Factors predictive of emotional and behavioural difficulties in children with refractory focal epilepsy

By

Margarita Sarri

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Royal Holloway, University of London

Abstract

Focal epilepsy in childhood is associated with increased risk for developing behavioral, emotional, cognitive and social–adaptive impairments. The present thesis focused on mental health difficulties in paediatric refractory focal epilepsy. It undertook a detailed evaluation of the predictive power of several demographic (gender, age at assessment), clinical (age at onset and duration of epilepsy, seizure frequency), localization (lobe and lateralization of pathology) and cognitive variables (performance in intellectual, memory and academic attainment measures) for mood, conduct, inattention/hyperactivity and peer relationship difficulties, as assessed by parental report. Data from a population of 282 children and adolescents, previously collected for clinical purposes, were examined, using a series of univariate and multivariate analyses. Mental health difficulties were found to be highly prevalent, with peer relationships the most frequently reported area of difficulty, followed by inattention/hyperactivity and emotional difficulties. Different patterns of associations between the variables examined here and individual emotional/behavioural difficulties were revealed, partially confirming and extending previous findings in the literature. Longer duration of epilepsy was found to increase the risk for developing emotional difficulties; male gender and earlier age at onset the risk for conduct difficulties; male gender, earlier age at onset, longer duration and frontal lobe localization the risk for attention/hyperactivity difficulties; and finally longer duration, higher seizure frequency and right hemisphere lateralization the risk for peer difficulties. Lower cognitive functioning was found associated with overall increased mental health difficulties and a lower VIQ was predictive of all types of difficulties. Developing a firm understanding of the risk factors that contribute to mental health comorbidities in focal paediatric epilepsy can help identify and provide assessment and intervention to children who are at higher risk earlier, thus significantly improving quality of life.

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Chapter 1

Introduction

An introduction to risk factors associated with emotional and behavioural difficulties in paediatric focal epilepsy

1.1 Introduction

Epilepsy is a neurological disorder characterized by an enduring predisposition of the brain to generate recurrent, unpredictable and typically unprovoked epileptic seizures (Fisher et al., 2005). The burden of epilepsy is much more complex than the mere presence of seizures suggests. Epilepsy in childhood is associated with increased risk for behavioral, emotional, psychiatric, cognitive and social–adaptive impairments as a result of chronic and persistent seizures (Austin & Caplan, 2007; Lin et al., 2012). These comorbidities are a major potential source of disability in children and adults with epilepsy and occur with higher frequency in epilepsy than in other chronic medical illnesses, highlighting the importance of the underlying neurologic disorder in the etiology of the deficits (Smith et al., 2002).

Epilepsy is estimated to affect 1.2% of the adult population in England and 50 million people worldwide with a yearly incidence of 40–70/10,000 (Rai et al., 2012). Approximately two thirds of the epileptic seizures start during early childhood (Beletsky & Mirsattari, 2012). As a result of the high frequency of epilepsy and its adverse effects on the course and quality of life an extensive literature exists on understanding its etiology and associated features, as well as on developing appropriate interventions and management strategies. An understanding of the mechanisms and consequences of epilepsy is essential in developing interventions aimed at minimizing the impact of epilepsy during development and helping each child maximize his/her potential.

Emotional and behavioural comorbidities in epilepsy are very common and represent an area of major need for targeted interventions. Although the literature on emotional and behavioural difficulties associated with epilepsy is growing, a number of important questions remain unanswered. Are the emotional-behavioural problems caused by the same brain pathologies that lead to seizures? Could they be due to ongoing abnormal electrical activity which may have subtle

effects on wider brain function? Alternatively does the burden of epilepsy create psychosocial challenges that lead to emotional-behavioural difficulties independent of any organic pathology?

Overall, there are currently few firm conclusions with regards to the risk factors for developing emotional or behavioural difficulties in childhood epilepsy and no comprehensive theoretical framework for these exists (Austin & Caplan, 2007). A selective review of risk factors associated with emotional and behavioural difficulties associated with childhood focal epilepsy is presented below. Specifically it focuses on existing evidence with regards to possible risk factors for the development of emotional, conduct, attention-hyperactivity and peer problems in childhood focal epilepsy. In particular the review focuses on epilepsy-specific factors (e.g. age at onset of epileptic disorder), the localisation and lateralisation of the epileptic focus, as well as cognitive functioning. A broad overview of the research evidence related to each potential risk factor is provided first and then available findings are discussed individually with regards to emotional, conduct, attention and social problems. Finally, the specific aims of the study are outlined.

1.2 Focal epilepsy and surgical treatment

Epileptic syndromes can be broadly categorised as “generalised” or “focal”. In generalised epileptic syndromes seizures tend to begin from and/or affect the whole of the neocortex. In contrast, focal epileptic syndromes (also called ‘partial’), accounting for approximately 40–60% of childhood epilepsy syndromes (Cowan, 2002), are characterised by seizures which have an onset in a localised area of the brain. Based on their aetiology, focal seizures can be distinguished as symptomatic (or presumably symptomatic) when there is a known (or suspected) underlying pathology (e.g. lesion, malformation, tumour) or idiopathic when no underlying pathology is found or is suspected.

The International Classification of Epilepsies recognises four main types of focal epilepsies: temporal lobe epilepsies (TLE), frontal lobe epilepsies (FLE), parietal lobe epilepsies (PLE), and occipital lobe epilepsies (OLE). This classification is not tied to specific causes or aetiologies (with the exception of hippocampal sclerosis in TLE), but rather depends on the epileptogenic focus (see Figure 1.1). TLE is the most common focal epilepsy syndrome in both children and adults and is undoubtedly the most studied in terms of its psychopathological and cognitive profile (Beletsky & Mirsattari, 2012). Most frequently TLE has an onset in childhood or adolescence and is typically characterised by a prolonged and intractable course. Mesial TLE associated with hippocampal sclerosis in particular is recognised as a discrete syndrome, accounting approximately for 70% of all TLE cases (Jokeit et al., 2004). Representing the second largest subgroup of focal epilepsy syndromes, FLE accounts for approximately 30% of the cases (Elger et al., 2004). Finally PLE and OLE are much less frequent and are estimated to account for approximately 5% and 6–8% of individuals with focal epilepsy respectively (Gleissner et al., 2008; Manford et al., 1992).

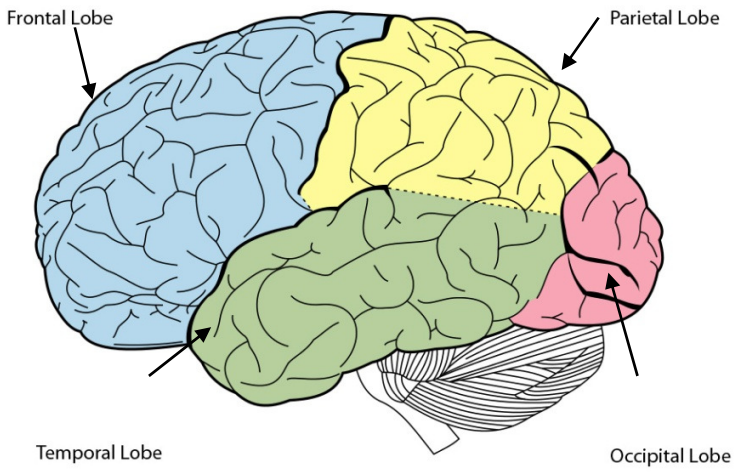

Figure 1.1. Lobes of the brain.

Current treatments for focal epilepsy in childhood include the use of antiepileptic medication, as well as non-pharmacologic options such as the ketogenic diet, vagus nerve stimulation and surgical intervention (Joshi et al., 2013; MacAllister & Schaffer, 2007). In recent times, epilepsy surgery for medically intractable epilepsy in carefully selected candidates with identified lesions has significantly increased in prominence as a treatment. Patients with TLE are frequently candidates for epilepsy surgery, due to circumscribed lesions and poor control by antiepileptic drugs. FLE is the second most frequent epilepsy type to receive surgical treatment representing 15% of intractable seizure disorders (Patrikelis et al., 2009).

Although traditionally, surgical interventions in focal epilepsy primarily aim to reduce or eliminate seizures, considerations for surgical success have now expanded to also include developmental, cognitive, emotional, behavioural and social outcome (Follett et al., 2012; Joshi et al., 2013). Obtaining neuropsychological baseline data is standard practice during the comprehensive pre-surgical workup and as a result many neuropsychological studies, including the one presented here, have employed samples of children during the pre-surgical stage to study the effects of focal epilepsy on mental health or cognition. As children with TLE are the most frequent candidates for epilepsy surgery, the mental health and cognitive profile of TLE is very well characterised (Deonna et al., 1986; Hermann & Seidenberg, 2007).

Surgical removal of lesions involved in the generation of seizures has been shown to stop or significantly decrease seizures in 50- 90% of children (Smith et al., 2002). Surgical interventions in children can also have a favourable cognitive and emotional/behavioural outcome along with positive effects on brain development (Andresen et al., 2014; Loddenkemper et al., 2007; Skirrow et al., 2011). To date, few studies have examined the impact of epilepsy surgery on emotional and behavioural functioning in children per se, however all indicate a favourable outcome. Using standardised measures of emotional and behavioural functioning, typically based

on parental report, these studies have demonstrated variable improvements in difficulties with attention and hyperactivity, internalizing and externalizing symptoms and social difficulties (Andresen et al., 2014; Lendt et al., 2000; McLellan et al., 2005; Titus et al., 2013; Williams et al., 1998). Cognitive functioning also appears to benefit from epilepsy surgery, as demonstrated by improvements in overall intellectual functioning (e.g. Hallböök et al., 2013; Ramantani et al., 2013; Skirrow et al., 2011). Furthermore, the freedom from seizures following surgery leads to a significant improvement in quality of life and is the most significant predictor of psychosocial outcome following surgery (Sabaz et al., 2006; Skirrow et al., 2011; Spencer & Huh, 2008; Titus et al., 2013). In contrast, poor seizure control has been associated with a gradual decrease in intellectual functioning and decreased quality of life over time (Bjornaes et al., 2001).

1.3 Overview of emotional and behavioural problems associated with focal epilepsy

Findings from epidemiological investigations unequivocally demonstrate an increased prevalence of emotional, behavioural and other mental health disorders in epilepsy (see Austin & Caplan, 2007; Lin et al., 2012 for recent reviews; also Ottoman et al., 2011 for recent epidemiological studies). A recent large epidemiological study in the USA (Russ et al., 2012) reported increased levels of psychopathology in children with epilepsy compared to healthy controls, highlighting an increased prevalence of depression (8% versus 2%), anxiety (17% versus 3%), attention deficit hyperactivity disorder (ADHD; 23% versus 6%), conduct disorder (16% versus 3%), developmental delay (51% versus 3%) and autism spectrum disorder (16% versus 1%). A recent meta-analysis (Quintas et al., 2012) further characterised the psychosocial effects of epilepsy by identifying the most frequently reported problems to be depression, anxiety,

poor quality of life (e.g., work, transportation, and interpersonal relationships), cognitive functions in general, memory functions, real and perceived stigma and locus of control. Overall there is now accumulated evidence suggesting that children and adolescents with epilepsy are at considerable risk of developing mental health difficulties, particularly depression, ADHD and conduct disorder compared to both the general child population and those with other non-neurological chronic health conditions (Davies et al., 2003; Turky et al., 2008).

Importantly, after several years of debate it is still unclear whether mental health problems experienced by individuals with epilepsy are integral parts of the same neurophysiological process or whether they represent independent comorbidities. While some mental health issues, such as anxiety disorders could be often attributed to an emotional response to living with a chronic and debilitating illness (for example as a result of stigma, social isolation, coping difficulties, parental depression etc.), others, such as ADHD symptoms, may be somewhat more difficult to explain. Indeed the literature suggests that while the pattern of some internalizing disorders (e.g. anxiety, adjustment disorder) in children with epilepsy often resembles that found in children with other chronic health conditions that do not involve the central nervous system (Boekaerts & Roder, 1999; Ettinger et al., 2004), the pattern of other mental health conditions (e.g. depression, ADHD) resembles that found in children with other conditions affecting the brain (e.g. head trauma; Luis & Mittenberg 2002; Max et al., 2004). A recent meta-analysis of findings from 46 studies, including data from 2,434 children with epilepsy, contrasted mental health problems in children with epilepsy to control groups, healthy siblings, and children with other chronic conditions (Rodenburg et al., 2005). The results indicated a specific association of cognitive, attentional and social problems with childhood epilepsy, whereas problems with withdrawal, somatic complaints, anxiety/depression, delinquency and aggression were found to be similar in children with epilepsy and their healthy siblings or children with other chronic health

conditions. These findings provide some support for the existence of some potentially common pathophysiological mechanisms between epilepsy and at least some specific mental health comorbidities which however are yet to be precisely identified (Beletsky & Mirsattari, 2012).

An obvious common pathophysiological mechanism under investigation is the seizure activity itself. Epileptic activity is known to cause enduring changes in brain function, structure and connectivity in many different ways, which can result in behavioural alteration (Holmes, 2005; Lin et al., 2012). There is evidence that focal or generalized seizures may be associated with neural damage (Rabinowicz, 1996; Racine et al., 2002) and that seizures may lead to a toxic increase of extracellular glutamate, which may have adverse effects on brain function (During & Spencer, 1993). Repeated seizures can also impact negatively on the normal neuronal development in infancy or early childhood (Engel et al., 2002). Indeed, children with epilepsy exhibit abnormalities in brain structure at or near the time of epilepsy onset and consequently often follow an altered developmental trajectory (Lin et al., 2012). In the mature brain, abnormal synaptic activity may induce further plastic changes, with adverse consequences on the normal neuronal function (Engel et al., 2002).

The role of seizures in the development of mental health problems is difficult to disentangle from the underlying neurological dysfunction that causes the seizures, the possible side effects of antiepileptic medication, as well as the child and family response to the condition (Austin & Dunn, 2002). Indeed, several other factors are likely to affect the development of emotional or behavioural difficulties in children and adolescents with epilepsy, including biological factors such as the localisation and lateralisation of the epileptic focus and other epilepsy specific factors including the age of onset, the duration and the severity/frequency of the epileptic seizures, as well as demographic, psychosocial (e.g. family and socio-economic characteristics; McDermott et al., 1995) and cognitive factors.

In the late 1980s Hermann and colleagues (1988) proposed a multifactorial model delineating possible mechanisms underlying emotional, behavioural and psychiatric comorbidities in paediatric epilepsy. This model considers epilepsy-related variables (such as age at onset, duration of illness, type of seizure disorder, EEG pattern), demographic variables (such as gender and family income), neuropsychological variables (such as intellectual ability), medication related variables (such as number and types of antiepileptic drugs) and psychosocial variables (such as parents' marital status). Since then, several studies have shown that epilepsy-related variables, such as seizure control (Austin et al., 1992; Kolfen et al., 2001; Lendt et al., 2000), type of seizure disorder (Aman et al., 1992; Mandelbaum et al., 1997), age at onset (Kolfen et al., 2001; O'Leary et al., 1983), duration of illness (Kolfen et al., 2001), severity of seizure disorder (Turky et al., 2008) are associated with psychopathology in children with epilepsy. Demographic (Alfstad et al., 2011), psychosocial (Aydemir et al., 2011; Ma et al., 2010) and medication (Reijs, 2004; Trimble et al., 2000; Weintraub et al., 2006) risk factors have also been examined. Less is known however about the contribution of cognitive factors to childhood psychopathology in paediatric epilepsy and the effects of the location and lateralization of the epileptic focus. Also, when considering possible risk factors often no distinction is made between different types of mental health problems in relation to various types of epileptic syndromes.

1.4 Emotional-behavioural difficulties and epilepsy specific factors

While epilepsy specific factors such as age at seizure onset, duration of illness and frequency of seizures have been somewhat reliably associated with cognitive outcome, academic performance and developmental delay in paediatric epilepsy (e.g. Buelow et al., 2003; Rantanen et al., 2011; Schoenfeld et al., 1999; Turky et al.,2011; Vasconcellos et al., 2001), less is known

about their association with mental health problems (Jones et al., 2010; Thome-Souza et al., 2004). Although several cross-sectional studies have shown age at onset and duration of epilepsy to be associated with the development of mental health problems in children with epilepsy (Hermann et al., 1988; Oguz et al., 2002), the most consistent finding is a link between higher seizure frequency and increased mental health problems (Austin & Dunn, 2002). Emotional or behavioural problems are also more frequently seen in individuals with drug-resistant refractory epilepsy and poor seizure control (Cornaggia et al., 2006).

From a neuropsychological perspective, several studies support the view that brain damage sustained early in life may be more detrimental to cognitive abilities than brain damage which occurs after a longer period of relatively normal growth and development (Boll, 1973; Cormack et al., 2007; Dikmen et al., 1975; Fitzhugh and Fitzhugh, 1965). It is likely that a similar principle applies to mental health issues. However, in studies investigating the association of age at onset of epilepsy with mental health issues, intellectual ability constitutes an important confounding variable, as early onset is more likely to be associated with reduced intellectual ability. Findings of studies that include children with very early onset of epilepsy without controlling for both IQ and other seizure variables such as seizure frequency may be thus difficult to interpret (Kolfen et al., 2001; Thome-Souza et al., 2004; Datta et al., 2005). It is therefore important to control for IQ when investigating the association of epilepsy-specific variables with different mental health presentations.

Antiepileptic drugs (AEDs) are also associated with a high incidence of unintended emotional and behavioural side-effects, such as depression, anxiety, irritability, reduced concentration, mood changes and even psychosis. These have been observed with essentially all AEDs at variable frequencies (Reijs, 2004; Trimble et al., 2000; Weintraub et al., 2006). Further, the traditional AEDs (Phenobarbital, Phenytoin, Carbamazepine, Valproic Acid) have all been

additionally associated with sedation and cognitive slowing (Hixson & Kirsch, 2009). Unfortunately, for obvious ethical purposes, it is not possible to study children with unmedicated epilepsy, so all studies to date, including the present one are confounded by medication side effects.

In summary, several characteristics of the epileptic syndrome are likely to influence the development of emotional or behavioural comorbidities in children suffering from epilepsy, including higher seizure frequency, earlier age at onset and longer duration of the epileptic syndrome, as well as the number and type of AEDs taken.

1.5 Emotional-behavioural difficulties and localisation/lateralisation of epileptic focus

The localization of the epileptic zone in focal epilepsy has also been considered as a risk factor for the development of mental health difficulties following the neuropsychological model of investigation, which aims to link specific cognitive or emotional functions to specific areas of the brain. Although some evidence supports an association between the localization of the epileptic zone and emotional/behavioural comorbidities, the literature remains equivocal. A long-standing controversy exists, with several studies in adults proposing an overall increased occurrence of mental health difficulties in patients with TLE compared to other types of epilepsy (e.g. Altshuler et al., 1990; Brown et al., 1986; Gibbs, 1951; Quiske et al., 2000; Rodin et al., 1976). Other studies, however, have failed to demonstrate this (e.g. Fiordelli et al., 1993; Standage and Fenton, 1975; Stevens, 1966; Swinkels et al., 2001). While TLE is undoubtedly associated with a high risk for developing emotional or behavioural comorbidities, this longstanding controversy in

the literature has now been replaced by the view that mental health disorders can occur across various epilepsy syndromes (Lin et al., 2012).

The laterality of the seizure focus has also been examined as a potential risk factor for the development of mental health problems in focal epilepsy. The evidence again is mostly based on investigations in adults and is varied and inconclusive, with most studies implicating the left hemisphere (e.g. Altshuler et al., 1990; Lindsay et al., 1979; Mendez et al., 1994; Perini and Mendius, 1984; Septien et al., 1993; Stores, 1978; Victoroff et al., 1994) or finding no association between lateralization and psychiatric comorbidities (e.g.Hermann et al., 1991; Schmitz et al., 1997; Helmstaedter et al., 2004; Feddersen et al., 2005). Studies in children with epilepsy also show that cognitive deficits do not demonstrate a clear effect of lateralization according to the hemispheric side of seizure onset but appear to be rather diffuse (Kolk et al., 2001).

The presence of localized structural or functional lesions which give rise to specific functional deficits is a core methodological and theoretical concept of neuropsychology. While several studies have supported some specific associations between specific emotional/behavioural or cognitive deficits and different types of focal epilepsy, it is important to keep in mind that the nature of focal epilepsy raises some difficulties for neuropsychological investigations. This is because it may be difficult to directly localise a cognitive deficit or mental health issue to a specific structural lesion or the seizure onset zone. Epileptic seizures will frequently spread from the zone of onset into functionally relevant remote brain regions, and cause as a result neuropsychological deficits that appear to be atypical for the localization of the lesion (Lin et al., 2012). As a result the impact of epilepsy on neuropsychological outcomes is mediated by the location and extent of the pathology, the location of the ictal onset zone, as well as the spread pattern of the seizures. Usually, these mediating factors are of greater importance for neuropsychological functioning than the specific aetiology itself, although aetiology itself can

also be important, as it may drive the spread pattern of seizures. Furthermore, studies examining the localisation pathology in relation to mental health profiles in focal epilepsy (e.g. Altshuler et al., 1990; Brown et al., 1986; Gibbs, 1951; Quiske et al., 2000; Rodin et al., 1976) are limited in their majority by focusing on focal areas as opposed to brain networks that maybe involved in a specific function.

Thus, although specific associations may be made between mental health profiles and different seizure onset foci, it is important to keep in mind that mental health difficulties are likely to be manifestations of widespread abnormalities in neuroanatomical networks involved in mood or behaviour regulation. For example while in TLE, there is a well documented link between hippocampal atrophy and memory impairments (e.g. Mueller et al., 2012; Stewart et al., 2009), considerable structural abnormality has also been uncovered outside temporal regions, including subcortical and cerebellar regions, and their direct and indirect connections, which may be associated with further deficits (Bell et al., 2011; Caplan et al., 2005; Cormack et al., 2007; Riley et al., 2010; Weber et al., 2007).

Finally, when investigating the effects of the localisation or lateralisation of pathology in the development of mental health difficulties in the context of childhood or adolescence it is imperative to take into account the characteristics of the developing brain. The developing brain at a young age undergoes constant maturational changes including cellular pruning, myelin deposition and a gradual increase in synaptic efficiency and complexity of neural circuits (Duchowny, 2007). Importantly, localisation and lateralisation of functions appears to be less prominent in children than adults. The evidence shows that the developing brain is initially highly interconnected and anatomically and functionally significantly less differentiated and modular than the adult brain (Chilosi et al., 2001; Huttenlocher & Dabholkar, 1997; Neville, 2006; Vargha-Khadem et al., 2000). The developing brain is characterised by dynamic and complex interactions

of multiple, emerging systems, as well as functional flexibility (Moses & Stiles, 2002). It is only over time that functional specialisation gradually takes place and that neural networks become relatively modularized (D'Souza & Karmiloff-Smith, 2011).

While focal damage in a consolidated adult brain system can lead to specific and localised neuropsychological deficits, the developing brain which sustains damage early in life may potentially find alternative developmental routes to accommodate different functions (D'Souza & Karmiloff-Smith, 2011). For example, children presenting with perinatal lesions to regions well known in the adult literature (Friederici & Gierhan, 2013; Martin, 2003) for their crucial involvement in language, such as Broca's area, can still acquire language abilities (D'Souza & Karmiloff-Smith, 2011; Liegeois et al., 2004; Vargha-Khadem et al., 1994; 2000). Significant variability may exist however in the amount of neuronal plasticity observed in the developing brain (Liegeois et al., 2008). In children with left hemispherectormy for example spoken language skills tend to be more preserved than written language skills (Moosa et al., 2013). Overall, after early brain insult more recovery is observed for 'lower order' skills such as simple language, visual and sensori-motor skills than more complex skills, such as attention, executive functions or social cognition, which are likely subsumed by more diffuse neural networks (see review by Anderson et al., 2011). So while brain damage in the adult brain can selectively compromise cognitive ability, the same damage in the developing brain, even if it affects large areas of the brain, may potentially result in milder (but possibly more diffuse) deficits (Stiles et al., 2005). The potential of the more immature brain for greater neural plasticity is often used as a rationale for performing earlier surgery in patients with refractory epilepsy (Duchowny, 2004).

In conclusion, models of adult cognition defined in terms of independently functioning and localised modules should be applied to developmental disorders with caution. Constant maturational changes, the lack of clear functional localisation and the increased neuronal

plasticity at an early age may account for some of the difficulties encountered in the literature in establishing clear associations between mental health difficulties and the localisation of epileptic pathologies. These efforts may be further compromised by the nature of the focal epileptic syndrome with seizures affecting multiple areas by spreading from the zone of onset into remote brain regions, causing functional changes.

1.6 Emotional-behavioural difficulties and cognition

Cognitive function in focal epilepsy

Several population-based and community-based studies in paediatric epilepsy suggest an increased occurrence of cognitive difficulties in children with epilepsy compared to children without epilepsy, as indicated by poorer performance on psychometric tests (see Elger et al., 2004; Hermann & Seidenberg, 2007; Hermann et al., 2009; Jokeit, 2004; Lin et al., 2012; MacAllister & Schaffer, 2007 for recent reviews). Academic achievement problems have also been identified in this population, resulting in significantly higher needs for educational interventions. The proportion of intellectual impairment (FSIQ <80) in children with focal epilepsy has been reported to vary between 26% and 57% (Berg et al., 2008; Cormack et al., 2007). Intellectual functioning in childhood focal epilepsies has been shown to decrease within 3–4 years following seizure onset, a deterioration that is not found in patients with adult onset epilepsy (Bjornaes et al., 2001).

Research investigating the relationship between intellectual function and seizure-related factors such as aetiology, age at onset, duration, seizure type and severity, antiepileptic medications is extensive and goes back several decades (Dodrill, 2004; Elger et al., 2004;

Hermann & Seidenberg, 2007; Hermann et al., 2009; Jokeit, 2004; Jokeit & Ebner, 2002; Lin et al., 2012; MacAllister & Schaffer, 2007). Age at seizure onset has consistently been highlighted in the literature as an important predictor of cognitive ability, with early age at seizure onset linked to lower intellectual status (Berg et al., 2012; Kaaden et al., 2009; Vendrame et al., 2009). Onset of epilepsy in childhood is generally associated with a poorer cognitive outcome and a greater risk of developing learning disabilities, than is onset in adulthood (Jambaque et al. 1993; Williams et al. 1996). Also, children with an onset of seizures before 5 years of age have been found to be more impaired on a broad range of intellectual functions than those whose seizures began later in life (Dikmen et al., 1975; O'Leary et al., 1983) and children with seizure onset during the first year of life are especially likely to have a poor cognitive outcome (Vanderlinden & Lagae, 2004; Cormack et al., 2007). Seizure duration has also been shown to be a contributing factor with longer seizure duration associated with poorer intellectual ability, albeit with less predictive power (Strauss et al., 1995). Longer duration of epilepsy can result in a poor long-term outcome, as a result of ongoing and progressive deterioration (Lespinet et al., 2002), and therefore early seizure control is important. Studies investigating the effects of age at onset or duration of epilepsy however may be limited by the fact that while diagnosis of epilepsy relies on seizures, there may be neural abnormalities disrupting cognitive development before the occurrence of these. The contribution of other epilepsy related variables to cognitive impairment is less certain.

In addition, extensive efforts have gone into establishing cognitive profiles for several individual focal epileptic syndromes, and in identifying any shared versus unique cognitive deficits present across these (see McAllister & Schaffer, 2007; Nolan et al., 2003 for reviews). In the current literature, cognitive profiles are most often described in children and adults with TLE, whereas other lobar syndromes have been less thoroughly investigated (Battaglia et al., 2006; Cormack et al., 2007; D'Argenzio et al., 2011).

The typical cognitive profile of TLE patients, as established mostly from studies in adults, involves a characteristic and prominent memory impairment (Herman & Seidenberg 2007; Milner, 1959; 1972; 2005). Helmstaedter and colleagues (2002) examined a large cohort of 1000 patients with refractory TLE and reported that 70–80% of patients this group showed impairment of either verbal or figural memory, depending on the side of pathology. Distinctive patterns between left and right TLE patients have also been described. Patients with left TLE tend to have more prominent deficits in verbal memory and learning (Lacritz et al., 2002; Moore et al., 2002), whereas those with right TLE have been shown to manifest more prominent deficits in visual memory, with their verbal memory performance comparable to that of controls [Gleißner et al., 1998; Lacritz et al., 2002; Milner, 2005). In addition to the memory deficits, a more generalised and diffuse pattern of cognitive dysfunction has also been described in TLE patients, as indicated by poorer performance across all cognitive domains, compared to controls (Oyegbile et al., 2004). Patients with TLE of the speech-dominant hemisphere (typically left) also present with word-finding deficits (Jokeit et al., 2004). Attention and executive functions are frequently spared (Jokeit et al., 2004).

The neuropsychology of FLE has been less studied and the findings are less consistent as available studies usually have to rely on much smaller samples. Impaired attention, working memory and executive functions are the most frequently reported deficits for both children and adults (Braaktman et al, 2011; Exner et al., 2002; Rise, 2006). Executive functions may be more impaired in patients with left FLE than those with right FLE (Upton & Thompson, 1997). Attention and working memory deficits however do not seem to be a unique characteristic of FLE as these appear to be similarly affected in FLE and TLE (Helmstaedter et al., 1996; Helmstaedter, 2001). Deficits in planning and impulse control and response inhibition however have been shown to be a unique characteristic of children with FLE (Hernandez et al., 2002). Further reported deficits

include psychomotor speed slowing (Helmstaedter et al., 1996) and memory problems, although the latter are not as pronounced as in TLE (Delaney et al., 1980). FLE patients typically have IQ patterns that fall within normal limits, something also seen in patients with frontal lesions without epilepsy (Patrikelis et al., 2009). Age at onset of FLE has been consistently reported to have considerable influence on cognitive outcome and the presence of specific frontal deficits (Braaktman et al, 2011; Upton & Thompson, 1997).

Finally occipital and parietal lobe epilepsy cases are rather rare and as a result, no comprehensive and systematic neuropsychological group studies of patients with occipital or parietal epilepsy have been published. Deficits in intellectual functioning, memory and attention have been found both in children with occipital lobe epilepsy (Gulgonen, 2000) and parietal lobe epilepsy (Gleissner et al., 2008), although sample sizes in these studies have been particularly small. Luerding and colleagues (2004) reported relative impairments in performance IQ in patients with posterior epilepsy, compared to verbal IQ measures.

Association between emotional and behavioural and cognitive problems in paediatric focal epilepsy

Although behavioural/emotional and cognitive difficulties are both frequent comorbidities in paediatric focal epilepsy (see Austin & Caplan, 2007; Lin et al., 2012 for recent reviews) very few studies have attempted to examine the relationship between the two. In addition, the few studies that have, offer a limited insight due to a number of methodological limitations. Existing studies often focused solely on single measures of overall intelligence (typically the Full Scale IQ index from the WISC) or estimates of overall intelligence based on the presence of special educational needs (Turky et al., 2008). The degree to which impairments in other cognitive domains, such as

memory, increase the risk of developing emotional/behavioural difficulties remains to be identified. Further most studies have used very restricted samples of patients (e.g. Thome-Souza et al., 2004; Turky et al., 2008) or have failed to distinguish between different types of emotional-behavioural difficulties (e.g. Schoenfeld et al., 1999) or the type of epileptic disorder (e.g. Jones et al., 2010), frequently only focusing on TLE (e.g. Schoenfeld et al., 1999). The majority of studies that have not focused on a specific lobar syndrome, such as TLE, lack well-defined syndrome classification not distinguishing between children with generalised and focal seizures (e.g. Turky et al., 2008). Thus to date I am aware of no comprehensive study that has examined the role of a) different domains of cognition and b) the localization of epilepsy (by considering different lobar syndromes) as potential risk factors for the development of specific emotional or behavioural problems in paediatric epilepsy.

The few existing studies however imply a possible link between emotional/behavioural difficulties and level of cognitive functioning, which warrants further investigation. The overall picture implies that poorer intellectual functioning is associated with a higher risk for developing emotional or behavioural difficulties. In a study of 56 children with unspecified types of epilepsy Turky and colleagues (2008) found that cognitive impairment, broadly identified by the presence of special educational needs, was associated with behavioural problems, specifically conduct problems, hyperactivity/inattention and peer problems, as assessed by parental ratings. In a separate study, Caplan and colleagues (2004) found that, when taking into account seizure-related variables and demographic factors, Verbal IQ was the most robust predictor of the presence of a psychiatric diagnosis in children with TLE. However, this association was reported in relation to overall psychopathology levels. Population-based studies have also indicated an increased occurrence of psychopathology in children with epilepsy and intellectual disability (Steffenburg et al., 1996) or learning, language or other neurological disabilities (Davies et al.,

2003). Children with mild to moderate cognitive or linguistic deficits without epilepsy are also known to have an increased risk of developing emotional or behavioural problems (Handwerk and Marshall, 1998).

There are several theoretical reasons for expecting cognitive ability to be associated to emotional or behavioural difficulties. One is that higher cognitive ability, as problem solving aptitude, is likely to have an impact on how different stressors are perceived, how threat or available resources are assessed or healthier environments and relationships are sought (Masten et al., 1999). Children's intellectual abilities also play a significant role in their social and academic functioning and development, as well as in their self-esteem and sense of competence (Austin & Caplan, 2007). From a different perspective, neurobiological models of self-regulation propose that 'higher-order' cognitive functions play a significant role in self control and modulation of 'lower-order' emotional reactions (Banfield et al., 1999; Shamosh et al., 2008). In addition, a relationship between emotional/behavioural and cognitive comorbidities in epilepsy may reflect the effects of underlying structural and/or functional changes in brain areas associated with the seizures and/or the underlying pathology.

1.7 Specific emotional and behavioural problems associated with focal epilepsy

Mood and Anxiety Problems

Depression and anxiety are the most frequent mental health disorders in patients with epilepsy (Caplan et al., 2005; Cornaggia et al., 2006; Kanner et al., 2012; Tellez-Zenteno et al., 2007). The risk of depression is similar in children and adults with epilepsy and in the range of 23-

33% (Alwash et al., 2000; Dunn et al. 1999) and as high as 55% in some reports (Devinsky et al., 2003). Anxiety disorders are estimated to occur in 10–25% of patients with epilepsy, increasing in adolescence (Gaitatzis et al., 2004) and frequently co-existing with mood disorders (Kanner et al., 2004). By the time that patients with epilepsy reach adulthood up to 60% carry a formal diagnosis of depression or anxiety (Beyenburg et al., 2005). Individuals with epilepsy are also twice as likely as individuals without epilepsy to report lifetime suicidal thoughts (Tellez-Zenteno et al., 2007). Girls are more likely than boys to experience emotional difficulties, especially during adolescence (Zahn-Waxler et al., 2008).

A recent nationwide population-based psychiatric investigation in the UK involving 7403 adults (Adult Psychiatric Morbidity Survey 2007; Rai et al., 2012) found that one in three individuals with epilepsy satisfied the International Classification of Diseases, Tenth Revision (ICD-10) criteria for anxiety or depressive disorder (compared with one in six people without epilepsy). This study also investigated whether any overrepresentation of comorbidities in epilepsy could be explained by the chronicity or neurological nature of epilepsy or by the confounding effect of demographic and socioeconomic factors or other health conditions. After adjusting for confounders, Rai and colleagues found that adults with epilepsy exhibited significantly higher rates of depression, suicidality, generalised anxiety disorder, social phobia and agoraphobia compared with the general population of England without epilepsy. These associations were consistently stronger than those in individuals with asthma or diabetes, but similar to those in people reporting migraine or chronic headaches.

While psychosocial factors such as stigmatization or learned helplessness undoubtedly play a large role in the development and maintenance of emotional disorders in epilepsy (de Souza, & Salgado, 2006), a growing literature supports the influence of organic structural or functional lesions on mood disturbance in epilepsy (Hixson & Kirsch, 2009). Traditionally depression is

considered to be more common in individuals with either TLE or FLE and patients with mesial TLE are thought to be at higher risk of developing depression compared to patients with generalized seizures or other types of focal epilepsy (e.g. Devinsky et al., 1993; Hixson & Kirsch, 2009; Sanchez-Gistau et al., 2010). This is because seizures originating in the mesial temporal lobe can induce functional changes in limbic areas (particularly the amygdala, hippocampus, and cortical regions) that have a well known and established role in emotional regulation and the manifestation of affective psychopathology (Cornaggia et al., 2006; Kanner et al., 2012). Depression in TLE has been associated with metabolic abnormalities in the amygdala and anterior cingulate gyrus (Drevets, 1998), as well as to hippocampal atrophy, with the degree of atrophy inversely associated with the severity and/or duration of depression (Finegersh et al., 2011). Other studies however have not supported this (Swinkels et al., 2006). Finally, substantial evidence also exists for the involvement of the medial prefrontal network in mood disorders (Price & Drevets, 2012). Children with major depressive disorder have been shown to have functional changes in both limbic and orbitofrontal areas, particularly in the left hemisphere (Arnsten & Rubia, 2012).

Anxiety disorders in epilepsy may also be linked to limbic dysfunction (Blackford & Pine, 2012; Hamid et al., 2011). In particular, the amygdala has been shown by neuroimaging and neuropsychological lesion studies to play a key role in the mediation of verbal and nonverbal recognition of emotions as well as fear-induced anxiety (Adolphs et al., 2005; LaBar et al., 1995). Frontal and temporal structures such as the orbitofrontal cortex, anterior insula and anterior cingulate gyrus have also been associated with anxiety (Fiddick, 2011).

In terms of seizure lateralization, some evidence suggests that adult patients with left hemisphere foci tend to be more susceptible to depression in particular (Dulay et al., 2004; Helmstaedter et al., 2004; Hermann et al., 1991; Mendez et al., 1994). However other studies

focusing on children with complex partial seizures, most of whom have left temporal involvement, have questioned this (Hermann et al., 1988; Caplan et al., 2004). Seizure severity has also been identified as a risk factor for emotional problems and depression (Turky et al., 2008).

Cognitive impairments in depressive disorders have been consistently reported in the adult literature, implicating working memory, attention, executive function and processing speed abilities (Elderkin-Thomson et al. 2010; Marazziti et al. 2010; Nakano et al. 2008; Rosenberg et al. 2010; Weiland-Fiedler et al. 2004). Cognitive symptoms, such as impairments in concentration and decision making, are also included in the DSM-IV diagnostic criteria for major depression (APA, 1994). Executive function, processing speed as well as memory impairments have also been found to be associated with depression in children and adolescents (e.g. Favre et al., 2009; Günther et al., 2004; Lauer et al., 1994).

In summary, mood and anxiety disorders are frequent comorbidities in both paediatric and adult focal epilepsy. These comorbidities are more likely to be associated with TLE and FLE, as a result of the involvement of limbic areas and frontal structures in emotional regulation. A possible differential involvement of the left hemisphere has also been proposed, although this has not been a consistent finding. Finally, cognitive impairments, such as impairments in attention and memory, are associated with mood disorders in the neurologically healthy population, although this association has not been investigated in the population with focal epilepsy.

Hyperactivity and Inattention Problems

Disorders of attention, such as Attention Deficit Hyperactivity Disorder (ADHD), are amongst the most frequent behavioural comorbidities in childhood epilepsy, and may be a contributing factor to the well known risk for academic underachievement in this population.

Epidemiological studies have reported 20% to 37% children with epilepsy as having ADHD (Barkley, 1990; Cohen et al., 2012; Hauser et al., 1998), while the reported prevalence in the non-epileptic population of school-aged children is 5% (Dunn et al., 2003). A recent study found the incidence of ADHD to be 7.76/1000 in patients with epilepsy as opposed to 3.22/1000 in those without epilepsy (per 1000 person-years; Chou et al., 2013). ADHD, a behavioural syndrome typically arising in early childhood, is characterized by hyperactivity, impulsivity and inattention which are pervasive and cause significant impairment in daily functioning (DSM-IV; APA, 1994). ADHD is known to often co-occur with conduct disorder (Nigg & Casey, 2005) and has a male:female ratio of 2:1 (Ramtekkar et al., 2010).

Attention Deficit Hyperactivity Disorder in childhood has long been associated with abnormalities in frontal (neostriatal and prefrontal) brain regions that that mediate attention, inhibitory control and motivation (Castellanos, 2001; Cubillo et al., 2012). Functional abnormalities however have also been found in neuroimaging studies to extend beyond frontal circuits to include parietal areas, limbic regions and the cerebellum (Arnsten & Rubia, 2012; Vaidya & Stollstorff, 2008). A differential involvement of the right hemisphere specialized for behavioural regulation and attention in adults has also been proposed (Stefanatos & Wasserstein, 2001) and ADHD in children has been associated with predominantly right frontal deficits (Arnsten & Rubia, 2012).

Given the neural basis of ADHD, it is perhaps not surprising that attention and hyperactivity problems appear to be the most frequently reported disturbance associated with paediatric FLE (Braakman et al., 2011). This is also consistent with the fact that cognitive impairments associated with FLE damage include attention deficits and impairments of response inhibition and impulse control (Culhane-Shelburne et al., 2002; Hernandez et al., 2002, 2003; Lendt et al.,

2002). However, the risk of ADHD in children with FLE has not been systematically compared to that in other types of focal epilepsy.

Several cognitive domains are affected in children with ADHD including attention, working memory (and especially visual working memory) and executive functions such as response suppression (Nigg, 2005; Barnett et al., 2009), providing an explanatory model for the phenomenological features of the disorder. As part of a neuropsychological assessment of ADHD general intelligence, attention, executive functions, working memory and processing speed are typically assessed (Barkley, 1998; Young & Brahman, 2007) and a discrepancy between general intelligence and the other domains of cognitive functioning needs to be documented before the diagnosis of ADHD is made. Importantly, the neuropsychological profile of ADHD is very similar to that of highly associated (comorbid) disorders such as conduct disorder or oppositional defiant disorder (Sergeant et al., 2003).

Proposed risk factors associated with attention difficulties and disinhibition are seizure frequency and poor seizure control, as these disturbances tend to improve with adequate seizure control (Lendt et al., 2002; Riva et al., 2002). Attention and hyperactivity problems in children with epilepsy may be further aggravated by the presence of additional cognitive deficits (Dunn et al., 2003).

In summary, children with epilepsy, and particularly FLE, are at a high risk for developing disorders of attention, such as ADHD. The risk may be higher for children whose epileptic seizure onset is localised in the right frontal lobe in particular. Boys are at higher risk than girls and increased seizure frequency and poor seizure control can increase the risk of developing inattention or hyperactivity difficulties.

Conduct Problems

Epidemiological studies over the past several decades unanimously suggest that conduct problems are up to 5 times higher in children with epilepsy compared to the general child population and as high as 2.5 times more compared to children with chronic conditions that do not affect the brain (Alfstad et al., 2011; Austin & Caplan, 2007; Davies et al., 2003; Hoie et al., 2006; McDermott et al., 1995; Rutter et al., 1970). Behavioural disturbances which are more frequent in epilepsy include physical and verbal aggression, social disinhibition, and self-injurious behaviour (Cornaggia et al., 2006; Devinsky et al., 1993; Gaitatzis et al., 2004). Behavioural problems have been shown to occur early in the course of the disorder and even to be present in some cases before the first clinical seizure, suggesting a possible common neurobiological mechanism (Austin et al., 2001; 2011).

The evidence as to the effects of the localisation of focal epilepsy on the presentation of conduct problems is not conclusive. While several early epidemiological and clinical studies in children indicated that left TLE, was specifically related to both increased behavioural problems in general, as well as to specific types of behavioural disturbances, such as hyperactivity, antisocial behaviour and aggression (Hoare & Kerley, 1991; Lindsay et al., 1979; Rutter et al., 1970; Stores, 1978), later studies indicated no relationship between seizure localisation and behavioural difficulties (Hermann et al., 1988; Whitman et al., 1982). FLE has also been associated with behavioural problems, including agitation, reduction of social interaction, disinhibition (Braakman et al., 2011). This is in line with the well established fact that frontal lobe damage or dysfunction may result in a range of behavioural difficulties, including distractibility, disinhibition and aggression (Boone et al., 1988).

A possible involvement of temporal and frontal lobe structures in conduct problems in epilepsy could also be supported by the neuroimaging literature on children and adolescents with conduct disorder (without epilepsy). Although there is high co-morbidity between conduct disorder

and ADHD with substantial clinical, cognitive and behavioural overlap between the two clinical presentations, recent neuroimaging studies have identified a specific neural profile related to conduct disorder. Structural and functional imaging studies have suggested that children with conduct disorder show abnormalities in the paralimbic system, comprising ventromedial, lateral orbitofrontal and superior temporal cortices together with specific limbic regions, regulating motivation and emotion control (Arnsten & Rubia, 2012; Rubia, 2011).

Neuropsychological variables such as poor verbal IQ and poor academic performance have been shown to moderately predict conduct disorder and behavioural difficulties (Bassarath, 2001). In a group of school children Adams et al. (1999) showed that reading and arithmetic performance was negatively correlated with ratings of hyperactivity and conduct problems and positively correlated with prosocial behaviour ratings. Finally, boys are more likely to display conduct problems compared to girls (Hay, 2007; Zahn-Waxler et al., 2008).

In summary, conduct problems in paediatric epilepsy have been somewhat unreliably linked to both FLE and TLE. Conduct problems in the general child population have been shown to be related to both verbal IQ and academic attainments, but no available relevant data exists on the paediatric epilepsy population.

Social Problems

In addition to the neurobiological, emotional and behavioural consequences of epilepsy, the social effects of epilepsy can be profound. Epilepsy can have a devastating negative effect on daily life activities, such as peer interactions, independent living and employment. Children with epilepsy have been shown to be at increased risk for functional disabilities and poorer social competence (Rantanen et al., 2012; Russ et al., 2012). A link between epilepsy and autism is also supported by some studies, with the incidence of epilepsy in children with autism being reported

to be as high as 40% (Tuchman & Rapin, 2002). Hughes and Melyn (2005) found that 46% of children with autism in their study had epileptic seizures and up to 75% showed abnormal patterns of electrical brain activity in EEG recordings.

The development of social competence is one of the best predictors of later behavioural, social and academic success and is also linked to the development of current or future behavioural and emotional problems (John, 2001). Social competence can be defined as the ability to interact effectively in an age-appropriate manner, consistently with one's cognitive abilities and can be regarded as a manifestation of prosocial or antisocial behaviour (Rantanen et al., 2012). Different subcomponents of social competence entail social skills, social adjustment, and social performance (Cavell, 1990). Both neurophysiological factors (neurological dysfunction or lesions) and environmental factors (e.g. family or school environment) may affect the development of social competence.

The majority of the studies in childhood epilepsy have focused the effects of seizures on social adjustment, defined typically as the absence of behavioural problems or antisocial behaviour (e.g., aggression and disruptive behaviour) and the manifestation of prosocial behaviour (Rantanen et al., 2012). Typically such studies employ the ratings given by a parent, a teacher, or the child itself with regards to the frequency and/or severity of a given behaviour, using different rating scales such as the Child Behavior Checklist (Achenbach, 1991). Children with epilepsy have been found to have statistically significant higher rates of behavioural problems than siblings (Berg et al., 2007; Dunn et al., 2003; Schoenfeld et al., 1999) or children with other chronic illness (Davies et al, 2003; Dunn et al., 2002; 2003). A specific association between social adjustment problems and a deficit in recognizing emotional expressions in TLE has also been reported (Golouboff et al., 2008).

Very few studies have looked into the effects of epilepsy on social skills (required to perform competently social tasks) or social performance (the degree to which a child's responses to social situations meets socially valid criteria). The few existing studies however suggest that children with epilepsy have statistically lower social skills compared to siblings (Tse et al., 2007) or healthy children (Rantanen et al., 2009). Social performance tends to be less affected, and the ratings given are typically found to be within the normal range (Rantanen et al., 2012).

Children with epilepsy are also likely to face significant peer problems. Davies et al. (2003) found that parents of children with epilepsy reported more peer problems relative to parents of healthy children. Children with epilepsy have been found to be less active and to socialize less with peers compared to healthy controls (Jakovljevic et al., 2006). Children with epilepsy and comorbid mental health issues also experience significant stigma and demonstrate higher levels of disability and role limitation beyond what can be attributed to the epilepsy itself (Kessler et al., 2012). A recent study showed that children with epilepsy tend to rate social stigmatisation as more detrimental to their wellbeing than the seizures themselves (Vanstraten et al., 2012). Fifty percent of children reported that social stigmatization comprised the worst part of having epilepsy, whereas 38% chose physical seizures. Peer problems unfortunately may also frequently manifest in bullying behaviour. Hamiwka and colleagues (2009) reported children with epilepsy to be more frequently victims of bullying (42%) compared to healthy children (21%) or children with chronic kidney disease (18%).

Some associations have been reported between social competence and epilepsy-related variables and particularly seizure frequency and seizure type (Rantanen et al., 2012). Social problems may be more frequently encountered in children with recurrent seizures (Austin et al., 2002; Dunn et al., 2003). Associations between social competence and other epilepsy-related variables such as age at onset, duration and antiepileptic medication has been inconsistent

(Rantanen et al., 2012). However, in children with other early brain insults an earlier age at damage has been associated with an increased risk for social impairment compared to normative expectations (Greenham et al., 2010).

A recent study by Rogers and colleagues (Rogers et al., 2012) provides a possible neuroanatomical correlate for the risk of developing peer problems in early childhood, as measured by the Strengths and Difficulties Questionnaire (Goodman, 1999), identifying white matter abnormalities in the right orbitofrontal cortex. This area is known to be functionally involved with social regulation, social cognition and theory of mind, which are also affected in autism spectrum disorders (Völlm, 2006).

Finally, in terms of possible cognitive predictors of social functioning, verbal and non-verbal cognitive abilities have been shown to moderate the effects of psychosocial stressors such as family contextual factors or neighbourhood deprivation on peer problems in children (Flouri et al., 2012). Social problems may be more frequently encountered in children with low IQ (Buelow et al., 2003).

To sum up, social and peer problems are a common occurrence in the paediatric epilepsy population. Difficulties in social adjustment, such as behavioural problems or antisocial behaviour, reduced overall activity and socialization with peers, significant stigma and bullying are all frequently encountered in children with epilepsy. Increased seizure frequency may augment the risk for these difficulties, as also potentially the involvement of frontal lobe structures involved with social cognition and regulation functions in the epilepsy pathology. Lower IQ in the general child population has also been shown to significantly increase the risk for developing peer and social difficulties.

1.8 Current challenges in epilepsy research and thesis overview

Epilepsy has frequently been associated with emotional, behavioural and other mental health comorbidities. Children with epilepsy are at considerable risk of developing psychopathology, including depression, ADHD and conduct disorder (Turky et al., 2011). These disorders occur with higher frequency in epilepsy than in other chronic illnesses, highlighting a possible neurological component in the aetiology of the deficits (Smith et al., 2002). Epilepsy is also frequently associated with cognitive impairment, affecting intellectual, memory, attention and other higher order cognitive functions (e.g. Jokeit, 2004; MacAlister et al., 2007).

Undoubtedly emotional and behavioural comorbidities in focal paediatric epilepsy are likely to have a multi-factorial aetiology and the impact of different factors on mental health will be difficult to disentangle. Despite substantial progress in understanding the mechanisms behind psychopathological comorbidities in paediatric epilepsy within the last few decades, many issues still remain unresolved. Although a number of risk factors have been suggested in the literature, there are currently few firm conclusions and no comprehensive theoretical framework of the potential risk and protective factors associated with mental health problems in childhood epilepsy. The existing literature however suggests that several factors may contribute to the development of emotional and behavioural comorbidities in focal paediatric epilepsy, including the seizures themselves, any associated brain dysfunction and/or damage, psycho-social reactions to the condition (stigma, social marginalization and familial dynamics), several epilepsy-related variables (age at onset, duration, frequency of seizures), localisation of the epileptogenic focus, cognitive functioning and treatment of epilepsy with antiepileptic drugs.

Existing studies of risk factors in children with focal epilepsy have been scarce, with much of the available evidence on potential risk factors coming from studies on adults. Further, the characteristic lack of consistency among findings may reflect significant methodological limitations that most studies face. Investigations have typically based their findings on relatively small patient samples (less than 200 cases) and consequently results may reflect chance specific fluctuations. Furthermore, the lack of consistency across different studies is likely to reflect variability in the localisation of the seizures and/or the underlying pathology of the sample studied, emphasizing the need for more homogeneous patient groups (Swinkels, et al., 2006). Studies recruiting more homogenous patient groups have almost exclusively focused on TLE patients and few, if any, have compared TLE with other types of epilepsy. Also, importantly, studies often do not differentiate between risk factors for different mental health issues (e.g. Turky et al., 2008). Finally, few if any studies have examined risk factors related to cognitive status and those who have are typically restricted by the examination of limited cognitive domains (e.g. most frequently reporting FSIQ alone, e.g. Tukey et al., 2008; Sherman et.al., 2012). The omission of other predictive indexes such as verbal and nonverbal memory is particularly striking given the high incidence of memory impairments in patients with epilepsy, particularly those with temporal lobe epilepsy (TLE).

The present thesis aimed to examine the predictive role of several potential risk factors for the development of specific emotional or behavioural difficulties in children and adolescents with focal epilepsy. Specifically, it focused on mental health difficulties related to mood, conduct, inattention/hyperactivity and peer relationships. These were assessed based on parental ratings using the Strengths and Difficulties Questionnaire (SDQ), a well-validated measure of emotional-behavioural difficulties for children. The thesis aimed to evaluate the predictive power of potential risk factors in relation to the development of each one of these mental health difficulties with the

aim of building a predictive model based on these. The risk factors considered in the present thesis can be broadly split into four categories related to:

1. Demographic characteristics (gender, age at assessment)
2. Epilepsy-specific characteristics (age at onset of epilepsy, duration of the epileptic syndrome and seizure frequency)
3. Localisation of pathology (lobe and lateralisation)
4. Cognitive functioning (performance in IQ, memory and academic attainment measures)

The present study is based on data collected from a large number of children with intractable focal epilepsy who presented as candidates for epilepsy surgery in a tertiary paediatric hospital between 1997-2013. The present study thus is specific to children at a pre-surgical stage and provides a 'snapshot' of this cohort's mental health difficulties and associated risk factors during that time. The effect of paediatric epilepsy surgery on mental health difficulties in this group should be the focus of future studies.

The study extended previous investigations in several ways. First, the pool of potential subjects used represents one of the largest groups of paediatric epilepsy patients studied to date. Second, children with different focal epilepsy syndromes (TLE, FLE, PLE-OLE) were studied, with the aim to identify any similarities and differences in their psychopathology profiles. The study also aimed to further characterise the mental health profile of paediatric FLE, PLE and OLE syndromes, which have not been sufficiently studied, frequently being overshadowed by TLE in the literature. Third, three domains of cognitive functioning were used as predictors, assessed with a comprehensive battery of cognitive tests: general intellectual status (Full Scale IQ, as well as the individual sub-domains of Verbal IQ, Performance IQ, Working Memory and Processing

Speed), memory (General Memory, Verbal Memory, Visual Memory) and academic attainments (Literacy and Numeracy). Finally, statistical techniques were used to determine the combined and unique contribution of the different risk factors for emotional/behavioural outcome.

Although I hope that this study makes a significant and novel contribution to the current literature, it is, like all investigations, also subject to a number of limitations that will be discussed in detail in the discussion chapter later on. It may be important to flag up here however in advance that the present study focused specifically on a selective sample of pre-surgical candidates with refractory epilepsy, who had frequent seizures and epilepsy severe enough to warrant surgery, and may thus not be representative of the entire population of children with epilepsy.

Based on existing evidence reviewed above, the following general predictions were generated:

1. *Gender* differences were expected to emerge with girls presenting with more emotional problems and boys with more conduct, hyperactivity/inattention and peer problems (Alfstad et al., 2011; Zahn-Waxler et al., 2008). Earlier *age at assessment* was expected to be associated more to inattention/hyperactivity problems, and later age at assessment more to emotional difficulties, which are known to become more prominent later in life during adolescence (Ramtekkar et al., 2010; Zahn-Waxler et al., 2008).

2. In terms of *epilepsy-related factors* it was predicted that increased seizure frequency and possibly earlier age at onset and longer duration would be associated with overall higher ratings of emotional or behavioural difficulties (e.g. Hermann et al., 1988; Oguz et al., 2002).

3. The *localisation and lateralisation of the epileptic focus* was expected to be overall a weak predictor of emotional or behavioural difficulties, due to both the spread of the epileptic

seizures and the lack of clear localisation of function in the developing brain. However, it was hypothesised that attention/hyperactivity, conduct and peer problems were likely to be more linked to FLE (Braakman et al., 2011; Rogers et al., 2012) and emotional difficulties more to TLE (Sanchez-Gistau et al., 2010).

4. Finally, it was expected that overall poorer *cognitive and academic functioning* in general would be associated with increased risk for emotional and behavioural problems (e.g. Turky et al., 2008). More specifically, it was predicted that working memory and processing speed performance as well as general memory would be related to mood difficulties (e.g. Elderkin-Thomson et al., 2010); academic achievement and verbal IQ performance to conduct problems (e.g. Bassarath, 2001); working memory and academic achievement scores to inattention/hyperactivity problems (Adams et al., 1999; Nigg, 2005) and finally verbal and non-verbal IQ to peer problems (Buelow et al., 2003; Flouri et al., 2012).

The presented study aimed to build predictive models outlining the combined and unique contribution of the several risk factors discussed above for emotional/behavioural outcomes in paediatric epilepsy. I hope that these predictive models will have significant implications for the management of emotional and behavioural problems in children with epilepsy. The outcome of emotional or behavioural difficulties in paediatric epilepsy can be influenced greatly by early effective treatment with psychological interventions, medication or surgery (Ekinci et al., 2009). Being able to identify children at high risk of developing these conditions, could lead to the provision of early psychological assessment and intervention, with the aim of minimising any long-term consequences on psychosocial dvelopment and educational outcome.

Chapter 2

Method

2.1 Sample characteristics

Data from a population of 282 children and adolescents with intractable focal epilepsy, which had previously been collected for clinical purposes, were examined in the present study. All children and adolescents whose data were examined had undergone a comprehensive neuropsychological assessment as part of multidisciplinary investigations for surgical treatment of intractable epilepsy at Great Ormond Street Children's Hospital, NHS Trust, a tertiary hospital in London, United Kingdom, between May 1997 and May 2013. This epilepsy surgery programme accepts children with complex or intractable epilepsy who have been referred from local paediatricians or neurologists. All children accepted in the programme undergo an extensive pre-surgical evaluation including a clinical assessment and review of clinical history by paediatric neurologists, an ictal and an interictal EEG examination, an optimized magnetic resonance imaging scan (MRI), as well as comprehensive neuropsychological and neuropsychiatric evaluations. Additional investigations such as single-photon emission computed tomography (SPECT), positron emission tomography (PET), functional MRI as well as other investigations (e.g. ophthalmology, magnetoencephalography and so on) are performed when required. The data from all examinations and investigations are then collated and discussed at a multidisciplinary meeting where a decision is made with regards to surgical intervention or other further medical and pharmacological management.

All children whose data were included in the present study had received a diagnosis of focal epilepsy according to the International League Against Epilepsy guidelines (ILAE, 1981; 1989), following the detailed assessment process outlined above. The diagnosis of focal epilepsy was made by a paediatric neurologist on the basis of seizure semiology, clinical history, EEG and MRI examination findings. All children had intractable epilepsy, defined by the failure to become seizure free despite having tried two or more anti-epileptic medications. Children with generalised epilepsy, mixed seizure disorder, previous epilepsy surgery, no clear structural brain abnormality,

bilateral or multifocal epilepsy according to MRI or EEG data or not experiencing epileptic seizures at the time of assessment were excluded from the study.

All children had MRI evidence of a structural brain abnormality, consistent with their seizure onset, which allowed us to categorise them as having 'temporal' (n=117, 41.6%), 'frontal' (n= 64, 22.8%), 'parietal' (n= 26, 9.3%), 'occipital' (n= 15, 5.3%) or 'multilobar' (n= 59, 20.9%) pathology. Due to the relatively small number of cases with parietal and occipital pathology in the cohort, these cases were combined to form one group in the analyses considering the effects of localisation of pathology. Further, 151 (53.5%) of the children or adolescents had left hemisphere pathology and 131 (46.5%) had right hemisphere pathology. The exact numbers of children with left hemisphere or right hemisphere pathology within each lobe can be found below in Table 2.1.

Table 2.1. Number of children and adolescents categorised, on the basis of MRI and EEG findings, as having 'temporal', 'frontal', 'parietal', 'occipital' or 'multilobar' pathology within the left or the right cerebral hemisphere respectively.

	Hemispheric Side of Pathology		
Lobe of Pathology	*Left*	*Right*	*Total*
Temporal	75	42	117
Frontal	27	37	64
Parietal	16	10	26
Occipital	5	10	15
Multilobar	27	32	59
Total	150	131	281

Across the entire patient sample, the most frequent pathology underlying the focal epilepsy, based on MRI findings, was focal malformation (n=70, 28%), followed by tumour (n=57, 23%) and mesial temporal sclerosis (n=37, 15%). Mesial temporal sclerosis, tumours and focal

malformations each accounted for approximately a third of the Temporal epilepsy cases and all together accounted for 93% of all the Temporal epilepsy cases. Focal malformation was the leading pathology associated with Frontal lobe epilepsy as well as Parietal lobe epilepsy, accounting for 62% (n=30) of the Frontal cases and 66% (n=8) of the Parietal cases. Occipital lobe epilepsy was predominantly associated with focal malformation as well as hypoxia/ischaemia. Finally, as expected, patients who had structural abnormalities affecting more than one lobe (multilobar) presented with pathologies which affected larger areas of the brain, such as hypoxia/ischaemia (n=22, 38%), Rasmussen's encephalitis (n=20, 34%) and hemi-malformations (n=21, 15%). Unfortunately, it was not possible to obtain information with regards to the underlying pathology in 34 cases. Table 2.2. gives a detailed breakdown of the type of pathology corresponding to children with 'temporal', 'frontal', 'parietal', 'occipital' or 'multilobar' localisation of pathology respectively. See also the Glossary for a brief explanation of the different types of pathology.

Table 2.2. Number of children and adolescents presenting with different types of localised pathology as identified on MRI scans.

Type of pathology	*Localisation of Pathology*					
	Temporal	*Frontal*	*Parietal*	*Occipital*	*Multilobar*	*Total*
Mesial Temporal Sclerosis	37	0	0	0	0	37
Tumour	38	9	0	2	0	57
Focal Malformation	26	30	8	6	0	70
Hypoxia/Ischaemia	2	4	0	5	22	33
Rasmussen's Encephalitis	0	0	0	0	20	20
Hemi Malformation	0	0	0	0	12	12
Vascular Abnormality	5	2	2	0	0	9
Sturge Weber Disease	0	1	0	0	2	3
Other	1	2	2	0	2	7
Total						248

Data from children and adolescents with focal epilepsy between 3-18 years of age were included in the present study. The mean age at assessment was 10.9 years (sd=3.6). For a frequency distribution of the age at assessment see the histogram in Figure 1. There were 143 (50.7%) boys and 138 (48.9%) girls in the cohort. With regards to handedness 213 (75.5%) of the children were right-handed and 58 (20.6%) were left-handed. Six children were ambidextrous and handedness was not established for 2 children.

The mean age at onset of habitual seizures in the sample was 4.9 years (sd=3.9 years), with 25% (n=69) of the children having had an onset within the first year of life and 63% (n=179) within the first five years of life. By the time of assessment, the children whose data were included in the present study had been experiencing on average habitual seizures for 6.5 years (sd=3.8 years). Figures 2.2 and 2.3 display the frequency distributions for age at onset of habitual seizures and duration (in years) of the epileptic syndrome by the time of assessment in the sample.

Figure 2.1. Frequency distribution of age at assessment (in years).

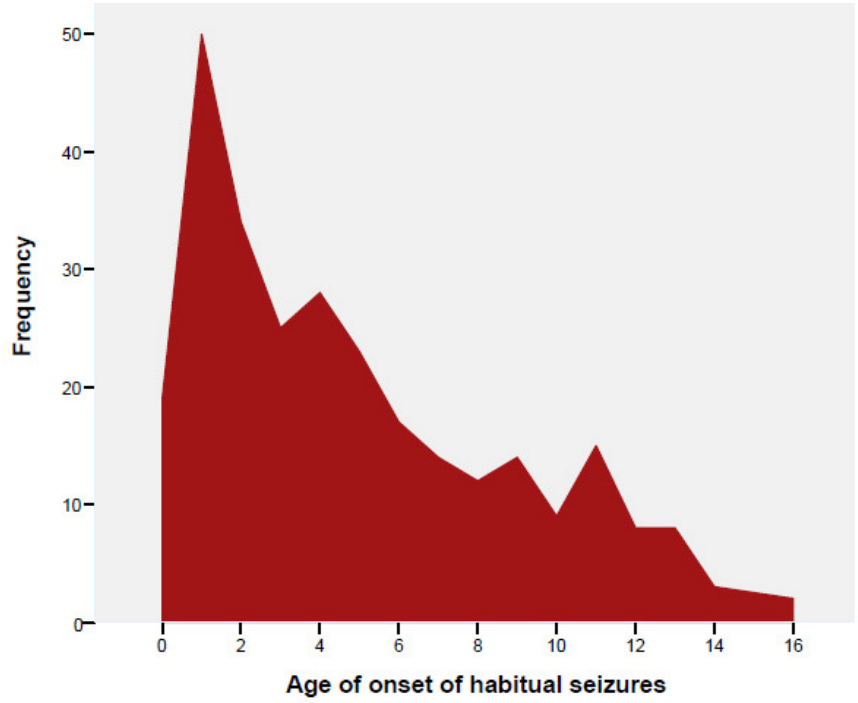

Figure 2.2. Frequency distribution of age at onset of habitual seizures (in years).

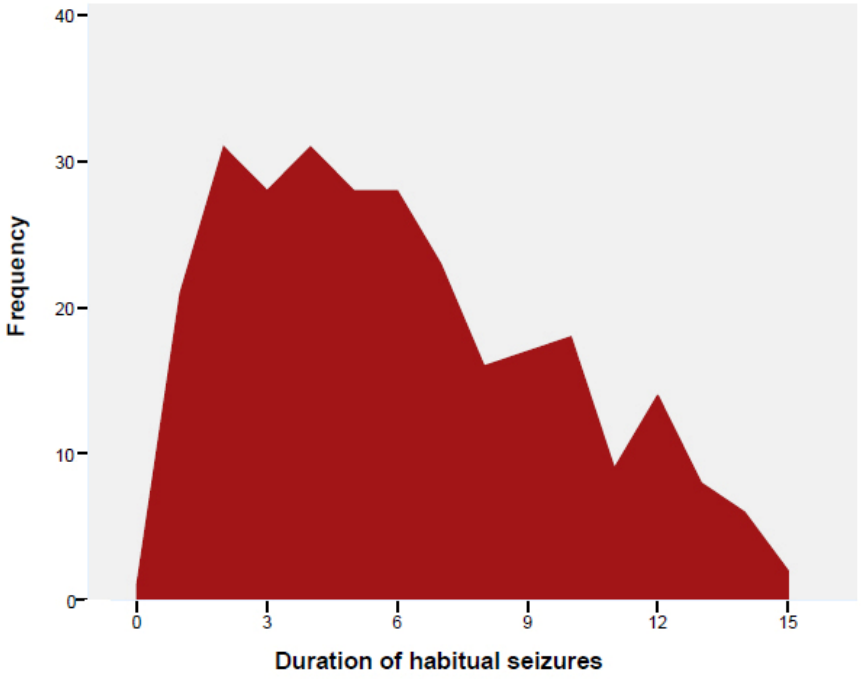

Figure 2.3 Frequency distribution of duration of epileptic syndrome at the time of assessment (in years).

Seizure frequency in the present study was measured by parental report and represents the reported frequency of epileptic seizures per month during the year prior to assessment. As epileptic seizures can vary substantially from month to month for many affected individuals, the seizure frequency reported here should be treated as an approximate estimate. Overall, the children whose data were used in the present study experienced several seizures per month, with more than half experiencing approximately 40 or more seizures per month. More detailed information with regards to the seizure frequency distribution in the sample is provided in Table 2.3. There was a high degree of variability for seizure frequency within the sample, with the average seizure frequency being 132 seizures per month (sd=218), after taking account of five outlier scores (3SDs above mean) that were treated by Windsorizing (Hasings et al., 1947).

Table 2.3. Number and percentage of children reportedly experiencing "1-10", "11-42", "43-150" or ">150" seizures per month in the year prior to assessment.. The seizure frequency groupings were formed so that each group accounts for approximately a quarter of the total cases.

Seizure frequency	*No*	*%*
1-10 seizures/month	64	25.4
11-42 seizures/month	62	24.6
43-150 seizures/month	66	26.2
>150/ seizures/month	60	23.8
Total	252	100%

2.2 Measures

All children and adolescents whose data were included in the present study had been assessed as part of their pre-surgical evaluation for the presence of emotional, behavioural and cognitive

difficulties using both clinical interviews and standardised neuropsychological protocols, to inform their medical care and management. Clinical interviews were conducted by a clinical neuropsychologist and occasionally were jointly conducted by both a clinical neuropsychologist and a psychiatrist. Psychometric assessments were carried out by clinical neuropsychologists or by graduate assistant psychologists under the supervision of clinical neuropsychologists. The present study uses quantitative estimates of emotional, behavioural and cognitive status obtained from participants' scores on standardised psychometric measures. Indices of behavioural and emotional difficulties were obtained in the current study using the Strengths and Difficulties Questionnaire (SDQ) completed by parents. Cognitive ability was assessed using the Wechsler Intelligence Scales, the Children's Memory Scale and the Wechsler Academic Achievements Test, measuring intelligence, memory and academic attainment abilities respectively. Each measure is described in detail below.

Note that as these data were obtained for clinical purposes, the measures considered here were administered to children on a case-by-case basis, based on clinical need and judgement at the time of assessment. Therefore, not all measures were administered to all children. While all children in the present study were assessed for behavioural and emotional difficulties, and almost all were assessed for intellectual functioning (n=275), only 175 cases (62% of the sample) were assessed for memory and 234 cases (83% of the sample) were assessed for academic achievements.

Behavioural and Emotional Difficulties

Children and adolescents' emotional and behavioural functioning was assessed using the Strengths and Difficulties Questionnaire (SDQ), a well-validated brief screening questionnaire of emotional and behavioural functioning for children and adolescents developed by Robert

Goodman (Goodman, 1999). The SDQ is widely used to briefly assess for common forms of psychopathology (Goodman & Goodman, 2011). It has been designed and normed for children and adolescents aged 3 to 16 years and can be completed by parents, teachers or the young people themselves (if aged 11 or above). As children's emotional and behavioural difficulties may not always be evident in all situations, ratings from both parents and teachers had been collected for clinical purposes where possible. In the present study only parental ratings were used which were available for all cases (n=282), as ratings from teachers were unfortunately available for approximately half the cases in the sample (n=130, 46%).

The SDQ questionnaire is designed to assess difficulties in the following five domains: emotional functioning, conduct, hyperactivity/inattention, peer relationships and prosocial behaviour. Ratings from the emotional, conduct, inattention/hyperactivity and peer relationships scales are then used to produce an estimate of 'total difficulty'. In the present study, data from the emotional, conduct, inattention/hyperactivity and peer relationships scales were analysed. The prosocial scale data was excluded from the analysis of the present study as it does not contribute to the total estimate of SDQ difficulties and I had no specific hypotheses with regards to this category of difficulties. Moreover, by excluding the prosocial scale data, the likelihood of Type I errors (the incorrect rejection of a true null hypothesis) in the present study was reduced, by limiting the number of statistical tests performed.

The five SDQ domains reflect the main areas of psychosocial disability according to the World Health Organization's (1996) multiaxial classification of child and adolescent psychiatric disorders (Goodman, 1999). The items included in each domain have been primarily selected to reflect key symptoms of DSM-IV diagnoses, and their groupings have been confirmed using multivariate structural analyses in a nationwide sample of British children and adolescents (Goodman, 1997; 1999; 2001). The criterion validity, predictive validity, concurrent validity and construct validity of the SDQ (Goodman, 1999; Goodman & Scott, 1999) and its sensitivity for identifying children and

adolescents with mental health difficulties (Goodman & Scott, 1999) have been found to be superior to those of other commonly used psychometric measures for psychopathology in children, such as the Child Behavior Checklist (Achenbach, 1991).

Each one of the five SDQ domains is represented in the questionnaire by five items, yielding a total of 25 questions. Example items representing each domain are: “The child often complains of headaches, stomach aches or sickness” (emotional domain); “Often fights with other children or bullies them” (conduct domain); “Is restless, overactive, cannot stay still for long” (hyperactivity/inattention domain); “Is rather solitary, tends to play alone” (peer relationship domain). The full SDQ questionnaire can be found in Appendix A.

For each item the respondent has to indicate for the child in question whether the statement is “not true”, “somewhat true” or “certainly true”, which is given a score of 0, 1 or 2 respectively. This makes the possible overall score range for each domain 0 to 10. For all domains (except for the prosocial behaviour domain) higher scores indicate more difficulties. The 20 items representing emotional symptoms, conduct, hyperactivity and peer problems are summed up to create a ‘total difficulty score’, with a possible score range from 0 to 40. The individual domain scores and the total score can be then classified as “normal”, “borderline”, or “abnormal” based on normative data providing established cut-off scores. The cut-off scores for the individual SDQ domains and the total difficulties score can also be found in Appendix A.

Intellectual Functioning

Intellectual functioning was measured in the present study using the Wechsler Intelligence Scales. The Wechsler Intelligence Scales are individually administered clinical instruments for assessing intellectual ability. Different versions of Wechsler Intelligence Scales exist for different

age ranges. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI; Wechsler, 1989) is designed for children ages 2 years 6 months to 7 years 3 months, the Wechsler Intelligence Scale for Children (WISC; Wechsler, 1991) for children 6 and 16 inclusive. Finally, the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955; 2008) is designed for individuals from 16 and above. In the current study, children who were aged 3-6 at the time of the assessment (n = 41) were administered the WPPSI (Wechsler, 1989), children aged 6-16 (n = 215) the WISC (Wechsler, 1991) and children aged 16-18 (n = 3) the WAIS (Wechsler, 1955; 2008). Finally, a total of 23 children whose low level of functioning did now allow for an intellectual ability assessment using one of the Wechsler scales mentioned above (7 temporal, 5 frontal, 1 parieto-occipital and 10 multilobar cases) were assessed for mental ability using the Bayley Scales of Infant and Toddler Development, third edition (Bayley, 2006). The Bayley Scales yield a developmental quotient indicating the neurodevelopmental status of the child.

Since their original publication all three versions of the Wechsler intelligence scales have been revised several times. Given the date employed in the present study were collected over a period of several years, different versions of the Wechsler intelligence scales were used for patients assessed at different time periods. The WPPSI-R (Wechsler, 1989) was administered to children tested from 1997 through 1998 (n=3) and the WPPSI-III (Wechsler, 2002) from 2003 onwards (n=38). Similarly the WISC-R (Wechsler, 1974) was administered to children tested from 1997 through 1998 (n=1), the WISC-III (Wechsler, 1991) was administered to children tested from 1999 through 2003 (n=47) and the WISC-IV (Wechsler, 2004) to children assessed from 2004 onwards (n=167). The only version of the WAIS administered (n = 3) was the WAIS-IV (Wechsler, 2008).

Each Wechsler Intelligence Scale (WPPSI, WISC, WAIS) consists of several subtests each measuring a different facet of intellectual ability. The subtests can be classified as core or supplemental. Core subtests are required for the computation of composite scores. The supplemental subtests provide additional information about cognitive abilities and can be used as

replacement to accommodate children in exceptional cases or for inconsistent/incomplete results which may occur because of interruptions or other unforeseen circumstances. A list and brief description of the subtests included in the Wechsler Intelligence Scales (WPPSI, WISC, WAIS) can be found in Table 2.4.

For each of the subtests, the raw scores are converted to a scaled score which takes into account the age of the individual. Scaled scores range from 1 - 19 with a score of 10 corresponding to the performance of the average child at a given age on that subtest. Scores between 7 and 13 are considered to fall within the average range. When the scores of all subtests are put together they provide a Full Scale IQ (FSIQ) representing an estimate of the child's overall level of intellectual ability. Composite scores representing the child's functioning in more discrete domains of cognitive functioning are also produced by splitting the subtests into individual sub-scales.

Table 2.4. List of subtests included in the WPPSI-III, WISC-IV and WAIS-III and supposed abilities measured by each. 'C' indicates that a particular subtest is a core subtest and 'S' indicates a supplementary subtest for a particular intelligence scale.

Subtest	**Supposed abilities measured**	**WPPSI**	**WISC**	**WAIS**
Verbal IQ				
Information	General information acquired from culture	**C**	**S**	**C**
Vocabulary	The degree to which one has learned, been able to comprehend and verbally express vocabulary	**C**	**C**	**C**
Word Reasoning	Reasoning with verbal material	**C**	**S**	**-**
Picture Naming	Expressive language ability, word retrieval from long-term memory and association of visual stimuli with language.	**C**	**-**	**-**
Similarities	Abstract verbal reasoning and concept formation	**S**	**C**	**C**

Comprehension	Ability to deal with abstract social conventions, rules and expressions	**S**	**C**	**S**
Receptive Vocabulary	Comprehension of verbal directions, auditory and visual discrimination, auditory memory, auditory processing and the integration of visual perception and auditory input.	**S**	**-**	**-**
Performance IQ				
Block Design	Spatial perception, visual abstract processing and problem solving	**C**	**C**	**C**
Matrix Reasoning	Nonverbal abstract problem solving, inductive reasoning, spatial reasoning	**C**	**C**	**C**
Picture Concepts	Fluid reasoning, perceptual organisation and categorisation	**C**	**C**	**-**
Object Assembly	Visual-perceptual organisation, integration and synthesis of part-whole relationships, non-verbal reasoning and trial-and-error learning	**S**	**-**	**-**
Picture Completion	Ability to quickly perceive visual details	**S**	**S**	**S**
Visual Puzzles	Spatial reasoning	**-**	**-**	**S**
Processing Speed Q				
Coding	Visual-motor coordination, motor and mental speed, visual working memory	**C**	**C**	**C**
Symbol Search	Visual perception/analysis, scanning speed	**C**	**C**	**C**
Cancellation	Visual-perceptual speed	**-**	**S**	**S**
Working Memory Q				
Digit span	Attention, concentration, mental control	**-**	**C**	**C**
Letter-Number Sequencing	Attention, concentration, mental control	**-**	**C**	**C**
Arithmetic	Concentration while manipulating mental mathematical problems	**-**	**S**	**S**

All Wechsler scales provide an estimate of verbal intelligence, a Verbal IQ composite score (VIQ; called Verbal IQ in WPPSI-III and Verbal Comprehension Index in WISC-IV and WAIS-IV), an overall measure designed to assess a child's ability for verbal expression, grasp of verbal concepts and abstract reasoning. The Verbal IQ is based on the sum of scores of subtests indicating how a child performs at a verbal level, acquires verbal information and subsequently uses it to establish relationships between words and concepts.

All Wechsler scales also provide an estimate of a Perceptual IQ (PIQ; called Performance IQ in WPPSI-III and Perceptual Reasoning Index in WISC-IV and WAIS-IV). The Perceptual IQ provides a measure of the ability of the child to make sense of visual information, organise objects into space and establish relationships between verbal instructions and visual concepts. The performance subtests consist of tasks which often require the child to "do" things (e.g., puzzles) in a given time limit. These subtests help to assess visual and spatial organisation and perceptual ability.

The WISC, WAIS and the WPPSI (for children aged 4 to 7 years and 3 months) scales also provide a Processing Speed Index. The Processing Speed Index (PRI) offers an indication of the individual's ability to make sense of abstract visual information and to quickly respond to it. It is measured by subtests requiring timed motor responses to simple abstract visual information.

Finally, the WISC and WAIS (with the exception of the WISC-R) yield an additional composite score, the Working Memory Index (formerly known as the Freedom from Distractibility Index). The Working Memory Index (WMI) is an indicator of the individual's ability to retain information in memory in the short term, sustain attention and maintain sufficient concentration to perform mental operations.

The FSIQ and additional composite index scores (VIQ, PIQ, PRI, WMI) are measured in standard scores with a mean of 100 and a standard deviation of 15. A score of 100 corresponds to the performance of the average child of a given age on that scale. According to the qualitative descriptions provided by the Wechsler scales (Wechsler, 1989, 1991, 1998) a composite score of 69 and below is classified as “extremely low”; a score of 70–79 as “borderline”, a score of 80–89 as “low average”, 90–109 as “average”, 110-119 as “high average”, 120-129 as “superior” and 130 and above as “very superior”. About two thirds of all children obtain scores between 85 and 115. Intellectual dysfunction is typically defined as a FSIQ below 79.

Memory

Memory functions were assessed in 175 participants (83 Temporal cases, 36 Frontal, 30 Parieto-Occipital and 25 Multilobar; 93 left hemisphere cases and 74 right hemisphere cases) using the Children’s Memory Scale (CMS; Cohen, 1997; for reviews, see Baron, 2004; Vaupel, 2001). The CMS is a widely used standardised test assessing short and long term, verbal and visual memory functions, and recall and recognition processes in children from 5 to 16 years of age. The CMS consists of several subtests each measuring learning and memory functions of the declarative memory system. The declarative memory system is involved in encoding, learning, consolidation, long-term storage and retrieval of information and is predominantly supported by medial temporal lobe structures, with the hippocampus playing a pivotal role in long term memory in particular (Squire, Stark, & Clark, 2004; Vargha-Khadem et al., 1997; Mishkin et al., 1997).

In particular, the CMS assesses memory and learning functioning for auditory/verbal and visual/non-verbal learning and memory. The verbal scale assesses learning and memory for verbal material and the sum of all the scores on this scale produces a Verbal Memory Index. The

subtests on the visual scale measure memory for visuo-spatial/non-verbal material and the sum of scores obtained on these subtests produce a Visual Memory Index. Each scale contains two core subtests and one supplemental subtest. Moreover, each subtest in the verbal and visual scale contains both an immediate and a delayed memory component. This allows for separate estimates of immediate memory (memory tested immediately after all the to-be-learnt material has been presented) and delayed memory (retention of learnt information on retesting after a delay) for both visual and verbal information to be obtained. When the scores of all CMS subtests are put together they provide an overall estimate of a child's general memory ability (General Memory Index). A detailed description of all the CMS core subtests employed in the present study can be found in Table 2.5.

Raw scores from each subtest are converted to a standardized scaled score with a mean of 10 and standard deviation of 3, based on normative data, taking into account the age of the child. Standard scores on CMS are derived on the same scale as WISC–IV composite scores, with a mean of 100 and a standard deviation of 15.

Table 2.5. Subtests included in the Children's Memory Scale (Cohen, 1997) and supposed abilities measured. All subtests have an immediate and a delayed memory component.

CMS Subtest	**Abilities measured**
Verbal Memory Scale	
Stories	Learning free recall of stories presented in the auditory modality
Word Pairs	Learning and recall of a list of paired-associate words (semantically unrelated) presented in the auditory modality
Visual Memory Scale	
Dot Locations	Learning and free recall of the spatial locations of dots
Faces	Learning and recognition of unfamiliar faces

Academic Attainments

Finally, academic achievement was measured in the present study using selected subtests from the Wechsler Individual Achievement Test, 2nd UK Edition (WIAT-IIUK; Wechsler, 2005), a test frequently used to assess academic strengths and weaknesses. The WIAT-II is a test consisting of several subtests (Word Reading, Pseudoword Decoding, Reading Comprehension, Numerical Operations, Mathematical Reasoning, Spelling, Written Expression, Listening Comprehension, and Oral Expression) each measuring a different facet of academic achievement including reading, writing, oral language and mathematics. In the current study data from five individual subtests of the WIAT-II were used: Spelling, Word Reading, Reading Comprehension, Numerical Operations and Mathematical Reasoning. Performance data for these subtests were available for 234 children and adolescents (100 Temporal cases, 56 Frontal, 33 Parieto-occipital and 44 Multilobar; 126 left hemisphere cases and 108 right hemisphere cases). A brief description of the WIAT-II subtests included in the present study is presented in Table 2.6.

Table 2.6 Wechsler Individual Achievement Test 2nd UK Edition (Wechsler, 2005) subtests which were used in the present study and supposed abilities measured.

WIAT-II Subtest	**Abilities measured**
Literacy	
Word Reading	Reading single words
Reading Comprehension	Understanding and interpreting information from written text
Spelling	Writing single words to dictation
Numeracy	
Mathematical Reasoning	Application of mathematical operations to solve problem scenarios
Numerical Operations	Performing operations of addition, subtraction, multiplication, division

Administration of each individual WIAT-II subtest yields a raw score which is converted to a scaled score taking into account the age of the child. Scaled scores have a mean of 10 which corresponds to the performance of the average child at a given age on that subtest, and a standard deviation of 3. The WIAT-II is directly linked to the WISC-IV so that a child's achievements can be compared with what would be predicted from his/her general ability.

2.3 Procedure and Data Analysis

As previously explained, the present study is a retrospective case review, examining data from a population of 282 children and adolescents with intractable focal epilepsy, previously collected for clinical purposes. The data employed for the purposes of the present study were extracted from clinical reports and were fully anonymised prior to being accessed by the investigators. The data included demographic, pathology and epilepsy-specific information as well as SDQ parental rating scores and scores achieved in the cognitive tests outlined above.

The SDQ ratings were used in the present study to provide estimates of emotional and behavioural difficulties for each participating child. The total SDQ score and the four SDQ scaled scores (Emotional, Conduct, Hyperactivity/Inattention and Peer Relationhsip), based on parental ratings, each served individually as dependent variables in the analyses outlined below.

Independent variables included demographic, epilepsy-specific, pathology localisation variables, as well as the scores on cognitive tests. The following demographic and epilepsy-specific features served as independent variables: gender, age at assessment, age at onset of habitual epileptic seizures, seizure frequency in the preceding 12 months and duration of epilepsy (in years).

Cognitive variables considered here included scores on tests of intelligence (WPPSI, WISC or WAIS), memory (CMS) and academic achievement (WIAT-II) measures. Specifically, an overall measure of intellectual ability (FSIQ or DQ) was used as an independent variable for all children, as well as indices of more discrete subdomains of intellectual functioning (VIQ, PIQ, WMI and PRI) where available (depending on the measure used for the assessment: WPPSI, WISC or WAIS). Similarly, an overall measure of memory was used (General Memory Index), as well as separate scores for Verbal Memory and Visual Memory, based on performance on the CMS. Finally, standard scores from the Word Reading, Spelling and Reading Comprehension subtests of the WIAT-II were averaged to provide an overall Literacy Index. Similarly, standard scores from the Numerical Operations and Mathematical Reasoning subtests of the WIAT-II were averaged to provide an overall Numeracy Index. The average standard score from all available WIAT-II subtests served as an overall Academic Achievements Index.

The association between each outcome measure (Total SDQ score and individual SDQ scale ratings) and individual independent variables was initially examined using a series of univariate analyses (independent-sample t tests, One-way ANOVAs, chi-squares, Pearson and Spearman correlations). Following these univariate analyses, the Total SDQ score and each SDQ domain score were modelled individually as a function of suitable predictors using multivariate linear regression models. The univariate analyses enabled us to identify suitable predictor variables for inclusion in the regression models. SPSS version 19 was used for the statistical analyses. For all statistical tests, correlations and differences were considered to be statistically significant at $p<0.05$. For univariate analyses, where no prior hypothesis existed however, the significance level was set to $p<0.01$, to take into account the issue of multiple statistical tests performed in this study and guard against type I errors.

As the data used were already collected prior to the start of this study, it was not possible to perform a priori power analyses on the reported statistics. The usefulness of retrospective post-hoc power analyses techniques is somewhat controversial (see Thomas, 1997), with the post-hoc power in its simplest form being a function of the p-value (Hoenig & Heisey, 2001). Nevertheless, a series of post-hoc power analyses in relation to the reported regression analyses is reported in this thesis for completeness. Post-hoc power analyses were conducted using the software package, Post-hoc Statistical Power Calculator for Multiple Regression (Soper, 2014).

2.4 Ethics

Ethical approval for this study was granted by the Research and Development office of Great Ormond Street Hospital for Children, NHS Foundation Trust (R&D reference number: 13CN05) and the Department of Psychology of Royal Holloway University of London (see Appendix B). As a retrospective case note review this study did not require ethical approval from the Local Research Ethics Council.

Chapter 3

Results

3.1 SDQ ratings

We first report here observations based on SDQ ratings given by parents. Table 3.1 below provides averages and standard deviations of parental ratings for each of the SDQ domains. Overall, children in this sample (n=282) received the highest ratings by their parents for hyperactivity/inattention problems which were significantly higher than emotional problems ($t(277)=8.22$, $p<0.001$), conduct problems $t(277)=18.78$, $p<0.001$) and peer relationship problems ($t(278)=9.32$, $p<0.001$). This was followed by emotional and peer problem ratings, with no significant difference between them. The lowest ratings were obtained for conduct problems.

Table 3.1. Average ratings and standard deviations (in parentheses) given by parents for each SDQ domain and the classification ('Normal', 'Borderline' or 'Abnormal') in which this average rating falls (n=282).

	Parental Ratings	
SDQ scale	*Average (sd)*	*Classification*
Emotional	3.7 (2.6)	Borderline
Conduct	2.4 (2.1)	Normal
Hyperactivity	5.4 (2.8)	Normal
Peer	3.7 (2.6)	Abnormal
Total Difficulties	15.2 (7.2)	Borderline

However, as individual SDQ domains have different cut-off scores for indicating difficulties based on normative data (see Appendix A), differences in raw ratings between individual SDQ scales do not necessarily reflect actual differences in the level of difficulty presented by the same child. To get a more accurate picture of the level of difficulties reported in this sample I looked at the

classification of the level of difficulty ('Abnormal', 'Borderline' or 'Normal') for each SDQ scale based on normative data. Figure 3.1 shows the percentages of children (n=281) falling within the 'Abnormal', 'Borderline' and 'Normal' range for each SDQ scale based on parental ratings.

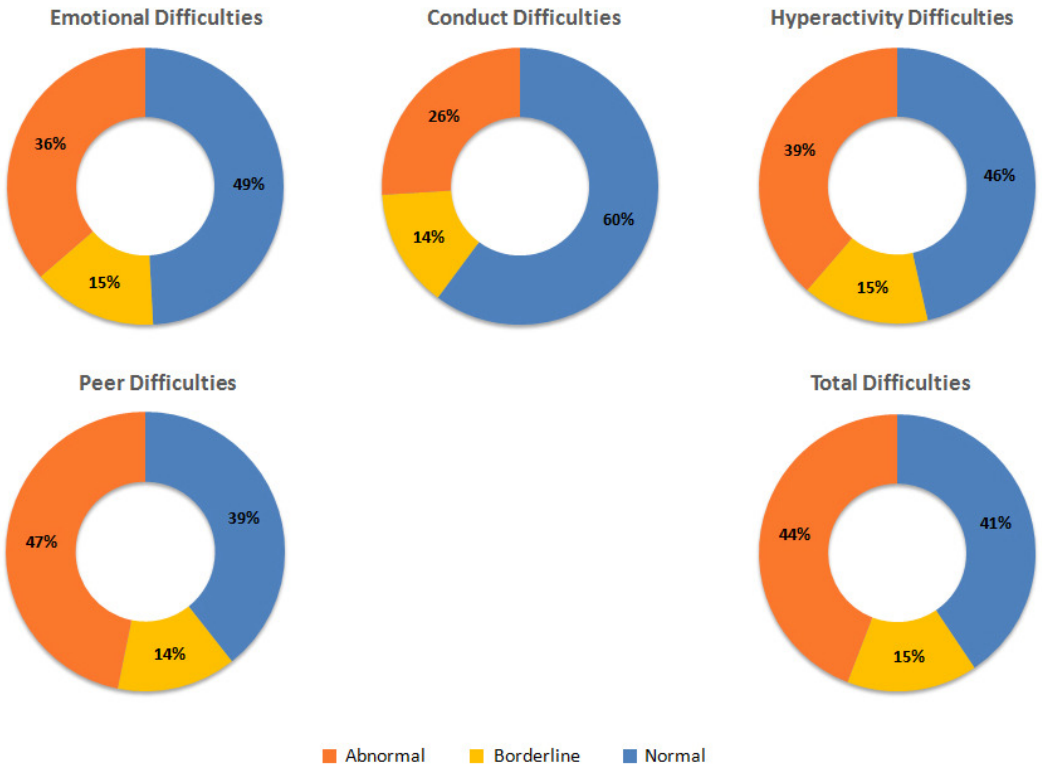

Figure 3.1. Percentages of ratings given by parents falling within the 'Abnormal', 'Borderline' or 'Normal' range for each SDQ scale and the SDQ Total Difficulties score for the whole study sample (n=281).

According to the classification results based on normative data presented in Figure 3.1, parental ratings indicated that more than half (59%) of the children in this sample presented with overall significant emotional and behavioural difficulties, with a Total Difficulties score falling in the 'Abnormal' or 'Borderline' range. The most commonly reported difficulty affecting children in this cohort related to peer relationship problems, with ratings for this domain falling in the 'Abnormal'

range for 47% of the cases. This was followed by problems with hyperactivity/inattention, which were reported to be a significant difficulty in 39% of the cases and emotional difficulties, which were reported to be a significant problem in 36% of the cases. Finally, difficulties with conduct were reported to be 'Abnormal' in 26% of the cases.

In order to identify any significant differences between the core SDQ domains (emotional, conduct, hyperactivity/inattention and peer relationships) as indicated by parental ratings, chi-square analyses were performed. These revealed that overall parents reported significantly more problems in the domain of peer relationships and hyperactivity than that of conduct (with scores falling in the 'Abnormal' or 'Borderline' range as opposed to the 'Normal' range; $\chi^2(1)=24.313$, $p<0.001$ and $\chi^2(1)=10.595$, $p=0.001$ respectively). No other significant differences were found between parental ratings of the SDQ domains.

I also performed here a validation analysis, examining the relationship between individual SDQ domains using Spearman's correlations. Table 3.2 shows the cross-scale correlation coefficients between the individual SDQ domains. As expected, there was a significant correlation between all individual SDQ domains (see also similar results in the original paper by Goodman, 2001). This suggested that children presenting with a higher level of difficulty in one domain also tended to present with more difficulties in other domains of the SDQ. The highest correlation was observed between the conduct and hyperactivity/inattention ($r_s(280)= -.503$, $p<0.001$) domains, with higher ratings of conduct problems being associated with higher ratings of hyperactivity/inattention problems. Despite the inter-correlation between the individual SDQ scales, Goodman (2001) has shown that the individual SDQ scales load onto separate factors in a discrete way and can thus be analysed independently (see for examples Tanabe et al., 2012; Turky et al., 2008).

*Table 3.2 Cross-scale Correlations for SDQ Scores. Spearman's correlation coefficient values (top rows) and significance levels of the correlations (p; bottom rows) reported (n=282). **Indicates significant correlations with p<0.001.*

	SDQ scale			
	Emotional	*Conduct*	*Hyperactivity*	*Peer*
Emotional		.281 **	.245 **	.250 **
		.000	.000	.000
Conduct	.281 **		.503 **	.358 **
	.000		.000	.000
Hyperactivity	.245 **	.503 **		.360 **
	.000	.000		.001
Peer	.250 **	.358 **	.360 **	
	.000	.000	.001	

3.2 The role of demographic characteristics

Gender

Table 3.3 below displays the means and standard deviations for parental SDQ ratings received for girls and boys, respectively. A series of One-way ANOVAs revealed a significant effect of gender on parental ratings for conduct ($F(1,279)=8.497$, $p=0.004$), hyperactivity/inattention ($F(1,279)=16.342$, $p<0.001$) and total difficulties ($F(1,279)=10.041$, $p=0.002$), with boys reportedly displaying significantly more problems than girls in these domains. There was no effect of gender on parental ratings for emotional or peer difficulties, suggesting that in this cohort boys and girls in this study experienced emotional and peer difficulties to the same degree.

Table 3.3. Average SDQ parental ratings (and standard deviations in parentheses) for boys (n=143) and girls (n=138) respectively.

	Gender	
SDQ scale	*Male*	*Female*
Emotional	3.8 (2.6)	3.7 (2.5)
Conduct	2.8 (2.3)	2.1 (2.0)
Hyperactivity	6.1 (2.7)	4.7 (2.8)
Peer	3.9 (2.6)	3.4 (2.6)
Total Difficulties	16.5 (7.0)	13.8 (7.1)

Age at assessment

The mean age at assessment in this study was 10.9 years (sd=3.6). In order to establish if there was any relationship between age at assessment and the degree of emotional or behavioural difficulties presented, as reflected in the SDQ ratings, individual Pearson correlation analyses between age at assessment and ratings in each SDQ domain rating were carried out. A weak but highly significant negative correlation was found between age at assessment and parental ratings for hyperactivity/inattention ($r=-.288$, $p<0.001$), indicating that younger children tended to receive higher ratings for hyperactivity/inattention problems. Table 3.4 lists all correlation coefficients between age at assessment and ratings on SDQ domains.

*Table 3.4 Pearson correlation coefficient values (top rows) and significance levels of the correlations (p; bottom rows) between age at assessment and each of the SDQ scales. **Indicates significant correlations with p<0.001.*

	SDQ scale				
	Emotional	*Conduct*	*Hyperactivity*	*Peer*	*Total*
Age at assessment	0.113	-.102	-.288 **	.049	-.088
	.059	.089	.000	.414	.143

3.3 The role of epilepsy-specific factors

Age at onset and duration of epilepsy

In order to investigate the effect of age at onset of habitual epilepsy on the presentation of emotional or behavioural problems at the time of assessment as indicated by SDQ parental ratings, partial correlations were performed between age at onset and each SDQ domain, while controlling for the duration of epilepsy. Similarly, in order to investigate the relationship between the duration of epilepsy (in years) at the time of assessment and the SDQ ratings, partial correlations controlling for age at onset of habitual epilepsy were carried out. Results of these partial correlations are presented in Table 3.5.

Weak but significant partial negative correlations were found between age at onset of habitual epilepsy (after controlling for duration) and parental ratings for conduct ($r=-.179$, $p=0.003$) and hyperactivity/inattention ($r=-.310$, $p<0.001$) difficulties, indicating that an earlier onset of epilepsy was associated with higher levels of conduct and hyperactivity/inattention difficulties as indicated by parental ratings, when controlling for the duration of epilepsy. A significant negative partial

correlation was also found between age at onset of habitual epilepsy (after controlling for duration) and the Total difficulties SDQ score (r=-.181, p=0.002), indicating that earlier onset of epilepsy was associated with overall higher levels of emotional and behavioural difficulties, as indicated by parental ratings.

Weak but significant partial positive correlations were found between duration of habitual epilepsy and parental ratings for emotional (r=.163, p=0.006) and peer difficulties (r=.194, p=0.001) indicating that a longer duration of the epileptic syndrome was associated with more emotional and peer difficulties, after controlling for the age at onset of habitual seizures. Surprisingly, a significant negative partial correlation was also found between duration of habitual epilepsy and parental ratings for hyperactivity/inattention difficulties (r=-.198, p=0.001), indicating that longer duration of the epileptic syndrome was associated with less problems in hyperactivity/inattention, after controlling for age at onset of habitual seizures.

*Table 3.5. Partial correlation coefficients between age at onset of habitual seizures and ratings on each of the SDQ domains (controlling for duration of habitual epilepsy; top row). Partial correlation coefficients between duration of habitual seizures and ratings on each of the SDQ scales (controlling for age at onset; bottom row). *Indicates significant correlations with p<0.01, **Indicates significant correlations with p<0.001.*

	SDQ scale				
	Emotional	*Conduct*	*Hyperactivity*	*Peer*	*Total*
Age at onset	.064	-.179 *	-.310 **	-.075	-.181 *
(controlling for Duration)	.290	.003	.000	.212	.002
Duration	.163 *	.021	-.198 **	.194 **	.064
(controlling for Age at onset)	.006	.722	.001	.001	.290

Seizure Frequency

We next examined the relationship between seizure frequency and SDQ ratings. Seizure frequency was found to be significantly positively skewed ($z=17.65$, $p<0.01$) and thus, a log10 transformation was applied on seizure frequency values, which resulted in the values becoming normally distributed ($z=1.58$). In order to investigate the relationship between seizure frequency and ratings on each of the SDQ domains, Pearson correlations between seizure frequency and each SDQ score were carried out. The results are presented below in Table 3.6.

*Table 3.6. Pearson correlation coefficients between seizure frequency and ratings on each of the SDQ domains. Correlation coefficients are presented in the top row and significance values (p) in the bottom row. * Indicates significant correlations with p<0.05, **Indicates significant correlations with p<0.001.*

	SDQ scale				
	Emotional	*Conduct*	*Hyperactivity*	*Peer*	*Total*
Seizure frequency	-.006	.113	.230 **	.130 *	.158 *
	.927	.073	.000	.040	.012

A weak but significant positive correlation was found between seizure frequency and parental ratings for hyperactivity/inattention ($r=.230$, $p<0.001$) and peer difficulties ($r=.130$, $p=0.040$), indicating that a higher frequency of epileptic seizures was associated with increased difficulties in these domains. A significant positive correlation was also found between seizure frequency and the Total difficulties score ($r=.158$, $p=0.012$), indicating that higher frequency of seizures was associated with a higher level of emotional and behavioural difficulties in the cohort overall, as indicated by parental ratings.

3.4 The role of localisation of pathology

Lobe of pathology

With regards to the localisation of pathology I first considered the possible effect of the affected lobe of pathology on SDQ parental ratings. Table 3.7 below displays the average ratings given by parents for each SDQ scale for children with Frontal, Temporal, Parieto-occipital and Multilobar pathology, respectively. Figures 3.2 and 3.3 further show the percentage of children with Frontal, Temporal, Parieto-occipital and Multilobar pathology falling within the 'Abnormal', 'Borderline' and 'Normal' range for the Total SDQ difficulty score and each individual SDQ scale respectively.

As can be seen in Figure 3.3 in children with Frontal lobe pathology peer difficulties was the most frequent area of reported difficulty, with 69% of these children receiving ratings in the 'Abnormal' or 'Borderline' range, followed by hyperactivity/inattention difficulties, with 61% of children in the 'Abnormal' or 'Borderline' range. Children with Temporal lobe pathology received most frequently ratings in the 'Abnormal' or 'Borderline' ranges for peer (57%) and emotional problems (53%). Finally, children with Parietal-Occipital lobe pathology received most frequently ratings in the 'Abnormal' or 'Borderline' ranges for peer problems (54%) and hyperactivity/inattention problems (51%).

In order to investigate any significant differences in SDQ ratings received between children with pathology in different lobes a one-way ANOVA with lobe of pathology as a factor was performed. This revealed a significant effect of lobe of pathology on parental ratings for hyperactivity/inattention problems ($F(3,277)=2.791$, $p=0.041$). Post-hoc analyses revealed that children with frontal pathology received significantly higher ratings for hyperactivity/inattention difficulties (mean=6.0, sd=2.8) than children with temporal pathology (mean=4.9, sd=2.8; $t(179)=2.438$, $p=0.016$). Localisation of pathology with respect to the lobe appeared to make no

significant difference on parental ratings for emotional, conduct or peer problems or the total difficulties score.

Table 3.7. Average SDQ parental ratings and standard deviations (in parentheses) for children with Frontal, Temporal, Parieto-Occipital and Multilobar pathology respectively.

	Average rating (sd)			
SDQ Scale	*Frontal*	*Temporal*	*Parieto-occipital*	*Multilobar*
Emotional	3.88 (2.7)	3.90 (2.7)	3.05 (2.3)	3.88 (2.3)
Conduct	2.39 (1.7)	2.39 (1.8)	2.10 (1.9)	2.88 (2.4)
Hyperactivity	6.03 (2.8)	4.95 (2.8)	5.07 (3.2)	5.88 (2.4)
Peer	4.14 (2.7)	3.45 (2.5)	3.29 (2.8)	3.69 (2.4)
Total	15.97 (6.5)	14.78 (7.3)	13. 61 (7.7)	16.54 (6.9)

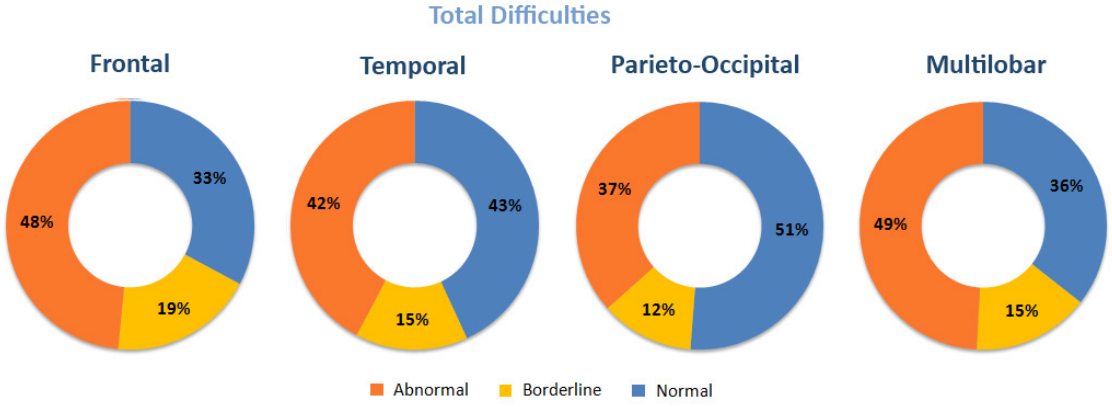

Figure 3.2. Percentage of Total Difficulties SDQ score based on parental ratings falling within the 'Abnormal', 'Borderline' and 'Normal' range for patients with Frontal (n=64), Temporal (n=116), Parieto-occipital (n=41) and multilobar pathology (n=60), respectively.

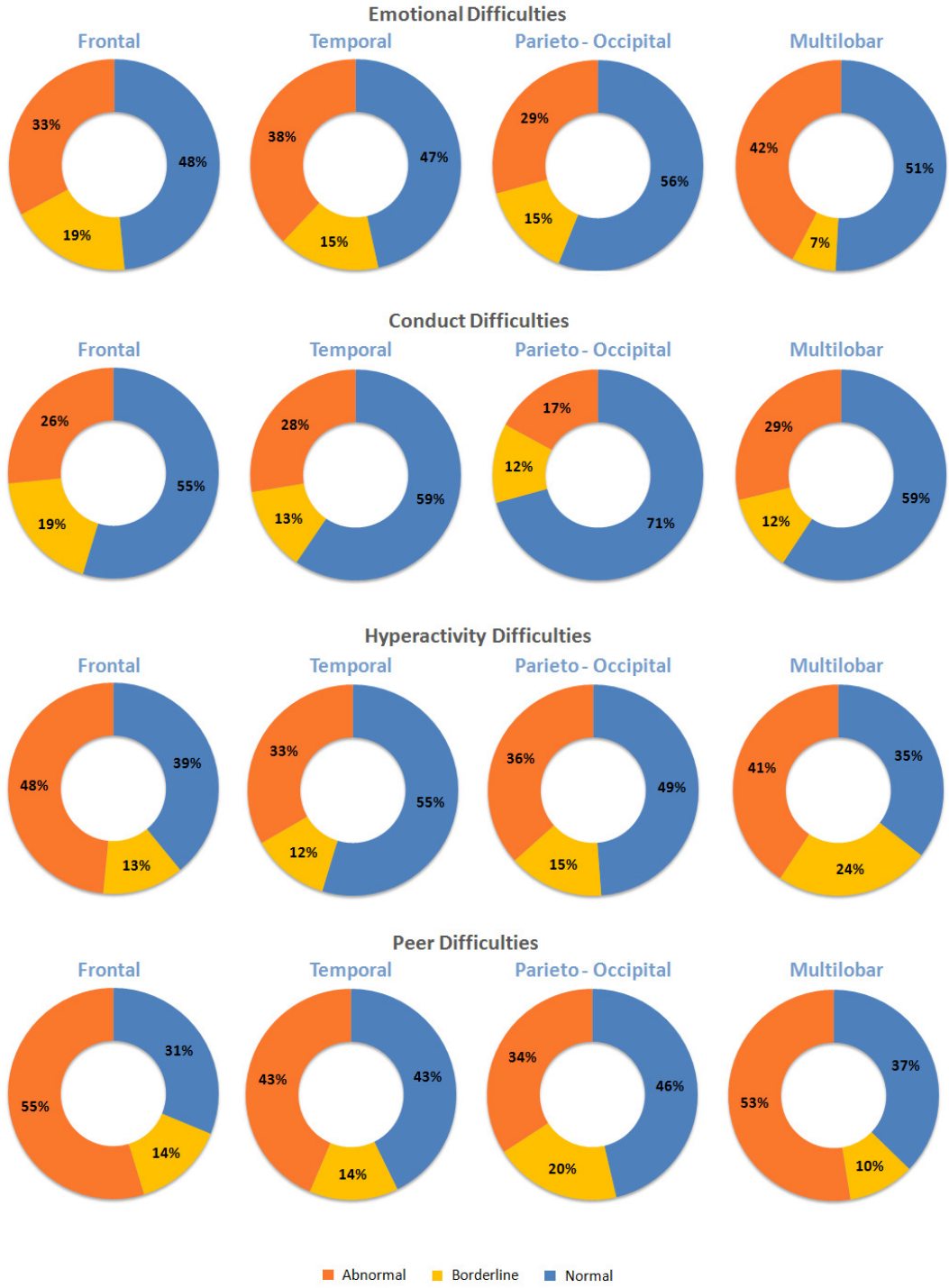

Figure 3.3. Percentage of SDQ individual scale ratings given by parents falling within the 'Abnormal', 'Borderline' and 'Normal' range for children with Frontal (n=64), Temporal (n=116), Parieto-occipital (n=41) and multilobar pathology (n=60), respectively.

Lateralisation of pathology

We next examined the effect of the hemispheric lateralisation of pathology underlying the epileptic syndrome on SDQ parental rating scores. Table 3.8 below displays the average parental ratings for each SDQ scale for children with left and right hemispheric pathology respectively. Figures 3.4 and 3.5 further show the percentage of children with left and right hemispheric pathology falling within the 'Abnormal', 'Borderline' and 'Normal' range for the Total Difficulties SDQ score and each individual SDQ scale respectively. As can be seen, children with right pathology received overall somewhat higher scores in all SDQ domains.

A one-way ANOVA with lateralisation of pathology as a factor and SDQ scale ratings as the dependent variables revealed significant differences for peer problems between children with left and right hemisphere pathology ($F(1,280)=5.776$, $p=0.01$). Specifically, children with right hemisphere pathology received higher ratings for peer problems (mean=4.1, sd=2.7) compared to children with left hemisphere pathology (mean=3.3, sd=2.5).

Further multivariate ANOVA analyses with both lobe and lateralisation of pathology as factors revealed no interaction effect between lobe and lateralisation for any of the SDQ scores.

Table 3.8. Average SDQ parental ratings and standard deviations (in parentheses) for children with left (n=150) and right (n=131) hemisphere pathology.

	Hemisphere of Pathology	
SDQ scale	*Left*	*Right*
Emotional	3.7 (2.5)	3.8 (2.7)
Conduct	2.3 (2.6)	2.6 (2.2)
Hyperactivity	5.1 (2.9)	5.7 (2.8)
Peer	3.3 (2.5)	4.5 (2.7)
Total Difficulties	14.5 (7.1)	16.0 (7.1)

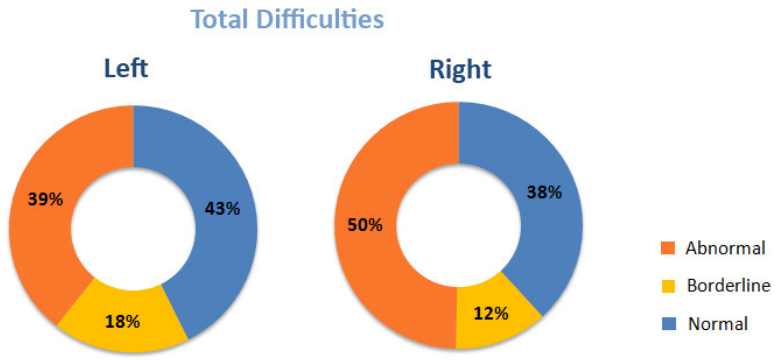

Figure 3.4. Percentages of the Total Difficulties SDQ score based on parental ratings falling within the 'Abnormal', 'Borderline' and 'Normal' range for patients with left hemisphere (n=150) and right hemisphere pathology (n=132) respectively.

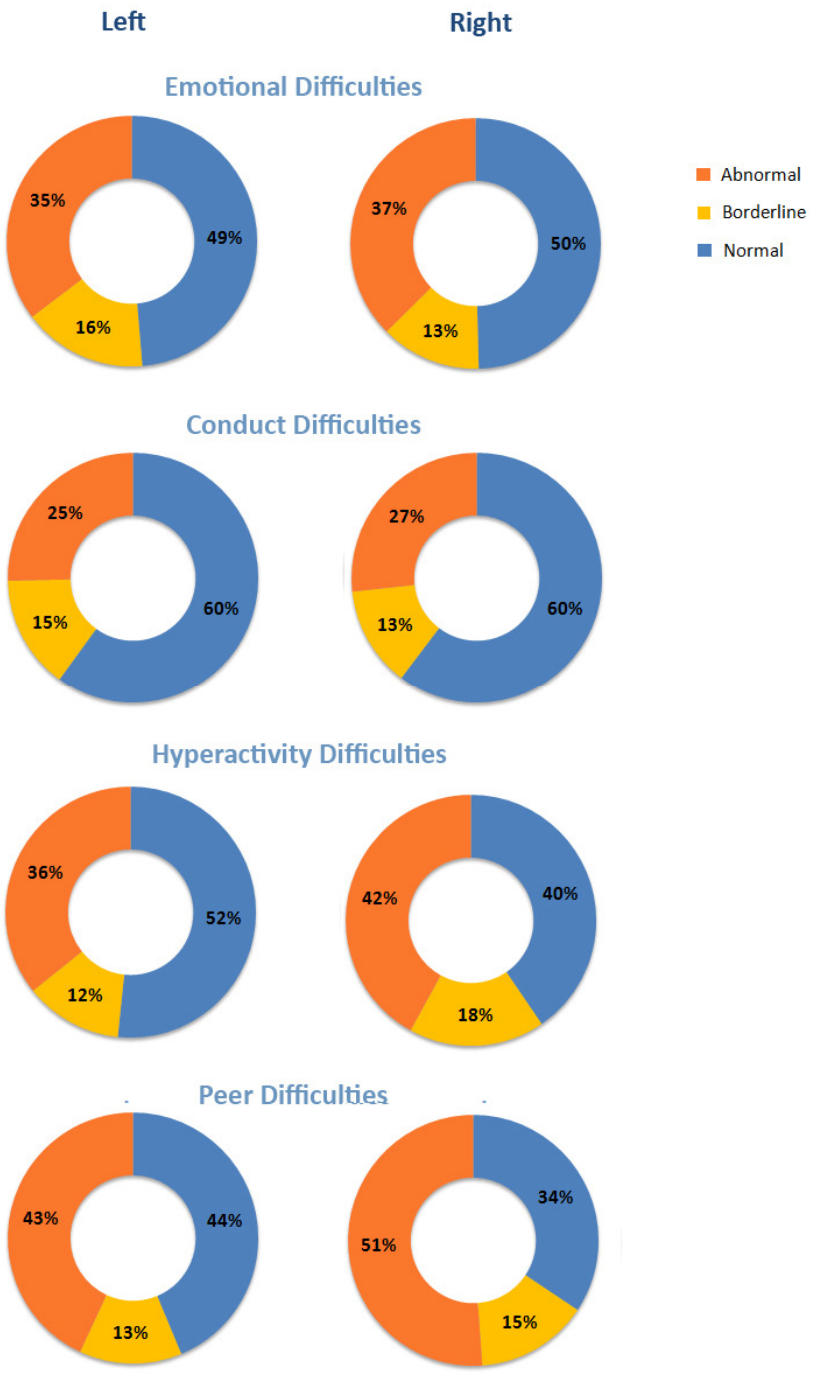

Figure 3.5. Percentages of parental ratings for each SDQ scale falling within the 'Abnormal', 'Borderline' and 'Normal' range for children with left hemisphere (n=150) and right hemisphere pathology (n=132) respectively.

3.5 The role of cognitive functions

Intellectual Ability

The next set of variables examined in the present study involved performance in cognitive tests including measures of intellectual ability (Wechsler Intelligence Scales or Bayley Scales). In the current study intellectual ability was examined based on indices of overall intellectual ability (FSIQ and DQ/FSIQ), as well as ability in more discrete domains of intellectual functioning (VIQ, PIQ, WMI and PSI). The average general intellectual or developmental ability score (FSIQ/DQ) obtained in this sample (mean standard score=75.96, sd=21.7) was found to be well below the mean of the population. 37% of children performed within the learning disability range (FSIQ/DQ<69, classified in Wechsler scales as "extremely low"), 21% performed in the Borderline range (70<FSIQ/DQ <80) and finally only 42% showed mild or no intellectual deficit by performing within the Low Average or above range (FSIQ/DQ >80). Table 3.9 below also provides average performance scores for individual domains of intellectual ability. Figure 3.6 displays the distribution of FSIQ/DQ standard scores for the whole sample.

Overall, intellectual or developmental ability was found to be highly correlated to SDQ ratings, with higher levels of emotional and behavioural difficulties associated with worse performance in intellectual ability measures (see Table 3.12 and Figure 3.7). As can be seen in Table 3.10 emotional and hyperactivity/inattention difficulty ratings were most highly correlated with the WMI index, while conduct and peer difficulties were most highly correlated with the VIQ index. The VIQ was also the IQ domain most highly correlated with the SDQ total difficulties score.

Table 3.9 Means and standard deviations for individual domains of intellectual ability. VIQ=Verbal Intelligence Quotient; PIQ= Performance Intelligence Quotient; WMI= Working Memory Index; PSI=Processing Speed Index; FSIQ= Full Scale Intelligence Quotient; FSIQ/DQ= Full Scale Intelligence Quotient or Developmental Quotient.

IQ scale	*Mean*	*sd*	*N*
VIQ	83.1	18.0	251
PIQ	81.9	17.8	251
WMI	84.7	17.3	163
PSI	82.7	16.5	166
FSIQ	79.5	18.5	252
FSIQ/DQ	75.9	21.7	275

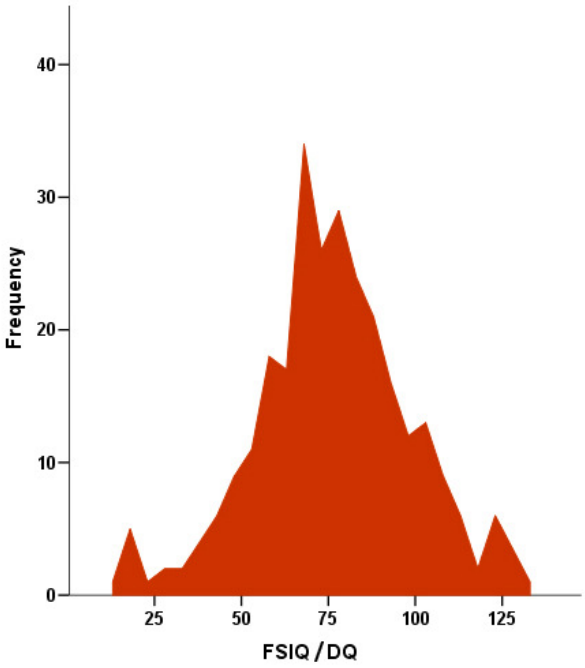

Figure 3.6. Frequency distribution of FSIQ/DQ standard scores for the whole cohort.

*Table 3.10. Correlation coefficients and level of significance (p) between the parental SDQ ratings and indices of intellectual ability. *Indicates significant correlations with p<0.01, **Indicates significant correlations with p<0.001.*

		SDQ scale				
	N	*Emotional*	*Conduct*	*Hyperactivity*	*Peer*	*Total*
VIQ	251	-.192 *	**-.265 ** **	-.289 **	**-.211 ** **	**-.351 ** **
		.002	**.000**	.000	**.001**	**.000**
PIQ	251	-.116	-.244 **	-.273 **	-.204 **	-.309 **
		.068	.000	.000	.001	.000
WMI	163	**-.235 ** **	-.177	**-.326 ** **	-.115	-.301 **
		.003	.024	**.000**	.144	.000
PSI	166	-.141	-.110	-.196 *	-.200 *	-.243 **
		.070	.159	.011	.010	.002
FSIQ	251	-.160 *	-.259 **	-.297 **	-.217 **	-.345 **
		.011	.000	.000	.001	.000
FSIQ/DQ	274	-.036	-.224 **	-.302 **	-.242 **	-.306 **
		.548	.000	.000	.000	.000

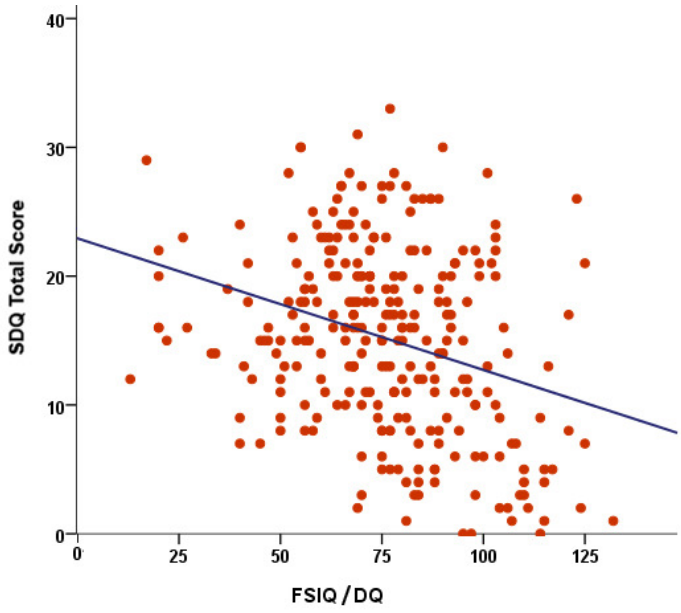

Figure 3.7. The SDQ Total Difficulties score as a function of general intellectual or developmental ability (FSIQ/DQ) across the whole sample. A significant negative correlation can be noted indicating that lower levels of intellectual or developmental ability are associated with higher levels of reported emotional and behavioural difficulties.

Memory

Memory functioning was examined here based on a Verbal, a Visual and a General Memory ability Index, as assessed by the Children's Memory Scale (CMS). Table 3.11 below displays mean performance scores in these three memory indices across the whole cohort. The distribution of the General Memory ability scores can also be seen in Figure 3.8. As can be seen, children in this cohort performed overall below the normative population mean (mean General Memory score=83.7, sd=19.4). Moreover, children in this study performed on average better in measures of Visual memory (score=92.7, sd=14.1) than Verbal memory (score=82.9, sd=19.3).

A series of Pearson correlations were run to investigate the relationship between performance in memory measures (CMS Verbal, Visual and General Memory composite scores) and parental SDQ ratings (see Table 3.12). Emotional and hyperactivity/inattention difficulty ratings were found to be negatively correlated to all three composite memory scores, with the highest correlation for emotional difficulties being with the Visual Memory index and the highest correlation for hyperactivity/inattention difficulties being with the General Memory index. Conduct difficulty ratings were significantly correlated to both Verbal and General Memory, with the highest correlation being with the Verbal Memory index. Finally the Total Difficulties SDQ score was significantly correlated negatively with all three indices of memory and most highly with the General Memory composite score (see Figure 3.8).

Table 3.11. Mean standard scores, standard deviations and available case numbers for Verbal, Visual and General Memory ability composite indices based on performance in the CMS.

CMS Composite Index	*Mean*	*sd*	*N*
Verbal Memory	82.9	19.3	170
Visual Memory	92.7	14.1	175
General Memory	83.7	19.4	167

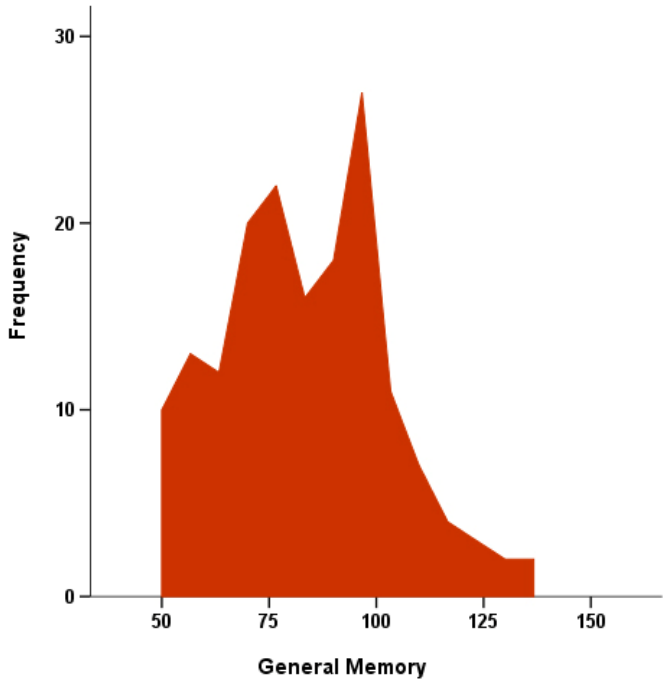

Figure 3.8. Frequency distribution of standard scores on the CMS General Memory ability index for the whole sample.

*Table 3.12. Pearson correlation coefficients (top rows) and significance values (bottom rows) between the CMS memory composite scores and the SDQ scales. *Indicates significant correlations with p<0.01, **Indicates significant correlations with p<0.001.*

	SDQ scale				
CMS Composite Index	*Emotional*	*Conduct*	*Hyperactivity*	*Peer*	*Total*
Verbal Memory	-.160 *	**-.195 ***	-.260 **	-.090	-.278 **
	.011	**.011**	.001	.242	.000
Visual Memory	**-.234 ***	-.038	**-.314 ****	-.173	**-.286 ****
	.002	.623	**.000**	.022	**.000**
General Memory	-.228 *	-.190 *	-.339 **	-.144	-.337 **
	.003	.014	.000	.063	.000

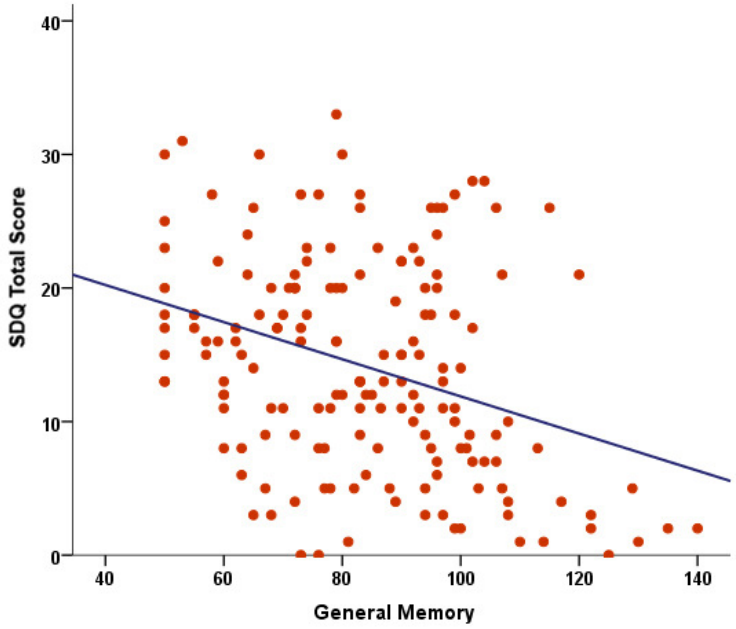

Figure 3.9 SDQ total difficulties score as a function of the CMS General Memory Index (n=167). A significant negative correlation can be noted between the level of overall emotional and behavioural difficulties reported by parents in the SDQ and the overall performance in the CMS memory measures.

Memory performance in the CMS however is known to be highly correlated to intelligence scores measured by Wechsler scales and particularly the FSIQ (Drozdick et al., 2008). In order to investigate the relationship between memory functions and emotional-behavioural difficulties irrespective of intellectual functioning a series of partial correlations were also carried out, investigating the relationship between SDQ scores and CMS memory indices while controlling for FSIQ (See Table 3.13). These revealed that after partialling out the effects of FSIQ, emotional and hyperactivity/inattention difficulty ratings were still significantly negatively correlated to CMS Visual and General memory composite scores, with the highest correlation for both being with Visual Memory.

*Table 3.13. Pearson partial correlation coefficients (top rows) and significance values (bottom rows) between the CMS memory composite scores and the SDQ scales, after controlling for FSIQ. *Indicates significant correlations with p<0.05, **Indicates significant correlations with p<0.001.*

	SDQ scale				
CMS Composite Index	*Emotional*	*Conduct*	*Hyperactivity*	*Peer*	*Total*
Verbal Memory	-.097	-.028	-.086	.078	-.066
	.210	.717	.268	.318	.393
Visual Memory	-.179 *	.119	-.196 *	-.072	-.133
	.019	.120	.010	.351	.083
General Memory	-.164 *	- .007	-.190 *	.017	-.138
	.035	.932	.014	.833	.076

Academic Attainments

The final factor examined in this study was the level of academic attainments achieved as estimated by performance in subtests from the Wechsler Individual Achievement Test, 2nd UK

Edition (WIAT-IIUK). In the current study performance in the WIAT-II was represented by a Literacy Index, a Numeracy Index and a General Academic Abilities Index. Table 3.14 displays the mean scores achieved in this cohort for the three indices. The distribution of standard scores on the General Academic Attainment index can also be seen in Figure 3.10. Similarly to the intelligence and memory results presented above, the average academic attainment performance was also found to be compromised in this cohort compared to the normative population (mean General Academic Attainments Index = 84, sd=18.6).

A series of Pearson correlations were run to investigate the relationship between academic attainments as measured by the three WIAT-II indices and parental SDQ ratings (see Table 3.15). Overall, emotional and behavioural difficulties as measured by the SDQ were found to be significantly correlated to academic attainments (See Table 3.15 and Figure 3.11). Specifically, emotional and peer difficulties were found to be most highly correlated to the Literacy Index, hyperactivity/inattention difficulties to the Numeracy Index and conduct difficulties to the General Academic Attainments Index.

Table 3.14. Mean standard scores, standard deviations and available case numbers for Literacy, Numeracy and overall Academic Attainment Indices, as measured by the WIAT-II.

WIAT-II Index	*Mean*	*sd*	*N*
Literacy	84.8	19.7	234
Numeracy	82.4	19.1	223
General	84.0	18.6	234

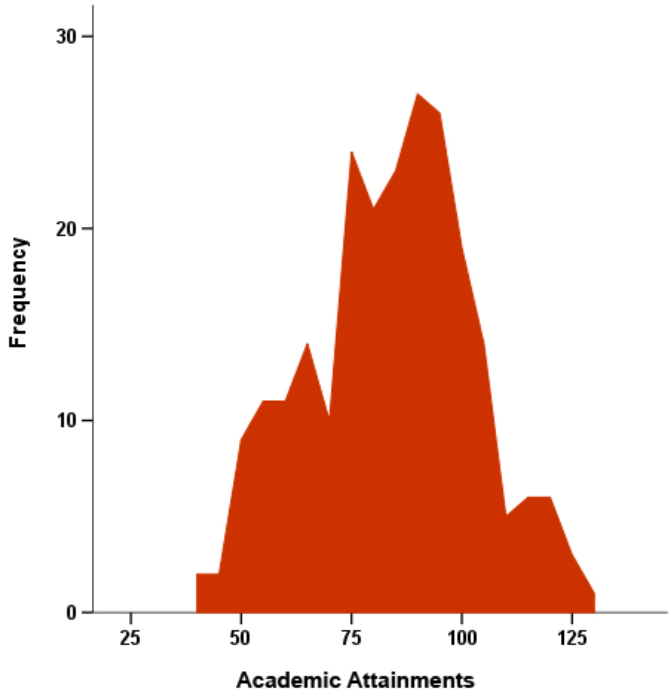

Figure 3.10.Frequency distribution of the WIAT-II General Academic Attainment Index score for the whole cohort.

*Table 3.15. Pearson correlation coefficients (top rows) and significance values (bottom rows) between performance scores in WIAT-II composite index scores and parental ratings in each of the SDQ scales. * Indicates significant correlations with p<0.01; ** Indicates significant correlations with p<0.001.*

	SDQ scale				
WIAT Index	*Emotional*	*Conduct*	*Hyperactivity*	*Peer*	*Total*
Literacy	-.203 *	-.269 **	-.276 **	-.240 **	-.349 **
	.002	.000	.000	.000	.000
Numeracy	-.122	-.246 **	-.306 **	-.194 **	-.304 **
	.070	.000	.000	.004	.000
General Academic	-.191 *	-.271 **	-.286 **	-.224 **	-.348 **
Attainments	.003	.000	.000	.001	.000

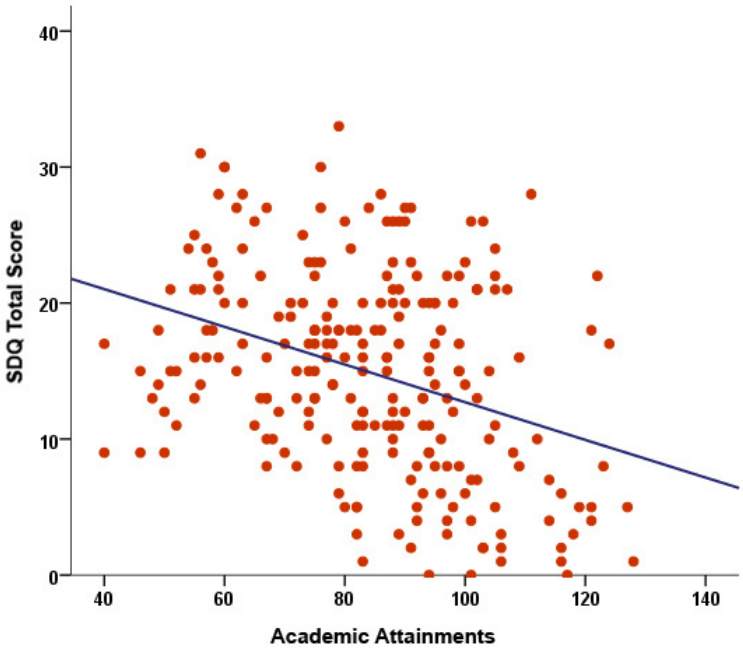

Figure 3.11 SDQ total difficulties score as a function of the WIAT-II General Academic Attainments Index (n=234). A significant negative correlation can be noted, with higher levels of emotional and behavioural difficulties being associated with lower academic attainments performance.

A further analysis looked at partial correlations between academic achievement indices and SDQ scores while controlling for the FSIQ (See Table 3.16). After partialling out the effects of the FSIQ, the SDQ Total difficulties score was still found to be significantly correlated to the WIAT-II Literacy Index, with lower performance in literacy measures associated with increased emotional and behavioural difficulties overall. After partialling out the effect of the FSIQ, no other correlations were found between SDQ scales and WIAT-II indices.

*Table 3.16. Partial correlation coefficients (top rows) and significance values (bottom rows) between WIAT-II composite index scores and parental ratings in each of the SDQ scales, after controlling for FSIQ. *Indicates significant correlations with p<0.05.*

	SDQ scale				
WIAT Index	*Emotional*	*Conduct*	*Hyperactivity*	*Peer*	*Total*
Literacy	-.127	-.117	-.086	-.119	-.147 *
	.059	.083	.198	.075	.028
Numeracy	.012	-.066	-.118	-.033	-.048
	.862	.337	.082	.624	.484
Academic Attainments	-.106	-.108	-.080	-.084	-.124
	.112	.106	.229	.209	.062

3.6 Multivariate Analyses

Finally, a series of multivariate linear regression analyses aiming to identify factors predictive of emotional and behavioural difficulties in children with epilepsy as measured by parental ratings is presented here. These regressions were aimed at producing tentative models of risk factors related to the development of mental health difficulties in children with epilepsy. I used the following model-building strategy to determine which of the demographic, epilepsy-specific, localisation and lateralisation and cognitive variables were predictive of the outcome measures (individual SDQ domain scores) after being jointly entered in multivariate linear regression analyses. For each SDQ outcome measure I included in the multivariate regression analysis as factors the demographic, epilepsy-specific, localisation and lateralisation variables that were

found in univariate analyses to be significantly associated with that specific outcome measure. Cognitive predictors were also included in these regression analyses as explained below.

I first considered cognitive factors related to intellectual ability. Due to the high degree of intercorrelation between individual scores in the different IQ domains, it was not possible to include in the regression analyses all the IQ domains which had shown an association to each SDQ outcome measure. I thus included in all regression analyses the VIQ score as a) the IQ domain for which most data were available and b) the IQ domain which was most highly correlated to the overall level of emotional and behavioural difficulty as represented by the Total SDQ score. As previously seen (see Table 3.10), the VIQ was the IQ domain showing the highest correlation with SDQ scores for conduct, peer and total difficulties. Although ratings for hyperactivity/inattention and emotional difficulties were found to be more strongly correlated with the WMI, as WMI data were available here for a much smaller sample (58% and 59% of the patients respectively), the VIQ was selected as a possible predictor instead so as not to reduce the statistical power of these analyses, as the IQ domain most correlated with the overall level of SDQ-measured difficulties and the second in line IQ domain correlating to hyperactivity/inattention and emotional outcome measures. Similarly, as memory data were only available for 60% of the sample, it was decided not to include memory performance variables (Verbal Memory Index, Visual Memory Index) in the regression analyses, so as not to limit the power of the statistical calculations. Practically, this resulted in the exclusion of Visual Memory as a possible predictor for emotional difficulties. Academic attainment scores (Literacy Index, Numeracy Index) were only included in the analyses if they were found to be significantly correlated to the SDQ scores after controlling for the effects of FSIQ. However, if found to show a high degree of collinearity (variance inflation factor; VIF>1) with VIQ scores after being included in the regression analyses

they were subsequently dropped. This practically resulted in the exclusion of all academic attainment predictors from the regression analyses. The Enter method was used for all the linear regression analyses presented here. See Table 3.17 for a summary of all the regression analyses results.

The first model examined predictive factors for the presence of emotional difficulties as measured by parental SDQ ratings. Duration of epilepsy and VIQ were entered as predictors in a linear regression model. A significant model emerged ($F(2,248)=7.075$, $p<0.001$, Adjusted R square =.138), with duration of epilepsy (beta =.137, p=0.032) and VIQ (beta = -.161, p=0.012) being both significant predictors for emotional difficulties as measured by the SDQ. These results indicated that longer duration of epilepsy and a lower VIQ score were predictive of more emotional difficulties as measured by parental ratings.

The next model aimed to identify predictors for conduct difficulties as measured by parental rating scores. Gender, age at onset of epilepsy and VIQ were entered as predictors. A significant model emerged ($F(3,244)=11.722$, $p<0.001$, Adjusted R square =.115), with gender (beta =-.161, p=0.008), age at onset (beta =.190, p=0.002) and VIQ (beta = -.223, $p<0.001$) being all significant predictors for conduct SDQ ratings. These results suggest that when considering the above factors together, in our cohort boys with epilepsy were more likely to develop conduct difficulties compared to girls. Also that later age at onset of epilepsy and a lower VIQ score were predictive of a higher level of conduct difficulties as measured by SDQ ratings.

Gender, age at onset of epilepsy, duration of epilepsy, frequency of seizures, VIQ and localisation of pathology were entered as predictors in a linear regression model with hyperactivity/inattention SDQ ratings as an outcome measure. A significant model emerged ($F(8,211)=7.380$, $p < 0.001$,

Adjusted R square = .182), with gender (beta = -.198, p=0.002), age at onset of epilepsy (beta =-.343, p<0.001), duration of epilepsy (beta = -.272, p<0.000), VIQ (beta = -.265, p<0.001) and localisation of pathology (Frontal versus Temporal; beta =.140, p=0.039) being all significant predictors for the hyperactivity/inattention SDQ score. These regression results indicate that when considering the above factors together in our cohort, boys with epilepsy were likely to develop more hyperactivity/inattention difficulties compared to girls. Also that earlier age of onset of epilepsy, shorter duration of epilepsy, the localisation of pathology in the frontal lobes (as compared to the temporal lobes) and a lower VIQ score were predictive of higher levels of hyperactivity/inattention difficulties as measured by SDQ ratings.

Finally, the predictors of peer SDQ score were examined using a linear regression model with duration of epilepsy, frequency of seizures, lateralisation of pathology and VIQ as predictors. A significant model emerged (F(4,215)=7.633, p<0.001, Adjusted R square = .101), with duration of epilepsy (beta =.214, p=0.001), frequency of seizures (beta =.139, p=0.034), lateralisation of pathology (beta = .154, p=0.017) and VIQ (beta = -.140, p=0.039) being all significant predictors for the peer SDQ score. Longer duration of epilepsy, higher frequency of seizures, the presence of right hemisphere pathology and lower VIQ score were thus found to be significant risk factors for the presence of peer problems as measured by parental SDQ ratings.

Post hoc power analyses were also conducted to assess whether the sample size was adequate for the regression analyses presented above. The alpha level used for these power analyses was adjusted from the nominal p<.05 to .01 to take into account the multiple hypotheses tested. I used the conventional minimum power=.80 (indicating the probability that I correctly rejected the null hypothesis when the null hypothesis was false; see Cohen 1988) to make judgements on adequate statistical power for the reported regression analyses. The post hoc power analyses

confirmed that with the sample sizes used in the reported regression analyses (n=211-248), the statistical power was equal or larger than .97 in all cases, suggesting that there was more than adequate power (i.e. power >.80) to detect the observed effects.

*Table 3.17. Summary of linear regression results, marking the factors (*) that were found to be significant predictors for each SDQ scale. *Indicates significance with p<0.05. Note that not all factors listed on the leftmost column were included in each analysis.*

	SDQ scale			
Predictors	*Emotional*	*Conduct*	*Hyperactivity*	*Peer*
Gender		*	*	
Age at onset		*	*	
Duration	*		*	*
Frequency				*
Localisation			*	
Lateralisation				*
VIQ	*	*	*	*

Chapter 4

Discussion

4.1 Introduction

The present thesis focused on mental health difficulties in paediatric refractory focal epilepsy. Specifically, it undertook a detailed evaluation of the predictive power of several demographic (gender, age at assessment), clinical (age at onset of epilepsy, duration of the epileptic syndrome and seizure frequency), localization (lobe and lateralization of pathology) and cognitive variables (performance in intellectual, memory and academic attainment measures) potentially associated with the development of mood, conduct, inattention/hyperactivity and peer relationship difficulties in paediatric refractory focal epilepsy. As previously summarized in the introduction of this thesis, although a number of risk factors for developing such difficulties has been suggested in the literature, to date there are few firm conclusions, with many studies employing small samples, using limited or unreliable measures or focusing exclusively on temporal lobe epilepsy. Moreover, there has been a dearth of research systematically investigating the combined contributions of potential risk factors to mental health outcome in paediatric epilepsy.

The study presented here expanded on previous studies in several ways. First, the pool of subjects examined here consists of one of the largest groups of paediatric epilepsy patients studied to date in relation to risk factors for mental health. Secondly, statistical techniques were used here to determine both the unique and combined contribution of several factors for mental health outcome. Third, the role of cognitive functioning as a potential determinant of mental health outcome was examined using three broad domains of functioning: general intellectual status (Full Scale IQ, Verbal IQ, Performance IQ, Working Memory and Processing Speed), memory (General Memory, Verbal Memory, Visual Memory) and academic attainment level (Literacy and Numeracy). This study also aimed to fill gaps in the existing literature by examining the role of localization and lateralization of pathology in the development of emotional or behavioural difficulties in intractable focal epilepsy by examining and comparing patients with temporal, frontal and parieto-occipital epilepsy.

The presented study partially confirms and extends previous findings regarding predictors of psychopathology in children and adolescents with focal epilepsy disorders. A summary of the main findings is presented and discussed below. The limitations of the presented study are also acknowledged and implications for clinical practice and future research are considered. Unless otherwise indicated, the findings discussed below are based on the results of the multivariate regression analyses.

4.2 Emotional and behavioural difficulties in refractory paediatric focal epilepsy

Mental health difficulties were widely present in this sample of children and adolescents with medication-resistant focal epilepsy based on parental report. 44% of the children had overall emotional and behavioural difficulties falling within the clinical ('abnormal') range and another 15% had difficulties in the 'borderline' range. Thus, an increased prevalence for all types of measured psychopathology was observed in this population as compared to the general child and adolescent population in the United Kingdom using the parent SDQ (Goodman, 1997). In interpreting these results, it has to be emphasized that the presented study is based on data collected from individuals with refractory epilepsy attending a tertiary service and is thus likely to over-represent children with significant difficulties. In this respect the presented results are most likely not representative of the entire paediatric population with focal epilepsy. In general, mental health problems are known to be more prevalent in both children and adults with refractory epilepsy (Inoue & Mihara, 2001).The rates of mental health difficulties reported here are reassuringly consistent with those reported in previous studies of children with chronic and refractory epilepsy studied at the presurgical stage (20–40%; Ott et al., 2003).

Problems with peer relationships was the most frequently reported area of difficulty in this sample, affecting one out of two children in the cohort, with ratings falling in the clinically 'abnormal' range for 47% of the cases. The rate of peer difficulties found here is slightly higher than that reported previously by Turky and colleagues (2008) using the same measure (SDQ), who found peer difficulties in 39% of their cases. Hyperactivity/inattention and emotional difficulties were also reported to be very common, present in 39% and 36% of the cases respectively, consistent with the literature highlighting these as areas of main concern for paediatric epilepsy. ADHD is amongst the most frequent behavioural comorbidities in childhood epilepsy (Thome-Souza et al., 2004; Turky et al., 2008; Russ et al., 2012) with reported rates in the literature ranging between 20-40% (Barkley, 1990; Cohen et al., 2012; Hauser et al., 1998). Emotional difficulties are also very frequently reported in paediatric epilepsy (36% in Thome-Souza et al., 2004; 34% in Turkey et al., 2008). Finally, difficulties with conduct were less common in this sample, present in 26% of the cases. Differences in the rate of psychopathologies reported here and in other studies are likely to reflect sampling issues (see below), as well as the use of different rating or diagnostic instruments (see Ott et al., 2003).

4.3 The role of demographic characteristics

Gender

Based on previous findings in epileptic as well as normative samples (e.g. Alfstad et al., 2011; Zahn-Waxler et al., 2008) I had expected gender differences to emerge with boys presenting with more conduct, hyperactivity/inattention and peer problems and girls presenting with more emotional problems. The literature suggests a gender difference in coping mechanisms for stress of adverse life situations with girls using more emotional coping strategies and rumination about

problems and boys relying more on distraction and aggressive strategies (Nolen-Hoeksema & Girgus, 1994; Zeman & Shipman, 1998). Here, I found that boys were rated as having overall more significant emotional and behavioural difficulties than girls, as demonstrated by a higher Total Difficulties SDQ rating on average. More specifically, boys were reported to have more difficulties than girls in the domains of conduct and hyperactivity/inattention as predicted. The presented findings are consistent with the literature supporting a marked male preponderance for mental health difficulties that typically have an early age onset such as conduct disorder and ADHD (Ramtekkar et al., 2010; Zahn-Waxler et al., 2008). Contrary to my prediction, I found no gender difference in emotional or peer relationship difficulties.

Sex differences in psychopathology are most likely rooted in the interaction of several factors including biological, cognitive and psycho-social differences in boys and girls. Girls and boys have different developmental trajectories and undergo different biological processes. For example, prenatal exposure to testosterone has been proposed to account for greater disinhibition in boys than in girls (Baron-Cohen 2002; Keenan & Shaw 1997). Higher fetal testosterone has also been linked to boys' lower empathy (Knickmeyer et al. 2005b) and lower quality of social relationships (Knickmeyer et al. 2005a). In adults, biological sex differences in relation to psychopathology have been observed at the level of genes, neurotransmitters, hormones, as well as brain structure and function (Zahn-Waxler, et al. 2006).

Moreover, faster maturation of cognitive and language abilities in girls relative to boys during childhood could explain why girls may be more resilient to behavioural problems during childhood (Zahn-Waxler, et al. 2006). Several brain areas including the frontal and temporal lobes are known to develop considerably faster in girls, by as much as 20 months (Zahn-Waxler, et al. 2006), potentially enhancing girls' abilities for problem solving, decision making and inhibitory

control. Boys have reduced language abilities compared to girls during childhood, which may reduce social problem solving abilities during conflict, and instead increase physical aggression and conduct problems (Keenan & Shaw 1997; Ruble & Martin 1998).

Finally, boys and girls may also experience different environmental risk factors and the gender-specific patterns of psychopathology may reflect in part normative gender-role traits and stereotypes. For example, stereotypical gender-specific behaviours promoting dependence, passivity and self-sacrificing, have been hypothesised to increase the risk for depression in girls (Hill & Lynch, 1983). From an early preschool age and continuing through childhood and adolescence, girls have been demonstrated to have higher empathy and prosociality, increased ability for understanding others' emotions and intentions, better social skills and more remorse after transgression compared to boys (Brody, 1999; McClure, 2000; Zahn-Waxler et al., 2006). Moreover, similar environmental factors may interact with biological factors to differentially shape outcomes for the two genders. For example Davies and Windle (1997) found that family conflict was more crucial for the development of conduct problems for girls than boys.

Although research unequivocally supports an increased prevalence of adolescent-onset emotional difficulties for girls compared to boys, including mood and anxiety disorders (Zahn-Waxler et al., 2008), girls were not found here to have more difficulties in the emotional domain. It is possible that I was not able to pick up a gender difference in the current sample, as the mean age of assessment in our sample was 10 years of age. However a separate analysis looking at participants aged 12 or above, also failed to demonstrate a difference between genders in the emotional domain.

The risk-by-gender interaction notable here suggests that gender plays a significant role in the development of mental health difficulties in boys and girls with focal refractory epilepsy. However

the pattern observed here with regards to conduct and hyperactivity/inattention difficulties, with boys having more difficulties than girls, is similar to that observed in the general population and therefore may not be epilepsy-specific. On the contrary, the pattern observed here with regards to emotional difficulties is unlike that of the general population, suggesting that in children or adolescents with epilepsy, boys may be as likely as girls to develop emotional difficulties.

Age at assessment

Due to high collinearity between age at assessment and other predictors examined in the present study it was not possible to include age at assessment as a factor in the multivariate regression analyses. The results from the univariate analyses however clearly support an association between younger age at assessment and more inattention/hyperactivity problems. This echoes the literature which reliably supports an early onset for attention deficit-hyperactivity disorder, as compared to emotional difficulties, for example, which become more prominent later in life during adolescence (Ramtekkar et al., 2010; Zahn-Waxler et al., 2008). Previous studies have also highlighted age as an important factor for mental health outcome specifically in paediatric epilepsy, with a predominance of ADHD during childhood (Thome-Souza et al., 2004). The much higher incidence of inattention/hyperactivity difficulties in our epilepsy sample compared to the general population however suggests that the presence of epilepsy at an early age may increase the risk for developing ADHD type difficulties.

4.4 The role of epilepsy-specific factors

The next group of factors examined in this study included variables related to the epileptic syndrome itself: the age at onset of habitual epileptic seizures, the duration of habitual epilepsy and seizure frequency in the year prior to the assessment. A relationship between such epilepsy-related factors and the occurrence of mental health difficulties epilepsy is not yet established in the literature. However, while age at onset and duration of epilepsy have been repeatedly and reliably linked to cognitive outcome (Cormack et al., 2007; Hermann & Seidenberg, 2007; Smith et al., 2002; Vasconcellos et al., 2001; Vendrame et al., 2009), seizure frequency has been pointed out as a potential predictive factor for mental health outcome (e.g. Hermann et al., 1988; Oguz et al., 2002). Age at onset and duration of epilepsy have been deemed to be potentially less important for mental health (Austin et al., 2001; Hermann et al., 1990; Oguz et al., 2002). Based on previous findings I had thus expected that increased seizure frequency predominantly and less possibly earlier age at onset and longer duration to be associated with higher ratings of emotional or behavioural difficulties.

Importantly, in the present study I was able to examine the predictive value of these epilepsy-related factors, while controlling for intellectual ability, which has been an important confounding variable in several previous studies (Kolfen et al., 2001; Thome-Souza et al., 2004; Datta et al., 2005). This is crucial as lower intellectual ability functioning is a known risk factor for the development of psychopathology (e.g. Dietz et al., 1997; Kusche et al., 1993) and particularly conduct disorder (Goodman, 1995), and poorer intellectual outcome in paediatric epilepsy has been reliably associated with earlier age at onset (Hermann et al., 2002).

In the present study, and contrary to previous findings, I found that age at onset of epilepsy was the only epilepsy–specific factor to be predictive of the overall level of emotional and behavioural

difficulties, even after controlling for the level of (verbal) intellectual ability. This implies that even if intellectual functioning is not affected by epilepsy, earlier onset of epilepsy is more likely to lead to increased mental health difficulties. More specifically, earlier age at onset was a significant predictor for the presence of conduct and inattention/hyperactivity difficulties. This finding may be in line with the notion of sensitive periods in brain development, according to which early brain development lays down the foundation for higher-order cognitive skills, such as problem solving, inhibition control and planning (Cormack et al., 2007; Knudsen, 2004). It may therefore not be surprising that early disruption of developmental processes may lead to an increased risk for difficulties with hyperactivity/inattention and conduct. In general, conduct disorder and ADHD are well known in the literature for typically arising in early childhood (Ramtekkar et al., 2010; Zahn-Waxler et al., 2008). It is also possible of course that an earlier onset of epilepsy may increase the risk for conduct and inattention/hyperactivity difficulties due to a greater impact on psycho-social development and family life.

In the present study, higher seizure frequency was found to be specifically associated with increased peer difficulties. Seizure frequency has been previously associated with behavioural and social problems in children with epilepsy (Austin et al., 2002; Espie et al., 2003) and controlling the frequency of seizures has been shown to dramatically improve the quality of life in this population (Boylan et al., 2004). It is conceivable that children with less frequent seizures may have more opportunities for social activities, allowing them to develop and maintain more stable peer relationships and better prosocial attributes. Although seizure frequency was also found in univariate analyses to be associated with the overall level of emotional and behavioural difficulties, as well as attention/hyperactivity difficulties specifically, when other factors were also taken into consideration (including gender, age at onset of epilepsy and VIQ) in multivariate regression analyses, these associations were no longer found to be present.

In interpreting the results related to seizure frequency and in comparing these results to those of previous studies several methodological limitations need to be taken in consideration. To start with, children in the present series represent mostly the severe end of the spectrum, having frequent enough seizures to warrant surgery. Secondly, seizure frequency was based on parental estimates here, which are unlikely to capture the fluctuating course of the illness, and may possibly be an underestimate, as subtle seizures may often go unnoticed.

Finally, longer duration of the epileptic syndrome was specifically associated with more emotional and peer difficulties, irrespective of the age at onset. Previous studies in children, have also found longer duration of epilepsy, but not age at onset of seizures, to be associated with mood difficulties (Baki et al., 2004). It is likely that chronic and longer exposure to real and perceived social stigma, the fear of seizures, the repeated experience of loss of personal control, as well as the effect of epilepsy on many crucial aspects of life (e.g. schooling, transportation, peer relationships), which have all been shown to reduce the quality of life in epilepsy (Schneider & Conrad, 1983), may increase the risk for depression.

4.5 The role of localisation factors

Although the study of lesion localization in focal epilepsies follows the methodological and theoretical concepts of neuropsychology, due to a number of theoretical and methodological limitations outlined in the introduction, very few studies have actually attempted to evaluate the influence of localization or lateralisation of epilepsy on mental health. Here I attempted to study in a comprehensive way the impact of the localization and lateralisation of the epileptic pathology on mental health, given that this may be a key parameter for consideration of surgical treatment. Based on the nature of the epileptic seizures and the lack of clear localisation of function in the developing brain, I had expected the localisation and lateralisation of the epileptic focus to be

overall a weak predictor of emotional or behavioural difficulties. Despite this, I had made some specific hypotheses: that inattention/hyperactivity, conduct and peer problems were more likely to be linked to FLE (Braakman et al., 2011; Rogers et al., 2012) and emotional difficulties more to TLE (Sanchez-Gistau et al., 2010). The presented study significantly complements the literature in having compared directly patients with temporal, frontal and parieto-occipital focal epilepsy. While the mental health profile in children with temporal lobe epilepsy has frequently been described, the impact of frontal lobe epilepsy on mental health has been less frequently reported and knowledge of the mental health outcome in parietal-occipital cases is almost absent (Austin & Caplan, 2007).

Importantly, I showed here that the presence of FLE is a specific risk factor for the development of inattention and hyperactivity problems. I found that children with frontal pathology were at significantly higher risk for developing inattention/hyperactivity difficulties compared to children with temporal pathology. Although ADHD has been previously reported to be the most common difficulty in children with FLE (Braakman et al., 2011), I have shown here for the first time a specific association of ADHD type difficulties with FLE in comparison to other focal epilepsy types. This finding may not be surprising given that ADHD in childhood has been reliably associated with abnormalities in frontal brain regions that that mediate "top-down" regulation of attention, inhibitory control and motivation (Castellanos, 2001; Cubillo et al., 2012). Recently, ADHD in epilepsy has also been associated with structural changes in the frontal lobes, and specifically with increased gray matter volume (Valera et al., 2007).

In terms of the lateralisation of pathology I found here that children with right hemisphere pathology presented on average with more peer relationship problems compared to children with left hemisphere pathology. A similar trend was found for hyperactivity difficulties and total difficulties, but did not reach significance. These findings are consistent with the implication of

right frontal regions in social regulation, social cognition and theory of mind (Völlm, 2006), as well as in behavioural regulation and attention (Stefanatos & Wasserstein, 2001).

With the exception of the findings described above, and as expected, localization and lateralisation of pathology was overall a weak predictor of mental health outcome in paediatric focal epilepsy. Indeed, localisation of pathology by lobe was not a differentiating risk factor for the presence of emotional or conduct problems. This could suggest a need for examining the influence of localisation and lateralisation of pathology in larger samples (Swinkels et al.,2006). However, it is likely that mental health outcome in paediatric epilepsy may be largely independent of the specific localisation of the epileptic foci, being in fact influenced by disruption in wider range neural networks following the spread of seizures into remote but functionally relevant brain areas (Jokeit et al., 2004). Given the nature of the developing brain, involving constant maturational changes, lack of clear functional localisation and increased neuronal plasticity (D'Souza & Karmiloff-Smith, 2011), future studies focusing on the role of epilepsy localization may in fact be more tailored to the adult population.

4.6 The role of cognitive factors

Intellectual Ability

I found that a large percentage of children and adolescents in this sample presented with cognitive impairments, with 37% of children performing clearly within the learning disability range on measures of intellectual/developmental ability and only 42% showing no intellectual deficit by performing within the 'normal' range. On average, the FSIQ/DQ in children with epilepsy in our study was 25 points lower than that of healthy, age-matched peers. These findings thus add to

several studies in refractory paediatric epilepsy suggesting an increased prevalence of intellectual deficits in this population (Elger et al., 2004; Hermann & Seidenberg, 2007; Hermann et al., 2009; Jokeit, 2004; Lin et al., 2012; MacAllister & Schaffer, 2007).

Importantly, in accordance to my initial predictions, I also found that poorer intellectual functioning was associated with increased risk for developing emotional and behavioural problems. Overall, intellectual ability was highly correlated to SDQ ratings, with higher levels of emotional and behavioural difficulties being associated with worse performance in intellectual ability measures. This is also consistent with previous findings suggesting that poorer intellectual functioning is associated with a higher risk for developing emotional or behavioural difficulties both in children and adolescents with epilepsy (Caplan et al., 2004; Jones et al., 2010; Turky et al., 2008) as well as the general child and adolescent population (e.g. Dietz et al., 1997; Kusche et al., 1993).

Based on univariate analyses findings, and again consistently with my predictions, I found that the VIQ was the intellectual subdomain most highly correlated with conduct and peer difficulties. The VIQ has been previously linked to conduct difficulties, being consistently lower than the PIQ in children with conduct disorder, suggesting specific difficulties with language in this population (e.g. Bassarath, 2001). The VIQ has also been previously associated with peer problems (Buelow et al., 2003; Flouri et al., 2012).

Further in line with my predictions, the univariate analyses results demonstrated that working memory (WMI) was the intellectual subdomain most highly correlated with emotional and attention/hyperactivity ratings. Indeed, working memory is known to be compromised both in individuals with mood difficulties and individuals with ADHD type problems. Working memory, attention and executive function abilities are the most affected areas of cognition in individuals with depressive disorders (Elderkin-Thomson et al. 2010; Marazziti et al. 2010; Nakano et al.

2008; Rosenberg et al. 2010; Weiland-Fiedler et al. 2004). And of course, working memory and attentional difficulties are core features of ADHD (Barkley, 1998; Young & Brahman, 2007).

In the current study, the VIQ was the intellectual ability subdomain most highly correlated with the overall level of emotional and behavioural difficulties. I considered the predictive value of the VIQ in regression analyses alongside several other epilepsy-related and demographic factors. These analyses revealed that the VIQ was a robust predictor for the presence of all types of emotional and behavioural difficulties considered here (mood, conduct, inattention/hyperactivity and peer relationship difficulties) for children with refractory epilepsy. Previous studies have also emphasised the special role of the VIQ in moderating psychopathology (Caplan et al., 2004).

Memory

Children assessed for memory in this cohort were also found to demonstrate compromised memory functioning. On average, children performed below the normative population mean, with the average general memory performance score falling 16 points below the age-matched population mean. Due to a) the high collinearity of performance in memory measures and intellectual ability measures and b) the limited availability of memory data in this cohort, it was not possible to examine the predictive value of memory functioning as a risk factor for the development of psychopathology in regression analyses. I thus examined the association of memory functioning to emotional and behavioural difficulties in a series of univariate analyses, after partialling out any effects of FSIQ.

I found that poorer performance in general and visual memory measures was specifically associated with increased emotional and inattention/hyperactivity difficulties. In addition to difficulties with working memory, as described above, and possibly as a result of that, depression

is also known to impact on the ability to form long term memories (Antikainen et al., 2001; Hammar & Schmid, 2013). Memory problems are also a frequently reported symptom in ADHD, and it is well-documented that children and adults with ADHD perform poorly on tests of long-term memory (see Skodzik et al., 2014 for a recent meta-analysis; Rhodes et al., 2012). A general consensus exists that such long term memory difficulties in both attention/hyperactivity as well as mood disorders may be secondary to attentional dysfunctions, reflecting difficulties in concentration (Marazziti, 2010).

Children in this study performed on average significantly worse on measures of verbal memory than measures of visual memory. A recent study by Liik and colleagues (2013) also found patients with focal-onset epilepsy to show disturbances predominantly in the verbal as opposed to the visual memory domain. Liik and colleagues also found that patients with focal epilepsy scored significantly worse on memory measures than patients with generalized epilepsy. The discrepancy between verbal and visual memory performance here however, is also likely to reflect a sampling bias in this study, as more children with left hemisphere pathology (n=93) than right hemisphere pathology (n= 74) were assessed. Previous studies have shown children with left hemisphere pathology to be more affected on measures of verbal memory and children with right hemisphere pathology more affected on measured of visual/spatial memory (Alessio et al., 2004; Cohen, 1992).

Academic Attainments

In line with the average intellectual and memory ability findings described above, academic performance as measured by literacy and numeracy measures was also found to be compromised in this cohort, falling on average 16 points below the normative population mean. Again, unfortunately, due to high collinearity with intellectual ability measures I was not able to

test the potential of academic achievement as a predictive factor for mental health in regression analyses. I therefore examined the relationship between academic achievement and emotional or behavioural difficulties through a series of univariate analyses, after partialling out any effects of FSIQ.

Based on previous findings I had hypothesised an association between academic achievement and inattention/hyperactivity as well as conduct problems (Adams et al., 1999; Bassarath, 2001; Nigg, 2005). Despite my predictions however, academic achievement was not found to be related to either inattention/hyperactivity or conduct difficulties, after taking into account the FSIQ. In combination with the robust correlations found between FSIQ and inattention/hyperactivity and also conduct difficulties, this finding may suggest that the FSIQ alone may principally account for variations in inattention/hyperactivity and conduct outcome. I did find here however that lower performance in literacy measures was associated with an overall increased level of emotional and behavioural difficulties (SDQ Total difficulties score).

4.7 Study limitations

It is important to acknowledge that the results of the present study are subject to a number of methodological limitations, restricting the extent to which the presented conclusions can be generalised to the wider paediatric epilepsy population. Firstly, my study is limited by the fact that the cohort studied here may not be representative of the general population of children and adolescents with epilepsy. Paediatric patients included in this study were candidates for epilepsy surgery attending a tertiary epilepsy centre and underwent neuropsychological assessment as part of their routine pre-surgical evaluation. Patients considered for surgical treatment typically

present with severe refractory epilepsy and have seizures frequent and severe enough to warrant surgery. In addition, patients may often be referred to epilepsy surgery programmes due to heightened concerns about behavioural difficulties, developmental delay or specific cognitive problems. On the contrary, children and adolescents with epilepsy and typical neurodevelopmental trajectories are often not referred for epilepsy surgery evaluation. Furthermore, children with severe refractory epilepsy considered for surgery have typically undergone extensive antiepileptic medication treatments, with known side effects on both mental health and cognitive functioning (Oguz et al., 2002; Schmitz, 2002). In conclusion, emotional, behavioural and cognitive problems are likely to be overrepresented in surgical candidates. This indicates that children and adolescents included in the present study represent most likely the more severe end of the spectrum. As a result, it is possible that while the presented findings are relevant to children and adolescents with refractory focal epilepsy, they may not generalise to the larger population of children and adolescents with uncomplicated epilepsy.

Another potential sampling confound in the present study relates to the recruitment of the data from a tertiary service. Previous studies have shown systemic inequalities in access to secondary and tertiary health care between social groups. For example, there is evidence that individuals belonging to ethnic minorities or with lower socio-economic position are less likely to access secondary and tertiary medical care compared to individuals from a white ethnic background or more affluent social groups (Adamson et al., 2003; Ibrahim et al., 2012). Such findings suggest that paediatric populations recruited from tertiary centres are likely to come from more privileged families and social groups and as a result have a higher baseline of academic achievement (Sacker,et al., 2002), perform better in tests of general intelligence (Gottfredson, 2004) and grow up in an environment associated with overall lower risk for developing mental health difficulties (e.g. Hafton, 2014; McKenzie et al., 2014). The evidence taken together suggests then that the

results of this study could also be an underestimate of the impact of intractable focal epilepsy on mental health, cognitive and academic functioning.

In addition, this study is limited by the fact that it was based on retrospective data collection. One of the implications of this is that there was substantial missing data for several of the clinical or psychometric variables investigated here. It is possible that this introduced biases in the sample, for example with memory measures being obtained for more 'highly' functioning children or for children with specific memory complaints (memory data were available for 60% of the sample). Missing data also limited the power in the statistical analyses, leaving a smaller sample size for testing and limiting the variables that I could include in regression analyses. For example, while almost complete data for the VIQ and PIQ were available (with data available for 89% of the sample), WMI and PSI data were available only for 58% and 59% of the patients respectively, which prevented me from including the latter indices in multivariate regression analyses. Notably, based on the univariate analyses results it would have been preferable to include the WMI over the VIQ as a possible predictor for inattention/hyperactivity and emotional difficulties.

Using data obtained from the medical records via retrospective review involves a number of other methodological difficulties. Records often lack specific patient information, there may be difficulty in interpreting or verifying documented information, and there is often variability in the quality of information documented by different health care professionals (Gearing et al., 2006). Finally, while the retrospective procedure employed here allows for possible associations, it does not allow us to draw conclusions on possible direct effects of epilepsy on emotional and behavioural functioning. Further prospective and controlled evaluations would be necessary to evaluate any causal effects between paediatric epilepsy and mental health. Although future prospective studies

may be able to provide more accurate results, a large number of patients would be necessary to sufficiently address the issues raised here.

There are also probable limitations in the present study with regards to the accuracy of my psychometric estimates. To start with the estimates of mental health difficulties were based on parental report and not on formal professional assessment. Previous studies however have reassuringly demonstrated that parental estimates based on the SDQ are reliable estimates of paediatric psychopathology (e.g. Goodman, 2001; Goodman & Goodman, 2011). In addition, there was no opportunity for longitudinal observations, with the measurements being collected during a single time-point of assessment and that occurring during hospital admission, presumably a stressful time for many children and their families. Identification of exact seizure localisation may also present a limitation to the study. Although localisation groups were determined on the basis of combined underlying brain pathology and primary seizure foci, due to the nature and heterogeneity of epilepsy, epileptogenic focal zones may not always be clearly identifiable. The use of multiple measures to identify these however, such as MRI and EEG, provides reasonable assurance of localization in this sample.

Furthermore, it is important to acknowledge here the fact that the results of the presented study will need to be validated in future investigations to safeguard against possible errors potentially committed here as a result of multiple testing. In the presented study, I lowered the acceptable significance level to 0.01 for findings with no prior hypotheses to account for the increased likelihood of type I errors as a result of multiple testing, given the number of variables investigated here. As most of the findings of the current study however are in accordance with the pre-existing theoretical framework, this provides substantial assurance as to their validity.

As a final note, a recognized limitation of studies similar to this is the lack of an appropriate control group. On the basis of these data, I cannot definitively determine whether the mental health difficulties presented are based on the epilepsy itself, the underlying pathology or the effects of living with a long-term health condition. To discern whether the epilepsy itself and not the underlying pathology is the major cause of mental health deterioration, a prospective control group with children with similar underlying pathologies but without epilepsy would be needed.

4.8 Implications for clinical practice and future research

Children and adolescents with epilepsy are at increased risk for developing mental health difficulties (Salpekar et al., 2013). Strikingly, almost half children and adolescents in the sample had significant emotional or behavioral issues, as reported by their parents. I found here that children with intractable focal epilepsy were at particular risk for developing difficulties with mood, attention/hyperactivity and relationships with peers. Despite the large prevalence of mental health problems in epilepsy however, and although the most significant predictor of quality of life in epilepsy is emotional health (Hixson 2009), this continues to be a relatively underdeveloped area in epilepsy care. Typically more emphasis is being placed on controlling seizures and medication side effects while neuropsychological and psychological assessment remain sources of limited availability (Caplan et al., 2004).

The findings presented here have thus several important clinical implications. Importantly, these results highlight the need for routine psychological assessment in children and adolescents with focal epilepsy undergoing pre-surgical evaluation. Developing a firm understanding of the risk factors that contribute to mental health difficulties in focal paediatric epilepsy may help identify and provide earlier psychological or psychiatric assessment and intervention to children who are

at higher risk of facing such difficulties. Knowledge of potential risk factors can be crucial in helping clinicians to make timely decisions with regards to drug treatments and psychological support. Early effective treatment with psychological interventions or medication can significantly change mental health outcome in epilepsy (Ekinci et al., 2009). For example, cognitive–behavioural therapy for mood disorders has been found to improve mood difficulties for both children (Martinovic, 2001) and adults (Crail-Melendez et al., 2012) with epilepsy.

More specifically, these findings highlight the importance of evaluating the negative impact of several risk factors, including gender, earlier onset and longer duration of epilepsy, higher seizure frequency, the localisation of the epileptic focus and cognitive functioning on the development of emotional or behavioural difficulties in pediatric focal epilepsy. The presented study identified that several of these factors were predictive of the presence of emotional, conduct, attention/hyperactivity and peer difficulties. Specifically, it was found here that having a lower VIQ increased the risk for all these types of difficulties. Moreover, a risk factor for developing emotional difficulties was longer duration of epilepsy; Risk factors for developing conduct difficulties included male gender and earlier age at onset of epilepsy; Risk factors for developing attention/hyperactivity difficulties included male gender, earlier age at onset of epilepsy, longer duration of epilepsy and localization of seizure pathology in the frontal lobes; and finally, risk factors for developing peer relationship difficulties included longer duration of epilepsy, higher frequency of seizures and lateralization of seizure pathology in the right hemisphere.

The robust association between cognitive impairment with all types of emotional and behavioural difficulties assessed here further emphasises the importance of prioritising psychological assessment in children with cognitive impairments or learning difficulties. From a clinical perspective, this study indicates that cognitive impairment and particularly Verbal IQ deficits may

increase the vulnerability of children with focal epilepsy for emotional and behavioural difficulties. From a methodological perspective, it also flags up the need to control for the effects of intellectual functioning, and particularly of Verbal IQ, in studies comparing mental health difficulties in children with epilepsy and controls or studies investigating the association between emotional/behavioural outcome and memory functions or academic achievement.

Identifying children at higher risk for increased mental health needs, as well as intellectual impairments, is also crucial for arranging appropriate educational support and interventions. Early psychological and neuropsychological assessment may provide essential information for tailoring educational programs and providing appropriate treatment to children with increased mental health needs, thus reducing the risks for poor educational outcomes. Reducing the long-term consequences of mental health difficulties on educational outcomes in turn has the potential of enhancing future quality of life, including social functioning and employment opportunities. It has been shown for example that children with untreated ADHD are at greater risk for poor academic, social and vocational outcomes (Pritchard et al., 2012).

Although our study adds to a growing number of studies addressing the impact of focal paediatric epilepsy on mental health, a number of questions remain unanswered. For example, more work is needed in establishing the distinct contribution of the seizures themselves and the underlying brain pathology on mental health difficulties in epilepsy.

Unfortunately it was not within the remit of the presented study to evaluate the effect of paediatric epilepsy surgery on mental health. It is possible that surgical treatment for focal epilepsy has a significant impact on the emotional and behavioural difficulties described here. The few existing studies to date assessing the emotional or behavioral outcome following surgery, indicate overall a favorable outcome, including improvements in attention and hyperactivity, internalizing and

externalizing symptoms, social difficulties and cognitive functioning (Andresen et al., 2014; Lendt et al., 2000; McLellan et al., 2005; Titus et al., 2013; Williams et al., 1998). There are also reports of some improvement in intellectual functioning post surgery, suggesting that the seizures themselves may be detrimental to cognition and that the earlier the surgery is performed the greater the potential is for better developmental and cognitive outcomes (e.g. Loddenkemper et al., 2007; Skirrow et al., 2011). However, more research is needed to understand the aetiology behind these improvements. For example, while the lack of or reduction of seizures following surgery undoubtedly has a significant impact, interestingly there is also evidence to suggest that the strongest predictor of IQ increase following surgery is the cessation of antiepileptic medication (Skirrow et al., 2011).

Importantly, more research is also needed in identifying risks to mental health related to epilepsy treatments themselves. Unfortunately, many epilepsy treatment options can also contribute aversely to mental health, whether due to medication side effects or as a result of lesions following surgical resections. This can make treatment decisions difficult for both clinicians and patients as the treatment may sometimes carry several undesirable effects. Finally, further research will also be necessary to investigate the contribution of psychosocial factors such as the stress of living with a chronic disease or long-term stigmatization, which were not investigated here. For example few studies have considered seizures as a potential “trauma”, yet this may in fact play an important role in generating emotional difficulties (Hixson, 2009).

In conclusion, the presented findings echo the current literature in highlighting the pressing need for prioritizing assessment and treatment of mental health difficulties in paediatric focal refractory epilepsy. Although this has been previously unequivocally demonstrated, there is still significant unmet clinical need as well as considerable demand for further research. The multifaceted

aetiology of emotional and behavioural difficulties in epilepsy means that future studies will need to employ large samples to be able to address further demographic, epilepsy-related, cognitive and psychosocial variables and their interrelationships in predicting psychopathology. Importantly, prospective studies will also be needed to identify risk factors for the development of emotional or behavioural difficulties.

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Appendix A

Strengths and Difficulties Questionnaire forms and scoring

Strengths and Difficulties

QUESTIONNAIRE

TO BE COMPLETED BY A MAIN CARER OF A CHILD AGED BETWEEN 3 AND 4

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain, or the items seem daft! Please give your answers on the basis of the child's behaviour over the last six months.

Child's Name _____ **Male/Female** **Date of Birth** _____

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐

Often fights with other children or bullies them	☐	☐	☐
Often unhappy, downhearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often argumentative with adults	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Can stop and think things over before acting	☐	☐	☐
Can be spiteful to others	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Please turn over – there are a few more questions on the other side…

Strengths and Difficulties
QUESTIONNAIRE
TO BE COMPLETED BY A MAIN CARER OF A CHILD AGED BETWEEN 4 AND 16

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain, or the items seem daft! Please give your answers on the basis of the child's behaviour over the last six months.

Child's Name _____ **Male/Female** **Date of Birth** _____

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot sit still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, downhearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Please turn over – there are a few more questions on the other side …

Scoring the Informant-Rated Strengths and Difficulties Questionnaire

The 25 items in the SDQ comprise 5 scales of 5 items each. It is usually easiest to score all 5 scales first before working out the total difficulties score. Somewhat True is always scored as 1, but the scoring of Not True and Certainly True varies with the item, as shown below scale by scale. For each of the 5 scales the score can range from 0 to 10 if all 5 items were completed. Scale score can be prorated if at least 3 items were completed.

Emotional Symptoms Scale	Not True	Somewhat True	Certainly True
Often complains of headaches, stomach-aches ...	0	1	2
Many worries, often seems worried	0	1	2
Often unhappy, downhearted or tearful	0	1	2
Nervous or clingy in new situations ...	0	1	2
Many fears, easily scared	0	1	2

Conduct Problems Scale	Not True	Somewhat True	Certainly True
Often has temper tantrums or hot tempers	0	1	2
Generally obedient, usually does what ...	2	1	0
Often fights with other children or bullies them	0	1	2
Often lies or cheats	0	1	2
Steals from home, school or elsewhere	0	1	2

Hyperactivity Scale	Not True	Somewhat True	Certainly True
Restless, overactive, cannot stay still for long	0	1	2
Constantly fidgeting or squirming	0	1	2
Easily distracted, concentration wanders	0	1	2
Thinks things out before acting	2	1	0
Sees tasks through to the end, good attention span	2	1	0

Peer Problems Scale	Not True	Somewhat True	Certainly True
Rather solitary, tends to play alone	0	1	2
Has at least one good friend	2	1	0
Generally liked by other children	2	1	0
Picked on or bullied by other children	0	1	2
Gets on better with adults than with other children	0	1	2

Prosocial Scale	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	0	1	2
Shares readily with other children	0	1	2
Helpful if someone is hurt, upset of feeling ill	0	1	2
Kind to younger children	0	1	2
Often volunteers to help others	0	1	2

The Total Difficulties Score:

is generated by summing the scores from all the scales except the prosocial scale. The resultant score can range from 0 to 40 (and is counted as missing if one of the component scores is missing).

Interpreting Symptom Scores and Defining "Caseness" from Symptom Scores

Although SDQ scores can often be used as continuous variables, it is sometimes convenient to classify scores as normal, borderline and abnormal. Using the bandings shown below, an abnormal score on one or both of the total difficulties scores can be used to identify likely "cases" with mental health disorders. This is clearly only a rough-and ready method for detecting disorders – combining information from SDQ symptom and impact scores from multiple informants is better, but still far from perfect. Approximately 10% of a community sample scores in the abnormal band on any given score, with a further 10% scoring in the borderline band. The exact proportions vary according to country, age and gender – normative SDQ data are available from the web site. You may want to adjust banding and caseness criteria for these characteristics, setting the threshold higher when avoiding false positives is of paramount importance, and setting the threshold lower when avoiding false negatives is more important.

	Normal	Borderline	Abnormal
Parent Completed			
Total Difficulties Score	0 - 13	14 - 16	17 - 40
Emotional Symptoms Score	0 - 3	4	5 - 10
Conduct Problems Score	0 - 2	3	4 - 10
Hyperactivity Score	0 - 5	6	7 - 10
Peer Problems Score	0 - 2	3	4 - 10
Prosocial Behaviour Score	6 - 10	5	0 - 4
Teacher Completed			
Total Difficulties Score	0 - 11	12 - 15	16 - 40
Emotional Symptoms Score	0 - 4	5	6 - 10
Conduct Problems Score	0 - 2	3	4 - 10
Hyperactivity Score	0 - 5	6	7 - 10
Peer Problems Score	0 - 3	4	5 - 10
Prosocial Behaviour Score	6 - 10	5	0 - 4

Appendix B

Ethical Approval

UCL INSTITUTE OF CHILD HEALTH

Great Ormond Street Hospital for Children
NHS Foundation Trust

Joint Research and Development Office
Division of Research and Innovation

Direct Line: 020 7905 2637
Email: Sibylla.warrington-brown@gosh.nhs.uk

02/05/2013

Prof Faraneh Vargha-Khadem
Head of Clinical Neuropsychology Department
Great Ormond Street Hospital for Children NHS Foundation Trust

Dear Prof Vargha-Khadem

PROJECT TITLE	Factors predictive of emotional and behavioural difficulties in children with focal epilepsy
Protocol version	N/A
Protocol date	N/A
REC Reference	N/A
R&D Reference	13CN05
Sponsor	Great Ormond Street Hospital for Children NHS Foundation Trust
Chief Investigator (CI)	Prof Faraneh Vargha-Khadem

Notification of Great Ormond Street Hospital NHS Permission – Retrospective Case Note Review

The research approval process for the above named study has been completed successfully. I am pleased to issue approval on behalf of Great Ormond Street Hospital for Children NHS Foundation Trust (GOSH) for the above study to proceed.

All research carried out within this Trust must be in accordance with the principles set out in the Research Governance Framework for Health and Social Care (April 2005, 2nd edition, Department of Health).

This approval is issued on the basis of the project documentation submitted to date. This study is a Case Note Review, with access to previously collected, non-identifiable information/data and as a result is exempt from REC approval under GAfREC 2011.

The conditions for host site approval are as follows:

- The Principle Investigator (PI) must ensure compliance with protocol and advise the Joint R&D Office of any change(s) to the protocol. Failure of notification may affect host approval status.
- The PI is responsible for the set up and maintenance of the Investigator Site File (ISF) generated to store all documentation relating to this project.
- The PI must ensure that all named staff are compliant with the Data Protection Act (DPA) 1998 and all other applicable statutory guidance and legislation.

- The PI must allow monitoring and auditing by the Sponsor and the Joint R&D Office.
- The PI must report any cases of suspected research misconduct and fraud to the Joint R&D Office.
- The PI must provide an annual report to the Joint R&D Office for all research involving NHS patients, staff and/or resources. The PI must notify the Joint R&D Office of any presentations of such research at scientific or professional meetings, or on the event of papers being published and any direct or indirect impacts on patient care.

Failure to comply with the above conditions and regulations will result in the suspension of the research project.

Please contact the Joint R&D Office if you require any further guidance or information on any matter mentioned above. We wish you every success in your research.

Yours sincerely,

S Warrington

Siby Warrington
Research Management and Governance Officer
Joint Research and Development Office

Subject: RE: GOSH research project query
From: Sibylla Warrington-Brown <Sibylla.Warrington-Brown@gosh.nhs.uk>
Date: 21/01/2013 17:10
To:"'sejjms0@live.ucl.ac.uk'" <sejjms0@live.ucl.ac.uk>

Dear Margarita,

I'm very sorry for the delay in getting back to you.

Yes, as this is a retrospective case note review using anonymised data, you are correct that only R&D approval is required, not ethics.

For case note reviews, we now request that an R&D form is completed in IRAS:

https://www.myresearchproject.org.uk/

Please give the contact person as 'Emma Pendleton', Deputy Director of R&D, with the address of the R&D Office.

If questions in the form are not applicable to a case note review (e.g. A76 regarding Insurance, please just detail N/A).

When you have completed a draft of the form, grateful if you would email me a copy. I will then register the study and let you know who will need to authorise the form as the Sponsor's contact (apologies, my manager is leaving next week so this will depend on when the form is received). The CI will also need to sign the form. When we have the final signed form and it has been reviewed, we will be able issue approval.

I would also be grateful if you would email me a copy of the CI's CV. If this is Prof Vargha-Khadem, we already hold this, so no need to resend. If you are the CI, grateful if you would forward a copy of your CV.

I hope this is clear. Please let me know if you have any queries.

Many thanks.

Kind regards,

Siby

Siby Warrington
Research Management and Governance Officer
Joint Research and Development Office
Division of Research and Innovation
Great Ormond Street Hospital for Children NHS Foundation Trust
UCL Institute of Child Health, 30 Guilford Street, Bloomsbury, London, WC1N 1EH
Internal T: x2637 - External T: 02079052637
Internal F: x2201 - External F: 02079052201
Email: Sibylla.Warrington-Brown@gosh.nhs.uk

From: Psychology-Webmaster@rhul.ac.uk [mailto:Psychology-Webmaster@rhul.ac.uk]
Sent: 17 May 2013 17:53
To: Sarri, Margarita (2011); Langdon, D
Cc: PSY - Ethics Admin; Leman, Patrick
Subject: Ref: 2013/042 Ethics Form Approved

Application Details:

Applicant Name: Margarita Sarri

Application title: Emotional and behavioural difficulties in children with focal epilepsy

Glossary

Focal malformation: Disorganized arrangement of tissue types in a focal brain area.

Hemi-malformation: Disorganized arrangement of tissue types in a large area of a brain hemisphere.

Hippocampus: A brain area belonging to the limbic system, playing important role in the consolidation of information from short-term to long-term memory and spatial navigation.

Hippocampal **sclerosis:** A neuropathological condition resulting to severe neuronal cell loss and gliosis in the hippocampus. Frequently associated with epilepsy.

Hypoxia: A pathological condition in which the brain or a region of the brain is deprived of adequate oxygen supply, leading to neuronal death.

Ictal**:** The period and physiologic state during a seizure.

Interctal**:** The period between seizures

Ischaemia: A restriction in blood supply to tissues, causing a shortage of oxygen and glucose, which are needed to keep tissue alive.

Mesial Temporal Sclerosis: See Hippocampal sclerosis.

Paediatric: The branch of medicine that deals with the medical care of infants, children, and adolescents.

Rasmussen's encephalitis: A rare inflammatory neurological disease, characterized by inflammation of the brain, frequent and severe seizures, loss of motor skills and speech, hemiparesis and dementia.

Sturge Webber syndrome: A rare congenital neurological and skin disorder, often associated with port-wine stains of the face, glaucoma, seizures and mental retardation. Normally, affects only one side of the brain.