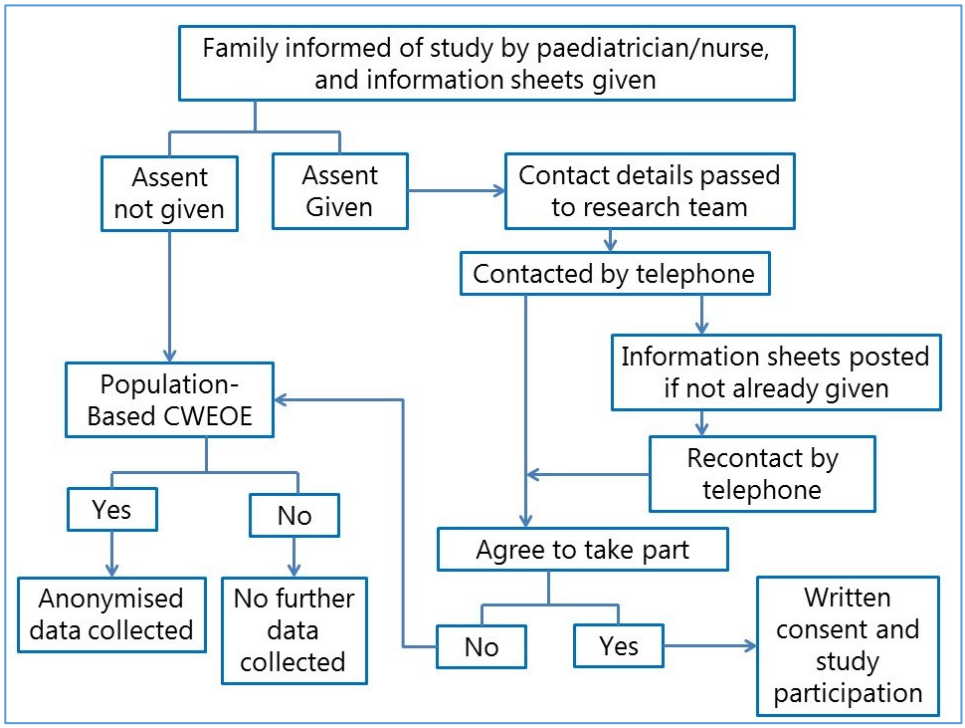
2.6.2 Participant Recruitment

Families of CWEOE were informed of the study by their paediatrician or epilepsy specialist nurse, during routine clinic, or as a Hospital inpatient. They gave eligible patients study information sheets, if available, and asked for permission to pass on the family's contact details to the research team. Once assent had been granted, the candidate contacted the family at least 24 hours after information sheets had been provided, to allow time to read the material. For those that did not receive information sheets, these were emailed or posted to the family after telephone contact. Contact was then made again by the candidate no less than five days after posting information sheets. If the family agreed to take part in the study, arrangements were made to undergo neuropsychological assessment and eye-tracking. A flow diagram of

the recruitment process is illustrated in figure 2.4. The target time from diagnosis to assessment was three months. Families who assented to be a part of the study but who failed to attend the appointment, were given repeated attempts to do so. Those who failed to attend on three occasions without notice were considered not to have consented for study participation. If assent was not granted at initial contact or through repeated non-attendance, anonymised data on demographic and epilepsy characteristics (appendix D) were obtained by the research team through a paediatrician within the child's care team, for population-based children only. This data was held under a unique non-patient identifiable study identification number, and used for incidence cohort characteristics.

Families of control children responded to public advertisement by contacting the candidate directly via email or telephone. Inclusion and exclusion criteria, including the neurological health of the child, were checked with the family, and information sheets were then emailed or posted if criteria were met. The same recontact latency period given to families of CWEOE was followed. If the family agreed to take part, arrangements for assessment were then made. Controls identified through the MRI department for the sibling study were approached immediately post-scan, by Dr Michael Yoong, and informed of the study. The same recruitment procedure for controls was then applied.

Figure 2.4 Recruitment process



2.6.3 Consent Procedure

Written consent was gained from the parent/legal guardian, when families attended for neuropsychological assessment. Consent was gathered for entry onto the study, to access medical records including EEG and MRI, to access routinely stored data on NHS and educational databases, and to retain contact information for further follow-up studies. Like those participants who did not assent to be contacted by the research team, anonymised data was gathered for those CWEOE from the population-based region who did not did not consent to the study, (see section 2.6.2, and appendix D).

Parents or legal guardians are required by law to give consent for children under the age of 16 for medical treatment (The Children (Scotland) Act 1995). This can be extrapolated to research other than clinical trials of medical products (Medical Research Council, http://www.hra-decisiontools.org.uk/consent/principles-children-Scotland.html). Although the Children (Scotland) Act considers age 12 years as sufficient for the child to give consent, personal research observations by Rosie Flewitt (2005) suggest that preschool children can often have sufficient understanding of what is being asked of them. As such, 'assent' was gained from the children, when appropriate, and on an ongoing basis. A children's information sheet was provided that the parent could read to their child prior to study assessment. It consisted of short direct statements with child friendly pictures. It directly asked the child if they would like to take part. On the day of assessment, verbal consent from the child was gathered prior to assessment, where appropriate. Mood and behaviour was monitored throughout each assessment, and verbal assent was reiterated periodically.

2.6.4 Study Assessment Procedure

All potential CWEOE and controls identified for the study were invited to take part in neuropsychological assessment and eye-tracking. Specific details on neuropsychological and eye-tracking test measures, and procedures are detailed in sections 8 and 12, respectively. Elements common to both are reported here.

Each family/child who agreed to participate completed a comprehensive assessment, involving age-appropriate standardised face-to-face assessment of cognitive functioning, eye-tracking, and parent-rated questionnaires of various aspects of behaviour. Assessments were planned to be conducted within three months of diagnosis. However, this varied depending on the personal circumstances of the families, and the time between diagnosis and identification.

Face-to-face neuropsychological assessment and eye-tracking took place at The Child Development Lab, Moray House of Education, School of Education, University of Edinburgh. In September 2014 (16 months into data collection) the venue for the Lab was changed, due to administrative reasons, to Kennedy Tower, Department of Psychiatry, University of Edinburgh. Home visits were arranged for families who could not, or did not want to, travel to appointment locations. Families of children who assented to take part were given details of what to expect on the day of neuropsychological assessment, and directions to the place of testing. Participants who had home visits did not undergo eye-tracking, unless they had attended and completed eye-tracking on a previous occasion. Study participation included a single or multiple visits to the Lab, depending on the child's attention and fatigue levels. Each assessment session lasted between 1-3 hours in total, including breaks. Participants were reimbursed for travel expenses but no other financial incentives were offered.

Study questionnaires were sent to parents upon receiving verbal assent to participate in the study. Questionnaires were completed prior to arrival for face-to-face assessment, but were not collected until written consent was obtained. If parents did not bring questionnaires to the assessment appointment, they were asked to post questionnaires directly to the research team. If parents were unsure of questions or questionnaires, for whatever reason, they were then completed at the end of assessment with support from the candidate. Families who did not have a parent literate in English were not asked to complete questionnaires.

Parents also completed a short standardised proforma via direct interview (appendix E), which gathered clinical and background information on the child and family. The interview collected information that was not routinely collected in clinic or recorded in medical notes (e.g. family history of psychiatric or developmental disorder), and gathered up-to-date clinical information at the time of assessment (e.g. current seizure frequency). Epilepsy-related information gathered here was used to supplement missing or dated information in medical records. Medical records were reviewed, supplemented by the proforma introduced above, by the research team after the date of neuropsychological assessment.

Face-to-face assessments and parent interview were carried out by the candidate, and all standardised assessments, including questionnaires, were scored by the candidate. Administration of eye-tracking was also carried out by the candidate. Face-to-face assessment, eye-tracking, parent interview, and collection of the questionnaires completed the child's active participation in the study.

2.7 Data and Analysis

Chapter specific analyses for the three main aims of the study are detailed and described in chapters II-IV. Data and analyses common to all chapters are described here.

2.7.1 Epilepsy- and Non-Epilepsy-Related Variables

The following variables were collected from medical records and/or parent interview, in order to establish clinical and sociodemographic characteristics of the cohort; or to use during analysis of risk factors.

Non-Epilepsy-Related Variables

(a) Age (at neuropsychological assessment), (b) Gender (male/female), (c) Birth weight (normal ≥2500g/low birth weight <2500g), (d) Prematurity (full-term ≥37 weeks/pre-term <37 weeks), (e) Ethnicity (White UK/White European/Asian/Black), and (f) SES (high/low).

Epilepsy-Related Variables

(a) Epilepsy classification (Berg et al., 2010), (b) Mode of seizure onset (focal/general/both), (c) Seizure type(s), (d) Seizure frequency at time of neuropsychological evaluation (low <one seizure per day/high ≥one seizure per day), (e) Aetiology (1989 and 2010 ILAE Classifications), (f) Number of AEDs at time of neuropsychological evaluation (0-1/≥2 polytherapy), (g) MRI status (normal/abnormal-minor/abnormal-major), (h) EEG status (normal/abnormal epileptiform/abnormal slow-wave), (i) Family history of epilepsy, (j) Family history of psychiatric or developmental disorder, (k) Age (at first unprovoked seizure), (l) Age (at diagnosis), and (m) Time delay from diagnosis to assessment.

2.7.2 MRI and EEG Ratings

MRI images were rated by consensus agreement of two neuroradiologists who were blinded to the child's clinical history. Ratings were classified as normal, minor structural abnormality, or major structural abnormality.

As children may have multiple EEG recordings, the child's EEG closest to the date of neuropsychological assessment was chosen. EEG recordings were rated by one of four neurophysiologists using a locally developed proforma (appendix F). Each EEG and proforma

were then reviewed by one consultant paediatric neurologist (KKT). KKT used other EEG recordings for guidance if more information was required. EEGs were rated as normal or abnormal. For the purposes of this study, abnormal EEGs were characterised as having epileptiform, non-epileptiform (i.e. slow-wave) features, or both.

2.7.3 Statistical Analysis

Statistical analysis techniques relevant to the specific chapters are detailed in the respective methods sections. Elements of statistical analysis common to all chapters are outlined here.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0.0 (Armonk, NY: IBM Corp., Released 2012), with the exception of the systematic review on the incidence of early-onset epilepsy (section 3) where Stata-MP v13.1 (2013, Statacorp LP, College Station, TX) was used.

Normality of all variables was assessed according to Shapiro-Wilk test and upon visual inspection of histograms and QQ-plots. Data transformation was attempted for variables with a non-normal distribution. Parametric tests were applied preferentially, with non-parametric analyses applied for non-normal data that could not be transformed. Fisher's exact test (FET) was applied for all 2x2 or 2x3 contingency tables comparing associations of nominal variables.

Estimates of effect size, or equivalent, were reported throughout. Mean difference between group scores (MD) with 95% confidence intervals were reported for t-tests. Pearson's r was reported for nonparametric Mann-Whitney U or Wilcoxon signed rank tests. Eta squared (η^2) was reported for analysis of variance tests (ANOVAs), and partial-eta squared (η_p^2) for analysis of covariance tests (ANCOVAs). Group differences of $p<.05$ were considered significant. The relative strength of effect sizes were qualitatively assessed using guidance from Cohen (1988; table 2.4). Odds Ratios (OR) and 95% confidence intervals were reported for all 2x2 contingency tables as an estimation of effect size.

Table 2.4 Qualitative guidance on strength of effect size (from Cohen, 1988)

	small	medium	large
r	.1	.3	.5
eta or partial squared	.01	.06	.14

Chapter II. Incidence of Early-Onset Epilepsy

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This chapter describes and reviews the literature on early-onset epilepsy incidence, with additional focus on infantile spasms/West Syndrome. It describes the specific methods for this part of the NEUROPROFILES study, the process of establishing an early-onset epilepsy cohort, and presents the study's findings. The annual incidence of early-onset epilepsy, applying an ascertainment-corrected adjustment, was 61.71 (95% CI 40.22 – 88.14) per 100,000 children ≤4 years. Risk factors were explored, with ethnicity identified as a potential risk factor for early-onset epilepsy but not socioeconomic status. The cumulative incidence of West Syndrome was estimated at 4.01 per 10,000 live births, 95% CI (1.47-8.72). The relationship of the findings are then discussed in relation to those from the systematic review.

***

3. Incidence of Early-Onset Epilepsy: Introduction

3.1 Introduction

The aim of this chapter was to ascertain the incidence of early-onset epilepsy (i.e. onset ≤4 years of age) in the existing literature base, and in a new, unique, population-based prospective cohort of CWEOE, whilst providing a rationale for doing so. A systematic review of the literature was conducted in order to estimate the incidence of early-onset epilepsy in the knowledge base, and to identify any gaps that could be addressed through the NEUROPROFILES study. The approach toward estimating the incidence of early-onset epilepsy in the present study is then described, followed by results and discussion.

3.2 Systematic Review and Meta-Analysis of the Incidence of Early-Onset Epilepsy

As mentioned above, to meet the aim of estimating the incidence of CWEOE in the existing literature base, a systematic review and meta-analysis of incidence studies in CWEOE was completed. Particular attention was placed on data from the United Kingdom (UK), due to its relevance to the current study.

3.2.1 Systematic Review: Introduction and Background

The incidence of epilepsy across the lifespan is 50.4/100,000/year (interquartile range, IQR, 33.6-75.6) (Ngugi et al., 2011). It is not evenly distributed but follows a U-shaped curve, with peak incidence in infancy and old age (Annegers, 2004; Christensen et al., 2007; Hauser et al., 1993) - a pattern also replicated in the UK population (MacDonald et al., 2000). The reason for such a pattern is due to age-related risk factors in the determinants of epilepsy. Knowledge on age-specific incidence data, and corresponding aetiological information, is therefore necessary in order to better understand epilepsy, to identify age-relevant risk factors, and determine prognostic implications. Such data will then aid resource provision, and targeted intervention strategies.

The Rochester Epidemiology Project has contributed to the understanding of the causes of epilepsy across the lifespan (Annegers et al., 1996; Annegers, 2004; Hauser et al., 1993), with the causes of structural related epilepsies much better understood. Data from the Rochester studies also indicate that the cause of epilepsy is unknown in approximately two thirds of cases.

Brain trauma and tumours are common to all ages, but are the leading precipitant of epilepsy in young people and adults. Cerebrovascular and degenerative diseases are leading causes in the elderly, while congenital and developmental causes are the main antecedents in childhood epilepsy. Identified genetic causes of epilepsy are more often syndrome specific (Berkovic et al., 1998), with most syndromes having onset in infancy and childhood. While the aetiological profile differs broadly between childhood, adulthood, and old age, it is also important to note that it varies markedly within childhood. This relates to different aetiological risk factors associated with different stages of development, and the occurrence of age-dependent epilepsy syndromes (Appleton and Camfield, 2011). For instance, structural related epilepsies are common in the neonatal period and infancy, often caused by developmental abnormalities such as congenital malformations or hypoxic-ischemic encephalopathy, whilst syndromes such as CAE, Dravet Syndrome, or BECTS occur in childhood, and Juvenile Myoclonic Epilepsy, or Temporal Lobe Epilepsy more often occur in adolescence (Appleton and Camfield, 2011; Berg et al., 2010). Ascertaining incidence estimates and clinical characteristics across childhood is therefore necessary.

Numerous epidemiological studies have addressed childhood-onset epilepsy, and have been summarised in three reviews (Cowan, 2002; Forsgren et al., 2005; Kotsopoulos et al., 2002) - although none have specifically addressed the early-onset period. From these reviews, the annual incidence of epilepsy in children ≤15 years, was estimated between 25 and 82, per 100,000 children, per year. The incidence of childhood epilepsy in the UK specifically, has been reported in eight studies (Cockerell et al., 1995; Eltze et al., 2013; Heaney et al., 2002; Kurtz et al., 1998; Martinez et al., 2009; MacDonald et al., 2000; Meeraus et al., 2013; Wallace et al., 1998). The incidence of epilepsy across childhood in the UK is presented in table 3.1, and estimates range between 41.4 and 114.8, per 100,000 children. As with other epidemiological studies of epilepsy, there is considerable heterogeneity in age stratifications reported, making it unclear how the incidence of early-onset epilepsy relates to general childhood estimates.

As argued in chapter I, the first five years of life are an extremely important period in neural and functional development (National Scientific Council on the Developing Child, NSC, 2007). The early-onset period is the time at which epilepsy is most common, the most severe forms occur, and where epilepsy may be likely to result in increased risk of neurobehavioural problems (see section 1 for further details). Age-specific point estimates of epilepsy are likely to vary over this period given that there are a number of age-related syndromes (Appleton

and Camfield 2011; Berg et al., 2010). As such, it is pertinent to detail the incidence of epilepsy during the first five years of life so that age-appropriate interventions can be better directed.

Table 3.1 Incidence of Childhood Epilepsy in the UK (per 100,000)

Author (year)	Cohort	Age (y)	Incidence Rate (95 % CI)
Cockerell et al (1995)	1983 GP cohort	0-20	60.9 (33.0 – 103.3)
Kurtz et al (1998)	1958 Birth Cohort	0-15	41.0 (33.3 – 49.8)
Wallace et al (1998)	GPRD cohort 1995	5-14	58.7 (49.7 – 68.8)
MacDonald et al (2000)	Unselected GP cohort 1995-1996	0-14	75.3
Heaney et al (2002)	Unselected GP cohort 1995-1997	0-14	114.8 (88.6 – 146.3)
Martinez et al (2009)	GPRD cohort 2005	0-9	48.0 (39.1 – 58.2)
Eltze et al (2013)	GP survey 2005-2006	0-2	70.1 (56.3 – 88.5)
Meeraus et al (2013)	THIN 1994-2008 birth cohort	0-7	70.6 (65.6 – 75.9) to 116 (100 – 123)†

GP – General practitioner
GPRD – General Practice Research Database; 5.5% of UK population
THIN – The Health Improvement Network Database; 5% of UK population
† Least to most sensitive criteria for epilepsy

As incidence estimates vary markedly between studies, it is additionally important to understand the factors that contribute to that variance. Methodological factors are important (Ngugi et al., 2011), whilst SES and ethnicity are two factors that also require consideration. Differences in SES within an area or culture may reflect health inequalities via the availability of health and social resources, knowledge and attitudes to care, and health and lifestyle choices. Low SES is associated with increased risk for abnormal development, adverse health, and incidence of neurological disorders in children (Bradley and Corwyn, 2002; Kumar et al., 2013). There is strong evidence that lower SES increases risk of epilepsy (Hesdorffer et al., 2005; Pickrell et al., 2015), although this relationship appears less robust in children, including within the UK (Hesdorffer et al., 2005; Reading et al., 2006). Contrary to this, Heaney et al. (2002) reported higher incidence of epilepsy in areas of lower socioeconomic status in children 0-14 years in the UK, raising the possibility of regional, temporal, or circumstantial variations in risk.

Data on differences in incidence across ethnicities are scarce (Banerjee et al., 2009). Of those available, similar incidence rates were reported between non-Hispanic, Hispanic, and African-

American ethnicities in North America (Annegers et al., 1999; Benn et al., 2008). In the UK, no significant difference was found in the incidence of recurrent nonfebrile seizures between South Asian and non-South-Asian children in Bradford (Hamdy et al., 2007), although Eltze et al. (2013) found a higher incidence of epilepsy among Asian infants in London, raising the possibility of ethnicity-specific regional variations. How the incidence of Asian and other ethnic groups of children compare in Scotland is unknown. Such data may be particularly important given that epileptic syndromes may differ based on ethnicity (Friedman et al., 2013), which may signify different risk or causal factors. Such knowledge may be useful for resource planning.

The main aim of the systematic review was to identify studies with incidence data reported on children with epilepsy under the age of five years, and to explore heterogeneity in estimates between studies. This is the first review specifically targeting the incidence of early-onset epilepsy.

3.2.2 Systematic Review: Search Strategy

This review follows guidance set out in the PRISMA report (Moher et al., 2009). Early searches and screening revealed a significant number of incidence studies on Infantile Spasms/West syndrome (herein referred to as infantile spasms), an early-onset epilepsy syndrome. Infantile spasms is a prevalent syndrome, typically manifesting in the first year of life. Therefore, infantile spasms specific studies were extracted and reviewed separately to those based on general cohorts of mixed early-onset epilepsies.

The electronic databases Medline (Ovid), Web of Science (Thomson Reuters), and EMBASE Classic + EMABSE (Ovid) were searched for original research articles between years 1946-2015 (appendix G). Searches were conducted on 8th May 2015, and search terms included MeSH terms (Ovid databases) 'epilepsy', AND 'preschool/child/infant/toddler/infancy' [or] 'minors', AND 'incidence' [or] 'epidemiology'. Indexed searches were supplemented with free-text searches of titles and abstracts using truncation of search terms. Web of Science search used topic searches of target terms, including truncated searches, of (1) epilepsy: 'epilepsy', 'p[a]ediatric epilepsy', 'childhood epilepsy', 'epileptic encephalopathy'; (2) children: 'preschool', 'infant', 'children', 'childhood', 'toddler'; and (3) incidence: 'incidence', 'epidemiology'. References and review articles were screened for additional articles.

3.2.3 Inclusion and Exclusion Criteria

Articles included were: (1) English language, (2) original research articles, (3) published on or after 1946 as identified from electronic database search, (4) population-based or community-based study design, (5) children with epilepsy diagnosed ≤4 years of age, (6) reported annual incidence figures, or cumulative incidence data from which annual figures could be calculated, for general epilepsy populations, and (7) cumulative incidence for studies of infantile spasms. Research studies often publish data on children with ≥1 unprovoked seizures. The operational definition of epilepsy in epidemiological studies is defined as two or more unprovoked seizures (Thurman et al., 2011; ILAE, 1993). Therefore, incidence data was only gathered when reported from cohorts of children where the study defined epilepsy as ≥2 unprovoked seizures, when the study classified epilepsy as 'recurrent' seizures, or when based on diagnostic codes for epilepsy.

Study articles were excluded if: (1) data were not reported for any age stratification below five years of age (e.g. <1 year, <2 years, 0-4 years), (2) were cross-sectional, single or multi-centre studies, (3) were review articles including systematic reviews, letters, abstracts, single-case studies, or other non-original research articles, or (4) if the study described incidence of epilepsy syndromes other than infantile spasms, epilepsy within special populations (e.g. ASD), or of solely seizure types.

3.2.4 Data Extraction and Synthesis

Early-onset epilepsy, restated here, is epilepsy onset ≤4 years of age. Pilot searches revealed that data was typically reported for ages <1, 1-4, and 0-4 years. Therefore, these were the main target ages for data extraction, and focus for review. Less often, studies reported on children <2 years. These were included here for the purposes of completeness. Several studies reported data for more than one age stratification, and as such, extracted age-stratification specific datasets were labelled as 'observations', so that there may be more than one incidence age observation per study. For age groups of interest, the total number of incident cases, and total-person-years were extracted from reviewed articles. To achieve standardisation across studies, incidence rates, standard errors, and 95% confidence intervals were independently calculated from available data for all studies, and presented in the data tables to follow. Where insufficient data was available to calculate incidence rates, standard errors, or confidence intervals,

available data on incidence rates and confidence intervals were extracted from the published results, and transferred directly to tables, but those studies were not included in meta-analysis.

Meta-analysis was used to provide pooled estimates, and meta-regression to explore the heterogeneity in incidence estimates. Incidence rates for epilepsy were reported per 100,000 children per year, and per 10,000 live births for studies of infantile spasms.

Extracted data included study authors, year of publication, study location, years of data collection, age group, incidence rate, 95% confidence intervals, total-person-years, study design (i.e. retrospective or prospective design), population type (i.e. cohort, population/community-based), case identification strategy (i.e. surveillance methods or medical registries, with case validation if completed), and case identification source (i.e. single-source or multi-source). Case identification is often a heterogeneous process, involving a combination of strategies from single or multiple data sources. For simplicity, strategies and sources of identification were considered separately. Independent resources of case identification included general practitioners, paediatricians, EEG departments, hospital or clinic departments, or medical registries (e.g. general practitioner database or medical records), for example. Multiple sources were defined as the use of more than one independent resource.

3.2.5 Individual Study Assessment of Risk of Bias

Risk of bias is a phenomenon in any research study where the findings may be unduly influenced by methodological factors. The Cochrane Collaboration (2009) recommends that an appraisal of quality be conducted in systematic reviews and meta-analyses. The use of a scoring system for assessing risk of bias is debated, but recommended by at least one group for observational studies (Stroup et al., 2000). A risk of bias assessment proforma was constructed by the candidate based on one produced for a previous systematic review of incidence studies (Kotsopoulos 2002). It was developed further, for the specific purposes of this review, and included factors that could potentially influence incidence estimates. There were six factors in total, and was made up of epilepsy definition, case identification methods, availability of confidence intervals or underlying population denominators, and length of time each population was observed for. Each factor was scored between 0 and 3 points depending on the risk for potential bias, and each study received a total score which was treated as a continuous variable. Rationale for factors, and scoring system can be found in appendix H.

3.2.6 Meta-Analysis with Meta-Regression

Analyses were performed using Stata-MP v13.1 (2013, Statacorp LP, College Station, TX). The Metaprop command (Nyaga et al., 2014) for Stata applies random-effects modelling for proportional data based on the binomial distribution, and was used to calculate pooled incidence rates and 95% confidence intervals. Heterogeneity explained by sampling variability is represented by the I^2 statistic. In addition to meta-analysis, this study explored the heterogeneity in incidence estimates using the meta-regression command Metareg (Harbord and Higgins, 2008). The random-effects regression model relates the contribution of study-level covariates to the heterogeneity of studies, applying both within- and between-study variance. The standard error was used as the coefficient for within-study variance; calculated using the formula: $sqrt[p * \frac{1-p}{n}]$, where p is the proportion (i.e. incidence). The standard error is a marker of the relative accuracy of the incidence estimate based on the dispersion of values around the sampling distribution. Larger standard errors indicate more variability in the estimate. Between-study variance explained by the covariate(s) is represented by the adjusted R^2 statistic (R^2_{adj}), and residual between-study variation due to heterogeneity is measured with the I^2_{res} statistic. The remaining variation not explained by I^2_{res} is attributable to within-study sampling variability (Harbord and Higgins 2008).

Heterogeneity was explored firstly through univariate analyses using study-level covariates that may influence incidence estimates: gross national income status (World Bank 2016), study design, cohort age stratification, case identification strategy, and case identification source. Covariates were included in multivariable meta-regression analysis if significant at the .05 level on univariate analyses. In addition, infantile spasms is typically classified according to broad aetiological category; i.e. symptomatic or cryptogenic/idiopathic – the risk factors for which may vary temporally or culturally. Therefore, aetiology was included as a study-level covariate for regression in studies of infantile spasms. For comparison of incidence estimates within study-level covariates, incidence rate ratios were calculated (i.e. incidence rate of one level of the covariate level divided by the incidence rate of the opposing level). 95% confidence intervals were calculated using the following formula, where a is the number of observations with one level of the covariate, and b is the number of observations of the opposing level:

$$e\left(\ln(incidence\ rate\ ratio) \pm 1.96 * \sqrt{{}^{1}/_{a} + {}^{1}/_{b}}\right)$$

Figure 3.1 Systematic review exclusion flow chart

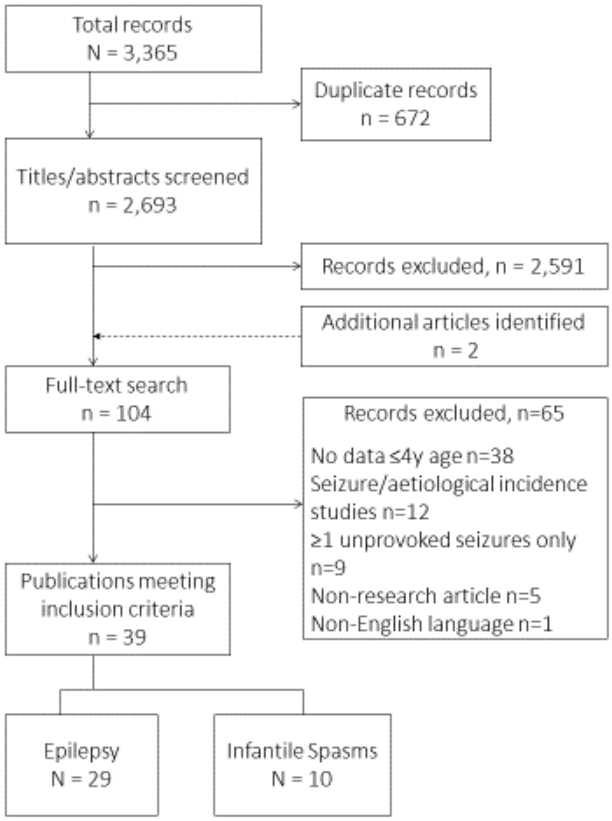
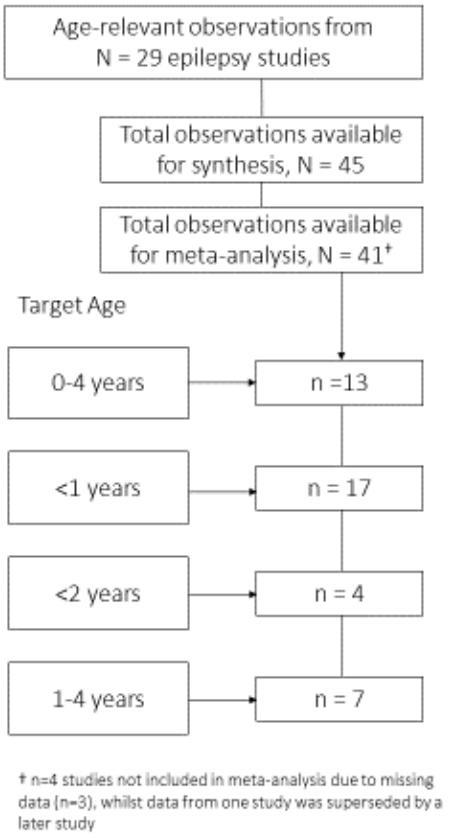


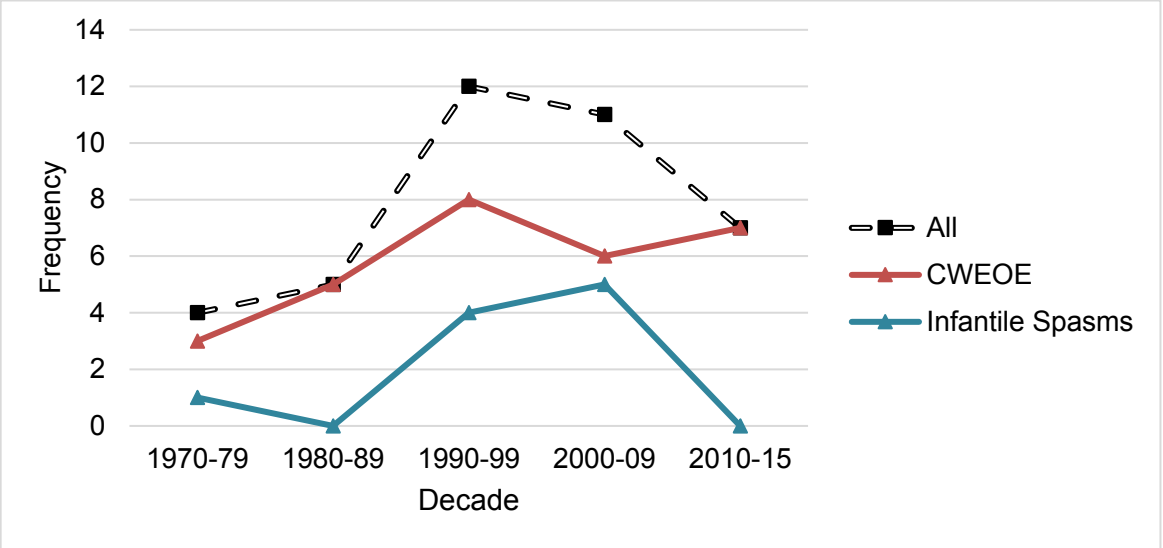
Figure 3.2 Age-specific data observations extracted from all studies



3.2.7 Systematic Review: Results

See figure 3.1 for PRISMA flow chart of inclusion/exclusion process. 2693 articles were screened, and two additional studies were included from screening references (Riikonen, 2001a; Sillanpaa, 1973). One article was missing from the original search after being indexed as a review but contained original data (Riikonen 2001a). The other was missed from database searches due to a combination of non-indexing, and because the specific synonym used in the article title, 'epidemiological', was not covered by free-text title searches where the term 'epidemiology' was used. 39 articles were accepted for final review: 29 studies described the annual incidence of epilepsy ≤4 years, and 10 reported the incidence of infantile spasms. Studies were published between 1973 and 2013 (figure 3.3), reporting on incident samples observed from 1935 to 2008. 26% (n=10) were published on or prior to 1993, the year of the publication of the ILAE guidelines for epidemiological studies on epilepsy (ILAE, 1993). Only three studies were from low or middle income countries across different age stratifications (Banerjee et al., 2010; El-Tallawy et al., 2013; Saha et al., 2008).

Figure 3.3 Study frequency by publication date



Epilepsy Studies

Of the 29 studies of annual incidence rates in early-onset epilepsy populations, figure 3.2 lists how many unique observations were available for data synthesis, and how many were available in each target age for meta-analysis. One study provided a vague incidence estimate for children <1 year of "up to 200 new cases" (Christensen et al., 2007, p62), and was not synthesised further. This, and three further studies, were not included in meta-analysis. Two studies published incidence rates without underlying population data (Doose and Sitepu, 1983; MacDonald et al., 2000), and the populations reported in Hauser et al. (1975) were reported and extended in (Hauser et al., 1993), which was preferred instead. Consequently, 41 unique age-specific observations from 25 studies were included in the meta-analysis and regression.

There was a total of 2137 incident cases from 2,129,516 total-person-years for all included studies on children with epilepsy of onset 0-4 years. Study characteristics for age-specific observations (i.e. 0-4 years, <1, <2 years, and 1-4 years) are listed in tables 3.2, 3.3, 3.4, and 3.5, respectively. Corresponding forest plots were produced (figures 3.4, 3.5, 3.6, and 3.7).

The pooled incidence estimate for observations of children 0-4 years only (n=13 studies) was 79.79 (95% CI 60.19 – 102.06), with considerable heterogeneity (I^2=92.54%). For observations

Table 3.2 Study characteristics and annual incidence rates of epilepsy per 100,000 children 0-4 years

Author (year)	Location	Incidence years	Design	Case Identification:		Incidence Rate /100,000 (95% Confidence Interval)
				Strategy	Source	
Blom et al. (1978)	Västerbotten, Sweden	1973-1974	Prospective	Surveillance	Multiple	130.86 (84.73 – 202.05)
Hauser et al. (1993)	Rochester, USA	1935-1984	Retrospective	Medical registry	Single	67.13 (56.55 – 79.70)
Olafsson et al. (1996)	Iceland	1993	Retrospective	Medical registry	Multiple	112.30 (59.10 – 213.31)
Kurtz et al. (1998)	UK	1958	Prospective	Questionnaire	Single	58.15 (43.46 – 77.79)
Annegers et al. (1999)	Texas, USA	1988-1994	Retrospective	Medical registry	Single	67.0 (48.82 – 91.94)
Beilmann et al. (1999)	Estonia	1995-1997	Prospective	Surveillance	Multiple	76.08 (60.52 – 95.64)
MacDonald et al. (2000)	London, UK	1995-1996	Prospective	Medical registry & surveillance	Multiple	86*
Freitag et al. (2001)	Heidelberg/ Mannheim, Germany	1999-2000	Prospective	Surveillance	Multiple	76.80 (46.55 – 126.68)
Saha et al. (2008)	West Bengal, India	1992-1998	Prospective	Questionnaire	Single	129.45 (70.33 – 238.14)
Martinez et al. (2009)	UK	2005	Retrospective	Medical registry	Single	56.97 (43.78 – 74.14)
Banerjee et al. (2010)	Kolkata, India	2003-2008	Retrospective	Questionnaire	Single	63.35 (34.42 – 116.59)
Casetta et al. (2012)	Ferrara, Italy	1996-2005	Prospective	Medical registry & surveillance	Multiple	68.76 (54.78 – 86.31)
Cesnik et al. (2013)	Ferrara, Italy	2007-2008	Prospective	Medical registry & surveillance	Multiple	63.69 (30.85 – 131.42)
Meeraus et al. (2013)	UK	2001-2008	Retrospective	Medical registry	Single	130.06 (122.45 – 138.13)

*excluded from meta-analysis (no population statistics)

Table 3.3 Study characteristics and annual incidence rates of epilepsy per 100,000 children <1 year

Author (year)	Location	Incidence years	Design	Case Identification:		Incidence Rate /100,000 (95% Confidence Interval)
				Strategy	Source	
Sillanpää (1973)	SW Finland	1961-1964	Retrospective	Medical registry	Single	92.0 (72.58 – 116.60)
Blom et al. (1978)	Västerbotten, Sweden	1973-1974	Prospective	Surveillance	Multiple	95.72 (32.56 – 281.08)
Doose and Sitepu (1983)	Kiel, Germany	1957-1966	Retrospective	Medical registry	Single	201.6*
Granieri et al. (1983)	Ferrara, Italy	1964-1978	Retrospective	Surveillance	Multiple	212.02 (137.30– 327.28)
Benna et al. (1984)	Alba-bra, Italy	1974-1978	Retrospective	Medical registry & surveillance	Multiple	211.14 (133.60 – 333.53)
Joensen (1986)	Faroe Islands	1970-1980	Retrospective	Medical registry	Multiple	202.87 (124.91 – 329.30)
Tsuboi (1988)	Fuchu, Tokyo	1974-1980	Retrospective	Surveillance	Single	193.62 (137.90 – 271.78)
Hauser et al. (1993)	Rochester, USA	1935-1984	Retrospective	Medical registry	Single	86.30 (62.34 – 119.44)
Camfield et al. (1996)	Nova Scotia, Canada	1977-1985	Retrospective	Medical registry	Single	118.14 (98.20–142.12)
Olafsson et al. (1996)	Iceland	1993	Retrospective	Medical registry	Multiple	256.41 (99.76 – 657.45)
Kurtz et al. (1998)	UK	1958	Prospective	Questionnaire	Single	90.35 (53.83 – 151.60)
Freitag et al. (2001)	Heidelberg/Mannheim, Germany	1999-2000	Prospective	Surveillance	Multiple	145.86 (62.32 – 341.01)
Dura-Trave et al. (2008)	Navarre, Spain	2002-2005	Prospective	Surveillance	Single	95.30 (62.95 – 144.27)

Table 3.3 continued

Martinez et al. (2009)	UK	2005	Retrospective	Medical registry	Single	84.25 (56.63 – 125.34)
Wirrell et al. (2011)	Rochester, USA	1980-2004	Retrospective	Medical registry	Single	102.40 (77.69 – 134.96)
Cassetta et al. (2012)	Ferrara, Italy	1996-2005	Prospective	Medical registry & surveillance	Multiple	109.42 (72.93 – 164.14)
Eltze et al. (2013)	London, UK	2005-2006	Prospective	Surveillance	Single	82.10 (63.24 – 106.59)
Meeraus et al. (2013)	UK	2001-2008	Retrospective	Medical registry	Single	220.19 (201.56 – 240.54)

*excluded from meta-analysis (no population statistics)

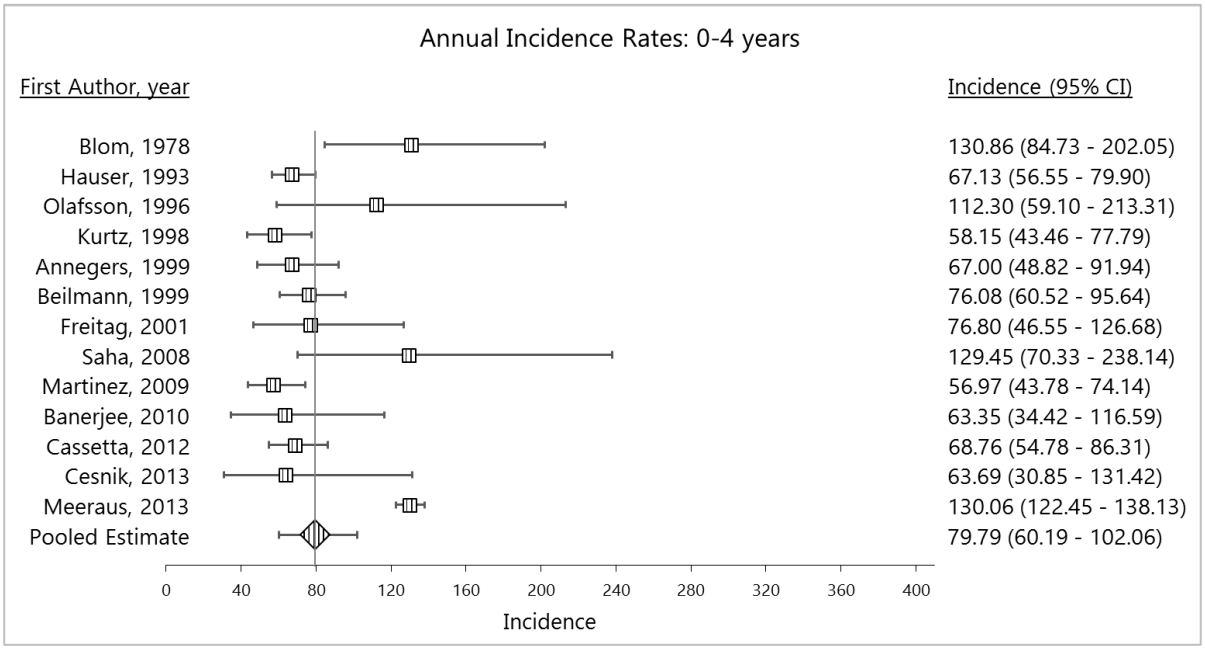
Table 3.4 Study characteristics and annual incidence rates of epilepsy per 100,000 children 1-4 years

Author (year)	Location	Incidence years	Design	Case Identification:		Incidence Rate /100,000 (95% Confidence Interval)
				Strategy	Source	
Blom et al. (1978)	Västerbotten, Sweden	1973-1974	Prospective	Surveillance	Multiple	139.92 (87.38 – 223.97)
Granieri et al. (1983)	Ferrara, Italy	1964-1978	Retrospective	Surveillance	Multiple	100.40 (72.20 – 139.59)
Hauser et al. (1993)	Rochester, USA	1935-1984	Retrospective	Medical registry	Single	61.87 (50.57 – 75.70)
Olafsson et al. (1996)	Iceland	1993	Retrospective	Medical registry	Multiple	77.47 (33.10 – 181.24)
Freitag et al. (2001)	Heidelberg/Mannheim, Germany	1999-2000	Prospective	Surveillance	Multiple	62.10 (33.73 – 114.28)
Wirrell et al. (2011)	Rochester, USA	1980-2004	Prospective	Medical registry	Single	65.30 (54.70 – 77.96)
Cassetta et al. (2012)	Ferrara, Italy	1996-2005	Prospective	Medical registry & surveillance	Multiple	58.89 (44.80 – 77.42)

Table 3.5 Study characteristics and annual incidence of epilepsy per 100,000 children <2 years

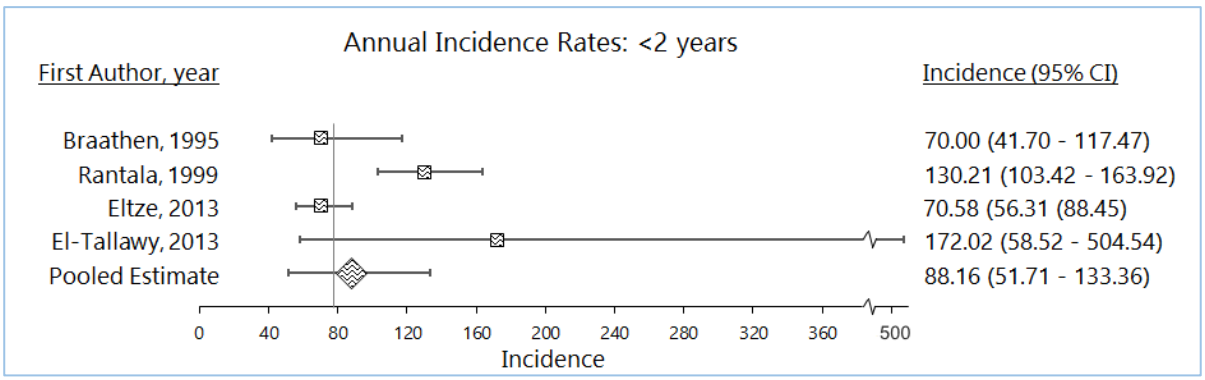
Author (year)	Location	Incidence years	Design	Case Identification:		Incidence Rate (95% CI)
				Strategy	Source	
Braathen and Theorell (1995)	Huddinge, Sweden	1990-1992	Prospective	Surveillance	Multiple	70 (41.70 – 117.47)
Rantala and Ingalsuo (1999)	Oulu, Finland	1976-1986	Prospective	Medical registry	Multiple	130.21 (103.42 – 163.92)
Eltze et al. (2013)	London, UK	2005-2006	Prospective	Surveillance	Single	70.58 (56.31 - 88.45)
El-Tallawy et al. (2013)	Al Kharga, Egypt	2007-2008	Prospective	Surveillance	Single	172.02 (58.52 – 504.54)

Figure 3.4 Forest plot: Annual incidence rate per 100,000 children 0-4 years



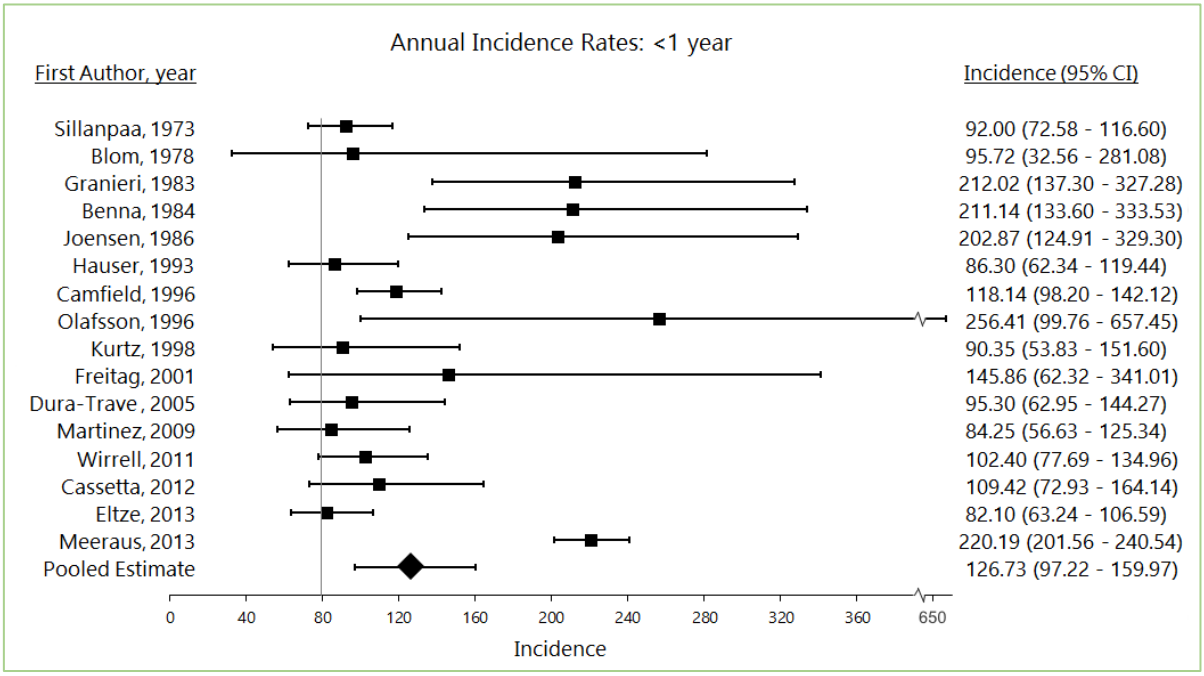
Vertical line represents 0-4 years pooled estimate

Figure 3.5 Forest plot: Annual incidence per 100,000 children <2 years



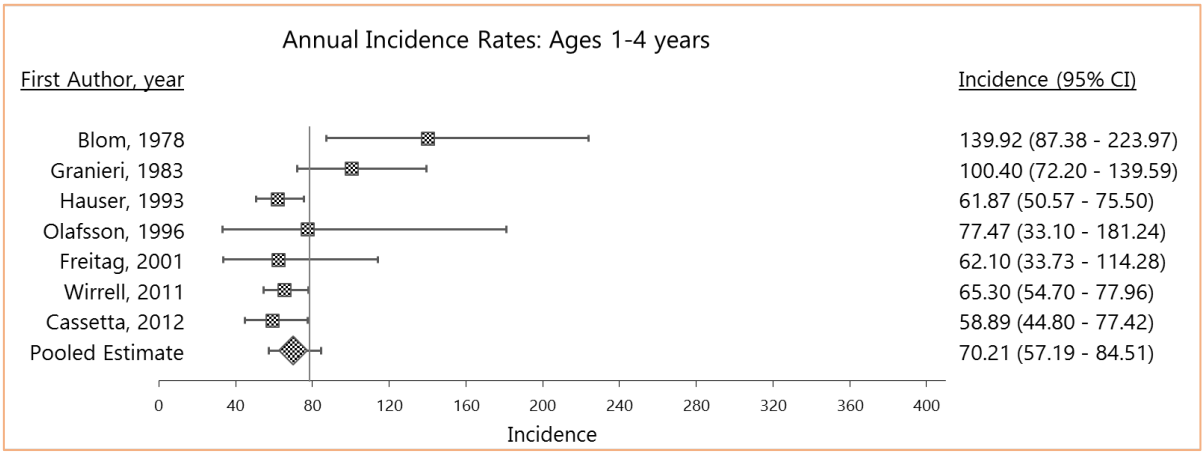
Vertical line represents 0-4 years pooled estimate

Figure 3.6 Forest plot: Annual incidence rates per 100,000 children <1 years



Vertical line represents 0-4 years pooled estimate

Figure 3.7 Forest plot: Annual incidence 1-4 years (per 100,000)



Vertical line represents 0-4 years pooled estimate

of children <1 years only (n=17 studies), the estimated pooled incidence was 126.73 (95% CI 97.22 – 159.97), and was 70.21 (95% CI 57.18 – 84.51) in observations of children aged 1-4 years only (n=7 studies). There was greater heterogeneity in <1 age group (I^2=90.21%), compared to 1-4 years (I^2=56.49%). Age was directly compared by inputting observations of ages <1 and 1-4 into a regression model (24 observations from n=17 studies). Age explained 19.45% of the variance (R^2_{adj}) (p=.024), with heterogeneity remaining substantial (I^2_{res}=86.27).

Univariate analysis of heterogeneity using study-level covariates revealed that heterogeneity was not significantly explained by study design, case identification strategy, case identification source, or risk of bias, in any of the age stratifications.

Incidence rate ratios were examined by including data from all unique observations from ages <1, <2, 1-4, and the remaining unique studies for ages 0-4 years - done in order to avoid duplication of underlying populations between observations (32 observations from n=25 studies). Incidence rates of covariate levels were similar, whilst all had considerable variance, and are displayed in table 3.6. Additionally, risk of bias did not significantly explain heterogeneity in incidence estimates (ß=1.51 (95% CI -4.54, 7.56), p=.6). No single covariate could significantly explain variance in incidence estimates.

Table 3.6 Rate Ratios for study covariates

Covariate	*Rate Ratio (95% CI)*
Study design: retrospective vs prospective	1.31 (-1.15, 2.62)
Case identification strategy: medical registry vs surveillance	1.05 (-1.90, 2.14)
Case identification source: multiple vs single	1.03 (-1.80, 1.97)
Income: Low/Middle vs High	0.94 (-3.40, 3.06)

Only four studies looked directly at socioeconomic aspects of incidence rates (Banerjee et al., 2010; El-Tallaway et al., 2008; Meeraus et al., 2013; Granieri et al., 1983). No difference in incidence rates were found between urban and rural communities in Egypt or Italy (El-Tallaway et al., 2008; Granieri et al., 1983), slums and nonslum communities in India (Banerjee et al., 2010), between areas of increasing social deprivation in the UK (Meeraus et al., 2013), or between populations in Italy when based on occupation status (Granieri et al., 1983), although this latter finding was based on both children and adults. Similar to data on socioeconomic status, there was extremely limited data on ethnicity, with only two studies reporting incidence based comparisons. In the United States, Annegers et al. (1999) found increased incidence of epilepsy in African-American and Hispanic children <5 years, compared to non-Hispanic white children. In the UK, Eltze et al. (2013) reported a higher incidence of epilepsy in Asian children ≤2 years compared to white children, but there was no increased risk in Black and mixed Asian-white children.

Data on age-gender-specific incidence rates were limited. There were 17 age-gender-specific observations from 13 studies (table 3.7). Population denominators were available in only four studies (n=8 observations) (Banerjee et al., 2010; Beilmann et al., 1999; Cassetta et al., 2012; Olafsson et al., 1996), which were inputted into a meta-analysis. In observations of children 0-4 years, estimates ranged between 51.9 and 145.1 in males, and between 68.17 and 82.9 in

Table 3.7 Age-gender-specific epilepsy incidence rates per 100,000 children per year

Author, year	*Age*	*Males* *Incidence (95% CIs)*	*Females* *Incidence (95% CIs)*
Olafsson et al, 1996†	0-4	145.14 (53.26-315.90)	77.34 (15.95-226.02)
Annegers et al, 1999	0-4	51.8	82.9
Beilmann et al, 1999†	0-4	74.96 (52.78-103.33)	77.27 (54.12-106.98)
Banerjee et al, 2010†	0-4	59.17 (1.50-329.68)	68.17 (1.73-379.80)
Cassetta et al, 2012†	0-4	66.00 (46.47-90.98)	70.80 (49.85-97.59)
Pooled	0-4	71.09 (45.66-96.52)	73.76 (46.99-100.52)
Sillanpaa 1973	<1	110	75
Doose et al, 1983	<1	230.5	170.6
Granieri et al, 1983	<1	353.2	81.3
Benna et al, 1994	<1	214.4	207.2
Olafsson et al, 1996†	<1	375.47 (77.43-1097.28)	131.41 (3.33-732.15)
Freitag et al, 2001	<1	158	109
Cassetta et al, 2012†	<1	79.77 (36.48-151.43)	134.13 (73.33-225.04)
Eltze et al, 2013*	<1	85 (70-103)	79 (60-95)
Pooled	<1	149.65 (-1446.52, 1745.83	133.94 (-305.15, 573.04)
Granieri et al, 1983	1-4	81.4	118.8
Olafsson et al, 1996†	1-4	89.96 (18.55-262.89)	64.14 (7.77231.71)
Freitag et al, 2001	1-4	72	51
Cassetta et al, 2012†	1-4	62.53 (41.55-90.38)	55.00 (34.87-82.53)
Pooled	1-4	63.88 (-82.44, 210.20)	55.55 (-85.63, 196.72)

† Data inputted into meta-analysis

* Data estimated from figure

females. Pooled estimates (n=4 observations) were roughly equivalent in males 71.09 (95% CI 45.66-96.52), and females 73.76 (95% CI 46.99-100.52). Gender-specific estimates for children <1 years were higher in males in all but one study, ranging from 79.8 to 375.5, and 75 to 207.2 in females. Pooled estimates (n=2), however, were similar. 149.65 (95% CI -1446.52, 1745.83) in males, and 133.94 (95% CI -305.15, 573.04) in females. In observations of children 1-4 years, estimates were narrower. Pooled estimates in males were 63.88 (95% CI -82.44, 210.20), and 55.55 (95% CI -85.63, 196.72) in females.

Infantile Spasms Studies

There were 10 studies reporting the cumulative incidence of infantile spasms based on 553 cases over 1,551,977 live births. Study characteristics are presented in table 3.8. Infantile spasms was defined in most studies by the presence of spasms, and hypsarrhythmia on EEG, although definitions were not always stated. The majority of studies were published in a narrow time period, with eight of the ten studies published between 1994 and 2002, with the remaining two studies published in 1979 and 2009. Despite this, population birth cohorts were monitored between 2 and 21 years within studies, and in a notable 31 consecutive years in Uusimaa County, Finland (Riikonen and Donner, 1979; Riikonen, 2001a). All studies were retrospective design, with three studies unclear about case identification methods (Hino-Fukuyo, Haginoya, Iinuma, Uematsu, and Tsuchiya 2009; Riikonen 2001a; Riikonen & Donner 1979).

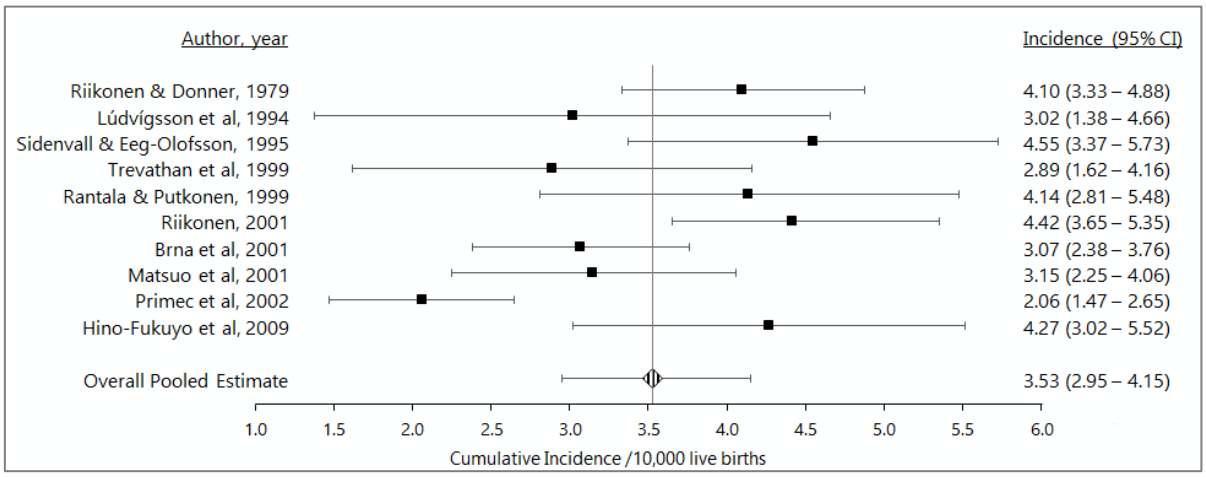
The range of cumulative incidence estimates for infantile spasms was relatively narrow, ranging between 2.06 and 4.55 per 10,000 live births (forest plot figure 3.8). Pooled incidence was estimated at 3.53 (95% CI 2.95 – 4.15) per 10,000 live births, with significant heterogeneity in between-study incidence estimates (I^2 73.24%). There was insufficient sub-group sample sizes for study-level covariates to perform meaningful meta-regression. Aetiological data was reported in 9 studies. Symptomatic causes were reported in 50-83% (median 75%) of cases, and cryptogenic or idiopathic aetiologies in 17-50% (median 25%). Aetiology was univariately assessed using the proportion of cases with symptomatic aetiology as a continuous variable. Aetiology explained 50.30% (R^2_{adj}) of between-study variance, although this, marginally, did not reach statistical significance (p=.053). With each one percent increase in the number of symptomatic cases, cumulative incidence increased by 0.05 (95% CI -.001, .103).

Table 3.8 Incidence of Infantile Spasms per 10,000 live births

Author (year)	Location	Incidence years	Study Design	Case Identification:		Cumulative Incidence (96% Confidence Interval)
				Strategy	Source	
Riikonen & Donner (1979)	Uusimaa, Finland	1960-1976	Retrospective	Unclear	Unclear	4.10 (3.40 – 4.96)
Lúthvígsson et al. (1994)	Iceland	1981-1990	Retrospective	Medical Registry & Surveillance	Multiple	3.02 (1.76 – 5.16)
Sidenvall and Eeg-Olofsson (1995)	Central Sweden	1987-1991	Retrospective	Medical Registry	Multiple	4.55 (3.51 – 5.89)
Trevathan et al. (1999)	Atlanta, USA	1975-1977	Retrospective	Surveillance	Multiple	2.89 (1.87 – 4.46)
Rantala and Putkonen (1999)	Oulu, Finland	1976-1986	Retrospective	Medical Registry	Multiple	4.14 (3.01 – 5.71)
Riikonen (2001a)	Uusimaa, Finland	1977-1991	Retrospective	Unclear	Unclear	4.42 (3.65 – 5.35)
Brna et al. (2001)	Nova Scotia/ Prince Edward Island, Canada	1979-1998	Retrospective	Medical Registry	Multiple	3.07 (2.45 – 3.85)
Matsuo et al. (2001)	Nagasaki, Japan	1989-1998	Retrospective	Surveillance	Single	3.15 (2.37 – 4.19)
Primec et al. (2002)	Slovenia	1985-1995	Retrospective	Medical Registry & Surveillance	Multiple	2.06 (1.55 – 2.74)
Hino-Fukuyo et al. (2009)	Miyagi, Japan	2000-2005	Retrospective	Surveillance	Unclear	4.27 (3.19 – 5.72)

There was insufficient information to statistically analyse gender differences. Eight of 10 studies stated the absolute number of males and females with infantile spasms but gender-specific population denominators were not reported (Brna et al., 2001; Hino-Fukuyo et al., 2009; Matsuo et al., 2001; Primec et al., 2002; Rantala and Putkonen, 1999; Luthvigsson et al., 1994; Riikonen, 2001a; Sidenvall and Eeg-Olofsson, 1995). Gender-specific incidence was reported in only one study, with a male predominance (4.5 vs 1.4 per 10,000 live births; Luthvigsson et al., 1994). In total, across studies, there were 239 males with infantile spasms, and 189 females reported.

Figure 3.8 Forest plot: Cumulative incidence of infantile spasms per 10,000 live births



Vertical bar represents pooled estimate

3.2.8 Systematic Review: Discussion

Children with Early-Onset Epilepsy

The incidence of early-onset epilepsy was estimated at 79.79 (95% CI 60.19 – 102.06) per 100,000 children ≤4 years. As expected, annual incidence rates in CWEOE were highest in the first year of life compared to years 1-4. In the few studies which reported incidence data for each year, peak incidence was in the first year of life as expected (Beilmann et al., 1999; Kurtz et al., 1998; Meeraus et al., 2013). There was no definitive pattern across individual years 1 through 4, with both a gradual decline (Meeraus et al., 2013), and variable age point estimates (Beilmann et al., 1999; Kurtz et al., 1998) reported. In those latter two studies, a second peak at age three years was noted.

Gender differences in children with epilepsy were inconclusive. Inconsistent findings were driven by inadequate data, due to limited reporting of gender-population denominators, as

well as considerable variability in incidence or absolute values between-studies and resulting wide confidence intervals. Although there is a slight male bias observed across the lifespan (Christensen et al., 2007; Forsgren et al., 2005; Kotsopoulos 2002), pooled estimates between genders in children ≤4 years were similar.

There was limited data on the incidence of early-onset epilepsy in the UK, with four studies reporting incidence estimates for the selected age stratifications. For observations of age 0-4 years, two studies reported annual incidence rates of 57 and 58 (Kurtz et al., 1998; Martinez et al., 2013), with one further study recording a notably larger estimate of 130 (Meeraus et al., 2013). There was no data for children 1-4 years, but the incidence for <1 years was estimated at 82-90 in three studies (Eltze et al., 2013; Kurtz et al., 1998; Martinez et al., 2013), and 220 in Meeraus et al. (2013). The large discrepancy between these data reported by Meeraus et al. and three alternative studies may be partially explained by first stage case identification methods, resulting in possible underestimation (Eltze et al., 2013; Kurtz et al., 1998), or overestimation (Meeraus et al., 2013). To explain, Meeraus et al. used three indicators for epilepsy classification with differing levels of sensitivity. The data above was formulated on their most liberal indicator (i.e. a prescription for an AED, epilepsy diagnosis code, or code for two or more non-febrile seizures). Although they found lower incidence rates based on more restrictive criteria in 0-7 year old children, that information was not available for children ≤4 years only. Interestingly, Kurtz et al. (1998) also noted higher estimations when similar selection criteria was applied in their prospective birth cohort (table 1, p316), but their final estimations were based on validation of individual cases through extensive interview and review of medical records. Meeraus et al. did perform a validation on 10% of their sample by examining medical records for further evidence of epilepsy - or for the absence of other diagnoses that could explain AED prescription. The authors found corroboratory evidence in 82-100% of children. This suggests that a combination of case identification and validation methods may play a role in these discrepancies. Kurtz et al. (1998) suggested that their data may be an underestimation due to uncertainty surrounding cases who died, particularly those in the early-onset period, where no medical information was obtained other than that stated on the death certificate. In the remaining UK studies, Eltze et al. (2013) used multi-tiered capture-recapture methods for first stage case identification, statistically compensating for potentially missing cases. Under-ascertainment was estimated at 24%, and additional studies are needed to corroborate estimations. Whilst all studies mentioned here, contributed extremely important and useful incidence data, complementary research in the UK that uses comprehensive case detection

methods with individual case validation for all cases in a prospective population-based cohort is required, in order to provide further clarification.

As well as providing pooled incidence estimates, this systematic review explored the variance in estimates using study-level covariates. Whilst age explained some of the variance between studies, most of the heterogeneity remained unexplained. An attempt was made in this review to partition study-level variables based on broad methodological variables that could theoretically influence estimates. In practice, studies varied in their approach often using combinations of these methodological factors, with individual differences often within the same methodological covariate. Above, it was suggested that the variance in incidence estimates between studies in the UK could be partially explained by close scrutiny of methodological differences. This suggests that any single methodological factor may not be enough in and of itself to explain variability in estimates, although further exploration of covariates in larger sample sizes is required. Modest study and observation sample sizes restricted the ability to investigate interaction effects between these variables in meta-analysis. It should also be noted that the risk or bias assessment used in this study attempted to take into consideration methodological biases. However, this had two potential limitations. The first is that, the risk of bias gave an assessment of methodological bias but did not indicate the direction of bias. That is, it was not determined if the specific study bias could lead to overestimation, or to underestimation. Second, the methodological factors were scored equally, and it may be the case that certain factors have greater or lesser influence on heterogeneity. Therefore, further development of such a system is needed to weight the variables appropriately. Although, heterogeneity could not be adequately explained in this study, it is important to note that incidence estimates are likely to vary temporally and across geographical locations (Sillanpaa et al., 2011). As such, it is important to ascertain incidence estimates in different locations in order to plan targeted resource provision.

Several of the study-level covariates necessitate further mention. First, in a meta-analytic review of epilepsy incidence in adults and children, Ngugi et al. (2011) found higher estimates in prospective studies compared to retrospective. The current review found no significant difference. The reason for this is unknown, although differences in methodologies and inclusion/exclusion criteria may offer potential explanation. Ngugi et al. included hospital-based studies and research database studies, and their review was based on studies of adults and children of all ages, where the present review included only children ≤4 years. It is unclear however, what effect these methodological differences might have had. Second, higher income

countries have higher incidence estimates than low/middle income countries (Kotsopoulos, 2002; Ngugi et al., 2011). There were limited studies from lower/middle income countries in the present study with which to make a robust comparison. Based on the very limited data available, income status of the country did not explain variance in incidence estimates.

Similarly, few studies directly investigated SES or ethnicity as a risk factor for epilepsy incidence in children with early-onset epilepsy. In those that did, no effect of SES was apparent. This finding was based on only four studies using different indicators of SES (i.e. rural vs urban dwellers, slum vs nonslum, and social deprivation), meaning that the relationship still remains unclear. Only two studies reported data on ethnicity, making this a particularly neglected area of study in early-onset epilepsy. It is interesting to note that while adult studies have found no difference in incidence estimates between ethnicities, the two studies of early-onset epilepsy reported here did so (Annegers et al., 1999; Eltze et al., 2013). This raises the possibility that different ethnicities present different risk factors for early-onset epilepsy, and studies reporting incidence estimates of various childhood and adult populations should take this into consideration. Direct evidence for this came from Annegers et al. (1999), who found higher incidence rates in African-American and Hispanic children <5 years, but similar rates in other childhood and adult age stratifications.

Infantile Spams/West Syndrome

The incidence of infantile spasms appears relatively stable across studies, ranging between 2.06 and 4.55 per 10,000 live births. Primec et al. (2002) reported the lowest incidence figure. The authors assumed that all cases from community hospitals would be redirected to their centre, but it was unclear if attempts were made to verify this, raising the possibility of missing cases lost to sampling bias. Nevertheless, all estimates lay in a relatively narrow band. Three commonly cited studies, which were not included in this review -because of estimates drawn from single or multiple centres with limited population coverage - provided lower estimates of 0.6 (Chen et al., 2004) and 1.68 (Hwang and Korean Child Neurology, 2001), with the third providing a population adjusted estimate of 3.1 (Lee and Ong, 2001), similar to the estimates from studies reviewed in this article.

A relationship across time could not be directly addressed in the analysis due to a narrow period of study publication. Three studies did find a high degree of stability across time within their respective populations (Riikonen and Donner 1979; Riikonen 2001a; Sidenvall and Eeg-

Olofsson 1995), with two of those showing stability across a 32 year observation period from 1960-1991 in one region of Finland (Riikonen & Donner 1979; Riikonen 2001a). In contrast, Brna et al. (2001) found a notable decrease in overall trend after 1993 – suggesting the possibility that incidence is in decline. However, the authors also found a high degree of yearly variability, and noted that this variability may distort any true overall trend. One study in this review was conducted solely after 1993, reported an incidence estimate at the higher end of the scale; 4.27 (Hino-Fukuyo et al., 2009), providing contradicting evidence. Should a relative overall stability in incidence remain, it would suggest that improvements in pre- and perinatal care have had little impact in decreasing the risk of infantile spasms over time.

Gender differences in infantile spasms could not be reliably assessed due to an absence of gender-specific population denominators. However, there were more male cases in absolute terms, cautiously suggesting that males may be at more at risk of developing infantile spasms than females. It is recommended that future studies include gender statistics for a robust evaluation.

Between-study heterogeneity remained unexplained. The small number of studies reviewed here had considerable homogeneity in methods, meaning that only aetiology could by factored into meta-regression. A trend toward aetiology was found, with higher proportions of symptomatic cases positively correlated with cumulative incidence. There was evidence of regional variation in incidence estimates (Hwang and Korean Child Neurology, 2001; Sidenvall and Eeg-Olofsson, 1995), as well as annual variations in incidence rates (Brna et al., 2001), and are two further factors that have the potential to explain some of the additional heterogeneity.

Limitations

The main limitation of the findings presented here, was that the exploration of heterogeneity was limited by the number of studies that could be modelled in meta-regression. Each study used various methodological approaches, and multivariate linear regression would have been preferred in order to explore combinations of methodological approaches. An attempt was made to assess risk of bias, which may have partly taken this into consideration. However, this did not significantly explain heterogeneity. One alternative possibility to explain between study heterogeneity could be argued, and which rests with differences in case identification sources. In this review, we considered single vs multiple identification sources, and surveillance vs medical registries. However, different studies may use different practices subsumed under the

same covariate. Medical coding procedures for instance may be defined differently according to country or site, or response rates from human informers during active surveillance may be variable between studies. Such variability would not have been identified in the current review. Nevertheless, the non-significant differences between study level covariates suggests that significant variation between study estimates remains, and which could be explained by other factors, such as regional and temporal variations in epilepsy incidence.

A methodological limitation of this review itself was that the study search was conducted by, and inclusion/exclusion criteria applied by, a single reviewer. Consequently, it is possible that some articles may have been missed. Additionally, infantile spasms specific articles were not the original intention of this review at conception, which increases the possibility that studies focused on infantile spasms were missed. However, epidemiological studies are well defined, and easily identifiable in literature searches, which would have reduced the risk of missing data. As one study was missed despite a comprehensive systematic approach, it highlights the benefits of using a systematic review search strategy than relying only on electronic searches only. To reduce this risk further, the systematic search was supplemented by screening papers for additional references.

Conclusion

In conclusion, this review was aimed at describing the pooled incidence estimates of CWEOE, and factors influencing heterogeneity in estimates between studies. It did so in general populations of epilepsy, and in those with infantile spasms, a common and well-studied early-onset syndrome. As expected, incidence estimates were higher in the first year of life compared to years 1-4. Whilst age explained some of the variance in epilepsy, most remained unexplained. In infantile spasms studies, methods were relatively narrow, and the heterogeneity of incidence in studies of infantile spasms was unexplained, although aetiology was a likely contributor. It is recommended that future incidence studies using early-onset epilepsy populations take into account age-gender-specific estimates, whilst reporting underlying population characteristics. It is also recommended that data on ethnic groups, and SES be examined in order to better understand the relative risk.

3.3 Requirement for a Prospective Incidence Study in Early-Onset Epilepsy in the UK

In addition to synthesising data from a review of studies, the systematic review identified several issues in the current literature on the incidence on early-onset epilepsy in the UK. First, there was limited up-to-date data on early-onset epilepsy in the UK. Most of the incidence data from the UK were gathered in the 1990s, and with evidence suggesting the incidence of childhood epilepsy is decreasing over time in children (Cowan, 2002; Kotsopolous, 2002), including in the UK (Meeraus et al., 2013), new data are required to monitor trends as well as to help identify time-relevant risk factors. Second, there is a need for population-based studies, with prospective case identification, and with well-defined and validated epilepsy. The four UK studies identified in the review used different methods of first stage case identification (i.e. pre-validation stage), and epilepsy verification. Eltze et al. (2013) and Kurtz et al. (1998) surveyed data sources at first stage, which can have varying levels of response rates. The two remaining studies retrospectively accessed medical registry coding (Martinez et al., 2009; Meeraus et al., 2013), which are reliant on the accuracy of diagnostic coding, potentially increasing risk of miscoding, and under- or over-diagnosis. In addition, Meeraus et al. (2013) demonstrated that incidence varies depending on the selection criteria used when using coding systems. All studies validated or partially validated the diagnosis of cases, providing improved accuracy of validated epilepsy post-case identification. That said, there is a need for complementary, prospective, population-based data that includes both a comprehensive approach to case identification, and full validation of epilepsy diagnoses. Third, prospective studies on the incidence of infantile spasms are required to supplement the existing retrospective data, and to provide up-to-date information. Fourth, there is very limited data on SES and ethnic risk factors for epilepsy in the UK. Lastly, data on the incidence of epilepsy and infantile spasms has not been gathered in Scotland, and such data will allow comparison of geographical data to past and future studies in the UK.

In addition to a basic knowledge requirement, incidence studies can provide detailed descriptive information on the age-related profiles of children with epilepsy. They provide a platform from which to identify age-related risk factors of epilepsy, and region or economic-specific data from which to guide policy making and advise on resource provision. Incidence data at different time points allows the assessment of change, and provides valuable information on the development of risk factors, and to determine the successes or failures of health policy changes and preventative measures. The establishment of a population-based cohort in the present study provided the platform on which to investigate the cognitive and behavioural development of a representative sample of CWEOE. The remainder of this chapter describes the study methods and resulting findings.

4. Incidence of Early-Onset Epilepsy: Methods

The systematic review on the incidence of early-onset epilepsy (section 3) revealed that updated data was required in the UK, and, for the first time, Scotland. From the UK studies identified in that review, it was concluded that complementary incidence estimates based on prospective population-based data with comprehensive case ascertainment methods and individually validated diagnoses were needed. Furthermore, socioeconomic data, and age- and gender-specific data using population denominators was required. This section describes the methods for the ascertainment of the incidence sample and estimates in the present NEUROPROFILES study.

4.1 Aims

As outlined in the previous chapter, the objective of Chapter II was to establish a population-based cohort of CWEOE with the primary research aim of determining the incidence of newly diagnosed early-onset epilepsy. Secondary research aims were as follows:

i) To describe the clinical and sociodemographic characteristics of the CWEOE cohort

ii) To provide gender and age-specific epilepsy incidence rates

iii) To provide ascertainment-adjusted epilepsy incidence rates, in order to account for potential missing cases, thereby providing the most accurate and comprehensive estimate

iv) To investigate SES and ethnicity as risk factors for epilepsy

v) To determine the cumulative incidence of infantile spasms

4.2 Participants

CWEOE were identified and recruited from the pre-defined population-based region. The description of which, and methods for case identification, can be found in Chapter I, section 2.

The reference population for analysis was comprised of all resident children aged ≤4 years (table 4.1) from the defined geographical location. Population statistics, including data on

ethnicity (table 4.3), were obtained from the 2011 Scottish Consensus (http://www.scotlandscensus.gov.uk/ods-web/standard-outputs.html). Statistics by age and gender can be found in table 4.2.

Table 4.1 Area population for children ≤4 years

Area	**Total**	**Male**	**Female**
Edinburgh	26,163	13, 234	12, 929
West Lothian	11,565	5, 952	5, 613
Fife	7,516	3, 886	3, 630
Total	45,244	23, 072	22, 172

Table 4.2 Total population by age and gender

Age (m)	**Total**	**Male**	**Female**
<12	9, 527	4, 856	4,671
12-23	9, 348	4, 775	4,573
24-35	9, 174	4, 605	4, 569
36-47	8, 917	4, 604	4, 313
48-59	8, 278	4, 232	4, 046

Population data on SES were based on Scottish Index of Multiple Deprivation 2012 data (SIMD; http://www.gov.scot/Topics/Statistics/SIMD; for more details on SIMD, see section 2.4). SIMD quintiles 1-3 were classified as low SES, and quintiles 4-5 as high SES. In the pre-defined general population, 63% of people reside in areas of low SES, and 37% in high SES areas.

The cumulative incidence of infantile spasms is typically reported according to the number of live births within the reference population. Statistics on live births was accessed from the Information Services Division Scotland (http://www.isdscotland.org/Health-Topics/Maternity-and-Births/Publications/data-tables.asp), with geography specific data supplied by the Information Services Division upon request from the candidate. Data was available for Edinburgh and West Lothian only. No gender-specific data was available. There were 13,825 live births from 1st April 2013 to 31st March 2015. Because the present study collected data over a 26 month period (May 2013 – June 2015), the total live births in Edinburgh and West Lothian over the study period was estimated at 14,977.

4.2.3 Statistical Analyses

(i) Cumulative Incidence and Annual Incidence Rates

Cumulative incidence, and annual incidence rates were calculated, applying the formulae described below, using the general population of 0-4 year old children from the defined geographical region. Age- and gender-specific values were calculated for age bands 1-11months, 12-23months, 24-35 months, 36-47 months, and 48-59 months using age and gender specific population statistics detailed in tables 4.2 and 4.3; and further summarised for ages 1-4 year and 0-4 years for comparison with studies identified from the systematic review (section 3).

Cumulative incidence was defined as the proportion of new cases of epilepsy over the period of data collection (1st May 2013 – 30th June 2015) from amongst the general population in our defined geographical region, i.e.

$$Cumulative\ Incidence\ = \frac{number\ of\ new\ cases\ over\ time\ period}{population\ at\ risk\ at\ beginning\ of\ time\ period} \times 100$$

Incidence rate was defined as the frequency of new cases from amongst the general population in our defined geographical regions per year. Incidence estimates were calculated using the following formula:

$$Incidence\ Rate = \frac{mean\ number\ of\ new\ cases\ over\ one\ year}{population\ at\ risk\ at\ beginning\ of\ time\ period} \times 10^5$$

95% Confidence intervals (CI) for rates were calculated in excel using Byar's approximation for Poisson distributions as described by the Association of Public Health Observatories (Eayres, 2008) (resource available from http://www.apho.org.uk/).

Cumulative incidence for infantile spasms was reported per 10,000 live births using the estimated number of live births in the general population. As identified in the systematic review in section 3, studies reporting the incidence of infantile spasms did not always provide a definition. Infantile spasms and West Syndrome are terms often used interchangeably. Both

terms reflect age-related onset of infantile spasms (usually in the first year of life) but with the definition of West syndrome including documented hypsarrhythmia on electroencephalograph (EEG) (Wong and Trevathan, 2001). In the present study, cumulative incidence calculation was based on those fulfilling criteria for West Syndrome only.

(ii) Ascertainment-adjusted Incidence Rate

Using the capture-recapture methods set out in chapter I section 2, the frequency of children identified from source 1, the neurology department, and from source 2, EEG departments, were used to estimate the number of possible missing cases. An adjustment to incidence rates accounting for missing cases was then made using Chao's lower bound estimator (figure 4, adapted from Brittain & Böhning, 2008). This is less sensitive to dependency of sources in a two-source model (Brittain & Böhning, 2008). Both unadjusted and adjusted incidence rates were reported for overall, and age- and gender-specific data.

Figure 4 Chao's estimator

	Neurology Department		
EEG Depts.	Identified	Not identified	
Identified	*f11*	*f01*	
Not identified	*f10*	*f00*ǂ	Nc

ǂ *estimated number of cases missing from both sources*
Nc Chao's estimated population size

$$f00 = \frac{(f10+f01)^2}{4f11}$$

$$Nc = f11 + f01 + f10 + f00$$

Under-ascertainment percentage = $\frac{f00}{Nc} \times 100$

(iii) SES and Ethnicity as Risk Factors for Epilepsy

The relative risk of developing epilepsy in the general population was determined for (i) SES, and (ii) ethnicity. Risk ratios were calculated for the likelihood of developing epilepsy for children residing from low SES areas compared to children residing from high SES areas. Risk ratios for developing epilepsy were also calculated for children from non-white ethnicities (i.e.

African/Caribbean and Asian) compared to children from white ethnicity (i.e. white-UK and white-European). In addition, risk ratios were calculated for individual ethnic sub-groups (i.e. African/Caribbean, Asian, and white-European), using white-UK as the comparator. Population statistics on SES and ethnicity were obtained from the Scottish 2011 Consensus (see section 4.2).

Risk ratios and 95% confidence intervals were calculated using the following formulae;

	Epilepsy	**Non-epilepsy**	**Total**
Subgroup 1	x_1	y_1	$x_1 + y_1$
Subgroup 2	x_2	y_2	$x_2 + y_2$

$$Risk\ Ratio = \frac{x_1/x_1 + y_1}{x_2/x_2 + y_2}$$

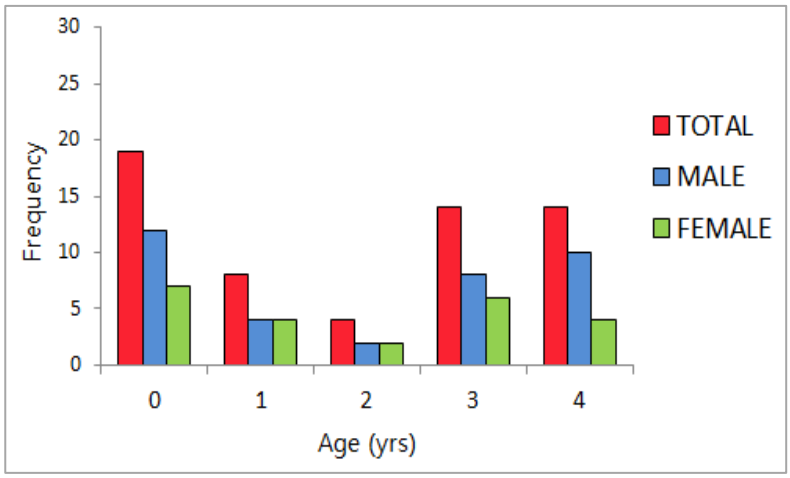
$$95\%\ CI = exp\left(Ln(Risk\ Ratio) \pm 1.96 \sqrt{\frac{(y_1/x_1)}{x_1 + y_1} + \frac{(y_2/x_2)}{x_2 + y_2}} \right)$$

5. Incidence of Early-Onset Epilepsy: Results

5.1 Population Descriptives

59 (36 Male, 23 Female) children from the general population were identified in the 26 months of data collection. 46 were recruited into the study and anonymised data were collected on the remaining 13. As explained in Chapter I, section 2, anonymised data on demographic and epilepsy characteristics (appendix D) were passed to the research team by a paediatrician within the child's care team. Children were predominantly white (n=51, 86%) vs non-white (n=8, 14%). 61% (n=36) of children were from a lower SES, and 39% (n=23) from a higher SES. Median age at epilepsy diagnosis was 28.52 (IQR 9.43 – 47.74), 1-59, months. Median age at first unprovoked seizure was 18.0 (IQR 6.0 – 36.0), <1-55, months. Epilepsy was most frequent at <1 years of age, with further spikes at ages three and four (figure 5.1). The median interval from age of onset (i.e. age at first unprovoked seizure, Thurman et al., 2011) to diagnosis was 4.4 (IQR 1.03 – 10.47), months.

Figure 5.1 Age at epilepsy diagnosis



Clinical characteristics are presented in table 5.1, and aetiological information is visually depicted in figure 5.2. Known structural causes were more common in the first two years of life, regardless of classification system. Examining the ILAE 1989 classification, symptomatic/cryptogenic and idiopathic aetiologies displayed a clear trend of increasing idiopathic cases with age. Across ages 0-4 years, idiopathic causes were most common,

Table 5.1 Clinical characteristics by age at epilepsy diagnosis

	Age (years)	Total N=59	0 n=19	1 n=8	2 n=4	3 n=15	4 n=13
	Sub-category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Aetiology (1989 ILAE Classification)	Unclassifiable	1 (1.7)	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)
	Idiopathic	33 (55.9)	6 (31.6)	5 (62.5)	2 (50.0)	9 (60.0)	11 (84.6)
	Cryptogenic	13 (22.0)	6 (31.6)	0 (0)	2 (50.0)	3 (20.0)	2 (15.4)
	Symptomatic	12 (20.4)	7 (36.8)	2 (25.0)	0 (0)	3 (20.0)	0 (0)
Aetiology (2010 ILAE Classification)	Genetic	22 (37.3)	5 (26.3)	3 (37.5)	2 (50.0)	7 (46.7)	5 (38.5)
	Structural/Metabolic	11 (18.6)	7 (36.8)	2 (25.0)	0 (0)	2 (13.3)	0 (0)
	Unknown	26 (44.1)	7 (36.8)	3 (37.5)	2 (50.0)	6 (40.0)	8 (61.5)
Mode of Seizure Onset	Focal	20 (33.9)	7 (36.8)	3 (37.5)	1 (25.0)	6 (40.0)	3 (23.1)
	Generalized	34 (57.6)	10 (52.6)	5 (62.5)	3 (75.0)	8 (53.3)	8 (61.5)
	Both	5 (8.5)	2 (10.5)	0 (0)	0 (0)	1 (6.7)	2 (15.4)
Pre-term Birth		5 (8.5)	2 (10.5)	1 (12.5)	(0)	2 (13.3)	0 (0)

Figure 5.2 Proportion of children with epilepsy by aetiological classification

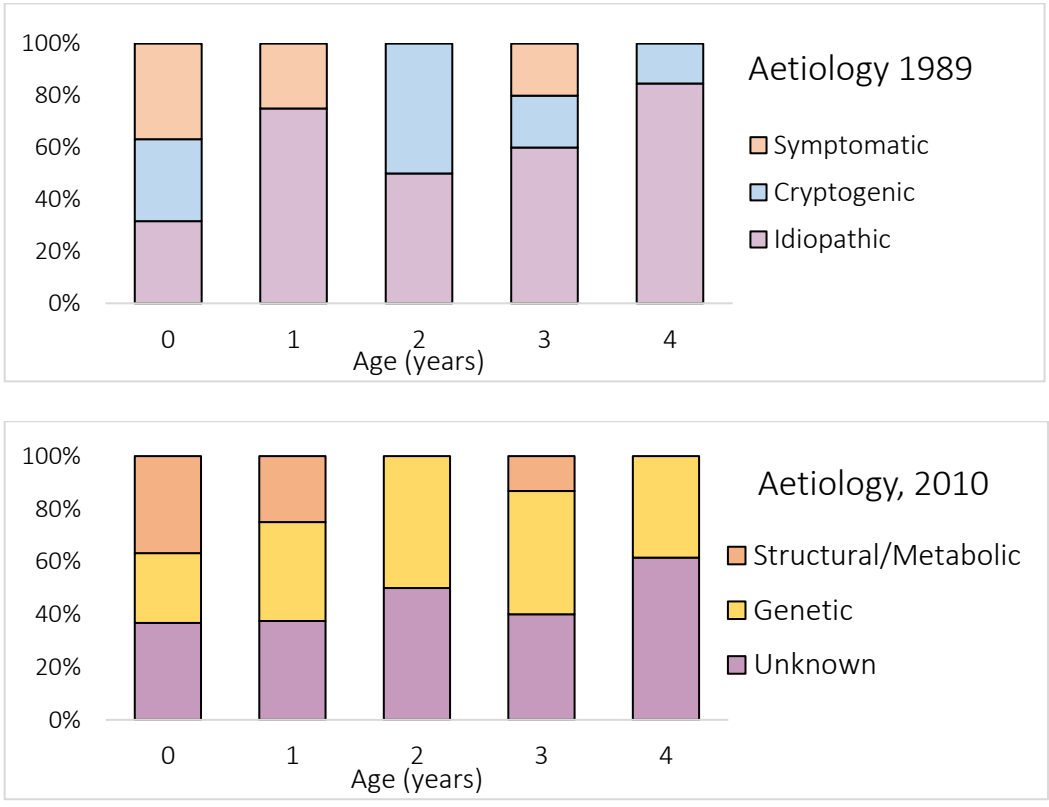


Table 5.2 Epilepsy syndrome classification table (developed according to ILAE, Berg et al., 2010)

Epilepsy Classification		*Syndrome*	*n=59*	*Known Causes*
Electroclinical Syndromes	Neonatal Period	Otahara Syndrome	1 (1.7%)	
	Infancy	Infantile Spasms/West Syndrome	10 (16.9%)	5x Structural - 2x HIE - 3x CM 5x Unknown
		Benign Infantile Epilepsy	3 (5.1%)	
		Benign Myoclonic Epilepsy of Infancy	1 (1.7%)	
	Childhood	Panayiotopoulos Syndrome	1 (1.7%)	
		Childhood Absence Epilepsy	5 (8.5%)	
		Generalised Epilepsy with Febrile Seizures +	1 (1.7%)	
		Benign Epilepsy with Centrotemporal Spikes	1 (1.7%)	
Distinctive Constellations		MTLE with HS	1 (1.7%)	
		Genetic Generalised Epilepsy	10 (16.9%)	
		Genetic Focal Epilepsy	4 (6.8%)	Presumed Genetic
Other Structural-Metabolic Causes		Focal Epilepsy	5 (8.5%)	3xCM 1xGliosis 1xTBI
Epilepsies of Unknown Cause		Mixed Focal & Generalised Epilepsy of Unknown Origin	2 (3.4%)	
		Generalised Epilepsy of Unknown Origin	8 (13.6%)	
		Focal Epilepsy of Unknown Origin	6 (10.2%)	

CM – Cerebral Malformation
HIE – Hypoxic-ischaemic encephalopathy
MTLE with HS – Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis
TBI – Traumatic Brain Injury

occurring in over half of children. In the 2010 classification system, the frequency of unknown and genetic causes were similar across ages.

Epilepsy classifications and seizure characteristics are described in table 5.2 and 5.3, respectively. Of the 59 children identified, 23 (39%) had two seizure types, and 4 (7%) had three seizure types.

Table 5.3 Seizure Type

Seizure Type	*n*	*%*
Focal	22	37.3
GTCS	20	33.9
Absences	17	28.8
Spasms	14	23.7
Myoclonic	5	8.5
Atonic	3	5.1
Unclassified	3	5.1
Clonic	2	3.4

5.2 Incidence

59 children (36M:23F) were diagnosed with early-onset epilepsy between 01.05.2013 and 30.06.2015 inclusive, providing a crude incidence rate of 60.19/100,000 children ≤4 years/year. Case ascertainment was high, with under-ascertainment estimated at 2.46%. Capture-recapture ascertainment-adjusted incidence was estimated at 61.71 (95% CI 40.22 – 88.14) (figure 5.3).

Figure 5.3 Capture recapture ascertainment adjusted estimate

		Neurology Departments		
		Identified, n	Not identified, n	
EEG Departments	Identified, n	43	6	Nc=61.71
	Not identified, n	10	1.49[ǂ]	

ǂ estimated number of missing cases

Nc Chao's estimated population size

Under-ascertainment percentage = ǂ/Nc*100 = 2.46% (M=1.02%, F=4.21%)

Age-specific cumulative incidence, unadjusted incidence rate, and ascertainment-adjusted incidence rates are listed in table 5.4. Incidence rate peaked in the first year of life, and was lower for years 1-4; 51.61 (95% CI 35.62 – 67.60) unadjusted, and 54.04 (95% CI 37.67 – 70.40) after ascertainment-adjustment. Incidence was lowest at age two years.

Table 5.4 Age-specific incidence

Age (year)	n	Population	Cumulative (100/26m)	Incidence rates per 100,000/y (95% CI)	
				Unadjusted	Ascertainment-adjusted
0	19	9527	.20	92.05 (39.70–172.42)	92.34 (39.70 – 172.42)
1	8	9348	.09	39.50 (9.04–101.75)	44.44 (11.66 – 109.56)
2	4	9174	.04	20.12 (1.18–69.94)	20.12 (1.18 – 69.94)
3	14	8917	.16	72.46 (24.69-146.46)	73.55 (28.09 – 154.13)
4	14	8278	.17	78.06 (26.60-157.76)	87.81 (34.00 – 174.23)
0-4	59	45244	.13	60.19 (39.33-86.83)	61.71 (40.22 – 88.14)

Variations in age-specific incidence reflected differences in age-related seizure types. The prevalence of GTCS and focal seizures was relatively stable across ages, while spasms and absence seizures had an age-related disposition. Peak incidence in the first year of life was attributed to spasms. 92% of children with spasms had onset <1 years of age. Likewise, the higher incidence at ages three and four years were attributed to the onset of absence seizures; 50% of children with absences had onset at age three, and 50% at age four.

Point incidence estimates were higher for males (table 5.5) than females (table 5.6), particularly at ages <1 and 4 years (figure 5.4). Confidence intervals of estimates between males and females overlapped at all ages, indicating uncertainty between true gender differences. Unadjusted incidence rate for age range 1-4 years in males was 60.72 (95% CI 36.43 – 85.00), and 42.13 (95% CI 21.49 – 62.77) for females. Ascertainment-adjusted incidence rate for ages 1-4 years was 62.54 (95% CI 37.89 – 87.18) in males, and 45.71 (95% CI 24.21 – 67.21) in females.

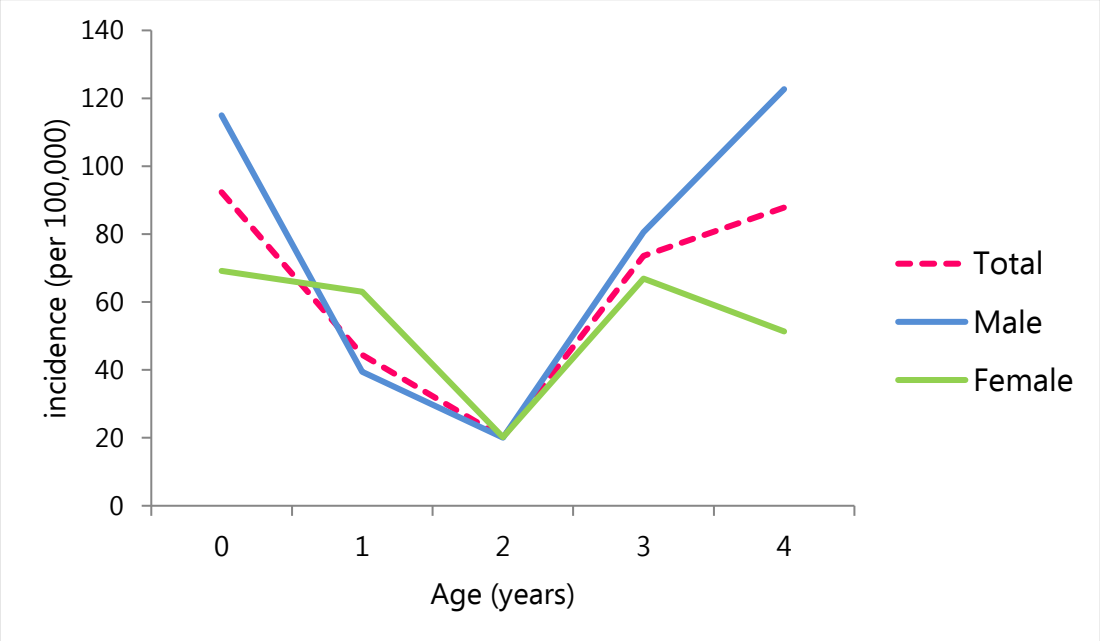
Table 5.5 Age-specific incidence estimates: Males

Age (year)	n	Population	Cumulative (100/26m)	Annual incidence per 100,000/yr (95% CI)	
				Unadjusted	Ascertainment-adjusted
0	12	4856	.25	114.05 (39.29 – 254.69)	115.0 (39.29 – 254.69)
1	4	4775	.08	38.66 (2.26 – 134.37)	39.44 (2.26 – 134.37)
2	2	4605	.04	20.05 (0.01 – 101.50)	20.05 (0.01 – 101.50)
3	8	4604	.17	80.20 (18.35 – 206.59)	80.60 (18.35 – 206.59)
4	10	4232	.24	109.06 (31.90 – 258.98)	122.69 (38.36 – 275.72)
0-4	36	23072	.16	72.02 (41.28 – 115.30)	73.52 (41.28 – 115.30)

Table 5.6 Age-specific incidence estimates: Females

Age (year)	n	Population	Cumulative (100/26m)	Annual incidence per 100,000/yr (95% CI)	
				Unadjusted	Ascertainment-adjusted
0	7	4671	.15	69.17 (13.24 – 187.70)	69.17 (13.24 – 187.70)
1	4	4573	.09	40.37 (2.36 – 140.31)	63.08 (9.09 – 175.08)
2	2	4569	.04	20.20 (0.01 – 102.30)	20.20 (0.01 – 102.30)
3	6	4313	.14	64.21 (9.64 – 185.63)	66.88 (9.64 – 185.63)
4	4	4046	.10	45.63 (2.67 – 158.58)	51.33 (5.99 – 178.56)
0-4	23	22172	.10	47.88 (23.19 – 85.86)	49.48 (23.19 – 85.86)

Figure 5.4 Ascertainment-adjusted Incidence by age and gender



There were 10 (7M:3F) children with infantile spasms. Six (3M:3F) had hypsarrhythmia on clinical EEG, and thus met criteria for West Syndrome. The cumulative incidence of West Syndrome was 4.01/10,000 live births, 95% CI (1.47-8.72). Mean age at diagnosis of West Syndrome was 5.10 months (SD=2.13, range 3-9 months). Three children had an unknown cause of West Syndrome, and three had a structural/metabolic cause viz: hypoxic-ischaemic encephalopathy, cerebral malformations associated with lissencephaly, and tuberous sclerosis.

5.3 Socioeconomic and ethnicity as risk factors for epilepsy

36 CWEOE resided in an areas of lower SES, with 23 from a higher SES. Risk ratio for lower SES compared to higher SES was 1.42 (95% CI 0.84, 2.39), p=.19, indicating that low SES was not associated with an increased risk of epilepsy.

Of the 59 children who developed epilepsy, 51 were white (43 white-UK, and 8 white-European) and 8 were non-white (1 African/Caribbean, and 7 Asian). The risk of developing epilepsy was not statistically different for non-white children compared to white children; risk ratio for non-white ethnicities was 1.40 (95% CI 0.66, 2.94), p=.38, compared to white children. However, there was increased risk of epilepsy identified during sub-group analysis. Whilst African/Caribbean ethnic origin was not associated with higher risk of developing epilepsy compared to white-UK origin (risk ratio = 1.11 [95% CI 0.15, 8.04], p=.92), increased risk was found for children from white-European origin (risk ratio= 2.46 [95% CI 1.16, 5.24], p=.02), and for Asian children (risk ratio = 2.32 [95% CI 1.05, 5.10], p=.04).

6. Incidence of early-onset epilepsy: Discussion

The aim of this chapter was to estimate the incidence of early-onset epilepsy in the existing literature base, and in a newly-diagnosed unique population-based sample of children in the South-East of Scotland. The systematic review in section 3 identified a number of studies providing incidence data on CWEOE. One of the main gaps in the literature was a lack of up-to-date data on incidence within the UK. The review also emphasised the need for data that provided a prospective, population-based approach with comprehensive case identification and full validation of epilepsy diagnoses. The review also highlighted the need for data on sociodemographic risk factors for epilepsy in CWEOE. The NEUROPROFILES study provided a means to address those gaps.

The ascertainment-adjusted annual incidence estimate of newly diagnosed early-onset epilepsy was 61.7 (95% CI 40.2 – 88.1) per 100,000 children ≤4 years per year. This was similar to that reported by Kurtz et al. (1998) and Martinez et al. (2013) in the UK, and toward the lower end of that found in the systematic review for this age range, i.e. 60.2 – 102.1. Age explained some of the variance between incidence estimates in the systematic review but most remained unexplained, suggesting that temporal and regional variations may be likely influences, although methodological factors may also play a role (see systematic review discussion; section 3.2.8). The robust methodological parameters used in the current study add confidence to the current estimate. All epilepsy cases were prospectively made, confirmed diagnoses, and comprehensive active surveillance methods were used, resulting in an extremely low under-ascertainment estimation.

In the current study, incidence rate was highest in the first year of life compared to years 1-4, echoing the pattern found in the systematic review; whilst incidence estimates were within the confidence intervals of the pooled estimates of the systematic review. The pattern of age-specific point estimates over the first five years of life - which peaked at age <1 year, followed by decline and further peaks at ages 3 and 4 years - was similar to that observed in two other studies that provided year-by-year estimates (Beilmann et al., 1999; Kurtz et al., 1998). However, this pattern was not observed in Meeraus et al. (2013), where a decreasing linear trend was observed. It is unknown why this difference in pattern was observed, although it could potentially be attributed to natural variance in time and age-specific point estimates. Alternatively, the case inclusion criteria leading to a masking effect could be another potential explanation. The specific data extracted from Meeraus et al. was based on the most sensitive

criteria for epilepsy (i.e. AED prescription, or codes for epilepsy, or ≥2 non-febrile seizures). Misdiagnosis is common in childhood epilepsy, including those prescribed AED medication (RCPCH, 2013; Hindley et al., 2006; Uldall et al., 2006), and overestimation particularly in younger children may have been possible. However, the candidate is not aware of data on age-specific AED prescribing rates during the data collection period, and this possibility is purely speculative.

Consistent with the systematic review, a gender difference in epilepsy incidence rates was uncertain, with overlapping confidence intervals, despite a male predominance in the first year of life and at age four. Inconsistent gender estimates are also found in general childhood epilepsy populations (Wallace et al., 1998). The majority of children with absence seizures in this study were male, including all five diagnosed with Childhood Absence Epilepsy (CAE). The prevalence of absence seizures is slightly higher in females compared to males, although significance values or confidence intervals are not always stated, or the differences are not statistically significant (Christensen et al., 2005; Lennox, 1960; Loiseau, 1985; Waaler et al., 2000). Asadi-Pooya et al. (2012) found no significant gender difference in early-onset CAE, whilst there may be a higher male presence in children with absence seizures and myoclonus (Tassinari and Bureau, 1985). However, only one child in the current cohort had myoclonus. Therefore, the increased presence of male CAE is unclear but may be a chance occurrence.

The development of epilepsy was not associated with SES, supporting previous findings in childhood epilepsy (Hesdorffer et al., 2005; Reading et al., 2006). The role of ethnicity as a risk factor in childhood epilepsy is unclear. In the current study, an increased risk of epilepsy was found in children from white-European, and Asian descent. This is now the second study in the UK to observe a higher incidence of CWEOE in those with Asian descent (Eltze et al., 2013), and the third to report ethnic-related differences in CWEOE (Annegers et al., 1999; Eltze et al., 2013). It is not known why higher incidence rates are reported in these studies, although genetic factors are a potential explanation. Environmental factors, such as cultural differences in child rearing, diet, attitudes to care and medicine, may be another. To the candidate's knowledge the higher risk of epilepsy seen in white children from European families has not previously been reported. This may be an erroneous result, although cultural or genetic differences cannot be ruled out.

In addition to the incidence of CWEOE in general, the cumulative incidence of West Syndrome in Edinburgh and West Lothian was also estimated. To the candidate's knowledge, this is the

first UK study to do so. The cumulative incidence was 4.01 per 10,000 live births, and was similar to estimations found in the systematic review; 3.53 (95% CI 2.06-4.55). As expected, all children were diagnosed in the first year of life (3-9 months). An equal number of male and female children were diagnosed with West Syndrome. No gender-specific birth statistics were available in order to calculate gender-specific incidence. Nevertheless, population statistics of resident children in the South-East Scotland over this time period were roughly equivalent for genders, suggesting that West Syndrome, in the UK, is likely to hold a similar risk for both genders. Given the relative rarity of West Syndrome, the total number of cases identified in this study was small. Nevertheless, the syndrome was well-defined, and the estimate is similar to that reported elsewhere, providing further credibility of the estimate. The findings also offer further evidence of global and temporal stability in the occurrence of West Syndrome.

In conclusion, this study was the first Scottish prospective population-based study, with high ascertainment, and has provided up-to-date data on the incidence of newly diagnosed early-onset epilepsy, and is the first in the UK to provide incidence data on children with West Syndrome. The sample size with which to assess sociodemographic risk factors was arguably modest, meaning an in-depth analysis of SES using individual stratifications of social deprivation quintiles was not possible. Nevertheless, ethnicity was identified as a significant risk factor despite a modest sample size, and requires further investigation in future studies.

This study has focused on children 0-4 years of age providing detailed and comprehensive information on demographic, aetiological, and syndromic characteristics in this highly vulnerable infant, toddler, and preschool group. Incidence rates, including, age- and gender-specific incidence rates, are rarely reported for each individual year of life, and may be useful when formulating targeted intervention/prevention strategies. A major strength of this study was the use of a comprehensive prospective case identification strategy, with ascertainment adjusted corrections, and confirmation of epilepsy diagnoses. The findings presented here, can therefore be considered more robust to measurement error related to misclassification of cases (e.g. coding errors) or missing cases.

Chapter III. Neurobehavioural Profile of Children With Early-Onset Epilepsy

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Chapter III details the construction and implementation of the comprehensive age-appropriate neurobehavioural assessment battery in the NEUROPROFILES study. Results are reported, and showed that CWEOE had an abnormal neurobehavioural profile compared to control children. That is, CWEOE had poorer cognitive functioning, and less age-appropriate social behaviour/more parent-reported behaviour problems compared to controls. The spectrum of neurobehavioural problems in CWEOE was broad, with a prevalence of 63% in CWEOE versus 27% in controls. The degree of comorbidity was varied. Risk factors varied but predominantly included aetiology, prematurity, and family history of developmental or psychiatric issue. These findings are then discussed in relation to the existing literature.

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7. Neurobehavioural Profile of CWEOE: Introduction

It is now widely recognised that neurobehavioural problems are overrepresented in childhood, adult, and elderly epilepsy populations (Duchowny and Bourgeois, 2003; Hermann et al., 2008; Lin et al., 2012a; Pellock, 2004). In children of all ages, the spectrum of problems are broad, and are wide reaching across the spectrum of epilepsies (Berl et al., 2015; Fastenau et al., 2009; Hoie et al., 2006; Jackson et al., 2013; Menlove and Reilly, 2015). These problems include cognitive impairment (Camfield and Camfield, 2007; Sidenvall et al., 1996; Sillanpaa, 1992), specific neuropsychological impairments - including memory, attention, executive functioning, and language (Elger et al., 2004; Lassonde et al., 2000)-, and behaviour problems, including ADHD, ASD, conduct disorders, and affective disorders (Berg et al., 2011b; Cohen et al., 2013; Davies et al., 2003; Suren et al., 2012; Reilly et al., 2015a; Russ et al., 2012). The prevalence of problems are greater than that found in the general population, in sibling controls, or in children with other chronic health conditions (Caplan and Austin, 2000; Dunn and Austin, 2004; Ekinci et al., 2009; Hamiwka et al., 2011; Maulik et al., 2011; Otero, 2009; Plioplys et al., 2007; Rantanen et al., 2012; Reilly et al., 2011; Reilly et al., 2013; Rodenburg et al., 2005; Verrotti et al., 2014). Thus, epilepsy is a serious neurological condition, with serious adverse cognitive and behavioural consequences.

As evidenced from the systematic review in chapter I, section 1.3, the data above has largely come from studies of children of all ages, or older childhood epilepsy populations. The review identified a major need for detailed knowledge surrounding the neurobehavioural profile of CWEOE, especially *during* the first five years of life. The systematic review specifically acknowledged the need for a population-based, prospective, case-control study, with the aim of determining the spectrum and prevalence of, and risk factors for, neurobehavioural problems in CWEOE in the UK. In chapter I it was argued that early-onset epilepsy could be an important independent risk factor for neurobehavioural problems (section 1.2), and combined with recent calls for research into childhood epilepsy (section 1.1), the case for pursuing this knowledge was strongly established.

Thus, the NEUROPROFILES study was designed with the aim of understanding the burden of early-onset epilepsy by determining the neurobehavioural profile of a cohort of CWEOE as identified in chapter II. Restated here, the neurobehavioural profile is defined as the quantitative representation of neurobehavioural characteristics, including distributions of

assessment scores and prevalence of neurobehavioral problems, as determined by psychometric assessment.

Additionally, the neurobehavioural profile of children is multi-dimensional, yet few studies provide detailed information on the degree to which cognitive and behavioural problems co-occur within a given population. This data is useful considering the rate of comorbidity can be high, and knowledge of comorbidities should inform patient and disease management. In the Children with Epilepsy in Sussex Schools study, in the UK, Reilly et al. (2014a) reported that 40% of children had cognitive impairment and 60% met criteria for a behavioural problem. When considered together, 80% of children had a cognitive and/or behavioural problem. Children had up to four coexisting disorders, highlighting the need for better understanding and improved reporting of multi-dimensional difficulties. Gathering such data could aid in the development of targeted strategies toward the provision of comprehensive healthcare, psychosocial, and educational resources.

The remainder of the current chapter will now detail the methods of determining the neurobehavioural profile of CWEOE in the NEUROPROFILES cohort, followed by results of the neurobehavioral assessment, and a discussion of the findings.

8. Neurobehavioural Profile of CWEOE: Methods

8.1 Aims and Objectives

The primary objective of this chapter was to describe the neurobehavioural profile of CWEOE by comparing performance on cognitive and behavioural psychometric assessment tools to that of control children; and to describe the spectrum and prevalence of neurobehavioural problems. Neurobehavioural problems were defined here as cognitive impairment or behaviour problems, as determined by empirically defined, and literature evidenced, cut-off points on those assessment tools. Operational definitions and cut-off points are described in detail in section 8.7.2.

The secondary objective was to identify potential risk factors associated with poor performance on the psychometric tools, or with neurobehavioural problems, in CWEOE. Research questions were as follows;

I. Does the distribution of neurobehavioural assessment scores differ between CWEOE and controls?

II. What are the types, and prevalence, of neurobehavioural problems in CWEOE and controls?

III. What are the sociodemographic and epilepsy-related variables associated with neurobehavioural problems in CWEOE?

8.2 Participants

CWEOE and controls were prospectively identified and recruited from the pre-defined population-based region. Methods for which are described in Chapter I, section 2.6. Whilst data was gathered for all children who were identified as having epilepsy in the analysis of early-onset epilepsy incidence, only data for those who consented for neurobehavioural assessment were included here. Inclusion and exclusion criteria are detailed in section 2.5.2. In addition, the face-to-face assessment tools were English language based, and children were excluded from face-to-face assessment if the child was exclusively foreign-language taught. Attending a Scottish nursery or preschool, or learning English in addition to the parent's native

language was considered sufficient for inclusion. Study questionnaires were also English language based, and were not issued if no parent or main caregiver (herein referred to as parent) was literate in English. No child who consented for study entry was excluded based on this criteria, and all families had at least one parent who was literate in English.

8.3 Neurobehavioural Assessment Battery: Rationale and Materials

The neurobehavioural profile of the children was assessed through an age-appropriate battery of validated face-to-face assessment tools and parent-rated social-emotional behaviour questionnaires. A mixed approach of questionnaires and face-to-face assessment has been used successfully in school-aged children with epilepsy (Reilly et al., 2014a) and in a large longitudinal childhood epilepsy cohort (The Connecticut Study of Epilepsy, http://medicine.yale.edu/lab/ctepilepsy/publications/). The battery was divided broadly into cognitive functioning and behavioural functioning. The former included domains of general cognitive ability, and more specific neuropsychological domains of memory, social perception, and attention & executive functioning. Behavioural functioning included domains of adaptive behaviour, internalising behaviour, externalising behaviour, executive functioning, social functioning, and ASD associated behaviours (table 8.1).

The neurobehavioural assessment battery was designed with the intention of generating psychometric scores across as much of the early-onset age as possible in each of the domains described above. Only age-appropriate validated tools with strong psychometric properties were selected. A lack of research and development of standardised psychometric tools for preschool-aged children (Baron and Anderson, 2012), and gross developmental differences throughout the early years, meant that standardised instruments were not available across the age span within each of the domains. Instead, different age-appropriate tools were used, and paired within domains. The domains of interest themselves were included based on their particular relevance to childhood epilepsy populations, and which are typically investigated in epilepsy research. The rationale for domain selection, and psychometric properties of the tools used to assess each domain, are described below;

8.3.1 Cognitive Functioning

General Cognitive Ability (GCA) is a term used within this study to describe general intellectual, or global cognitive, functioning in the study population. Intelligence Quotient (IQ) is often

Table 8.1 Neurobehavioural assessment battery tools and main outcome variable; by domain and age

<table>
<tr><th rowspan="2">Domain</th><th colspan="5">Age (months)</th><th rowspan="2">Age</th></tr>
<tr><th>1-11</th><th>12-23</th><th>24-35</th><th>36-47</th><th>≥48</th></tr>
<tr><td>General Cognitive Ability</td><td colspan="2">Bayley III Cognition</td><td colspan="3">WPPSI III FSIQ</td><td>≥1m</td></tr>
<tr><td>Neuropsychological Skills</td><td colspan="3"></td><td colspan="2">NEPSY II Memory, Social Perception, and Attention & Executive Functioning</td><td>≥36m</td></tr>
<tr><td>Adaptive Behaviour</td><td colspan="5">ABAS II General Adaptive Composite</td><td>≥1m</td></tr>
<tr><td>Executive Functioning</td><td colspan="2"></td><td colspan="3">BRIEF-P General Executive Composite</td><td>≥24m</td></tr>
<tr><td>Internalising Behaviour</td><td></td><td>ITSEA Internalising</td><td colspan="3">CEC Anxiety
CEC Mood/Affect</td><td>≥12m</td></tr>
<tr><td>Externalising Behaviour</td><td></td><td>ITSEA Externalising</td><td colspan="3">CEC Inattention/ Hyperactivity
CEC Defiance/Aggression</td><td>≥12m</td></tr>
<tr><td rowspan="2">Social Functioning</td><td rowspan="2">SEGC</td><td rowspan="2">ITSEA Competence</td><td colspan="3">CEC Social/Atypical</td><td rowspan="2">≥1m</td></tr>
<tr><td></td><td colspan="2">SDQ Peer Relationship Problems
SDQ Prosocial Behaviour</td></tr>
<tr><td>ASD Behaviours</td><td colspan="2"></td><td>M-CHAT</td><td colspan="2">SRS-2 Total</td><td>≥16m</td></tr>
<tr><td>Completion Time</td><td>1.0hr</td><td>1.5hrs</td><td>1.5hrs</td><td>1.5 – 2hrs</td><td>2 – 3hrs</td><td></td></tr>
</table>

Bayley III – Bayley Scales 3rd ed.

WPPSI III – Wechsler Preschool and Primary Scales of Attention 3rd ed.

NEPSY II – The Dev. Neuropsych. Assessment 2nd ed.

ABAS II – Adaptive Behaviour Assessment System 2nd ed.

ITSEA – Infant and toddler Social Emotional Assessment

CEC – Conners Early Childhood

BRIEF-P – Behaviour Rating Inventory of Executive Function - Preschool

SEGC – Greenspan Social-Emotional Growth Chart

M-CHAT – Modified Checklist for Autism in Toddlers

SDQ – Strengths and Difficulties Questionnaire

SRS2 – Social Responsiveness Scale 2nd ed.

used to describe this concept in children and adults. However, IQ tools are not available across the infant/toddler ranges, where developmental abilities are more appropriately ascribed to indicate cognitive function. GCA was assessed using the Bayley Scales of Infant and Toddler Development, 3rd Edition (Bayley III; Bayley, 2006a), for children aged 1-29 months (m), and the Wechsler Preschool and Primary Scales of Intelligence, 3rd UK Edition UK (WPPSI III; Wechsler, 2002), for children aged ≥30m. Memory, social perception, and attention & executive functioning were assessed using The Developmental Neuropsychological Assessment-2nd Edition (NEPSY II; Korkman and Kemp, 2007), for children ≥36m. These were all face-to-face assessment tools.

(i) General Cognitive Ability

The Bayley III consists of three scales; Cognition, Language (Receptive and Expressive subscales), and Motor (Fine and Gross motor subscales). The Bayley III is standardised on 1700 U.S. children and normed to ages 1-42m (Bayley, 2006b). It is validated in a UK & Ireland sample of 221 children aged 1-27m (Bayley, 2010). The Bayley III generates scaled scores of 1-19 with a mean of 10 and standard deviation (SD) of 3, and composite scores with a mean of 100 and SD of 15.

The WPPSI III measures the intellectual ability of children between the ages of 2:6 years and 7:3 years. There are two age-based versions; 2:6-3:11 years, and 4:0-7:3 years. The former consists of four main subtests and generates scaled scores for each, as well as a composite Verbal IQ (VIQ), Performance IQ (PIQ), and Full Scale IQ (FSIQ). The latter version consists of 8 main subtests with corresponding scaled scores, and composite VIQ, PIQ, and FSIQ scores. This version also includes a processing speed quotient (PSQ). Normative data is based on 805 UK children and the UK version has been anglicised. Scaled scores have a mean of 10 and SD of 3, and IQ index scores have a mean of 100 and SD of 15.

The term GCA reflects the fact that both the Bayley III Cognition scale and WPPSI III FSIQ aim to measure general/global intellectual or cognitive functioning. The Bayley III Cognition scale is founded on the development of cognitive features of play – including symbolism, relationships, information processing, memory, problem-solving and concept development. Despite its basis in sensorimotor play, the Bayley III Cognition scale has a strong correlation with the WPPSI III FSIQ (.79, Bayley, 2006b). The language domain of the Bayley III also offers a strong correlation with the WPPSI III VIQ (.83). The Bayley III and WPPSI III are gold standard

measurements of development and IQ respectively, and have been extensively used in both clinical and research settings.

(ii) Memory, Social Perception, and Attention & Executive Functioning (NEPSY II)

The NEPSY II consists of 32 age-specific subtests that can be tailored for individual assessment or administered according to any of eight preset combinations of subtest batteries designed for specific referral types (e.g. language delay, attention, or school readiness) (Korkman et al., 2007). The subtests are categorised into six domains: Attention & Executive functioning, Language, Memory & Learning, Sensorimotor, Social Perception, and Visuospatial Processing. Unlike the NEPSY I, composite scores are not generated based on the clinical sensitivity of subtest scores alone (Korkman et al., 2007). The NEPSY II was standardised on 1200 U.S. children aged 3-16 years. It generates scaled scores of 1-19 with a mean of 10 and SD of 3. Internal consistency (.62-.89) and test-retest reliability (.62-.82) for subtests are satisfactory (Korkman et al., 2007).

The Memory & Learning, Social Perception, and Attention & Executive Functioning domains of the NEPSY II were selected for the current study due to their applicability to an epilepsy population, and in order to directly complement the specific goals of the assessment battery by assessing aspects of cognitive functioning, social cognition/behaviour, and attention/executive functioning, respectively. Of the NEPSY II domains, all age-relevant subtests were selected. Popular face-to-face standardised alternatives for memory assessment (e.g. Children's Memory Scales) and attention (e.g. Test of Everyday Attention for Children, TEA-Ch) are not available for children under five years, meaning the NEPSY II was one of the few face-to-face tools standardised to preschool-aged children that assess specific neuropsychological skills.

The Memory & Learning domain consisted of three memory subtests: Memory for Designs, Narrative Memory, and Sentence Repetition. Memory for Designs measures immediate visuospatial recall and learning; Narrative Memory assesses immediate cued verbal recall and recognition memory; and Sentence Repetition assesses immediate verbal recall of short sentences. The Social Perception domain includes Theory of Mind, and Affect Recognition subtests. These assess the ability to understand the beliefs and perspectives of others, and the ability to discriminate emotional faces, respectively. Theory of mind and emotional facial discrimination are aspects of social cognition which are known to be compromised in children

with ASD (Baron-Cohen, 2000; Uljarevic and Hamilton, 2013). The subtests complemented the social behaviour aspects of the assessment battery. The Attention & Executive Functioning domain consisted of only the Statue subtest. The Statue subtest assesses the ability of the child to maintain a defined statue position over a 75 second period whilst inhibiting the impulse to move or speak in the face of distractions, thereby relying on executive functions such as inhibition, and on the ability to attend to internal and external cues. The BRIEF-P and CEC Inattention/Hyperactivity (described in 8.3.2 below) complemented the Statue subtest by offering a behaviour based assessment of executive functioning and attention, respectively. Performance based and questionnaire based measures of executive functioning may tap into different mechanisms (Mahone and Hoffman, 2007), and was further justification for considering these tools separately.

8.3.2 Behavioural Functioning

Behavioural functioning was assessed via parent-rated social-emotional behaviour questionnaires. Parent-rated questionnaires offer quick and cost-effective means of surveying a broad spectrum of behaviours, whilst maintaining predictive diagnostic validity (e.g. Reilly et al., 2014c; Charman et al., 2007). Questionnaires used aimed to assess social-emotional behaviour issues pertinent to children with epilepsy. The battery assessed the domains: adaptive behaviour, internalising behaviour, externalising behaviour, executive functioning, social functioning, and ASD behaviours. Study specific questionnaires are described according to domain, below.

(i) Adaptive behaviour

Adaptive behaviour is commonly assessed in the clinical setting and is used in conjunction with an IQ assessment to diagnose intellectual disability (Alves et al., 2000). It is commonly measured in young children, and has previously been used in preschool-aged children with epilepsy (Berg et al., 2004; Berg et al., 2013). It provides a measure of everyday age-appropriate functional abilities that should be reached in order to achieve independent functioning. The *Adaptive Behaviour Assessment System-2nd Edition (ABAS II) (0-5 years; Harrison and Oakland, 2003a)* was used here. The ABAS II is a questionnaire consisting of 7 (<1 year age), or 10 (1-5 years), adaptive skills areas. Skill areas generate composite scores for: Practical Adaptive Behaviour, Social Adaptive Behaviour, Conceptual Adaptive Behaviour, and an overall General Adaptive Composite. Normative data is standardised on 1350 U.S. parent/primary caregiver

reports. Scaled scores have a mean of 10 and SD of 3, and composite scores have a mean of 100 and SD of 15. The ABAS-II has good internal consistency (α) for composite domains (.91 - .97), test-retest reliability (.86 - .88), and inter-rater reliability between different parents (.72 - .86) (Harrison and Oakland, 2003b).

(ii) Executive Functioning

The *Behavioural Rating Inventory of Executive Function - Preschool (BRIEF-P; Gioia et al., 2003b)* is a 63 item questionnaire consisting of clinical scales measuring five aspects of executive functioning in children aged 2-5 years. The subscales (Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize) form three index scales (Inhibitory Self-Control Index, Flexibility Index, and Emergent Metacognition Index) and a global composite score (General Executive Composite). All scales and indices generate T-scores with a mean of 50 and SD of 10. Internal consistency (.80 - .95), and test-retest stability (.78 - .90) for indices and scales is high (Gioia et al., 2003a). The BRIEF-P has shown discriminant validity in children with a clinical diagnosis of ADHD, who have higher scores than typically developing children (Gioa et al., 2003a; (Mahone and Hoffman, 2007; Skogan et al., 2015). Children with anxiety disorders also score higher, as do children with ASD, although scoring profiles differ (Gioia et al 2003a; Skogan et al., 2015). The normative sample was standardised on 460 parents of U.S. children. Although executive functioning can be considered a cognitive skill, the questionnaire assesses the behavioural impact of executive functioning. The BRIEF-P is the only executive functioning rating scale for preschool children, and has only a modest correlation with the other executive functioning measure in the battery, the NEPSY II Statues subtest (r=0.35, Mahone, 2005).

(iii) Internalising Behaviour, Externalising Behaviour, and Social Functioning

The internalising, externalising, and social functioning domains were constructed by selecting relevant infant/toddler or preschool-aged questionnaires, or questionnaire scales, and merging them into the relevant domain of interest in order to maximise age coverage (table 8.1). Scales from two questionnaires, the Infant and Toddler Social Emotional Assessment (ITSEA) for ages 12-23m, and Conners Early Childhood-Behaviour Scales (CEC), for ages ≥24m, were allocated into all three domains. The social functioning domain included two additional questionnaires which are described in the relevant section below. Note that scores for each domain were not pooled. The internalising, externalising, and social functioning domains are detailed as follows;

Internalising Domain

The internalising domain consisted of the ITSEA Internalising scale (12-23m; table 8.2), and CEC Anxiety and CEC Mood/Affect scales (≥24m).

Externalising Domain

The externalising domain consisted of the ITSEA Externalising scale (12-23m; table 8.2) and the CEC Inattention/Hyperactivity and CEC Defiant/Aggressive scales (≥24m).

Social Functioning Domain

The social functioning domain consisted of the Greenspan Social-Emotional Growth Chart (SEGC; Greenspan, 2004)) (≤12m), the ITSEA Competence scale (12-23m; table 8.2), and the CEC Social Functioning/Atypical Behaviour scale (≥24m).

The terms internalising and externalising were first conceptualised by (Achenbach, 1966). Internalising behaviours consist of emotional or introverted behaviours, such as anxiety or depression, whilst externalising behaviours are more extroverted and socially apparent, such as disruptive behaviour, ADHD, or conduct disorder. Social competence is a term used to describe age- and culturally-appropriate social interactive behaviour. Inadequate childhood social competence can adversely affect social relationships, workplace relations and success, and mental health in later life (Jones et al., 2015). However, social competence is not well defined conceptually or operationally (Cavell, 1990; Rantanen et al., 2012). To avoid problematic conceptualisation, and to make a clear distinction from other social-behaviour domains and concepts, in the current study a 'social functioning' domain was created and defined here as reflecting the behaviour scales associated with social skill development, social interaction and social relationships. Individual questionnaires and scales in these domains are now described.

The ITSEA (Carter and Briggs-Gowan, 2005), was constructed in order to identify social and emotional problems in children from ages 12-35 months. It was standardised on 600 U.S. children, and consists of four scales: Internalising, Externalising, Competence, and Dysregulation. Each scale is made up of several subscales (table 8.2), and each generates a T-score with a mean of 50 and SD of 10. No overall composite is generated. Internal consistency

(.85 - .89), inter-rater agreement (parent-pairs; .72 - .79), and test-retest reliability (.76 - .91) of scales are good (Carter and Briggs-Gowan, 2006). The ITSEA offers discriminant validity for children with mental health problems, and development delay (Carter and Briggs-Gowan, 2006), and for those at high-risk of social-emotional difficulties as early as 12m of age (Sanner et al., 2016).

Table 8.2 ITSEA selected scales, and subscales

Scale	*Internalising*	*Externalising*	*Competence*
Subscales	- Depression/Withdrawal - General Anxiety - Separation Distress - Inhibition to Novelty	- Activity/Impulsivity - Aggression/Defiance - Peer Aggression	- Compliance - Attention - Mastery Motivation - Imitation/Play - Empathy - Prosocial Peer Relations

The CEC (Conners, 2009) is a 110 item questionnaire designed to assess a range of social and emotional behavioural concerns in children aged 2-6 years. The CEC generates an overall total score, three global index scores, and six behaviour scale scores (Inattention/Hyperactivity, Defiant/Aggressive behaviours, Social Functioning/Atypical Behaviour, Anxiety, Mood/Affect, and Physical Symptoms). The Defiance/Aggressive behaviours and Social Functioning/Atypical behaviour scales are subdivided further into subscales. Individual scales provide discriminant validity for corresponding clinical groups of ADHD, behaviour problems, adaptive problems, and social-emotional problems, providing positive predictive power between 69-98% (Conners, 2009). Scales have good internal consistency (.64 - .94), test-retest reliability (.73 - .92), and inter-rater reliability (parent-pairs; .62 - .85) (Conners, 2009) – and were thus used for domain analysis in this study. Each CEC scale generates T-scores, with a mean of 50 and SD of 10.

The SEGC measures social-interactive and emotional milestones – which are important indicators of social functional development – in children aged 0-42 months. It is an accompaniment to the Bayley III and validated on the Bayley III standardisation sample. It has high internal consistency (.90), and was standardised on 456 children aged 15 days to 42 months (Bayley, 2006b). It returns a standard score with a mean of 100 and SD of 15. The SEGC has a moderately strong correlation with the ITSEA (r=.48; Carter and Briggs-Gowan, 2006).

To provide a complementary and focused examination of social relationships in CWEOE and controls, the Peer Problems and Prosocial Behaviour scales of the Strength and Difficulties Questionnaire (SDQ; Goodman, 1999) was used. The SDQ is widely used in clinical practice and in research, with parent report forms available for children aged 3-4 years, or 4-16 years. The SDQ provides raw scores and qualitative descriptors (i.e. low score, average, high, very high). Both age versions of the questionnaire were used, which have minor differences in comparative scores. Thus, qualitative descriptors were preferred. Internal consistency for Peer Problems and Prosocial Behaviour is 0.57 and 0.65, respectively, while test-retest correlations are 0.61 in both scales (Goodman, 2001). The parent versions of the SDQ were used for children ≥36m in this study.

(iv) ASD behaviours

Two ASD assessment tools were included in this study: The *Modified Checklist for Autism in Toddlers* (M-CHAT; Robins et al., 1999; Robins et al., 2009), and The *Social Responsiveness Scale - Second Edition* (SRS-2; Constantino and Gruber, 2012). ASD screening tools, such as the M-CHAT and SRS-2, offer quick, validated, standardised evaluations of abnormal social behaviour used to identify children for further clinical evaluation from general, or 'at risk', populations.

The M-CHAT is a 23 item questionnaire designed to screen for ASD behaviours in toddlers aged 16-30 months. The M-CHAT has been validated on a sample of children with Pervasive Developmental Disorders (Robins et al., 2001; Snow and Lecavalier, 2008) and is an extension of the original Checklist for Autism in Toddlers (CHAT; Baron-Cohen et al., 1992). The M-CHAT generates a binary outcome of "risk" or "low risk" for ASD. It has good internal consistency (.85), and variable sensitivity (.70-.82), specificity (.38-.54), and positive predictive value (.36-.79) (Charman et al., 2016; Chlebowski et al., 2013; Kleinman et al., 2008; Snow and Lecavalier, 2008). The M-CHAT is widely used, freely accessible (via http://www.M-CHAT.org/), and has similar outcome properties to the few screening tools available for toddlers (Dudova et al., 2014; Smith et al., 2013).

The SRS-2 is a 65 item questionnaire which measures typical features of ASD and associated social reciprocal behaviours. It includes a preschool version (30-54 months) and a school-aged version (4-18 years). The SRS-2 generates T-scores for five subscales (Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive

Behaviour), a composite Social Communication Index, and a Total score. Constantino and Gruber (2012) suggest that T-scores above 60 indicate levels of social communication and reciprocal social behaviour deficiencies; 60-65 indicate mild to moderate deficiencies, 66-75 suggests behaviours typical for children with moderate ASD, and >75 is strongly associated with a clinical diagnosis of ASD. Normative data was standardised using 247 U.S. preschool children (30-54 months) and 1014 U.S. school-aged children (4-19 years). The SRS-2 is a recent derivative from the SRS questionnaire published in 2012, and therefore, has only limited, but promising, validation from clinical populations in children aged 2-5 years (Constantino, 2011; Turner-Brown et al., 2013). The school-aged version has shown good predictive value (Bruni, 2014), and has been validated in a UK sample of children (Wigham et al., 2012). Internal consistency is high (.94), and inter-rater reliability (.77) is good (Constantino and Gruber, 2012).

The M-CHAT and SRS-2 complemented one another by spanning ages 16-63m in the current cohort. These screening tools were preferred to the popular performance-based measure of ASD evaluation, the Autism Diagnostic Observation schedule (ADOS), due to their acceptable psychometric properties, applicability as broad first stage screening tools in 'at risk' populations, and their timely use in an already large assessment battery. The ADOS is a semi-structured face-to-face instrument requiring clinical expertise, with its administration time a considerable disadvantage (Akshoomoff et al., 2006).

8.4 Procedure

General procedures for study identification, entry, consent, and involvement are detailed in chapter I, section 2.6. To remind the reader, after identification of CWEOE and controls, families were invited to take part in the study, and those who consented were sent age- and domain-appropriate parent-rated questionnaires (table 8.1) to the family's home. These were completed prior to face-to-face assessment, or in situ if parents requested further clarification of questionnaire items from the candidate. Face-to-face assessments were completed at the child development lab or in the family home if they were unable/unwilling to attend the lab. Eye-tracking was also completed at the lab (see section 12). Further details specific to procedures surrounding neurobehavioural assessment are described below.

Face-to-face neurobehavioural assessment was carried out by the candidate. The candidate received training and supervision from RS, Consultant Clinical Psychologist, and KV, Paediatric Neuropsychologist. The candidate also received Bayley-III training from two physiotherapists,

and attended a two-day training course from Pearson UK. Parents were briefed on what assessment tool would be used and what to expect during the assessment, and were given the opportunity to ask questions before face-to-face assessment. The candidate was sensitive to the needs of the families during assessments and would introduce breaks as necessary or when requested.

Children <30 months of age completed the Bayley III assessment. Children ≥30 months of age completed the WPPSI-III, and children ≥36m also completed the NEPSY II. In children ≥36m, FSIQ was seen as the relatively more fundamental aspect of the study, compared to the specific neuropsychological functions measured by the NEPSY II. Therefore, the WPPSI III was completed first to reduce any potential attrition from fatigue or failure to return to appointments. For those that attended the child development lab, the eye-tracking battery was completed, typically after cognitive assessment. Occasionally, eye-tracking was performed first if the child was nervous or uncooperative, or during break time if the child was uncooperative or fatigued from cognitive assessment. After face-to-face assessment and eye-tracking was completed, parents were interviewed with the medical questionnaire (appendix E) to obtain information on the child's epilepsy-related characteristics and family history of epilepsy or developmental/psychiatric issues (see section 2.6 for further details). At the end of face-to-face assessment, families were given the opportunity to ask questions about the study and their child's participation. This may have been about the study purpose or progress, or about the child's performance, for example. Families were reminded that this was not a clinical evaluation and that a feedback report would be generated.

Figure 8 Reward stickers

8.5 Assessment Engagement

The anticipated length of each assessment session was expected to vary according to age, being appropriately shorter in duration for younger children (see table 8.1). Face-to-face

assessment duration was also expected to vary according to the child's temperament, cognitive abilities (including attention), familiarity with an assessment environment, and personal preferences for these types of tasks. One of the challenges during assessment was to promote attention and engagement. To manage this, stickers were created (figure 8) as a motivational tool and issued for task completion.

8.6 Assessment Feedback

Guidance on informing patients on assessment results was taken from Lefaivre et al. (2007). All families who participated received written feedback of their child's assessment. The language was accessible for the lay person, and sensitive in nature, particularly when relaying information on subnormal findings. Each feedback report was reviewed by a member of the research team, KV, Paediatric Neuropsychologist, who has years of experience of paediatric assessment and parent liaison. Assessment reports were not treated as clinical interpretations, as this was not the nature of the assessment. Each report summarised the findings of the assessment across each neuropsychological domain tested, and indicated if the child was "below average", within the "normal ranges", "above average" or within the "elevated ranges", depending on the tool reported. Individual test scores were not given, as they should not be interpreted by someone not trained in their use and limitations.

Every child's GP and paediatrician, if the child had one, was informed of their patient entering the study, and was given a copy of the feedback report with adjoining cover letter, summarising the findings of the assessment - unless the child's family did not provide written consent for this to happen. Although it was made clear that the report was not a clinical evaluation, parents of children taking part were recommended to contact the child's GP, paediatrician, or Health Visitor, if they had any developmental concerns about the child. GPs and paediatricians were invited to refer the child to the appropriate clinical services using existing referral systems if they had concerns. Feedback reports were offered upon completion of the study, although reports were compiled and sent when time permitted; typically between 3-6 months of the individual completing face-to-face assessments.

8.7 Analysis

Analyses were aimed at: (1) examining intergroup differences (CWEOE vs controls) in assessment scores, (2) detailing the spectrum and prevalence of neurobehavioural problems

in CWEOE and controls, and (3) examining the association between study variables and assessment scores/neurobehavioural problems.

Descriptive data on seizure and epilepsy-related characteristics were reported according to the ILAE Commission on Classification and Terminology 2005-2009 (Berg et al., 2010), as well as the Commission on Classification and Terminology of the International League Against Epilepsy 1989 (ILAE, 1989) (see section 2.4 for rationale), and were presented first.

The order of intergroup analyses [of assessment scores, and prevalences of neurobehavioural problems] followed the domain structure laid out in table 8.1. Analyses were conducted for each questionnaire or scale within each domain of interest using the overall composite score of the tool, if applicable, or individual scale score (see table 8.1 for primary outcome variable). The relationship between scores/prevalences and study variables were examined throughout. Secondary analysis using subsidiary composite scores or subscales, where applicable, were conducted if group differences were found on the main outcome variable.

Study variables were selected, a priori, based on the published literature, and included: gender, SES, prematurity, family history of epilepsy, seizure frequency, number of AEDs, mode of seizure onset, aetiology (ILAE 1989 & 2010 classifications), MRI status, EEG status, assessment age, and age at first seizure. There was insufficient subgroup sample sizes for analysis of family history of psychiatric issue or developmental disability by disorder type (e.g. anxiety, depression, ASD, etc), and this variable was reserved for global analysis of presence/absence of any neurobehaviour problem. Study variable categories are described in section 2.7.1. Bivariate analyses tables were presented throughout, in order to appraise the strength of, and trends in, relationships with study variables, due to small subgroup sample sizes, and absence of corrections for multiple comparisons.

Multiple comparisons are not recommended by some statisticians (Rothman, 1990; Saville 1990), and potentially increase type II errors by reducing type I errors. This study examined a relatively understudied age group, and thus serves as a platform for further and focused analysis. Thus, an increased risk of false positives was considered acceptable, and p-values and/or confidence intervals/effect sizes were presented throughout. Given a p-value of .05, 5% of any significant findings may be expected to have occurred by chance alone.

8.7.1 Assessment Scores Analysis

T-tests were used to assess group differences in neurobehavioural assessment scores when data was normally distributed. Between-group differences were followed by analysis of covariance (ANCOVA) to control for differences in SES or age, when appropriate. Additionally, mixed ANOVAs were used to assess between- and within-group differences in WPPSI III IQ scales, and ABAS II composite scales. For group comparisons following non-normal distributions, data transformation was attempted. When unsuccessful, Mann-Whitney U tests were applied, as well as rank-based ANCOVAs (Quade, 1967) when adjusting for SES and/or age.

Relationships between assessment scores and sociodemographic and clinical study variables were assessed via Pearson or Spearman's Rank correlations for continuous variables, and T-tests or Mann-Whitney U tests for categorical variables. FET was applied for all 2x2 or 2x3 contingency tables comparing sub-group associations of nominal variables. In CWEOE, multiple linear regression was used to assess the contribution of variables identified at the $p<.01$ level from bivariate analysis toward the neurobehavioural assessment outcome score, when sample sizes were sufficiently powered. If variables were highly correlated, the main variable of clinical interest was included in the model and explained in the relevant model.

The Bayley III Cognition scale (for children aged 1-29m) and WPPSI III scales (≥30m) were analysed individually for group differences in cognition and IQ scales, respectively. Index scores were then converted to z-scores and pooled for comparison (Jackson et al., 2013; Reilly et al., 2015b), under the concept of GCA. This was done in order to increase power for bivariate analysis and multiple linear regression with study variables, and to examine the effects of age and tool type across the early-onset age range. Conversion to z-scores allows the comparison of scores from different tools by standardising the scores to a mean of zero and SD of one. Positive scores indicate performance above the mean, and negative scores indicate performance below mean. Increasing scores indicate better performance, and vice versa.

The Bayley III is used in the clinical assessment of infants with suspected developmental delay, meaning that all children <30m could be reliably assessed with this tool. The WPPSI III relies on understanding verbal task instructions, and having sufficient psychomotor ability to carry out certain subtests. Children ≥30m but under the upper age limit of the Bayley III (i.e. 42m)

could be alternatively assessed using the Bayley III, should WPPSI III administration have been unsuccessful. Children who were >42m could not be entered into analysis of assessment scores, but could be included in the analysis of GCA impairment if sufficient evidence of impairment was present from medical history (e.g. history of global developmental delay). Sensitivity analyses of group comparisons on the Bayley III/GCA were performed by re-running analyses without outlying children (i.e. cases ≥3SDs below the mean) in order to address potential uncertainty in the group estimates caused by participants with floor scores due to severe developmental delay.

Most behaviour questionnaires in the battery produced T-scores for scales and subscales. T-scores are standardised scores with a mean of 50 and SD of 10, where increasing scores represent increases in problem behaviours, or absences of age-expected behaviours. For consistency, the ABAS II and SEGC, which produced standard scores with a mean of 100 and SD of 15, were converted to T-scores and inverted for comparison with other scales. The ITSEA Competence scale was also inverted for comparison with other scales. Conversion and introversion does not alter the meaning of scores, but only the scale and direction. Note that the M-CHAT provides only a categorical classification and was not included in analysis of ASD behaviour scores.

Some previous studies on childhood epilepsy have conducted subgroup analysis using complicated and uncomplicated epilepsy groups (e.g. Berg et al., 2008; Rantanen et al., 2011; Rutter et al., 1970). Definitions often vary but uncomplicated epilepsy typically consists of idiopathic or cryptogenic epilepsies, whilst complicated epilepsy consists of structural or symptomatic epilepsies, or those with epilepsy and additional neurological disorders. This is a useful distinction but has some drawbacks. Children with cryptogenic aetiologies can have poor cognitive outcome, and those with structural/symptomatic aetiologies may have typical outcomes. As brain imaging techniques advance it is also likely that lesions will be identified more often on clinical imaging, and the suggested changes to aetiological classification (Berg et al., 2010) means the definition must evolve. As the sample size in the present study was modest, and to provide a comprehensive picture of CWEOE, the cohort was analysed as a whole. For closer comparison with previous studies, a supplementary analysis of assessment scores was made. As unknown and genetic aetiologies (Berg et al., 2010) may now include cases previously classified as symptomatic/cryptogenic, supplementary analysis with children with idiopathic aetiology was preferred. None had neurological disorders, making this group comparable to children classified as uncomplicated epilepsy.

8.7.2 Neurobehavioural Problem Analysis

In order to determine the spectrum and prevalence of neurobehavioural problems (i.e. GCA impairment or behaviour problem), cut-off points on psychometric tools were assigned and children were categorised as having, or not having, a neurobehavioural problem in each of the relevant scales. Cut-off points were based on tool author recommendations and the published literature, rather than a blanket approach.

Table 8.3 Neurobehavioural problems cut-off points: Cognitive Impairments

Tool	*Scale specific*	*SD below mean*	*Percentile*	*Note on cut-off point*
Bayley III WPPSI III	z-score ≤ -2	2	≤2.5	Widely used, including in epilepsy research (e.g. Berg et al., 2008; Rantanen et al., 2011; Reilly et al., 2014; Sidenvall et al., 1996)
NEPSY II	scaled score ≤5	1.5	<10	Cut-off point used in Barron-Linnankoski et al. (2015); Bender et al. (2007); Rasmussen et al. (2013) and Lind et al. (2011)

Information on cut-off points for cognitive impairments are listed in table 8.3. Table 8.4 details scale cut-offs for behaviour problems. Scale cut-offs captured at least the ≥90th percentile of children. Two behaviour scales used a higher cut-off of ≥2 SD above mean (T-score ≥70), based on tool author comparison with clinical groups. A lower threshold with greater sensitivity in the SEGC has been suggested for use in screening for ASD (Casenhiser et al., 2007), but as this was not the specific purpose of use in this study, original cut-off was retained. The remainder used a cut off at approximately the 90th percentile (≥1.5 SD above mean). Whilst a stricter criterion for behaviour problems of ≥2 SD above mean may reduce false positives, it may be too stringent to identify all those who will go on to develop psychopathological problems (Edelbrock and Costello, 1988; Petty et al., 2008; Shekim et al., 1986). Edelbrock and Costello (1988), for example, found a surprising 63% of children with a T-score of 66-70 (1.5-2 SD) in their sample went on to receive a conduct disorder diagnosis. Cut-off points at or below 1.5SD are common in the analysis of behaviour problems (e.g. Briggs-Gowan and Carter, 2007; Mazefsky et al., 2011; Rantanen et al., 2009). To assess low/high risk for ASD, the M-CHAT and SRS-2 were pooled. The M-CHAT categorises children into low or high risk of ASD, whilst children scoring < or ≥1.5 SDs on the SRS2 Total score were categorised as low and high risk, respectively.

Table 8.4 Neurobehavioural problems cut-off points: Behaviour Problems

Tool	*T-score*	*SD above mean*	*Percentile*	*Note on cut-off point*
ABAS II	≥70	2	≥98	Used for clinical validity analysis (Harrison & Oakland, 2003), and recommended cut-off in assessment of intellectual disability (Joyce et al., 2015)
SEGC	≥70	2	≥98	Used for analysis of clinical groups (Bayley, 2006b)
BRIEF-P	≥65	1.5	≥90	Author recommended threshold for abnormally elevated score that is of 'potential clinical significance'
M-CHAT	-	-	-	Author recommended: three total failed items or ≥2 critical items failed, equates to a risk of ASD
SRS-2	≥65	1.5	-	Author recommended threshold for 'clinically significant deficiencies in social behaviour that interference with everyday social interactions, and are typical for children with moderate severity'
CEC	≥65	1.5	≥93	Author recommended threshold that indicates significant concerns
ITSEA	≥65	1.5	≥90	Author recommended threshold that identifies children at risk for delayed, deficient, or deviant behaviour
SDQ	-	-	≥90	Scores associated with a substantial increase in psychiatric risk (Goodman, 2001)

Note: T-scores are standard scores but corresponding percentiles may differ depending on scale. Figures here are those reported by scale author(s). ABAS II and SEGC have been converted to T-scores and inverted. ITSEA Competence scale has been inverted to match direction of other scales.

FET was applied to between-group (CWEOE vs controls) differences in the prevalence of neurobehavioural problems at the scale and domain levels, and to subgroup analysis of associations with study variables in CWEOE (i.e. number of children with problem vs no problem). Associations with age-related variables applied Mann-Whitney U tests. Study variables significant at the $p<.01$ level in bivariate analyses were entered into multivariable logistic regression analysis.

Lastly, the extent of comorbidity of neurobehavioural problems was ascertained by calculating the proportion of children who met criteria for each problem at the domain level.

8.8 Epilepsy and ESSENCE – Screening for coexisting disorders

As identified in section 7, neurobehavioural problems in epilepsy are often multi-factorial, and there is a need for the identification of coexisting neurobehavioural problems, in order to provide comprehensive targeted care. The term ESSENCE, which is an acronym for Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations, was coined by Gillberg (2010), in order to aid in the recognition and management of children who have an ESSENCE disorder. ESSENCE syndromes describe a group of neurodevelopmental disorders, such as ASD, ADHD, learning disability, Tourette Syndrome, and rare epilepsy syndromes, mainly in children under 5 years of age, in which there is high likelihood of the coexistence of those disorders. By identifying disorders subsumed under ESSENCE, a child with an ESSENCE disorder could then be screened for other coexisting disorders under the ESSENCE umbrella (Neville, 2013). An ESSENCE questionnaire was devised by Gillberg (http://gillbergcentre.gu.se/english) with the primary motive to help in the process of identifying children with coexisting symptoms that require further investigation or follow-up with specialist services, and thus promote a multi-faceted approach to the child's care.

Epilepsy is a neurodevelopmental disorder, and whilst it was beyond the scope of this study to identify ESSENCE disorders in CWEOE, the ESSENCE questionnaire was used to identify children that may potentially have an ESSENCE disorder or other co-existing disorders aside from epilepsy itself, and relate that to the outcome of the neurobehavioural assessment battery. In such a way, the viability of the ESSENCE questionnaire as a pre-screening instrument in CWEOE could be explored.

The first version of the ESSENCE questionnaire (ESSENCE-Q, appendix I; now replaced by a revised edition, Gillberg, 2012, http://gillbergcentre.gu.se/english /research/essence--early-symptomatic-syndromes-eliciting-neurodevelopmental-clinical-examinations-), is an 11 item questionnaire that asks the parent if they have been "concerned" about their child's development in any one or more of 11 categories (e.g. general development, communication, and behaviour). It is scored on a "yes", "no", or "maybe" format. The ESSENCE-Q has recently been validated in a Japanese sample of 130 children ≤6 years of age (Hatakenaka et al., 2016), offering sensitivity of .87 and specificity of .77 using a cut off score of at least two yeses or three maybes. Reaching this criteria prompts a recommendation for further assessment and may be indicative of a child fulfilling a disorder subsumed under ESSENCE.

In the current study, the number of children meeting essence criteria was recorded, and the findings were then compared to the presence of neurobehavioural problems identified from the assessment battery. Subgroup analysis between those who did and did not meet ESSENCE criteria and study variables was assessed using FET for associations with nominal variables, and Mann-Whitney U test for age variables.

9. Neurobehavioural Profile of CWEOE: Results

9.1 Participants

46 of the population-based sample of 59 CWEOE (78% [95% CI 65.9, 86.6]) and 37 controls consented for the study, and received neurobehavioural assessment, the details of which are provided in section 8. However, in brief, the assessment was comprised of a battery of validated parent-rated questionnaires, and face-to-face assessments. There were no significant differences in sociodemographic or clinical variables between those CWEOE who had neurobehavioural assessment, and those who did not (table9.1A and B). Therefore, the CWEOE cohort who received assessment were representative of the entire population-based cohort.

Table 9.1 CWEOE who received (n=46), or did not receive (n=13), neurobehavioural assessment: Comparison of sociodemographic and clinical characteristics

A. Gender, SES, and aetiology

Variable	*Levels*	*Assessed, n (%)*		*FET*	*OR (95% CI)*
		Yes	*No*		
Gender	Male	27 (58.7)	9 (69.2)	.54	0.63 (0.17, 2.36)
	Female	19 (41.3)	4 (30.8)		
SES	Lower	28 (60.9)	8 (61.5)	1.0	1.03 (0.29, 3.64)
	higher	18 (39.1)	5 (38.5)		
Aetiology (1989)	Idiopathic vs Symptomatic/Cryptogenic	24 (52.2)	10 (79.6)	.20	0.33 (0.08, 1.35)
		22 (47.8)	3 (23.1)		
Aetiology (2010)	Genetic	15 (32.6)	7 (53.8)	.43	-
	Structural/Metabolic	9 (19.6)	2 (15.4)		
	Unknown	22 (47.8)	4 (30.8)		

B. Age (months)

Age	*Assessed*	*Median Age (IQR)*	*Mann-Whitney U, p (r)*
At diagnosis	Yes	25.54 (9.18, 47.93)	.72 (.05)
	No	36.01 (8.25, 46.44)	
At first seizure	Yes	17.5 (6.0, 36.0)	.65 (.06)
	No	24.0 (7.0, 37.0)	

The 46 CWEOE who were enrolled onto the study, did not significantly differ in gender, age, family history of developmental disability or psychiatric problems, or the proportion of children born prematurely (table 9.2), compared to controls. A higher proportion of controls were resident in areas of higher SES compared to controls. As such, SES was included across the analyses as a confounder.

Table 9.2 Sociodemographic comparisons between CWEOE and control children

Variable		*Group, n (%)*		*Group Comparison FET (OR [95% CI])*
		CWEOE	Controls	
Gender	Male	27 (59)	18 (49)	.38 (1.50 [0.63, 3.59])
	Female	19 (41)	19 (51)	
SES	Low	28 (61)	8 (22)	**<.001 (0.18 [0.07, 0.47])**
	High	18 (39)	29 (78)	
Family history of developmental disability or psychiatric issues	No	30 (65)	27 (73)	.63 (0.77 [0.28, 2.08])
	Yes	13 (28)	9 (24)	
	(Unknown)	3 (7)	1 (3)	
Prematurity	No	42 (91)	36 (97)	.38 (3.43 [0.37, 32.08])
	Yes	4 (9)	1 (3)	
Age at assessment (months)	Median (range)	31.21 (3-63)	31.47 (3-59)	†p=.65, r= .05

†Mann-Whitney U test

Emboldened p<.05

CWEOE were diagnosed at a median age of 31.21 (3-63) months (m), and received neurobehavioural assessment a median of 2.97 (IQR 1.51 – 4.95)m after diagnosis. CWEOE were characterised according to ILAE's 1989 and 2010 aetiological classifications (table 9.3), and by epileptic syndrome classification (Berg et al 2010) (table 9.4). Focal seizures were the most predominant seizure type, occurring in 37% of cases, followed by Generalised Tonic Clonic Seizures (24%), and spasms (20%). The remainder was

Table 9.3 Aetiological Classification ILAE 1989 and 2010

ILAE Classification	*Aetiology*	*n (%)*
ILAE 1989	Symptomatic	10 (21.7)
	Cryptogenic	12 (26.1)
	Idiopathic	24 (52.2)
ILAE 2010	Structural/Metabolic	9 (19.6)
	Genetic	15 (32.6)
	Unknown	22 (47.8)

made up of absences (13%), atonic (2%), myoclonic (2%), and clonic (2%) seizures. 8.7% percent of CWEOE had one seizure type, 34.8% had two, and 6.5% of children had three seizure types.

Table 9.4 Epilepsy syndromes and classifications (N=46)

Epilepsy Classification		**Syndrome**	**n (%)**
Electroclinical Syndromes	Neonatal Period	Otahara Syndrome	1 (2.2%)
	Infancy	West Syndrome	7 (15.2%)
		Benign Infantile Epilepsy	3 (6.5%)
	Childhood	Panayiotopoulos	1 (2.2%)
		CAE	4 (8.7%)
		Generalised Epilepsy with Febrile Seizures +	1 (2.2%)
Distinctive Constellations		MTLE with HS	1 (2.2%)
		Genetic Generalised Epilepsy	7 (15.2%)
		Genetic Focal Epilepsy	4 (8.7%)
Other Structural-Metabolic Causes		Focal Epilepsy	5 (10.9%)
Epilepsies of Unknown Cause		Mixed Focal & Generalised Epilepsy of Unknown Origin	1 (2.2%)
		Generalised Epilepsy of Unknown Origin	5 (10.9%)
		Focal Epilepsy of Unknown Origin	6 (13.0%)

9.2 Cognitive Functioning

In this section, analysis of group differences in cognitive functioning are reported. Data on the Bayley III Cognition scale (0-29m) and WPPSI III IQ scales (≥30m) are reported individually, and then pooled to provide analysis of General Cognitive Ability (GCA). The effects of age, tool type, and sociodemographic variables across the early-onset period on GCA are examined. Data on NEPSY II: Memory, Social Perception, and Attention & Executive Functioning, in children (age ≥36m) are then presented. For all tools, the distribution of scores for CWEOE and controls are presented first, followed by the prevalence of cognitive functioning impairments.

41 of the 46 population-based CWEOE completed face-to-face cognitive assessment using the Bayley III or WPPSI III. Demographic details and comparisons of the 41 CWEOE and 37 controls who completed a Bayley III or WPPSI III are listed in table 9.5.

Five children could not be assessed with the WPPSI III, despite attempted administration. Four of the five could not be reliably assessed due to learning, language, and/or psychomotor difficulties. All had previously diagnosed global developmental delay according to medical records, and were over the upper age limit of the Bayley III; and an assessment score could not be generated. These children were consequently classified as GCA impaired. Additionally, all four could not be assessed on the NEPSY II for the same reasons. The fifth child, who was 31m of age and was eligible for alternative assessment on the Bayley III, did not return for assessment. This child was unsuccessfully assessed in a community care setting by an associate psychologist using a similar developmental assessment tool, and was therefore classified as GCA impaired. Similar methods of qualitatively classifying children have been used elsewhere (e.g. Cormack et al., 2007; Rantanen et al., 2011).

Table 9.5 Group demographics, and age and gender comparisons

	CWEOE		*Controls*		*Group Comparison (p-value)*	
Tool	N (M:F)	Age, m (SD)	N (M:F)	Age, m (SD)	Age	Gender
Bayley III	22 (12:10)	13.05 (7.48)	19 (9:10)	19.10 (8.14)	**.02**	.76
WPPSI III	19 (14:5)	49.63 (8.85)	18 (9:9)	47.58 (9.97)	.51	.18
GCA	41 (26:15)	30.00 (20.14)	37 (18:19)	32.96 (16.98)	.49	.25

9.2.1 Bayley-III Cognition Scale

Mean Bayley III cognition score for CWEOE was significantly poorer than that of controls (Group Mean difference (MD)= -22.00 (95% CI -12.13, -31.86), p<.001). A one-way analysis of covariance (ANCOVA) found a significant main effect of group on Bayley III cognition, after adjusting for age and SES (F(1,37)=15.01, p<.001, η_p^2=.29), with lower estimated marginal means (EMM) in CWEOE compared to controls. Unadjusted and adjusted means are displayed in table 9.6.

Seven CWEOE and zero controls scored ≥3 SD below the normative mean, and were excluded as part of a sensitivity analysis (see section 8.7.1 for discussion and rationale). The ANCOVA was reran, and a group (η_p^2=.34) and SES (η_p^2=.29) main effect remained. Therefore, poor performance in CWEOE could not be explained by children with severe developmental delay disproportionately decreasing the group mean.

Table 9.6 Bayley III Cognition scores

Group Analysis	*CWEOE (n=22)*	*Controls (n=19)*	*Group Comparison MD (95% CI) or effect size*
Unadjusted Mean (SD)†	79.32 (20.43)	101.32 (9.11)	**-22.00 (-12.13, -31.86)**
SES and Age Adjustment EMM (95% CI)	78.75 (71.15, 86.36)	101.97 (93.69, 110.26)	η_p^2**=.29**
Sensitivity Analysis EMM (95% CI)	88.18 (82.55, 93.82)‡	103.28 (98.34, 108.21)	η_p^2**=.34**

† unequal variances t-test
‡ CWEOE n=15
Emboldened p<.05

9.2.2 WPPSI III IQ Scales

CWEOE (n=19) had poorer FSIQ compared to controls (n=18) (p=.001), although FSIQ lay close to the normative mean in CWEOE (table 9.7). Group difference in FSIQ remained after controlling for SES (ANCOVA; F(1,34)=9.9, p=.003, η_p^2=.23) (table 9.7). There was no main effect of SES (η_p^2=.02). This suggests that despite FSIQ in the normal range, CWEOE were not reaching peer expectations.

Table 9.7 WPPSI III FSIQ scores

Group analysis	*CWEOE (n=19)*	*Controls (n=18)*	*Group Comparison MD (95% CI) or effect size*
Unadjusted Mean (SD)	98.16 (14.80)	114.11 (12.18)	**-15.95 (-6.88, -25.03)**
SES Adjustment EMM (95% CI)	98.70 (92.17, 105.22)	113.54 (106.83, 120.26)	**η_p^2=.23**

Emboldened p<.05

A mixed (split-plot) ANOVA examined group differences across WPPSI III subscales: VIQ and PIQ (table 9.8). There was a significant interaction effect between group and WPPSI III subscales (Wilks' Lambda=.89, F(1,35)=4.52, p=.041, η_p^2=.11), with control children scoring significantly higher than CWEOE (η_p^2=.27). Simple effects tests using pairwise comparisons revealed poorer performance in CWEOE compared to controls in VIQ (MD= -18.62 [95% CI -980, -27.45]), and in PIQ (MD= -9.56 [95% CI .35, 18.77]). Taken together, controls scored significantly higher in VIQ and PIQ compared to CWEOE, and the within-groups relationship between VIQ and PIQ was inverse; that is, VIQ was higher, but not significantly so, compared to PIQ in controls but vice versa in CWEOE. PSQ was available for children from 4 years of age (n=11 per group). CWEOE had lower PSQ score than controls but there was no significant difference between groups; MD= -8.09, 95% CI (-18.42, 2.23), p=.118.

Table 9.8 WPPSI III IQ subscale scores

Group	*VIQ mean (SD)*	*PIQ mean (SD)*	*PSQ† mean (SD)*
CWEOE (n=19)	96.21 (12.91)	101.11 (15.20)	n=11, 98.91 (14.60)
Controls (n=18)	114.83 (13.54)	110.67 (12.13)	n=11, 107.00 (7.50)

VIQ - Verbal IQ
PIQ - Performance IQ
PSQ - Processing Speed Quotient; † children ≥4 years

9.2.3 General Cognitive Ability (GCA)

To remind the reader, the Bayley III Cognition and WPPSI III FSIQ scales were converted to z-scores in order to compare GCA between groups across the entire age range, as well as to assess the impact of age, tool type, and study variables.

(i) General Cognitive Ability Scores

The distribution of GCA scores in CWEOE and controls is depicted in figure 9.1. CWEOE had significantly poorer unadjusted GCA scores compared to controls (table 9.9). After adjusting for SES in an ANCOVA, a significant main effect of group remained ($F(1,75)=23.79$, $p<.001$, $\eta_p^2=.24$). There was no main effect of SES ($\eta_p^2=.004$). In a sensitivity analysis (see section 8.7.1), excluding children with Bayley III cognition score ≥3 SD below normative mean (n=7), did not alter the findings (table 9.9), indicating that poorer GCA in CWEOE could not be attributed simply to more severe cases of epilepsy.

Figure 9.1 Boxplot of GCA scores

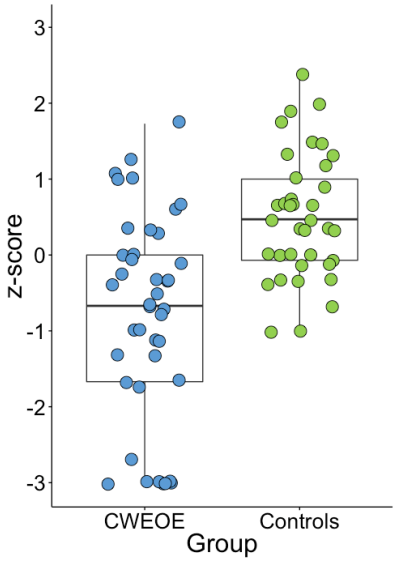


Table 9.9 GCA unadjusted and adjusted means

Group Analysis	*CWEOE (n=41)*	*Controls (n=37)*	*Group Comparison MD (95% CI) or effect size*
Unadjusted Mean (SD)†	-0.80 (1.35)	0.50 (0.83)	**-1.30 (-0.80, -1.80)**
SES Adjusted EMM (95% CI)	-0.82 (-0.46, -1.19)	0.53 (0.14, 0.92)	**η_p^2=.24**
‡ Sensitivity analysis; SES adjusted EMM (95% CI)	-0.40 (-0.08, -0.72)	0.56 (0.25, 0.86)	**η_p^2=.21**

Emboldened p<.001
† unequal variances t-test
‡ Excluding 7 outliers, CWEOE n=34

GCA improved with increasing age in both CWEOE ($r_s=0.41$, $p=.008$) and controls ($r_s=0.50$, $p=.002$). To investigate the possibility that GCA score improved with changes in assessment tool type (i.e. Bayley III, WPPSI III 30-47m version, or WPPSI III 48-84m version) rather than age

per se, assessment tools were factored into linear regression models and compared to a model with assessment age only. It was found that tool type did not significantly increase predictive power beyond that predicted by assessment age alone, which showed that GCA improved with age in CWEOE and controls, rather than tool type.

Table 9.10 Bivariate analysis of GCA and study variables in CWEOE (n=41)

Variable	*Sub-group*	*N*	*Mean GCA (SD)*	*p*	*MD (95% CI) or effect size*
Gender	Male	26	-0.57 (1.11)	.07‡	0.89 (-0.06, 1.84)
	Female	15	-1.36 (1.57)		
SES	Lower	24	-0.85 (1.39)	.76	0.14 (-0.74, 1.01)
	Higher	17	-0.72 (1.33)		
Prematurity	Pre-term	4	-1.33 (1.15)	.41	0.59 (-2.03, 0.85)
	Full-term	37	-0.74 (1.37)		
Family History of Epilepsy	No	24	-1.06 (1.53)	.13	-.65 (-1.47, 0.19)
	Yes	15	-.42 (1.03)		
Seizure Frequency	Low	25	-0.50 (0.89)	.12‡	.77 (-0.08, 1.62)
	High	16	-1.27 (1.78)		
No. of AEDs	None/monotherapy	35	-0.58 (1.22)	**.009**	1.51 (0.40, 2.63)
	Polytherapy	6	-2.09 (1.45)		
Seizure onset	Localised	17	-0.83 (1.30)	.85	η^2 = 0.008
	Generalised	20	-0.70 (1.51)		
	Both	4	-1.12 (0.73)		
Aetiology (1989)	Idiopathic	24	-0.13 (0.87)	**<.001**	η^2 = 0.37
	Symptomatic	9	-1.93 (1.46)		
	Cryptogenic	8	-1.54 (1.28)		
Aetiology (2010)	Unknown	20	-0.51 (1.34)	**.013**	η^2 = 0.20
	Genetic	12	-0.42 (0.77)		
	Structural/Metabolic	9	-1.93 (1.46)		
MRI	Normal	18	-0.66 (1.04)	**.012**	η^2 = 0.24
	Minor abnormality	6	-0.66 (0.59)		
	Major abnormality	11	-1.95 (1.38)		
EEG	Normal	11	-.033 (0.85)	**<.001**	η^2 = 0.37
	Epileptiform *or* slow-wave	23	-0.59 (1.26)		
	Both	6†	-2.72 (0.53)		
Assessment age, months	(median)	41		**.008**	r_s = .41
Age 1st seizure, months	(median)	41		**.013**	r_s = .39

‡ unequal variances t-test

†4 had infantile spasms, 1 had Otahara syndrome, 1 had structural focal epilepsy

The association between GCA and sociodemographic and epilepsy-related variables was explored in CWEOE via bivariate analyses (table 9.10). Polytherapy, structural or symptomatic/cryptogenic aetiology, major brain abnormality recognised on MRI, presence of epileptiform *and* slow-wave background activity on clinical EEG, and younger age at assessment/first seizure were associated with poorer GCA score in CWEOE.

A standard multiple linear regression model was fitted including variables identified from bivariate analyses at the $p<.01$ significance level. Although EEG status was significant, it was not included in modelling due to collinearity with aetiology. Both ILAE classifications were modelled separately. Symptomatic and cryptogenic aetiologies were collapsed into a single subgroup, as were genetic and unknown aetiologies, due to non-significant differences in bivariate analyses. Age at first seizure was selected over age at assessment, due to greater clinical applicability. Gender was also modelled but did not significantly improve model fit, and was excluded from final models.

Models including old and new aetiological classifications were significant (table 9.11 A and B, respectively). Model A, including the 1989 classification, explained more of the variance in GCA score than the newer classification (R^2*adj* = 42.4% vs 33.9%, respectively). In the former, aetiology (1989) and number of AEDs independently predicted GCA. GCA decreased by 1.05 SD in children treated with more than one AED (i.e. polytherapy) compared to those untreated or on monotherapy. GCA decreased by 0.63 SD with symptomatic/cryptogenic aetiology compared to idiopathic aetiology in model B. Age at first seizure was non-significant in both models.

Table 9.11 Regression coefficients for study variables GCA in CWEOE

A. Model including 1989 aetiology

Variable	*ß*	*95% CI*		*p*
		Lower	*Upper*	
Constant	-0.10	-0.54	0.34	.640
0/1 AED vs polytherapy	-1.05	-0.11	-1.99	**.030**
Aetiology (1989)[1]	-0.63	-0.26	-0.99	**.001**
Age at first seizure	0.01	-0.01	0.04	.175

1-Idiopathic vs symptomatic/cryptogenic

B. Model including 2010 aetiology

Variable	*ß*	*95% CI*		*p*
		Lower	*Upper*	
Constant	-0.36	-0.77	0.06	.090
0/1 AED vs polytherapy	-1.24	-2.23	-0.24	**.016**
Aetiology (2010)[2]	-1.05	-1.94	-0.17	**.021**
Age at first seizure	0.02	-0.001	.043	.062

2-Unknown/genetic vs structural/metabolic

In summary, CWEOE had significantly poorer GCA than control children - which could not be explained by differences in SES. Results held equally true for infants and toddlers assessed by the Bayley-III (0-29m), and preschool children assessed with the WPPSI-III (≥30m). GCA improved with age in CWEOE and controls, whilst poorer GCA in CWEOE was independently predicted by structural or symptomatic aetiology, and polytherapy.

(ii) GCA impairment

While GCA scores were generated for 41 CWEOE, five CWEOE were qualitatively classified with GCA impairment based on unassessability due to previously diagnosed learning, social or developmental difficulties (see section 9.2). Thus, data for 46 CWEOE and 37 controls were available for the current analysis on GCA impairment. The prevalence of GCA impairment can be found in table 9.12. Of the eight children scoring in the impaired range on the Bayley-III, seven had global impairment (i.e. cognitive, language, and motor domain impairment). The remaining child had cognitive and motor impairment, with normal language functioning.

Table 9.12 Cognitive functioning classification by group and tool

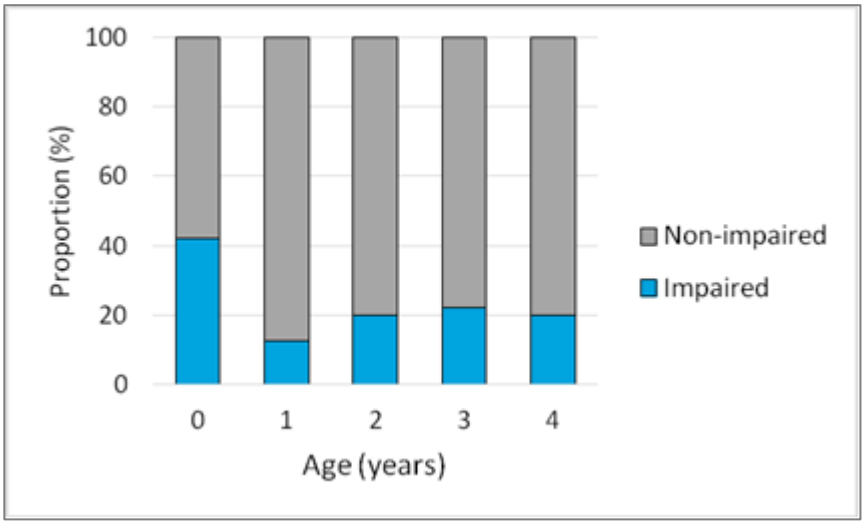
Classification (SD below mean)		Bayley III (≤29m*)		WPPSI III (≥30m)		Total (GCA)	
		CWEOE (n=22) % (n)	Controls (n=19) % (n)	CWEOE (n=24) % (n)	Controls (n=18) % (n)	CWEOE (n=46) % (n)	Controls (n=37) % (n)
Normal	(≤1SD)	40.9 (9)	89.5 (17)	62.5 (15)	100 (18)	52.2 (24)	94.6 (35)
Subnormal	(1-2SD)	22.7 (5)	10.5 (2)	16.7 (4)	0 (0)	19.5 (9)	5.4 (2)
Impaired	(≥2SD)	36.4 (8)	0 (0)	20.8 (5)	0 (0)	28.3 (13)	0 (0)

*one control child was 33m at test

Peak GCA impairment was in the first year of life. Figure 9.2 displays the proportion of CWEOE with *or* without GCA impairment by year of age (at first seizure). The proportion of CWEOE with GCA impairment <12m (42.1%) was considerably higher, but not significantly so, compared to the proportion of children impaired aged 1-4 years (18.5%); FET, p=.10, OR=3.20 (95% CI [.85, 12.12]). The difference in percentages between year 0 and 1-4, can be explained by the presence of infantile spasms. All seven children with infantile spasms had onset in year 0, five of which (71.4%) had GCA impairment. For the remaining 12 children with other epilepsies, 3 (25.0%) had GCA impairment, closer to the overall prevalence of impairment

across all ages (n=8, 20.5%). The odds of impairment was greater for infantile spasms than other epilepsies; OR 9.69 (95% CI 1.58, 59.47).

Figure 9.2 Proportion of CWEOE with/without GCA impairment by age at first seizure



Bivariate analyses of GCA impairment and sociodemographic and clinical variables revealed that GCA impairment occurred more often in females, and in those with high seizure frequency, those on polytherapy, those with both epileptiform *and* slow-wave background activity on clinical EEG, and those with symptomatic/cryptogenic aetiology (table 9.13). All 13 CWEOE with GCA impairment had symptomatic/cryptogenic aetiology. There was no significant association between GCA impairment and 2010 aetiological classification. Due to modest sub-group sample sizes, a multiple linear regression was unsuitable.

Table 9.13 Bivariate analysis of GCA impairment and study variables in CWEOE (n=46)

Variable	*Sub-group*	*Impaired N (%)*		*FET*	*OR (95% CI)*
		No	*Yes*		
Gender	Male Female	24 (88.9) 9 (47.4)	3 (11.1) 10 (52.6)	**.003**	8.89 (1.98, 39.86)
SES	Higher Lower	14 (77.8) 19 (67.9)	4 (22.2) 9 (32.1)	.52	1.66 (0.42, 6.49)
Prematurity	Pre-term Full-term	3 (75.0) 30 (71.4)	1 (25.0) 12 (28.6)	1.0	1.20 (0.11, 12.71)
Family History of Epilepsy	No Yes	17 (65.4) 14 (77.8)	9 (34.6) 4 (22.2)	.51	0.54 (0.14, 2.13)

Table 9.13 continued

Variable	*Sub-group*	*Impaired N (%)*		*FET*	*OR (95% CI)*
		No	*Yes*		
Seizure Frequency	Low High	24 (88.9) 9 (47.4)	3 (11.1) 10 (52.6)	**.003**	8.89 (1.98, 39.86)
No. of AEDs	None/monotherapy Polytherapy	31 (81.6) 2 (25.0)	7 (18.4) 6 (75.0)	**.004**	13.29 (2.2, 80.23)
Seizure onset	Localised Generalised Both	14 (77.8) 15 (62.5) 4 (100)	4 (22.2) 9 (37.5) 0 (0)	.26	-
Aetiology (1989)	Idiopathic Symptomatic Cryptogenic	24 (100) 4 (40.0) 5 (41.7)	0 (100) 6 (60.0) 7 (58.3)	**<.001**	OR for sympt/crypt vs idiopathic = 2.44 (1.48, 4.04)
Aetiology (2010)	Unknown Genetic Structural/Metabolic	17 (77.3) 12 (80.0) 4 (44.4)	5 (22.7) 3 (20.0) 5 (55.6)	.15	-
MRI*	Normal Minor abnormality Major abnormality	16 (72.7) 6 (85.7) 5 (45.5)	6 (27.3) 1 (14.3) 6 (55.5)	.18	-
EEG*	Normal Epileptiform *or* slow-wave Both	11 (100) 20 (8.0) 1 (12.5)	0 (0) 5 (20.0)† 7 (87.5)	**<.001**	-
Assessment Age, months (median)		39	31	p=.10‡	r_s=.24
Age at 1st seizure, months (median)		18	8	p=.11‡	r_s=.24

*6 children did not have an MRI, and EEG data was unavailable for 2

† All 5 had epileptiform activity only

‡ Mann-Whitney U test

9.2.4 Specific Neuropsychological Skills: Memory, Social Perception, and Attention & Executive Functioning (NEPSY II)

The NEPSY II consisted of six subtests which assessed memory, social perception, and attention & executive functioning in children ≥36m (section 8.3.1). Of the 22 CWEOE who were age-eligible for NEPSY II assessment, four children were excluded due to developmental delay (see section 8.7.1). 18 (13M:5F) CWEOE (M=50.66, SD=7.83m) and 15 (8M:7F) controls (M=50.66, SD=7.71m) completed the NEPSY II subtests. CWEOE and control groups did not significantly differ in gender or age. Each specific neuropsychological domain is described below.

(i) Memory Scores

The NEPSY II Memory domain consisted of three memory subtests: Memory for Designs (visuospatial memory), Narrative Memory (verbal recall and recognition memory), and Sentence Repetition (verbal recall memory). Controls performed better than CWEOE in each subtest, although both groups scored within the average ranges - significantly so for Memory for Designs and Sentence Repetition (table 9.14). ANCOVAs were conducted to adjust for possible effects of SES. In Memory for Designs, a group effect (η_p^2=.05) was no longer evident when SES (p=.022, η_p^2=.16) was adjusted for. In contrast, after adjustment for SES (η_p^2=.10), poor performance in CWEOE relative to controls remained in the Sentence Repetition subtest (p=.002, η_p^2=.30).

Table 9.14 NEPSY II Memory subtests with group comparisons

Subtest	*Group (N)*	*M (SD)*	*MD (95% CI)*	*SES adjustment EMM (95% CI)*	η_p^2
Memory for Designs	CWEOE (18) Controls (15)	9.72 (3.21) 12.40 (4.27)	**-2.68 (-5.34, -.18)**	10.21 (8.49, 11.93) 11.81 (9.92, 13.71)	.05
Narrative Memory	CWEOE (18) Controls (15)	8.56 (3.24) 10.00 (3.02)	-1.44 (-3.69, .80)	n/a	-
Sentence Repetition*	CWEOE (17) Controls (14)	8.0 (3.14) 12.0 (2.15)	**-4.0 (-6.02, -1.98)**	**8.24 (6.89, 9.58)** **11.72 (10.22, 13.21)**	**.16**

*1 CWEOE and 1 control child did not complete Sentence Repetition due to non-compliance
Emboldened= p<.05

(ii) Social Perception Scores

Social Perception consisted of Affect Recognition and Theory of Mind subtests. One control child did not complete the Theory of Mind subtest due to non-compliance. CWEOE scored close to the normative mean on both subtests, but significantly lower than control children (table 9.15). After adjustment for SES in Affect Recognition, there was no longer a significant effect of group (p=.055), or main effect of SES (η_p^2=.03). A moderate-large effect size (η_p^2=.12), however, suggests a noteworthy trend toward group difference. In contrast, a group effect remained in the Theory of Mind subtest (p=.014), but not for SES, suggesting that CWEOE are scoring poorer than should be expected regardless of SES.

Table 9.15 NEPSY II Social Perception Subtests with group comparisons

Subtest	*Group (N)*	*M (SD)*	*MD (95% CI)*	*SES adjustment EMM (95% CI)*	η_p^2
Affect Recognition	CWEOE (18)	10.06 (2.29)	**-1.9 (-0.34, -3.55)**	10.18 (9.06, 11.30)	.12
	Controls (15)	12.00 (2.20)		11.85 (10.62, 13.09)	
Theory of Mind	CWEOE (18)	9.61 (2.20)	**-2.46 (-0.52, -4.40)**	**9.53 (8.20, 10.87)**	**.19**
	Controls (14)	12.07 (3.17)		**12.17 (10.65, 13.70)**	

Emboldened= p<.05

(iii) Attention & Executive Functioning Scores

Attention & Executive Functioning was assessed via the Statue subtest. One CWEOE and one control child did not complete this subtest due to non-compliance.

CWEOE scored significantly poorer than control children (table 9.16). However, after adjustment for SES, group was no longer significant (p=.068), albeit with a moderate effect size (η_p^2=.11), suggesting a trend toward a group difference. There was no main effect of SES (η_p^2=.08).

Table 9.16 NEPSY II Attention & Executive Functioning

Group (N)	*M (SD)*	*MD (95% CI)*	*SES adjusted EMM (95% CI)*	η_p^2
CWEOE (17)	8.47 (3.41)	**-2.67 (-0.42, -4.92)**	8.71 (7.20, 10.22)	.11
Controls (14)	11.14 (2.54)		10.85 (9.18, 12.53)	

Emboldened p<.05

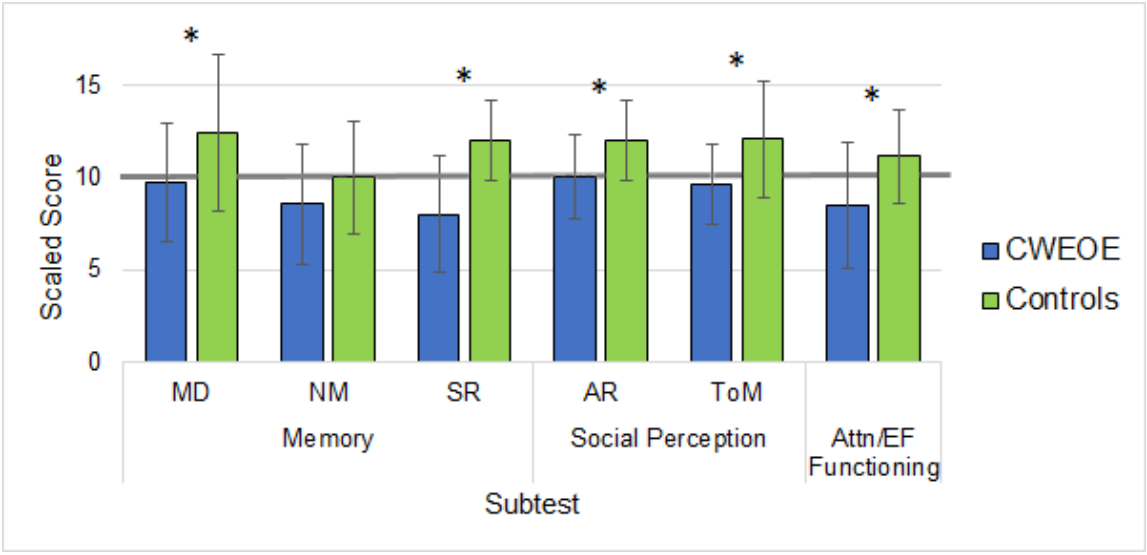
(iv) Specific Neuropsychological Skills: Scores Summary

CWEOE consistently scored lower than controls across all subtests of the NEPSY-II. This was significantly so for Memory for Designs, Sentence Repetition, Affect Recognition, and Theory of Mind (figure 9.3A). After adjustment for SES, a group difference remained in Sentence Repetition and Theory of Mind subtests (figure 9.3B), indicating that epilepsy itself remained a strong influence on aspects of neuropsychological functioning beyond SES. Whilst group differences in Affect Recognition and Attention & Executive Functioning were non-significant after SES adjustment, it is important to note that moderate-large effect sizes remained,

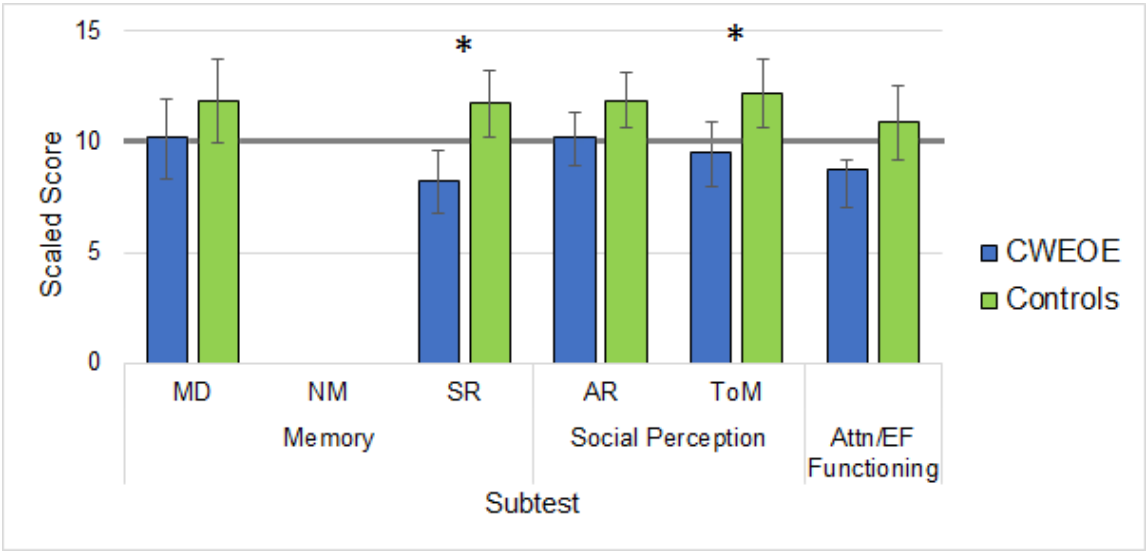
suggesting that the scores in CWEOE were lower than expected potentially as a result of having epilepsy.

Figure 9.3 Unadjusted and SES adjusted NEPSY II subtest means scaled scores

A. Unadjusted mean scaled scores and standard deviations (error bars)



B. Mean SES adjusted sclaed scores and 95% confidence intervals



Horizontal grey line represents normative mean

* Group difference p<.05

AR – Affect Recognition

Attn/EF – Attention & Executive Functioning

MD – Memory for designs

NM – Narrative Memory

SR – Sentence Repetition

ToM – Theory of Mind

As a group, CWEOE who completed the NEPSY II had GCA within the normal range (M= -.07, SD= 0.98 [range -1.73 to 1.73]) but had lower GCA scores compared to controls (MD= -1.10 [95% CI -0.48, -1.72]). Thus, it is unclear if group differences observed in the Sentence Repetition and Theory of Mind subtests, or trending differences in other subtests, could be attributed to an effect of epilepsy or to intergroup differences in GCA. In support of an epilepsy effect, a one-samples t-test in CWEOE revealed poorer performance in Sentence Repetition (M=8.0, SD=3.14) compared to the test normative mean (M=10.0); p=.018, MD=-2.00 (95% CI -0.38, -3.62). However, a similar result was not found in the Theory of Mind subtest (M=9.61, MD= -.39 [95% CI -1.48, 0.71]), Affect Recognition (M=9.72, MD= -0.28 [95% CI -1.88, 1.32]), or Attention & Executive Functioning (M=10.06, MD= -.06 [95% CI -1.08, 1.19]). These results suggest stronger evidence for a disproportionate influence of epilepsy on the Sentence Repetition task at this age, beyond any difference in GCA.

(v) Specific Neuropsychological Skills: Impairment

No significant differences were found between group prevalences of impairments (scaled score ≥1.5SD below mean) on the NEPSY-II subtests (table 9.17). Statue, and Sentence Repetition, were most notably affected, with 4 CWEOE scoring in the impaired range on the former, and four different children on the latter, indicating domain specific impairments.

Table 9.17 Prevalence of impairment on NEPSY II subtests

Domain	*Subtest*	*Group*	*Impaired N (%)*		*FET*
			No	*Yes*	
Attention & Executive Functioning	Statues	CWEOE Controls	13 (76.5) 14 (100)	4 (23.5) 0 (0)	.11
Memory	Memory for Designs	CWEOE Controls	17 (94.4) 15 (100)	1 (5.6) 0 (0)	1.0
	Narrative Memory	CWEOE Controls	15 (83.3) 14 (83.3)	3 (16.7) 1 (6.7)	.61
	Sentence Repetition	CWEOE Controls	14 (77.8) 14 (100)	4 (22.2) 0 (0)	.11
Social Perception	Affect Recognition	CWEOE Controls	17 (94.4) 15 (100)	1 (5.6) 0 (0)	1.0
	Theory of Mind	CWEOE Controls	18 (100) 13 (92.9)	0 (0) 1 (7.1)	.44

9.3 Behavioural Functioning

The previous subsection described and compared the distribution of cognition-based psychometric assessment tools in CWEOE and controls. This subsection addresses the results of the parent-rated social-emotional behaviour rating scales. Results are structured according to the domains of interest and corresponding domain relevant scales, which have been described in section 8.3.

9.3.1 Completeness of the neurobehavioural assessment battery

Questionnaire return rate was high. Between 90 and 97% of questionnaires were returned by those who consented. Of the 46 CWEOE who had, or attempted, face-to-face cognitive assessment, only four did not return behaviour questionnaires. Two of these children had normal GCA and were neurologically normal. The third had severe global delay, and the fourth child was unassessable due to uncooperativeness and social interaction difficulty. This child was under investigations from community paediatricians for suspected learning/social difficulties. A further three CWEOE had partial completion of the behaviour questionnaires. One did not return an ITSEA, one a CEC questionnaire, and one a SES questionnaire. Of the 37 controls, four had partial completeness due to non-return of questionnaires or incomplete questionnaires. Table 9.18 details the completeness of behaviour assessment questionnaires for CWEOE and controls, describing how many returned a questionnaire (n) from those who were age-eligible for that questionnaire (N). The table also includes between-group (i.e. CWEOE vs Controls) gender and age comparisons for each questionnaire.

Table 9.18 Behaviour questionnaire assessment completeness

Assessment Tool	*Completeness n/N (%)*		*Group Comparisons (FET)*	
	CWEOE	*Controls*	*Gender*	*Age ǂ*
ABAS II	42/46 (91)	37/37 (100)	.37	.80
ITSEA	9/11 (82)	13/13 (100)	.42	.17
CEC	23/26 (88)	20/20 (100)	.76	.39
BRIEF-P	24/26 (92)	22/22 (100)	.77	.28
SEGC	9/11 (82)	2/4 (50)	.46	.81
M-CHAT	7/7 (100)	11/11 (100)	1.0	.56
SRS2	22/24 (92)	17/19 (90)	.53	.75
Total	90.07%	96.83%		

ǂ T-test or Mann Whitney U

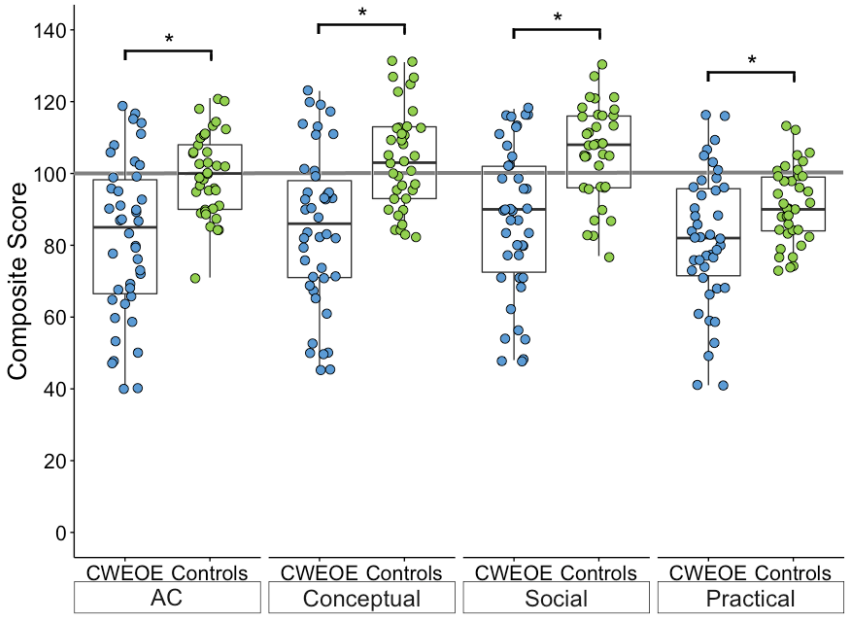
9.3.2 Adaptive Behaviour

Adaptive Behaviour was assessed using the ABAS II (≥1m), and consisted of Conceptual, Social, and Practical domain composites scores, and an overall General Adaptive Composite (AC). 42 CWEOE (25M:17F) and 37 controls (18M:19F) completed the ABAS-II.

(i) Adaptive Behaviour Scores

Figure 9.4 displays the unadjusted distributions of AC and adaptive behaviour composite domain scores. CWEOE (M=62.13, SD= 14.54) had poorer (i.e. higher) unadjusted AC score compared to controls (M=50.18, SD=7.62); MD= 11.95 (95% CI 6.81, 17.08) (unequal variances t-test). Likewise, CWEOE had poorer adaptive behaviour across all composite domains. To account for possible effects of SES, and due to unequality of variance, a rANCOVA was conducted. After adjustment for SES, poorer AC remained in CWEOE compared to controls; $F(1,77)=9.02$, $p=.004$, $\eta^2=.11$.

Figure 9.4 Scatter-box plot: Unadjusted ABAS II composite scores



Horizontal grey line represents normative mean

While mean AC was lower in CWEOE regardless of SES, stratifying children by SES revealed that the group difference was only seen in those with lower SES (table 9.19), indicating that having epilepsy and being from an area of lower SES increased the likelihood of adaptive behaviour problems.

Table 9.19 Mean AC score by group and SES

SES	*Group*	*N*	*Mean (SD)*	*MD (95% CI)*
High SES	CWEOE	17	56.71 (13.83)	9.13 (0.50, 18.76)
	Controls	29	50.62 (7.85)	
Low SES	CWEOE	25	65.81 (14.09)	**25.85 (9.89, 41.80)**
	Controls	8	48.58 (6.98)	

Emboldened p<.05

Table 9.20 Bivariate analysis AC and study variables in CWEOE (n=41)

Variable	*Sub-group*	*N*	*Mean (SD)*	*P*	*MD (95% CI) or effect size*
Gender	Male	25	58.19 (13.14)	**.031**	-9.74 (-0.92, -18.56)
	Female	17	67.92 (14.92)		
SES	Lower	25	65.81 (14.09)	**.045**	9.11 (0.22, 18.00)
	Higher	17	56.71 (13.83)		
Prematurity	Pre-term	4	71.67 (5.67)	.17	10.54 (-4.73, 25.82)
	Full-term	38	61.12 (14.86)		
Family History of Epilepsy	No	25	64.85 (14.33)	.16	6.94 (-2.76, 16.64)
	Yes	15	57.91 (15.23)		
Seizure Frequency	Low	26	60.44 (12.76)	.34	-4.44 (-13.79, 4.91)
	High	16	64.88 (17.13)		
No. of AEDs	None/monotherapy	35	59.30 (13.09)	**.003**	-16.99 (-5.93, -28.05)
	Polytherapy	7	76.29 (13.90)		
Seizure onset	Localised	17	59.76 (14.24)	.64	η^2 = 0.02
	Generalised	21	64.25 (15.58)		
	Both	4	61.00 (11.16)		
Aetiology (1989)	Idiopathic	22	54.85 (9.73)	**.002**	η^2 = 0.28
	Symptomatic	10	70.40 (14.98)		
	Cryptogenic	10	69.87 (15.68)		
Aetiology (2010)	Unknown	20	61.67 (14.40)	.32	η^2 = 0.06
	Genetic	13	58.62 (14.82)		
	Structural/Metabolic	9	68.22 (14.12)		
MRI*	Normal	20	61.30 (15.14)	.59	η^2 = 0.03
	Minor abnormality	7	62.48 (16.83)		
	Major abnormality	10	67.33 (13.49)		
EEG*	Normal	9	59.41 (8.88)	**.015**	η^2 = 0.20
	Epileptiform *or* slow-wave	24	59.06 (14.98)		
	Both	7†	75.71 (8.17)		
Assessment Age, months	(median)	42		1.0	r_s=-0.001
Age at first seizure, months	(median)	42		.79	r_s=0.042

*5 children did not have an MRI, and EEG data was unavailable for 2 children

†All 7 had symptomatic/cryptogenic aetiology, 4 had infantile spasms

Bivariate analyses of study variables and AC score in CWEOE revealed poorer adaptive behaviour was associated with female gender, lower SES, polytherapy, symptomatic/cryptogenic aetiology, and a having both epileptiform *and* slow-wave background activity on clinical EEG (table 9.20). All children with epileptiform and slow-wave EEG activity had symptomatic/cryptogenic aetiology. Unlike ILAE 1989 classifications, ILAE 2010 aetiological classification was not statistically significant. Variables significant at the p<.01 level were inputted into a standard multiple linear regression model, with the exception of EEG, due to collinearity with aetiology. Gender and SES were included as control terms.

Aetiology (1989) remained the only significant predictor when gender and number of AEDs were adjusted for (table 9.21). The overall model was significant (F(3,38)=7.10, p=.001), explaining 31% of the variance in AC score (*adj*R^2). Having a symptomatic or cryptogenic cause for epilepsy resulted in a 6.26 point increase in AC T-score, compared to idiopathic aetiology.

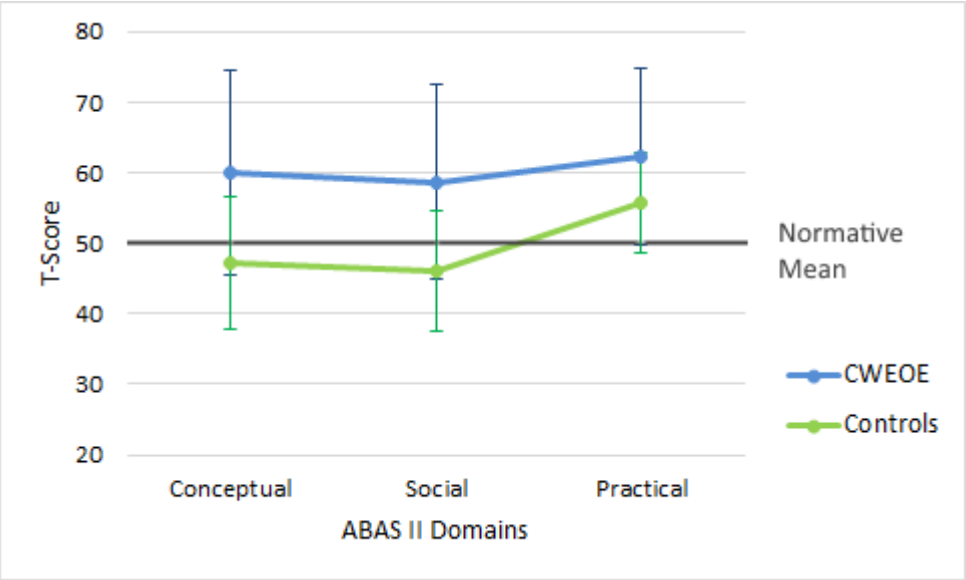
Table 9.21 Regression coefficients for AC and selected variables in CWEOE

Variable		*ß*	*95% CI*		*P*
			Lower	Upper	
Constant		50.30	43.45	57.15	**<.001**
Gender	Male vs Female	5.62	-2.41	13.64	.17
SES	High vs Low SES	6.03	-1.84	13.89	.13
Aetiology (1989)	Idiopathic vs Symptomatic/cryptogenic	6.26	2.25	10.27	**.003**

A two-way mixed ANOVA explored the relationship within and between-groups across ABAS II composite domains (i.e. Social, Conceptual, and Practical), whilst controlling for SES. Levene's test of equality of variance was violated and an alpha level of .01 was set (Tabachnick and Fidell, 2007). There was a significant main effect of ABAS II composite domain (p<.001, η_p^2=.31) but not of SES (η_p^2=.01), and a significant interaction effect between group and ABAS II composite domain (p=.002, η_p^2=.15). To explain, CWEOE scored significantly poorer in the conceptual and social domains compared to controls, but there was no between-group difference in the practical domain (figure 9.5). Post-hoc within-group comparisons using one-way ANOVAs with Bonferroni adjusted pairwise comparisons revealed significant differences

across domains in CWEOE (p=.013, η_p^2=.20), and across domains in controls (p<.001, η_p^2=.62). CWEOE scored higher (i.e. poorer) in the practical domain compared to the social domain, whilst in control children, poorer scores were found in the practical domain compared to the conceptual and social domains.

Figure 9.5 ABAS II Composite Domains, means and SDs



In summary, CWEOE had significantly poorer general adaptive behaviour than control children. ABAS II domain analysis revealed that CWEOE had poorer conceptual and social adaptive behaviours than controls, but not practical adaptive behaviour. Exploration of the variance in AC in CWEOE revealed that poorer adaptive behaviour was associated with female gender, polytherapy, symptomatic/cryptogenic aetiology, low SES, and epileptiform & slow-wave activity on EEG monitoring. Aetiology was the only independent predictor after multiple linear regression, suggesting that cause of epilepsy is perhaps one of the most important precursors to poor adaptive functioning in CWEOE.

(ii) Adaptive Behaviour Problems

Fourteen CWEOE (33.3%) scored ≥2SD above the mean, and met criteria for an adaptive behaviour problem. No control children had an adaptive behaviour problem. In CWEOE, adaptive behaviour problem was significantly associated with female gender, polytherapy,

Table 9.22 Analysis of Adaptive Behaviour problems and study variables in CWEOE (n=42)

Variable	*Sub-group*	*Problem, n (%)*		*FET*	*OR (95% CI)*
		No	*Yes*		
Gender	Male	20 (80.0)	5 (20.0)	**.045**	4.50 (1.15, 17.65)
	Female	8 (47.1)	9 (52.9)		
SES	Higher	14 (82.3)	3 (17.7)	.10	3.67 (0.84, 16.04)
	Lower	14 (56.0)	11 (44.0)		
Prematurity	Full-term	27 (71.1)	11 (28.9)	.10	7.36 (0.69, 78.72)
	Pre-term	1 (25.0)	3 (75.0)		
Seizure Frequency	Low	20 (76.9)	6 (23.1)	.10	3.33 (0.87, 12.72)
	High	8 (50.0)	8 (50.0)		
Family history of epilepsy	No	13 (52.0)	12 (48.0)	**.040**	0.17 (0.03, .90)
	Yes	13 (86.7)	2 (13.3)		
No. of AEDs	None/monotherapy	27 (77.1)	8 (22.9)	**.003**	20.25 (2.12, 193.91)
	Polytherapy	1 (14.3)	6 (85.7)		
Seizure onset	Localised	12 (70.6)	5 (29.4)	.89	-
	Generalised	13 (61.9)	8 (38.1)		
	Both	3 (75.0)	1 (25.0)		
GCA impairment	Non-impaired	27 (87.1)	4 (12.9)	**<.001**	67.50 (6.71, 678.87)
	Impaired	1 (9.1)	10 (90.9)		
Aetiology (1989)	Idiopathic	20 (90.9)	2 (9.1)	**.001**	OR for idiopathic vs symptom/crypto =15.00 (2.72, 82.67)
	Symptomatic	4 (40.0)	6 (60.0)		
	Cryptogenic	4 (40.0)	6 (60.0)		
Aetiology (2010)	Unknown	13 (65.0)	7 (35.0)	.14	-
	Genetic	11 (84.6)	2 (15.4)		
	Structural/Metabolic	4 (44.4)	5 (55.6)		
MRI*	Normal	13 (65.0)	7 (35.0)	.66	-
	Minor abnormality	5 (71.4)	2 (28.6)		
	Major abnormality	5 (50.0)	5 (50.0)		
EEG*	Normal	7 (77.8)	2 (22.2)	**.006**	OR for both vs normal/ epileptiform or slow-wave= 22.29 (2.29, 216.92)
	Epileptiform or slow-wave	19 (79.2)	5 (20.8)†		
	Both	1 (14.3)	6 (85.7)¤		
Assessment Age, months (median)		34	36	.88‡	r=.02
Age at first seizure, months (median)		18	13.5	.98‡	r=.004

*5 children did not have an MRI, and EEG data was unavailable for 2 children

† All 5 had epileptiform activity

‡ Mann-Whitney U

¤ 4 CWEOE had infantile spasms, 2 had generalised epilepsy of unknown cause

cognitive impairment, cryptogenic/symptomatic aetiology, and EEG status (table 9.22). Those with epileptiform activity and slow-wave activity on clinical EEG, were associated with adaptive behaviour problem – most of whom had infantile spasms. Those with a family history of epilepsy were less likely to have an adaptive behaviour problem. A protective factor here is unlikely, and the finding is presumably due to more children with symptomatic/cryptogenic aetiologies having an adaptive behaviour problem than those with idiopathic aetiology, who are more likely to have a positive family history of epilepsy.

A direct logistic regression model was fitted using gender, aetiology (1989), and number of AEDs, in CWEOE. EEG status and cognitive impairment were not included due to multicollinearity. Gender was not a significant predictor, and did not improve model fit. Thus, the model with the least amount of variables was preferred. Model including aetiology (1989) and number of AEDs was significant ($x^2(2,42)=21.60$, $p<.001$), and explained between 40.2 (Cox & Snell R^2) and 55.8% (Nagelkerke R^2) of the variance. Number of AEDs (p=.019) and aetiology (p=.007) independently predicted an adaptive behaviour problem; being on polytherapy was associated with increased odds of adaptive behaviour problem of 32.03 (95% CI 1.76, 584.33) compared to monotherapy/no medication, and having symptomatic/cryptogenic aetiology increased the odds of an adaptive behaviour problem by 20.99 (95% CI 2.28, 193.31) compared to idiopathic aetiology.

9.3.3 Executive Functioning

Executive functioning behaviour assessed using the BRIEF-P, and spanned ages 24-63m in this cohort. Parents of 24 CWEOE (15M:9F) and 22 Controls (12M:10F) completed the BRIEF-P.

(i) Executive Functioning Scores

Mean General Executive Composite (GEC) score was significantly higher in CWEOE than that of controls (p=.046), indicative of increased reporting of executive problems in CWEOE (table 9.23). However, an ANCOVA (data transformed) with SES as a covariate found no main effect of group ($F(1,43)=2.36$, p=.13, $\eta_p^2=.05$), or of SES ($\eta_p^2=.04$), indicating a non-significant difference in executive functioning between groups. Moderate effect sizes suggest the possibility that executive functioning behaviour may be unduly influenced by both SES and epilepsy at this early age.

Table 9.23 BRIEF-P General Executive Composite means and group comparisons

Group (N)	*M (SD)*	*MD (95% CI)*	*SES adjustment EMM (95% CI)*
CWEOE (24)	57.79 (16.87)	**9.06 (0.17, 17.96)**	56.84 (50.59. 63.09)
Controls (22)	48.73 (12.53)		49.77 (43.23, 56.31)

Emboldened p<.05

The inhibit subscale and working memory subscale of the BRIEF-P are associated with ADHD (Skogan et al., 2015). Analysis of these individual scales in CWEOE and controls here found a significant, unadjusted, group difference in the working memory subscale. CWEOE scored significantly higher (i.e. more working memory problems) than controls (MD=8.92 [95% CI 0.59, 17.26], p=.037). This difference dissipated after adjustment for SES (p=.25). There was no significant difference in the inhibit subscale (MD=7.25 [95% CI -1.64, 16.14], p=.11). Of the remaining subscales (shift, emotional control, and planning/organising), only the shift subscale was of statistical significance (p=.008), and which remained significant after rANCOVA adjusting for SES - potentially reflecting rigidity and inflexibility in behaviour across social situations in CWEOE.

(ii) Executive Functioning Problems

Eight CWEOE (33%) had an executive functioning problem (i.e. T-score ≥65 on the General Executive Composite), compared with three (14%) control children. The difference between groups was not statistically significant (FET=.17, OR=3.13 [95% CI 0.72, 14.29]). Variables associated with executive functioning problems included prematurity and symptomatic/cryptogenic aetiology (table 9.24). A regression could not be carried out due to quasi-complete separation in the prematurity variable.

Table 9.24 Analysis of Executive Functioning Problems and study variables in CWEOE (n=24)

Variable	*Sub-group*	*Problem, n (%)*		*FET*	*OR (95% CI)*
		No	*Yes*		
Gender	Male	10 (66.7)	5 (33.3)	1.0	1.0 (0.17, 5.77)
	Female	6 (66.7)	3 (33.3)		
SES	Higher	8 (80.0)	2 (20.0)	.39	3.00 (0.46, 19.59)
	Lower	8 (57.1)	6 (42.9)		
Prematurity	Pre-term	0 (0)	3 (100)	**.028**	-
	Full-term	16 (76.2)	5 (23.8)		

Table 9.24 continued

Variable	*Sub-group*	*Problem, n (%)*		*FET*	*OR (95% CI)*
		No	*Yes*		
Family history of epilepsy	No	9 (64.3)	5 (35.7)	1.0	1.08 (0.18, 6.54)
	Yes	5 (62.5)	3 (37.5)		
Seizure Frequency	Low	10 (55.6)	8 (44.4)	.066	-
	High	6 (100)	0 (0)		
No. of AEDs	None/monotherapy	13 (65.0)	7 (35.0)	1.0	0.62 (0.05, 7.12)
	Polytherapy	3 (75.0)	1 (25.0)		
Seizure onset	Localised	4 (50.0)	4 (50.0)	.33	-
	Generalised	11 (78.6)	3 (21.4)		
	Both	1 (50.0)	1 (50.0)		
GCA impairment	Non-impaired	14 (70.0)	6 (30.0)	.58	2.33 (0.26, 20.66)
	Impaired	2 (50.0)	2 (50.0)		
Aetiology (1989)	Idiopathic	13 (86.70	2 (13.3)	**.021**	OR for sympt/crpyt vs idiopathic = 13.00 (1.70, 99.38)
	Symptomatic	1 (33.3)	2 (66.7)		
	Cryptogenic	2 (33.3)	4 (66.7)		
Aetiology (2010)	Unknown	9 (64.3)	5 (35.7)	.068	-
	Genetic	7 (87.5)	1 (12.5)		
	Structural/Metabolic	0 (0)	2 (100)		
MRI*	Normal	9 (75.0)	3 (0)	.22	-
	Minor abnormality	3 (50.0)	3 (50.0)		
	Major abnormality	0 (0)	1 (100)		
EEG*	Normal	2 (40.0)	3 (60.0)	.15	-
	Epileptiform *or* slow-wave	13 (81.2)	3 (18.8)		
	Both	1 (50.0)	1 (50.0)		
Assessment age, months (median)		50	45	.71ǂ	r=.08
Age at first seizure, months (median)		36	29	.52ǂ	r=.13

*5 children did not have an MRI, and EEG data was unavailable for 1
ǂ Mann-Whitney U

9.3.4 Internalising, Externalising, & Social Functioning Domains

The internalising domain, externalising domain, and social functioning domain consisted of scales originating from several questionnaires (figure 9.6). For a detailed explanation, see section 8.3.2. The SEGC (ages 1-11m) was included in the social functioning domain only, while the scales of the ITSEA and CEC questionnaires were included in the internalising, externalising, and social functioning domains. Therefore, the demographics of those who completed the ITSEA and CEC questionnaires are described here. The ITSEA questionnaire was completed by parents of children aged 12-23m, and the CEC questionnaire for children aged ≥24m. Nine

(6M:3F) CWEOE and 13 (6M:7F) controls completed an ITSEA questionnaire. 23 (14M:9F) CWEOE and 20 (11M:9F) controls completed the CEC questionnaire. Each domain is described below.

Figure 9.6 Internalising, externalising, and social functioning scales, and inclusive ages

Domain	***Scale***	***0-11m***	***12-23m***	***24-35m***	***≥36m***
Internalising	ITSEA Internalising				
	CEC Mood/Affect & Anxiety				
Externalising	ITSEA Externalising				
	CEC Inattention/Hyperactivity				
	CEC Defiance/Aggression				
Social Functioning	SEGC				
	ITSEA Competence				
	CEC Social Atypical				
	CEC Social Functioning				

9.3.4.1 Internalising Behaviour Domain

Internalising behaviour was assessed via the ITSEA Internalising scale and CEC Anxiety and Mood/Affect scales, spanning ages 12-63m – including 32 (20M:12F) CWEOE and 33 (17M:16F) controls.

(i) Internalising Behaviour Domain Scores

Parents of CWEOE reported more internalising behaviours than controls, but the difference did not reach statistical significance (table 9.25).

Table 9.25 Internalising behaviours; scale means and group comparisons

Group	ITSEA Internalising		CEC Mood/Affect		CEC Anxiety	
	Mean (SD)	MD (95% CI) ǂ	Median	p (r) †	Median	p (r) †
CWEOE	48.78 (12.30)	2.93 (-6.89, 12.76)	60.0	.09 (.26)	54.0	.08 (.27)
Controls	45.85 (6.38)		51.0		46.5	

ǂ Unequal variances t-test

† Mann-Whitney U test

(ii) Internalising Domain Problems

Internalising problems (T-score ≥65) were more often found in the CEC scales (table 9.26). Of the children identified on the CEC, one had an anxiety problem, one had a mood/affect problem, and 8 met criteria on both scales. One control child had a CEC mood/affect problem, and two had both an anxiety and mood/affect problem. When the domain was considered as a whole, CWEOE had significantly more internalising problems; eleven (34.4%) CWEOE had an internalising problem compared with three (9.1%) controls; (FET=.017, OR=5.24 [95% CI 1.30, 21.28).

Table 9.26 Prevalence of internalising problems with group comparisons

	Prevalence of problem, n/N (%)		
	ITSEA Internalising	CEC Anxiety	CEC Mood/Affect
CWEOE	1/9 (11%)	9/23 (39%)	9/23 (39%)
Controls	0/13 (0%)	2/20 (10%)	3/20 (15%)
FET (OR [95% CI])	.41	**.039** (5.79 [1.07, 31.16])	.10 (2.61 [.62, 10.98])

n=number of children with problem, N=total number of age-eligible children

Emboldened p<.05

Prematurity was the only significant variable associated with a problem in the internalizing domain (table 9.27).

Table 9.27 Analysis of internalising domain problems and study variables in CWEOE (n=32)

Variable	*Sub-group*	*Problem, n (%)*		*FET*	*OR (95% CI)*
		No	Yes		
Gender	Male	14 (70.0)	6 (30.0)	.70	1.67 (0.37, 7.42)
	Female	7 (58.3)	5 (41.7)		
SES	Higher	9 (69.2)	4 (30.8)	1.0	1.31 (0.29, 5.89)
	Lower	12 (63.2)	7 (36.8)		
Prematurity	Pre-term	0 (0)	3 (100)	**.03**	-
	Full-term	21 (72.4)	8 (27.6)		
Family history of epilepsy	No	12 (66.7)	6 (33.3)	.71	1.43 (0.32, 6.46)
	Yes	7 (58.3)	5 (41.7)		
Seizure Frequency	Low	16 (66.7)	8 (33.3)	1.0	1.20 (0.23, 6.34)
	High	5 (62.5)	3 (37.5)		
No. of AEDs	None/monotherapy	17 (65.4)	9 (34.6)	1.0	0.94 (0.14, 6.19)
	Polytherapy	4 (66.7)	2 (33.3)		

Table 9.27 continued

Variable	*Sub-group*	*Problem, n (%)*		*FET*	*OR (95% CI)*
		No	Yes		
Seizure onset	Localised	6 (54.5)	5 (54.5)	.74	-
	Generalised	13 (72.2)	5 (27.8)		
	Both	2 (66.7)	1 (33.3)		
GCA impairment	Non-impaired	16 (61.5)	10 (38.5)	.64	0.32 (0.03, 3.15)
	Impaired	5 (83.3)	1 (16.7)		
Aetiology (1989)	Idiopathic	13 (65.0)	7 (35.0)	.33	-
	Symptomatic	2 (40.0)	3 (60.0)		
	Cryptogenic	6 (85.7)	1 (14.3)		
Aetiology (2010)	Unknown	10 (62.5)	6 (37.5)	.67	-
	Genetic	9 (75.0)	3 (25.0)		
	Structural/Metabolic	2 (50.0)	2 (50.0)		
MRI*	Normal	9 (60.0)	6 (40.0)	1.0	-
	Minor abnormality	5 (71.4)	2 (28.6)		
	Major abnormality	3 (60.0)	2 (40.0)		
EEG*	Normal	4 (44.4)	5 (55.6)	.19	-
	Epileptiform *or* slow-wave	12 (66.7)	6 (33.3)		
	Both	4 (100)	0 (0)		
Assessment age, months (median)		44	43	.81ǂ	r=.04
Age at first seizure, months (median)		28	24	.77ǂ	r=.05

*5 children did not have an MRI, and EEG data was unavailable for 1

ǂ Mann-Whitney U

9.3.4.2 Externalising Behaviour

The externalising domain consisted of the ITSEA Externalising scale, CEC Defiance subscale, CEC Aggression subscale, and CEC Inattention/hyperactivity scale – and included 32 (20M:12F) CWEOE and 33 (17M:16F) controls (ages 12-63m).

(i) Externalising Domain Scores

Parents of CWEOE reported more ITSEA Externalising and CEC Defiance/Aggression behaviours than controls but the differences did not reach statistical significance (table 9.28A). Parents of CWEOE reported significantly more problems on the CEC Inattention/Hyperactivity scale compared to controls (table 9.28B). A group difference remained after adjustment for SES

(F(1,40)=5.36, p=.026, η_p^2=.12), indicating an effect of epilepsy on attention/executive functioning in CWEOE. There was no main effect of SES (η_p^2=.07).

Table 9.28 Externalising behaviours; scale means and group comparisons

A. ITSEA Externalising and CEC Defiance/Aggression

	ITSEA Externalising		*CEC Defiance/Aggression*	
Group	*Mean (SD)*	*MD (95% CI)*	*Mean (SD)*	*MD (95% CI)*
CWEOE	47.78 (9.24)	4.93 (-2.41, 12.28)	59.04 (16.04)	5.14 (-3.99, 14.27)
Controls	42.85 (4.49)		53.90 (13.18)	

B. CEC Inattention/Hyperactivity

Group	*Mean (SD)*	*MD (95% CI)*	*SES adjustment EMM (95% CI)*	η_p^2
CWEOE	61.30 (15.76)	**12.10 (3.74, 20.47)**	60.26 (54.54, 65.98)	**.12**
Controls	49.20 (10.75)		50.40 (44.25, 56.56)	

Emboldened p<.05

(ii) Externalising Domain Problems

More CWEOE (n=12, 37.5%) met criteria for an externalising domain problem (T-score ≥65) compared to controls (n=6, 18%), but the difference was not significant (FET=.10, OR= 0.37 [95% CI 0.12, 1.16]). Individual scale analysis (table 9.29) revealed a significant group difference in CEC Inattention/Hyperactivity problems.

Table 9.29 Prevalence of externalising problems

	Prevalence of impairment, n/N (%)			
	ITSEA Externalising	*CEC Defiance*	*CEC Aggression*	*CEC Inattention/ Hyperactivity*
CWEOE	0/9 (0)	6/23 (26)	7/23 (30)	9/23 (39)
Controls	0/13 (0)	4/20 (20)	3/20 (15)	2/20 (10)
FET	n/a	.73	.29	**.039**
OR (95% CI)		0.71 (0.17, 2.98)	0.40 (.09, 1.84)	**0.17 (0.03, 0.93)**

n=number of children with problem, N=total number of age-eligible children

Emboldened p<.05

Prematurity and low seizure frequency were the only study variables that were significantly associated with having an externalising domain problem in CWEOE (table 9.30).

Table 9.30 Analysis of externalising domain problems and study variables in CWEOE (n=32)

Variable	*Sub-group*	*Problem, n (%)*		*FET*	*OR (95% CI)*
		No	*Yes*		
Gender	Male	13 (65.0)	7 (35.0)	.72	1.33 (0.31, 5.77)
	Female	7 (58.3)	5 (41.7)		
SES	Higher	9 (69.2)	4 (30.8)	.71	1.64 (0.37, 7.25)
	Lower	11 (57.9)	8 (42.1)		
Prematurity	Pre-term	0 (0)	3 (100)	**.044**	-
	Full-term	20 (69.0)	9 (31.0)		
Seizure Frequency	Low	12 (50.0)	12 (50.0)	**.014**	-
	High	8 (100)	0 (0)		
Family history of epilepsy	No	11 (61.1)	7 (38.9)	1.0	1.12 (0.25, 4.97)
	Yes	7 (58.3)	5 (41.7)		
No. of AEDs	None/monotherapy	16 (61.5)	10 (38.5)	1.0	0.80 (0.12, 5.20)
	Polytherapy	4 (66.7)	2 (33.3)		
Seizure onset	Localised	5 (45.5)	6 (54.5)	.37	-
	Generalised	13 (72.2)	5 (27.8)		
	Both	2 (66.7)	1 (33.3)		
GCA impairment	Non-impaired	16 (80.0)	4 (20.0)	1.0	0.80 (0.12, 5.20)
	Impaired	4 (66.7)	2 (33.3)		
Aetiology (1989)	Idiopathic	14 (70.0)	6 (30.0)	.52	-
	Symptomatic	3 (60.0)	2 (40.0)		
	Cryptogenic	3 (42.9)	4 (57.1)		
Aetiology (2010)	Unknown	10 (62.5)	6 (37.5)	.89	-
	Genetic	8 (66.7)	4 (33.3)		
	Structural/Metabolic	2 (50.0)	2 (50.0)		
MRI*	Normal	8 (53.3)	7 (46.7)	.76	-
	Minor abnormality	4 (57.1)	3 (42.9)		
	Major abnormality	4 (80.0)	1 (20.0)		
EEG*	Normal	6 (66.7)	3 (33.3)	1.0	-
	Epileptiform *or* slow-wave	11 (61.1)	7 (38.9)		
	Both	3 (75.0)	1 (25.0)		
Assessment age, months	(median)	30	45	.17ǂ	r=.24
Age at first seizure, months	(median)	22.5	29	.41ǂ	r=.15

*5 children did not have an MRI, and EEG data was unavailable for 1

ǂ Mann-Whitney U

9.3.4.3 Social Functioning Domain

The social functioning domain was made up of the SEGC, ITSEA Competence scale, and CEC Social Functioning and Atypical subscales. All scales included a total of 41 (25M:16F) CWEOE and 35 (17M:18F) controls, spanning ages 3-63m.

(i) Social Functioning Scores

9 CWEOE (M=62.96, SD=18.22) and 2 controls (M=43.33, SD=0.00) <12m completed the SEGC. No formal analysis could be completed due to the small sample size in the control group. CWEOE had a median T-score of 73.33 (range 40-80), which is two SDs above the mean, reflecting a strong tendency toward atypical social-emotional development in CWEOE <12m.

Two CWEOE were excluded from group analysis of the ITSEA Competence Scale due to incomplete questionnaire responses on the relative subscales which meant a T-score could not be generated for the overall scale. Of the data available from the five subscales that make up the Competence scale, both children had four subscales scoring in the <5th percentile, with the data from the fifth subscale missing. This indicated that these two children were displaying a high degree of IITSEA Competence scale problems.

Table 9.31 Social Functioning; scale means and group comparisons

A. ITSEA Competence and CEC Social Functioning/Atypical Behaviour scales group comparisons †

	ITSEA Competence		*CEC Social Functioning/Atypical Behaviour*	
Group	*Mean (SD)*	*MD (95% CI)*	*Median*	*p (r)*
CWEOE	59.43 (2.99)	-4.66 (-11.63, 2.31)	64.0	**.006 (.42)**
Controls	54.77 (8.41)		47.0	

B. CEC Social Functioning and Atypical subscales group comparisons

	CEC Social Functioning		*CEC Atypical Behaviour*		
Group	*Median*	*p (r)*	*Median*	*p (r)*	*rANCOVA*
CWEOE	56.0	.06 (.29)	61.0	**.001 (.53)**	**F(1,42)=10.12, η^2=.20**
Controls	47.0		45.0		

† ITSEA: CWEOE n=7, controls n=13; CEC: CWEOE n=23, controls n=20

Emboldened, significant at p<.05 level

Parents of CWEOE reported more abnormal social functioning behaviours across the ITSEA Competence and CEC Social Functioning/Atypical Behaviour scales. The difference was not significant in the ITSEA Competence scale but was significant in CEC Social Functioning/Atypical scale (table 9.31A). Subscale analysis revealed the difference was more prominent in the CEC Atypical Behaviour subscale compared to the Social Functioning subscale (table 9.31B). A significant group difference in Atypical Behaviour remained after adjustment for SES.

(ii) Social Functioning Problems

The prevalence of children meeting criteria for a social functioning domain problem (T-score ≥65) within each scale can be found in table 9.32. More CWEOE met criteria for behaviour problems on each scale, except the ITSEA Competence scale. The difference was significant in the CEC Atypical scale. Overall, significantly more CWEOE (n=18, 46%) than controls (n=6, 17%) had a social functioning domain problem (FET=.01, OR= 4.14 [95% CI 1.41, 12.21]).

Table 9.32 Prevalence of social functioning problems by scale

	Prevalence of problems, n/N (%)			
	SEGC	*ITSEA Competence*	*CEC Social Functioning*	*CEC Atypical Behaviour*
CWEOE *Controls*	5/9 (55.6) 0/2 (0)	0/7 (0) 2/13 (15)	7/22 (32) 3/20 (15)	11/23 (48) 2/20 (10)
FET *OR (95% CI)*	.46	.52	.28 2.64 (0.58, 12.10)	**.009** **8.25 (1.55, 44.02)**

n=number of children with problem, N=total number of age-eligible children

Emboldened p<.05

Variables significantly associated with Social Functioning domain problems included female gender, prematurity, cognitive impairment, and symptomatic/cryptogenic aetiology (table 9.33). A multivariable logistic regression including all variables could not be completed due to quasi-complete separation in the premature, and GCA impairment variables.

Supplementary analysis of social functioning specific to peer relationships was conducted using the SDQ. Parents of children aged 36-63m completed the SDQ Peer Relationship Problems, and SDQ Prosocial Behaviour subscales. CWEOE (n=21) had more peer relationship

problems (i.e. rated as having 'high' or 'very high' peer problems on the SDQ) compared to control children (n=15); 38% vs 13% (OR= 4.00 [95% CI 0.71, 2.56]). There was no statistical difference between groups in Prosocial Behaviour (FET=1.0), with 62% of CWEOE and 67% of controls rated as displaying typical levels of prosocial behaviour.

Table 9.33 Analysis of social functioning domain problems and study variables in CWEOE (n=39)

Variable	*Sub-group*	*Problem, n (%)*		*FET*	*OR (95% CI)*
		No	*Yes*		
Gender	Male	8 (53.3)	7 (46.7)	**.003**	9.43 (2.01, 44.27)
	Female	3 (21.4)	11 (78.6)		
SES	Higher	11 (68.8)	5 (31.2)	.19	2.86 (0.75, 10.93)
	Lower	10 (43.5)	13 (56.5)		
Prematurity	Pre-term	0 (0)	4 (100)	**.037**	-
	Full-term	21 (60.0)	14 (40.0)		
Family history of epilepsy	No	9 (40.9)	13 (59.1)	.18	0.35 (0.09, 1.36)
	Yes	10 (66.7)	5 (33.3)		
Seizure Frequency	Low	15 (60.0)	10 (40.0)	.34	2.0 (0.53, 7.54)
	High	6 (42.9)	8 (57.1)		
No. of AEDs	None/monotherapy	20 (58.8)	14 (41.2)	.16	5.71 (0.58, 56.73)
	Polytherapy	1 (20.0)	4 (80.0)		
Seizure onset	Localised	7 (46.7)	8 (53.3)	.65	-
	Generalised	11 (55.0)	9 (45.0)		
	Both	3 (75.0)	1 (25.0)		
GCA impairment	Non-impaired	21 (70.0)	9 (30.0)	**<.001**	-
	Impaired	0 (0)	9 (100)		
Aetiology (1989)	Idiopathic	16 (76.2)	5 (23.8)	**.01**	OR for Symp/crypt vs idiopathic = 8.32 (1.97, 35.10)
	Symptomatic	2 (22.2)	7 (77.8)		
	Cryptogenic	3 (33.3)	6 (66.7)		
Aetiology (2010)	Unknown	9 (50.0)	9 (50.0)	.059	-
	Genetic	10 (76.9)	3 (23.1)		
	Structural/Metabolic	2 (25.0)	6 (75.0)		
MRI*	Normal	11 (61.1)	7 (38.9)	.66	-
	Minor abnormality	3 (42.9)	4 (57.1)		
	Major abnormality	4 (44.4)	5 (55.6)		
EEG*	Normal	5 (55.6)	4 (44.4)	.12	-
	Epileptiform *or* slow-wave	14 (63.6)	8 (36.4)		
	Both	1 (16.7)	5 (83.3)		
Assessment age, months (median)		27	43	.77ǂ	r=.05
Age at first seizure, months (median)		18	23	.92ǂ	r=.02

*5 children did not have an MRI, and EEG data was unavailable for 2

ǂ Mann-Whitney U

9.3.5 Autism Spectrum Disorder Behaviours

ASD behaviours were assessed using the SRS-2, a tool measuring social reciprocal behaviour in children ≥30m. Risk of having ASD was assessed using classification from the M-CHAT (16-29m), and cut-off T-score of ≥65 on the SRS-2 (tools and methods described in section 8.3.2). The M-CHAT was completed in 7 (4M:3F) CWEOE and 11 (5M:6F) controls, and the SRS-2 was completed by 22 (14M:8F) CWEOE and 17 (9M:8F) controls.

(i) ASD Behaviour Scores (SRS-2)

SRS-2 Total score and all index scales and subscales in CWEOE were significantly elevated compared to controls, although remaining within a standard deviation of the normative mean (figure 9.7A). A one-way ANCOVA (log transformed data) revealed a main effect of Group ($F(1,36)=9.01$, $p=.005$, $\eta_p^2=.20$), and a main effect of SES ($F(1,36)=15.86$, $p<.001$, $\eta_p^2=.31$), with those from low SES having more elevated SRS-2 total scores than high SES. Parents of CWEOE reported more atypical social reciprocal behaviours (geometric mean=51.88 [95% CI 48.64, 55.34]) compared to control children (geometric mean=44.67 [95% CI 41.50, 48.19]). A significant group difference remained across indices and subscales after adjustment for SES, with the exception of Social Awareness (figure 9.7B).

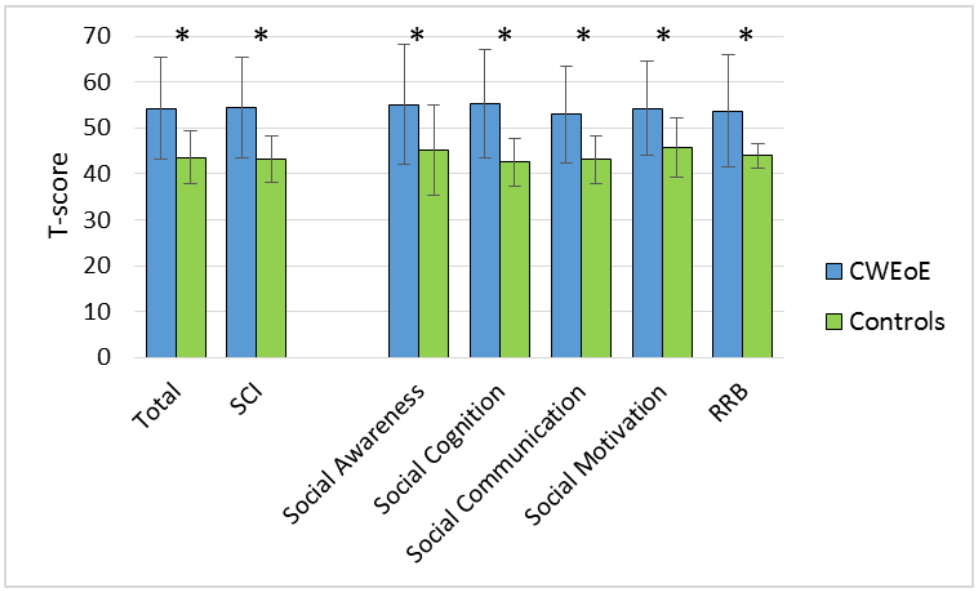
ASD is commonly associated with cognitive impairment in children with epilepsy (Berg and Plioplys, 2012; Tuchman et al., 2010). Consequently a sensitivity analysis was explored using ANCOVA (applying log transformation), dropping four cases of CWEOE with cognitive impairment (see section 9.5.2 for cognitive impairment assessment). A main effect of group remained after SES adjustment ($F(1,32)=5.63$, $p=.024$, $\eta_p^2=.15$), as did a main effect of SES ($F(1,32)=15.29$, $p<.000$, $\eta_p^2=.32$). Back transformed estimated marginal means for CWEOE were 50.23 (95% CI 46.77, 53.95), and 44.46 (95% CI 41.30, 47.86) in controls. These findings suggest that more ASD behaviours compared to controls cannot be explained by GCA impairment in CWEOE.

Bivariate analyses explored study variables on SRS-2 Total score in CWEOE (all cases; table 9.34). Higher T-scores (indicative of increased reporting of atypical social reciprocal behaviour/higher risk of ASD) were associated with lower SES, prematurity, symptomatic/cryptogenic aetiology, and normal EEG status. Although a significant association with normal EEG status was found, this is likely to be due to a type I error, owing to small

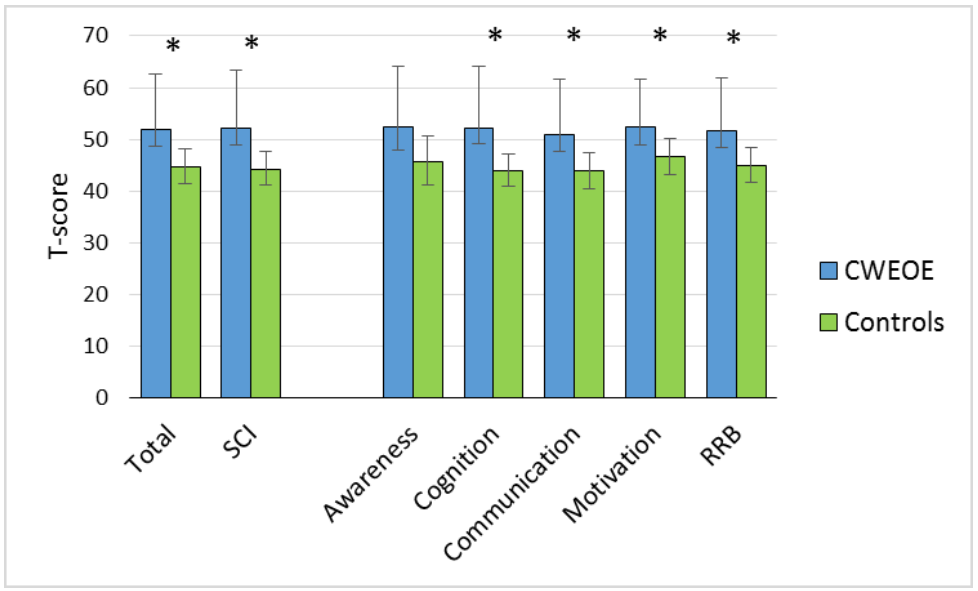
subgroup sample sizes, as it is unlikely that epileptiform activity or slow-wave background activity provides a protective factor against the development of ASD behaviour.

Figure 9.7 SRS-2 indices and subscales means

A. Unadjusted means and standard deviations (error bars)



B. SES adjusted geometric means and 95% confidence intervals



RRB – Restrictive Interest and Repetitive Behaviour * p<.05

SCI – Social Communication Index

Table 9.34 Analysis of SRS2 Total and study variables in CWEOE (n=22)

Variable	*Sub-group*	*N*	*Mean (SD)*	*P*	*MD (95% CI) or effect size*
Gender	Male	14	52.79 (12.21)	.41	-4.09 (-14.32, 6.15)
	Female	8	56.88 (8.56)		
SES	Lower	13	59.69 (9.33)	**.003**	-13.25 (-5.15, -21.35)
	Higher	9	46.44 (8.35)		
Prematurity	Pre-term	3	72.00 (3.46)	**.001**	20.53 (9.51, 31.54)
	Full-term	19	51.47 (8.88)		
Family history of epilepsy	No	13	54.54 (11.54)	.96	.29 (-10.55, 11.13)
	Yes	8	54.25 (11.50)		
Seizure Frequency	Low	17	55.59 (10.78)	.31	5.58 (-5.85, 17.43)
	High	5	49.80 (11.71)		
No. of AEDs	None/monotherapy	18	53.00 (10.40)	.26	-7.00 (-19.57, 5.57)
	Polytherapy	4	60.00 (13.37)		
Seizure onset	Localised	8	57.00 (10.56)	.59	η^2 = .05
	Generalised	12	52.00 (11.65)		
	Both	2	57.00 (11.31)		
Aetiology (1989)	Idiopathic	14	49.50 (11.11)	**.018**	η^2 = .35
	Symptomatic	3	62.67 (4.62)		
	Cryptogenic	5	62.60 (1.82)		
Aetiology (2010)	Unknown	12	55.58 (12.60)	.11 ǂ	η^2 = .14
	Genetic	8	49.88 (7.51)		
	Structural/Metabolic	2	64.00 (5.66)		
MRI*	Normal	11	52.91 (10.04)	.27	η^2 = .17
	Minor abnormality	5	58.60 (8.96)		
	Major abnormality	1	68.00 (0)		
EEG*	Normal	3	67.33 (7.02)	**.018**	η^2 = .36
	Epileptiform *or* slow-wave	16	50.31 (9.92)		
	Both	2	62.50 (11.12)		
Assessment age				.21	r_s=-.28
Age at first seizure				.41	r_s= -.18

*5 children did not have an MRI, and EEG data was unavailable for 1

ǂ Brown-Forsythe robust test of equality of means

A standard multiple linear regression including aetiology (1989, idiopathic vs symptomatic/cryptogenic) and SES in CWEOE was ran. EEG and prematurity could not be included in modelling due to small subgroup sample sizes and collinearity. Prematurity was

not included due to collinearity. Aetiology and SES both independently predicted SRS2 Total score. Symptomatic/cryptogenic aetiology (ß=10.44, [95% CI 3.22, 17.66]) and lower SES (ß =10.75 [95% CI 3.67, 17.81]) resulted in increased SRS-2 Total scores. The overall regression model was significant (p<.001) explaining 53% of the variance in SRS-2 Total score (R^2*adj*).

(ii) Autism Spectrum Disorder Risk

Eight (32%) of 25 CWEOE and zero of 28 controls, screened with the M-CHAT and SRS2 questionnaires between the ages 16-63m, were considered at higher risk of ASD. The difference in prevalence of children at risk of ASD between groups was significant (FET=.004). Four (57%) of seven CWEOE, and 0 of 11 controls screened 'at risk' on the M-CHAT questionnaire. Four (18%) of 22 CWEOE, and 0 of 17 controls met criteria for ASD risk (SRS2 Total T-score ≥65) on the SRS2 questionnaire.

Study variables associated with ASD risk were explored through bivariate analysis in CWEOE (n=29). ASD risk was associated with lower SES, prematurity, and lower age at first seizure (table 9.35). A multivariable logistic regression could not be completed due to quasi-complete separation. No child from a high SES was at risk of ASD, compared to 47% from a low SES. Despite the recognised link between intellectual impairment and ASD, only one of the five children with GCA impairment was deemed at risk of ASD. However, the remaining four children with GCA impairment had a mean SRS-2 T-score of 61.75 (SD=1.71), which was significantly higher than non-GCA impaired children (M=52.61, SD=11.52); p=.004 (unequal variances t-test), suggesting that ASD risk is still increased albeit not reaching the pre-defined threshold.

Table 9.35 Analysis of ASD risk and study variables in CWEOE (n=29)

Variable	*Sub-group*	*ASD risk, n (%)*		*FET*	*OR (95% CI)*
		Lower Risk	*Higher Risk*		
Gender	Male	13 (72.2)	5 (27.8)	1.0	0.98 (0.18, 5.24)
	Female	8 (72.7)	3 (27.3)		
SES	Higher	12 (100)	0 (0)	**.009**	-
	Lower	9 (52.9)	8 (47.1)		
Prematurity	Pre-term	0 (0)	3 (100)	**.015**	-
	Full-term	21 (80.8)	5 (19.2)		
Family history of epilepsy	No	12 (70.6)	5 (29.4)	1.0	1.03 (0.19, 5.68)
	Yes	7 (70.0)	3 (30.0)		

Table 9.35 continued

Variable	*Sub-group*	*ASD risk, n (%)*		*FET*	*OR (95% CI)*
		Lower Risk	*Higher Risk*		
Seizure Frequency	Low	15 (68.2)	7 (31.8)	.64	0.36 (0.04, 3.56)
	High	6 (85.7)	1 (14.3)		
No. of AEDs	None/monotherapy	18 (75.0)	6 (25.0)	.60	2.00 (0.27, 14.98)
	Polytherapy	3 (60.0)	2 (40.0)		
Seizure onset	Localised	7 (63.6)	4 (36.4)	.34	-
	Generalised	13 (81.2)	3 (18.8)		
	Both	1 (50.0)	1 (50.0)		
GCA impairment	Non-impaired	17 (70.8)	7 (29.2)	1.0	0.61 (0.06, 6.44)
	Impaired	4 (80.0)	1 (20.0)		
Aetiology (1989)	Idiopathic	13 (72.2)	5 (27.8)	.72	-
	Symptomatic	3 (60.0)	2 (40.0)		
	Cryptogenic	5 (83.3)	1 (16.7)		
Aetiology (2010)	Unknown	11 (73.3)	4 (26.7)	.63	-
	Genetic	8 (80.0)	2 (20.0)		
	Structural/Metabolic	2 (50.0)	2 (50.0)		
MRI*	Normal	11 (78.6)	3 (21.4)	.11	-
	Minor abnormality	5 (83.3)	1 (16.7)		
	Major abnormality	1 (25.0)	3 (75.0)		
EEG*	Normal	3 (42.9)	4 (57.1)	.18	-
	Epileptiform *or* slow-wave	14 (77.8)	4 (22.2)		
	Both	3 (100)	0 (0)		
Assessment age, months	(median)	45	35	.10 ǂ	r=.31
Age at first seizure, months	(median)	36	13.5	**.04** ǂ	r=.38

*5 children did not have an MRI, and EEG data was unavailable for 1

ǂ Mann-Whitney U

9.4 Assessment Scores and Neurobehavioural Problems: Summaries

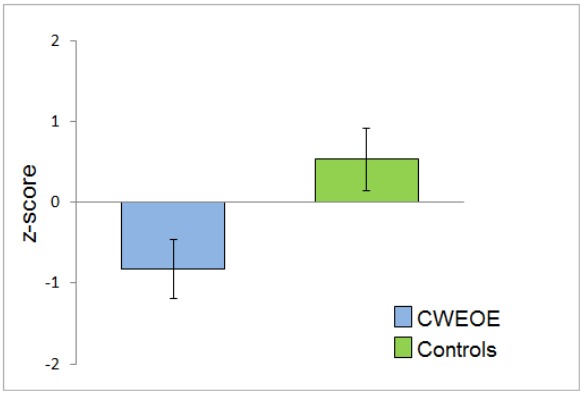
In the sections above, the distribution of neurobehavioural assessment scores, and estimates of the prevalence of neurobehavioural problems, in CWEOE and controls were reported, in order to provide a detailed description of the pattern, and group differences in, cognitive and behavioural functioning. What follows here is a summary of those findings, and an overview of the, psychometrically-based, neurobehavioural profile of CWEOE and controls in South-East Scotland.

9.4.1 Neurobehavioural Scores Summary

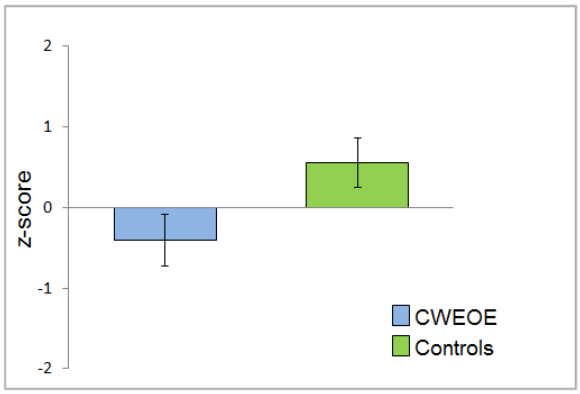
CWEOE had poorer GCA compared to control children (figure 9.8A), even when cases who 'floor scored' on the assessment were excluded (figure 9.8B). Additionally, across every domain and scale of the behaviour questionnaires, parents of CWEOE reported more problems, or fewer age-appropriate behaviours, compared to controls (figure 9.9). Group differences were significant in the scales of adaptive behaviour, executive functioning, inattention/hyperactivity, atypical behaviour, and ASD behaviours. After adjustment for SES, significant group differences remained in all but executive functioning.

Figure 9.8 GCA scores in CWEOE and Controls

A. SES adjusted means and 95% Cis

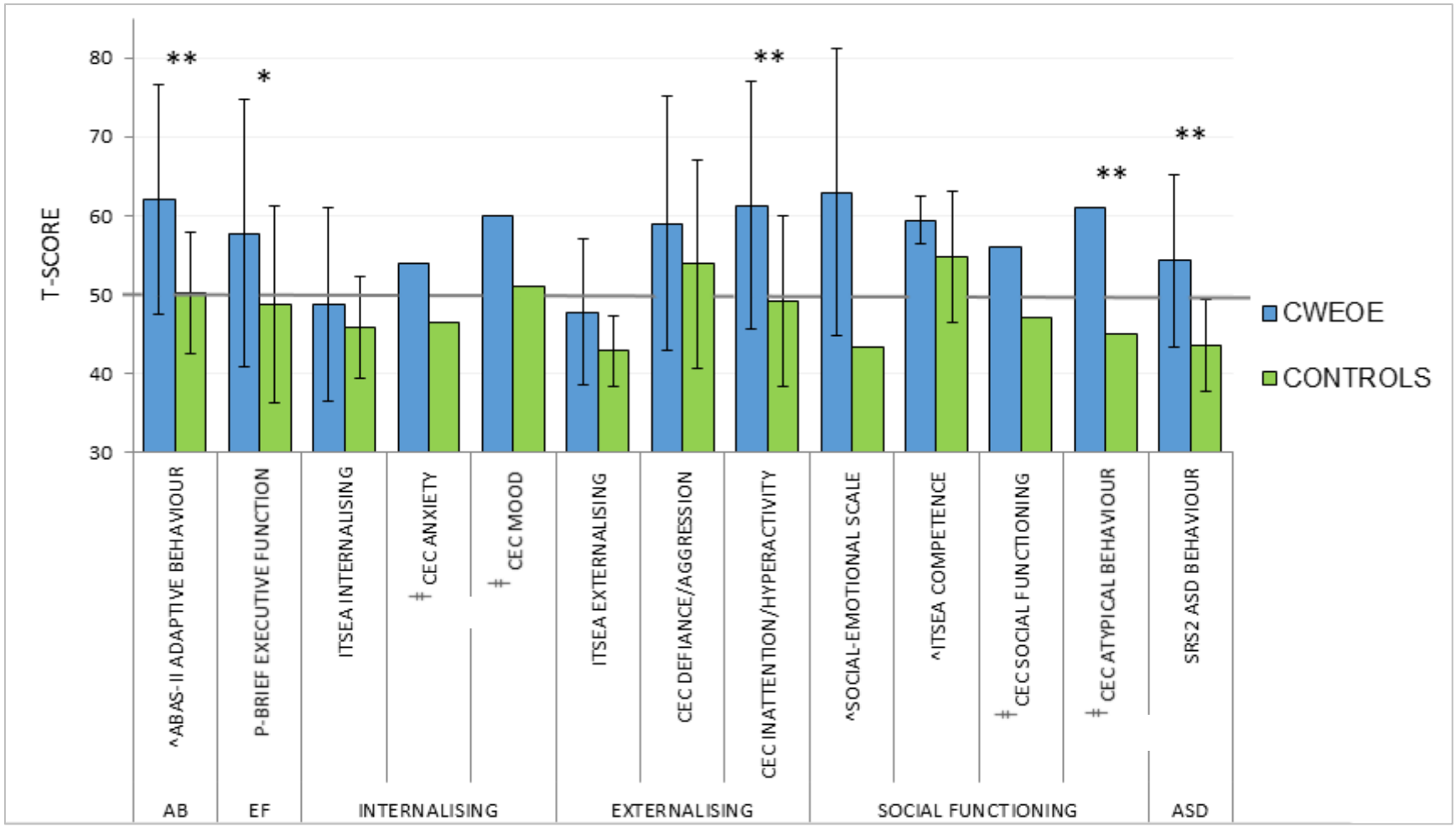


B. Sensitivity analysis* means and 95% CIs



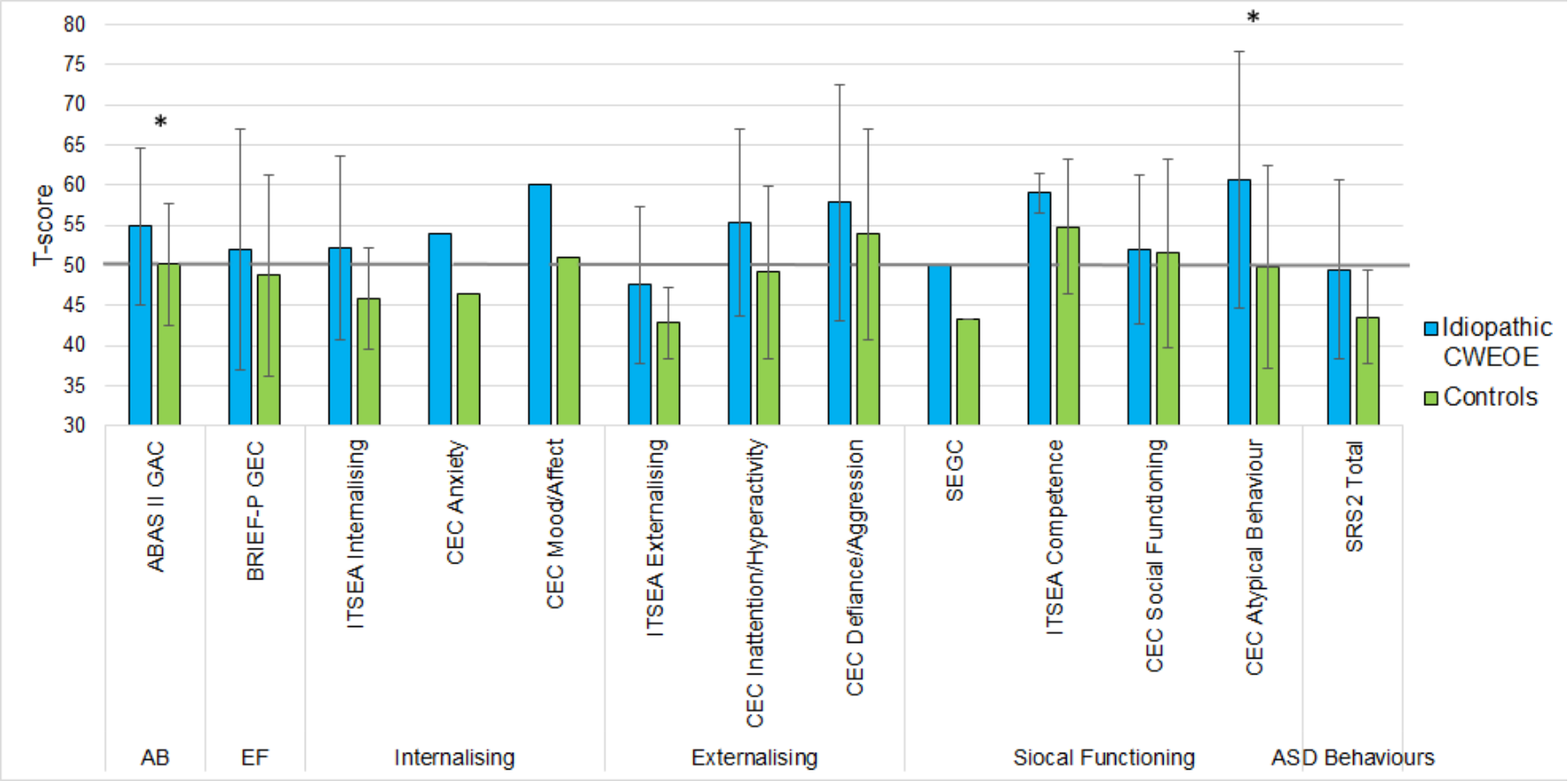
*Outlying cases who scored ≥3SD below mean (i.e. 7 CWEOE, 0 controls) were excluded

Figure 9.9 Behaviour scales mean/median T-scores (error bars represent standard deviation)



AB – Adaptive Behaviour
EF – Executive Function
^ Scale converted and/or inverted
‡ Median t-score
* Significant group difference (p<.05)
** Group difference remained (p<.05) after adjustment for socioeconomic status
Horizontal grey line represents normative mean

Figure 9.10 Behaviour assessment scores in CWEOE (idiopathic aetiology only) and controls



Horizontal grey line represents normative mean

Error bars represent standard deviation

AB – Adaptive behaviour

EF – Executive functioning

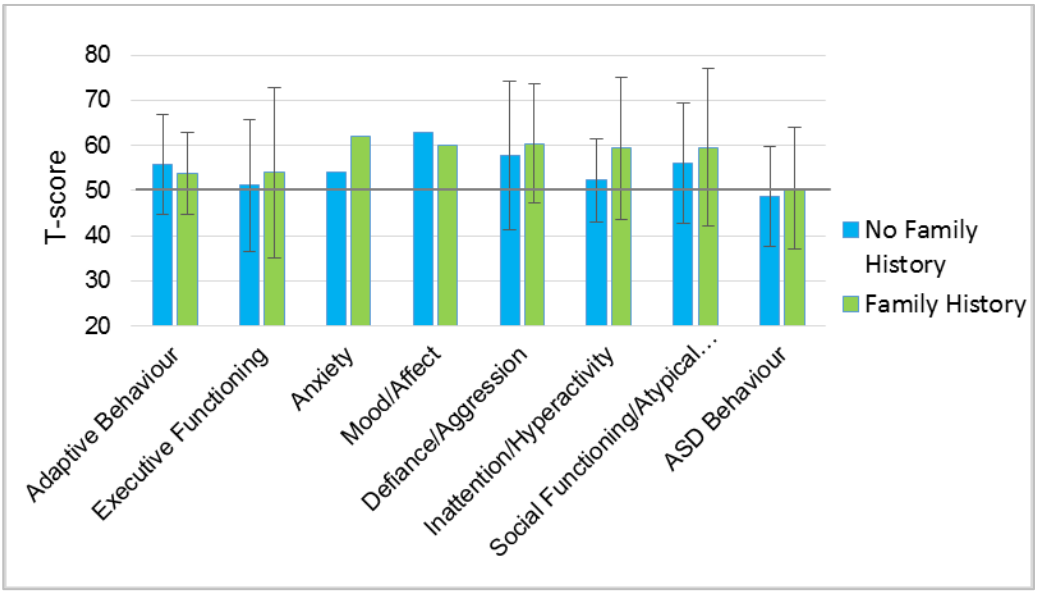
*p<.05

When only CWEOE with idiopathic epilepsy were considered (figure 9.10), elevated scores persisted across all behaviour scales. A significant difference was found in ABAS II Adaptive Behaviour and CEC Atypical Behaviour scale. As subgroup sizes were smaller, there was less power to detect group differences. Nevertheless, a clear pattern of increased reporting of abnormal behaviour is persistent even in those without a suspected or known cause for their epilepsy, suggesting the early emergence of behaviour problems, or a global impact on behavioural functioning influenced by the presence of epilepsy.

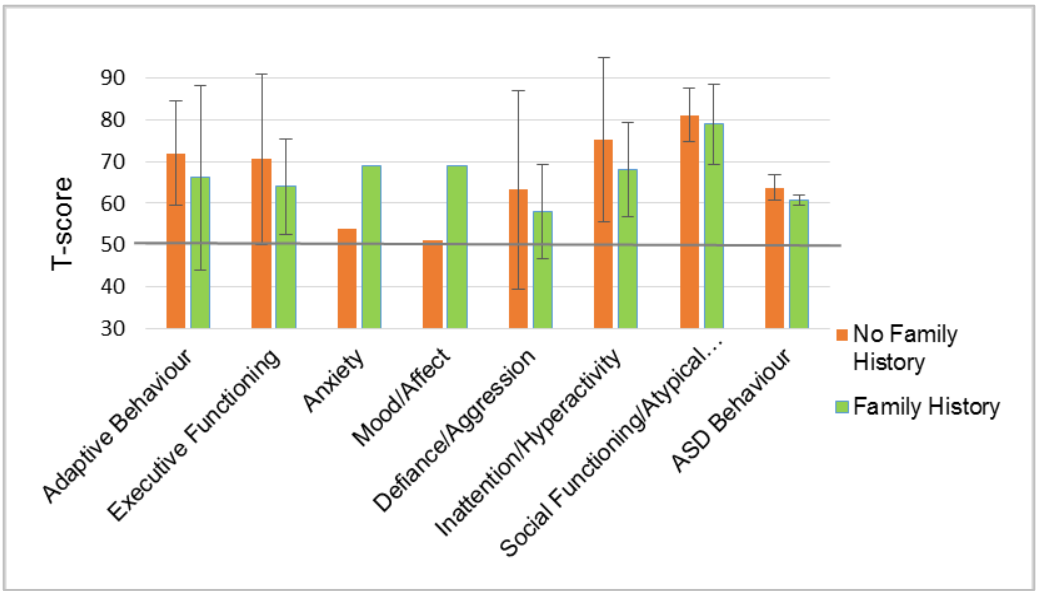
Family history of epilepsy in CWEOE was not significantly associated with GCA or behavioural assessment scores throughout the analysis. This relationship was explored further, by aetiology, with assessment scores summarised in figure 9.11; (A) children with idiopathic epilepsy, and (B) children with cryptogenic/symptomatic epilepsy. Subgroup sample sizes were small, and while no significant differences were found, moderate effect sizes of r=.26 and .32 were noted in CEC scales of Anxiety and CEC Mood/Affect in children with symptomatic/cryptogenic epilepsy, respectively. Only a small effect size was seen in children with idiopathic epilepsy. This may indicate increased predisposition to, or earlier expression of, anxiety or mood problems in children with epilepsy when the cause has a clinically recognised lesion or abnormality, or is strongly suspected of one. Note that subgroup scores for the SEGC or ITSEA were not included as subgroup sample sizes were less than n≤2 in several cells.

Figure 9.11 Behaviour assessment scores for children with and without family history of epilepsy by aetiology (ILAE, 1989)

A. Idiopathic epilepsy mean/median scores (error bars represent standard deviation)



B. Symptomatic/Cryptogenic epilepsy mean/median scores (error bars represent standard deviation)



Horizontal grey line represents normative mean

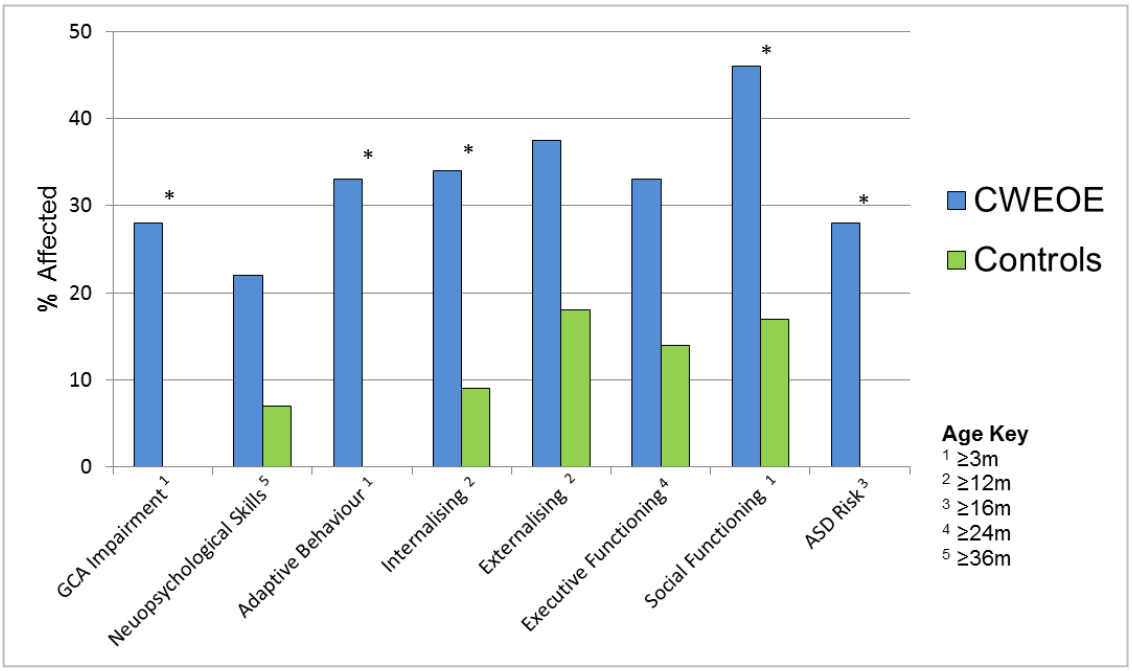
Scale Tools:

Adaptive behaviour – ABAS II
Executive functioning – BRIEF-P
ASD Behaviour – SRS2

Anxiety, Mood/Affect, Defiance/Aggression, Inattention/Hyperactivity ,and social Functioning/Atypical Behaviour - CEC

9.4.2 Neurobehavioural Problems Summary

Figure 9.12 Prevalence of neurobehavioural problems



*significant group difference (p<.05)

Table 9.36 Prevalence of neurobehavioural problems

Major Domain	*Domain*	*Assessment Tool*	*Age Range (months)*	*Prevalence of problem (n/N) %*		*Group Comparison FET (OR [95% CI])* ŧ
				CWEOE	*Controls*	
Cognition	General Cognitive Ability	Bayley III Cognition/WPPSI III FSIQ	3-63	(13/46) 28%	(0/37) 0%	**<.001**
	Memory	NEPSY II Memory for Designs/ Narrative Memory/ Sentence Repetition	36-63	(4/18) 22%	(0/14) 0%	.11 (9.62 [0.48, 194.84])
	Social Perception	NEPSY II Affect Recognition/Theory of Mind	36-63	(0/18) 0%	(1/15) 7%	.46 (0.26 [0.01, 6.90])
	Attention/Executive Functioning	NEPSY II Statues	36-63	(1/17) 6%	(0/14) 0%	1.0 (2.49 [0.09, 65.76])
Behaviour	Adaptive Behaviour	ABAS II General Adaptive Composite	3-63	(14/42) 33%	(0/37) 0%	**<.001**
	Internalising	ITSEA Internalizing/ CEC Mood/Affect/ CEC Anxiety	12-63	(11/32) 34%	(3/33) 9%	**.017 (5.24 [1.30, 21.28])**
	Externalising	ITSEA Externalizing/CEC Inattention/Hyperactivity/CEC Defiance/Aggression	12-63	(12/32) 37.5%	(6/33) 18%	.10 (0.37 [0.12, 1.16])
	Executive Functioning	BRIEF-P General Executive Composite	24-63	(8/24) 33%	(3/22) 14%	.17 (0.32 [0.07, 1.39])
	Social Functioning	SEGC/ITSEA Competence/CEC Social/Atypical	3-63	(18/39) 46%	(6/35) 17%	**.01 (0.24 [0.08, 0.71])**
	ASD Risk	M-CHAT/SRS2 Total	16-63	(8/29) 28%	(0/28) 0%	**.004**

Problem in cognition domain defined as score ≥2SD below mean; Problem in behaviour domain defined as score ≥1.5SD above mean, with exceptions for ABAS II and SEGC which were ≥2SD above mean

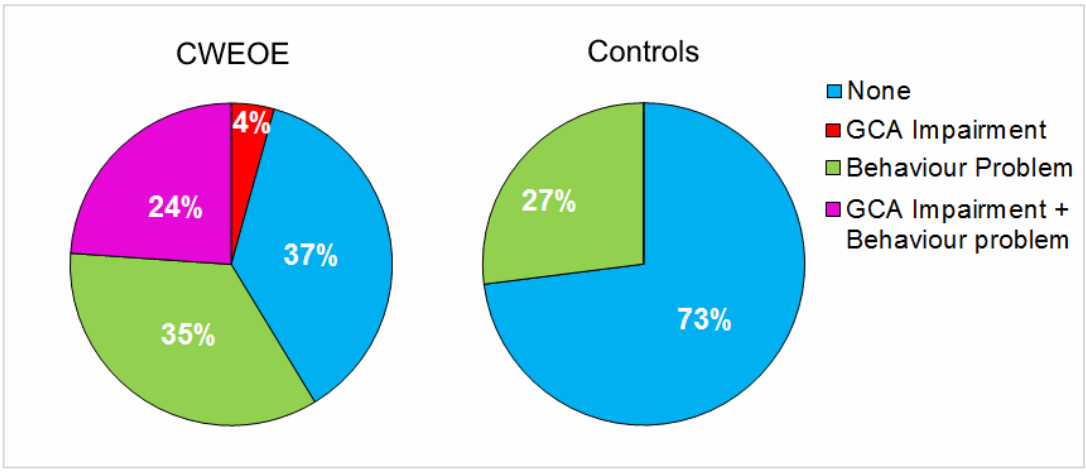
n=number of children with problem, N=total number of age-eligible children

ŧ Odds Ratio (OR) cannot be calculated when ≥1 cells in contingency table = 0

The prevalence of GCA impairment and behavioural problems are visually depicted in figure 9.12, and described in detail in table 9.36. CWEOE consistently had more children meeting criteria for neurobehavioural problems than controls. This was significantly so in the domains of GCA, adaptive behaviour, internalising behaviour, social functioning, and ASD risk.

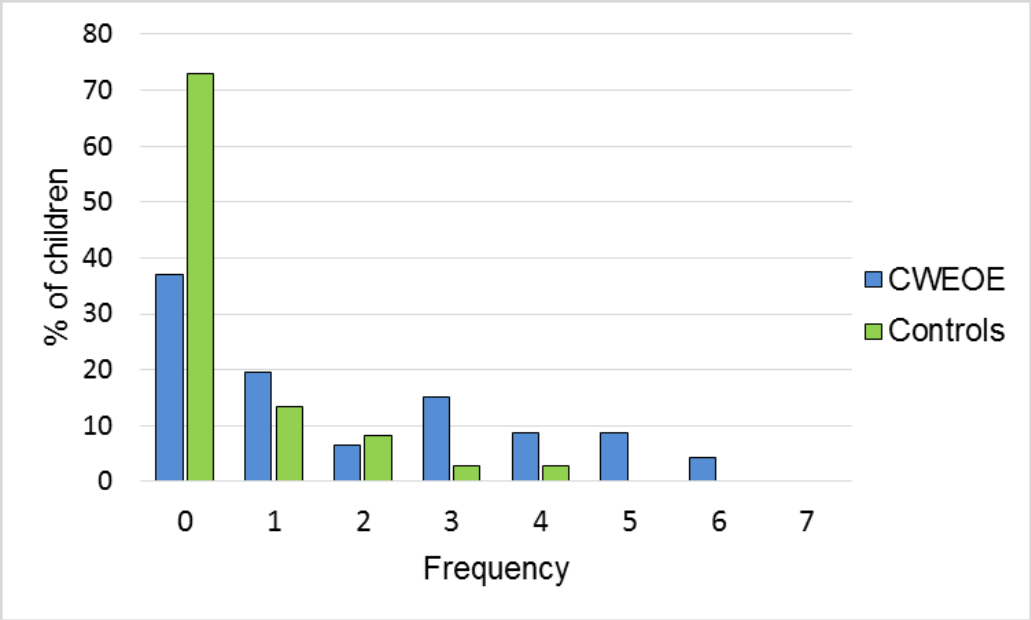
Focusing on GCA and behaviour scales, overall, a neurobehavioural problem was found in 63% (95% CI 48.6-75.5) of CWEOE, compared to 27% (95% CI 15.4, 43.0) of controls. No control child had a GCA impairment, but a GCA impairment was found in 28% (95% CI 17.3, 42.5) of CWEOE. Whilst behaviour problems were evident in 59% (95% CI 44.3, 71.7) of CWEOE, almost one quarter had a cognitive and comorbid behavioural problem. A GCA impairment in the absence of behavioural problem was rare, at 4% (95% CI 1.2, 14.5). The nature of the problems are visually dichotomised in figure 9.13.

Figure 9.13 GCA Impairment and/or Behaviour Problem by Group



To understand the degree of comorbidity across domains, figure 9.14 breaks down the information above by detailing the frequency of neurobehavioural problems according to the number of domains in which a neurobehavioural problem was identified. 20% of CWEOE had a problem in only one domain, compared with 13.5% of control children, while multi-domain problems of 3-6 domains were more common in CWEOE. These data demonstrate that the high prevalence of problems found in CWEOE is not due to any particular subgroup of children scoring consistently in the problem ranges across all tools, but that problems are spread across the sample to differing degrees.

Figure 9.14 Frequency of neurobehavioural problems



Risk factors for neurobehavioural problems differed depending on the domain of interest. Risk factors identified from bivariate analysis, and from multivariable regressions, are listed in table 9.37. Symptomatic/cryptogenic aetiology and prematurity were the most common variables associated with neurobehavioural problems.

In several of the predictor variables, within domains, all CWEOE belonged exclusively in the problem category. For instance, all prematurely born children met criteria for executive functioning problems, social competence problems, and positive ASD risk. Consequently, multiple regressions could not be completed due to quasi-complete separation.

Interestingly, a family history of developmental disability or psychiatric issue was not associated with GCA impairment (OR=2.05 [95% CI 0.51, 8.34]), but was associated with ≥1 behavioural problems in any of the domains of interest, in 100% (n=11) of cases. That is, any child with a family history of developmental or psychiatric issue had at least one behavioural problem. In contrast, 16 (55.2%) children without any family history of developmental disability or psychiatric issue had at least one behaviour problem; FET=.007. Therefore, a positive family history may pose a general risk factor for the development of behavioural problems. There was no such association with family history of epilepsy, and GCA impairment or ≥1 behaviour problems (FET=1.0, OR=0.94 [95% CI 0.24, 3.68]).

Table 9.37 Significant (p<.05) risk factors associated with neurobehavioural problems in CWEOE

Major Domain	*Domain*	*Bivariate analysis: Risk Factors*	*Multivariable analysis: Risk Factors*
Cognitive Functioning	General Cognitive Ability	Females, polytherapy, high seizure frequency, symptomatic/cryptogenic aetiology, EEG status	n/a
Behavioural Functioning	Adaptive Behaviour	Females, polytherapy, GCA impairment, symptomatic/ cryptogenic aetiology, and EEG status	Polytherapy, symptomatic/ cryptogenic aetiology (EEG status and GCA impairment not modelled)
	Executive Functioning	prematurity and symptomatic/cryptogenic aetiology	n/a
	Internalising	Prematurity	n/a
	Externalising	Prematurity and low seizure frequency	n/a
	Social Functioning	females, prematurity, GCA impairment, and symptomatic/cryptogenic aetiology	n/a
	ASD Risk	lower SES, prematurity, and lower age at first seizure	n/a

9.5 ESSENCE criteria

42 CWEOE (25M:17F) and 37 controls (18M:19F) completed an ESSENCE-Q. Four CWEOE (9%) did not return an ESSENCE-Q. 100% of questionnaires were returned by controls. 28 (66.7%, [95% CI 51.6, 79.0]) CWEOE and 3 (8.1% [95% CI 2.8, 21.3]) controls scored at least two "yeses" or at least three "maybes" and met criteria as potentially having a disorder subsumed under the ESSENCE umbrella. These figures are close in approximation to CWEOE who met criteria for neurobehavioural problems on the assessment battery, but less so in controls. 29 (63%) CWEOE and 10 (27%) control children met criteria for at least one neurobehavioural problem (section 9.4.2). This comparison must be treated with caution as ESSENCE disorders were not the focus of this assessment battery. The findings do however provide some support for the

ESSENCE-Q as a pre-screening instrument to identify children who may need further investigations (Carlsson et al., 2013; Hatakenaka et al., 2016).

In control children, there was no statistical difference between those who did not meet ESSENCE criteria and those who did, in age, gender or SES. In CWEOE (table 9.38) no study variable, with the exception of symptomatic/cryptogenic aetiology, was significantly associated with meeting ESSENCE criteria. This suggests that disorders or problems potentially identifiable under the ESSENCE-Q in CWEOE are diverse and have different associated risk factors, but, as evidenced in the neurobehavioural assessment, symptomatic/cryptogenic aetiology is a potentially broad risk factor for disorders identified under the ESSENCE-Q.

Table 9.38 Study variables and CWEOE who did (n=28), or did not (n=14), meet ESSENCE criteria

Variable		*Met ESSENCE criteria, n (%)*		*Group Comparison*
		No	*Yes*	*FET (OR [95% CI])*
Gender	Male	10 (71.4)	15 (53.6)	.33 (2.17 [0.55, 8.59])
	Female	4 (28.6)	13 (46.4)	
SES	Low	8 (57.1)	9 (32.1)	.18 (2.82 [0.75, 10.57])
	High	6 (42.9)	19 (67.9)	
Family history of epilepsy	No	9 (36.0)	16 (64.0)	1.0 (1.13 [0.29, 4.34])
	Yes	5 (33.3)	10 (66.7)	
Aetiology (1989)	Idiopathic	11 (78.6)	11 (39.3)	**.02 (5.67 [1.28, 25.02])**
	Symptomatic/Cryptogenic	3 (21.4)	17 (60.7)	
Aetiology (2010)	Genetic	6 (42.9)	7 (25.0)	.26
	Structural/Metabolic	1 (7.1)	8 (28.6)	
	Unknown	7 (50.0)	13 (46.4)	
Seizure frequency	Low	19 (67.9)	7 (50.0)	.32 (.47 [0.13, 1.76])
	High	9 (32.1)	7 (50.0)	
Seizure Onset	Localised	6 (42.9)	11 (39.3)	1.0
	Generalised	7 (50.0)	14 (50.0)	
	Both	1 (7.1)	3 (10.7)	
MRI	Normal	8 (72.7)	12 (46.2)	.28
	Minor Abnormality	2 (18.2)	5 (19.20	
	Major Abnormality	1 (9.1)	9 (34.6)	
EEG	Normal	2 (14.3)	7 (26.9)	.27
	Epileptiform *or* slow-wave	11 (78.6)	13 (50.0)	
	Both	1 (7.1)	6 (23.1)	

Table 9.38 continued

Variable		*Met ESSENCE criteria, n (%)*		*Group Comparison*
		No	Yes	*FET (OR [95% CI])*
AED	0-1	14 (100)	21 (75.0)	.08
	≥2	0 (0)	7 (25.0)	
Prematurity	Yes	0 (0)	4 (14.3)	.28
	No	14 (100)	24 (85.7)	
Assessment age (months)	Median (IQR)	32.9 (6.9, 56.0)	34.4 (14.4, 45.1)	†p=.86, r= .03
Age first seizure (months)	Median (IQR)	21.0 (4.0, 44.3)	17.5 (6.3, 36.0)	†p=.93, r=.01

Emboldened= p<.05

*5 children did not have an MRI, and EEG data was unavailable for 2

†Mann-Whitney U test

10. Neurobehavioural Profile of CWEOE: Discussion

The aim of this chapter was to describe the neurobehavioural profile of CWEOE using a comprehensive battery of cognitive and behavioural assessment tools. These generated group level distributions of scores, and estimations of the types, and prevalence, of neurobehavioural problems (i.e. GCA impairment and behaviour problems - as defined by the study cut-offs on those assessment tools). From the findings of the systematic review (chapter I, section 1.3), this is the first study to describe comorbid cognitive and behavioural functioning in a single cohort of children with epilepsy during the first five years of life. As hypothesised, the neurobehavioural profile of CWEOE was unfavourably different to that of control children. Neurobehavioural problems were highly prevalent in CWEOE, exceeding that found in control subjects, and were more often multiple in nature. Given the large assessment battery and analysis, the study results are discussed by cognitive and behavioural functioning separately.

10.1 Cognitive Functioning

10.1.1 General Cognitive Ability

Cognitive functioning was compromised in CWEOE. In line with other population-based studies, GCA was poorer in children with epilepsy compared to control children (Hoie et al., 2008; Rantanen et al., 2011; Reilly et al., 2014a). GCA was 0.8 SD below test normative mean and 1.3 SD below control mean. When 'floor' scoring children were excluded, GCA lay 0.4 SD below normative mean and 0.96 SD below controls, meaning the poorer performance could not simply be attributed to more severe cases of epilepsy. No other published data is available for direct comparison to the entire early-onset age range. Instead, the findings can be compared to studies of infants/toddlers, and preschool-aged children.

In CWEOE, GCA score lay in the borderline (i.e. between 1.5 and 2 SD below mean), to low-average (i.e. between 0.75 and 1.5 SD below mean) range in infants/toddlers, with and without floor cases, respectively; and close to the normative mean in preschool children. To the candidate's knowledge, there have been no peer-reviewed journal publications of psychometric GCA data in a general population-based cohort of infants/toddlers with epilepsy. One study published in a MD dissertation by Eltze in 2010 did provide supportive evidence of poorer than expected cognitive functioning in infants/toddlers with epilepsy. Similar to the

present study Eltze reported borderline Bayley III Cognition in her population-based cohort of infants <2 years with epilepsy in London, UK.

Preschool CWEOE in the current study scored at normative mean level but which remained significantly below that of control children. There are two potential explanations. The first is that children from this region of Scotland score higher than the WPPSI III standardisation sample, and supports the use of a comparator control group taken from the same population. The second is that a larger proportion of control children from a high SES background in this study, which is associated with better cognitive status, may have positively distorted the true population estimate. However, control children from both a high and low SES scored well above the normative mean, and statistical adjustment for SES did not alter between-group findings, failing to support that assertion. As SES based on neighbourhood deprivation may not represent an individual's level of deprivation or socioeconomic characteristics, such as parent education, it is possible that control children here were unrepresentative of the population. However, neighbourhood level factors influence developmental and psychosocial outcomes, and can do so more than individual factors (Duncan et al., 1994; Garner and Raudenbush, 1991; Kalff et al., 2001). In further support of the findings here, Rantanen et al. (2010) reported on a population-based subgroup of preschool children aged 36-83m with uncomplicated epilepsy (i.e. epilepsy without chronic illness or neurological disorder). These children had a mean IQ of 94.6 (SD 12.2) which was significantly lower than control IQ despite being matched for parental education level. Indeed, older children with epilepsy have been found to perform lower than expected based on parent IQ (Walker et al., 2012). In direct comparison to Rantanen et al., the preschool CWEOE with idiopathic epilepsy only from the current study, who also had no neurological disorders, scored at the normative mean level (101.33, SD 14.48), without notable difference between low and high SES children. Taken together, findings suggest that preschool-aged children may show average levels of GCA on testing, but could be performing lower than peers, irrespective of SES.

A key factor in describing the cognitive profile of CWEOE was determining the prevalence of GCA impairment (i.e. GCA score ≥2 SD below mean). The prevalence of 28% was similar to that reported in other population-based studies of older childhood epilepsy (Hoie et al., 2005; Reilly et al., 2014a; Sillanpaa 1992; Waaler et al., 2000). Around 40% of children whose epilepsy onset began <12m of age had GCA impairment, compared to approximately 20% of children with onset during years 1 to 4. The presence of infantile spasms in the first year of life accounted for the majority of that difference, and suggests that onset of epilepsy at any age during the

early-onset period, in the absence of infantile spasms, poses similar risks to the occurrence of GCA impairment. The proportion of children with GCA impairment whose onset was in the first year of life here, is less than the 58-82% previously reported elsewhere (Altunbasak et al., 2007; Battaglia et al., 1999b; Czochanska et al., 1994; Cormack et al., 2007). These data with higher reported proportions were derived from single centre, cross-sectional or special population, studies, which are likely to have a biased sample source, and are not generalisable to the overall epilepsy population with onset <12 months.

Referring to preschool-aged children only, Rantanen et al. (2011) reported GCA impairment in 50% of children with epilepsy, whereas only 21% were impaired here. The epilepsy cohort in Rantanen et al. were slightly older, but this was unlikely to account for the discrepancy. In that study, children had active epilepsy, and were seen 38 (2-83) months after epilepsy onset. Consequently, that cohort may not have included some children with benign or better controlled epilepsies. The proportion of children with symptomatic/cryptogenic aetiologies, which is strongly associated with GCA impairment, was 91%, compared to 36% in the present study. Therefore, a higher proportion of symptomatic/cryptogenic aetiology is the most likely explanation. Elsewhere, Berg et al. (2008) also found a higher prevalence of GCA impairment (33.4%) in their community-based study of persons ≤29 years of age whose onset began at 0-5 years. Because children were assessed *during* the early-onset period, and shortly after the onset of their epilepsy, in the present study, it is possible that the prevalence of GCA impairment may rise with age as the epilepsies evolve in some children. Children with Dravet Syndrome, for example, have normal cognitive development before developmental stalling by four years of age (Nabbout et al., 2013; Wolff et al., 2006a).

Whilst GCA was clearly affected in CWEOE, the influence of epilepsy on attention & executive functioning, memory, and social perception, in children ≥36m, was not as widely apparent. CWEOE did not perform as well as controls on all six NEPSY II subtests, but significantly poorer mean scores were only observed in the Theory of Mind and Sentence Repetition subtests. Therefore, only selective features of memory and social perception were affected in CWEOE, whilst the attention & executive functioning domain was relatively spared. Few studies have used the NEPSY in children with epilepsy. Some have used the previous NEPSY version with construct differences to the second, and all have used varied subtests and populations (Bender et al., 2007; Kolk et al., 2001; Parisi et al., 2012; Rantanen et al., 2010a; Verrotti et al., 2013; Zilli et al., 2015). Deficits in the attention & executive functioning domain were observed in all those studies except Rantanen et al. (2010) and the present study. As both of these studies were

focused on preschool children, and attention & executive functioning was non-significantly poorer, it could be argued that attention & executive difficulties have not yet emerged in preschool children. That said, almost one quarter of CWEOE had an attention & executive impairment compared to zero controls. A moderate effect size at group level was also observed, suggesting that attention & executive difficulties are indeed emerging in some CWEOE. Because different subtests within the NEPSY I and II are used to evaluate preschool children and school-aged children, the findings may be different as a result of using subtests with different constructs. A parent questionnaire of executive functioning issued in the present study (BRIEF-P) did not reveal significant differences between CWEOE and controls, yet the attention/hyperactivity scale of the CEC did. Given that executive functioning deficits are common in later childhood epilepsy (Berl et al., 2015; Fastenau et al., 2009; Hoie et al., 2006; Jackson et al., 2013), it is possible that differences in the NEPSY II attention & executive functioning subtest did not emerge because executive functioning abilities do not mature until the end of, or beyond, the early-onset period (Garon et al., 2008).

In regards to memory, a deficit in Sentence Repetition was seen in this study, and also in a study of preschool children with uncomplicated epilepsy (Rantanen et al., 2010). Performance on the Narrative Memory and Memory for Designs subtests were comparable to controls in the present study, as noted elsewhere (Rantanen et al., 2011; Verrotti et al., 2013; Zilli et al., 2015). The Memory for Designs and Narrative Memory subtests reflect visual memory and learning, and cued verbal recall, respectively, whereas Sentence Repetition reflects immediate unaided verbal recall. Thus, one explanation for the difference between performance on these memory subtests is increased task difficulty of the Sentence Repetition task in CWEOE. Age of epilepsy onset has the potential to affect brain structure and function differentially, and is another possibility (Gonzalez et al., 2014; Hermann et al., 2002; Kaaden et al., 2011). The Sentence Repetition task is normed for children 3-6 years, and direct comparison with older childhood studies was not possible, with the exception of Zilli et al. (2015), who used an Italian version of the NEPSY II with wider age norms. Zilli et al. did not find a memory deficit on the Sentence Repetition task, thus providing some support for early age of onset as a potential factor. The use of a different language version of the subtest may confound this explanation. Memory deficits have been reported in older children with epilepsy using the NEPSY (Bender et al., 2007; Kolk et al., 2001; Verrotti et al., 2013), and from the evidence presented here, some memory deficits are apparent in preschool aged children, but it is difficult to draw any firm conclusions about age-related differences in memory performance due to limited studies, and the use of different age-appropriate and versioned NEPSY memory subtests.

In the assessment of Social Perception, Zilli et al. (2015) reported poorer mean Theory of Mind scores and Affect Recognition in older children with epilepsy compared to controls. Here, CWEOE had poorer Theory of Mind, and a moderate between group effect size was noted in Affect Recognition. As discussed later in this section, CWEOE had elevated atypical social behaviours, and ASD associated behaviours - a common feature of childhood epilepsy. It seems plausible then, that social cognition difficulties, including those underpinning the Social Perception subtests, may be features of CWEOE that emerge early and persist into later childhood.

Given that control children performed better than CWEOE across subtests of the NEPSY II in this study, as well as that of Rantanen et al. (2010), it suggests that cognitive functions that are involved in these specific skills are at least partially affected in CWEOE. This could signify emerging problems in CWEOE, or that a detriment to GCA has an overarching impact on more specific cognitive functions. This latter explanation cannot, however, account for the disproportionate difference observed in Sentence Repetition and Theory of Mind subtests. The differentiation hypothesis (Garrett, 1946) states that as children age, a general factor of intelligence differentiates to more specific cognitive functions. It is therefore plausible that early problems are more difficult to detect due to ongoing specialisation. Nevertheless, a consistent pattern of subtle underperformance seen in preschool children here indicates that early cognitive functions are measurable, and difficulties may be detectable. Thus, further attention from researchers, and likewise, those involved in clinical care or educational policy and management, is warranted.

10.2 Behavioural Functioning

Having established that cognitive functioning was unfavourably affected in CWEOE, it was then shown that behaviour was also widely compromised. Behaviour scores were variable and on average, were within one SD of the mean. But a clear pattern of increased levels of abnormal behaviour were reported by parents of CWEOE across all domains and scales, even in those with idiopathic epilepsy only. This indicates that at least subtle increases in abnormal behavioural functioning in those with epilepsy is evident. CWEOE group scores were significantly elevated in adaptive behaviour, inattention/hyperactivity, atypical behaviour, and ASD behaviours, while 59% of CWEOE compared to 27% of controls met criteria for a behaviour problem. This prevalence of behaviour problems is within that previously reported by population-based studies of later childhood epilepsy (30-60%; Alfstad et al., 2011; Berg et al.,

2011a; Davies et al., 2003; Hoie et al., 2008; Lossius et al., 2006; McDermott et al., 1995; Reilly et al., 2014a). These studies included children with onset above and below age five, and thus, the current study provides a more focused study of problem prevalence during the early-onset period itself. A higher prevalence of problems was found across all domains, and significantly so in adaptive behaviour, internalising behaviour, social functioning, and ASD risk - indicating a similar spectrum of behavioural problems to that found in older childhood studies.

The pattern of findings described above are reflective of Rodenburg et al's (2005) findings that attention and social difficulties are more prominent, and possibly unique compared to other chronic conditions, characteristics of childhood epilepsy. Scores on the Internalising and externalising scales, with the exception of inattention/hyperactivity, were not significantly different between control children and CWEOE. Rodenburg et al. suggest that family factors might play a more influential role in the development of internalising or externalising behaviours. Without sibling data the contributory role of epilepsy in the development of anxiety and mood problems is uncertain, but the data do suggest that by early childhood internalising difficulties are emerging, and that epilepsy may increase individual susceptibility to the development of emotional problems. This was seen through a moderate effect size and higher problem prevalence in the CEC Anxiety and CEC Mood/Affect scales. CWEOE showed increased atypical behaviour, ASD behaviours (reflective of social cognition and communication abilities), and peer relationship problems, but comparable prosocial behaviours and CEC social functioning. This pattern may reflect the opinion that children with epilepsy have poorer social skills and increased peer problems, yet are able to participate in social activities to a similar degree as controls (Hamiwka et al., 2011; Rantanen et al., 2012).

Differences in social cognition were evident in the assessment of ASD behaviour in the current study. Both group scores, and the prevalence of those meeting criteria for ASD risk, were significantly higher compared to control children. ASD is overrepresented in children with epilepsy, with prevalence rates reported between 6-28% (Davies et al., 2003; Berg et al., 2011b; Suren et al., 2012; Reilly et al., 2014a; Russ et al., 2012). The data in CWEOE is unclear, although there is a known risk in those with epileptic encephalopathies (Brunklaus et al., 2011; Besag, 2004; Li et al., 2011; Riikonen and Amnell, 1981; Wolff et al., 2006a). In the current study, 32% screened positive for ASD risk. This figure was similar to other studies of early and later childhood epilepsy who screened for ASD (Clarke et al., 2005; Fisher et al., 2012a). Although those studies assessed children in tertiary epilepsy care settings, these data converge to suggest a high risk of ASD, or ASD-like behaviour, in children with epilepsy. Children with

epilepsy can express ASD behaviour despite not meeting criteria for a diagnosis of classic ASD (Berg et al 2011), and coupled with evidence that ASD features are impairing without meeting clinical thresholds even in the general population (Skuse 2009), it is clear that there is a strong argument for screening all children with epilepsy to identify those with social communication and social cognitive difficulties.

10.3 Neurobehaviour and Risk Factors

Sociodemographic and epilepsy-related factors were variably associated with assessment scores and neurobehavioural problems. Aetiology had an extensive effect on neurobehavioural expression, and the 1989 ILAE classification system was a better predictor of assessment scores and neurobehavioural problems than the 2010 classification system. Both systems independently predicted GCA impairment, but the 1989 classification was associated with several behavioural problems when the 2010 system was not. That said, abnormal assessment scores and more problems were associated with structural/metabolic aetiologies as expected, but the overall utility of the 2010 categorisation to detect subgroup differences was diluted primarily by the transition from cryptogenic classification to the unknown or genetic categories. Given that the sample size was moderate, the 2010 classification system may be better suited on larger sample sizes. The discussion on risk factors to follow focuses on the ILAE 1989 classification system when discussing aetiological factors because of its utility in this context, and its clinical applicability.

In this study, adaptive behaviour was spared in CWEOE with idiopathic aetiologies when compared to test normative mean although CWEOE still performed significantly more poorly than control children. The finding of relative sparing in idiopathic epilepsy has been reported in children with epilepsy elsewhere (Berg et al 2004; Berg et al., 2013). An unexpected finding in the current study was that control children had significantly poorer practical adaptive behaviour compared to their respective social and conceptual domains - albeit remaining within the average range. Given there was a small standard deviation around the mean, this finding may reflect cultural differences between this South-East Scotland sample of control children and the ABAS II US normative sample, rather than a difficulty with practical adaptive behaviour per se. A discrepancy in scores was found in motor scales between the US and UK standardisation samples on the Bayley III (Bayley, 2010), and likewise, any disproportionate deficit in the practical domain seen in CWEOE may also have been influenced by sampling differences, rather than due to an epilepsy effect. Parents often commented on the subjectivity

or uncertainty surrounding questions on the ABAS II, to the candidate. Parents commented that they did not allow their children to perform certain actions as queried by the ABAS II practical domain (e.g. carrying hot liquids, or using electrical sockets), and their ratings reflected this rather than the child's ability to carry out the action. They also commonly reported that they aided the child in certain situations due to fussiness rather than inability (e.g. feeding, brushing teeth, dressing, or going to bed), but rated them negatively because of this. Nevertheless, this finding did not alter the overall finding that CWEOE had poorer overall adaptive behaviour compared to control children, particularly so in children with symptomatic/cryptogenic aetiologies. Additionally, it provides further support for the use of local comparator control data rather than test normative scores.

With the exception of aetiology, epilepsy-related variables were rarely associated with neurobehavioural problems, suggesting that aetiology is the predominant factor. The population was heterogeneous with insufficient sample sizes for sub-syndrome analysis. Accordingly this may have impacted the power to detect true effects of these variables should they have existed within certain syndromes. That said, epilepsy-related variables are not strongly or consistently linked with behaviour problems in the childhood epilepsy literature (Dunn & Austin 2004; Ekincini 2008; Otero 2009; Plioplys 2007; Rantanen 2012; Reilly 2011; Reilly 2013), suggesting the same could apply to CWEOE.

Contrary to Berg et al. (2011), we did not find an association, or trend, between family history of epilepsy, and behaviour problems in CWEOE. Moderate effect sizes were seen in anxiety and mood scores in those with symptomatic/cryptogenic aetiology, where anxiety and mood behaviours were reported in those with a positive family history. Sample sizes were smaller in these aetiological subgroups, and although there is currently little evidence in the literature suggesting a link between structural lesions and anxiety or mood disorders, this relationship could be explored further in larger sample sizes of CWEOE.

Non-epilepsy-related variables including gender, SES, and age, had rare and variable relationships with scores or neurobehavioural problems. Prematurity was the exception. It was strongly associated with several of the behaviour domains, which reflected the known risk of premature birth to behaviour problems (Cassiano et al., 2016). Gender was associated with two neurobehavioural problems. More females were identified with GCA impairment and adaptive behaviour problems than males. Given the modest sample size, this is likely to be an incidental finding. Children with GCA impairment were more likely to have an adaptive behaviour

problem, and after multivariable regression in adaptive behaviour, gender was no longer a significant independent predictor. A biological explanation of female predominance of GCA impairment in CWEOE is unlikely, and may be partly due to the result of the precursors to the epilepsy itself. All had symptomatic/cryptogenic causes. And of those with known causes, one had epilepsy as a result of a TBI, and two others had lissencephaly – which has no gender prevalence bias (de Rijk-van Andel et al., 1991). It is plausible then, that a gender association occurred by chance.

Adverse cognition and behaviour are more common in children from more deprived social backgrounds, including those with chronic health conditions (Bradley and Corwyn, 2002; Gortmaker et al., 1990), or those with epilepsy (Carson et al., 2015). In this cohort, low SES (reflecting higher social deprivation) was not significantly associated with GCA impairment, or any of the behavioural problems, with the exception of ASD risk in CWEOE. Odds ratios were notably higher in several of the behaviour domains, and modest sample sizes may have masked true differences. The finding that all children at risk of ASD were from a low SES was unexpected. The association between SES and ASD has inconsistent findings, with reports linking ASD with low SES (Burd et al., 1999), high SES (Durkin et al., 2010; Thomas et al., 2012), or no relationship (Fombonne et al., 1997; Larsson et al., 2005). Delobel-Ayoub et al. (2015) linked ASD and severe GCA impairment with low SES. In children with epilepsy, a relationship between ASD and GCA impairment has been established, although the role of SES in this is unknown (Berg et al., 2011b; Berg and Plioplys, 2012; Reilly et al., 2014a; Tuchman et al., 2010). In the current study, only one child at higher risk of ASD had GCA impairment, with the remaining children having variable GCA scores, making this explanation unsatisfactory. West syndrome is also associated with ASD (Berg et al., 2011b), but those with Infantile Spasms/West Syndrome were too young in the present study to be assessed with the ASD screening tools. Therefore, the relationship between ASD and low SES in the current study remains unknown. Further evaluation and longitudinal follow-up is needed to corroborate the extent of ASD diagnosis, and evolution of ASD behaviour symptoms in this cohort, to make firmer comparisons.

Some evidence indicates that child psychopathology in children with epilepsy is associated with psychopathology in the parent (Shore et al., 2002; Shore et al., 2004; Hoare and Kerley, 1991; Lothman and Pianta, 1993), although this is not always supported (Baki et al., 2004). A family history can signify both genetic factors, and family environmental factors, in the development of behaviour problems (Breaux et al., 2014; Fristad and Clayton, 1999). Here,

100% of children with a family history of developmental disability or psychiatric issue screened positive for some type of behaviour problem. Only chance levels were observed in children without such family history. As the association was non-domain specific, this may indicate a general predisposition to behaviour problems with a positive family history. This data requires validation in larger studies, but if the finding persists, it could be used as an easily identifiable risk factor. Furthermore, the family environment could provide a potential avenue for early therapeutic intervention.

Age of epilepsy onset is consistently associated with cognitive impairment but not behaviour in the childhood epilepsy literature (see section 1.4). Here, *within* the early-onset period, the association was weak. For GCA younger age at first seizure was associated with poorer scores, but after multivariable regression, age at first seizure was no longer an independent predictor. Instead, aetiology was the main predictor, with more structural or symptomatic/cryptogenic cases occurring at an earlier age. In the behaviour domains, the association with age was weaker still. The assessment of internalising, externalising and social functioning domains included assessment by an infant/toddler aged tool, the ITSEA, and a preschool-aged tool, the CEC. No infant/toddler tool was available for executive functioning. Neurobehavioural problems were found more often in the CEC, the preschool-aged tool. This suggests that behavioural problems could emerge with increasing age, particularly during the preschool years. However, because no significant relationships were found between age and assessment scores on the individual scales, or between age and the prevalence of behaviour problems, it's unlikely that age itself is a driving factor. Differences in scale structure and parent beliefs surrounding age-appropriate behaviour is an alternative possibility (Cox et al., 2010), and in turn suggests that behaviour problems are likely throughout the early years but which are more obvious or easier to discriminate during the preschool years.

10.4 Neurobehavioural Comorbidity

Having established that neurobehavioural problems were highly prevalent and widespread, it was also important to establish the extent of comorbidity. Whilst the wide spectrum of neurobehavioural problems in children with epilepsy is well recognised, few studies have provided information on the degree to which problems co-occur within the populations (c.f. (Berg et al., 2011a; Caplan et al., 2005; Hoie et al., 2008; Reilly et al., 2014a; Suren et al., 2012). Such information is necessary, and this view has been recently championed in children with ESSENCE disorders (Gillberg, 2010). In the current study, despite 28% of CWEOE having GCA

impairment, only 4% had one in the absence of a behaviour problem. Approximately one quarter of all CWEOE had GCA impairment and a comorbid behavioural problem, whilst one quarter had a behaviour problem in the absence of GCA impairment. Multi-behavioural-domain problems were also common and variable in volume. One fifth of CWEOE met criteria for a single neurobehavioural problem, while 43% had problems in 2 to 6 domains. This raises the possibility of different neurobehavioural phenotypes (Hermann et al., 2007a), who may have different associated risk factors. The results here clearly portray a diverse and multidimensional neurobehavioural profile, and echoes the sentiment laid down by ESSENCE, in that CWEOE require comprehensive evaluation beyond any single neurobehavioural dimension that may be the cause for initial investigation.

Overall, the proportion of CWEOE meeting criteria for cognitive impairment and/or behaviour problem was 63%. Control children met criteria for behaviour problems only, and at 27% was at the higher end of normal (Brauner and Stephens, 2006). One hypothetical explanation for these high figures is that parents had pre-existing concerns about their children which were reflected by study entry, and in scoring response styles. This explanation is unlikely in CWEOE in the current study for several reasons. One, there was a high study ascertainment rate, and was thus representative of the cohort rather than a sampling bias. Two, the differences between CWEOE and controls were consistent in direction across domains, reflecting a general and consistent pattern of poorer cognition and behaviour in CWEOE. Three, such a high prevalence of neurobehavioural problems in school-aged children with epilepsy has been demonstrated recently in the UK using a similar comprehensive assessment - and it is therefore not unreasonable in CWEOE. Reilly et al. (2014a) found 80% of children with epilepsy met criteria for intellectual impairment and/or a DSM-IV-TR behaviour diagnosis. Four, behaviour problem under-diagnosis has been reported in several studies, albeit in children of older age groups (Carson et al., 2015; Ott et al., 2003; Reilly et al., 2014a). This suggests that prevalence rates based on diagnoses or medical registries reported in the literature may be higher than previously considered. Finally, the multiplicity of neurobehavioural problems with problems in 1-6 domains indicates that neurobehavioural problems are widespread, and not the result of a negative scoring response in a small subgroup of children.

10.5 Conclusions

The study has several limitations. The main limitation was a modest sample size with which to investigate risk factors. Validation of the results in a larger cohort of CWEOE would be

recommended. Although the study provides important data for policy development in CWEOE, the sample nonetheless consisted of a heterogeneous sample of children with epilepsy, and sub-syndrome analysis was not possible. Such data on epilepsy syndromes is useful in determining syndrome specific profiles (Nolan et al., 2003; Nolan et al., 2004; Fastenau et al., 2009; Jackson et al., 2013; Kernan et al., 2012), and identifying syndrome specific risk factors that are potentially diluted by mixed samples. One *possible* limitation is the potential overestimation of neurobehavioural problems. The operational definitions used here were based on validated face-to-face assessment tools and questionnaires. Formal diagnosis of neurobehavioural disorders by qualified psychiatrists or clinical psychologists via comprehensive clinical investigations is the gold standard approach. However, the assessment tools used here are routinely adopted in clinical practice to aid diagnosis, meaning the data is based on reliable tools. They can provide excellent discriminant validity (e.g. Reilly et al., 2014c)) but can also help identify children who meet criteria for a diagnosis but have not been identified by clinical services (Ott et al., 2003; Reilly et al., 2014a). These tools also have the ability to identify children who do not reach clinical thresholds but may be impaired all the same (Gigi et al., 2014; Seltzer et al., 2005; Skuse et al., 2009).

A final limitation is the difficulty in attributing neurobehaviour to effects associated with epilepsy rather than AED medications. AEDs are believed to affect cognition and behaviour, yet their degree of influence is uncertain and difficult to untangle from other confounding epilepsy-related factors as well as methodological limitations (Loring and Meador, 2004; Ijff and Aldenkamp, 2013; Mula and Trimble, 2009). Polytherapy, for example, is more detrimental to cognitive outcome than monotherapy (Aldenkamp and Bodde, 2005; Hermann et al., 2010; Mula and Trimble, 2009), yet those on polytherapy have chronic, difficult to control seizures, high seizure frequency, and structural brain lesions, which are also associated with adverse outcomes. In the current study, polytherapy was associated with cognitive impairment, and adaptive behaviour problems, but no other behaviour problem. Assessments were made close to diagnosis, too early to assess GCA and adaptive behaviour outcomes in those on AED with or without seizure control. Nevertheless, an effect of AED in these areas cannot be ruled out. Converse to an AED explanation, problems are increasingly reported at or before epilepsy onset (Austin et al., 2001; Dunn et al., 2002; Hermann et al., 2006; Hesdorffer et al., 2004; Jones et al., 2007; Oostrom et al., 2003) and prior to AED treatment (Goldberg-Stern et al., 2010; Kolk et al., 2001; Taylor et al., 2010; Masur et al., 2013), clearly implicating epilepsy and its associated pathology with comorbid neurobehavioural functioning beyond that of any medication effects.

This study has a number of strengths. It is the first to provide a comprehensive neurobehavioural profile of CWEOE in a population-based sample during the first five years of life, and is one of the few to provide details on the multidimensional nature of neurobehavioural comorbidities within the same cohort. Rantanen and colleagues (2009; 2010; 2011) provided valuable data on a population-based cohort of children aged 3-6 years with established epilepsy. This study extends that data to a UK population of preschool children, including an extended neurobehavioural battery, and adds a new dimension by including infants and toddlers, and by focusing on children with recent onset epilepsy as opposed to established active epilepsy. The preschool aged-sample in this cohort also reflects the UK preschool age prior to formal schooling at age five. The current study also complements the CHESS study in the UK (Reilly et al., 2014a) which provided a neurobehavioural profile of school-aged children with epilepsy. As this study investigated recent-onset epilepsy, one of its main strengths was providing information prior to any long-term effects of chronic epilepsy. This data could form the impetus for earlier detection of neurobehavioural problems, and influence strategies for the development of educational/behavioural support as children prepare to start school.

In conclusion, neurobehavioural problems are detectable and highly prevalent in CWEOE. The children here had recent onset epilepsy which lends further support to the growing consensus that neurobehavioral problems are associated with underlying pathology. Although further studies with larger cohorts are required to corroborate these findings, the evidence strongly suggests that young children with epilepsy should be considered for further evaluation. As problems in the preschool years can persist across childhood and adolescence (Asendorpf et al., 2008; Bayer et al., 2011; Bosquet and Egeland, 2006), and that childhood epilepsy is associated with adverse psychosocial consequences in adulthood (Camfield and Camfield, 2009; Camfield and Camfield, 2010; Chin et al., 2011; Jalava et al., 1997; Sillanpaa et al., 1998; Wakamoto et al., 2000; Wirrell et al., 1997) (c.f. (Camfield and Camfield, 2014), there is a strong case for identification, evaluation, and intervention at the earliest possible time. This may take the form of blanket screening of children with new-onset epilepsy via cognitive and behavioural screening tools. Even when a single problem has been identified, this study, and others, suggest that multidimensional screening should be considered in order to identify all potential problem areas, in order to provide a comprehensive treatment approach. As social problems are consistently reported and were found in CWEOE, attention may be drawn particularly to socially aimed interventions. Not all children with epileptic seizures are brain imaged. The finding here that structural or symptomatic/cryptogenic aetiologies are very often

associated with neurobehavioural problems, suggests routine imaging to identify those who may be at an increased risk. Finally, parents should be made aware of the potential for cognitive or behavioural problems, even when a benign pathology is suspected, so that informed decisions about the child's care and educational needs can be met.

Chapter IV. Eye-gaze Behaviour in Children with Early-Onset Epilepsy

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Chapter IV explores eye-gaze behaviour via eye-tracking as a marker of visual attention and neurobehavioural problems in CWEOE and control children. The concept and practicalities of eye-tracking is introduced, and its rationale for use in CWEOE is described. Methods used in the current study are detailed, which includes the description of five tasks designed to measure cognition/memory, attention/inhibition, and social cognition. It was found that, CWEOE exhibited abnormal visual attention to naturalistic social scenes, which was related to behavioural functioning. Other subtle atypicalities in sustained engagement of attention were found, and are discussed. The findings from this exploratory study suggest that eye-tracking is viable, particularly in less severe epilepsy, and has the potential to be used to aid in the detection of neurobehavioural problems.

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11. Eye-gaze Behaviour in CWEOE: Introduction

The NEUROPROFILES study was created with the intention of determining the neurobehavioural profile of children with early-onset epilepsy (CWEOE; onset ≤4 years). To do this, a cohort of CWEOE, with newly diagnosed epilepsy, was identified from the general population (Chapter II). The neurobehavioural profile of those who consented for the study was determined (Chapter III), with over 60% of CWEOE meeting criteria for cognitive impairment and/or a behavioural problem. The types of neurobehavioural problems were wide reaching, encompassing almost all domains covered by the neurobehavioural battery, and with a high degree of comorbidity. The current chapter was concerned with how control children and CWEOE, including those with and without neurobehavioural problems, performed on eye-tracking paradigms designed to assess some of these cognitive/behavioural areas, in order to explore the utility of eye-tracking as tool for identifying neurobehavioural problems.

In the introduction, the assessment of eye-gaze behaviour using eye-tracking technology is explained, as is its rationale for its use in CWEOE. The main aims of the chapter are laid out, and an overview of the specific tasks used in this study are outlined. In the subsequent sections, further details on each specific eye-tracking task is presented, including individual task backgrounds, methods, results, and discussions. In the final section, the findings from all eye-tracking tasks will be synthesised and discussed.

11.1 Introduction

As outlined in the general introduction to this thesis (section 1.5), eye-gaze behaviour, as measured through eye-tracking, provides an empirical method of assessing or exploring diverse aspects of cognition and behaviour. It has the potential to provide a quick and cost effective means of detecting atypical neuropsychological development, and neurobehavioural problems. This introduction will briefly outline how eye-gaze behaviour relates to neuropsychological processes, followed by a brief introduction to eye-tracking technology used in the measurement of eye-gaze behaviour. Lastly, the aims of this chapter are outlined, and the neuropsychological areas to be explored through eye-tracking will be specified.

The brain processes incoming visual information in a highly complex and selective way. These processes are driven by physiological and neuropsychological factors which have corresponding neurological networks and substrates. The visual system is composed of various

visual pathways (e.g. dorsal stream) that link the retina to brain regions involved in visual processing, such as depth and spatial awareness, attention mechanisms, colour and motion perception, programmed saccades, object tracking, and smooth pursuit (Greenlee and Tse, 2008; Grill-Spector and Malach, 2004). Selective or broad injury to any of these areas can negatively affect eye-gaze behaviour. For instance, the posterior parietal cortex, superior colliculus, and pulvinar (Palmer, 1999) are involved in engaging, disengaging, and relocating visual attention, respectively. Anterior or posterior damage to the pulvinar region selectively impairs temporal and spatial vision (Arend et al., 2008). Thus, gaze-behaviour can be symptomatic of neural abnormality.

The visual system selectively attends to information in the visual field. Various models of selective attention have been proposed to explain what, how and why humans attend to information in the visual field (Heinke and Humphreys, 2005; Itti and Koch, 2001). To understand selective attention, an integrative approach involving bottom-up (e.g. saliency feature maps) and top-down processing (e.g. task-orientated goals), as well as neuromodulators and biomechanics is needed. However, the present study is concerned with how neuropsychological functioning and development, in children with epilepsy, affects eye-gaze behaviour. Neuropsychological processes that drive eye-gaze behaviour include goals and context (Yarbus, 1967; Neider and Zelinsky, 2006), social relevance (Castelhano et al., 2008), and memory and expectations (Torralba et al., 2006). Thus, eye-tracking can tap into such mechanisms, and act as a cognitive marker for abnormal neuropsychological functioning.

Abnormal eye movements themselves are regularly used in the diagnosis of neurological disorders (Bedell and Stevenson, 2013). In disorders of psychiatry, mental health, developmental disorders, and neurodegenerative disorders, eye-tracking is not yet used as a diagnostic measure. However, evidence for the potential utility of eye-tracking as a diagnostic tool in clinical populations have come from childhood and adult studies in a variety of fields including schizophrenia (Benson et al., 2012), anxiety and depression (Armstrong and Olatunji, 2012), ADHD (Deans et al., 2010; Fried et al., 2014), ASD (Pierce et al., 2011b), and dementia (Crutcher et al., 2009). As eye-tracking paradigms are not yet sufficiently sensitive or specific enough to offer suitable diagnostic discrimination between clinical groups and similar disorders, studies typically perform comparative analysis at the group level. Nevertheless, as eye-tracking paradigms and statistical methods evolve, sensitivity will improve. Benson et al. (2012), for example, recently found that a probabilistic model predicted schizophrenia with 98.3% accuracy, based on abnormal eye-gaze behaviour.

A major advantage of eye-tracking is its suitability for use in infant and childhood populations, where it has been extensively used to understand the development of visual attention, and cognition (Feng, 2011; Gredeback et al., 2010). Research has covered a broad array of topics, offering insight into the existence, and development, of mechanisms involving perceptual completion, object permanence, oculomotor and saccade production, priming, social cognition, language, and memory. Eye-tracking research has also been increasingly used in clinical populations in order to understand atypical childhood development, including Learning Disability, ADHD, ASD, prematurity, and other developmental and psychiatric disorders (Karatekin, 2007).

Whilst other neurodevelopmental disorders have received interest, eye-tracking has received limited attention in children with epilepsy. This may in part be due to the heterogeneous nature of epilepsy, including its broad developmental and neurobehavioural spectrum. Nevertheless, atypical gaze-behaviour has been reported in children with epilepsy. Asato et al. (2011), for example, reported increased response inhibition errors and slower visual reaction times in epileptic children from eight years of age. Macchi et al. (2003) found poorer performance in children with epilepsy on a backward masking task compared to controls, and Bedoin and colleagues (2012) found attentional deficits that were dependent on syndrome, lateralisation of epileptic focus, and presence of ADHD in BECTS and Panayiotopoulos syndrome. Recent investigations by Djukic and colleagues (Djukic and McDermott, 2012; Djukic et al., 2014; Djukic et al., 2012), in children with Rett Syndrome, a neurodevelopmental disorder where the majority of children have epileptic seizures, have reported on typical and atypical aspects of development. The authors identified typical orientation toward salient and novel stimuli, and attention toward complex social stimuli, but also reported atypical gaze toward faces, and difficulties with emotional recognition. Taken together, the evidence suggests the validity of using eye-tracking in children with epilepsy, including those with developmental and communication difficulties. Indeed, an advantage of eye-tracking in children with epilepsy is the flexibility of task design which allows targeting of children at all levels of intelligence or verbal ability. Eye-tracking provides a blank canvas for task design, and paradigms can be created that do not require verbal commands or instructions - ideal for use in infants, or in children with communication or learning disorders. Before outlining how eye-gaze behaviour will be assessed in CWEOE in the current study, and in what way, it is necessary to provide a brief introduction to eye-tracking technology mechanics.

11.2 Eye-Tracking Technology Mechanics

The primary function of the eye is to bring into focus that which is of relative importance to the observer. Items in the visual field cannot be processed with clarity without coming into alignment with the fovea – an area on the retina on the interior rear surface of the eye. The retina is covered with photoreceptor cells called rods and cones. Rods need little light to function and have resulting low spatial acuity, creating a less defined 'blurry' area of the visual field known as peripheral vision. Cones require more light, and process colour, with resulting high acuity. The fovea has the highest concentration of cones, and thus the greatest sensitivity to light. The brain interprets data from the visual field, including the peripheral region, and sends signals to the eye on where to move the eye in order to align with the foveal region. The act of focusing the fovea on items within the visual field for further processing is known as a fixation.

There are four basic types of eye movements which result in a fixation, or help maintain a fixation (Purves et al., 2001). These are saccades, vergence movements, smooth pursuit movements, and vestibulo-ocular movements. Saccades are the rapid oculomotor eye movements made between fixations. No object in the visual field can be registered on the fovea during a saccade. Vergence is a corrective movement made by the eyes in which each eye rotates along the vertical plane toward one another (i.e. convergence) as an object gets closer to the observer, or when they rotate away from each another (i.e. divergence) if the object is further away, in order to bring that object into focus. Smooth pursuit is when the eyes keep track of an object that is in motion by following it with smooth steady focus, as opposed to intermittent saccadic movements. Vestibulo-ocular movements are those initiated by the vestibular system to keep the gaze steady in the context of head movements. It prevents objects being lost from focus as the head moves. Fixations and saccades are typically the primary aim of behavioural research, and are the focus of the current study.

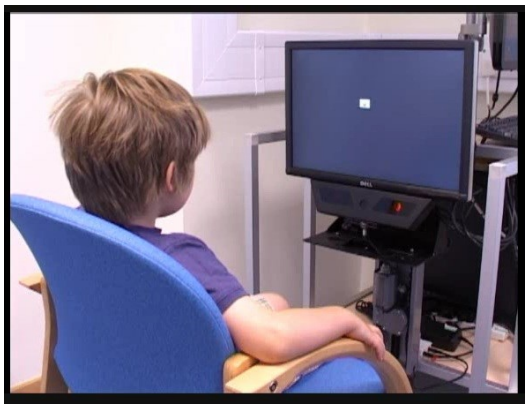
Eye-trackers have been in use for over 100 years (Duchowski, 2007; Holmqvist et al., 2011; Young and Sheena, 1975), and were developed to study eye movements and eye-gaze behaviour, with different eye trackers and methods better suited to certain tasks or environments. Eye-trackers can be divided into four main types (Duchowski, 2007): (1) Eye-attached; a highly invasive method of attaching a metal coil to the eye that produces an electromagnetic signal in response to eye movements. It is accurate, and can detect even microsaccades (brief eye movements), but is impractical for most uses, especially in children,

given its invasiveness. (2) Electrooculography; uses electrodes placed around the eye to measure electrical signals produced by physical movements of the eye. It is minimally invasive, and has the advantage of being used when the eyes are closed. However, this method is inaccurate in regard to the location of gaze fixations. (3) Photo/Video-oculography; uses mounted cameras (including infrared cameras) which record eye movements by tracking the pupil - which has been illuminated by the tracker. When applied in research, a coder will often judge the direction of eye movements based on captured video, in order to relate eye-gaze to visual stimuli. Thus, this method may be prone to human error, and will likely have poor spatial accuracy for fixation points. (4) Pupil centred corneal reflection (PCCR); Corneal reflection is the dominant technique in modern history (Holmqvist et al, 2011), and is discussed in further detail below.

In PCCR based eye-trackers, infrared light is emitted by the tracker, which is reflected off the cornea and pupil (known as Purkinje images 1 and 4). Images are captured by the tracker and a vector is created based on the relative position of these reflections to one another. The direction of the vector in combination with other geometric features of the eye captured by the tracker are used to calculate gaze direction with high accuracy. Advanced PCCR eye trackers use two methods of corneal illumination: dark and bright. Each have advantages and disadvantages based on the characteristics of the participants, or environmental conditions. Bright pupil eye-tracking places illumination close to the optical axis of the imaging device, which causes the pupil to appear lit up. In dark pupil tracking the illumination is placed further away from the optical axis, and the pupil remains dark. Modern eye-trackers may use both methods. One major advantage of PCCR over other eye trackers is the ability to estimate fixation points with high accuracy as the participant concurrently views a visual stimulus. Software then interprets the data and produces meaningful temporal and spatial data with which eye-gaze behaviour can be mapped directly onto the viewed stimuli. Another major advantage is the versatility with which they are produced. PCCR eye trackers are available mounted onto head gear, on glasses, in built-in desktop monitors, or via remote units (figure 11.1). They are, however, not without their limitations. The major disadvantage of remote eye-tracking units in infants and young children is data loss (Haith, 2004). Children are often distractible, turning attention away from the display, perform excessive head movements, or 'scrunching' their eyes, reducing eye data capture. However, this disadvantage is outweighed by their benefit in infant and childhood populations, as they require no physical apparatus attached to the child. Accordingly, a remote PCCR eye-tracker was the preferred choice for the current study.

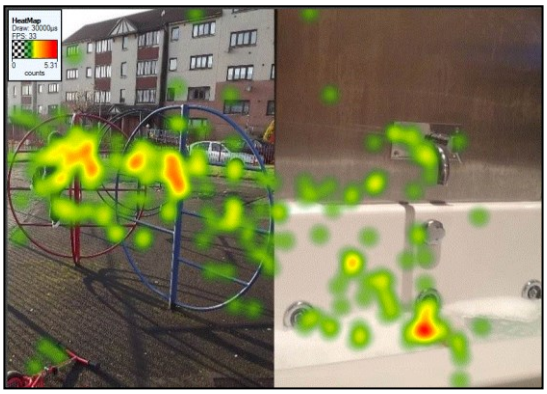
PCCR eye trackers typically involve a participant viewing a static image, video, or interactive stimuli, presented on a monitor attached to the tracking device which has been calibrated to the participant (figure 11.1) – although mounted glasses offer eye-tracking in real world situations. The eye tracker software calculates x/y coordinates and temporal data for fixation points, with which a number of metrics can be produced for analysis. Total Fixation Duration (TFD) and Time To First Fixation (TTFF) are two common fixation metrics reported in studies of cognitive development. These metrics are approximate measures for how important or relevant a particular element within the stimuli is to the observer, and are those used in statistical analysis in the present study. Viewing something more often, or for longer, is indicative of more detailed processing. Eye-tracking software can also produce visual outputs to conceptualise eye-gaze data, such as fixation maps or heat maps (figure 11.2), to visually represent individual or group data. The quantitative statistics produced from the eye-tracking metrics are then used for statistical analysis.

Figure 11.1 Remote eye tracker



PCCR eye tracker and child observer

Figure 11.2 Heat map



Heat maps indicate the proportion of time fixating for an individual, or group. The spectrum runs from green to red, with longer average durations signified by red, and shorter durations by green.

11.3 Eye-Tracking Battery Overview

The CWEOE and controls enrolled onto the NEUROPROFILES study were a heterogeneous group, consisting of infants, toddlers, and pre-school children, with varying levels of development and cognitive ability. In order to reduce outcome bias, the eye-tracking tasks used in the study were chosen, and the battery was administered, in a standardised manner for the entire cohort. This scenario was possible with eye-tracking, given the freedom of the method to select or develop specific tasks suited to individual goals and requirements. The

eye-tracker was a remote PCCR device, allowing accessibility for all children. Tasks were selected that required no verbal instructions, so as to be suitable for infants and preverbal-children as well as those with learning or communication difficulties.

There are a broad spectrum of neurobehavioural problems in children with epilepsy in general (Rantanen et al., 2012; Reilly et al., 2013; Rodenburg et al., 2005; Lin et al., 2012a). Three of the most prominent neurobehavioural domains associated with childhood epilepsy are General Cognitive Ability (GCA), attention, and social problems. Similarly, in the NEUROPROFILES study, CWEOE had a broad spectrum of neurobehavioural problems, including GCA impairment, inattention/hyperactivity problems, and social cognitive and social functioning problems (see chapter II for detailed description). The eye-tracking tasks chosen for the study were based on visual attentive mechanisms associated with these three domains. As yet, no standardised eye-tracking measures with psychometric properties exist for the diagnosis of cognitive or social behaviour problems. Instead, eye-tracking tasks were selected based on the theoretical relationship between the visual attention mechanism elicited during the task, and the behavioural outcome of interest. Five tasks were selected, and were assigned to one of three domains; cognition/memory, attention/inhibition, and social cognition. The structure is outlined in table 11. Each of the domains, and tasks selected, will be discussed in more detail in sections 13, 14, and 15, respectively - complete with background, methods, results, and discussion. General methods that apply to all tasks are described in section 12.

Table 11 Eye-tracking tasks by neurobehavioural domain

Domain	**Eye-Tracking Task**	**Overview**
Cognition/Memory	1. Memory Task	Visual paired comparison paradigm assessing incidental recognition memory. Associated with GCA.
Attention/Inhibition	2. Oculomotor Control Task	Saccadic inhibition task. Also measures production of antisaccades.
	3. Spatial Negative Priming Task	Negative priming task assessing selective attention with spatial inhibition.
Social Cognition	4. Face Scanning Task	Selective preference for facial features during free viewing of neutral faces.
	5. Social Preference Task	Selective preference for social or non-social natural-scene images.

11.4 Primary Aims and Hypotheses

As outlined in chapter I, epilepsy is associated with a high prevalence of neurobehavioural problems, and the initial goal of treating or preventing any adverse condition is to identify it at the earliest possible time. Early intervention for cognitive and behavioural problems is advantageous (see section 1.1), and eye-tracking is one tool that could potentially identify problems at an early stage through simple viewing tasks. Therefore, the primary aim of this chapter was to explore eye-gaze behaviour as a potential marker of neurobehavioural problems in CWEOE.

To meet that primary aim, the relationship between psychometric assessment scores from neurobehavioural assessment tools, and eye-gaze behaviour in the eye-tracking tasks listed above, were statistically evaluated in CWEOE, and typically developing control children. This included an evaluation of linear relationships between outcome variables from eye-gaze tasks and neurobehavioural tools, and eye-gaze performance between those CWEOE with, and without, neurobehavioural problems. Prior to analysis including neurobehavioural assessment, broad group differences in eye-gaze behaviour between CWEOE and controls were explored, with the intention of determining if there was a general effect of having epilepsy on eye-gaze.

Given that epilepsy is a heterogeneous condition with variability in the prevalence of neurobehavioural problems, it was hypothesised that CWEOE would exhibit eye-gaze behaviour similar to that of controls across eye-tracking tasks, but with greater variability in performance. It was expected that CWEOE with neurobehavioural problems would exhibit abnormal gaze behaviour compared to CWEOE without neurobehavioural problems. Hypotheses specific to each eye-tracking task are described in the relevant sections to follow.

12. Eye-gaze Behaviour in CWEOE: General Methods

Methods that apply to all five eye-tracking tasks are presented here, with an overview of statistical analysis for all tasks. Methods relevant to specific tasks are detailed in the relevant domain sections; cognition/memory in section 13, attention/inhibition in section 14, and social cognition in section 15.

12.1 Participants

75 CWEOE and 52 control children were identified and consented into the NEUROPROFILES study, and were eligible to participate in eye-tracking (see chapter I, section 2 for identification and recruitment methods, including consent procedures). All children who completed eye-tracking partook in the neurobehavioural assessment battery which has been described in chapter II, section 9.

12.2 General Procedure

Children completed eye-tracking after the face-to-face elements of the NEUROPROFILES assessment battery (i.e. Bayley III, WPPSI III, and NEPSY II). As described in Chapter II, not all children completed neurobehavioural assessment and eye-tracking in one session. Some completed eye-tracking in a separate session. Additionally, several children were nervous or uncooperative upon arrival, and eye-tracking was completed first, in order to complete the assessment battery and also to help the child relax prior to neurobehavioural assessment. The estimated completion time for eye-tracking was approximately 20-30 minutes including short breaks between tasks.

Children sat alone or on their parent's/carer's lap (herein referred to as parents) 50-60cm from the monitor. Toddlers and preschool children were informed verbally by the candidate that they would be watching some pictures and animations. No task specific instructions were given in order to maintain standard operating protocol for verbal and nonverbal children. To promote engagement and sustained attention, verbal encouragement was given to those children who required it by the candidate. General statements were chosen that would not influence the direction of gaze (e.g. "What's happening here?", "Wow, look at that!", "What did you see?"). Parents were asked to remain quiet, except to offer the child encouragement if

required, or to direct the child's attention back to the monitor if the child became inattentive and was unresponsive to the candidate.

The five eye-tracking tasks – outlined in section 11.1.3, and detailed in subsequent sections - were presented across four presentation blocks, which allowed breaks between presentations to minimise attentional fatigue. The Spatial Negative Priming (SNP) Task and Oculomotor Task were each presented in blocks one and two, respectively. The Memory Task, Face Scanning Task, and Social Preference Task were amalgamated into blocks three and four. Each of these two blocks consisted of stimuli from all three tasks. A similar approach was used in Gillespie-Smith et al. (2016), and Telford et al. (2016). Initially tasks in the two blocks were ordered randomly, but observations suggested that attention was being moderately reduced or lost after presentation of the Memory Task, particularly in older children. Subsequently the Memory Task stimuli were re-ordered to be presented at the end of each of those two blocks. Thus, Face Scanning Task stimuli were presented at the beginning of block three, followed by Social Preference Task stimuli, then Memory Task stimuli. In block four, the order was switched so the Social Preference Task stimuli would be viewed first, followed by Face Scanning stimuli then Memory Task stimuli. Approximately half of the children in the study were administered the initial order, and half the adjusted order. Anecdotally, children displayed a reduction in overt signs of fussiness (e.g. fiddling, getting off seat, or expressing verbal dissatisfaction) during the adjusted presentation order. All four blocks were administered in a random order across participants. Breaks were administered between blocks if necessary. Calibration was performed at eye-tracking onset, and after any prolonged break.

Visual acuity and visual field was assessed as a control measure. Visual acuity was assessed in children <18 months using Keeler Acuity Cards (Keeler Ltd. Windsor, UK). A novel locally developed visual field test (Murray et al., 2009) was carried out in all children to assess for visual field deficits. No child with successful calibration had visual acuity/field deficit. One child wearing corrective lenses, had successful calibration.

12.3 Eye-tracker and Fixation Filter

Eye movements were detected using a Tobii x60 eye-tracker, which tracks both eyes to a rated accuracy of 0.3° at a data rate of 60 Hz. Eye-tracking stimuli were presented in Tobii Studio 3.2.2, and displayed on an LCD monitor with a screen size of W40.8cm and H25.0cm, and resolution of 1440 x 900 pixels. Calibration used a fully automated five-point calibration

procedure as standard with Tobii Studio. During calibration the child tracks a coloured circle as it moves to five calibration points situated at standard uniform positions around the screen. Infant calibration is a semi-automated alternative, available in Tobii Studio, and uses large animations at each calibration point instead of a coloured circle. Infant calibration was performed when the child could not sustain attention to the regular calibration procedure, having resulted in failed calibration.

The latest Tobii fixation filter, the I-VT, was used to determine fixation data. The I-VT filter uses averaged binocular eye data, interpolation at 75 milliseconds (ms), with minimum fixation duration of 60ms. Multiple-fixations within 75ms and 0.5° are counted as single fixations (Olsen, 2012).

Fixation data was captured on manually drawn areas of interest (AOI); the size and dimensions of which was determined by the user (section 12.5.1). Tobii Studio collects X Y coordinate data and a time stamp – with which spatial location and temporal order of fixations can be determined. AOIs were predefined 2D physical regions of space marked on visual stimuli using Tobii Studio's definition tools. In a dynamic stimulus, such as a movie animation or series of images within a single trial, the AOI can be 'active' or 'inactive'. Fixation data is captured only during the active phase of the AOI. In this way, fixation data can be collected for when it is appropriate to gather, such as after the appearance of a target stimulus or cue for example.

12.4 Interstimulus Interval Stimuli

Individual task stimuli are described in the relevant task methods sections. Stimuli used during the interstimulus intervals (ISI), i.e. the time period between trials or between presentations of stimuli within trials, consisted of animated objects (e.g. rotating rattle) paired with non-distinct sounds presented at the centre of the screen. These stimuli were uploaded directly from Tobii Studio. ISI stimuli were used to maintain attention, and to improve standardised presentation by orienting eye-gaze to the centre of the screen prior to trial/stimulus onset.

12.5 General Analysis

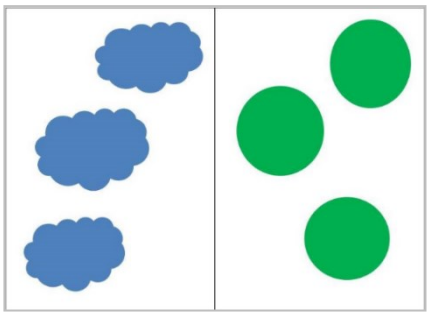
12.5.1 Areas of Interest (AOI)

An AOI is constructed in order to capture gaze data directed toward an object of interest, or toward particular spatial and/or temporal locations of a stimulus, often in situ with competing

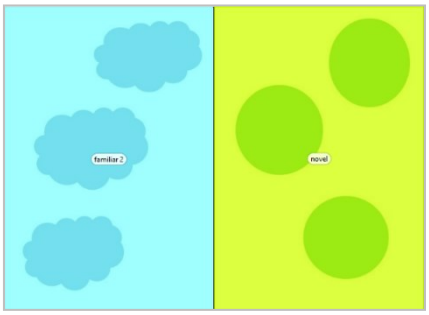
AOIs. An aim of constructing an AOI is to find balance between fixations which are truly intended for the target location- including those fixations that may fall outside of it -, and fixations that fall outside the target location and were not intended for that target (Orquin et al., 2016). As yet, there is little guidance or standardised approach toward the construction of AOIs, with most studies manually drawing AOIs to researcher-defined shapes and sizes (Hessels et al., 2016; Holmqvist et al., 2011; Orquin et al., 2016). Different sized AOIs can lead to different statistical results in some cases (Hessels et al., 2016; Orquin et al., 2016), but this may also depend upon the nature of the stimulus itself (e.g. stimulus complexity, or object sparseness) (Orquin et al., 2016). In addition, the accuracy of fixations as detected by an eye tracker can be compromised by the inaccuracy of programmed saccades themselves (Palmer, 1999), and by the accuracy and success of the eye-tracker and its calibration procedures. It could be argued that inconsistencies in calibration accuracy may be expected more so in very young children for the same reasons described in the introduction to this chapter. Accuracy in the capture of fixations truly intended for the target can be supplemented by increasing the AOI boundary beyond the object to create a buffer zone (Holmqvist et al., 2011). Increased boundaries are preferred when target objects where distal from one another (Orquin et al., 2016). AOI sizes for the current study were manually constructed, allowed for buffer zones, and were defined a priori, to avoid any potential preferential result bias as a result of a posteriori analysis of multiple AOI sizes. The location of AOIs were guided by previous research where appropriate.

AOIs for each task are illustrated in figure 12. Tasks using AOIs that competed for attention employed AOIs of equal size in order to avoid potential spatial bias. Specifically, the Memory Task and Social Preference used a forced choice design, with the AOIs splitting the selection equally between two halves of the screen. This design has been used previously (Fletcher-Watson et al., 2008; Gillespie-Smith et al., 2016; Telford et al., 2016), and was considered acceptable given that each half of the screen was considered the target, as opposed to the specific objects within each half. The SNP Task AOIs used the natural topography of the display grid in order to define AOI size whilst allowing a reasonable buffer margin. The Oculomotor Task used equal sized AOIs that became temporally activated after offset of the central stimulus (i.e. smiling sun). The original authors of the task used video recording to code gaze direction (Scerif et al., 2005), and therefore larger AOIs were preferred to maximise false negatives, and to replicate the broad direction of saccades as captured by the authors.

Figure 12 Examples of task specific areas of interest (AOIs)



1(A)



1(B)

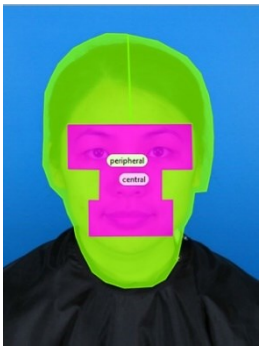
1 - Memory Task stimuli (A) were divided into two equal AOI halves (B)

2(A)

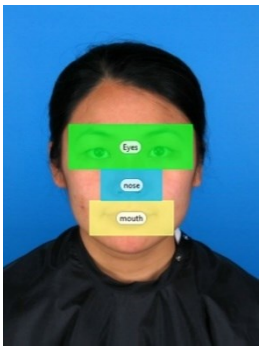
2(B)

2 – Social Preference Task (A) was divided into two equal halves (B), with the addition of AOIs for the child/children (2B green) and head region (2B light blue). Fixation data was captured by each AOI regardless of AOI overlap.

3(A)

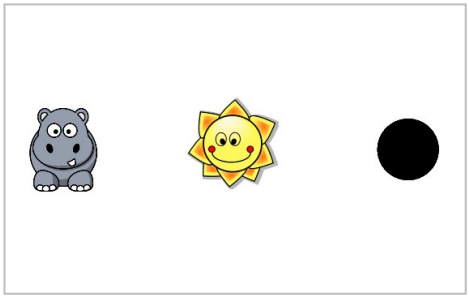


3(B)

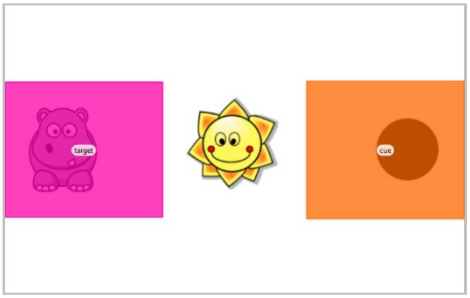


3(C)

3 – Face Scanning Task AOIs were analysed by central facial region and peripheral facial features (B), with further analysis of the central features individually (eyes, nose and mouth, fig. C).



4(A)

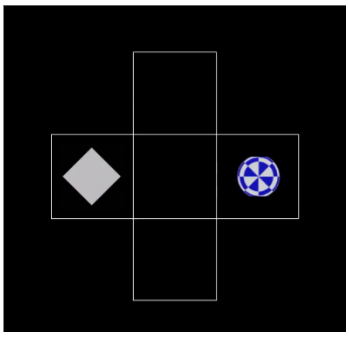


4(B)

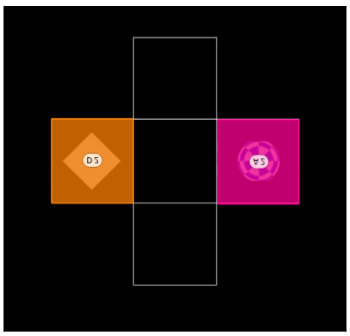
4 – Oculomotor Control Task stimuli (A) AOIs were situated over target and cue regions (B). Note that AOIs only became active at cue onset. Note that figures are for illustration purposes. The central stimulus, cue, and target did not appear at at the same time.

Figure 12 continued

5(A)



5(B)



5 – Figure 5A illustrates the probe condition of the Spatial Negative Priming Task, with AOIs superimposed on the respective grids (5B). AOIs became activated immediately following probe onset.

In the Social Preference Task, AOIs were additionally crafted for child/children regions and head regions to explore within-social scene eye-gaze preferences for persons (Buswell, 1935). AOI boundaries extended approximately 1-1.5° of visual angle around the AOIs in order to minimise false positives from fixations toward other items in these naturally complex scenes, whilst simultaneously accounting for inaccuracy. AOI selection on the Face Scanning Task was founded on Chawarska and Shic (2009) AOIs in typically developing and ASD children. AOIs were created for central facial features (i.e. eyes, nose, and mouth) and peripheral facial features (i.e. hair, ears, forehead, cheeks, and neck). As facial dimensions differed between stimuli, new AOIs was manually drawn for each target within the stimulus, using a rectangular AOI tool in an effort to maximise a standardised approach. As previously employed in Chawarska and Shic (2009), AOIs touched but did not overlap.

12.5.2 Image-wise Analysis

Three tasks were locally-created and novel: Memory Task, Social Preference Task, and Face Scanning Task (Gillespie-Smith et al., 2016; Telford et al., 2016). Prior to main analyses, image-wise analysis was carried out using t-tests or Mann-Whitney-U tests, depending on normality, to explore image bias (e.g. bias for male or female faces), or to identify individual images with disproportionate gaze data. Analysis was conducted for the sample as a whole, and for CWEOE and controls separately. The proportion of TFD was compared for: (1) Memory Task; right vs left images, (2) Social Preference Task; right vs left social images, and (3) Face Scanning Task;

Males vs Females. There were no disproportionate patterns of visual attention identified, indicating that image types were equally as attractive, and image position did not bias direction of gaze. Thus, all images were analysed together.

12.5.3 Eye-Tracking Metrics

Tobii Studio (v3.2.2) has a number of eye-tracking metrics. These include the number of fixations before fixating an AOI, the time from stimulus onset to first fixation (time to first fixation, TTFF), the duration of the first fixation, the number of fixations on each AOI (fixation count), the total time duration of fixations within an AOI regardless of the number of fixations (total fixation duration, TFD), the duration of time spent in each AOI including time not fixated (visit duration), the number of visits to each AOI independent of fixations (visit count), the percentage of subjects who fixated an AOI (percentage fixated), and other metrics based on mouse clicks before, or within, an AOI.

The two metrics deemed most appropriate for the purposes of the current study were TFD, and TTFF. In addition to saccade programming, the duration of a fixation is thought to correspond to the amount of perceptual and cognitive load and processing (Just and Carpenter, 1980; Meghanathan et al., 2014; Pannasch et al., 2011). Thus, TFD can be used as a measurement of attentional importance when assessing the selection of competing stimuli, and thus visual preference. Indeed, studies show, for example, that increased fixation duration is associated with visual decision making (Glaholt et al., 2009), and consumer choice (van der Laan et al., 2015) in adults, and novelty and social preferences in infants (Burbacher and Grant, 2012); Gillespie-Smith et al., 2016). Therefore, TFD was used in the present study to assess preferential selection between competing AOIs.

TTFF is the latency from stimulus onset to the first fixation within an AOI. It is a useful metric in determining reaction times, intervals between spatial or temporal events, or in understanding immediate preferences. In this latter respect, TTFF may be used as a proxy for attentional priority in naturalistic scenes (Fletcher-Watson et al., 2009), where the AOI viewed first (i.e. quickest) could be considered to hold immediate relative importance to the observer. In the present study, TTFF was used in this way for the Face Scanning Task and Social Preference Task, and to calculate dependent variables in the SNP Task and Oculomotor Control Task. Metrics used in the calculation of dependent variables for each task are listed in table 12.1.

It can be argued that using TTFF to assess which AOI subjects attended to first on average is liable to error. Across *n* trials, disproportionately small or large latencies can distort the latency of the sample mean. An alternative, and novel, method of identifying attentional priority, developed by the candidate, was based on the proportion of first fixations made to each AOI. Termed 'first fixation preference' here, the first AOI fixated within each trial, based on TTFF, was manually recorded, and the total number of first fixations toward each AOI across trials was calculated for each child. The proportion of first fixations to each AOI within a task stimulus was then expressed as a percentage of the total number of trials the child completed. As this ascertains how often an AOI is looked at first, it could be considered a more reliable measure than TTFF latencies alone, which ascertain more definitively how *quickly* an AOI is viewed.

12.5.4 Data Cleaning Procedures

Prior to analysis, the data was expurgated to remove or amend unsuitable data via the following procedures. Trials with a TTFF <100ms post trial onset represent pre-programmed saccades (Liversedge and Findlay, 2000), and were replaced with the next subsequent fixation point post 100ms. Using the gazeplot, through the visualisation tab of Tobii Studio, it was possible to determine this first "true" volitional fixation. This method was devised by the candidate, and was applied in Telford et al. (2016).

Average fixation duration during natural scene viewing is highly variable (Henderson, 2003). Trials with a total fixation duration time of <500ms were excluded (Fletcher-Watson et al., 2008; Fletcher-Watson et al., 2009; Gillespie-Smith et al., 2016; Telford et al., 2016) as they may represent only brief attention to a scene that may have been pre-programmed and unrepresentative of true stimulus-goal fixation preferences.

An individual child's data on the Memory Task, Social Preference Task, and Face Scanning Task were included in analysis if there was eye-gaze data available for at least 33% of trials after data cleaning procedures were applied. This standardised cut-off point was chosen by the candidate to ensure representative natural eye-gaze behaviour, and reduce bias resulting from data obtained from children who were inattentive to the specific task. Two tasks, the Oculomotor Control Task and SNP Task, had task specific exclusion criteria, due to the sequential nature of data collection required during these tasks. That is, eye gaze data were only meaningful when certain criteria where met during each stage of the trial. During the Oculomotor Control Task, children's data were excluded when the child looked at the cue

<40% of trials in the first half of trials, or if <12 trials were scorable (Johnson, 1995). Individual trials were excluded if the child's gaze was not fixated on the central stimulus prior to the onset of the cue. As explained in section 13, the SNP Task is based on the suppression of one spatial location and the simultaneous selection of another. To ensure this occurred, SNP Task trials were excluded if there were no looks toward the prime display, if the target animation in prime display was not fixated, if the distractor was fixated in the prime display, if distractor was fixated first during probe display, and when gaze was not maintained from prime to probe displays (Amso and Johnson, 2005).

12.5.5 Attention to eye-tracking Tasks and Battery

To exclude the possibility that any potential group differences in eye-gaze behaviour could be attributed to differences in general visual attention, rather than group differences in eye-gaze behaviour, general attentiveness to the tasks and eye-tracking blocks were measured in two ways. The first was based on the percentage of the total number of trials that were included in analysis after exclusion criteria above were applied. Meeting inclusion criteria was a reflection of general attention to trials. The second method was based on the Tobii Studio eye-tracking metric of samples collected, which pertained to general attention to the eye-tracking blocks, and quality of data collected by the eye-tracker (Tobii Studio 3.2, user manual). It is a combination of the eye-tracker's success in tracking eye position and movement, and the time spent looking at any particular block of trials. The quality of the sample is affected by how often the tracker can record one or both eyes. A sample collection of 50%, for example, might indicate 100% tracking with one eye, 50% collection with both eyes, or a combination of both. T-tests or Mann-Whitney U tests were used to compare attention in CWEOE vs controls, in order to determine if group differences existed in attention to the eye tracking battery.

12.5.6 General and Task Specific Analysis

Normality was assessed according to Shapiro-Wilk test and upon visual inspection of histograms and QQ-plots. T-tests and ANOVAs were used to assess group differences in gaze behaviour when data was normally distributed, and Mann-Whitney U/Wilcoxon signed rank tests and Kruskal-Wallis/Friedman tests when data followed a non-normal distribution. Relationships between gaze behaviour and sociodemographic variables or neurobehavioural assessment scores were assessed via Pearson or Spearman's Rank correlations for continuous

variables, and t-tests or Mann-Whitney U tests for categorical variables. FET was applied for all 2x2 or 2x3 contingency tables comparing sub-group comparisons of nominal variables.

Table 12.1 Analysis of attentional importance and priority by task

Task	Between-group outcome	Dependent Variable(s)
Memory Task	Preference for 'familiar' vs 'novel' shapes	Fixation Preference/ First Fixation Preference
Oculomotor Control Task	Extent of inhibition of reflexive saccades	Percentage of trials with look toward cue; first half vs second half of trials*
	Saccade type produced	Percentage of corrective, reactive, and anti-saccades produced*
Spatial Negative Priming	Presence of negative priming	Latency to target in 'repeated distractor' vs 'control' trials*
Social Preference Task	Preference for 'social' vs 'non-social' scenes	Fixation Preference/ First Fixation Preference
	Time spent fixating children and head regions	Total Fixation Duration/ First Fixation Preference
Face Scanning Task	Preference for 'central' vs 'peripheral' features	Fixation Preference/ First Fixation Preference
	Preference for eyes, nose, and mouth regions	Fixation Preference/ First Fixation Preference

*Dependent variable derived from time to first fixation (TTFF)

ISI – interstimulus interval

A summary of analyses and outcome variables for each of the five eye-tracking tasks can be found in table 12.1, and described in context in the relevant sections to follow. Several tasks (i.e. Memory Task, Social Preference Task, and Face Scanning Task) were primarily focused on the preference for one AOI versus a competing AOI. As such, a common dependent variable was calculated and is introduced here. This variable was labelled 'fixation preference', and was calculated as the difference in mean TFD, expressed as a percentage of TFD to the whole scene, for one AOI minus the TFD of the competing AOI. Expressing mean TFD as a percentage standardised data by taking individual variation in total fixation duration to the overall stimulus into account. Fixation preference allowed the production of positive and negative directional values. One sample T-tests were used to assess novelty preference (Memory Task: novel vs

familiar shapes) or social preference (Social Preference Task: social image vs non-social image) against chance levels (i.e. fixation preference of 0). As reasoned earlier, for the purposes of this study, fixation preference was considered a measure of attentional importance, and first fixation preference as a measure of attentional priority. TFD and TTFF were used to calculate dependent variables for the Oculomotor Task and SNP Task.

12.5.7 Neurobehavioural Assessment Analysis

One intention of eye-tracking in the current cohort was to explore the association between eye-gaze behaviour and neurobehavioural outcomes in CWEOE and controls. This was done in order to explore the potential utility of eye-tracking as a predictive tool for cognition and behaviour, and for the identification of those meeting criteria for neurobehavioural problems.

All children completed a neurobehavioural battery of cognitive and social-emotional behaviour tools as part of the NEUROPROFILES study (see chapter II). The dependent variable of each eye-tracking task was correlated with General Cognitive Ability (GCA, i.e. z-score derived from Bayley III Cognition scale or WPPSI-III FSIQ, ages >1m), and with the most relevant neurobehavioural tools (table 12.2), in order to establish any linear relationships. In addition, the dependent variables were compared between children meeting criteria for neurobehavioural problems and those who did not, including those at lower or higher risk of ASD (≥16m).

Table 12.2 Eye-tracking tasks and relevant neurobehavioural assessment tool

Task	**Neurobehavioural Tool (age coverage, m)**	
Memory Task	NEPSY-II: Memory for Designs; Narrative Memory; Sentence Repetition (≥36)	
Oculomotor Control Task SNP Task	1. CEC Inattention/Hyperactivity (≥24) 2. NEPSY-II Statues (≥36)	3. P-BRIEF GEC (≥24) 4. ITSEA Externalising (12-23)
Social Preference Task Face Scanning Task	1. Social Functioning (i.e. Social-Emotional Scale (1-11); ITSEA Competence (12-23); or CEC Social Functioning (≥24))	2. NEPSY-II Affect Recognition (≥36) 3. NEPSY-II Theory of mind (≥36) 4. SRS2 Communication & Interaction Index, and SRS2 Total (≥30)

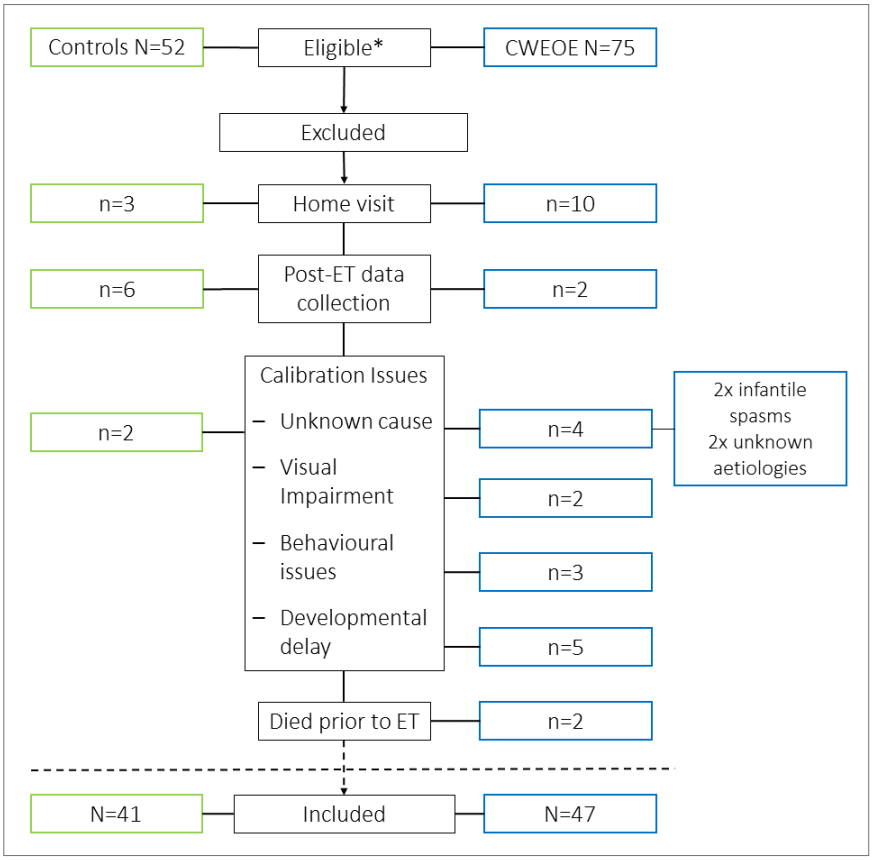
†Risk based on positive M-CHAT screen, or SRS2 Total T-score ≥65

13. Preface to Individual Eye-Tracking Tasks and Results

As outlined at the beginning of this chapter, the eye-tracking battery consisted of five tasks: Memory Task, Oculomotor Control Task, SNP Task, Face Scanning Task, and Social Preference Task. The remainder of this chapter describes each of these five tasks in turn, and is organised by domain: cognition/memory (section 14), attention/inhibition (section 15), and social cognition (section 16). Backgrounds, methods [not covered in section 12], and results are presented, along with a discussion for each of the three domains. This is followed by a general discussion of the eye-tracking battery. Preceding sections 14-16 is an overview to the children who completed the eye-tracking battery - including epilepsy characteristics -, and an analysis of attentiveness to the eye-tracking battery.

13.1 Participants

Figure 13 Eye-tracking Exclusion Flow Chart



* Eligible children were those who consented and had neuropsychological assessment

Of the 75 CWEOE and 52 controls who were eligible for eye-tracking (i.e. consented for the study and had neuropsychological assessment), 47 CWEOE and 41 controls completed the eye-tracking battery. 28 CWEOE and 11 controls did not complete the battery (figure 13). Of those who attempted eye-tracking but no data could be gathered, two control children and 14 CWEOE could not be calibrated. The reason for unsuccessful calibration in controls was unknown. In CWEOE, calibration was not successful due to visual impairment, uncooperative or hyperactive behaviour, developmental delay or psychomotor difficulties leading to poor attention, and unknown reasons.

CWEOE (n=28) who did not complete the eye-tracking battery had a significantly different clinical profile than those who did. They were younger (Median=16.31 [IQR 7.12 – 41.55]m, p=.016), were more likely to have symptomatic epilepsy (FET=.004) or structural/metabolic aetiology (FET=.03), had a major brain abnormality on MRI (FET=.017), had a higher seizure frequency (FET=.042), and were on more than one AED (FET=.028). Six of the 7 infants who were born prematurely did not receive eye tracking. This suggests that the results presented were more likely to be gathered from children with less severe epilepsy.

47 (32M:15F) CWEOE and 41 (19M:22F) controls successfully completed eye-tracking. Median age at assessment was 37.85m (IQR 17.25 - 51.19) in CWEOE, and 27.60m (15.59 – 48.71) in controls. Groups did not significantly differ in age (p=.42, r=.09). Gender difference was marginally non- significant (FET=.052).

The aetiological composition of the CWEOE cohort, and syndromic classification (Berg 2010), are reported in tables 13.1 and 13.2, respectively. In terms of antiepileptic drug therapy (AED), 15% of CWEOE were not on an AED at the time of assessment, 79% were treated with monotherapy, and 6% polytherapy.

Table 13.1 Aetiological Classification ILAE 1989 and 2010

ILAE Classification	Aetiology	n (%)
ILAE 1989	Symptomatic Cryptogenic Idiopathic	6 (13) 8 (17) 33 (70)
ILAE 2010	Structural/Metabolic Genetic Unknown	5 (11) 19 (40) 23 (49)

Table 13.2 Epilepsy classifications according to Berg et al (2010)

Classification		Syndrome	N=47
Electroclinical Syndromes	Infancy	West Syndrome	2 (4.3%)
		Benign Infantile Epilepsy	4 (8.5%)
	Childhood	Panayiotopoulos	1 (2.1%)
		Childhood Absence Epilepsy	6 (12.8%)
		Generalised Epilepsy with Febrile Seizures +	2 (4.3%)
Distinctive Constellations		Genetic Generalised Epilepsy	9 (19.1%)
		Genetic Focal Epilepsy	3 (6.4%)
Other Structural-Metabolic Causes		Focal Epilepsy	4 (8.5%)
		Generalised Epilepsy	1 (2.1%)
Epilepsies of Unknown Cause		Generalised Epilepsy of Unknown Origin	6 (12.8%)
		Focal Epilepsy of Unknown Origin	7 (14.9%)
		Unclassified	2 (4%)

13.2 General Attentiveness to the Eye-Tracking Battery

The percentage of trials included in analysis – for the Memory task, Oculomotor Control Task, Face scanning task, and Social Preference task - in CWEOE (median= 79.17 [IQR 63.89 – 91.67]) was not significantly different to that of controls (median= 83.33 [IQR 71.88 – 91.49]) (p= .67, r= .05). More specifically, there were no significant differences between CWEOE and controls in any of the tasks. Similarly, the mean percentage of samples collected across eye-tracking blocks were not significantly different between CWEOE (M=53.82, SD=16.70) and controls (55.78, SD=17.43); MD=-1.96 (95% CI -9.20, 5.27). Taken together, CWEOE and controls displayed similar levels of attention to trials, and across the eye-tracking blocks. CWEOE (M= 62.48, SD= 15.17) had significantly more CEC inattention/hyperactivity behaviours than controls (M= 50.45, SD=11.27) on the neurobehavioural assessment, indicating that despite

poorer behavioural-level attention, visual attention was not affected. Thus, the eye-tracking tasks were suitable in this population. The percentage of inclusive trials and percentage of samples collected were not correlated with age - indicating that the eye-tracking tasks captured attention equally well at all ages, and analysis of the battery was applicable for the entire sample.

Of the 47 CWEOE and 41 controls who were able to carry out eye tracking, not all were included in each specific task analysis after exclusion criteria was applied (exclusion criteria detailed in section 12.5.4). Table 13.3 lists the number of children whose data were included in each task. The number of children included in data analysis for each task was highly variable, and was dependent on task specific inclusion/exclusion attentional demands for each task, which are detailed in each subsequent section below.

Table 13.3 Children included in analysis after exclusion criteria applied

Task	Included N (%)	
	CWEOE	Controls
Memory Task	32 (68)	21 (48)
Oculomotor Control Task	27 (57)	33 (80)
SNP Task	14 (30)	23 (56)
Social Preference Task	47 (100)	38 (93)
Face Scanning Task	46 (98)	41 (100)

14. Cognition/Memory Domain

The analysis of cognition in eye tracking was focused on memory, using a visual paired comparisons paradigm. This is described below.

14.1 Memory Task: Background

Memory problems are common in children with epilepsy (Menlove and Reilly, 2015), and have been found in children as young as three years of age (Danielsson and Petermann, 2009; Rantanen et al., 2010a). Problems have been found in both verbal and visual memory and occur across epilepsy syndromes (Fastenau et al., 2009), differing in severity (Jackson et al., 2013; Nolan et al., 2004). Memory problems in verbal children and adults are identifiable through anecdotal report, and via standardised self-report and performance assessment. In very young children it is more difficult to formally assess memory due to the immature development of executive functions, and verbal ability. The visual paired comparisons design (VPC) (Fantz, 1964) is one method by which memory can be partly assessed, and which has been successfully and commonly used in infants. VPC designs measure visual preference between sets of paired images, one familiar to the child, and one novel. Preference for the novel stimulus is thought to reflect successful memory encoding and retrieval of the familiar stimulus, as the visual system preferentially selects new information over known information. Performance on VPC designed tasks in infancy has been associated with working memory ability by age 11 (Rose et al., 2012), indicating the utility of the task as a predictive memory tool.

Memory ability is correlated with intelligence (Ackerman et al., 2005), and performance on VPC designed tasks may be potentially indicative of GCA. Indeed, novelty preference within the first year of life has been associated with developmental outcome by age two or three years of age (Rose et al., 2005), and IQ at 21 years (Fagan et al., 2007). Although these were moderate associations, indicating limited applicability, these results signify the usefulness of VPC design in assessing memory and GCA in very young populations where standardised and validated memory instruments are extremely scarce. Additionally, performance on VPC designed tasks are adversely affected in clinical groups such Down's Syndrome (Miranda and Fantz, 1974), and preterm infants (Rose, 1983; Rose et al., 2005), also signifying its use as a cognitive biomarker in clinical childhood populations of abnormal development.

The aim of the current study was to assess incidental recognition memory in CWEOE and controls, through preferential visual selection in a VPC eye-tracking task. And to assess if task could identify CWEOE with GCA (ages ≥1m) or memory impairment (ages ≥36m). Childhood epilepsy is often accompanied by speech/communication impairment or learning disability, and it was anticipated that some CWEOE may also have had these conditions. The VPC-based memory task selected for the current study was a novel and locally developed for a pilot study of typically developing infants (Gillespie-Smith et al., – memory task results unpublished). It was chosen because it did not require verbal instruction or direction, increasing its applicability and standard operating protocol across infants and other nonverbal children with epilepsy.

As epilepsy has a heterogeneous neurobehavioural profile, it was hypothesized that CWEOE would display a novelty preference but with a weaker preference compared with that of control children. It was also hypothesised that those CWEOE with GCA or memory impairment would exhibit weaker, or absent, novelty preference than other CWEOE.

14.2 Memory Task: Methods

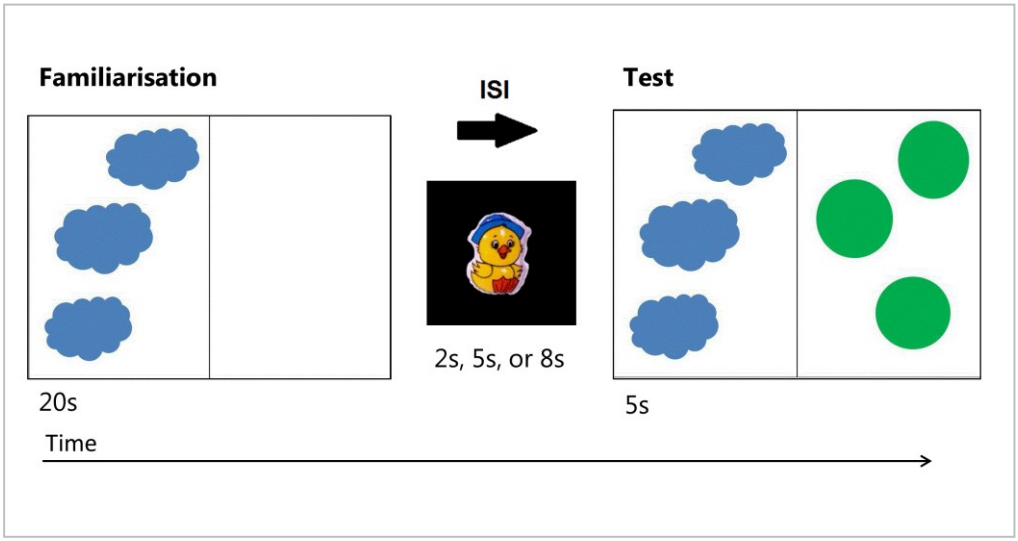
The original version of the Memory Task constructed by Gillespie-Smith and colleagues contained highly variable, and non-standardised, ISI timings. The task was then corrected to standardise ISI timings, and stimuli were modified to increase attention grabbing properties. This modified design substituted static images with animated images. Accordingly, data collected with the original design (pre-July 2014) were excluded, and only data from the modified design were used in the final analysis, and the design of which is described here.

The Memory Task followed a VPC design to assess eye-gaze preference for novel or familiar shapes. Each trial consisted of a familiarisation phase, where a set of three same-coloured shapes were presented, followed by an ISI of 2, 5, or 8 seconds to explore processing time (Gillespie-Smith et al., unpublished), and a test phase, where the familiar shapes were paired with novel shapes. The trial process is illustrated in figure 14.1. There were a total of 9 trials, allowing three trials per ISI delay, delivered across two blocks of the eye-tracking battery.

Stimuli were presented on a white rectangle (840x362 pixels), and the remainder of the screen border was black. Stimuli consisted of 18 different coloured angular or curved shapes (e.g. squares, rhombus, stars, or clouds). Familiar and novel objects were presented on one equal vertical half of the white rectangle. In the familiarisation phase one set of shapes was presented

continuously for 20 seconds to allow habituation (Frick and Richards, 2001). Shapes were presented on the left half of the white rectangle on five trials, and right in the remaining four, in a pseudorandom order across trials. Test phase included the familiar (habituated) shapes, with novel shapes presented on the contra half of the white rectangle. Location of familiar shapes remained constant across phases. Colour of familiar and novel shapes differed to aid visual discrimination. Each object animated (i.e. rotated or luminance faded then returned in cyclical manner) in turn sequentially from top to bottom and was paired with a non-distinct sound in order to promote the capture of attention. In test phases, objects in the familiar and novel categories animated in the same way and in the same sequence. Test phases lasted 5 seconds. Trials were manually ordered by ISI in order to minimise risk of attentional drop-off. Trials in block one consisted of ISIs at 2, 5, 5, 5, and 8 seconds, and 2, 8, 2, and 8 seconds in block two.

Figure 14.1 Memory Task



ISI – Interstimulus interval
s - seconds

Statistical analysis, AOIs, and metrics were described in section 12.5. Two dependent variables were acquired: (1) first fixation preference; which was the proportion of total trials where either the familiar or novel shapes were viewed first during the test phase, and (2) fixation preference; which was the proportion of total looking time toward the novel minus the familiar shapes. The former was considered a marker of attentional priority, and the latter, a marker of attentional importance. Analyses were conducted on all trials in the first instance, then

repeated for each ISI. Lastly, fixation preference was compared with neurobehavioural measures of memory (see section 12.4.7). Neurobehavioural tools assessing memory were only available for children ≥36m of age.

14.3 Memory Task: Results

Participants

32 CWEOE (68%) and 21 controls (48%) were included in Memory Task analysis. 7 CWEOE and 17 controls had completed the initial version of the Memory Task and were therefore excluded from analysis. 8 CWEOE and 3 controls who attempted the current version of the Memory Task, did not meet inclusion criterion (i.e. ≥33% of trials included). There were no significant differences in sociodemographic or clinical characteristics between those CWEOE who did, or did not, meet inclusion criteria.

Table 14 Group comparisons of GCA z-scores, and NEPSY II memory scaled scores

	GCA		*NEPSY II*			
	N	Mean (SD)	N	Memory for Designs	Narrative Memory	Sentence Repetition
CWEOE	30	**-.11 (.87)**	17	9.71 (3.29)	9.18 (2.88)	**9.00 (2.99)**
Controls	21	**.60 (.70)**	9	12.11 (4.51)	10.89 (3.14)	**11.75 (2.87)**

Emboldened p<.05

GCA and NEPSY II memory scores are reported in table 14. Control children had significantly higher GCA score (MD=-.70 (95% CI -1.16, -.24), p=.004), and Sentence Repetition (MD= -.2.75, 95% CI -.10, -5.40), p=.04), but comparable Memory for Designs and Narrative Memory.

First Fixation Preference

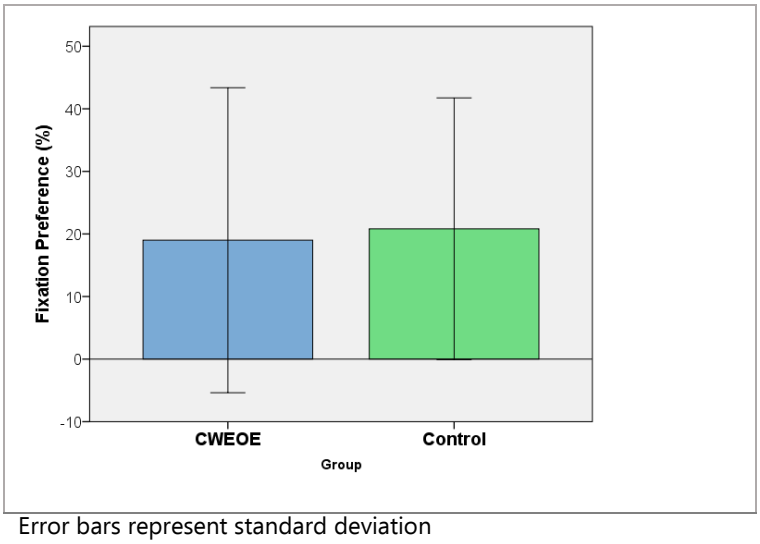
Across all trials, control children looked first more often toward the novel shapes compared to the familiar (M=65% vs 35%, p=.002), but CWEOE did not (M=55% vs 45%, p=.20). However, the between group difference was not statistically significant (MD= -19.89%, 95% CI [-42.15, 2.37], p=.08), indicating considerable variability in first look preferences. A significant positive correlation was found between the proportion of first looks to the novel stimuli and age in CWEOE (r_s=.60), but not in controls (r_s=.18) – reflecting a greater tendency in CWEOE to look

first at the familiar shapes during the first years of life, but a consistent preference for the novel shapes across age in controls. Exploration of ISI conditions revealed that the novelty preference exhibited in controls, but not in CWEOE, existed only at the 2s ISI. Here, controls looked first more often at the novel shapes compared to CWEOE (p=.02) - who displayed no clear preference. In the 5s and 8s ISI conditions, there were no significant within- or between-group differences in first fixation preference. There was no significant association with gender. To summarise, controls exhibited a first fixation preference toward the novel shapes but only at 2s ISI. CWEOE showed no first fixation preference toward novel or familiar shapes across ISI conditions, but did show a tendency toward looking first at the familiar shapes more often in infancy.

Fixation Preference: Across All Trials

CWEOE (M=19.00%, SD=24.38) and controls (M=20.82%, SD=20.91) spent a similar duration of time fixating the novel shapes compared to the familiar shapes (figure 14.2); MD= -1.83% (95% CI -14.84, 11.19). This equated to a mean total fixation duration toward the novel shapes of 59.5% for CWEOE, and 60.4% for controls, meaning that both CWEOE (t(31)=4.41, p<.001) and controls (t(20)=4.56, p<.001) displayed a novelty preference above chance levels. This signified successful memory recognition in CWEOE and controls. Across both groups, fixation preference was positively correlated with age at assessment (r_s=.38, p=.005), but was not associated with gender (MD=3.61 [95% CI -9.38, 16.59]), signifying increased attentional importance to novel shapes with increasing age.

Figure 14.2 Memory Task bar chart: Mean fixation preference

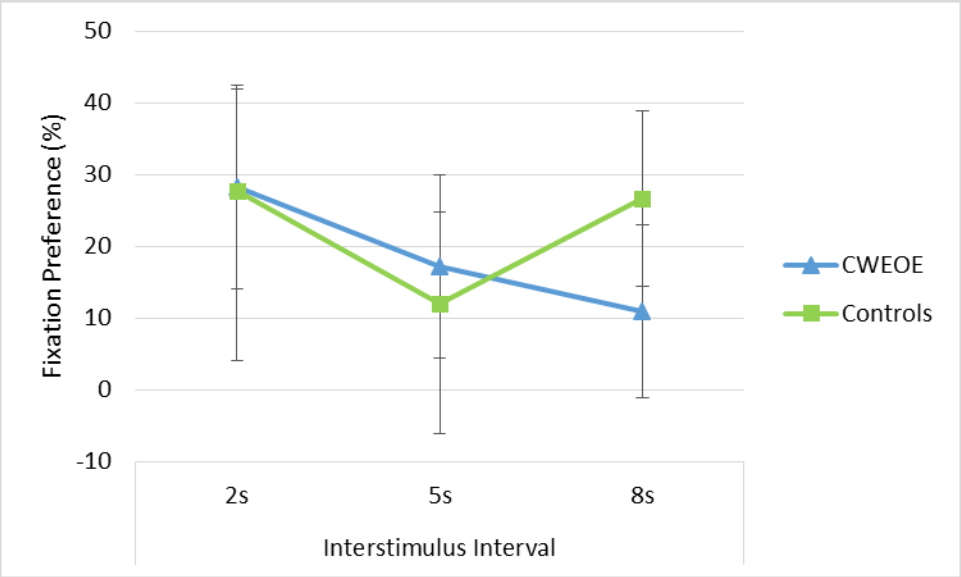


Error bars represent standard deviation

Fixation Preference: by ISI

Analysis of fixation preference at 2s, 5s, and 8s using a two-way repeated measures ANOVA found no main effect of group (η_p^2=.003), or ISI (η_p^2=.03), and no group*ISI interaction effect (η_p^2=.05), meaning that both CWEOE and controls displayed similar fixation preferences at each interval delay. Mean between-group difference in fixation preference at 8s ISI showed a trend towards statistical significance (MD=19.55%, p=.057) but confidence intervals overlapped implying significant within-ISI variability (figure 14.3). Fixation preference was highly similar at 2s ISI (MD=5.35%), and at 5s ISI (MD=6.36%).

Figure 14.3 Mean fixation preference by ISI



Error bars represent 95% confidence intervals

Within-group fixation preferences were directly assessed via one-sample t-tests. Both CWEOE and controls exhibited a significant novelty preference at each ISI, with the exception of CWEOE at the 8s ISI (t(31)=1.66, p=.11). Taken with the above, unlike controls, CWEOE had an absence of recognition memory at an interval of 8s, but a group difference was absent due to considerable variability in performance. The absence of novelty preference at 8s ISI is potentially suggestive that recognition memory differences may exist at larger ISIs in CWEOE. This could be explored in future research.

Fixation Preference and Neurobehavioural Data

As both CWEOE and controls showed a novelty preference across all trials, analysis was conducted on all children together. There was no correlation between fixation preference and GCA (n=51, r=.14, p=.33), even when age was controlled for (r=.07, p=.62). Additionally, there was no correlation between fixation preference and NEPSY II measures of memory in children ≥36m (n=26); Narrative Memory (r=-.27, p=.19), Sentence Repetition (r=-.25, p=.24), or Memory for Designs, although a moderate correlation was noted (r_s=-.38, p=.059). There were insufficient sample sizes of children who met criteria for GCA impairment or memory problems to make sub-group comparisons with fixation preference. Two CWEOE had GCA impairment, with fixation preference scores of -23.90% and 25.94%. One CWEOE had impairment in NEPSY II Memory for Designs, three on Sentence Repetition, and one on the Narrative memory, scoring 24.90, 32.09, and 32.98% respectively – scores above the CWEOE mean (19.0%). From the available data, the eye-tracking Memory Task does not adequately predict neurobehavioural measures of GCA and memory in the 0-4 year age group. As the task was originally designed for infants, it is unclear if a lack of relationship with GCA or NEPSY II measures of memory and fixation preference is due to ceiling effects, or because the task itself does not sufficiently tax memory or GCA in children ≤4 years. There were insufficient numbers of children <12m of age to explore relationships between fixation preference and GCA in infancy only.

14.4 Memory Task: Discussion

The Memory Task assessed incidental recognition memory through selective visual attention for familiar versus novel shapes. Contrary to expectations the results revealed that both control children and CWEOE displayed a novelty preference to a similar degree. This signified typical recognition memory over short periods of time. Despite a group difference in GCA, fixation preference between groups remained similar. There was no significant correlation between fixation preference and GCA, suggesting that fixation preference was independent of GCA. The correlation of .14 found here was weaker compared to that found in Rose et al. (2005) and Fagan et al. (2007). There are two possible contributing factors. First, Rose et al. and Fagan et al. included, in part or in whole, pictures of faces in their stimuli. Although debated (Gauthier et al., 2014), face recognition may involve unique neural correlates (Kanwisher et al., 1997), that may influence memory performance. Second, both studies assessed 6-12 month old infants on a VPC paradigm, whereas the NEUROPROFILES cohort were aged up to 59 months. Age-

related functional differences in face and object recognition are likely (e.g. Gathers et al., 2004), and age-related increases in task complexity may be required in order to negate ceiling effects and match cognitive ability to older children.

There was one subtle nuance noted in the Memory Task. There was a first fixation preference for novel shapes in control children at 2s ISI but not CWEOE – where controls viewed the novel image first more often than CWEOE. A first fixation novelty preference was absent in either group at 5s and 8s ISI, suggesting that all children needed to compare paired images and retrieve representations from longer term memory. Previous work has found sudden decay in short-term memory after approximately five seconds (Cowan et al., 1997; Ricker and Cowan, 2010), and in the current study, this might suggest that at a 2s interval control children maintained a visual representation of the familiar shapes in short-term memory, improving the accuracy of swiftly detecting the novel stimulus. This was absent in CWEOE and may indicate an extremely subtle deficit in the rate at which visual objects decay from immediate short-term memory.

There was a lack of correlation between performance on the Memory Task and neurobehavioural measures of memory, or GCA (GCA discussed above). There were limited sample sizes to robustly test the validity of the Memory Task to discriminate those CWEOE with cognitive impairment or memory problems. Based on the small number of results available, there was a lack of supporting evidence for any strong association. The lack of a strong and significant correlation between NESPY II memory scores and fixation preference suggests that this manifestation of the VPC task was not an adequate assessor of memory in children ≥36m. It should be noted that a moderate correlation was found between fixation preference and NEPSY II Memory for Designs. This might potentially indicate better task applicability to visual memory than memory or cognition as general constructs, as may be expected given the nature of the task.

Several factors should also be considered when considering the results of the Memory Task. Firstly, the Memory Task was made up of a small number of trials at each ISI (three in each), and there may have been insufficient trials to detect group or sub-group differences at different ISI delays. Secondly, the Memory Task was originally designed and developed for infants which raises the possibility that the Memory Task was too simplistic to detect memory problems in children up to four years of age. Indeed, memory development across infancy to early childhood involves changes in object representation (Ross-Sheehy et al., 2003), memory

span (Gathercole, 1999), and long-term memory (Hayes et al., 2002), and more complex design, or tasks with age-appropriate memory loading should be implemented. Lastly, CWEOE displayed a decrease in novelty preference with longer ISIs, with no novelty preference at the longest ISI. Although there was no statistically significant difference between CWEOE and controls, difficulties in long-term memory consolidation have been found in children with idiopathic epilepsy (Gascoigne et al., 2012), and it does raise the question of how memory performance in CWEOE could be affected at longer delays.

In conclusion, the Memory Task provided evidence that children up to four years of age display a novelty preference in a simple object-based VPC task. VPC based eye-tracking designs can therefore be successfully used in infants and preschool children with epilepsy. Visual recognition memory over very short delays is not impaired in CWEOE, although further research and evaluation is required with manipulation of experimental design, including increased trial volume, length of ISI, and age-appropriate memory loading. Nevertheless, the methods and results from the current study can be used as a platform from which to base future experimental design. Finally, eye-gaze behaviour assessment in children with epilepsy is a worthwhile pursuit given that cognition and memory is commonly impaired in children with epilepsy. There are limited memory measures in the early-onset age, and eye-tracking provides an accessible means of potential identification and assessment.

15. Attention/Inhibition Domain

Attention problems, including Attention-Deficit Hyperactivity Disorder (ADHD) are a highly prominent feature of childhood epilepsy (Chou et al., 2013; Davies et al., 2003; Reilly et al., 2014b; Rodenburg et al., 2005). ADHD is detectable in preschool children, and can persist into later childhood causing detrimental academic, functional, and social outcomes (Lahey et al., 2004; Washbrook et al., 2013). Similarly, other types of attention related functions, such as working memory (Reilly et al., 2015b; Myatchin and Lagae, 2011; Myatchin et al., 2009) and executive functioning (Hoie et al., 2006; Parrish et al., 2007; Pulsipher et al., 2009) are commonly impaired in childhood epilepsy, and impact social and academic achievement. Improving attentional control may produce positive cascade effects in related cognitive functions (Wass et al., 2012), providing significant justification for the early identification of attention problems in CWEOE.

Attention is a theoretical construct that consists of four broad processes (Knudsen, 2007): working memory, top-down sensitivity, competitive selection, and automatic bottom-up filtering. These processes are embedded in visual attention - as is eye biomechanics (Itti and Koch, 2001) – and here we are concerned with competitive visual selection. One important function of visual selection is inhibition. Inhibition refers to covert and overt processes that selectively impede areas of visual space, stimulus features, or prevent programmed eye movements, in order to allow the selection of competing targets (see Itti & Koch, 2001; Knudsen, 2007; Müller and Krummenacher, 2006, for reviews of selective attention). Inhibition of return, for example, is a well-known phenomenon whereby a previously attended location in visual space is covertly suppressed, leading to a delay in return to that location. An antisaccade is a top-down inhibitory mechanism of visual attention, involving prefrontal and parietal pathways (McDowell et al., 2002; McDowell et al., 2008; Schaeffer et al., 2013). In antisaccade paradigms covert attention is drawn toward a cue, and the observer must actively inhibit the ensuing reflexive saccade to that cue in lieu of a competing saccade in the opposite direction. Tapping into inhibitory aspects of visual attention is one potential avenue in eye-tracking research for detecting attention problems in CWEOE. Children with ADHD, for instance, show broad oculomotor control difficulties, particularly with saccadic inhibition (Karatekin, 2007). These can include premature saccades, and increased antisaccade errors (Karatekin, 2007).

To the candidate's knowledge, eye tracking has not been used to detect attention problems in children with epilepsy. In the NEUROPROFILES study, inhibitory aspects of attention were explored in CWEOE and controls using two inhibitory based eye tracking tasks. One, the Oculomotor Control Task, assessed inhibition of reflexive saccades, and production of antisaccades; and the second, the SNP Task, was a spatial negative priming paradigm where visual inhibition and simultaneous target selection was assessed. Performance on these tasks was related to neurobehavioural measures of attention and executive functioning.

15.1 Oculomotor Control Task

15.1.1 Oculomotor Control Task: Background

The Oculomotor Control Task assessed the inhibition of reflexive saccades and the production of antisaccades by following the paradigm and procedure described by Scerif et al. (2005). A reflexive saccade is an automatic shift in gaze toward a particular location or object. Children as young as 4 months can inhibit reflexive saccades (Johnson, 1995), which is a vital component of visual selection. Inhibiting a gaze shift to something in peripheral vision allows continued visual attention to be placed on a preferred stimulus, or to produce a shift in an opposing direction. Scerif et al. (2005) found that children from 8 to 38 months, like those in Johnson (1995), implicitly learned to inhibit saccades toward a peripheral cue across trials. The authors failed to find the same effect in children with Fragile X syndrome – a chromosomal disorder with increased risks of attention problems (Cornish et al., 2004) – which provided evidence that this task was successful in detecting atypical gaze behaviour in a clinical population of children with known attention problems.

As mentioned in the introduction to this section, inhibition of saccades and antisaccade production errors are commonly reported in children with ADHD (e.g. Munoz, 2003); and one of the goals of this study was to identify children with attention problems, including ADHD. Young infants do not produce antisaccades (Johnson, 1995; Scerif et al., 2005), but Scerif et al. (2005) found that toddlers did so from around 20 months of age. As well as inhibiting reflexive saccades toward the peripheral cue, the children in Scerif et al. produced antisaccades by using the cue as a signal to direct gaze toward the contralateral half of the screen in anticipation of a visual reward (i.e. coloured circle and cartoon animation). The children with Fragile X produced antisaccades despite difficulty with inhibition, indicating that the task could detect inhibition of saccades in addition to antisaccade production.

The authors suggested that Fragile X and ADHD share a commonality in that both disorders affect frontostriatal pathways. Similarly, frontostriatal pathway disruption has been proposed as a mechanism for executive dysfunction in temporal lobe epilepsy (Riley et al., 2011), whilst imaging studies of children with epilepsy and attention problems have also implicated frontal regions, as well as parietal and insular regions (Bechtel et al., 2012; Dabbs et al., 2013; Killory et al., 2011). Neurological deficits observed in children with epilepsy and neurobehavioural problems may echo those observed in those with problems but without epilepsy (Bechtel et al., 2012), suggesting that children with epilepsy and attention problems may display similar atypicalities in visual attention as children without epilepsy.

The task described in Scerif et al. (2005) was replicated for the current study for the reasons outlined here; it has been validated in infants and preschool aged children, including a clinical population of young children. The task targets inhibitory mechanisms of saccadic control, and the production of antisaccades – two factors known to be affected in those with attention problems. The task relies on implicit visual attention and learning, and is therefore suitable for young nonverbal and preverbal children. Thus, its administration can be standardised across the NEUROPROFILES cohort. Given that the cohort was heterogeneous in epilepsy characteristics as well as neurobehaviourally, it was hypothesised that CWEOE would display a less dramatic increase in inhibition of reflexive saccades across trials, and which would be related to behavioural measures of attention. It was also hypothesised that the number of antisaccades produced by CWEOE would be less than control children, and which would be negatively correlated with behavioural attention measures.

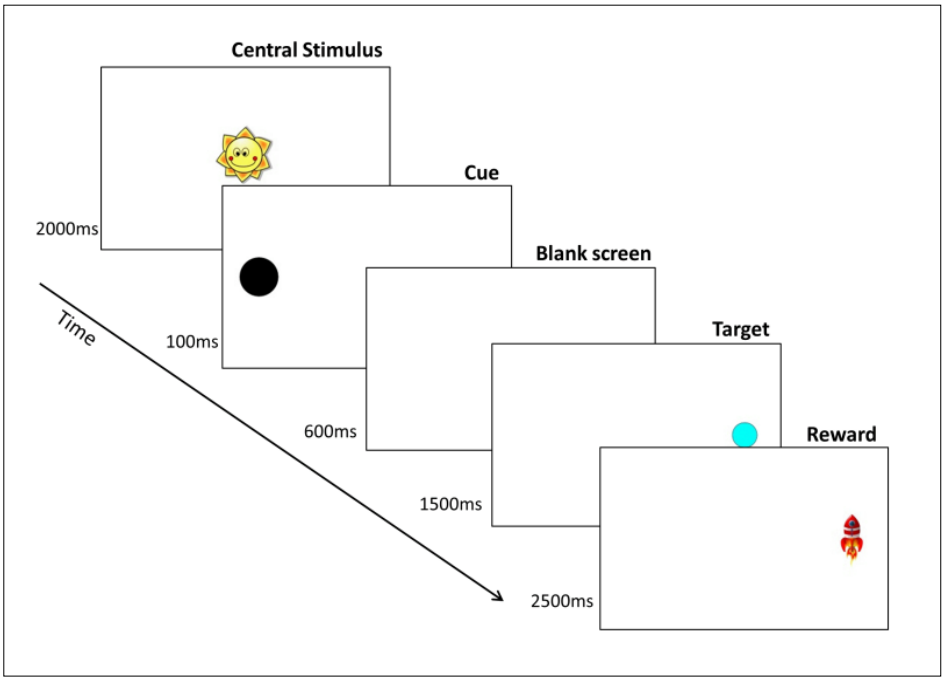
15.1.2 Oculomotor Control Task: Methods

The Oculomotor Control Task replicated the paradigm design and timing used by Scerif et al. (2005, adapted from Guitton et al., 1985). The task evaluated inhibition of reflexive saccades toward an unenticing cue by determining the change in proportion of overt looks toward that cue from one half of trials compared to the second half of trials. The number, and type, of saccades toward a contralateral salient target were also calculated. These included reactive saccades, corrective saccades, and antisaccades.

In replication of Scerif et al., each trial was made up of a central fixation stimulus, cue, target, and reward. Trial sequence is illustrated in figure 15.1, with each trial lasting 6700ms. The central fixation stimulus (i.e. bright cartoon sun with smiling face) appeared at trial onset on a

white background for 2000ms accompanied by a short beep sound, to orient the child's attention toward the centre of the screen. The stimulus, subtending 20° of visual angle, either rotated or zoomed in and out. A brief 100ms cue (black circle, 5.5°) appeared immediately post-central stimulus offset, 18° either to the right or the left of the central stimulus. A blank screen was presented for 600ms followed by the target (i.e. a coloured circle) which zoomed in and out (6°-9.25°) for 1500ms. The target appeared contralateral to cue presentation and was immediately followed by a colourful reward (i.e. cartoon image of an animal or object) subtending 20° and lasting 2500ms. The reward was paired with a sound (e.g. clapping, car horn, animal noise). On half of trials the cue was presented on the right side, and half on the left, with target and reward on the contralateral half. Each subsequent trial was presented immediately following reward offset. Trials were presented in a randomised order across participants to negate any ordering bias.

Figure 15.1 Oculomotor Control Task: trial sequence



The task paradigm and timing replicated Scerif et al., whilst the individual stimuli and trial animations were constructed by the candidate, following the same structure (i.e. circles, child-friendly rewards, etc) set out by the authors. Nineteen reward stimulus images were selected and downloaded from http://all-free-download.com/. Child friendly images that were colourful, enticing, and recognisable were chosen by the candidate. Cue and reward stimuli

were designed, and individual animations (i.e. rotating or zooming stimuli) were built, in paint.net (v3.5), and animated using Windows Movie Maker (v16.4). Each trial was then converted to AVI movie format. Stimuli size was determined based on degrees of visual angle reported in Scerif et al. Target stimuli colour varied to promote attention.

Scerif and colleagues used 32 trials with an average loss rate of 5 unusable trials per child. The minimum number of trials required for analysis in their study was 12. The number of total trials in the current study was reduced to 24 in order to attain a reasonable 50% trial-target minimum while reducing overall test load. All 24 trails were viewed consecutively in one block.

General statistical analysis was described in section 12.4.6. To assess inhibition of reflexive saccades, the dependent variable was the change in percentage of trials with a saccade toward the cue, as determined by a fixation on the cue AOI, from the first half of trials to the second half (i.e. % of cue looks in second half of trials - % of cue looks first half of trials). As the number of successfully completed trials varied between participants (see section 12.4.4 for criteria), the halves were based on the total number of trials per individual. When there was an uneven number of trials, the last trial was excluded. The type of saccade (reactive, corrective, or antisaccade), and proportion produced, toward the target was also ascertained, with particular focus on antisaccade production. An antisaccade was an anticipatory look toward target up to 100ms post target onset (Scerif et al.) without a preceding look toward the cue. A corrective saccade was a look toward the cue followed by a look toward the target up to 100ms post onset. A reactive saccade was a look toward the target preceding a look toward the cue. Analysis was planned for the percentage of cue change, and proportion of saccades produced, between groups (CWEOE versus controls), as well as the relationship between performance and age, and neurobehavioural scores on tools of attention and executive functioning (see section 12.4.7 for tools used).

15.1.3 Oculomotor Control Task: Results

Participants

27 (19M:8F) CWEOE (57% of total N), and 33 (15M:18F) controls (80% of total N), were included in analysis. CWEOE, median age 37.85 [IQR 17.25 – 51.19] months, and controls, median age 25.96 [IQR 16.51 – 50.18] months, did not statistically differ in age (p=.67, r=.06) or gender (p=.07). CWEOE had poorer GCA (MD= -.67 [95% CI -.21, -1.14], p=.006). GCA was not

significantly correlated with the main outcome variable, change in cue looks (r= -.03), and was therefore not factored into between-group analysis as a control variable.

Of the 20 CWEOE who did not reach inclusion criteria, 13 (65%) had <12 scorable trials, and 7 (35%) had <40% looks toward cue in the first half of trials. There was no difference in age (p=.98, r=.003), gender (FET=.76), or GCA (MD= .32, 95% CI [.86, -.22], p=.23), between those CWEOE who were or were not included in analysis. Additionally, there were no differences in their clinical characteristics; aetiology (1989 or 2010 ILAE classifications), seizure frequency, seizure origin, MRI status, EEG status, number of AEDs, or GCA impairment. The reason why some children did not meet inclusion criteria could not be attributed to general attention to this specific task. The average total fixation duration to the stimuli (MD=.63 [95% CI -.24, 1.50] seconds, p=.15), and average number of fixations per trial (MD=1.48 [95% CI -.23, 3.18, p=.09]), were not significantly different between those who met or did not meet criteria. All CWEOE had adequate visual field assessment, therefore, it is plausible that CWEOE who did not meet inclusion criteria simply did not, or could not, adequately maintain attention to the task animation sequence often enough. In other words, they were more likely to disengage from key elements of the trial and look elsewhere, and thus meet exclusion criteria.

Of the 8 control children (median age 30.62 [IQR 9.35 – 42.60] months), who were not included in analysis, 6 (75%) had <12 scorable trials. Two (25%) controls completed an earlier version of the task which had a technical fault with playback and which could not be scored. There was no significant demographic differences between controls who were or were not included in analysis; age (p=.66, r=.07), gender (FET=1.0), or SES (FET=1.0).

Inhibition of Reflexive Saccades: Percentage Change in Cue Looks

CWEOE and controls looked less often at the cue in the second half of trials compared to the first (table 15.1). A two-way mixed ANOVA revealed a significant main effect of trial half (F (1,58)=13.89, p<.001, η_p^2=.19), but no main effect of group (η_p^2=.003) or interaction effect (η_p^2=.015). That is, both groups of children implicitly learned to inhibit reflexive saccades toward the cue to a similar degree.

Table 15.1 Percentage of trials with fixations on cue

	First half trials mean % (SD)	Second half trials mean % (SD)
CWEOE (n=27)	69.37 (16.49)	60.5 (24.23)
Controls (n=33)	74.04 (17.08)	59.23 (19.09)

The percentage change in looks toward the cue across trial halves was not significantly associated with gender (MD=9.20% [95% CI -3.43, 21.84]). Scerif et al. (2005) found a significant correlation between increasing age and a reduction in cue looks during the second half of trials in their analysis – signifying improved saccadic inhibition with age. However, no correlation was found between age and percentage of cue looks in the second half on trials in the present study (r_s= -.19, p=.15), nor was there a correlation present between age and percentage of cue change (r_s=-.02, p=.91 [group comparison illustrated in figure 15.2]) – which took individual performance into account.

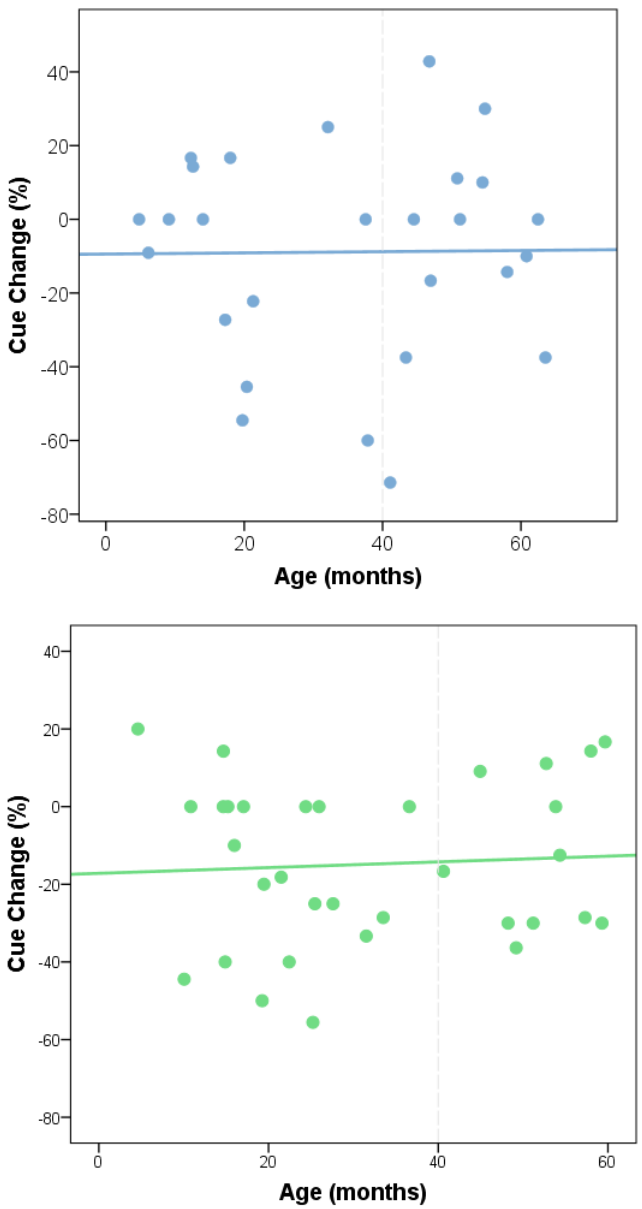


Figure 15.2 Scatterplot: Age and percentage cue change by group

A comparison of cue change from first half of trials to second half in CWEOE (blue), and controls (green). Negative direction indicates a decrease in cue looks from first half of trials to second half of trials. Dashed vertical line references age 40m.

The reason for this between study discrepancy is unclear, although the present study had a slightly larger sample size, and included children up to 63m, compared to 38m in Scerif et al. When only children <40m were included in analysis, there was a moderate but significant correlation of rs=-.35, p=.04 (n=35), indicating that decreasing cue looks were moderately associated with increasing age. This result suggests that the Oculomotor Control task may be more sensitive to age changes in children <40m. Children >40m exhibited a decrease in looks toward the cue in the second half of trials (65.9% to 56.9%) albeit non-significantly, on account of looking less toward the cue during the first half of trials. It is important to note that two-way ANOVA measuring cue change from the first to second half of trials, and the associations with neurobehavioural tools (described below), using only children <40m, were repeated with no change in findings. This indicates that the task remains suitable for the children in this cohort, but may be more demanding on inhibitory mechanisms in younger children.

Inhibition of Reflexive Saccades: Relationship with Neurobehavioural Tools

Percentage change in cue looks was not correlated with psychometric scores on neurobehavioural tools measuring attention and/or executive functioning (table 15.2) – meaning that the degree of reflexive saccadic inhibition was not a marker of the behavioural manifestations of attention or executive function, as measured by these neurobehavioural tools.

Table 15.2 Correlation coefficients for cue change and attention/executive functioning scales

Age	*12-23m*	*≥24m*	*≥24m*	*≥24m*	*≥36m*
Tool	ITSEA Externalising (n=20)	CEC Restless Index (n=31)	CEC Inattention/ Hyperactivity (n=31)	PBRIEF GEC (n=33)	NEPSY Statues (n=26)
Coefficient	r_s= .07	r= .11	r= .10	r= .03	r_s= -.27

BRIEF GEC – Behaviour Rating Inventory of Executive Function General Executive Composite

CEC – Conners Early Childhood

ITSEA – Infant Toddler Social Emotional Assessment

NEPSY – Developmental Neuropsychological Assessment

Similarly, percentage cue change on the Oculomotor Control Task was not significantly associated with executive functioning or inattention/hyperactivity problems (table 15.3). The number of children classified with a neurobehavioural problem in attention/hyperactivity or executive functioning was small, and larger sample sizes are required to adequately assess the

Oculomotor Control Task as an identification tool for attention or executive problems. Nevertheless, based on the data here, the Oculomotor Control Task was not sensitive enough to discriminate children with attention/hyperactivity or executive functioning problems. No child included in the Oculomotor Control Task met criteria for an ITSEA externalising problem, whilst only one child had cognitive impairment. As such, no further analysis could be completed using those tools.

Table 15.3 Percentage cue change in those with/without neurobehavioural problems

Domain	Neurobehavioural problem	N	Mean	MD	95% CI
Executive Functioning †	No	29	-16.17	-21.72	-47.75, 4.30
	Yes	4	5.56		
Inattention/hyperactivity ‡	No	24	-12.86	-5.83	-27.06, 15.40
	Yes	7	-7.03		

† P-BRIEF General Executive Composite

‡ Conners Early Childhood Restless Index or Inattention/Hyperactivity scale

Saccades Toward Target: Reactive, Corrective, and Antisaccades

Contrary to Scerif et al. (2005), CWEOE and controls here did not produce antisaccades or corrective saccades (<1% across all trials). Children invariably produced reactive saccades toward the target, suggesting that they did not implicitly learn the association between target and cue locations, or that they did learn this association but could not produce corrective or antisaccades.

Table 15.4 Median latency to target (seconds)

	1st half trials Median [IQR]	2nd half trials Median [IQR]	Wilcoxon p-value (r)
CWEOE (n=27)	1.38 [1.15 – 1.78]	1.66 [1.26 – 2.50]	.009 (.34)
Controls (n=33)	1.37 [1.18 – 1.59]	1.48 [1.32 – 1.66]	.20 (.16)

Time to target was expected to be longer during the second half of trials as reflexive inhibition improved, and antisaccades were produced – viz through additional steps in saccadic programming. The latency to target [from cue onset] for CWEOE and controls is listed in table 15.4. Both CWEOE and controls took longer to fixate on the target location in the second half of trials compared to the first. This was significant in CWEOE only, but there was no significant difference in latency change between groups (U=370.5, p=.27, r=.14), indicating the strength of the difference was small. In contrast, when only children <40m were included, the difference in latency between groups was significant (U=85.5, p=.04, r=.35). As only reactive saccades were produced, the additional latency in time to target in the second half of trials could be attributed to the impact of reflexive inhibition, meaning that reflexive inhibition came at an increased cost in the production of a subsequent saccade in CWEOE <40m.

Summary

CWEOE and control children exhibited a reduction in saccades toward the cue from the first half of trials to the second half of trials – indicating an increase in inhibition of reflexive saccades. Cue change was not correlated with age, except when only children <40m were considered. Additionally, the time to target was significantly longer during the second half of trials in CWEOE <40m of age, compared to controls, suggesting that inhibition came at an increased cost to CWEOE <40m. Whilst reflexive inhibition was not affected by the age of this cohort, the results in children <40m suggest the Oculomotor Control task may be more demanding in this age group, and thus, more appropriate. Contrary to Scerif et al. (2005), CWEOE and controls did not produce antisaccades at any age. Lastly, the Oculomotor Control Task was not associated with neurobehavioural scores, or children with neurobehavioural problems signifying that this visual attention based task was not directly related to attention or executive functioning at the behavioural level, as measured by these neurobehavioural tools.

15.2 Spatial Negative Priming (SNP) Task

15.2.1 SNP Task: Background

A basic facet of the human visual system is the ability to inhibit particular regions of visual space and instead attend to more preferred locations. SNP describes paradigms in which saccadic latencies are slower, or less accurate, to spatial locations which have been actively supressed. In SNP paradigms a target object and distractor are presented in a prime display, whilst in a subsequent probe display the target object is located either in a new spatial location

(control trial), or in the previously ignored space occupied by the distractor during the prime display (repeated distractor trial). The reasons for this location-related negative priming effect are not well understood (Frings et al., 2015) but hinges on inhibitory mechanisms or retrieval mechanisms.

SNP effects have been evidenced in infants from 9 months of age and in adulthood (Amso and Johnson, 2005; Amso and Johnson, 2008; Wright et al., 2005). SNP appears to function normally in those with ASD (Brian et al., 2003) but it is unclear if children with attention or executive functioning difficulties display atypical negative priming. ADHD is a disorder conceptualised by an impairment in the ability to inhibit responses or control conflicting responses (Barkley, 1997). There are mixed-results in non-spatial visual-auditory negative priming in ADHD (e.g. Gaultney et al., 1999; Nigg et al., 2002), that may be potentially and partially explained by the presence of other comorbid conditions (e.g. mood or conduct disorder) (Pritchard et al., 2008). As spatial-based and identity-based negative priming may involve different mechanisms (Frings et al., 2015), it may be useful to explore SNP in children with ADHD or other attention related difficulties. As mentioned previously, epilepsy commonly involves attentional (Rodenburg et al., 2005), and executive difficulties (e.g. Parrish et al., 2007), with a high prevalence of ADHD (Chou et al., 2013). In the present study SNP was explored in CWEOE compared to controls, and it was hypothesised that CWEOE with attention difficulties would display a marked reduction or absence of SNP.

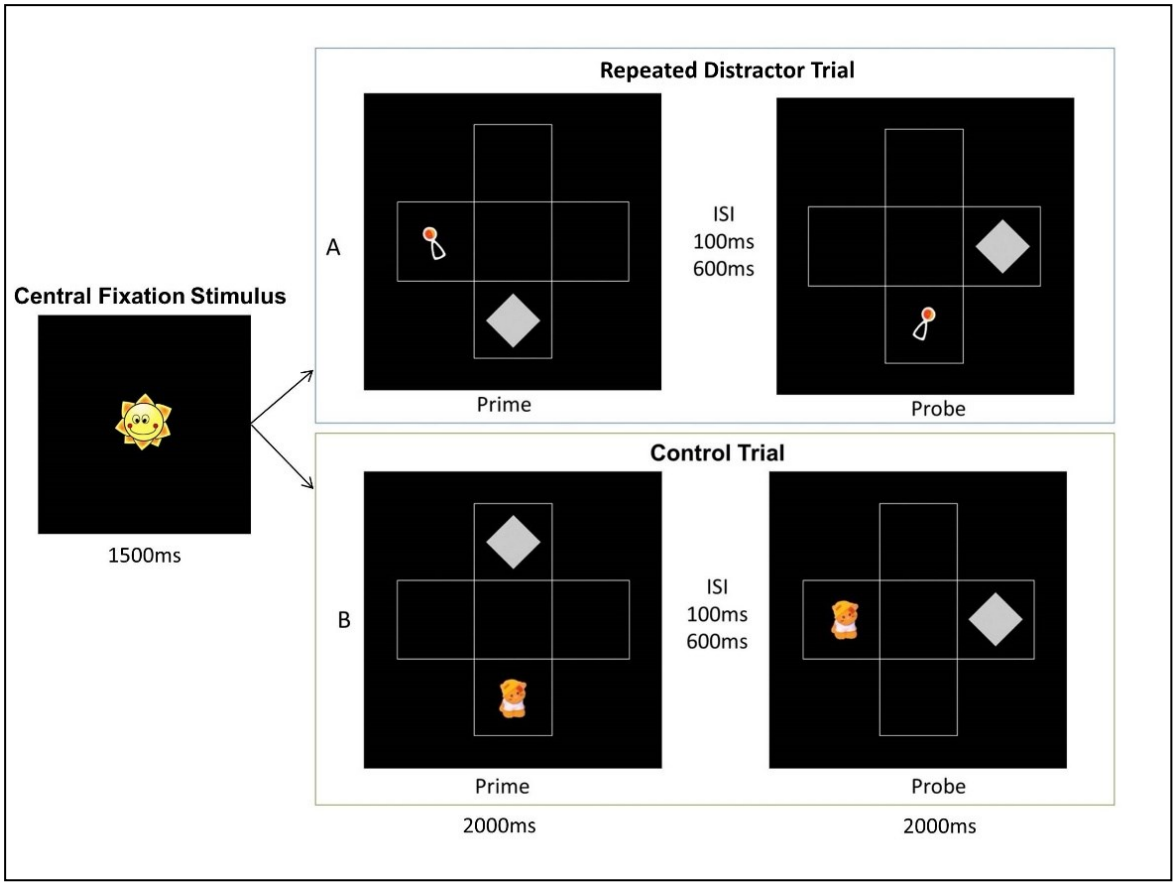
Therefore, the objectives of the SNP task in the current study were to: (1) determine if CWEOE display atypical SNP compared to controls, and (2) explore the relationship between SNP and behavioural manifestations of attention and executive functioning as measured by neurobehavioural assessment tools.

15.2.2 SNP Task: Methods

The SNP task in the current study was a procedurally modified version of the paradigm created by Amso and Johnson (2005; 2008), designed to extend their findings in 9m old infants and adults to typically developing children 0-4 years of age, and in a cohort of CWEOE. In this task, children and adults viewed a 2D grid with a target and distractor. There were two displays during each trial, a prime and a probe. In the prime, a target and distractor were presented in a grid, before the target shifted to a new location in the probe display. There were two types of trial; a control trial where the target moved to a previously unattended location, and a

repeated-distractor trial where the target moved to the location previously occupied by the distractor. Amso and Johnson found slower latencies to repeated-distractor trials, illustrating spatial negatively priming.

Figure 15.3 Spatial negative priming repeated distractor and control trials



ISI – Interstimulus interval

The SNP Task stimuli and procedure in the current study were replicated from Amso and Johnson, and is visually illustrated in figure 15.3. At the beginning of each trial a central fixation stimulus (i.e. bright smiling cartoon sun) was presented for 1500ms to orient the child to the centre of the screen, and to signify a new trial. The central fixation stimulus subtended 20° degrees of visual angle and either rotated 360° or zoomed in and out. In the prime display, children freely viewed the 2D grid (each of the 4 target grids were 7cm^2, with total grid size of H21cm x W21cm,) with target object (e.g. animated cat, bus, or rattle, subtending 18-20° degrees of visual angle) and distractor (i.e. unanimated grey diamond, 20° degrees of visual angle). Amso and Johnson did not include a distractor in probe trials, but it was retained here

to fit in line with similar methods employed in other SNP paradigms. In the probe, the target and distractor shifted grid locations to previously unoccupied locations (control trial), or the target shifted to the location previously occupied by distractor (repeated-distractor) while the distractor shifted to an entirely new location. Prime and probe displays were presented for 2000ms each and were separated by an ISI comprised of a blank black screen.

There were 32 trials in total; 16 repeated distractor trials and 16 control trials. Trials were divided equally into the two ISI conditions of 100ms or 600ms. Amso and Johnson (2005; 2008) originally presented 48 trials, exploring three ISIs of 67, 200, and 550ms. Given the overall heavy task load on children in the current study, an effort was made to reduce the overall number of trials by selecting only two ISIs. In their study, 9m old children did not display an SNP effect at the 67ms ISI but did so at 200 and 550ms. For the current study an ISI of 100ms, the lowest interval possible using Tobii Studio, was selected, together with an upper ISI of 600ms (Amso, personal communication 29/05/2013). As an SNP effect was found at 550ms, it was expected to be found at 600ms. It would be unlikely that a difference of 50ms would negate an SNP effect, given that inhibition of return lasts over 1000ms (Klein, 2000). Children were exposed to both ISI conditions to explore between-group and repeated measures performance across ISI conditions.

Stimulus design was derived from Amso and Johnson (2005). Animated target objects were uploaded from Tobii Studio, and were the same as those used by Amso and Johnson. The central fixation stimulus was downloaded from http://all-free-download.com/, and was chosen by the candidate based on its bright, colourful, and child-friendly enticing nature. The grid and distractor were created by the candidate, mimicking Amso and Johnson, using paint.net (v3.5), Microsoft Powerpoint 2010, and animated in Windows Movie Maker v16.4. Files were converted to AVI format for use in Tobii Studio.

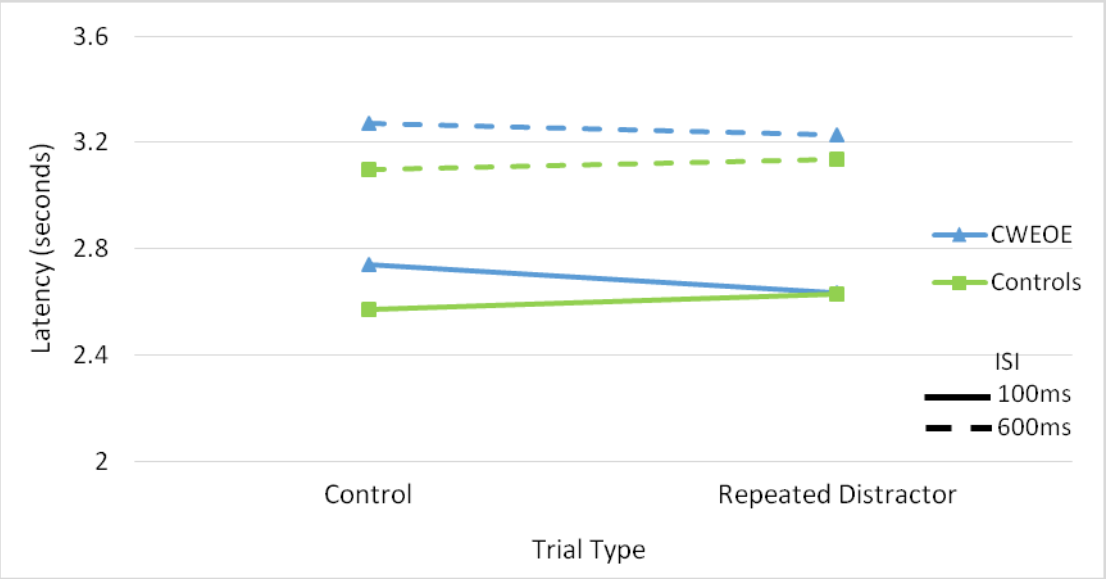
General statistical analysis was described in section 12.4.6. The dependent variable was latency to target in the probe display in the control trial compared to the repeated distractor trial. Wilcoxon signed rank tests were used to compare within-group differences in target latency due to skewed data. Between-group (i.e. CWEOE vs controls) differences in latency to target, within each ISI condition, were carried out by subtracting the control trial latency from the repeated distractor trial latency, and applying Mann-Whitney U tests. Within- and between-group performance was determined for both 100ms and 600ms ISI conditions. Correlations

were also planned between latency to target and performance on attention and executive functioning behavioural tools described in section 12.4.7.

15.2.3 SNP Task: Results

Preliminary analysis of 14 CWEOE and 23 control children revealed a high percentage of trial exclusion following inclusion/exclusion criteria (see section 12.4.4). The percentage of trials included in analysis was considerably lower in CWEOE (Median=31.25%) and controls (M=59.38%) than the average of the remaining four tasks (Median=79.19% and 83.33%, respectively). This potentially indicated age inappropriateness of the task, and/or poor ability to capture and maintain attention. Observationally, children were less attentive to the overall eye-tracking battery and displayed more signs of fatigue and irritation (e.g. fidgeting, getting out of seat, verbal complaints). For these reasons, and given the large assessment battery, the SNP Task was discontinued, and no further data was collected. Analysis of excluded trials found no significant between-group differences in the reasons for trial exclusion, although percentage of probe displays that were not attended to at all was moderately higher in CWEOE (68% [IQR 51.42, 77.38]) compared to controls (52% [IQR 29.13, 66.67]); p=.054, r=.32.

Figure 15.4 Median latency between control and distractor trials



Latency was measured from trial onset

Based on the data collected, there was no SNP effect identified in CWEOE or controls. That is, latency to target was not significantly different in the repeated distractor trials compared to

the control trials in either ISI condition (figure 15.4). This was in contrast to Amso and Johnson (2005; 2008). Additionally, there was no significant between group difference in the change in latency to target from control trial to repeated distractor trial (i.e. control trial latency – repeated distractor trial latency) (table 15.5). Nor was there a significant correlation with age and change in latency to target in either ISI, in CWEOE or controls. In other words, performance on the SNP Task was similar between CWEOE and controls. Analysis with neurobehavioural tools were not completed due to an absence of SNP.

Table 15.5 Change in latency to target in SNP Task (milliseconds)

	ISI Condition	
	100ms Median (IQR)	600ms Median (IQR)
CWEOE (n=12)	90 (-328, 333)	170 (-170, 280)
Controls (n=23)	-40 (-130, 60)	35 (-150, 240)
*Group comparison p-value (r)	.35 (.16)	.62 (.09)

*Mann-Whitney test

15.3 Attention/Inhibition Discussion

Two eye-tracking tasks were used to explore inhibitory mechanisms of visual attention in CWEOE compared to typically developing controls, and to relate potential atypicalities in visual attention to attention/hyperactivity and executive functioning at the behavioural level. Findings revealed that CWEOE and controls produced comparable results in both eye tracking tasks, and which were not associated with neurobehavioural measures of attention and executive functioning, where applied. That said, the SNP Task failed to elicit SNP in control children or CWEOE, which may have been due to task inappropriateness for this age group. Therefore, an understanding of the functioning of SNP in CWEOE remains unclear. Several other issues arose from the study and will also be discussed; the first was a lack of relationship between the Oculomotor Control Task and neurobehavioural tools. The second was an absence of antisaccades during the same task. And thirdly, as mentioned above, the SNP Task did not elicit a negative priming effect in controls or CWEOE. These latter two issues have may have implications for previous and future research using these tasks. Interestingly, subtle

abnormalities in gaze behaviour were noted in CWEOE during both tasks, but which were not derived from the intended design of the task. These are also discussed further below.

CWEOE displayed inhibition of reflexive saccades to a similar degree as controls during the Oculomotor Control Task. This was expected in this CWEOE cohort given its heterogeneous clinical and neurobehavioural presentation. However, task performance was not associated with neurobehavioural measures of attention/hyperactivity or executive functioning, contrary to expectation. This meant that inhibitory aspects of visual attention, as measured by these particular eye-tracking tasks, were not directly related to functioning at the behavioural level. This was a prospective study, and one of the major limitations as a result, was a small number of children who met criteria for an attention/hyperactivity, or executive functioning, problem being enrolled for the study, and having successful eye-tracking. Nevertheless, correlations with test measures were small, corroborating evidence of weak relationship. There is another caveat to consider when interpreting a lack of relationship between the Oculomotor Control Task and neurobehavioural tools. Inhibition errors have been associated with ADHD, yet it is unknown if the children who met criteria for an executive functioning problem or attention/hyperactivity problem in this sample would also have met clinical criteria for ADHD. It is possible that attention difficulties in this sample may be different in their neural underpinnings compared to classic ADHD. Therefore the task may not have been suited to detecting attention difficulties in this population.

An unexpected finding from this study was that antisaccades were not produced in the Oculomotor Control Task in typically developing control children (or CWEOE) - a contradictory finding to that of Serif et al. (2005). The reason for this is unknown, although differences in data collection may be a possibility. Scerif et al. recorded and coded gaze direction through video recordings of eye movements. This method may be liable to human error. However, interrater reliability - on a sample of trials - produced a Cohen's Kappa coefficient of 1.0 (Scerif et al. 2005), and is unlikely to be the explanation. The natural development of antisaccades during childhood is unclear, although there is evidence that development remains immature even by five or six years of age (Munoz et al., 1998; Munoz, 2003), and does not reach adult levels until adolescence (Munoz et al., 2003). The eye movements detected in Scerif et al. may, possibly, not have been antisaccades. Because video coding relies on the physical direction of a moving eyeball to donate gaze direction and point of regard, these movements may have reflected microsaccades rather than true saccades. Microsaccades can have the same amplitude as a typical saccade, and typically occur horizontally in humans, but have extremely

brief fixation durations (Martinez-Conde et al., 2009). Therefore, it is unclear if the antisaccades produced in Scerif et al. were true anticipatory saccades or involuntary brief oculomotor shifts. The authors found a positive correlation between the number of antisaccades and age, suggesting that eye movements were occurring in response to developmental maturity. However, microsaccades also increase with age (Port et al., 2016). The fixation duration parameter used in Tobii Studio for the current study (i.e. ≥60ms) would not have recorded a typical microsaccade, and may explain the difference in findings. Alternatively, it is also plausible that an infant's or preschooler's anticipatory saccade may take a different form than that of older children or adults, and the contradictory results found here as compared to previous work advocates the need for further clarification on antisaccade production in infants and young children.

It is unclear why an SNP effect was observed in Amso and Johnson (2005; 2008) but not in the current study. Our task differed from that of Amso and Johnson, in that the distractor was presented in the probe condition. Previous research has reported quicker latencies toward probe target in repeated distractor trials in the absence of a distractor compared to its presence (Neill et al., 1994). One explanation, therefore, may have been a weaker negative priming effect in the presence of the probe distractor. However, negative priming may still have been expected (Neill et al., 1994), yet no trend was observed. Another potential explanation may have been due to the relaxation of selection state (Tipper and Cranston, 1985). The selection state is when there is a balance of excitatory and inhibitory processes that keep one spatial location supressed, and another activated. Relaxation of the selection state may have occurred given that the probe distractor could be easily distinguished from the target, which may not have provided sufficient excitation to maintain the state. The SNP Task was validated in infants and adults (Amso and Johnson 2005; 2008), and its validity in preschool aged children had not been attained. A third reason for an absence of SNP might simply be explained by task unsuitability in toddlers and preschool aged children. There were not enough infants under one year of age to provide age sub-group analysis, but the low number of successful trials leading to the discontinuation of the SNP Task may be an indicator that the task did not capture attention in the intended way. The stimuli or process may not have been exciting enough for this age group, or not novel enough to maintain sustained attention. As explained in the methods section, the sight change in ISI timings were not expected to negate SNP, but this cannot be definitively ruled out.

Signs of potential attention deficits in CWEOE were found during the SNP Task and Oculomotor Control Task. Neither related directly to the original aims of the paradigms, and therefore explanation of their causes and interpretations are limited. Nevertheless, they do highlight possible deficits in attention that may form the basis of future experimental design. The SNP Task was discontinued after preliminary analyses revealed a low trial success rate. That rate was considerably lower in CWEOE compared to controls. This should not have been expected given that general attentiveness to the remaining four tasks of the battery were comparable between CWEOE and controls (section 13.3). The SNP task had more stringent trial exclusion criteria than other tasks on account of its design, and necessity to maintain sustained and sequential attention across prime and probe displays. Although marginally non-significant, CWEOE looked less at the probe display than controls, suggesting that the trial length and/or ISI was enough to cause sufficient distraction to disengage from the stimulus or disrupt underlying processes. This is suggestive of a difficulty in sustained attention, a component of attention commonly reported in children with epilepsy (Kavros et al., 2008; Killory et al., 2011; Sanchez-Carpintero and Neville, 2003). This finding was not reflected in the analysis of general attention to the trials and eye tracking battery because three of the remaining four tasks (Memory Task, Social Preference Task, and Face Scanning Task) did not rely on sustained sequential attention, and were unaffected by off-AOI or off-screen fixations. In a similar manner to the SNP Task, a greater number of CWEOE were excluded from the Oculomotor Control Task analysis than control children. Exclusion criteria in this task was also based on sustained attention across sequential within-trial stimuli presentation. The exclusion criteria here were less stringent than the SNP Task, and did not have the same level of trial dropout. But the pattern observed across these two tasks suggests a possible impairment in sustained visual attention in CWEOE.

A second potential abnormality in visual attention identified in CWEOE was found in the Oculomotor Control Task. CWEOE <40m took significantly longer to fixate the target in the second half of trials compared to the first, whereas control children did not. Coupled with increased inhibition of reflexive saccades toward the cue, longer latency to target was explained as a function of the additional information processing step involved in cue inhibition. As only reactive saccades were observed, the slower latency to target may have been explained by a need for additional time to either program or execute the saccade toward target. This finding is tentative given the task design was not created to specifically address that question, but could be explored more directly in future research. Relatedly, slower processing speed has

been reported in children with epilepsy (Reilly et al., 2015b; Sherman et al., 2012), which would lend support to this finding.

The findings presented here are based on exploratory work in a heterogeneous population of CWEOE. Therefore the results are limited in their interpretability to specific epilepsy syndromes, who may present with component specific deficits in attention (Sánchez-Carpintero and Neville, 2003). As stated above, this was a prospective cohort of CWEOE, who were assessed for behavioural level attention and executive problems using, primarily, behaviour rating scales. There is only moderate correlation between performance-based and rating-based measures of attention (Mahone, 2005), and it remains to be seen if the Oculomotor Control Tasks draws closer relationship to performance-based tools. One performance-based tool used in the current study (NEPSY II Statues) was only applicable to children ≥36m old and showed a stronger, albeit non-significant, moderate correlation. Attention tools are very limited in preschool aged children, particularly in children under four years (Mahone, 2005; Mahone and Schneider, 2012). But it may be of interest to replicate the study in a verbal preschool population with performance-based measures of attention. This would have an additional benefit. The Oculomotor Control Task paradigm was not an antisaccade task in the classic sense, in that children were not told to look in the opposing direction from the cue. Replicating the task, or other antisaccade paradigm, with verbal children would allow further exploration of antisaccade generation in children with epilepsy and its relationship with rating or performance-based measures of attention and executive functioning.

In conclusion, the attention/inhibition based eye-tracking tasks used in the current study had mixed success. Reflexive inhibition was found in CWEOE and controls but not antisaccades, whilst the SNP Task was discontinued due to poor attention, and did not elicit SNP. Nevertheless, the tasks have highlighted some potential areas of further investigation in CWEOE. Furthermore, the tasks raised issue with the measurement of antisaccade production in typically developing children that requires further investigation. In spite of some limited methodological differences in the eye-tracking tasks applied, the methodological points raised in this study, namely age-appropriateness of paradigm design, probe distractor placement in SNP design, and eye gaze recording methods may be of interest to visual attention researchers.

16. Social Cognition Domain

There is no clear and agreed upon definition of social cognition (Fiske and Mcrae, 2012), but it is defined here as the complex set of cognitive processes that underlie and influence social interaction. Social attention, which "can be considered as attention (orienting, focusing, and disengagement of visual systems) in the context of social streams of information" (Salley and Colombo, 2016, p689), assessed through eye-gaze behaviour, was used here as a marker for social cognition. Two naturalistic free viewing tasks were used: (1) Social Preference Task, and (2) Face Scanning Task. Each are discussed separately in the following sub-sections, whilst the rationale for using social attention tasks in CWEOE is outlined below.

Social problems are more common to childhood epilepsy compared to other chronic illnesses (Rodenburg et al., 2005), and social cognitive difficulties may underlie those social problems (Kennedy and Adolphs, 2012; Semrud-Clikeman, 2007). Identifying children with social problems at the earliest possible time is advantageous to successful intervention (section 1.1). Eye tracking provides an opportunity to assess social cognition through social visual attention in order to help understand where social cognitive difficulties may lie in CWEOE, and identify those with social functioning problems for earlier intervention.

ASD is a well-known neurodevelopmental disorder characterised by deficits in social attention and social interaction (Falck-Ytter et al., 2013; Johnson et al., 2016), and has received much attention in eye-tracking research. ASD is overrepresented in childhood epilepsy, with approximately 5% of children with epilepsy receiving an ASD diagnosis (Suren et al., 2012). Therefore, it may be possible to identify children at risk of ASD using eye-tracking based social attention tasks. Interestingly, the frequency of positive screens using ASD sensitive questionnaires can be as high as 47% (Clarke et al., 2005; Fisher et al., 2012), suggesting that a higher volume of children may have social communication or interaction difficulties, but which may not meet criteria for ASD. Deficits in social communication in the general population can be functionally impairing (Skuse et al., 2009), and highlights the need to identify children with social difficulties, not just those reaching criteria for ASD.

16.1 Social Preference Task

16.1.1 Social Preference Task: Background

Evidence suggests that infants who atypically attend to social information within a scene later develop ASD (Chawarska et al., 2012; Chawarska et al., 2013). Indeed, atypical attention and gaze patterns toward people and faces, compared to typically developing children, appears to be a feature of ASD (Falck-Ytter et al., 2013). There is also a tendency for children with ASD to prefer objects rather than faces (Pierce et al., 2011a; Sasson and Touchstone, 2013). However, Wilson, Brock, & Palermo (2010) found that both typically developing children and children with ASD preferred to orient toward people within social scenes when compared to objects, but typically developing children spent significantly more time looking at people than the ASD children. Fletcher-Watson et al. (2009) investigated gaze attention toward two competing natural scenes, some of which contained people (social scene) and others without (non-social scene), in adults with and without ASD. Adults with ASD, like controls, preferred the socially informative scene, being particularly drawn to the person within the social scene. However, Fletcher-Watson et al. noted a difference in how quickly the subjects fixated to people within the social scene, a reflection of attentional priority, where those with ASD took longer to fixate the person than typically developing adults.

Recently, premature infants, who are at higher risk of ASD, displayed differences in fixation duration compared to typically developing infants, on an adapted version of the task used by Fletcher-Watson et al. (Telford et al., 2016). Therefore, the task may be sensitive to atypical social cognitive development, and the NEUROPROFILES study adopted that child-adapted task, with the aim to assess eye-gaze behaviour toward social and non-social naturalistic scenes in CWEOE compared to control children. Performance was also related to behavioural measures of social cognition and social functioning. It was hypothesised that CWEOE would display a preference for social scenes, but those with social functioning problems, or those at risk of ASD, would display atypical gaze behaviour by showing reduced attentional priority and reduced fixation duration to social stimuli.

16.1.2 Social Preference Task: Methods

The Social Preference Task was a novel, locally designed paradigm, which assessed visual preference for competing naturalistic scenes (social versus non-social scenes). It was adapted

from an adult version of the task (Fletcher-Watson et al., 2008; Fletcher-Watson et al., 2009). The Social Preference Task was validated in typically developing infants (Gillespie-Smith et al., 2016; Telford et al., 2016), and in preterm infants (Telford et al., 2016), aged 6-12m. As older children with ASD have displayed abnormalities in social scene viewing tasks (Wilson et al., 2010), the Social Preference Task was deemed suitable to administer in the current infant and preschool-aged cohort. The stimuli consisted of photographs of real-world scenes taken locally by the developers. There were six real world scenes with two versions of each: one with 1-2 children (i.e. social scene), and one without children (i.e. non-social scene). Trials consisted of social and non-social scene pairs presented in a counterbalanced pseudorandom order. Images were never presented in a pair with their real world sibling in order to increase overall scene complexity and avoid a reduction in image competition. Stimulus pairs were presented side by side (figure 16.1), with a combined on-screen size of W24.0cm x H17.0cm. There were a total of 12 trials, six in each block. Each trial was presented for 5s (Gillespie-Smith et al., 2016).

Figure 16.1 Social Preference Task trial examples

A

B

Image (A) depicts an example of a social & non-social scene pair. Image (B) depicts the same real world scenes as in (A), but with social & non-social content reversed.

General statistical analysis was laid out in section 12.4.6. Attentional priority and attentional importance were assessed for competing scenes (social versus non-social scene) as a measure of social preference, using first fixation preference, and fixation preference, respectively. Fixation preference was calculated as the % of TFD on the social image, compared to the whole scene, minus % of TFD to the non-social image. Fixation preference score was associated with sociodemographic variables (age and SES), and neurobehavioural data. Additionally, the social scene was analysed for between-group differences in TFD (expressed as a proportion of the

total time spent fixating the social image) toward the child/children, and the head regions within the scene.

16.1.3 Social Preference Task: Results

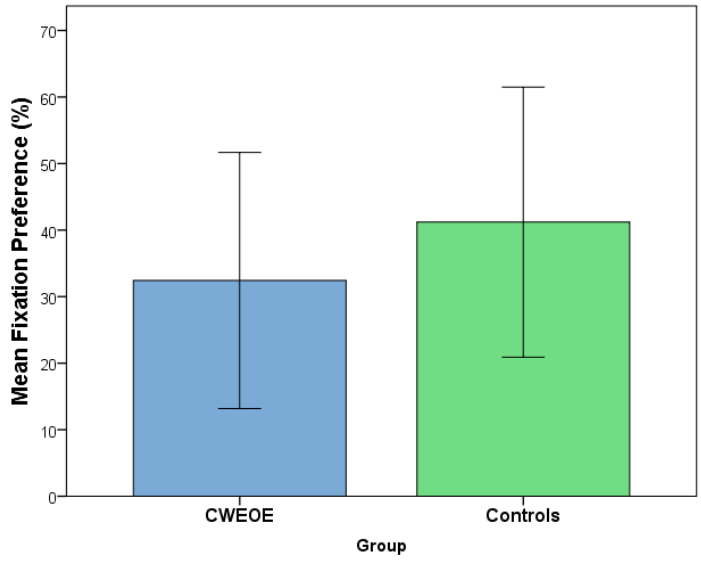
Participants

After trial exclusion criteria was applied, 47 CWEOE (100%) and 38 controls (93%) were included in analysis; three control children (2M:1F) aged 3-28m had <33% of scorable trials, and were excluded.

Social Preference: Fixation Preference and First Fixation Preference

Both CWEOE (t(46)=11.55, p<.001) and controls (t(37)=12.52, p<.001) displayed a significant fixation preference for the social image (i.e. the image including a child or children) (figure 16.2). This preference was stronger in control children compared to CWEOE (MD= -8.77 [95% CI -0.22, -17.33], p=.045). Mean fixation preference in CWEOE was 32.43% (SD 19.25), and 41.20% (SD 20.29) in controls, which equated to a mean percentage of TFD on the social image of 66.21% (SD 9.62) in CWEOE and 70.60% (SD 10.15) in controls. Similarly, both CWEOE and controls looked first toward the social scene more often than the non-social scene, but controls did so more often than CWEOE (MD= -15.00 [95% CI -3.41, -26.60], p=.012).

Figure 16.2 Bar chart: Fixation preference



Error bars represent standard deviation

Increasing scores indicate increasing fixation duration on social scene

Social Preference: Relationship with Sociodemographics, and Neurobehavioural Scores

Exploration of sociodemographic and neurobehavioural data revealed significant within-group associations between fixation preference and age, social functioning, and GCA, but not SES or ASD behaviours (table 16.1).

Table 16.1 Fixation Preference (%) associations with sociodemographic and neurobehavioural variables

	Age (r_s)	† Social functioning (r)	ǂ ASD Behaviours (r)	GCA (r)	SES (High vs Low) MD (95% CI)
CWEOE (n=47)	-.04	**.43****	.33	.18	.02 (-11.41, 11.46)
Controls (n=38)	**-.52****	.24	-.06	**-.36***	7.19 (-7.54, 21.91)

*p<.05, **p<.01, ***p<.001

† Social functioning = SEGC/ITSEA competence/CEC Social functioning scale (CWEOE n=42, controls n=36)

ǂ SRS-2 Total Score (CWEOE n=26, Controls n=16)

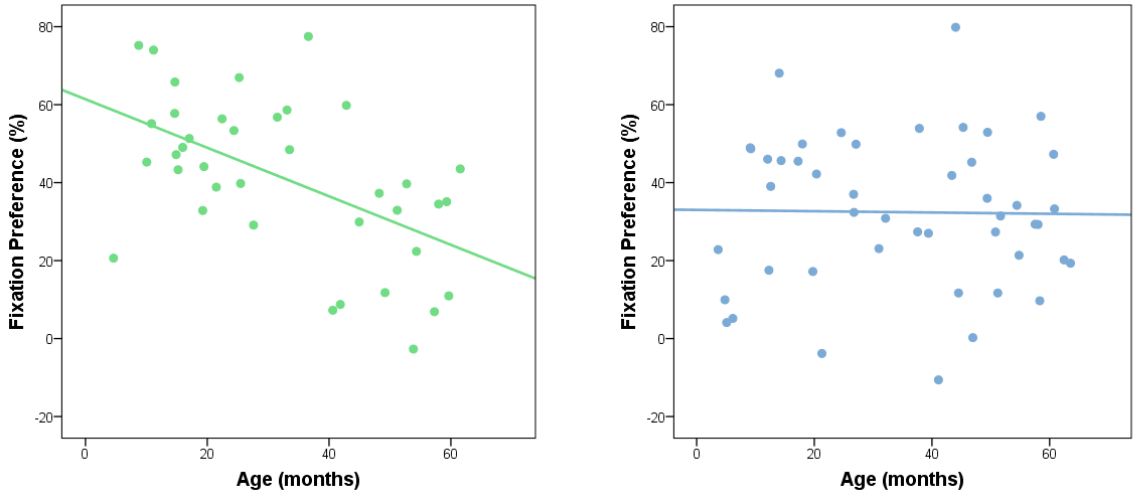
All variables significantly associated with fixation preference (i.e. age, social functioning, and GCA) were factored into multiple linear regression analysis. Interaction variables were also modelled. GCA was not a significant independent predictor when factored into multivariable models, and did not improve model fit, and was therefore dropped. The final model including group, age, group*age interaction, and social functioning was significant ($F(4,73)=8.68$, $p<.001$), explaining 28.5% (R^2_{adj}) of the variance in fixation preference. All variables independently predicted fixation preference (table 16.2). The model indicated that CWEOE looked less toward the social image than controls overall (B= -36.37), but there was also an influence of age, where children looked less at the social image with increasing age (B= -.70).

The group*age interaction revealed that control children had a strong fixation preference for the social image at a younger age but looked less toward that image with increasing age. CWEOE did not (figure 16.3). Despite considerable variability, the pattern of fixation preference in CWEOE indicated an overall fixation preference for the social image that remained stable with age.

Table 16.2 Regression coefficients for fixation preference

	ß	95% CI		p-value
		Lower	Upper	
Constant	37.34	13.61	61.06	.002
Group: Controls vs CWEOE	-36.37	-19.10	-53.63	<.001
Age (m)	-0.70	-0.36	-1.04	<.001
Group*Age interaction	0.74	0.30	1.18	.001
Social functioning T-score	0.55	0.18	0.91	.004

Figure 16.3 Social Preference Task fixation preference and age



Control children (green, left), and CWEOE (blue, right)

Higher social functioning scores, as measured via social functioning questionnaires, indicate poorer social functioning. Thus, with a Beta of 0.55, poorer social functioning was independently associated with increased fixation preference toward the social scene. It can therefore be taken that increased social scene fixation preference is, as measured in this particular task, indicative of less advanced, or poorer, social functioning.

Social Preference and Neurobehavioural Problems

Data on the relationship between fixation preference and those who met criteria for neurobehavioural problems (details of which were described in section 12.4.7) is presented in table 16.3. Only one CWEOE met criteria for NEPSY II Affect Recognition and Theory of Mind problems and thus, there were insufficient data for analysis, or presentation. Those with GCA

impairment, social domain problems, and those at higher risk of ASD had larger fixation preferences for the social image. This was significant for those with GCA impairment and social domain problems.

Table 16.3 Fixation preference in CWEOE with and without neurobehavioural problems

	Age range	Problem (n)*	Fixation Preference % (SD)	MD	95% CI	p
GCA impairment	≥1m	No (44) Yes (3)	30.76 (18.24) 56.80 (20.26)	-26.04	(-48.07, -4.00)	**.02**
Social Domain problem	≥1m	No (30) Yes (13)	28.27 (18.51) 41.16 (16.89)	-12.89	(-24.99, -0.78)	**.038**
ASD Risk	≥16m	Lower (29) Higher (6)	30.66 (19.66) 38.92 (15.04)	-8.53	(-25.63, 9.10)	.34
NEPSY II Theory of Mind Problem	≥36m	No (22) Yes (1)	-	-	-	-
NEPSY II Affect Recognition Problem	≥36m	No (22) Yes (1)	-	-	-	-

* The total number of children included is dependent on age-range of tool

Child/children and Head Region Analysis

CWEOE (N=47, M=14.41%, SD=9.33) and controls (N=38, M=15.27%, SD=9.93) spent a similar proportion of time within the social image fixating the head region (MD= -0.86% [95% CI -5.03, 3.30], p<.68), although controls (M=34.72%, SD=13.96) spent more time fixating the child/children than CWEOE (M=28.06%, SD=12.44); MD= -6.66% (95% CI -0.96, -12.36), p=.023. This indicates a reduced attraction to socially relevant stimuli in CWEOE. Control children fixated less on the child/children region with increasing age (rs=-.52, p=.001), but CWEOE did not (rs= -.04). This followed the same pattern observed toward the social scene itself, and supports the assertion that eye-gaze behaviour to the social scene is driven by the child/children.

Summary

Control children exhibited a stronger social fixation preference during infancy which reduced linearly by preschool age, and which coincided with time spent looking at the child/children region. The pattern of data suggest that a stronger social preference is indicative of less

mature social cognitive development; hence, a stronger social preference in infancy, that reduced with age, and why poorer social functioning scores were related to increased social fixation preference. CWEOE also displayed a social fixation preference, but this was weaker than controls, with no age-related correlation, suggesting a significant reduction in attraction to socially relevant information during the earlier years. CWEOE spent proportionately less time looking at the child/children regions. Taken together, CWEOE exhibited abnormal gaze behaviour toward socially relevant stimuli, as a function of being less drawn toward child/children within the social scene. The Social Preference Task was not sensitive toward ASD behaviour in this early-onset cohort, but was related to social functioning as measured by behavioural rating-scales, and to those with social functioning problems or GCA impairment.

16.2 Face Scanning Task

16.2.1 Face Scanning Task: Background

The face is a socially pertinent stimulus that conveys important communicative information such as gender, mood, and intention. In humans, the face is of particular social importance, being processed by a specialised brain region known as the fusiform face area (Kanwisher et al., 1997), and with development occurring earlier than body perception (Slaughter et al., 2002). Newborns, only minutes to hours old, prefer the face to face-like representations (Goren et al., 1975; Johnson et al., 1991; Maurer and Young, 1983), with face processing becoming increasingly specialised over the first months of life (Simion et al., 2007). The eye region of the face is of particular social importance, with newborns showing a preference for faces with eyes open compared to eyes closed (Batki et al., 2000), and with a preference for eyes rather than mouth by infancy (Gillespie-smith et al., 2016; Telford et al., 2016).

Visual preference for social information is atypical in children and adults with ASD, including gaze behaviour toward faces (Boraston et al., 2008; Chawarska et al., 2012; Chawarska et al., 2013; Dalton et al., 2005; Jones et al., 2008; Klin et al., 2002; Pelphrey et al., 2002). In a study investigating the processing of neutral static faces, Chawarska and Shic (2009) reported normal face scanning in two year old typically developing children and ASD children. However, children with ASD spent more time looking at outer-facial features (i.e. hair, cheeks and forehead) than typically developing children. This atypical fixation preference was more pronounced in 4 year old children with ASD, who looked at the eyes, nose and mouth regions less so than even their younger counterparts.

Recently, Telford et al., (2016) found gaze behaviour differences in facial scanning between typically developing infants, and infants born pre-term. Social communication difficulties are common in preterm children, yet only 1-8% develop ASD (Johnson et al., 2010; Kuzniewicz et al., 2014), suggesting face scanning may be a marker of social communication difficulties. As social problems including ASD are common in children with epilepsy, it is therefore of interest to explore face scanning in CWEOE. The fundamental model of viewing static neutral faces, as used by Chawarska and Shic (2009) and Telford et al., (2016), was adopted for this study as a base measure of face processing - as other factors such as emotion, context, or speech can influence gaze behaviour (Sasson and Touchstone, 2014; Shic et al., 2013; de Wit et al., 2008). Thus, the aim of the current study was to determine if atypical face scanning was evident in

CWEOE, and to determine to what extent gaze behaviour was related to behavioural measures of social cognition and problems, or risk of ASD. It was hypothesised that CWEOE would display typical eye gaze behaviour, but those at risk of ASD or with social problems would display atypical eye-gaze behaviour.

16.2.2 Face Scanning Task: Methods

The Face Scanning Task entailed free-viewing of photographs of human faces. Similar design has been used in infants (Gillespie-Smith et al., 2016; Telford et al., 2016), and preschool children (Chawarska and Shic, 2009). The task used six photographs (3 male and 3 female) of adult faces presented on a blue background, selected from the 2D face database at the University of Stirling (http://pics.psych.stir.ac.uk). Emotional expressions and direction of eye-gaze influence facial and neural processing (e.g. Hoehl and Striano, 2008; Leppanen et al., 2007). Therefore, emotionally neutral faces with direct gaze were selected as a baseline measure of face processing. The specific faces used were validated in a cohort of typically developing infants (Gillespie-Smith et al., 2016). Photographs were displayed on a computer screen at 16cm x 21.5cm. The task consisted of 6 trials, with three trials in each block. Each trial lasted 10s with an ISI of 4s (Gillespie-Smith et al., 2016).

General statistical analysis was described in section 12.4.6. Previous research has found fixation preference for central facial features (Chawarska and Shic, 2009), and for eyes compared to mouth (Gillespie-Smith et al., 2016). Therefore, analysis was focused on fixation preference and first fixation preference to: (1) central facial features (i.e. eyes, nose, and mouth) vs peripheral facial features (i.e. hair, forehead, ears, cheek, chin, and neck); and (2) within central features (i.e. eyes vs nose vs mouth), with focus on eyes vs mouth. AOIs for facial features were illustrated in 12.5.1. Both within- and between-group analysis was conducted for fixation preferences and first fixation preferences. Fixation preference was associated with neurobehavioural measures of social cognition and functioning, and compared between those with and without neurobehavioural problems in CWEOE (see section 12.4.7). For the purposes of comparisons to age and neurobehavioural tools/scales, fixation preference scores were calculated by subtracting the TFD on one face region (e.g. peripheral face features) - as a proportion of TFD to the entire image -, from the proportion of TFD on the competing region (e.g. central face features).

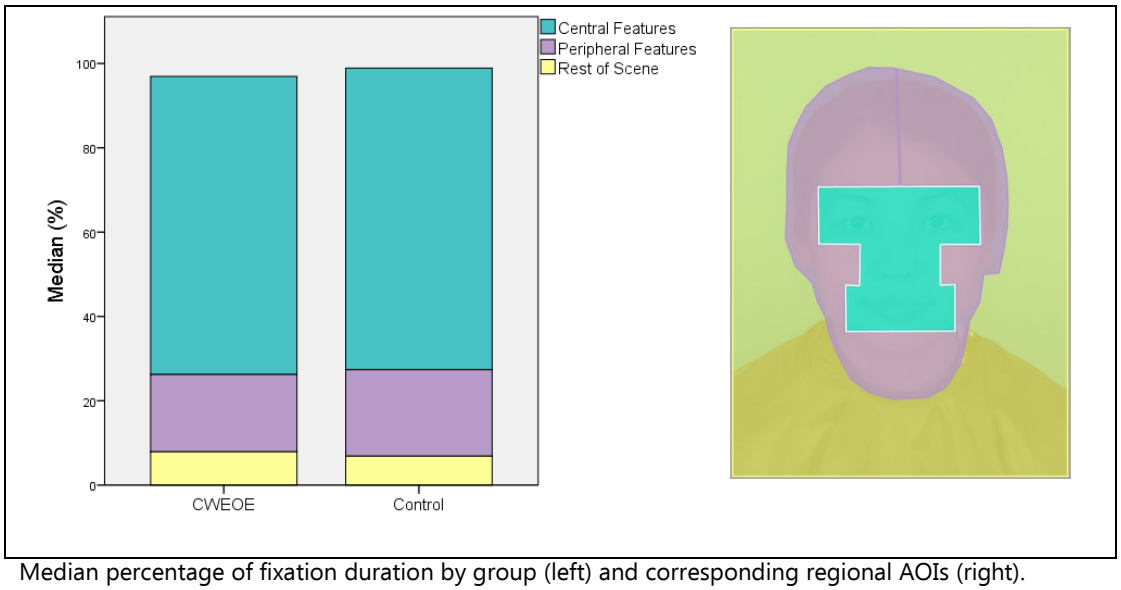
16.2.3 Face Scanning Task: Results

46 CWEOE (98%) and 41 controls (100%) were included in analysis. One CWEOE had fixation data available for only one trial, and was therefore excluded from analysis.

Central Facial Features vs Peripheral Features

Compared to one another, CWEOE and controls spent a similar proportion of time fixating on the central features, peripheral features, and rest of the image (p=.67, r=.05) (figure 16.4). Within-group analysis found that fixation preference (i.e. proportion of time spent fixating central features – peripheral features) in CWEOE (Median=53.31% [IQR 9.82, 72.55]) and controls (Median=51.99% [IQR 9.13, 63.21]) was stronger for central facial features compared to peripheral features. Both CWEOE (Median=67% vs 17%; p<.001) and controls (Median=75% vs 17%; p<.001) also fixated first more often on the central features than peripheral features. There was no significant relationship between fixation preference and age, or first fixation preference and age, in CWEOE or controls.

Figure 16.4 Percentage of fixation duration to facial feature regions



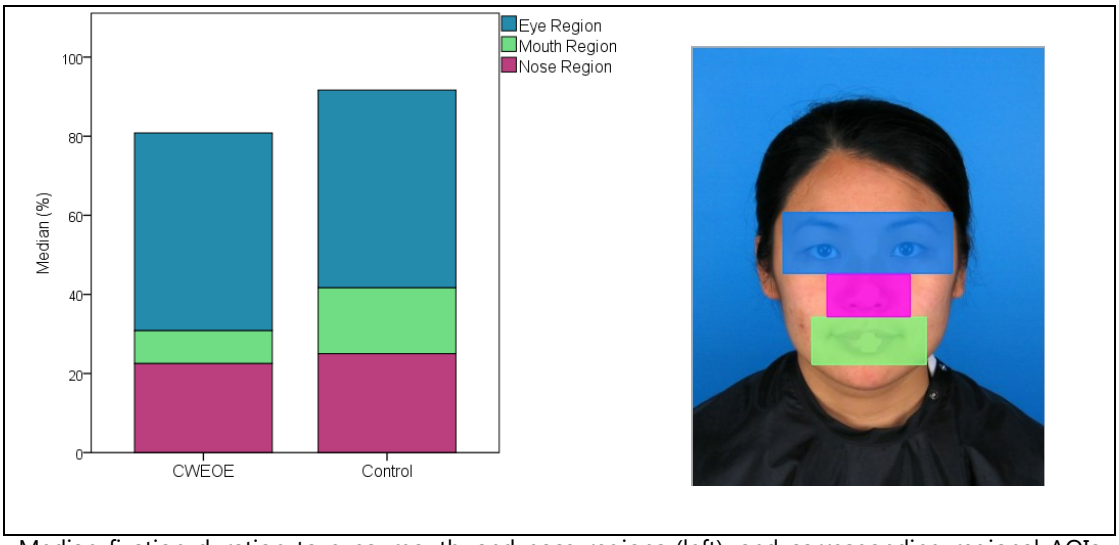
Median percentage of fixation duration by group (left) and corresponding regional AOIs (right).

Central Feature Analysis (Eyes, Nose, and Mouth)

Analysis of fixations toward the eyes, nose and mouth regions revealed significant within-group differences. Both CWEOE and controls preferred fixating on the eye region compared to

the nose or mouth regions (figure 16.5). Controls fixated the nose region longer than CWEOE (p=.036, r=.23), but looked at the eye and mouth regions to a similar degree. CWEOE (x^2 =20.78, p<.001) and controls (x^2 =6.27, p=.043) looked first more often toward the eye region compared to the nose or mouth regions, with no between-group differences. There were no significant correlations between fixation preference and age, or first fixation preference and age, in either CWEOE or controls.

Figure 16.5 Median percentage of fixation time on eye, nose, and mouth regions



Median fixation duration to eyes, mouth, and nose regions (left), and corresponding regional AOIs (right).

Neurobehavioural Assessment Scores and Facial Feature Processing

Spearman's rank coefficients for correlations between social behaviour tools/scales (i.e. Social functioning, ABAS-II Social Composite, NEPSY-II Affect Recognition, NEPSY-II Theory of mind, SRS2 Communication & Interaction Index, and SRS2 Total) and fixation preference to central facial features were small, ranging between .05 and .24. Likewise, correlations with fixation preference to the eye region (i.e. proportion of TFD on eye region – proportion of TFD on mouth region) ranged between .02 and .28. No correlations were statistically significant. Additionally, there was no significant correlation between fixation preference and GCA score, meaning that neither parent-reported social functioning behaviours nor GCA was related to eye-gaze behaviour in the processing of static faces.

Table 16.4 Central/peripheral fixation preference and neurobehavioural problems in CWEOE

	Age range	Problem (n)	Median (IQR)	p	r
GCA impairment	≥1m	No (43) Yes (3)	55.17 (18.12, 73.01) 6.72 (-33.32, n/a)	.15	.21
Social Domain problem	≥1m	No (29) Yes (13)	55.17 (7.93, 72.70) 53.64 (15.97, 69.63)	.90	.02
ASD Risk	≥16m	Lower (29) Higher (6)	55.17 (8.79, 72.70) 46.44 (-20.55, 71.47)	.90	.02
NEPSY II Theory of Mind Problem	≥36m	No (22) Yes (1)	-	-	-
NEPSY II Affect Recognition Problem	≥36m	No (22) Yes (1)	-	-	-

* The total number of children included is dependent on age-range of tool

Table 16.5 Eyes/mouth fixation preference and neurobehavioural problems in CWEOE

	Age range	Problem (n)	Median (IQR)	p	r
GCA impairment	≥1m	No (43) Yes (3)	55.22 (3.48, 80.60) -13.72 (-70.18,n/a)	.068	.27
Social Domain problem	≥1m	No (29) Yes (13)	55.22 (4.10, 78.09) 19.12 (-6.82, 79.18)	.78	.04
ASD Risk	≥16m	Lower (29) Higher (6)	30.67 (-2.81, 78.18) 51.98 (34.13, 87.30)	.24	.20
NEPSY II Theory of Mind Problem	≥36m	No (22) Yes (1)	-	-	-
NEPSY II Affect Recognition Problem	≥36m	No (22) Yes (1)	-	-	-

* The total number of children included is dependent on age-range of tool

Analysis of those with and without neurobehavioural problems in CWEOE revealed that fixation preference for central/peripheral facial features (table 16.4) or eye/mouth regions (table 16.5) was not significantly different. Sample sizes of those with GCA impairment or those at higher risk of ASD were small, and results should be treated with caution. Based on the data available, the Face Scanning Task was not a sensitive marker of social behavioural development in CWEOE, and did not identify those with neurobehavioural problems. It is important to reiterate that analysis of those with neurobehavioural problems were based on small sample sizes, and

it is also important to note that several of the behaviour tools were not applicable to infants (i.e. NEPSY II, MCHAT, and SRS2), and it is unclear how effective the Face Scanning Task is to this age group.

16.3 Social Cognition Discussion

Much previous work has focused on social attention in children with ASD. Here, we extended that growing body of work to focus on children with epilepsy, a disorder known to have increased risk of social problems including ASD. The CWEOE cohort here had poorer levels of social functioning, and it was hypothesised that performance on the social attention eye-tracking tasks would be atypical in those children meeting criteria for social problems, and those at higher risk of ASD. The results of the Social Preference and Face Scanning tasks provided a slightly more complex picture of social attention in CWEOE. Visual social attention atypicalities were dependent on the nature of the social stimulus. Namely, CWEOE with social problems or those at risk of ASD viewed faces normally, but at the group level, CWEOE had atypical gaze behaviour toward social scenes compared to non-social scenes. This latter finding was independently influenced by age and social functioning, both of which point toward abnormal social cognitive development in CWEOE.

Gaze behaviour in control children echoed that found in previous research of typically developing children. Control children preferred more socially relevant features of faces (i.e. the central features), particularly the eye region when compared to the mouth. This replicated previous findings in infants (Gillespie-Smith et al., 2016; Telford et al., 2016), and toddlers and preschool children (Chawarska and Shic, 2009). In the Social Preference Task, control children displayed attentional priority and attentional importance toward socially relevant scenes, which was driven by attention toward child/children within the scene. This has previously been noted in typically developing infants (Gillespie-Smith et al., 2016; Telford et al., 2016), and adults (Fletcher-Watson et al., 2009).

Whilst it was hypothesised that CWEOE with poor social functioning would display atypical social attention, the same was not expected in CWEOE as the whole. CWEOE's gaze behaviour in the Social Preference Task may therefore point toward a global immaturity in social cognitive development. Control children had a strong preference for the social scene in infancy, which reduced linearly with increasing age. This pattern was absent in CWEOE, with infants and older children displaying variable levels of fixation preference. Such a reduction in social preference

with age in controls may indicate that the task stimuli were not sufficiently complex enough to elicit prolonged gaze attention in typically developing toddlers/preschool children. Conversely it may reflect differences in age-related visual importance and processing. In any case, the fact that age was independently related to fixation preference suggests that the absence of that pattern in CWEOE was reflective of abnormal social attention.

It is unclear why CWEOE spent proportionately less time fixating the child/children within the social scene than controls. Attention to the child/children was the driving force behind the pattern of age-related gaze behaviour seen in control children. Time spent fixating on the head region was similar between groups, and results from the face scanning task clearly demonstrated typical attention to the face and eyes in controls and CWEOE. Therefore, orientation to the child/children themselves within the social scene may have a different gravitas than that of faces. As previously described, typically developing infants are drawn to social stimuli, and it is plausible that with age and advancing visual and cognitive development, that children may have shown an increased interest in scene context and objects within the social and competing non-social scenes. However, this could not be directly assessed in the current study because the stimuli were not designed for this purpose. Nevertheless, it does raise the possibility that CWEOE attend atypically to non-facial social stimuli (i.e. whole bodies). Therefore, one possibility is that CWEOE had less interest in child/children because the body had less social relevance to them. Bodies are socially informative, and the detection and recognition of faces and bodies may be served by different networks that develop at different age-related stages (Slaughter et al., 2004). Therefore, a second, and perhaps not mutually exclusive possibility, is that CWEOE have immature neural networks involved in body recognition, or processing. Given the absence of an age-related pattern of fixation preference in CWEOE, an alternative explanation may be offered. That being the presence of a dual age-related pathology rather than a global explanation. That is, there may have been a reduction in attention to the social scene in infants (i.e. social orientation), and an abnormal increase in social scene engagement in older children (i.e. attentional disengagement) – and this could be explored with future task manipulation.

Eye gaze behaviour in the Social Preference Task and Face Scanning Task was not associated with ASD behaviours, nor was performance different in those at higher risk of ASD. Thus, the eye-tracking tasks employed here were not effective predictors of those at risk of, or displaying behaviours associated with ASD. Several studies have now reported typical scanning of static faces in children and adults with ASD (Bar-Haim et al., 2006; Rutherford and Towns, 2008; Speer

et al., 2007). Children with ASD (or those at risk of ASD) may be drawn toward socially salient features in a similar way to typically developing children when viewing static images, but evidence suggests that gaze behaviour may differ when non-static stimuli are used. Speer et al. (2007) gave children with, and without ASD, static and dynamic social stimuli and found that atypical eye-gaze behaviour in ASD was only found for dynamic social stimuli. Similar abnormalities in face viewing in children with ASD using dynamic stimuli have been found elsewhere (Jones et al., 2008; Jones and Klin, 2013; Klin et al., 2002). Wass et al. (2015) found abnormalities in fixation duration to static social images related to presence of ASD, but when developmental level was considered, the role of ASD was no longer significant. This suggests that abnormal eye-gaze behaviour toward social stimuli may, alternatively, be a function of development rather than ASD. In support of this, Telford et al., (2016), using the same eye tracking tasks as in the current study, in addition to others, found that preterm infants spent less time looking at social stimuli than term infants. Thus, a lack of relationship between fixation preferences and ASD in the current study may be due to the use of static images, or because the CWEOE displaying ASD behaviours had sufficient neurological developmental. Interestingly, those CWEOE with GCA impairment, which may reflect poor general development, had increased fixation to the social image in the Social Preference Task compared to those with normal GCA – and perhaps offers supportive evidence of abnormal social gaze behaviour in those with poorer neurological development as opposed to neurological maldevelopment associated with ASD. One limitation of the current study was the tool used to measure ASD behaviour as a continuous variable (i.e. SRS-2) was available only for children from 36 months of age, and it was therefore not possible to correlate fixation preference in younger children with ASD-type behaviours. That said, no relationship was found between fixation preferences and 'risk of ASD', as measured through the SRS-2 and M-CHAT, which was applicable to children from 16 months of age. It should also be noted that the CWEOE included in the eye-tracking study tended to have less severe epilepsy, and the findings may only apply to less developmentally impaired children with ASD behaviours.

Interestingly, measures of social functioning used in the present study independently predicted fixation preference in the Social Preference Task. The social functioning construct used in this study was a reflection of social skill development, peer relationships, social engagement, and social temperament. Given that ASD behaviour was not associated with fixation preference, the findings then lend support to the notion that this task reflected a different social construct than that measured through ASD assessment tools. The same relationship was not found in the Face scanning Task, suggesting that that task measured a more fundamental level of social

attention. In the Social Preference Task, typically developing children fixated less toward the social scene with age, suggesting that, in this particular task, increased social preference was a marker of developmental immaturity. It makes sense, therefore, that poorer social functioning was related to increased fixation duration the social scene. Despite the evident relationship between social functioning and social preference, regression modelling revealed that social functioning, age, and epilepsy accounted for only 29% of the variance in fixation preference. This indicated that other unknown factors contributed toward gaze behaviour in the social preference task. As argued above, developmental level may also be one of those factors. Nevertheless, it is promising that such a task may be capable of identifying young children with social functioning problems.

One limitation of the eye-tracking tasks used here was that they had been originally created for infants, and perhaps lacked the developmental appropriateness to adequately assess social attention in toddlers and preschool children. Despite clear differences between CWEOE and controls in the Social Preference Task, the pattern of age-related gaze behaviour observed adds complexity to the interpretation, and future research should explore age related differences in social attention by manipulation of task design. Nevertheless, the eye tracking tasks used here have provided useful insight. Namely, that CWEOE display atypical attention to social scenes involving young children, but scan faces in a typical fashion. This suggests that CWEOE have underdeveloped social cognition, and that eye-tracking tasks such as the Social Preference Task may be useful tools in the early identification of children with cognitive impairment or poor social functioning. As mentioned previously, the tasks were not effective predictors of ASD, but that conclusion is somewhat tentative given the age restriction of the ASD tools. Therefore, it would be informative to follow infants longitudinally and relate their fixation preferences to ASD scores in the future. With particular regard to face scanning, future research in CWEOE could also assess other aspects of face scanning to dynamic stimuli, and emotional expression recognition. A number of studies have found impaired facial identity and emotional recognition in various childhood and adult epilepsy syndromes (Gomez-Ibanez et al., 2014; Golouboff et al., 2008; Lunn et al., 2015; Meletti et al., 2003; Meletti et al., 2009). Facial and emotional recognition is a valuable social skill (Harrigan, 1994), and deficits can be reflective of developmental disorder or social communication difficulties (Lunn et al., 2015; Uljarevic and Hamilton, 2012). It is therefore worth exploring in CWEOE.

In conclusion, the social attention based eye tracking tasks used here are the first in CWEOE, and have provided evidence of impaired early social cognition in that population. Social

problems may be a hallmark of childhood epilepsy (Rodenburg et al., 2005), and eye tracking provides a promising tool toward detecting early social functioning problems.

17. Eye-gaze Behaviour in CWEOE: General Discussion

The aim of this chapter was to explore eye-gaze behaviour in a cohort of CWEOE, with particular focus on exploring the potential of eye-gaze behaviour as a marker of neurobehavioural problems. In doing so, this is the first study to use eye-tracking in infants, toddlers, and pre-schoolers with epilepsy. The study focused on three broad domains: cognition/memory, attention/inhibition, and social cognition, using five tasks designed to measure certain aspects of visual attention associated with each domain. As a group, CWEOE showed largely similar gaze behaviour to that of typically developing control children. However, several issues were found that result in the conclusion that CWEOE do indeed display abnormalities in visual attention. In the most poignant, CWEOE were found to display abnormal visual attention to naturalistic social scenes containing child/children. This finding was related to behavioural measures of social functioning, and has therefore shown promise of clinical applicability. CWEOE were also found to have a slight delay in the speed at which a new stimulus was fixated following active inhibition. This finding was not related to the speed at which CWEOE could produce a typical prosaccade, which appeared to be normal, but with cost of information processing after saccadic inhibition. This was an incidental finding, and one which was not the initial subject of investigation. Likewise, indirect evidence from the study also pointed toward impaired sustained attention within trials in CWEOE, despite normal general attention to the battery.

This study was exploratory in nature with methodological considerations that require further refinement, but nevertheless, it does point out that eye-tracking in infants and young children with epilepsy is possible, that abnormalities are evident, and that it is of potential use as a marker for neurobehavioural problems. Identifying such abnormal eye-gaze behaviour is of interest from a neuroscientific, psychological and clinical perspective. Such data are informative in understanding the underlying cognitive processes involved in visual attention in children with epilepsy, the influence these processes may have on behaviour and learning, and the application to clinical diagnosis and markers of change. Social problems, for instance, are common, and possibly core manifestation of childhood epilepsy (Rodenburg et al., 2005). Accordingly, the findings of the current study may be indicative of early markers of impaired or immature social cognition, even at such an early age. They may also act as a marker of problems at the behavioural level, as evidenced by the association between fixation preference and parent-rated questionnaires of social behaviour.

One of the main goals was to indeed identify children with neurobehavioural problems through eye-gaze behaviour. Whilst that proved successful in the Social Preference Task, the remaining tasks were not sensitive to their respective neurobehavioural measures. This lends further support to the notion that the eye-tracking tasks were independent, and were not simply measuring visual attentive systems associated with an epileptic brain. The reason why those with neurobehavioural problems were not discriminated in the remaining tasks may have been influenced by two factors. First, there were limited numbers of children who met criteria for neurobehavioural problems to robustly assess the validity of those relationships. This was case for most of the tools used to determine problem behaviour, where only a small number of children met problem criteria. This was a prospective study, where the cognitive and behavioural status of the children were unknown prior to study enrolment, and replication of the analysis with greater sample sizes of children with problem behaviours would be advised before drawing any firm conclusions. Second, and alternatively, the mechanisms of visual attention involved in those eye-tracking tasks may not have been related to the respective neurobehavioural tools. The memory task for instance was a proxy for GCA (Rose et al., 2005; Rose et al., 2012; Fagan et al., 2007), yet it had only a weak correlation with it. Nor was it correlated with memory measures except for a moderate correlation with a visuospatial performance-based tool, the NEPSY II Memory for Designs. This task, and the others, may have been expected to discriminate children with neurobehavioural problems if a stronger relationship had been identified via correlations with those tools. As this wasn't the case, it is unlikely that given larger numbers the eye-tracking tasks would have been greatly different. It is also possible that other neurobehavioural tools of cognition and behaviour may provide a stronger correlation, and this could be explored in future work.

This study was limited through several methodological considerations. The cohort of CWEOE was prospectively gathered, and consisted of a heterogeneous population with variable verbal abilities, ages, and clinical characteristics. As a result, the eye-tracking findings are limited to a population of mixed epilepsy syndromes and presentations. Many of the more severely affected CWEOE were not successfully eye-tracked or enrolled, and the results are therefore more applicable to those less severely affected by the condition. This is understandable given that severe epilepsy, particularly in the very young, is often accompanied by developmental impairment or visual impairment, making it difficult for the child to orient themselves to the task, as well as achieve successful attention and calibration. West Syndrome for instance encompasses both developmental regression and visual impairment (Jambaque et al., 1993), and of the seven enrolled onto the NEUROPROFILES study, only two successfully completed

eye-tracking. Although this does not discredit the results, it must be made clear that the results are not generalisable to the entire CWEOE population, particularly the more developmentally compromised. In fact, it is encouraging that eye-tracking is successful in infants, toddlers, and pre-schoolers with epilepsy, and that it can detect abnormalities in those less severely affected, who may indeed have more subtle cognitive or behavioural problems.

As mentioned previously, the eye-tracking tasks were selected based on their intended psychophysiological mechanisms, and applicability to a developmentally mixed cohort. As such, they may not always be suitable for certain age groups - as was suspected to be the case in the SNP Task. Eye-tracking itself is still very much in early development in terms of its applicability to neuropsychological understandings, the clinical context, or as a diagnostic tool. Eye-tracking paradigms are not yet commercially available, nor do they have validated psychometric properties. In the present study, the Memory Task, Social Preference Task, and SNP Task were created for use primarily in infant populations, and as such may not have been best-suited for toddlers or preschool children. It is possible that null findings were due to task simplicity, and more cognitively demanding tasks may return different results. Abnormal behaviour to that of controls was observed in the Social Preference Task, and it may be the case that further evolution and refinement of these tasks may produce alternative results.

Naturally, future research in CWEOE could build on the work presented here. Namely by using more complex or cognitively demanding paradigms to gauge memory, social cognition, and attention in toddlers and preschool aged children. For example, the Memory Task used a VPC design of two competing stimuli. The stimulus design could feature increasingly discrete visual differences, or stimulus capacity could be increased to three or more items. It would also be advantageous to follow-up the existing cohort in order to track the trajectory of development in relation to their present eye-gaze behaviour. Rose et al. (2005; 2012), and Fagan et al. (2007), for example, have associated early eye-gaze behaviour with later working memory ability and cognitive development. Future research into CWEOE could also explore paradigms targeted at assessing the visual components of attention. As was evidenced by this study, CWEOE might have difficulty with sustained visual attention, which could potentially be a marker for attentive difficulties or school achievement for example. Finally, this was a heterogeneous population of epilepsy types and presentations. Epilepsy syndromes can present with differing neurobehavioural profiles, and future research should also take this into consideration by designing studies targeted at specific epilepsy syndromes.

To conclude, this study was exploratory, and serves as a first step in the study of eye-gaze behaviour in CWEOE. It has discovered a basic abnormality in how CWEOE view natural social scenes, which may help in the study of underlying mechanisms involved in social cognition and the development of social problems in children with epilepsy. The study also provided contradicting data on antisaccade production, and issues involving SNP, in typically developing children, which will be of interest to visual attention researchers. Whilst eye-tracking is an evolving technology, and its clinical application is only emerging, eye-tracking itself is a highly promising tool toward the identification of children with neurobehavioural problems.

Chapter V. Conclusions

18. Conclusions

This research study was created in order to understand the neurobehavioural burden of early-onset epilepsy. Given that a detailed description of the sociodemographic and clinical characteristics of early-onset epilepsy itself was provided, the findings presented here can be seen as truly representative of the early-onset epilepsy population. The addition of eye-tracking as a marker of neurobehavioural problems may provide the beginnings of a new direction of exploration with which neurobehaviour could be understood and problems detected in CWEOE.

This was the first population-based study in Scotland describing the sociodemographic and clinical characteristics of CWEOE, estimating the incidence of CWEOE and West Syndrome, and determining the risk factors for early-onset epilepsy. Thus, the results here provide up-to-date data in the UK, and new data in Scotland. Likewise, and to the candidate's knowledge, this was the first population-based study which has focused on a general cohort of children with epilepsy under the age of five years which has provided a detailed description of the patterns of cognitive and behavioural functioning of that population. Although several studies have provided data on children whose onset began in the first five years of life, the systematic review in section 1.3 revealed that very few had provided data *during* those first five years. Thus, this study has provided valuable data on cognition and behaviour in CWEOE during the early years, and compliments those conducted later in childhood.

The central hypothesis of this study was that CWEOE would have an abnormal neurobehavioural profile compared to the general population. That is, poorer cognitive functioning and more problematic social-emotional behaviour compared to controls, as well as having a greater prevalence of neurobehavioural problems. The findings of this study support that assertion, and notes that although some neurobehavioural domains appear to be affected more so than others in the general CWEOE population, the risk of neurobehavioural problems remained high throughout. As such, this study has highlighted the increased vulnerability to cognition and behaviour in individuals with epilepsy during this age.

As a result of the findings in this study, there are a number of possible implications that require addressing. The first is that a higher risk of epilepsy was found in white-European and Asian ethnicities. The causes of which are currently unknown but nevertheless provide opportunity

for further research and the formulation of preventative strategies for these particular populations within the health community.

Second, the high degree of neurobehavioural problems identified in this cohort necessitate closer scrutiny of how the early-onset epilepsy population is managed. Psychiatric diagnoses are more common in school-aged children compared to preschool aged children (Merikangas et al., 2009; Wichstrom et al., 2012). However, this may be partly driven by the inherent difficulty in distinguishing normal from abnormal behaviour in very young children but is also likely due to attitudes and beliefs by health care professionals toward the measurement and judgement of abnormal behaviour in very young children. There may be a tendency to dismiss problem behaviours in the young as temporary, yet contradictory evidence on the pervasiveness of neurobehavioural problems, reported in the section 1, and the results reported as a result of the current study suggest that these concerns should not be so quickly dismissed. Therefore, this has implications for policy and practice pertaining to the care and management of CWEOE. This is particularly relevant in Scotland, where over the last decade there has been a focus on policy aimed at improving development and mental health across infancy and the early years, with an aim to increase awareness, provide integrative holistic services, and identify individuals and groups at risk (Geddes et al., 2010; Puckering, 2007; Scottish Executive, 2005; Scottish Government, 2008). In addition, parents could be made aware of the possible risks to cognition and behaviour upon presentation of epilepsy when under clinical care. Thus providing opportunity for behavioural monitoring, as well as parental education in behavioural management. Furthermore, the fact that neurobehavioural problems were identified at an early age provides a strong case for early intervention in CWEOE. As noted in chapter I, section 1, the early identification of problems is highly beneficial for earlier and successful interventions. Such early childhood interventions are advocated by the Scottish Government (Geddes et al., 2010; Scottish Government, 2008), and the results found here suggest that CWEOE should be considered as an at risk group for early intervention.

Third, a high degree of comorbidity was found in CWEOE, the nature of which varied considerably. Comorbid problems in childhood epilepsy are under-recognised and often go untreated (Carson et al., 2015; Ott et al., 2003; Reilly et al., 2014a), making the case for identification more pertinent. The findings of this study, and others in later childhood, strongly suggest the need for multi-dimensional screening. As mentioned previously in this thesis, ESSENCE (Gillberg, 2010), is one method of crude screening that could be applied during

routine clinic. A comprehensive understanding of the child's needs is essential in order to provide targeted and holistic care.

Finally, the early detection of neurobehavioural problems in children was an issue raised at the beginning of this thesis. It was explained that there is a current lack of standardised and validated diagnostic tools at this age. One of the aims of this study was to explore eye-tracking as a marker of neurobehavioural problems in CWEOE. The results here suggest that eye-tracking *is* a viable technology worthy of further exploration and refinement, but one that may be more suited to those with less severe epilepsy. That said, eye-tracking is an evolving technology, and creative use of different hardware formats and eye-tracking paradigms may yet prove to be more suitable. Furthermore, the use of eye-tracking as a screening tool for neurobehavioural problems could offset the need for blanket screening using standardised assessment methods.

Limitations and Future Directions

The limitations and directions for future research of individual aspects of this study have been reported in the relevant chapters. Several wider issues are briefly described here.

In the introduction to this thesis it was argued that early-onset of epilepsy was an independent risk factor for neurobehavioural problems. Whilst this study has shown that abnormal cognition and behaviour is detectable, and that neurobehavioural problems are highly prevalent in CWEOE, it was beyond the scope of this study to directly compare these findings to older children with epilepsy in South-East Scotland. Therefore, it would be beneficial to follow up the current cohort to track the natural history of neurobehavioural problems in CWEOE over time, which currently remains unclear. Children were assessed near the onset of their disease, and following the development of these children over time would allow closer examination of the effects of chronic seizures, duration of epilepsy, seizure remission, and AED use on cognition and behaviour by later childhood.

The high rate of comorbidity, and evidence of problems at the beginning of the disease, also suggest that underlying factors contribute toward the neurobehavioural profile of CWEOE. Imaging studies have provided strong evidence that cortical abnormalities are present at distal sites from seizure locus. Temporal lobe epilepsy, for example, is typically characterised by a unilateral, localized seizure focus, originating in the temporal lobe. However, widespread

volumetric reductions have been found in temporal, parietal, and occipital cortices, as well as sub-cortical structures within, and extra to, the temporal lobes – and in hemispheres both ipsilateral and contralateral to the side of seizure focus (Keller and Roberts, 2008). The brain has billions of connections and cognitive functions operate on a network basis rather than via discrete structures (McIntosh, 2000; Price and Friston, 2005). Abnormal activation of synaptic projections coming from the initial site of epileptic lesion (Avanzini et al. 2014), may be one potential explanation of widespread brain abnormality and cognitive deficits. As no imaging studies have focused on CWEOE, it would be informative to explore the links between brain function and structure in CWEOEO and the presence of neurobehavioural comorbidities.

Eye-tracking was used on an exploratory basis in this cohort, and the tasks used in this study where chosen due to their applicability across a relatively diverse age group made up of differing age-related developmental and verbal abilities. Eye-tracking was successfully employed in this age group approaching it in this way. However, the findings here also suggest that certain tasks may be more suited to certain ages, and it is therefore recommended that future studies take this into consideration.

Concluding Comment

It can be argued that the body of work contained in this thesis has met its goal in contributing to the existing knowledge base, whilst meeting its primary aims and objectives. NEUROPROFILES has (1) estimated the incidence of early-onset epilepsy, (2) described the neurobehavioural profile of CWEOE, and explored risk factors for neurobehavioural problems, and (3) explored eye-tracking as a marker of neurobehavioural problems in CWEOE. In doing so, it has contributed toward the existing childhood epilepsy literature, by providing unique data on an understudied group of children. These findings may also provide new and influential information for the management and care of CWEOE in Scotland.

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Appendices

Appendix A – Search strategy for systematic review (chapter I, section 1.3)

Databases: (i) Medline (Ovid), (ii) Embase (Ovid), (iii) PsycINFO (Ovid), (iv) Web of Science (Thomson Reuters), and (v) CINAHL (EBSCOhost).

Search term targets: Children, epilepsy, cognition, and behaviour.

Search strategy by database:

(i) Medline

'Advanced Search' selected, and 'Match term to subject heading' checked (years 1970 – current). Terms;

1. Subject heading terms;
- Epilepsy (includes seizures and seizure disorders) - Preschool (subselect child preschool, child, infant) - Minors - Mental Processes (subselect cognition/executive function/learning [subselect memory]/Theory of mind/thinking/perception) - Intelligence - Psychological Tests (subselect intelligence tests(exp)/language tests/neuropsychological tests(exp)/psychometrics) - Psychology (subselect child psychology and child psychiatry) - Neuropsychology - Mental Disorders (subselect anxiety(exp)/impulse control/mood [expand 'mental disorders diagnosed in childhood' and select anxiety/attention(exp)/child behavior disorders/child development disorders [expand and select Asperger/autistic disorder]/communications/developmental disorder/learning disorder/intelligence disorder/motor/mutism/react/schizophrenia/stereo dis) - Comorbidity - Child Development - Neurobehavioral Manifestation (subselect communications/memory/intellectual disability/psychomotor disorders) -- Behavior (subselect Behavioral symptoms [subselect affective/aggression/depression/obsessive behavior/stress)) child behavior [select infant behaviour]/communications/impulsive behavior/inhibition/social behavior[expand and select aggression]/emotions[expand and select affect/anxiety/fear]) - Psychopathology

2. Title and abstract free-text searches;
- epilepsy.ti OR epilepsy.ab - children.ab. OR children.ti. OR infant*.ab. OR infant*.ti. OR toddler*.ab. OR toddler*.ti. OR preschool*.ab. OR preschool*.ti. - cogniti*.ab OR cogniti*.ti - behaviour.ti OR behaviour.ab OR behavior.ti OR behavior.ab

Main search supplemented with title and abstract free-text search of 'Ovid Medline In-Process & Other Non-indexed citations' for non-indexed items posted in last six months. Search terms were: epilep*, child*, cognit*, and behavio?r.

(ii) EMBASE

'Advanced Search' selected, and 'Match term to subject heading' checked (years 1970 – current). Terms;

1. Search terms;
- Epilepsy (subselect seizure, epilepsy, and convulsion) - Infant - Toddler (subselect child) - Newborn - Minor (person) - Intelligence (expand and select intellect/intelligence quotient) - Psychologic Test - Neuropsychological test - Cognitive defect - Cognition (subselect attention/cognitive reserve/executive function/learning/memory/mental cap/mental development/mental performance/social cognition/Theory of mind/thinking) - Mental deficiency (subselect intellectual impairment) - Psychophysiology (subselect attention/sensorimotor function) - Behavior (subselect behaviour/adaptive behaviour/aggression/antisocial behaviour/child behaviour/emotion/"inhibition(psychology)"/misconduct/motor activity/psychological aspect/psychosocial dev/social behavior) - Psychology (uncheck psychology and select child psychology & developmental psychology) - Neuropsychology - Mental disease (expand uncheck mental disease and subselect anxiety disorder/autism/behavior disorder/emotional disorder/learning disorder/memory/mental deficiency/mood/thought disorder) - Child Development (subselect postnatal development) - Comorbidity - Language disability

2. Title and abstract free-text searches;
epilepsy, children, infant*, toddler*, preschool*, cogniti*, and behavio*

(iii) PsycINFO

'Advanced Search' selected, and 'Match term to subject heading' checked (years 1970 – current). Terms;

1. Search terms;
- Epilepsy (subselect epileptic seizures) - Seizures - Encephalopathies - Infant development (subselect neonatal development) - Child development (subselect early childhood development) - Preschool Students (subselect nursery school and kindergarten) - Cognition (subselect cognitive development, cognitive impairment, and cognitive processes) - Cognitive ability (subselect spatial ability/verbal ability/cognitive processing speed/executive function) - Metacognition (subselect comprehension/memory/learning) - Intelligence (subselect intelligence quotient, intellectual development/reasoning/thinking) - Intellectual development disorder (subselect adaptive behaviour) - Psychological assessment (subselect behavioural assessment/ cognitive assessment/Neuropsychological Assessment) - Psychophysiology - Attention - Attention deficit disorder (subselect ADHD/impulsiveness/ODD) - Mental disorders (subselect autism/impulse/PDD) - Social Behavior (subselect aggressive behavior/prosocial behavior/social cognition/social perception/social skills) - Behavior (subselect adaptive behaviour/ antisocial behaviour) - Behavior disorders (subselect aggressive behaviour/behaviour problems/conduct disorder) - Emotional states (subselect anxiety/depression/fear /emotional disturbances) - Child psychopathology (subselect child psychiatry/child psychology) - Neuropsychology - Learning disabilities - Memory (subselect episodic/long term/short term/spatial/verbal/visual) - Comorbidity - Language disorders (subselect communication disorders/specific language impairment/language delay/speech disorders)
2. Title and abstract search terms;
- epilepsy, children, infant*, toddler*, preschool*, cogniti*, and behaviour

(iv) Web of Science

Search using free-text search under 'advanced search' (years 1970 – 2014);

Free-text search terms;	
- Epilep*	- "Non-verbal ability"
- "Pediatric epilepsy"	- Neurobehav*
- "Childhood Epilepsy"	- "Neurobehavio$ral Comorbidit*"
- "Epilep* Encephalopath*"	- "Psychiatric Comorbidity"
- Preschool*	- Psychopathology
- Infant*	- Comorbid*
- Children	- Behavio$r (returns a lot of hits)
- Childhood	- "Behavior disorder"
- Toddler*	- "Social behaviour"
- Cognition (gets a lot of irrelevant hits)	- "specific language impairment"
- "Intellectual Impairment"	- "speech disorder" (or)
- "Cognitive-Intellectual-Performance"	- "Communication disorder" (or)
- "Executive Function*"	- "Language impairment" (or)
- "Cognitive function*"	- "Attention deficit hyperactivity disorder" (or)
- "Cognitive assessment"	- ADHD
- IQ	- "Conduct Disorder"
- "neuropsychology"	- "Social Cognition"
- "neuropsychological function"	- "Autism Spectrum Disorders"
- Intelligence	- Anxiety
- "Processing speed"	- Depression
- "Cognitive ability"	- "Memory Impairment"
- "Verbal Ability"	

(v) CINAHL Plus (years 1970-2014)

Search using CINAHL Headings and free-text searches;

1. Search using CINAHL headings;
- Epilepsy (exp)
- Child (expand and select Child, Preschool and Infant [expand and select Infant, Newborn (exp)]
- Cognition (expand and select learning, perception, thinking, memory [expand and select short term and recognition])
- Cognition disorders
- Intelligence
- Psychological Tests (exp)

- Language disorders (expand and select speech disorders) - Behavior (expand and select Child behaviour [expand and select Infant Behavior], Social Behavior, Emotions [expand and select Anxiety], Neurobehavioral Manifestations [expand and select Intellectual Disability, Memory Disorders]) - Comorbidity - Psychopathology - Autistic Disorder - Mental Disorders (expand and select Mental Disorders Diagnosed in Childhood [expand and select ADHD, Child Behavior Disorders, Child Developmental Disorders (exp), Communication Disorders (exp), Developmental Disabilities, Learning Disability])
2. Free-text title and abstract search terms;
Epilep*, Children, toddler*, infant*, preschool*, cogniti*, “executive function*”, intelligence, IQ, “verbal ability”, “non-verbal ability”, memory, learning, language, speech, behavior, behaviour, neurobehavio*, psychopathology, anxiety, depression, autism, ADHD, and attention

Appendix B – Participant Information Sheet

Parent Information Sheet

Study Title: NEURO-PROFILES – Neurodevelopment in Preschool Children Of Fife and Lothian Epilepsy Study

You and your child are invited to take part in this research study on children with epilepsy. Please read through the information sheet before deciding if you would like to part. Contact details will be provided should you require more information. Thank you for taking the time to read this information sheet.

Who is conducting the study?

The study is being conducted by researchers from the University of Edinburgh in collaboration with colleagues from NHS Lothian and Fife. Further information about these organisations can be found in the "More Information" section.

What is the aim of the study?

We aim to investigate how epilepsy affects children in ways other than just seizures as some children also have behavioural or thinking difficulties. These difficulties can often go unrecognised or untreated. The aim of this study is to be the first of its kind to determine what kind of difficulties children with epilepsy have, how common they are, and factors that might contribute to them.

What we hope to achieve

By performing studies like these we hope to ultimately improve the overall care and treatment for children with epilepsy and their families. This will be done by using the findings to influence policies on epilepsy care and practice, and by improving treatment guidelines and educational resources.

Why have I been invited?

You have been invited because we hope to assess every child under the age of five with newly diagnosed epilepsy who are resident in the city of Edinburgh, West Lothian, or Fife

council areas or have received part of their care through a hospital in these regions. You have been identified through the Lothian and Fife NHS epilepsy network. We also hope to assess children without epilepsy for similar thinking and behavioural difficulties.

Do I have to take part?

You do not have to take part. If you decide not to take part this will not affect you or your child's legal rights and it will not affect the quality of care your child will receive.

What will happen in the study?

We will ask you some questions about your child and to complete some questionnaires. These questions may include how your child is affected by epilepsy and aspects of your child's behaviour. The questionnaires measure things like attention, mood, how a child behaves in social situations, and how they develop adaptive skills during childhood. You will be invited to the Royal Hospital for Sick Children, Edinburgh, Queen Margaret Hospital, Dunfermline, or the University of Edinburgh where we will ask your child to take part in some psychological tests to measure different aspects of their development such as memory, attention, and general development.

We will also use eye-tracking to assess memory and attention. This involves watching a screen with still or moving pictures while a remote device situated on the computer records eye movements. This is safe and requires no direct contact with the eyes. Eye-tracking will take approximately 30-40 minutes. Eye-tracking is suitable for children with attention difficulties such as short attention span.

As part of normal epilepsy clinical procedure your child will undergo an MRI scan. We will ask to obtain copies of your child's scan. During an MRI scan the child is placed under general anaesthetic. An MRI uses a magnetic field to build a picture of the brain. It is a painless and harmless procedure.

We will ask you as parent/legal guardian to sign a consent form on the day of assessment which will allow you and your child to take part.

Are there any benefits to taking part?

People take part in research for different reasons. Taking part in the research may be fun and/or of interest to you, and some people also feel they are giving back to the community. We will provide an individualized report of the neuropsychology assessment which you will receive upon completion of the study. Additionally this research may lead to a better understanding of childhood epilepsy and toward better treatment for those affected.

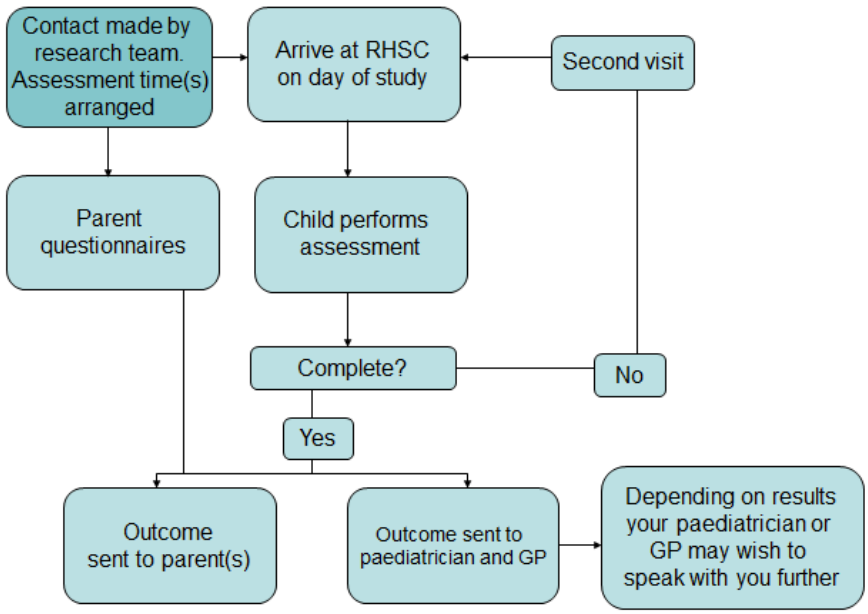
Are there any risks to taking part?

The assessments pose no physical risk to you or your child. The questionnaires and tasks are tried and tested standard clinical assessment tools. Eye-tracking is non-invasive and requires no contact with the eyes. This study has been reviewed by the NHS South East Scotland Research Ethics Service.

The assessment may take a few hours. The length of time will depend on factors such as the age of your child or attention and interest level. It is best to set aside a half day for assessment. There will be plenty of opportunity to take breaks as required. Assessment can be split over two or more occasions if you feel this would be better suited to your needs. If you or your child feel tired or stressed during assessment or for any other reason then you have the right to stop the assessment without giving explanation.

Travel costs and lunch expenses (if required) will be reimbursed to a maximum of £30. Please keep any travel and/or expenses receipts.

Should the testing reveal any implications for your child's development such as learning or behavioural issues then these will be discussed with you by your paediatrician (see diagram below).



Flow chart of study and outcomes

What will happen to the results of this study?

The results of the research will be published in appropriate peer-reviewed scientific journals for distribution to other healthcare professionals. Talks and presentations may be made. In all cases, your name and personal details will not be identified.

Will this information be kept confidential?

Yes. The study adheres to strict UK legislation, NHS and University confidentiality guidelines. All information collected will be anonymised and no personal information will be made public. All participants will be given a unique code number in place of personable data. Information may be passed to your paediatrician to enhance the care of the child. As per the Child Protection Act (1995), all information will be kept in the strictest of confidence except where there is risk to the safety of your child.

You have the right to end the study at any time without explanation. You also have the right to withdraw your data after the study if you so wish.

Can I get involved in future studies?

Yes. Tracking the progress of children's development is vitally important in understanding how epilepsy effects the individual throughout their lifetime and how epilepsy itself influences the course of natural development. We would like to follow-up your child to obtain a developmental profile over time.

To do this we will ask for your permission to access routinely stored data on the social, education, and health care of your child. In Scotland routine information is held on children by the Scottish Government and National Health Service. Access to this information is carefully controlled and we would seek permission from relevant bodies such as the Privacy Advisory Committee before accessing information on your child.

Such data might include statistics on hospital visits, pupil absence rates, or in-school support needs. By linking this kind of information with your data from the current NEUROPROFILES study, the research is more useful as we can look at the impact of early onset epilepsy on children's longer term health and wider circumstances which will allow us to inform policy makers on the additional educational, health, and social needs of children with early onset epilepsy.

Only relevant and necessary information would be made available to us. We would not have access to your child's full medical or other records. We will take great care to protect the confidentiality of the information we are given and it will be used for statistical research purposes only. No information will be released from this or future studies that could identify individual participants or families. If you do not wish the research team to access this information in the future it will not affect participation in the current study. When your child

reaches the age of 12 years they will have the option to consent for themselves. The research team will contact them personally and ask for consent in order to access any stored information.

Additionally we may invite you and your child to take part in future studies like this one which involve similar kinds of assessments. We do this to accurately track developmental paths which can vary greatly over time. However, you are under NO obligation to decide this now.

We will simply ask to retain your contact details in order to contact you at a future time. If you would not like to be contacted in the future this will not affect your involvement in the current study in any way.

Who do I contact if I have any more questions?

If you have any questions about the study or about research in general you can contact the Research Fellow **Matthew Hunter** on **0131 536 0801** or email M.Hunter-7@sms.ed.ac.uk or the Chief Investigator **Dr Richard Chin** on **0131 536 0841** or email r.chin@ed.ac.uk. If you wish to contact someone not involved in the study but who can provide information about the project then please contact **Dr Jay Shetty**, Consultant Paediatric Neurologist, RHSC on **0131 536 0727** or email Jay.Shetty@nhslothian.scot.nhs.uk.

What do I do now?

You will be contacted by telephone by a member of the research team in no less than 24 hours. You will have the opportunity to discuss anything further and decide if you would like to participate in the study.

Let us take this opportunity to thank you for taking the time to read this information leaflet and for your interest thus far.

What if I have a complaint?

If you wish to make a complaint about the study please contact your NHS Health Board;

NHS Lothian Complaints Team

2nd Floor

Waverley Gate

2-4 waterloo Place

Fife NHS Board
Hayfield House
Hayfield Road
Kirkcaldy

Edinburgh, EH1 3EG

Tel: 0131 465 5708

Fife, KY2 5AH
Tel: 01592 648 153

More Information

More information on the various organisations can be found here;

University of Edinburgh http://www.ed.ac.uk

Child Life and Health http://www.crh.ed.ac.uk/clah/

NHS Scotland http://www.show.scot.nhs.uk/

MMEC http://www.edinburghneuroscience.ed.ac.uk/MuirMaxwellCentre/

NHS National Services Scotland Information Services Division
http://www.isdscotland.org/

Appendix C – Participant Consent Form

NEURO-PROFILES – Neurodevelopment in Preschool Children Of Fife and Lothian Epilepsy Study

Consent Form

Please initial box

1. I confirm that I have read and understood the information sheet (12/11/13 version 5) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my child's and my own participation is voluntary and that we are free to withdraw at any time without giving any reason. ☐

3. I understand that the results as well as the participation in the current experiment will be confidentially treated. ☐

4. I agree to let my personal details be stored securely to enable contact by the research team in the future and I understand that I can request to withdraw this information at any time in the future. (In the event of loss of capacity you and your child will be withdrawn from the study. Data already collected will be retained and used in the study.) ☐

5. I allow the research team to access routinely stored data on education, health and social information for my child, as described in the study information sheet, to follow-up my child's development. ☐

6. I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by individuals from the sponsor(s), regulatory authorities or from the NHS Board, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my child's records. ☐

7. I agree to let my child's GP and/or Paediatrician be informed of entry onto the study and to be informed of assessment results if appropriate. ☐

8. I **c**onsent to my child and I taking part in the above study, and understand that not taking part will not affect the quality of my child's care in any way. ☐

Child's name:_____

Parent/guardian's name:_____

Parent/guardian's signature: _____ Date:_____

Person taking consent:_____ Date:_____

Appendix D – Anonymously gathered data

- Age (determined by age at diagnosis)
- Gender
- Socioeconomic status (determined using Scottish Index of Multiple Deprivation as described in - chapter I, section 2.4.3)
- Aetiology (ILAE 1989 and 2010 classifications)
- Mode of seizure onset
- Date of first seizure
- Seizure type(s)
- Ethnic origin
- Epilepsy syndrome

Appendix E – Medical History Questionnaire

1. Basic information

- Gender (male/female)
- Birth weight (kg)
- Gestation time (weeks)
- Birth order (sibling order)
- Twin (yes/no)
- Breast fed duration (months)
- Ethnicity
- Parent marital status

2. Epilepsy-related information

- Date or age at first seizure
- Diagnosis date or age
- Syndrome
- Seizure frequency (current)
- Time since last seizure (days/weeks)
- History of febrile seizures (yes/no)
- History of status epilepticus if known or longest seizure duration
- Status epilepticus frequency
- Current AED medication (type/dosage)
- Previous AED medication (type/dosage)
- Time on current AED (days/weeks)
- Other significant medications

3. Other relevant information

- History of pregnancy complications/medication during pregnancy/history of drug or substance abuse during pregnancy
- Family history of epilepsy or febrile seizures
- Family history of psychiatric/mental disorder, learning disability, or developmental disorder
- Other significant medical history of child

Appendix F – Electroencephalograph Characteristics Proforma

EEG No:	
Age/ DOB	
Medication	

SECTION A: OVERALL FINDINGS:

1. Conscious state recorded: Wake only
Sleep only
- record deepest sleep stage N1 N2 N3 REM

Wake and sleep
- record deepest sleep stage N1 N2 N3 REM

2. Attacks recorded: Yes
No

3. Overall impression of EEG: Normal
Abnormal
- Abnormal, non-epileptiform
- Abnormal, epileptiform

IF ABNORMAL, COMPLETE SECTION B

SECTION B
1. Non-epileptic abnormalities:
- slow activity (abnormal for age) recorded? YES / NO
  - intermittent
  - continuous
  - focal
  - generalised

2. Epileptiform abnormalities:

- Interictal epileptiform discharges recorded? YES / NO
    - Focal – single focus
    - Focal – multifocal, unilateral
    - Focal – multifocal, bilateral
    - Generalised

- Ictal changes recorded? YES / NO
    - Focal – single focus [temporal / extratemporal]
    - Focal – multifocal, unilateral
    - Focal – multifocal, bilateral
    - Generalised

3. Any syndrome-specific pattern? YES / NO
    - Idiopathic generalised epilepsy
        -CAE other
    - Symptomatic generalised epilepsy
        -West Syndrome Lennox Gastaut Syndrome Other
    - BECTS
    - Benign occipital epilepsy
    - Other (describe)

Appendix G – Search strategy for systematic review (chapter II, section 3.2)

Database Selection: (i) Medline (Ovid) from 1946, (ii) Embase classic and EMBASE (Ovid) from 1946, and (iii) Web of Science Core Collection (Thomson Reuters).

Main target search terms: Children, epilepsy, incidence, and epidemiology**.**

Database specific searches;

(i) Medline, and (ii) EMBASE classic and EMBASE

MESH search terms with relevant subheadings, and supplementary free-text searches were used;

1. MESH terms;
- Epilepsy (includes seizures and seizure disorders) - Preschool (subselect child preschool, child, and infant) - Minors - Incidence - Epidemiology

2. Title and abstract free-text searches;
- epilepsy - children, infant*, toddler*, or preschool* - incidence - epidemiology

(iii) Web Of Science

Terms searched using 'topic' searches;

1. epilep* OR "pediatric epilepsy" OR "paediatric epilepsy" OR "childhood epilepsy" OR "epilep* encephalopathy*"

2. preschool* OR Infant* OR Children OR Childhood OR Todller*

3. incidence OR epidemiolog*

Appendix H – Risk of Bias assessment

Methodological quality checklist from Kotsopoulos et al (2002)		
1. Definition of epilepsy, epileptic seizures	0 1 5	No Yes – not clear Yes - clear
2. Type of study	9 4 3 2 1	Prospective Review of medical records and re-examination of positive cases Review of medical records Survey and re-examination of positive cases Survey
3. Study population		
- a. Demography	0 2	No Yes
- b. Description of selection cases	0 1 3	No Yes – not clear Yes – clear
4. Epilepsy, epileptic seizures	3 2 3 0	Epilepsy Certain seizures Unprovoked seizures epileptic seizures (provoked and unprovoked)
5. Incidence rates	1 1 1 1 1 0 1	Age adjusted age specific syndrome specific Sex-specific Cumulative incidence rates time trends
Maximum possible score 30		

Risk bias assessment NEUROPROFILES		
1. Definition of epilepsy or infantile spasms/West Syndrome	0 1 2	No Yes – not clear Yes – clear
2. Population type	2 3	Cohort (e.g. GP or birth) Geographic only
3. Identification		
a. Prospective	1 2 3	Questionnaire survey Surveillance of medical departments Mixed surveillance and medical registries
b. Medical registry only	1 2	None or partial validation of positive cases Full validation of cases
4. Identification sources	2 3	Single Multiple
5. Population denominators or confidence intervals stated	0 3	No Yes
6. Incidence period	1 2 3	One year Two to five years ≥Six years
Maximum score 18*		

* Minimum score was 6, and a maximum score was 18. A score of ≤12 was considered a high risk of bias, and 13-18

Points for each subsection were determined on a scale of 0 to 3. 0 points reflected an absence of a factor that may have improved accuracy of the true estimate, to a maximum of 3 points for the inclusion of methods that maximally increase the accuracy of the estimate or reduce bias.

Subsection rationale;

1. Definition - A clear definition of epilepsy is required in order to determine the accuracy of the underlying population.

2. Population type – A cohort design (e.g. birth cohort or General Practitioner surgery) may potentially underestimate cases by excluding cases who have migrated into the area, or not registered with a General Practitioner.

3. Identification – prospective design was given more weight than retrospective studies as per Kotsopoulos (2002). Mixed sourcing given more weight as this increases potential identification.

4. Identification sources – multiple sources of case identification are preferred, as they are more likely to maximise case ascertainment.

5. Population denominators or confidence intervals stated – All incidence estimates are likely to differ, even within the same population. As such, a confidence interval allows an appraisal of the uncertainty around the estimate.

6. Incidence period – Incidence figures within a region may vary by year, and cases identified by underlying population size. Thus, longer identification phases increase total person-years and may improve certainty of the estimate.

Appendix I – ESSENCE Questionnaire

_____ _____ Girl Boy

Name of child Age

_____ _____

Completed by Date

Please take a few minutes to read and check the following items.

Have you (or anybody else, who?_____) been concerned for more than a few months regarding child´s

		Y	M/AL	N*
1.	General development			
2.	Motor development/Milestones			
3.	Reaction to sensory environment (sounds, light, smell, taste, heat, cold)			
4.	Communication/language/babble			
5.	Activity level (overactivity/passivity) or impulsivity			
6.	Attention/concentration/"listening"			
7.	Social interaction/Interest in other children			
8.	Behaviour			
9.	Mood ("depressed", "elated", "crying spells")			
10.	Sleep			
11.	Feeding			

Y=Yes; M/AL=Maybe/A little; N=No

Appendix J – Abbreviations

ABAS II – Adaptive Behaviour Assessment System, second edition
AC – General adaptive composite of ABAS II
ADHD – Attention Deficit Hyperactivity Disorder
AED - Antiepileptic drugs
ANCOVA – Analysis of covariance
ANOVA – Analysis of variance
AOI – Area of interest
ASD - Autism spectrum disorder

BRIEF-P - The Behavioural Rating Inventory of Executive Function – Preschool
BMEI - Benign Myoclonic Epilepsy of Infancy

CAE - Childhood Absence Epilepsy
CEC - Conners Early Childhood-Behaviour Scales
CI – Confidence interval
CWEOE – Children with early-onset epilepsy

DSM - Diagnostic and Statistical Manual of Mental Disorders
DQ – Developmental quotient

EEG – Electroencephalogram
EMM – Estimated marginal mean
ESSENCE-Q - Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations – Questionnaire

FET – Fisher's exact test
FSIQ – Full scale intelligence quotient

GCA - General cognitive ability
GEC – General executive composite
GQ - General quotient
GP – General Practitioner

ILAE - The International League Against Epilepsy
IQ - Intelligence quotient
IQR – Interquartile range
ISI – Interstimulus interval
ITSEA - Infant and Toddler Social Emotional Assessment

M – Mean
M-CHAT - The Modified Checklist for Autism in Toddlers
MD – Mean difference
MRI - Magnetic resonance imaging

NEPSY – The Developmental Neuropsychological Assessment

OR – Odds ratio

PRISMA - Preferred Items for Systematic Reviews and Meta-Analyses

rANCOVA – Rank analysis of covariance

SD – Standard deviation
SDQ – Strength and Difficulties Questionnaire
SEGC – Social Emotional Growth Chart
SES - Socioeconomic status
SIMD – Scottish Index of Multiple Deprivation
SNP – Spatial negative priming
SRS-2 - The Social Responsiveness Scale - Second Edition

TFD – Total fixation duration
TSC - Tuberous sclerosis complex
TTFF – Time to first fixation

VABS - Vineland Adaptive Behaviour Scales
VPC – Visual paired comparisons

WPPSI III – Wechsler Preschool and Primary Scales of Intelligence