Rasmussen Syndrome: Cognitive trajectories and brain changes

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Finally, and most of all I would like to thank the courageous young people I met with Rasmussen syndrome (RS) and their families. This disease is devastating to see in someone so young. I was struck by how in the face of their diagnosis they strive to lead their lives to the full. I hope this study may in some small way help the fight against RS and will ultimately improve their outcome and the quality of life.

Abstract

This study investigated the cognitive trajectory and brain changes of those with Rasmussen syndrome (RS), a rare childhood disease characterised by atrophy of one hemisphere of the brain. Neuropsychology performance was estimated from historical neuropsychology assessments and 10 new neuropsychological assessments carried out as part as clinical practice by the first author. This resulted in 39 RS participants (right hemisphere affected=21, left hemisphere affected=18). Analyses were conducted to elucidate the changing cognitive trajectory at two time points: (1) pre-surgery and (2) pre- to post-op. Differences between left and right hemisphere groups were also investigated. Our study also explored cortical changes pre-surgery in a subset of RS participants using Voxel Based Morphometry. The possible neurobiological substrates of cognitive change were explored through correlational analyses.

Our results revealed that pre-surgery there were significant declines in both left and right RS groups in a number of cognitive domains. In addition, between groups analyses showed the right RS group exhibited more difficulties with tasks of perceptual reasoning, whereas the left RS group had weaker abilities on tasks requiring verbal faculties. From pre- to post-op the left RS group declined in all IQ abilities, whereas the right group's abilities remained better preserved. The left RS group was also significantly weaker on tasks that required language than the right RS. VBM analyses showed that in a subset of our RS participants brain regions within the unaffected hemisphere of the brain significantly atrophied from 3 to 6 years post-onset of seizures. The decline in grey and white matter of the bilateral parietal and occipital lobes was significantly associated with decline in non-verbal IQ. These findings may have important implications for the medical and psychological care of those with RS, in particular, in regard to optimisation of clinical outcome.

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Chapter 1 - Introduction

The present study investigated the cognitive trajectory of children with Rasmussen syndrome (RS), a rare childhood disease presumed to be an autoimmune inflammatory process characterised by atrophy of one hemisphere of the brain. Those with RS experience progressive decline of neurological functions including cognitive deterioration and epilepsy. This investigation was the first to elucidate the trajectory of RS cognitive abilities at multiple time points before and after surgery. The impact of the hemisphere affected (left versus right) and neurosurgery on the RS individual's cognition were explored. Importantly, the impact of medical risk factors such as frequency of seizures and number of anti-epileptic drugs on an RS individuals' psychometric performance were also interrogated. The neural underpinning of the cognitive change was then explored by investigating the changes in cortical grey and white matter in a subset of RS individuals pre-surgery using Voxel Based Morphometry. Possible associations between the grey and white matter atrophy and cognitive change over time prior to neurosurgery were then explored in a subset of RS individuals.

To start, RS will be fully described and treatment options will be reviewed. Next, studies that have looked at the impact of medical factors on cognitive performance such as: aetiology, epilepsy duration and seizure frequency, age at onset and use of anti-epileptic drugs on those with epilepsy and RS *before* surgery will be considered. The review will next look at cognitive outcome *after* functional hemispherectomy (FH) surgery (i.e., when one hemisphere of the brain is disconnected from the other) in groups of individuals who are suffering from catastrophic and intractable epilepsies including those with RS. The studies that have looked solely at substantial groups of RS individuals' psychometric performance pre-FH and pre- to post-FH will then be considered. The effect of the timing of surgery on cognitive outcomes after FH, alongside a number of the key issues around deciding when surgery should take

place, will also be reviewed taking into account smaller N outcome studies of RS after FH.

In the final section a general introduction of Magnetic Resonance Imaging (MRI) will be presented. Non-automated MRI studies (radiologists reading or region of interest studies) that have investigated the brain changes that occur in RS over time will be discussed. Next, Voxel Based Morphometry (VBM), a fully automated whole brain neuroimaging technique that was utilized in this study, will be introduced. Results of VBM studies in temporal lobe epilepsy will be considered before two novel investigations that have used VBM to interrogate the neural correlates of neuropsychological change in children who have undergone epilepsy surgery are discussed.

1.1. **Rasmussen syndrome (RS)**

RS was first characterised by Rasmussen and colleagues (1958) who described three paediatric patients who were experiencing focal seizures caused by localised encephalitis which was lateralised to one hemisphere of the brain. This childhood disease is very rare and a recent UK surveillance study reported an incidence of 1.7 per 10 million people under the age of 16 years (Lamb, Scott, & Mensah, 2013). Over the last 57 years the clinical course of the disease has been characterised (Figure 1-1). Onset occurs any time from infancy to adulthood but typically around 6 years (Granata et al., 2003; Oguni, Andermann, & Rasmussen, 1992). Some patients experience a prodromal period, which precedes the acute stage by a number of years, and is characterized by infrequent seizures and mild hemiparesis (i.e., weakness and paralysis of one side of the body). Next, in the acute stage RS individuals experience frequent seizures arising from one hemisphere and around half will experience epilepsia partialis continua (EPC; i.e., recurrent focal motor epileptic seizures that implicate the hands and face, and recur every few seconds or minutes for extended periods; Obeso, Rothwell, & Marsden, 1985). Within a year of the onset of epilepsy those with RS typically experience a progressive neurological deficit

associated with the affected hemisphere, including cognitive deterioration, hemiparesis and hemianopia (i.e., decreased vision of one half of the visual field in both eyes). If the language-dominant hemisphere is affected (typically the left) then aphasia (i.e., the partial or complete impairment of the ability to communicate) is also experienced (Varadkar et al., 2014). Around 10% of RS cases do not follow this course and will present in adolescence and adulthood (Oguni et al., 1992). This later onset is characterised by a slower disease course that does not result in such severe neurological deficits as childhood onset RS (Bien et al., 2005).

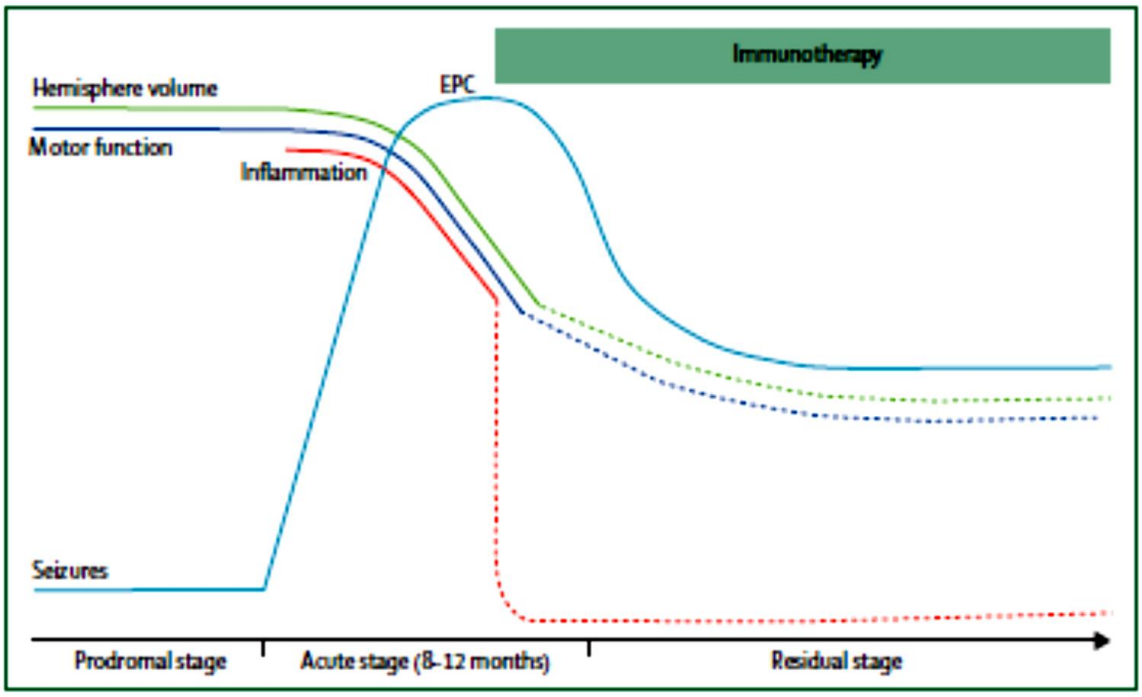

Figure 1-1: Natural clinical course and expected effect of immunotherapy in RS (Varadkar et al., 2014).

Despite research efforts the aetiology of RS has remained elusive. Rasmussen and colleagues (1958) suggested the aetiology of RS may be a slow-virus infection, however, so far there has been a lack of evidence for this hypothesis (for review see C G Bien et al., 2005). Other avenues of research have suggested the cause of RS is an antibody-mediated immune

response which is erroneously directed towards brain cells (Bien & Schramm, 2009). Indeed, recent research indicates that cytotoxic T cells (i.e., a type of white blood cell that destroys cells that are damaged) may cause the death of astrocytes and neurons in RS. This is currently the primary focus of research in an effort to help determine a cause and ultimately a potential treatment and cure for RS (Vining, 2006).

The diagnostic criteria for RS were proposed by a European consensus panel in 2005 (Bien et al., 2005; Figure 1-2). RS is diagnosed if all three criteria of Part A are present, or two out of three criteria from Part B are present (Bein et al., 2005). The diagnosis should be made by a paediatric neurologist based on clinical examination, electroencephalography (EEG) and MRI findings, seizure semiology, neuropsychological assessment results and clinical history.

Part A:

1 Clinical focal seizures and unilateral cortical deficit(s)

2 EEG- Unihemispheric slowing with or without epileptiform activity and unilateral seizure onset

3 MRI- Unihemisphereic focal cortical atrophy and at least one of the following: (1) Grey or white matter T2/FLAIR hyperintense signal; (2) Hyperintense signal or atrophy of the ipsilateral caudate head

Part B

1 Clinical epilepsia partialis continua or progressive unilateral cortical deficits

2 MRI- Progressive unihemispheric focal cortical atrophy

3 Histopathology- T cells dominated encephalitis with activated microglial cells and reactive astrogliosis.

Figure 1-2: Diagnostic criteria for Rasmussen syndrome (RS) as set out by Bien and colleagues (2005).

1.1.1. Treatment options for RS

Treatment options for RS include anti-epileptic medications (AEDs), anti-inflammatory therapy, immunomodulation and epilepsy neurosurgery (Bien & Schramm, 2009). AEDs are the first line of medical treatment for those with RS. Problematically, RS individuals also commonly experience seizures that are intractable, that is, seizures not brought under control by at least two AEDs which have been given over a 2-year period (Cross, 2002). This can result in RS individuals being trialled on increasing numbers of different AEDs which can be associated with potentially difficult side effects (as discussed in more detail below). More

recently, immunosuppressive therapy has been given to those with RS on the presumption that there is an underlying autoimmune process driving the disease (Bien et al., 2005, 2013). A randomised prospective treatment trial suggested that immunomodulators were effective in delaying deterioration and intractable seizures in comparison to historical controls (i.e., those with RS who had not been given immunomodulators; Bien et al., 2013). On the other hand, there is a potential difficulty in delaying the clinical course of RS. Indeed it has been suggested that immunomodulators may potentially delay neurosurgery at a time when the brain may have increased neuroplasticity (i.e., an ability to reorganise and form new neural connections) which is vital for successful rehabilitation after neurosurgery (Bien et al., 2013).

Functional hemispherectomy (FH) of the affected side of the brain is considered to currently be the only effective cure and surgical approach for RS (Bien & Schramm, 2009). FH is only considered in those who have seizures arising from one hemisphere of the brain when there is also a recognised pre-existing structural abnormality of that hemisphere (Devlin et al., 2003). The aim of surgery is seizure freedom, which it provides in approximately 50% of cases (Devlin et al., 2003; Vining et al., 1997). However, there are complex and disabling neurological side effects of surgery including: hemiplegia and difficulties with gait and fine motor movement, and hemianopia (Hartman & Cross, 2014). In addition, those with RS affecting their language-dominant hemisphere will often have language difficulties post-surgery (Boatman et al., 1999). Additional cognitive deficits and behavioural issues may also be seen after FH, however, there is currently a lack of research into the post-op cognitive outcome after FH (Boatman et al., 1999; Pulsifer et al., 2004). Intensive rehabilitation is often required post-surgery including: physiotherapy for gait and balance, occupational therapy for hand function and daily living skills, speech and language therapy if the left hemisphere was disconnected, and neuropsychology for cognitive function. Issues around the timing and outcomes of surgery will be discussed below.

1.2. **Cognitive trajectory pre-surgically and the impact of medical variables**

One of the main clinical features of RS is intractable epilepsy. Epilepsy is caused by abnormal and extreme axonal activity in the brain (Fisher et al., 2005). A wide body of literature has investigated the conditions under which those with epilepsy, including RS, experience cognitive impairment (Seidenberg, Pulsipher, & Hermann, 2007). The four risk factors that have been highlighted by this literature that may lead to cognitive decline are: (1) the underlying aetiological substrate, (2) seizure activity and severity, (3) anti-epileptic drug(s) prescribed and (4) age at onset (Hermann, Meador, Gaillard, & Cramer, 2010). The evidence for these variables will be discussed in turn and then the implications for the cognitive abilities of those with RS prior to surgery will be considered.

1.2.1. Aetiology

The aetiology of epilepsy often cannot be determined (i.e., idiopathic epilepsy); however, when it can, brain damage or abnormality is observed (i.e., symptomatic epilepsy; http://www.nhs.uk/CONDITIONS/EPILEPSY/Pages/Causes.aspx). Symptomatic epilepsies range from those with catastrophic localization-related epilepsies affecting a whole hemisphere like RS, to those who have small lesions in specific regions of the brain. Cross-sectional studies of children reveal that the localization and extent of brain lesions can directly inform the specific cognitive deficits experienced by the individual. For instance, circumscribed lesions to the hippocampus in either hemisphere leads to specific deficits in delayed verbal recall (Cormack, Vargha-Khadem, Wood, Cross, & Baldeweg, 2012). Hence, the cognitive deficit experienced by someone with a specific brain lesion is somewhat predictable considering knowledge of lesion location and functional localization in the brain.

The developing brain, however, can add a layer of complexity to the ability to predict

functional deficits based on brain insult or injury. A recent study suggested the developmental stage of the child when symptomatic focal epilepsy begins can significantly impacts the cognitive difficulties observed (Gonzalez et al., 2014), with those with epilepsy occurring in the critical period for language (2-5 years) exhibiting significant difficulties in phonological processing and vocabulary in comparison to those who experienced seizure onset in later childhood. In addition, studies have shown that those with the same localisation and extent of brain injury in childhood can have vastly different functional outcomes ranging from no change in their cognitive abilities to severe learning disabilities (Anderson et al., 2009; Anderson, Spencer-Smith, & Wood, 2011).

Children with large portions of their brain affected, like those with RS, cortical dysplasia and Sturge Weber syndrome, typically have uniformly poor cognitive outcomes and all areas of cognitive abilities can be affected (Hermann et al., 2010). Importantly, however, the area of the brain and its specific function can still affect the changes in cognition observed. For example, those with cortical dysplasia (i.e., congenital abnormality in which neurons in the brain fail to migrate in utero) in the left hemisphere have greater problems with verbal IQ, whereas cortical dysplasia in the right hemisphere leads to deficits in non-verbal IQ (Klein, Levin, Duchowny, & Llabre, 2000).

Since the 19th Century the left hemisphere of the brain has been characterised as lateralised for language (Broca, 1861). By investigating those with specific aphasias, a model of language functioning and brain architecture was put forward with Broca's area, a region within the left hemisphere's frontal cortex, supporting expressive language (Broca, 1861), and Wernicke's area, an area in the superior temporal gyrus, supporting language comprehension (Geschwind, 1970). Since the advent of functional MRI the large language networks of the normally functioning brain have been elucidated and numerous studies have shown phonology, semantic and sentence processing are typically supported by the left frontal and

temporal cortical regions (Vigneau et al., 2006). Interestingly, however, handedness appears to play an important role in the language lateralisation of the brain and research has shown that 96% of those who are right handed are lateralised for language to their left hemisphere, whereas this drops to 90% of those who are left handed (Knecht et al., 2000). This means a small proportion of individuals are right hemisphere lateralised for language or have a bilateral lateralisation (Knecht et al., 2000).

In those with RS affecting the left hemisphere (presumed language dominant), small group or single cases have suggested marked language difficulties pre-surgery. Boatman and colleagues (1999) found expressive and receptive language deficits, but not aphasia, in six left RS individuals pre-FH in comparison to age-matched controls. However, a single case study of a late onset (11 years) left RS individual was found to be markedly aphasic prior to FH at 16 years (Telfeian, Danielak, Simon, & Dunhaime, 2002).

Only one study has examined cognition in a large group of RS individuals (n=37) before and after FH (Pulsifer et al., 2004). Looking at the cognitive performance pre-surgery showed the left group had significantly lower scores on tests of expressive and receptive language at the pre-surgery assessment in comparison to the right hemisphere RS group (left = low range, right = low average range; Pulsifer et al., 2004). This investigation also showed that before surgery the left hemisphere RS individuals had non-significantly poorer Full Scale IQ scores, scoring in the low range, in comparison to those who had RS affecting the right hemisphere who were in the low average range (Pulsifer et al., 2004).

The right hemisphere was originally thought to possess no language function and to lack consciousness (Sperry, 1945). Pioneering experiments in split brain patients, however, revealed the right hemisphere is able to comprehend spoken and written language as will be discussed in more detail below (Moscovitch, 1976; Sperry, 1961). More recently, neuroimaging and investigations of those with right hemisphere brain damage have led to the idea that the

right hemisphere supports higher order visual perceptual processes, spatial and topographical processing, non-verbal reasoning, musicality and attention (Reeves, Rand, & Swenson, 2008).

Very few studies have investigated the cognitive profile of children with right hemisphere RS. The limited evidence discussed so far has indicated that pre-surgery those with right hemisphere RS have better preserved Full Scale IQ and language abilities in comparison to left hemisphere RS (Pulsifer et al., 2004). More detailed neuropsychological investigation into the memory, executive function and visuo-spatial abilities of gross right hemisphere damage has been infrequent. One single case study of an individual with early brain injury to the whole right hemisphere (not RS) had serial neuropsychological assessment before and after right FH (Chiricozzi et al., 2005). The one time point before surgery suggested damage to the right hemisphere was associated with deficits in non-verbal perceptual reasoning IQ but better preserved verbal IQ (PIQ < 45, VIQ = 65). In addition, visuoperceptual and visuospatial abilities were markedly reduced as measured by the Visual Object and Space Perception (VOSP) battery, but long-term memory was intact (Chiricozzi et al., 2005).

In summary, reviewed evidence suggests that those with progressive damage to their left hemisphere due to disease change, including those with left hemisphere RS, have specific language impairments and significant declines in their Full Scale IQ scoring into the low range. The cognitive abilities of those with progressive damage to their right hemisphere before surgery remain less well characterized, although available evidence hints they may experience particular difficulties in non-verbal perceptual reasoning IQ and visuospatial abilities.

1.2.2. Seizure frequency and duration of epilepsy

Animal studies show that epileptic seizures cause disruption in the functioning of specific brain regions through influencing functional organization, particularly in the developing brain (Sayin, Sutula, & Stafstrom, 2004). The impact of seizures in both adults and children has been

investigated using longitudinal designs that re-test the same cohort after a specific time interval to determine if cognitive changes are associated with seizure frequency. Longitudinal studies of adults with epilepsy localized typically to the temporal lobe have shown longer duration of epilepsy is significantly associated with cognitive decline across multiple domains, but most reliably in verbal memory, psychomotor speed and attention (Hermann et al., 2006; Piazzini et al., 2006). This effect is only seen in studies where the test-retest interval is greater than 18 years (Seidenberg et al., 2007). Other studies suggest seizure frequency is a more important factor than duration. For example, Thompson and Duncan (2005) investigated the IQ, memory and executive abilities in 136 patients with intractable epilepsy at two time points ten years apart. They found significant decline in all cognitive functions, with all scores dropping on average 10 points. Multiple regression analyses revealed the frequency of generalised tonic-clonic seizures (i.e., seizure in which the patient will become unconscious, their muscles will stiffen and they cry out (tonic phase) and then their arms and legs will rapidly jerk rhythmically (clonic phase) typically for around 1-3 minutes; http://www.epilepsy.com/learn/types-seizures/tonic-clonic-seizures) was the strongest predictor of this decline over and above duration of epilepsy. It also showed the timing of the onset of seizures (early vs. late onset) did not affect cognitive outcome (however, see section 1.2.4 below).

Very few longitudinal studies exist in children with epilepsy but those that do generally suggest poorer academic attainments in children with epilepsy over time in comparison to controls (Oostrom, Smeets-Schouten, Kruitwagen, Peters, & Jenneken-Schinkel, 2003). Interestingly, however, these deficits are observable not only at retest but at the time of epilepsy onset (Oostrom et al., 2003). This suggests seizure frequency and duration of epilepsy may have a lesser impact on cognition in children than indicated by the adult literature described above. This was further corroborated by a study that novelly looked at 3 assessment

time points (at diagnosis, 2 years and 5-6 years post-diagnosis) to determine the cognitive trajectory of 69 epileptic children in comparison to controls by carrying out assessment of IQ, academic achievement, language, executive function and psychomotor speed (Rathouz et al., 2014). Results showed deficits were exhibited in the epilepsy group in arithmetic, executive function and psychomotor control at the time of diagnosis and that this deficit remained stable over the next 6 years (Rathouz et al., 2014). The authors concluded that children with mixed epilepsies do not necessarily deteriorate over time but that their development lags behind children without epilepsy. Whilst this study would suggest that duration of epilepsy may not impact children's cognitive performance, a number of limitations must be considered. First, the frequency of seizures was not measured by Rathouz and colleagues (2014) so the impact of regular and severe seizures cannot be determined. In addition, the time of follow up was relatively short and further decline may have been seen if retest had been later, as suggested above (Thompson & Duncan, 2005) .

Taken together these findings suggest frequency of seizures and duration of epilepsy may have an important impact on cognition over longer durations greater than 10 years, but a lesser impact over shorter durations. It also suggests those with intractable epilepsy (like those with RS) may experience cognitive decline associated with very frequent seizures over a long duration (Thompson & Duncan, 2005).

1.2.3. Cognitive effects of anti-epileptic drugs

Anti-epileptic drugs (AEDs) act by decreasing neuronal irritability, which in turn reduces the likelihood of seizure development and propagation (Lagae, 2006). AEDs are thought to be related to mild-to-moderate cognitive side effects (Aldenkamp, 2001) by reducing neuronal excitability and causing electrophysiological slowing (Hermann et al., 2010). Separating out the effects of an AED on cognition from the impact of epilepsy itself is very difficult. To circumvent this issue the AED's impact on cognition has been investigated in healthy adults in

comparison to controls. These have shown that, in general, one month of AEDs leads to deficits in processing speed and sustained attention in comparison to controls (Hermann et al., 2010; Meador, Loring, & Ray, 2001).

Very few studies have investigated the cognitive effects of AEDs in children due to ethical problems and issues around controlling for medical factors (Lagae, 2006). In the studies that have been conducted, "older" AEDs (e.g., phenobarbital, phenytoin, carbamazepine and sodium valproate) are associated with psychomotor slowing in children (Aldenkamp et al., 1993) and long-term use of phenobarbital has been associated with a decrease of around 10 points in IQ and "hyperactivity" in children with epilepsy (Vining et al., 1987). On the other hand, some research suggests no significant adverse effects of older AEDs on cognition in epilepsy (Chen, Chow, & Lee, 2001). However, whilst the research is far from unanimous, it is generally accepted that there is more evidence that "older" AED's do have adverse cognitive side effects (Lagae, 2006).

There is currently a paucity of data for the cognitive side effects of newer AEDs, such as levetiracetam, lamotrigine and oxcarbazepine, in children. One recent investigation by Skirrow et al., (2011) that looked at the long-term cognitive outcome of those with temporal lobe epilepsy found through a stepwise multiple regression that current number of AEDs was negatively predictive of full scale IQ change over time (Skirrow et al., 2011). On the other hand, a few studies that have investigated adult epileptic individuals' neuropsychological profiles revealed lamotrigine, oxcarbazepine and levetriacetam are associated with no adverse cognitive effects (Mandelbaum & Burack, 1997; Sabers, Moller, & Dam, 1995) and at times have been associated with improvement in cognitive function (Buchanan, 1995; Sabers et al., 1995). Care should be taken not to extrapolate existing data in adults to children, however, as minor side effects in adults may cause significant learning and cognitive effects in children (Lagae, 2006).

No studies have specifically looked at the effect of AEDs on those with catastrophic epilepsies like RS. However, bearing in mind the intractable nature of the seizures experienced by RS individuals and the evidence already reviewed suggesting seizure frequency and epilepsy duration has a negative impact on cognition, some seizure control offered by an AED may lead to a better cognitive outcome for a child than failure to medicate (Hermann et al., 2010).

1.2.4. Age at onset

The impact of age at seizure onset on cognitive performance, especially in those with refractory catastrophic epilepsies, has also been explored. Correlational and regression analyses show that earlier age at onset is associated with lower IQ or developmental scores (Cormack, Cross, & Issacs, 2007; Freitag & Tuxhorn, 2005; Vasconcellos, Wyllie, & Sullivan, 2001). However, separating out the effects of age at onset and duration of epilepsy is difficult and many studies have failed to separate these two variables (Berg, Zelko, Levy, & Testa, 2012). One prospective study successfully achieved this by assessing children's cognition 8 years after first epilepsy diagnosis and investigating if age at onset of epilepsy, duration of seizures or an interaction of the two informed cognition (Berg et al., 2012). Linear regression analysis revealed age did not correlate with cognitive outcome but there was an interaction between duration of epilepsy and age (Berg et al., 2012). This suggests the deleterious impact of the duration of seizures decreases as age increases which led to the conclusion that those with early onset epilepsies should undergo early aggressive treatment to try to ensure seizure control (Berg et al., 2012). RS has a variable age at onset ranging from diagnoses in the first year of life to those who develop the disease in their early teens (Bien & Schramm, 2009). Hence, the possible influence of age at onset of epilepsy on cognition remains to be determined in RS.

1.3. **Cognitive outcomes after functional hemispherectomy**

1.3.1. In groups of children including those with RS

There has been intense interest in the effect of FH on the outcomes of those with catastrophic epilepsies, including RS. A number of studies have assessed medical outcomes, including neuropsychological performance, in groups of children who have undergone FH before and after surgery.

One of the earliest studies interrogated the clinical outcomes of a group of 33 children who underwent FH, including six RS individuals (Devlin et al., 2003). Pre- and post-surgery 15 children underwent cognitive assessment using formal measures, 10 were given a developmental assessment and the remaining 8 cases were evaluated based on a clinical assessment by a paediatric neurologist. From this children were put into intellectual categories of: normal, mild impairment, moderate impairment and severe impairment. Results showed that after FH most children experience no change in their cognitive abilities (i.e., they did not move from one intellectual category to another) and 4 children (none with RS) showed significant improvement in developmental trajectory, moving from the severely impaired range to moderately impaired (Devlin et al., 2003). Unfortunately, the abilities of the RS children were not described or documented separately. No changes in cognitive abilities after FH were also observed by Lettori and colleagues (2008) who looked at the outcome of 16 children (1 with RS) with catastrophic onset of epilepsy in the first 5 years of life who had undergone FH. Again they did not conduct psychometric assessment in all participants but categorised them according to their intellectual abilities (Lettori et al., 2008).

These studies' findings that functional removal (or disconnection) of half the brain does not result in further cognitive decline is perhaps surprising. Indeed it would be predicted that disconnection of the left and right hemispheres would lead to verbal and non-verbal

difficulties respectively (Vargha-Khadem, Isaacs, Papaleloudi, Polkey, & Wilson, 1991). These two studies, however, may lack sensitivity to pick up cognitive change as they failed to conduct detailed psychometric assessment in all children and instead categorised children into broad ability bands.

Other investigations have successfully carried out more detailed psychometric assessment of individuals before and after FH. One prospective longitudinal study assessed IQ, developmental age and language abilities in 16 children (9 RS) before and after FH (Thomas, Daniel, Chacko, Thomas, & Russell, 2010). Those with RS significantly improved in terms of their language scores in comparison to the rest of the cohort post-surgery and no effect of side of surgery was observed. Linear regression analysis of the whole sample also revealed age at onset and duration of epilepsy had a significant influence on the intellectual abilities of the child after surgery and the older the child at onset and the shorter the duration of epilepsy the better the outcome (Thomas et al., 2010). This study therefore showed more detailed psychometric assessment can detect positive changes in language irrespective of the hemisphere disconnected. In addition, it suggests age at onset and duration of seizures may continue to have an impact on cognitive outcome even after half the brain is disconnected. The validity of these findings, however, is difficult to determine considering the exceptionally low sample size for a linear regression (n=16).

Indeed, one of the main limitations of the studies described so far may be a lack of statistical sensitivity due to relatively small sample sizes (i.e., all $N < 33$) and very small groups of diagnoses to compare to one another (i.e., RS vs cortical dysplasia). However, smaller sample sizes are often a necessity due to difficulties accessing and then conducting assessment in this rare group of individuals. One study aimed to circumvent this issue by asking patients who had undergone FH about their functional outcome (i.e., ability to walk, speak, read, attend academically or gain employment and behaviour) before and after surgery

through questionnaires completed over the telephone (Moosa et al., 2013). This resulted in a large sample of 125 participants; however, only 10 had RS. Results showed 70% had satisfactory subjective spoken language skills after FH whilst 42% had satisfactory reading skills (Moosa et al., 2013). Multivariate logistic regression also showed seizure recurrence negatively affected all functional domains and young age at FH also correlated with poor language outcome. Hence, this study does support previous evidence that seizure frequency and early onset of epilepsy can have a negative impact on cognitive functions after FH.

1.3.2. Cognitive trajectory post-operatively in those with RS

A few studies have exclusively explored RS individuals' cognitive change over time by conducting psychometric assessment pre- and post-FH (Boatman et al., 1999; Caplan, Curtiss, Chugani, & Vinters, 1996; Pulsifer et al., 2004; Terra-Bustamante et al., 2009). One retrospective study looked at medical outcomes including cognition and language before and after FH in 25 RS individuals (Terra-Bustamante et al., 2009). Findings showed half of RS individuals' cognition stayed the same, 38% declined and 10% improved. In terms of language, 41% of RS individuals were dysphasic after surgery, however all of these individuals had had language problems pre-surgery (Terra-Bustamante et al., 2009). Very problematically, however, the way cognition and language were measured is not disclosed in this study and so it is difficult to ascertain the validity of these findings.

As already mentioned the most extensive investigation into the cognitive abilities of those with RS was conducted by Pulsifer and colleagues (2004). Using standardised psychometric assessment they assessed: intelligence, adaptive skills, language (expressive and receptive) and visuospatial performance before and an average of 5.1 years after FH in 37 RS individuals. Results showed that at both time points the left hemisphere RS patients scored significantly lower than the right in terms of IQ and expressive and receptive language (Pulsifer et al., 2004). The left group also scored lower on adaptive functioning than the right but this

did not reach statistical significance. The only significant effect of time of assessment (i.e., pre- vs. post-op) was in expressive language, which was lower at post-op irrespective of side of resection suggesting FH has an negative impact on language irrespective of RS side (Pulsifer et al., 2004). This indicated that post-op there was a deterioration in expressive language abilities in both groups. No interaction was found between side of surgery and time of evaluation on all measures, suggesting changes in test scores post-surgery were not affected by side of surgery.

Whilst this study is the only one to have conducted detailed psychometric assessment in a large group of RS individuals using a test-retest design, it does suffer from some limitations. Firstly, the follow up assessment occurred between 1 and 26 years after surgery. Considering some recent studies have shown that improvements in IQ after epilepsy surgery can be observed only after 5 years (Skirrow et al., 2011), a variable follow up time may severely affect the findings as time since surgery is not controlled. In addition, Pulsifer and colleagues (2004) did not conduct multiple regression analyses to determine the effect of medical risk factors on those with RS. Finally, there was no consideration of possible dissociations in cognitive performance and Full Scale IQ was considered as a single construct, meaning that it is unknown which cognitive domains were driving poor IQ performance. For example, it is possible those with left FH may have poorer verbal IQ abilities, whereas those with right FH may have more difficulties with tasks of perceptual reasoning.

In conclusion, in the largest study that has looked at the cognitive outcome of FH in RS children, those with left RS scored lower in their IQ and language scores in comparison to right before and after surgery. No separable effects of surgery were found, and there was no significant difference between those with right and left RS in terms of IQ or language post-surgery. Medical variables' effects on cognitive change were also not investigated.

1.3.3. Impact of medical variables on cognitive trajectory post-operatively in RS

Few studies have investigated the effect of medical variables on the outcome of those with RS after FH. One investigation suggested that a shorter duration of epilepsy pre- FH was associated with improved language and social communication in those with right hemisphere RS post-FH (N= 4; Caplan et al., 1996). It has been recently hypothesised in those with RS that seizure activity may not only damage the ipsilateral hemisphere but also the contralateral hemisphere through seizure propagation from the affected hemisphere to the unaffected RS hemisphere (Hartman & Cross, 2014). Indeed, a recent longitudinal EEG investigation of 19 RS individuals revealed by 3-6 months and 5 years follow up 25% and 62% respectively were experiencing interictal epileptiform abnormalities (IABNs; i.e., the epileptic activity detected in the brain between seizures; http://medical-dictionary.thefreedictionary.com/interictal) over the unaffected hemisphere (Longaretti et al., 2012). Those with IABNs in the unaffected hemisphere also experienced a marked cognitive decline over time with their IQ scores reducing at least 30 points in comparison to those without IABNs, who showed a more modest decline (FSIQ=<15). Whilst this study was unable to determine the pathogenesis of the IABNs, it hints that the prolonged epileptic activity may have damaging affects to the contralateral hemisphere resulting in a higher impact on cognitive functioning.

Another medical variable not yet considered is timing to surgery. The above evidence may suggest that early FH is advisable so that seizure propagation from the affected to the unaffected hemisphere cannot take place. However, the optimum timing to FH in RS remains largely unknown (Hartman & Cross, 2014). FH “early” in the disease course is particularly difficult to undertake in those with RS affecting their language dominant hemisphere because FH can lead to aphasia and severe language disorder (Boatman et al., 1999; Vargha-Khadem et al., 1991). The right hemisphere’s potential for language is known to markedly decrease after 4-5 years of age (Vicari et al., 2000). It is currently unknown whether language function

can be forced to reorganise to the non-dominant (typically right) hemisphere through FH, or if the surgery should be delayed until language function is reorganised naturally due to the disease process itself (Hartman & Cross, 2014). Boatman and colleagues (1999) followed six individuals with left hemisphere RS who had normal language prior to the onset of RS. One year post-surgery their receptive language abilities had improved in comparison to pre-surgery performance. Conversely, their expressive language abilities consisted only of single words and their vocabulary was highly impaired in comparison to pre-surgery ability. Whilst the authors concluded the isolated right hemisphere is able to support receptive language by one year post-FH, it highlights the devastating effect that FH can have on an RS individual's expressive language. This pattern of relatively preserved receptive language but severe deficits in expressive language after FH of the language dominant hemisphere has been found in a number of other studies where N<6, or in single cases (Mariotti, Iuvone, Giulia, & Silveri, 1998; Vargha-Khadem et al., 1991).

On the other hand, some single cases of language dominant RS individuals suggest that poor expressive language outcomes post-FH are not inevitable. For example, a single case study of a left RS case who was profoundly aphasic before surgery was able to speak 7-word sentences 2 years after FH at 16 years (Telfeian et al., 2002). This suggests that the isolated right hemisphere could reorganise to take on some language function even after damage to the left hemisphere is sustained after the critical period of 4 years old. Further evidence for this was found in an fMRI study that showed a left FH RS individual who had some limited expressive language ability post-surgery showed new activation in the right hemisphere in an area homologous to Broca's area during a language task (Liégeois, Connelly, Baldeweg, & Vargha-Khadem, 2008).

There continues to be considerable debate over the timing of FH in RS. Due to a lack of longitudinal investigations and the rarity of the syndrome the ideal timing of surgery

remains unknown (Hartman & Cross, 2014). It may be preferable to wait until decline in neurological functions have plateaued before surgery is offered. Alternatively, carrying out surgery earlier in the disease process may preserve some motor, vision, language and cognitive functions due to less potential damage and possible neuroplasticity of the contralateral hemisphere (Hartman & Cross, 2014). It is only through conducting studies in which neurological functions, including cognition, are followed longitudinally before and after surgery that impact of different medical variables will be able to be deduced and subsequently better decision making around medical care including surgery will be possible. Determining the possible grey and white matter changes before surgery in the affected and unaffected hemisphere and possible impacts these may have on cognitive functioning will also be vital, as will be discussed below.

1.4. **MRI**

1.4.1. Overview

Our bodies are principally made up of water molecules that contain two hydrogen protons or nuclei. Hydrogen protons are magnetic and so behave similarly to magnets spinning around an axis (Westbrook, 2014). MRI exploits the inherent magnetic properties of the hydrogen proton to produce images of any region of the body (Clinical Review, 2002). When a person is placed in an MRI scanner the powerful magnetic field, normally ranging from 0.5 to 3 tesla, causes the hydrogen protons' axes to line up in the direction of the magnetic field (Burghart & Finn, 2011). A radio wave frequency is then applied to deflect the hydrogen nuclei in this field (Clinical Review, 2002). The radiofrequency source is then switched off and this causes the magnetic vector to return to a resting state, which in turn causes a radio signal wave to be emitted. This radio signal is detected by receiver coils within the MRI scanner and is used to create the MRI images (Clinical Review, 2002).

Different tissues relax at different rates when the radiofrequency is turned off due to their different compositions of water. Hence, radiofrequency pulses can be sequenced or weighted to investigate different tissues of interest (Westbrook, 2014). T1 weighting, in which the time taken for the magnetic vector to return to its resting state (i.e., T1 relaxation) is measured, is typically utilized to investigate the cerebral cortex (Burghart & Finn, 2011). This is because in a T1-weighted image water and bone are dark and fats such as the myelinated white matter are bright (http://fmri.ucsd.edu/Howto/3T/structure.html#T1). Therefore, a T1-weighted image provides a very good contrast between grey matter, which appears dark grey, white matter that is lighter grey and cerebral spinal fluid which is black (http://fmri.ucsd.edu/Howto/3T/structure.html#T1). This contrast allows for high-level statistical analysis of the grey and white matter difference across participants.

1.4.2. MRI neuroimaging in RS

One of the diagnostic criteria of RS is progressive atrophy of one hemisphere of the brain that happens over months or years (Bien et al., 2005). Numerous studies in which radiologists have rated MRI scans of RS individuals have provided evidence for this using longitudinal designs (Varadkar et al., 2014). These studies also revealed that RS is associated with specific regional volume loss. Granata and colleagues (2003) studied 12 RS individuals' MRI scans serially from diagnosis (scan within the first 4 months) to up to 5 years post diagnosis. Radiologists' ratings suggested scans collected in the first 4 months post-diagnosis showed atrophy in the insular cortex, caudate head and widening of the ventricles in one hemisphere of the brain (Granata et al., 2003). Whilst this study is notable, aspects of the methodology are problematic as the radiologists reading the scans were not blind to the disease state.

Rajesh and colleagues (2006) used radiologists blinded to the clinical state of the patient to classify areas of change in 29 MRI scans collected from 12 RS individuals over time. This study again found atrophy in the insular region, caudate and also the putamen of one

hemisphere. This study is significant as it was the first to suggest the putamen and hence basal ganglion involvement in RS (Rajesh, Kesavadas, Ashalatha, & Thomas, 2006). Volume loss in the perisylvian region, caudate nucleus and enlargement of the ventricles in a single brain hemisphere during the acute stage of RS is now generally accepted as the pattern of atrophy most commonly seen (see Figure 1-3; Kim et al., 2002; Yamazaki et al., 2011; Varadkar et al., 2014).

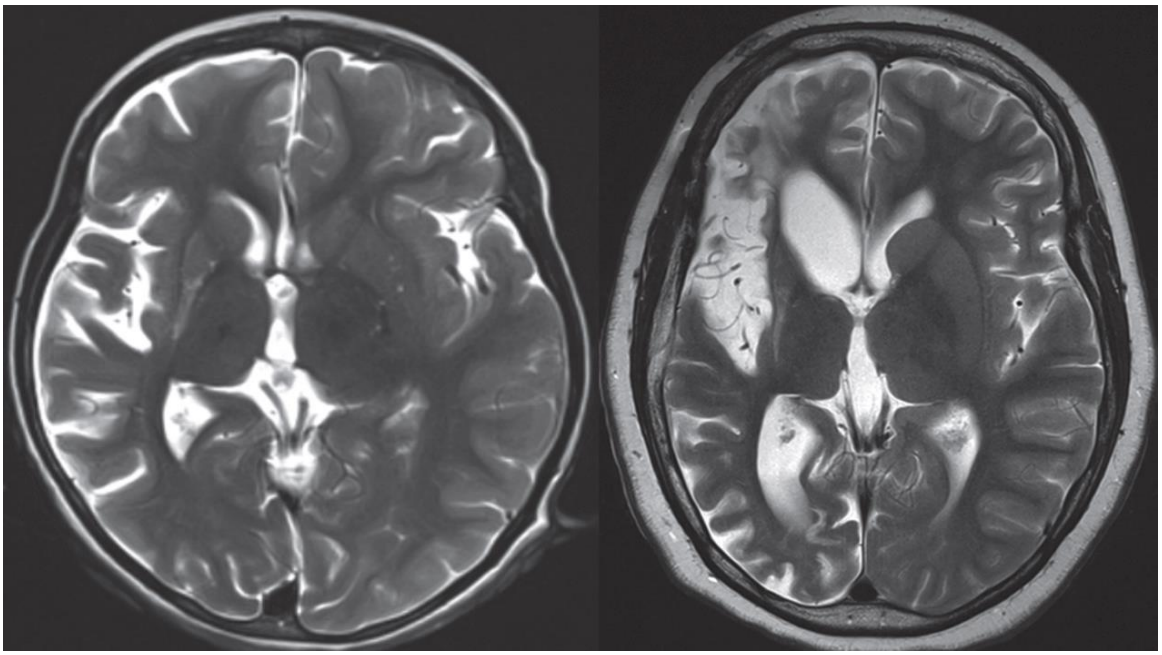

Figure 1-3: Two MRI scans taken one year apart in an individual with right hemisphere RS. They show progressive right hemisphere atrophy in the basal ganglia and sylvian fissure over 1 year (Kim et al., 2002; Varadkar et al., 2014).

So far all the RS MRI studies discussed have been based on radiologists reading scans and classifying areas of change and atrophy. The use of neuroimaging analysis techniques to objectively quantify volume loss (or increase), however, can provide insights into more subtle changes to grey and white matter in RS free of subjective visual assessments. Only two investigations have used imaging analyses to investigate brain volume change in RS. Larionov and colleagues (2005) used manual volumetry (i.e., manual tracking of bitmap images) to

calculate the relative volumes of the affected and unaffected hemispheres in 18 RS individuals with 63 MRI investigations over time. They manually traced around hemispheres and, to allow comparison between brains of different sizes, calculated the quotient of the absolute volume of the affected hemisphere (AH) and the unaffected hemisphere (UH) and vice versa to derive the relative volume of the AH and UH over time. Results revealed the AH underwent around 30 cm (cubed) of tissue loss annually, but that the UH also underwent some atrophy at a much slower rate. This was hypothesised to be reflective of degeneration of the commissural fibres that originate in the AH or the effect of chronic seizure and AEDs on the UH (Larionov et al., 2005). Whilst, this study was the first of its kind, it did not report the timing of the MRI scans in regards to the onset of RS. In addition, brain volumes were estimated through manual tracing and hence, difficulties can arise from investigators not being blinded to the disease state of the individual.

More recently Wagner and colleagues (2012) used an semi-automated system to extract volumes of the UH, AH and cortical and subcortical structures of interest using number of regions of interest (ROIs) using FMRI Software Library (FSL) in 12 RS individuals with 66 serial scans over time. In this investigation they only investigated RS individuals who had their first scan in the first 2 years after onset. Again they calculated the relative volume of brain regions to allow comparison between RS participants. The years from disease onset to MRI scan were reported and the first MRI scan ranged from 0.1 to 2 years with a median of 0.7 years since onset. The subsequent observation period in which additional MRI scans were collected ranged from 0.3 to 5.8 years with a median of 3 years. In agreement with Larinov et al (2005) the AH showed a catastrophic volume reduction over time in all RS individuals (Wagner et al., 2012). They found the frontal lobe and the insula in the AH showed the most severe atrophy at the most recent MRI in 9 out for 12 participants. There was a hint that the UH also declined in grey matter but only in half of their participants investigated (Wagner et al., 2012).

1.4.3. VBM

First pioneered by Ashburner and Friston (2000), VBM is a fully automated whole brain imaging analysis that allows the structural integrity of the grey matter at the voxel level to be investigated (i.e., basic unit of MRI in three dimensional space). One major methodological advantage of VBM is that it is conducted at the whole brain level and is hence not constrained by a priori ROIs, time consuming manual measurements or subjective visual assessments which can all be influenced by investigator bias (Whitwell, 2009).

Once pre-processing has taken place (see Chapter 2), voxel-wise parametric statistical tests, which compare the smoothed grey or white matter segments between or within participant groups, can be performed (Whitwell, 2009). For example, to determine the difference in patterns of regional anatomy between groups of participants t-tests are performed at every voxel of the image. Importantly, when VBM is compared to manual or visual measurements of particular brain structures VBM analyses show good correspondence (Giuliani, Calhoun, Pearlson, Francis, & Buchanan, 2005), suggesting the biological legitimacy of VBM (Whitwell, 2009).

1.4.4. VBM and epilepsy

No previous investigations have used VBM to explore the grey matter changes in those with RS. However, many studies have utilized VBM to explore the brain differences in those with temporal lobe epilepsy in comparison to controls. These have shown overwhelmingly that those with temporal lobe epilepsy have abnormalities in the hippocampus ipsilateral to the seizure focus (for review see Keller and Roberts, 2008). Interestingly, VBM studies of those with seizures arising in the temporal lobe have also found bilateral atrophy in regions outside the temporal lobe especially in the thalamus and parietal lobe (Keller & Roberts, 2008). This suggests that VBM is able to detect possible grey matter changes that are not commonly

observed in a radiologist's report.

Longitudinal VBM studies of those with temporal lobe epilepsy have shown that atrophy worsens over time and this is related to specific medical variables. Coan and colleagues (2009) conducted two MRI scans around 7 months apart in those with temporal lobe epilepsy and found using VBM analysis (i.e., paired t-test) that there is a significant reduction in grey matter in the hippocampus over time. Interestingly, the progression of atrophy was more intense in those with left temporal lobe epilepsy in comparison to right and higher seizure frequency and longer epilepsy duration were also associated with progression of grey matter atrophy (Coan et al., 2009). This has led to the suggestion that temporal lobe epilepsy is a progressive condition and one of the mechanisms for this may be through recurrent seizures (Coan & Cendes, 2013).

1.4.5. Relationships between neural change and cognitive function

Cross-sectional VBM studies have also allowed correlational analysis across voxels to assess the neuroanatomical correlates of cognitive or behavioural performance. This technique can aid understanding of how specific brain changes during disease or disorder may underpin specific clinical features (Whitwell, 2009). Of particular interest are the investigations that attempt to elucidate the neurobiological abnormalities that underline neuropsychological impairment. In adults with temporal lobe epilepsy, correlational VBM analyses have suggested there is a significant relationship between long-term memory indices and grey matter integrity of the medial temporal lobe (Bonilha et al., 2007). What is more, using VBM correlational analysis, adults with temporal lobe epilepsy's executive functioning scores have also been shown to be associated with the grey matter concentration of their prefrontal cortex (Keller, Baker, Downes, & Roberts, 2009). On the other hand, some studies have suggested that cognitive performance is not associated with specific regions of grey matter but is correlated with grey matter integrity at a global level (Focke, Thompson, & Duncan, 2008), implying a

cognitive impairment may be underpinned by a widespread network of brain abnormality (Bell, Lin, Seidenberg, & Hermann, 2011).

Very few longitudinal studies have explored the possible association between grey matter atrophy over time and changing neuropsychological abilities. Two recent notable exceptions used VBM to investigate the relationship between grey matter change and IQ and memory scores at long-term post-op follow up (over 10 years) in those who had undergone temporal lobe surgery in childhood (Skirrow et al., 2011, 2014). Skirrow and colleagues (2011), extracted grey and white matter values using MRIcron for the whole brain and revealed an association between the change in grey matter volume of the whole brain post-surgery (i.e., post-surgery grey matter – pre-surgery grey matter) and the change in IQ score (i.e., post-op IQ score – pre-op IQ score; Skirrow et al., 2011). This led the authors to conclude that a network of brain regions supports IQ. Next, manual tracing of the hippocampus and the temporal lobe using MRIcron and extraction of grey and white matter values, in the same group of participants, revealed that residual hippocampal and temporal lobe volumes at post-op were significantly associated with verbal memory scores (Skirrow et al., 2014). Notably however, there was no significant relationship between the changes in memory scores pre- to post-operatively and indices of brain structure derived from MRI.

1.4.6. Intelligence constructs and their neural correlates

Verbal comprehension and perceptual reasoning are two important dimensions of general intelligence and are estimated by standardized tests of intellectual functioning (Wechsler, 1997) as discussed in Chapter 2. Perceptual reasoning pertains to the ability to solve novel visuospatial problems by deriving and manipulating relational representations among different stimuli (Holyoak & Koger, 1995). Typically these tests require an individual to correctly pick out a missing component of a complex design or stimulus. In this way the ability to solve these visuospatial problems is not based on prior knowledge but novel problem solving

abilities (i.e., fluid intelligence). fMRI studies of children carrying out visuospatial perceptual reasoning tasks have indicated the bilateral superior parietal cortex in the region of the retrosplenial cortex, the bilateral dorsolateral prefrontal cortex and occipital-temporal cortex are all recruited during successful completion of these tasks (Eslinger et al., 2009). Uni-hemispheric activations were also found in the left caudate and right putamen and insula (Eslinger et al., 2009).

Typically those with bilateral lesions to their frontal and parietal lobes exhibit difficulties on visual-spatial reasoning tests (Duncan, Burgess, & Emslie, 1995). Interestingly, however, adults with damage to the left frontal lobe alone have difficulties with complex problem-solving even when tasks are non-verbal (Baldo et al., 2005; Langdon & Warrington, 2000). For example, a study indicated that poor performance on a relational reasoning task in those with left hemisphere stroke was related to damage in the left superior temporal gyri and inferior parietal cortex (Baldo, Bunge, Wilson, & Dronkers, 2010). The authors suggested this may be due to problems with covert language or inner speech which they postulated may be required to successfully complete challenging problem solving tasks (Baldo et al., 2005).

Verbal comprehension is the ability to understand spoken or written language. Early investigations of those with aphasia led to the classical idea that verbal comprehension is supported by the superior temporal gyrus (Wernicke's area; Geschwind, 1970) in language-dominant hemisphere. However, more recent fMRI studies of healthy individuals have suggested verbal comprehension is supported by a temporofrontal network of regions including: Broca's area, Wernicke's area, planum temporale and additional regions within the frontal lobe, parietal lobe and temporal areas (Binder, Frost, Hammeke, Rao, & Cox, 1996; Perani et al., 1996). Lesions to the language dominant temporofrontal network has led to catastrophic deficits in language comprehension in left hemisphere stroke patients (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004) and those with left RS (Boatman et al., 1999;

Pulsifer et al., 2004). Importantly though, as discussed above, the language non-dominant hemisphere does have the capacity to support some verbal comprehension (Boatman et al., 1999). Investigations into adults with damage to the language dominant hemisphere due to stroke show that language recovery may be supported by a upregulation of the remaining undamaged temporofrontal network (Warburton, Price, Swinburn, & Wise, 1999) and an involvement of homologous language areas in the non-dominant hemisphere (Rosen et al., 2000). This idea is supported by the single case RS fMRI study, that showed after left FH expressive language recovery was supported by activation in the temporofrontal regions of the right hemisphere (Liégeois, Connelly, et al., 2008).

The evidence summarised above suggests that bilateral regions of the brain support non-verbal relational problem solving and damage to either hemisphere within parietal, frontal and temporal regions can lead to deficits on these tasks. Language comprehension, however, is primarily supported by the language dominant hemisphere although regions within the right hemisphere do have some capacity for verbal comprehension.

1.5. **Thesis overview**

This study aimed to explore the neuropsychological performance of individuals with RS at multiple time points before and after surgery using standard psychometric assessment to measure IQ, academic achievement, language and memory. It differed from Pulsifer et al. (2004) and other previous investigations in a number of crucial ways: (1) it interrogated the trajectory (which is not necessarily linear) in cognition *before* neurosurgery (2) it endeavoured to determine the effect of a number of medical factors on cognitive abilities, (3) post-operative assessments were all around 1-2 years post-surgery (thus timing of assessment will not be a confounding factor as in Pulsifer et al. (2004)), (4) it looked in more detail at the neuropsychological scores of RS individuals examining, specifically, the verbal and non-verbal

domains.

The following key questions were investigated in regard to the neuropsychological data:

1. What is the neuropsychological performance associated with RS and what is the cognitive trajectory (a) pre-surgery and (b) pre- and post-FH?
2. Is there a difference between the cognitive profile of those with RS of the right or left hemisphere (a) pre-surgery and (b) pre- and post-FH?
3. Are certain medical factors such as: age at onset, frequency of seizures and duration of epilepsy, time to surgery and current use of AEDs associated with cognitive changes in individuals with RS (a) pre-surgery and (b) pre- and post-FH?

A further novel primary aim of this investigation was to explore the ability of VBM to detect grey and white matter change over two time points pre-surgery in 18 RS individuals (9 right hemisphere affected). Next, it investigated if the neural correlates of cognitive change could be determined by exploring if there was a relationship between the change in grey and white matter integrity of specific brain regions and neuropsychological performance change over time.

The following questions were investigated in regard to the neuroimaging data:

4. Can VBM analysis detect grey and white matter change in RS individuals over time at two time points pre-surgery?
5. Can the neurobiological correlates of neuropsychological decline in two important constructs of intelligence, verbal comprehension and perceptual reasoning, be determined at the whole brain level and within regions of interest in RS pre-surgery?

A greater understanding and characterization of the neuropsychological trajectory and its neurobiological correlates in individuals with RS will not only increase scientific knowledge but could also have important clinical implications. It may help hone assessment of RS and inform

the recommendations for ongoing individualised support. The progression of cognitive change and its relationship to brain change before surgery and information on the medical factors that impact decline may also aid treatment decisions around timing of surgery. This could ultimately have implications for RS individuals' preservation of cognitive functioning and quality of life.

Chapter 2 - Method

2.1. Design

This study used historical neuropsychological assessment data, clinical structural MRI scans and RS patient information from medical records, and was therefore classified as a case note review. In addition, the author, after gaining a honourary contract with Great Ormond Street Hospital for Children NHS Foundation Trust (GOSH), conducted 10 neuropsychological interviews and assessments with RS individuals as part of normal clinical practice between June 2014 and April 2015. As the assessments were completed as part of clinical practice, the first author received supervision and was required to give feedback and write up neuropsychological reports including recommendations for support required at school, at home and in the community.

2.2. Sample

2.2.1. Setting

All data in this study were collected from individuals with RS as part of normal clinical practice at GOSH, a tertiary hospital in London, United Kingdom between January 1991 and February 2015. The cognitive assessments and MRI scans were conducted as part of a multidisciplinary investigation for surgical treatment for intractable epilepsy or yearly reviews that monitor the progression of RS.

Once a diagnosis of RS is made, children and adolescents are seen every year at GOSH to check the progression of the disease. At this review neuropsychological assessment, MRI scan and ictal and interictal EEG examination are repeated. The results are passed to the paediatric neurologist to aid medical decision making and care. In the epilepsy surgery

program, RS individuals undergo extensive pre-surgical evaluation including: ictal and interictal EEG examination, MRI scan, functional MRI (fMRI) scan, clinical review, neuropsychological assessment and neuropsychiatric interview. The data from these investigations are gathered and discussed at the weekly epilepsy surgery multidisciplinary team meeting and decisions are made over surgical intervention (typically FH in RS).

2.2.2. Characteristics of whole sample

The main inclusion criteria in this study were that all children and adolescents had received a diagnosis of RS by a paediatric neurologist according to Bien and colleagues' (2005) formal diagnostic criteria (see Introduction Table 1-1.). In addition, they all had at least one neuropsychological assessment of intellectual functioning and were aged 4-18 years old. A total of 39 (16 male; 23 female) RS children and adolescents between the ages of 4-18 years were identified by searching medical notes and records at GOSH. Twenty-one children were diagnosed with RS affecting the right hemisphere of the brain and 18 the left hemisphere. The mean age at onset of epilepsy was 6.71 years (SD = 2.82; min = 2.54; max = 13.01) with 28 % of RS children experiencing their first seizure before the age of 5 years, 59 % from 5-10 years and 12 % after the age of 10 years (see Table 2-1). Initial handedness was 32 right-handed, five left-handed and two were ambidextrous. 28 RS individuals underwent FH. The average age at surgery was 11.67 years (S.D = 4.03; see Table 2-1). For demographic details of these groups see Table 2-1. 22 RS individuals underwent cognitive assessment post-operatively. However, note that not all of these participants had a pre-operative assessment.

Table 2-1: Demographic details of the whole RS sample and divided into those with the right and left hemispheres affected.

	Total RS Mean (S.D)	**Left RS Mean (S.D)**	**Right RS Mean (S.D)**
N	39	18	21
Male/Female	16/23	8/10	9/12
Age at onset of epilepsy	6.71 (2.82)	6.42 (2.46)	6.96 (3.14)
Surgery N	28	12	16
Age at Surgery	11.67 (4.03)	10.96 (3.86)	12.24 (3.86)

2.2.3. Characteristics at each cognitive assessment

Pre-surgery individuals with RS took part in one to six neuropsychological assessments. Post-op the number of assessments ranged from one to four. See Table 2-2 for the number and average age of those who underwent each assessment. The average age at the first assessment post-operatively was 13.33 years (S.D = 4.59; Table 2-2).

Table 2-2 : Demographic details of participants at each cognitive assessment.

	Pre-op Neuropsychological Assessments						**Post-op Neuropsychological Assessments**				
	1	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**
N	38	28	20	9	4	2	22	10	4	2	1
Average Age (S.D)	9.3 (3.01)	10.93 (2.9)	12.73 (2.89)	13.48 (3.08)	15.19 (1.62)	12.15 (8.95)	13.33 (4.6)	13.10 (3.7)	11.79 (2.95)	12.8 (1.24)	13.51

2.2.4. Characteristics of groups created for statistical analysis

To allow statistical analyses to investigate the cognitive trajectory of RS individuals at multiple time points before and after surgery two groups were created from our larger sample. The first group allowed the investigation of the trajectory of RS individuals pre-surgery and consisted of RS individuals who had at least two assessments prior to surgery (pre-surgery trajectory group): (1) Assessment 1 (AS1; i.e., the first assessment undertaken by the RS individual before surgery) and (2) Assessment 2 (AS2; i.e., the most recent assessment undertaken by this individual before surgery). The second group, which allowed the trajectory before and after surgery be investigated (pre- to post-op group), compared the last cognitive assessment prior to surgery (pre-op) to the first assessment post-operatively (post-op; Figure 2-1).

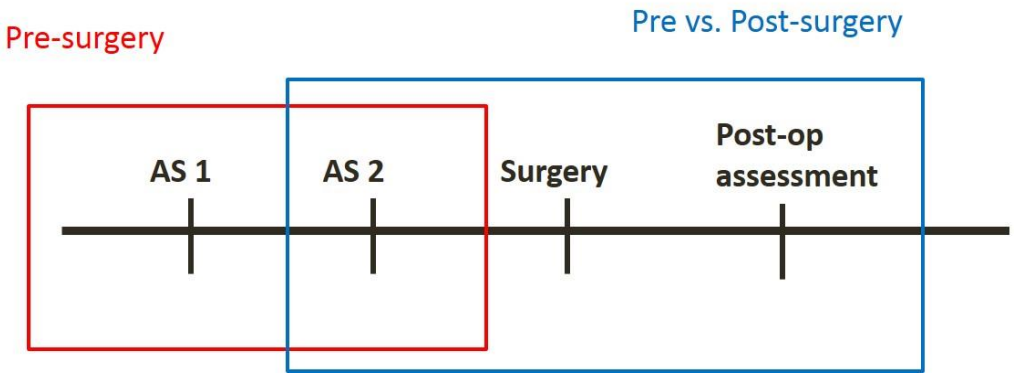

Figure 2-1: Schematic representation of the groups created to investigate the pre-surgery trajectory and pre- to post-op trajectory.

All individuals in the two groups exploring the pre-surgery trajectory and the pre- and post-op trajectory were taken from the larger group described above. As all data included were collected for clinical purposes, neuropsychological tests carried out in each assessment were based on clinical need and judgment. Consequently, cognitive scores available for each RS individual at each assessment varied greatly. The number of individuals who undertook each psychometric test of IQ, academic attainments, memory and language in each group is represented in Table 2-3. This shows that for the pre-surgery trajectory group the number who completed memory and language assessments was low. Indeed, the only substantial group of RS individuals to have language assessment were 6 left RS individuals who had at least two assessments pre-surgery (Table 2-3). For the pre- to post-op group the number of psychometric assessments fell again. Table 2-3 shows that few left RS individuals had spelling assessments. In addition, no individuals had language assessment pre- and post-op.

*Table 2-3: Table with the number of RS individuals in the pre-surgery trajectory group and the pre- to post-op trajectory group at each psychometric test; VCI= Verbal Comprehension Index, PRI = Perceptual Reasoning Index, WMI = Working Memory Index, PSI = Processing Speed Index, NO = Numerical Operations; * = Verbal Immediate Memory, Sp = Spelling, R = Reading.*

	IQ		**Academic Attainment**		**Memory**		**Language**	
Trajectory	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**
Pre-surgery	VCI/PRI=14 WMI/PSI= 12	VCI/PRI=10 WMI/PSI=9	12	12	6	4	0	6
Pre- to post-op	VCI/PRI=12 WMI/PSI= 6	VCI/PRI=9 WMI/PSI=4	R=7 Sp=6 NO=7	R=4 Sp=1 NO=4	5*	2	0	0

Medical variables of seizure frequency and anti-epileptic drugs (AEDs) prescribed at each assessment were gathered from parental report at the clinical interview or from medical records at each assessment for all individuals in the pre-surgery trajectory group and the pre- to post-op group. Estimates of seizure frequency were categorized as: monthly, weekly, daily or constantly and the number of seizures from the last previous assessment was calculated. The number of AEDs the RS individual was taking at each assessment was also recorded (see Table 2-4). Whilst the number of AEDs is typically used to measure the impact of AEDs on cognition it is possible that this is also an indirect measure seizure severity as more AEDs are given to those with more severe seizure disorders. It is worth noting, however, that dosage

will also play an important role in seizure management and so number of AEDs does not necessarily increase in direct proportion to seizure severity.

Table 2-4: Seizure frequency and total AEDs for the pre-surgery group and pre to post-op group.

	Average number of seizures since last assessment		**Current average AEDs**	
	Left	**Right**	**Left**	**Right**
Pre-surgery group	590	1049	2.7	3.44
Pre to post-op group	609	441	1.44	1.33

2.2.5. Characteristics of MRI participants

Another aim of this study was to investigate the relationship between grey and white matter and the cognitive change in RS individuals. 18 participants were identified as having had at least two MRI scans collected for clinical purposes before neurosurgery was undertaken. Nine of these had RS affecting the left hemisphere and nine had RS affecting the right. All of these participants were from the larger group as described above.

2.2.6. Ethical approval

All data including MRI and neuropsychological assessment were collected through normal clinical practice. NRES enquiries classified this study as a service evaluation (Appendix 1) and stated that NHS ethics was not required. The study was then registered with the GOSH audit

office and approved as a clinical evaluation (Appendix 2). The GOSH R & D office was contacted and they confirmed that this study did not required registration with them (Appendix 3). Finally, Royal Holloway Research Ethics was sought and received on the 5th of June 2014 (Appendix 4).

2.2.7. Service user involvement

Service user involvement was an important aspect of the study. During the clinical interview with RS individuals and their parents or guardians, their views and experiences of neuropsychological testing were sought. This consultation led to a number of individualized but generalizable amendments to neuropsychological testing sessions: (1) the need for more frequent rest breaks, (2) ensuring that hemiplegia and hemianopia were taken into account and (3) making testing fun! Short breaks were incorporated, rewards and play was utilized when appropriate, care was taken not to place items in the blind field of RS individuals and modifications were provided for items that require physical manipulation when an RS individual had hemiplegia (see section 2.3.1 below).

Clinical interviews with families affected by RS also revealed that there was often little understanding within schools about the nature or severity of RS. Families felt this was due to a lack of information generally available and poor communication within schools when children transitioned years or when they moved schools. RS adolescents also talked about a general lack of accessible information about RS available for them. This lead to issues around explaining to friends and family what was happening, with a negative impact on their adjustment and emotional health.

These conversations with service users lead me to write two guides: “Rasmussen syndrome for teenagers” (Appendix 4) and “Rasmussen syndrome for schools” (Appendix 5). The former guide was written to explain the brain, RS’s effects on it, common symptoms and

treatment options. This guide also focused on the emotional impact of the syndrome and where to get help. The guide for schools imparted similar information but focused on the cognitive and learning changes that those with RS may experience. It also discussed the physical, medical and emotional supports that RS children may require at school. Both these guides were given to an adolescent service user with RS, who made comments on them and changes were incorporated. As they both described medical symptoms and medication the guides will be checked over by a Consultant Paediatric Neurologist who specializes in RS for comments and amendments before they are widely disseminated. The aim is for these guides is for them to be given to RS individuals and their families to help them understand the disease in their own time away from the medical clinic. They will also be included in neuropsychological reports in the future to be given to schools that RS individuals attend.

2.3. **Measures**

2.3.1. Intellectual functioning

Intellectual functioning of RS individuals was estimated using the age appropriate version of the Wechsler Intelligence Scales. Four versions of the Wechsler Intelligence Scales allow assessment of different age groups: (1) Wechsler Preschool and Primary Scale of Intelligence (WPPSI^{UK}; Wechsler, 2003a) for children aged 2.6 years to 7.3 years, Wechsler intelligence Scale for Children (WISC^{UK}, Wechsler, 2003b) for those from 6 years-16 years, Wechsler Adult Intelligence Scale (WAIS^{UK}, Wechsler, 2008) for adults over 16 years-90.11 years and (4) Wechsler Abbreviated Scale of Intelligence (WASI^{UK}, Wechsler, 1999) for those aged between 6 years and 89:11 years.

Since its first publication (Wechsler, 1939) a number of editions of the Wechsler Intelligence Scales have been published. As a proportion of the data in this study were historical a number of different editions of the Wechsler intelligence tests were used. The

versions of the Wechsler intelligence tests used and the year of publication across all assessments can be seen in Table 2-5 below.

Table 2-5: The different Wechsler intelligence tests (UK edition) included in this study.

WPPSI-R^{UK} *(1989)*	**WPPSI-III^{UK}** *(2003)*	**WISC-R^{UK}** *(1974)*	**WISC-III^{UK}** *(1991)*	**WISC-IV^{UK}** *(2004)*	**WASI^{UK}** *(1999)*	**WAIS-III^{UK}** *(1997)*	**WAIS-IV^{UK}** *(2008)*
8	3	5	51	56	3	4	1

All Wechsler Intelligence Scales include a number of core subtests that give rise to composite standard scores of intellectual ability: Full Scale Intellectual Quotient (FSIQ) which measures general intellectual ability, Verbal Comprehension Index (VCI) or Verbal IQ (VIQ) that measures verbal intelligence, and Perceptual Reasoning Index (PRI) or Performance IQ (PIQ) that estimates non-verbal or perceptual intelligence. The WISC^{UK} and WAIS^{UK}, but not the WPPSI^{UK} and WASI^{UK}, also include the Working Memory Index (WMI) and Processing Speed Index (PSI) that measure the ability to hold information in mind over a few seconds and rate of test taking respectively. Each core subtest must be administered to allow successful calculation of the composite scores. However, one supplementary subtest per composite index can be administered if core subtests yield incomplete or inconsistent results. For details of the subtests involved in the Wechsler Intelligence Scales included in this study and which subtests comprise each composite index please see Table 2-6 below.

Table 2-6 : The subtests included in each Wechsler intelligence test and the cognitive abilities expert consensus agrees they measure (S = Supplementary, C = Core).

Subtest	Cognitive ability estimated	WPPSI-R^{UK}	WPPSI-III^{UK}	WISC-R^{UK}	WISC-III^{UK}	WISC-IV^{UK}	WASI^{UK}	WAIS-III^{UK}	WAIS-IV^{UK}
VCI/VIQ									
Similarities	Language development	S	S	C	C	C	C	C	C
Vocabulary	Lexical knowledge	C	C	C	C	C	C	C	C
Comprehension	General information	S	S	C	C	C	-	S	S
Word Reasoning	Lexical knowledge	-	C		-	S	-	-	-
Information	General information	C	C	C	C	S	-	C	C
Picture Naming	Association of visual stimuli with language	-	S	-	-	-	-	-	-
Receptive Vocabulary	Language development	-	S	-	-	-	-	-	-
Sentences	Verbal memory	S	-	-	-	-	-	-	-
PRI/PIQ									
Picture Completion	General information	S	S	C	C	S	-	C	S
Picture Arrangement	General information	-	-	-	C	-	-	S	-
Block Design	Spatial relations	C	C	C	C	C	C	C	C

Object Assembly	Spatial relations	S	S	C	C	-	-	S	-
Matrix Reasoning	Induction and general sequential reasoning	-	C	-	-	C	C	C	C
Picture Concepts	Induction	-	C	-	-	C	-	-	-
Visual Puzzles	Spatial reasoning	-	-	-	-	-	-	-	C
WMI									
Digit Span	Working memory	-	-	-	C	C	-	C	C
Letter-Number Sequencing	Working memory	-	-	-	-	C	-	S	S
Arithmetic	Mathematic achievement	-	-	C	C	S	-	C	C
Mazes	Spatial reasoning	S	-	-	S	-	-	-	-
Geometric Design	Visuospatial skill	C	-	-	-	-	-	-	-
PSI									
Coding	Rate of test taking	-	-	C	C	C	-	C	C
Symbol Search	Perceptual speed	-	-	-	C	C	-	C	C
Cancellation	Perceptual speed	-	-	-	-	S	-	-	S
Animal Pegs	Rate of test taking	S	-	-	-	-	-	-	-

Due to the high numbers of WISC-IV^{UK} and WISC-III^{UK} assessments administered in this study (see Table 2-5), whenever possible composite index scores (i.e. VCI, PRI, WMI and PSI)

were calculated and used in analyses. However, when this was not possible because the WPPSI^{UK} or WASI^{UK} were administered, VIQ and PIQ were used in analyses instead. This was necessary as the VIQ and PIQ were eliminated from the WISC-IV^{UK} and so the same composite scores do not exist across all Wechsler intelligence tests. However, it should be noted that factor analysis and expert ratings suggest that the subtests which make up the VCI/VIQ and PIQ/PRI measure the same intelligence constructs (Wechsler, 1999b, 2003a, 2003b). In this study the FSIQ was not used as many individuals had significant discrepancies between their VCI/VIQ and PRI/PIQ scores, invalidating the FSIQ.

2.3.2. Academic attainments

In this study academic achievement was measured primarily by the Wechsler Individual Achievement Test UK 2nd Edition (WIAT-II^{UK}; Wechsler, 2009). This test consists of 16 subtests that measure reading, mathematic ability, written language and oral language in those aged 4-85 years. Only three subtests of this test—Spelling, single Word Reading and Numerical Operations—were utilized because these are the subtests administered by the Clinical Neuropsychology team at GOSH as part of routine clinical practice (Table 2-7).

Those assessed before 2005 had their spelling and word reading assessed using the Wechsler Objective Reading Dimensions (WORD, Rust et al., 1993) and their numerical operations using the Wechsler Objective Numerical Dimensions (WOND, Rust et al., 1993b). In this study there were 41 WIAT-II^{UK}s administered and 13 WORD/WONDs. All raw scores on the WIAT-II^{UK}, WORD or WOND were converted into standard scores to control for age and sex of participant. These were scored as per section 2.4.5.

Table 2-7: The subtests used in this study from the WIAT-II^{UK} (Wechsler, 2009) and WOND/WORD (Rust et al., 1993a, 1993b).

Subtests	**Abilities measured**
Word Reading	Reading single words
Spelling	Writing single dictated words
Numerical Operations	Performing operations of addition, subtraction, multiplication and division

2.3.3. Memory

A proportion of RS individuals participating had their memory assessed during neuropsychological evaluation (see Table 2-3). Declarative long-term memory (LTM) was assessed using the Children's Memory Scale (CMS; (Cohen, 1997) for those aged between 5-16 years, Child Auditory Verbal Learning Test- 2nd Edition (CAVLT-2; (Taley, 1992) for children and adolescents from 6:6 years to 17:11 years, and the Wechsler Memory Scale- 3rd edition (WMS-III; Wechsler, 1999b) for those over 16 years.

The CMS is made up of 14 subtests designed to assess learning and memory in children and adolescents. Subtests give rise to composite scores of Verbal Immediate, Verbal Delayed, Visual Immediate and Visual Delayed memory, which were used in this study. See Table 2-8 for the subtests that make up each memory composite involved in this study, and the abilities they measure. The CMS also measures attention and concentration, learning, and delayed recognition; however, these are uncommonly administered at GOSH and so were not included here.

Table 2-8: The subtests used in this study from the Children's Memory Scale (Cohen, 1997) and supposed LTM abilities measured. Note that all subtests have an immediate and delayed memory component.

CMS subtest	Abilities measured
Verbal memory scale	
Stories	Encoding and recall of verbally presented information
Word Pairs	Encoding and recall of verbally presented information
Visual memory scale	
Dot Locations	Encoding and recall of spatial locations
Faces	Encoding and recognition of faces

The WMS-III measures LTM and learning in adults using 11 subtests (Wechsler, 1999a). It follows a similar format to the CMS and gives rise to indices of Immediate and Delayed Visual and Verbal Memory (see Table 2-9 for a description of the subtests). Additional indices not included in this study but measured by the WMS-III are the General Memory, Immediate Memory, Auditory Recognition, Delayed Memory and Working Memory. Both the CMS and WMS-III are scored as per section 2.4.5.

Table 2-9: The subtests used in this study from the WMS-III (Wechsler, 1999a) *and supposed LTM abilities measured. Note that all subtests have an immediate and delayed memory component.*

WMS subtest	Abilities measured
Verbal memory	
Logical Memory	Encoding and recall of verbally presented information
Verbal Paired Associates	Encoding and recall of verbally presented information
Visual memory	
Faces Recognition	Encoding and recognition of faces
Family Pictures	Encoding and recall of scenes

Finally, the Child Auditory Verbal Learning Test- 2nd edition (CAVLT; Taley, 1992) is a verbal memory test for children and adolescents. This test gives rise to estimates of immediate memory span, level of learning, an interference trial, immediate and delayed recall, recognition accuracy and total intrusions. In this study 39 CMS, 9 CAVLT and 3 WMS-III were included. So that the composites were comparable, immediate and delayed recall from the CAVLT were used in analysis as a measure of immediate and delayed verbal memory.

2.3.4. Language

Language was assessed in a proportion of our sample using the Clinical Evaluation of Language Fundamentals UK 4th Edition (CELF-IV^{UK}; Semel et al., 2003). This test is for children aged 5-16 years and is made up of 18 subtests that give rise to composite indices of Core Language,

Receptive Language, Expressive Language, Language Content and Language Memory. In this study only Receptive and Expressive Language indices were included. For full details of the subtests that make up these composite indices see Table 2-10. Note that different age groups in the CELF-IV^{UK} are administered different subtests as represented in Table 2-10. CELF-IV^{UK} subtests and composite indices are standardized as described in section 2.4.5. (Semel et al., 2003).

*Table 2-10: The subtests used in this study from the CELF-IV^{UK} and cognitive ability estimated (*5-8 years, ^9-12, ‘13-16 years).*

CELF-IV^{UK} subtest	
Receptive Language	**Abilities measured**
Concepts and Following Directions^*	Interpreting spoken directions
*Word Classes *^’*	Understanding relationships between words
*Sentence Structure **	Interpret spoken sentences and select pictures that illustrate meaning of sentence
Semantic Relationships ‘	Interpretation of sentences and semantic relationships within them
Understanding Spoken paragraphs ‘	Attend to, understand and answer questions about a narrative
Expressive Language	
*Word Structure **	Applying word structure rules and morphology
*Recalling Sentences *^’*	Learn and repeat spoken sentences
Formulated Sentences^’*	Formulating complete, semantically correct sentences
Word Classes Expressive ^’	Understanding relationships between words

2.3.5. Scoring neuropsychological assessments

All psychometric assessments in this study were scored and standardized in the following way unless specified. To calculate composite standard scores the raw subtest scores were converted into standardised scores to control for the individual's age. Subtest scaled scores range from 1-19 and have a mean of 10 and a standard deviation of 3. Scaled scores of 7-13 are considered to fall in the average range. Certain subtests' scaled scores are added together to produce norm-referenced standard composite scores (for the Wechsler Intelligence tests see Table 2-6 for the core subtests added together for each composite score). The composite scaled scores range from 40-160 with 100 as the mean and a standard deviation of 15. The Wechsler manual states that an Index (composite) standard score of <69 is classified as "extremely low", 70-79 as "borderline", 80-89 as "low average", 90-109 as "average", 110-119 as "high average", 120-129 as "superior" and finally >130 as "very superior" (Wechsler, 2003b).

2.3.6. Neuroimaging data acquisition and pre-processing

Only neuroimaging scans that allowed measurement of volumetric change of grey and white matter were included in this study. These included volumetric T1 scans, stealth scans (i.e., scans for planning surgery) and foreign volumetric T1 scans acquired at other hospitals in the UK. 18 pairs of structural scans were identified for our RS participants as mentioned above. For the first scan of each pair: seven scans were volume T1- weighted scans acquired at GOSH, seven were stealth scans acquired at GOSH and the remaining four were foreign T1 scans uploaded into medical records but acquired at different hospitals. At the second time point: nine scans were volumetric T1 scans, five were stealth scans and four scans were foreign T1 scans from other hospitals.

All GOSH T1 and stealth MRI scans were acquired on a 1.5-Tesla Siemens Vision Systems Scanner (Siemens, Erlangen, Germany). Acquisition for the volume T1-weighted

images and stealth scans was a 3-dimensional magnetization-prepared rapid gradient echo sequence (repetition time = 10 msec; echo time = 4 msec; flip angle = 123 degrees; voxel size =1 x 1 1 mm). The acquisition data of the foreign scans is unknown; however, much of it was of higher resolution than the scans collected at GOSH and was collected on a 3-Tesla scanner.

2.4. **Procedure**

2.4.1. Neuropsychological Assessment

This study acquired neuropsychological assessment results from two different sources: (1) historical neuropsychological data extracted from medical records and, (2) cognitive assessment of 10 RS individuals carried out by the author as part of routine clinical practice. All assessments consisted of a clinical interview conducted by a Clinical Neuropsychologist or the supervised Trainee Clinical Psychologist in which concerns around cognitive functioning and other relevant school, medical, behavioural and emotional information was sought.

After the clinical interview was completed the RS individual's cognitive ability was assessed. An Assistant Clinical Neuropsychologist under supervision or Clinical Neuropsychologist collected the historical data (i.e., collected prior to June 2014) and the Trainee Clinical Psychologist assessed patients from June 2014 onwards. Unless health or behavioural challenges disrupted testing a measure of intellectual functioning and academic attainments were always sought. A number of factors determined the protocol for the assessment of additional cognitive functions such as memory, language and visuospatial skills. Site of pathology played an important part in measure selection; those with left hemisphere RS were more likely to have language assessment whilst those with RS affecting the right hemisphere had visuospatial assessments. This is due to the left hemisphere's involvement in language functioning (Geschwind, 1970) and the right hemisphere's involvement in visuospatial skills. The child's specific needs and areas of cognitive weakness highlighted from

the clinical interview also informed testing and reported areas of weakness or concern in particular would be assessed. As mentioned above, when an RS individual had hemiplegia subtest substitutions were carried out to ensure, as much as possible, difficulty manipulating items did not negatively affect their performance. Specifically, in the Wechsler Intelligence tests the Picture Completion subtest was substituted for Block Design and the processing speed subtests were only conducted if the individual was able to write.

Following this a feedback session was conducted with families in person or over the phone to highlight cognitive strengths, discuss areas of weakness and make recommendations for support. This was followed up by a detailed neuropsychological report including test results and recommendations. The Trainee Clinical Psychologist prepared all neuropsychological reports for the 10 RS individuals involved in this study and these were reviewed by a Consultant Neuropsychologist.

2.4.2. MRI Neuroimaging

RS individuals undergo MRI neuroimaging during surgical work up or to assess the progression of the syndrome. To find clinically-acquired MRI structural scans, the hospital radiological records were searched for all 39 RS individuals in this study. All structural scans uploaded to the GOSH neuroimaging database or on hard CD copies were anonymized and all identifiable information was removed and moved to an analysis computer via an encrypted external hard drive. This drive was purchased on the advice of the Clinical Systems Team Manager at GOSH. All MRIs were converted from DICOM to analysable NIFTI format using SPM8 (Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk). As our research questions pertained to grey and white matter change prior to surgery, RS individuals who had had at least 2 scans prior to surgery were identified. This resulted in 18 participants with two pre-surgery scans. The mean time from onset to scan 1 and scan 2 are described in Table 2-11.

Table 2-11: Time from onset of epilepsy to scan 1 and scan 2.

	Time to scan 1 (Years)		Time to scan 2 (Years)	
	Range	**Mean (SD)**	**Range**	**Mean (SD)**
Total	-0.4 – 10.07	3.83 (3.13)	1.8 - 12.98	6.64 (3.47)

All processing and analyses took place using the VBM toolbox (developed by C. Gaser, University Jena, Germany, dbm.neuro.uni-jena.de/vbm/) for SPM8 (Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk). Before pre-processing took place a number of additional steps were conducted to correct for the differing acquisition of scans in this study. Each pair of scans was co-registered to one another so they were aligned in one native space and then they were re-sliced to a standard voxel size (1 x 1 x 1 mm).

Next pre-processing for longitudinal data was conducted. Pre-processing of VBM longitudinal data differs from cross-sectional data analysis and each participant's scans must be registered to a mean image created for each subject (http://dbm.neuro.uni-jena.de/vbm8/VBM8-Manual.pdf). The steps for longitudinal VBM pre-processing are as follows: (1) realignment of images, (2) calculation of the mean of realigned image, (3) bias correction of inhomogeneities in realigned images using the created mean image, (4) segmentation of grey matter, white matter and cerebrospinal fluid of the mean image and estimation of spatial normalization parameters, (5) realignment of segmented images using normalization parameters and (6) deformations applied so that normalized segmentations are finally realigned to one another (http://dbm.neuro.uni-jena.de/vbm8/VBM8-Manual.pdf). Following these pre-processing steps grey and white segments are available in standardized MNI space for analysis.

Finally, to increase statistical power for the VBM analyses, all right RS hemisphere

individuals' brains were flipped around the z axis using the flipdim command of the Imcalc tool in SPM8. This meant all brains now were in the same space, with the affected hemisphere on the left and the unaffected hemisphere on the right for all 18 individuals.

2.5. **Analysis**

2.5.1. Cognitive trajectory

The dependent variables to investigate cognitive trajectory of RS individuals were cognitive scores from neuropsychological assessment. These included: (1) Wechsler intelligence test estimates of VCI/VIQ, PRI/PIQ, WMI, PSI, (2) academic attainment estimates of word reading, spelling and numerical operations, (3) verbal and visual memory at immediate and delayed conditions as measured by the CMS/WMS or the verbal immediate and delayed memory from the CAVLT-2 and (4) expressive and receptive language scores as estimated by the CELF-IV^{UK}. Independent variables were: side of the affected hemisphere, FH conducted, seizure frequency and number of antiepileptic medications.

To start a number of descriptive analyses were conducted to examine the whole sample's average cognitive trajectory at 2-yearly intervals in those with assessments prior to surgery, and those with assessments before and after surgery. Then, as described above, two groups were created of those with two assessments pre-surgically, and those with an assessment pre- and post-op. Repeated measures ANOVAs were used to examine the trajectories of intellectual functioning and academic attainments. Any significant main effects or interactions were then interrogated using paired sample t-tests, independent t-tests, one-way ANOVAs or Wilcoxon t-tests, or Mann Whitney U tests, as appropriate. Due to small sample sizes, non-parametric analyses were used to investigate differences between groups for memory and language assessments in those with left and right RS. SPSS version 22 was used for the statistical analyses and results were taken to be significant if $p < 0.05$.

Pulsifer et al. (2004) used repeated measures ANOVAs to investigate differences in assessment pre- and post-FH, and found a significant reduction in expressive language scores post-surgery in comparison to pre-surgery in RS individuals with both left and right hemisphere disease. It should be noted that only a proportion of RS participants had undergone expressive language testing and the total N=20. No effect size is quoted in Pulsifer and colleagues (2004). However, it can be computed from the means and standard deviations provided that Cohen's d is between a small and medium effect size (d = 0.341; F=1.11). If a value between a small and medium effect size for ANOVA is selected (F effect size = 0.23) then the gpower program (http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/) indicates the number of participants needed for a significant effect to be found is 42.

In this study, the sample sizes for our pre-surgery trajectory group (N=24) and pre and post-op group (N=20) are similar to the sample size in Pulsifer et al., (2004) study but fall short of the sample size suggested by the above power analysis. Subsequently, parametric analyses should be considered with caution.

Following these statistical and descriptive analyses, changes in VCI and PRI scores from: (1) AS1 and AS2 (AS2 -AS1) and (2) pre- to post-op assessment (post-op assessment– pre-op assessment) were modelled individually as a function of suitable predictors using multivariate linear regression models. The factors entered in the regression model for cognitive change were planned to be: age at onset, seizure frequency, duration of epilepsy and antiepileptic medications. Whilst no previous study has looked at individuals with RS using multiple regression analysis, a similar investigation by Skirrow and colleagues (2011) interrogating the long-term intellectual outcomes of temporal lobe surgery in children with intractable epilepsy looked at similar medical factors associated with IQ change (Skirrow et al., 2011). Their results suggested current use of antiepileptic medication was a negative indicator of post-operative IQ with a large effect size (f2= 0.35). Extrapolating from this to investigate 5

factors in the current study 41 RS individuals would be required.

In this study the number of participants with two pre-surgery assessments (N=24) and pre-and post-op assessments (N=20) fell short of allowing a multiple regression analysis with four independent factors. Due to this an explorative multiple regression was conducted in which only two independent variables, seizure frequency and total number of AEDs were included to see the effect on the change in VCI and PRI. These two independent variables were selected as evidence suggests they have the greatest impact on cognitive ability (see section 1.2.2 and 1.2.3). Note that for two predictors ideally our sample size should have been 31.

2.5.2. VBM analyses

VBM was implemented to explore the changes in grey and white matter over the two scans prior to surgery in a subset of our participants. A paired t-test for the grey matter and white matter were separately conducted to explore the possible changes between scans 1 and 2. Images were threshold masked at 0.2 (i.e., any voxel intensities that fell below this threshold were then excluded from the analysis) and global normalisation was also conducted in which the whole brain volume (grey matter + white matter) for each participant at scan 1 was entered as a covariate of no interest in the GLM (i.e., an ANCOVA). This step ensures that overall differences in brain sizes across individuals were corrected for and do not affect our analyses.

For the grey and white matter two contrasts of interest were conducted: scan 1 greater than scan 2 ('scan 1-scan 2') and scan 2 greater than scan 1 ('scan 2-scan 1'). Since this is an explorative analysis a threshold of $p < 0.05$ uncorrected, cluster size ≥ 20 voxels was applied to identify regions of significant change in grey or white matter between scans 1 and 2.

2.5.3. Relationship between grey and white matter and cognition

MRIcron was used to create right and left regions of interest of the: whole hemispheres, frontal lobe, temporal lobe, parietal lobe and occipital lobe on a standard MNI brain template.

Using the “Easy Volume” toolbox in SPM these masks were then used to extract average grey and white matter volumes for each participant’s grey and white matter brains at scan 1 and scan 2. The changes in grey and white matter were then calculated ((scan 2 grey + white matter) – (scan 1 grey + white matter)).

For each participant in the MRI analyses the nearest cognitive assessment to each scan was found and the VCI and PRI score recorded. The change in the VCI and PRI scores from scan 1 to scan 2 was then calculated (nearest scan 2 assessment – nearest scan 1 assessment). The changes in VCI and PRI scores were then correlated with the changes in grey and white matter to determine if there was any relationship between cortical atrophy and cognitive deterioration.

Chapter 3 - Results

This study explored in detail the cognitive trajectory of RS individuals at time points before and after surgery. Pre-surgical trajectory of intellect, academic attainments, memory and language was explored. Next, cognitive performance was investigated pre- to post-op. Finally, the neuroimaging analyses and their relationship to these cognitive abilities will be considered. All groups of data met parametric assumptions unless stated in the text.

3.1. Cognitive trajectory pre-surgery

3.1.1. Intellect

3.1.1.1. Descriptive analyses

Cognitive ability was measured using the Wechsler intelligence tests, generating the following composite scores: Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI) and Processing Speed Index (PSI). So that the contribution of aetiology could be determined, the left and right RS individuals were grouped prior to surgery and their intelligence indices examined separately. To examine the performance trajectories over the time, the timing of each individual assessment in relation to the first seizure onset was calculated. Scores were then grouped together into 2-yearly categories (0-2 years post-onset, 2-4 years, 4-6 years and 6-8 years) and averaged as in Skirrow and colleagues (2011). This allowed the average IQ scores at two-yearly intervals in each group to be plotted (see Figure 3-1 and Figure 3-2).

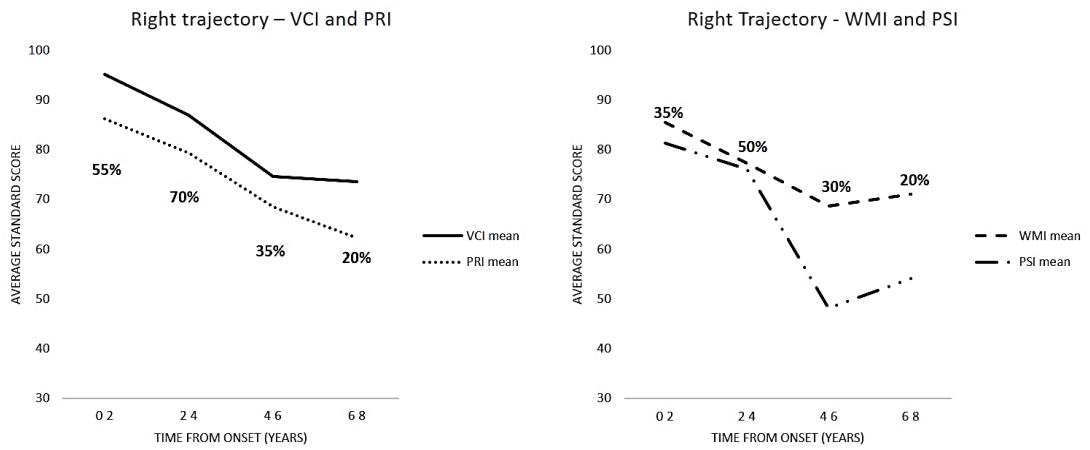

Figure 3-1: The right RS group's pre-surgery trajectory averaged every two years for their VCI, PRI, WMI and PSI scores. The proportion of the sample that contributed to each point is represented as a percentage. Note that if less than 15% of the sample contributed towards a point it was excluded.

For the right group Figure 3-1 reveals all IQ indices declined over time taking individuals from functioning in the low average-to-average range in the first two years after onset to the exceptionally low-to-borderline range (Figure 3-1). This suggests that after 6 years of RS disease process right individuals are functioning in the learning disabled range. A dissociable pattern in which the PRI score is weaker than VCI from the first 2 years post-onset and beyond is also observable. The WMI and PSI scores followed a similar declining trajectory until 4-6 years when there was steep drop in WMI performance, falling to the exceptionally low range, in comparison to the better-preserved PSI.

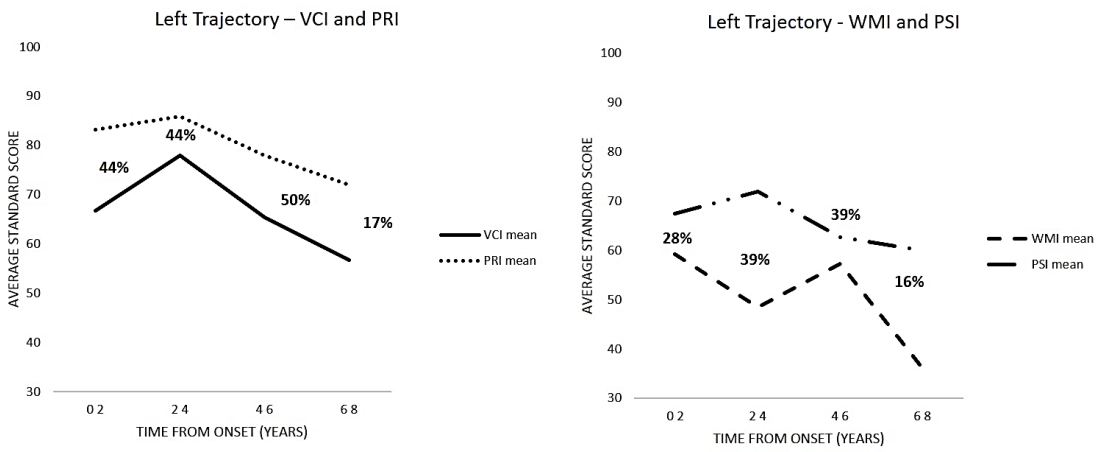

Figure 3-2: The left RS group's pre-surgery trajectory averaged every two years for their VCI, PRI, WMI and PSI scores. The proportion of the sample that contributed to each point is represented as a percentage. Note that if less than 15% of the sample contributed towards a point it was excluded.

For the left RS group, again, there was a pattern of decline in all IQ composite scores from 0-2 years to 6-8 years post-onset of seizures. It was noticeable however, that the left groups' VCI and WMI scores were already in the exceptionally low range at 0-2 years post-onset, in comparison to the PRI and PSI scores which were better preserved, and in the low average and low ranges, respectively. This pattern continued up to 6-8 years post-onset. The left group also experienced more variation in some trajectories; for example, the VCI improved at the second time point only to decline again.

3.1.1.2. Parametric analyses

The left and right group at AS1 and AS2 did not differ in terms of age at onset or time from onset to first or second assessment ($p > 0.05$). Right and left RS groups' VCI, PRI, WMI and PSI score distributions were individually investigated for skewedness and kurtosis. This revealed all were <2.58 ($p > 0.01$), suggestive of a normal distribution.

To investigate the effect of side and assessment (time) on VCI and PRI performance, a

repeated measures ANOVA was conducted. Right and left RS groups ('side') were compared on their VCI and PRI index scores ('index') at assessment 1 and 2 ('time'). The dependent variable was their VCI and PRI score at each pre-surgery assessment. A side (right vs left) x time x test repeated measures ANOVA showed a significant main effect of time ($F(1, 22) = 11.99$, $p = 0.002$) indicating a significant change in both left and right groups' VCI and PRI scores from AS1 to AS2 (Figure 3-3). The interaction of test and side was significant ($F(1, 22) = 7.21$, $p = 0.014$), suggesting that the right group's PRI scores are significantly lower than the left at both time points, and the left VCI scores are significantly lower than the right at both time points.

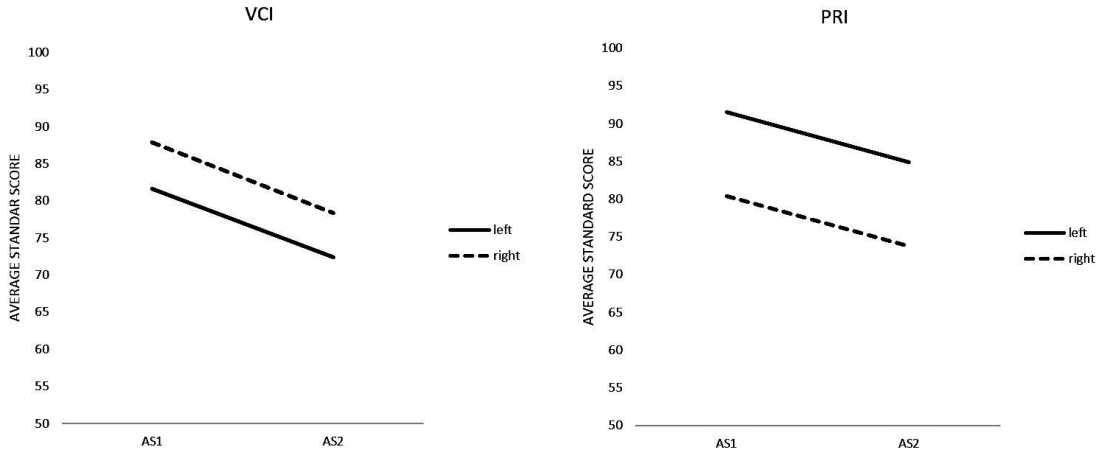

Figure 3-3: The VCI and PRI pre-surgery trajectory at AS1 and AS2 for the left and right RS groups.

There was no significant main effect of test indicating that right and left RS individuals do not differ significantly overall in their VCI and PRI scores ($F(1, 22) = 0.75$, $p= 0.39$). Furthermore, no interactions between the following were observed: time by side ($F(1, 22) = 0.001$, $p = 0.97$), time by test ($F(1, 22) = 1.11$, $p = 0.3$) and time by test by side ($F(1, 22) = 0.007$, $p = 0.93$).

Post-hoc analyses were conducted to explore the differences in VCI and PRI scores

between groups suggested by the above test by side interaction. Four independent t-tests were calculated in which the left and right groups' VCI and PRI scores were compared separately at AS1 and AS2. At AS1 there was no significant difference between the left and right groups' VCI performance ($t(22) = -1.15$, $p = 0.26$) and a trend towards a significant difference between their PRI scores ($t(22) = 1.76$, $p = 0.093$). For AS2 there was no significant difference between the left and right groups' VCI performance ($t(22) = -1.02$, $p = 0.32$) nor the PRI performance ($t(22) = 1.43$, $p = 0.17$). To investigate the significant main effect of time four paired t-tests within groups were conducted for the PRI and VCI scores. These suggested that both groups' VCI scores significantly declined over time (left: $t(9) = 2.78$, $p = 0.021$; right: $t(13) = 3.8$, $p = 0.002$), whereas PRI there was a trend for the right group and the left group failed to reach significance (right: $t(13) = 1.78$, $p = 0.099$; left: $t(9) = 1.32$, $p = 0.22$).

For the WMI and PSI scores the same repeated measures ANOVA revealed a significant main effect of time ($F(1, 19) = 17.27$, $p = 0.001$) indicating both the WMI and PSI scores decreased in the left and right RS group from AS1 to AS2. There was a trend towards a significant interaction between time and side ($F(1, 19) = 0.33$, $p = 0.057$), suggesting that performance in the groups differentially changes from AS1 to AS2. There were no other significant main effects or interactions found from this investigation (see Table 3-1, Figure 3-4).

Table 3-1: Non-significant main effects and interactions from the WMI and PSI repeated measures ANOVA.

Main effect	F value	Significance (p)
Test	1.19	0.29
Test x side	0.83	0.37
Test x time	0.17	0.69
Test x time x side	0.66	0.43

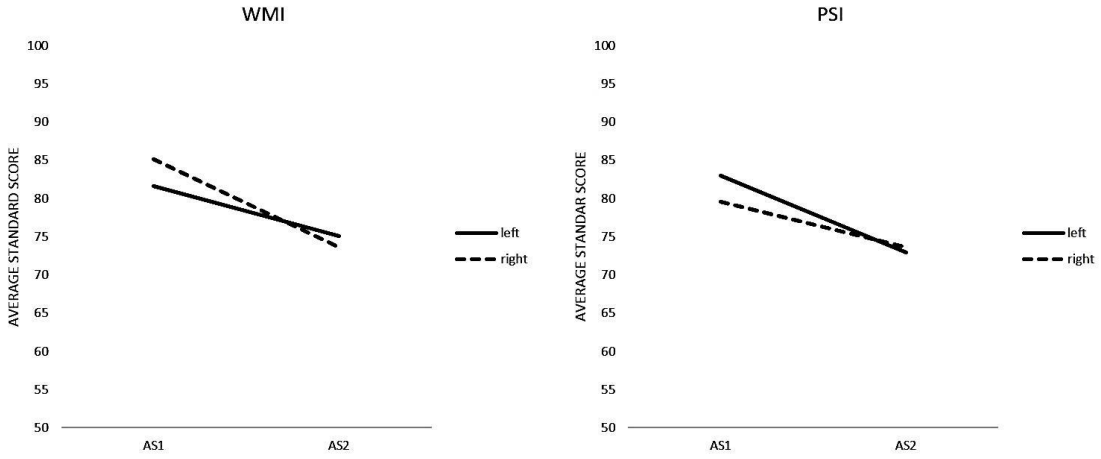

Figure 3-4: The WMI and PSI pre-surgery trajectory at AS1 and AS2 for the left and right RS groups.

To interrogate the main effect of time four post-hoc paired t-tests were conducted. These suggested that the within each group both WMI (left: t (8) = 2.5, p = 0.05; right: t (11) = 3.57, p =0.004) and PSI (left: t (8) = 2.85, p 0.02; right: t (11) = 2.23, p = 0.047) significantly declined to from AS1 to AS2.

3.1.2. Academic attainments

3.1.2.1. Descriptive analyses

For the academic attainment tests pre-surgery trajectories were plotted (Figure 3-5). This showed the right group was performing in the low average range by 0-2 year's post-onset of seizures and declined further into the borderline range by 4-6 years. Reading and spelling, on the other hand, remained relatively intact and declined from the average to the low average range by 4-6 years.

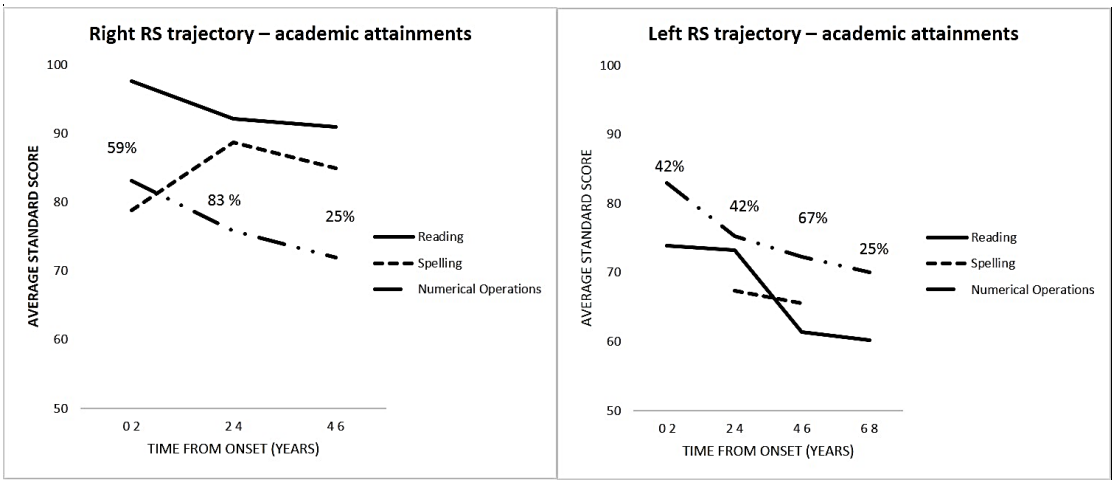

Figure 3-5: The right and left RS group's pre-surgery trajectory averaged every two years for their academic attainment scores. The proportion of the sample that contributed to each point is represented as a percentage. Note that if less than 15% of the sample contributed towards a point it was excluded.

The left RS group's academic attainment abilities were less well preserved and by 0-2 years after onset all scores were already in the boarderline or low average ranges (Figure 3-5). Although relative, the opposite pattern was observed in the left group to that in the right; numerical operations were comparably preserved relative to reading and spelling (which were markedly impaired), beginning in the low average range and declining to the borderline range 6 -8 years after seizure onset. Note, however, that there does not appear to be a difference in

the numerical operations performance between groups.

3.1.2.2. Parametric analyses

The left and right group at AS1 and AS2 for reading, spelling and numerical operations did not differ in terms of age at onset or time from onset to first or second assessment ($p > 0.05$). Spelling scores at AS1 did not fulfil parametric assumptions (kurtoisis = 3.39, $p < 0.001$), therefore spelling was not included in the following parametric analyses and will be explored using non-parametric analyses below.

The same repeated measures ANOVA as above was conducted for the reading and numerical operations scores. This showed a significant main effect of time ($F(1, 15) = 7.5$, $p = 0.015$) indicating that reading and numerical operation scores declined over time (Figure 3-6). In addition, there was a trend towards a test by side interaction ($F(1, 15) = 3.93$, $p = 0.066$). This hints that the left group's reading and numerical operations scores were significantly lower than the right at all pre-operative assessments apart from numerical operations at AS2 (Figure 3-6). No other main effects or interactions were significant (see Table 3-2).

Table 3-2: Non-significant main effects and interactions from the academic attainment repeated measures ANOVA.

Main effect	**F value**	**Significance (p)**
Test	2.82	0.11
Test x side	0.46	0.51
Test x time	0.67	0.43
Test x time x side	0.014	0.91

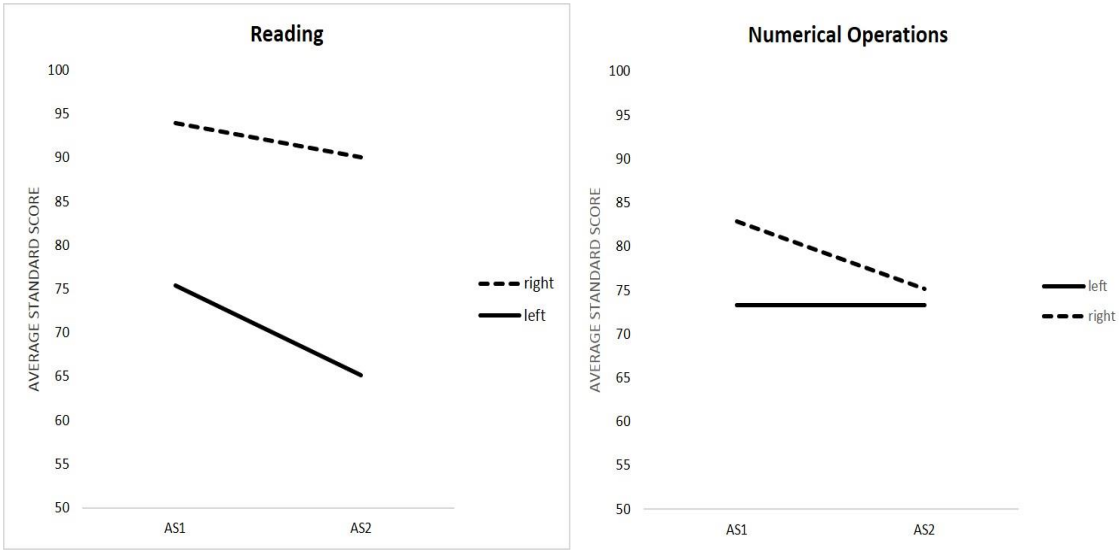

Figure 3-6: The reading and numerical operations pre-surgery trajectory at AS1 and AS2 for the left and right RS groups.

Post-hoc independent t-tests were conducted to investigate possible group differences at each assessment. These confirmed the left group had significantly lower reading scores at AS1 (t (18) = -2.35, p = 0.031) and AS2 (t (18) = -3.79, p =0.001) than the right group. For numerical operations there was a trend towards the left group having a lower numerical operations score than the right at AS1 (t (18) = -1.14, p = 0.17) but not at AS2 (t (18) = -0.26, p = 0.79).

To investigate the significant main effect of time four paired t-tests were conducted within groups and showed that for reading there was a significant decline from AS1 to AS2 in the left group (t(9) = 3.16, p = 0.012) and a trend towards a decline in the right (t (9) = 1.86, p = 0.096). However, there was no significant decline in numerical operations from AS1 to AS2 for either group (left: t (9) = 0.54, p = 0.61; right: t (9) = 1.54, p = 0.16).

3.1.2.3. Non-parametric analyses

For the spelling scores a Mann-Whitney U test was used to compare the groups' performance

at each assessment. At AS1 there was a trend towards a significant difference between the left and right groups' performance (p = 0.099), whereas at AS2 there was a significant difference between the groups' performances (p = 0.005). This suggests that whilst the left group's performance was poorer than the right group's at both assessments, this difference had increased by AS2 (Figure 3-7).

To investigate the change in spelling performance over time in the two groups a Wilcoxon Signed Rank test revealed there was no significant decline in each group's spelling performance from AS1 and AS2 (left p = 0.27; right p = 0.26).

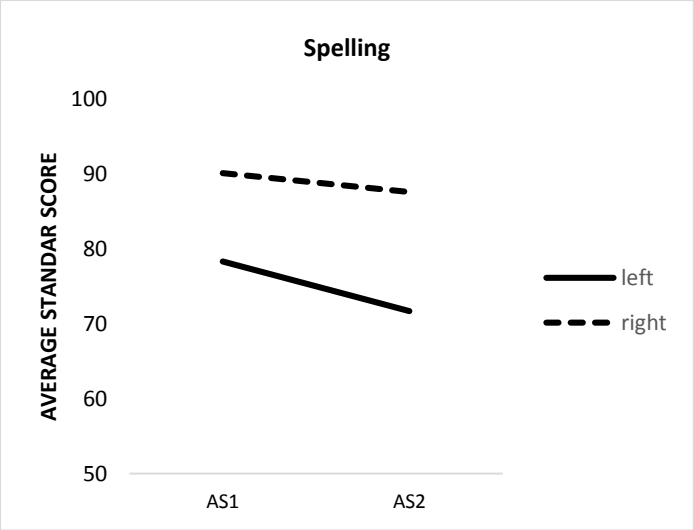

Figure 3-7: The spelling pre-surgery trajectory at AS1 and AS2 for the left and right RS groups.

3.1.3. Memory

Only a small group of the sample had completed two pre-surgery assessments of the CMS, WMS or CAVLT (see Methods). This meant that the average trajectory at two-yearly intervals could not be plotted as above. To gain an idea of the pattern of performance at AS1 and AS2 the groups' average scores were plotted (Figure 3-8). This graph suggests that in both groups verbal memory scores declined or remained the same from AS1 to AS2, whereas the visual memory indices improved from AS1 to AS2.

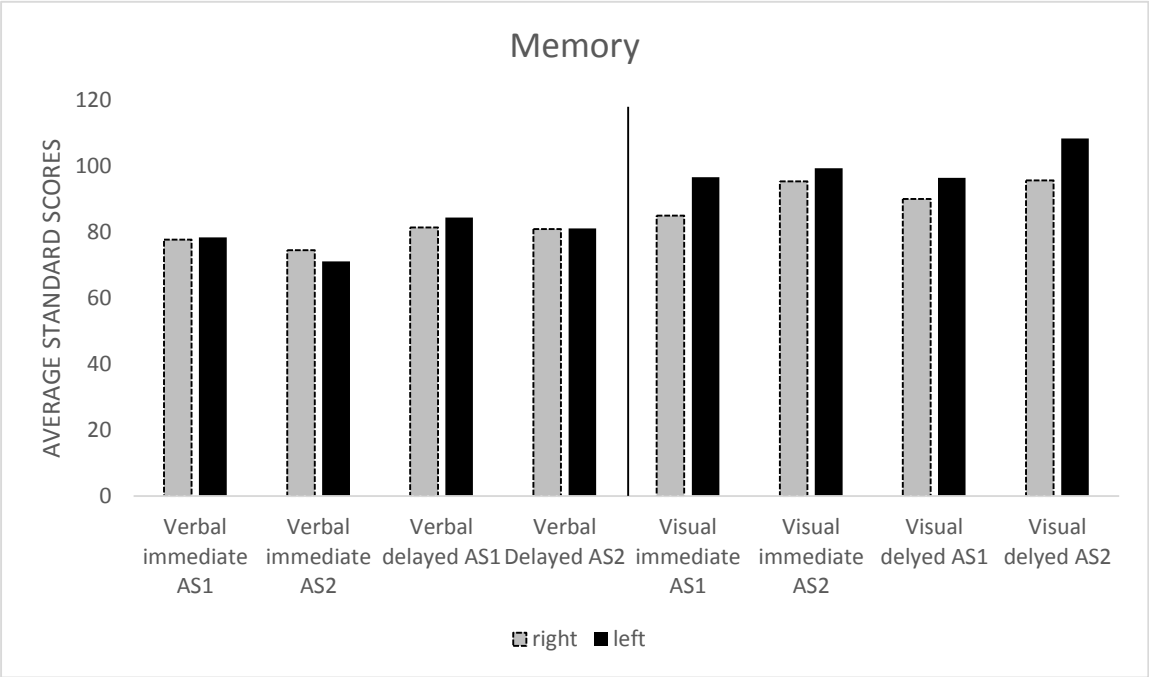

Figure 3-8: The memory pre-surgery trajectory at AS1 and AS2 for the left and right RS groups.

3.1.3.1. Non-parametric analyses

The right and lefts groups' memory estimates did not fulfil parametric assumptions (skewedness > 0.27) and so non-parametric analyses were conducted. To investigate any differences between groups, a number of independent samples Mann Whitney U tests were conducted at each assessment. These showed there were no significant differences between the left and right RS groups' performance on any of the memory estimates regardless of assessment time point (see Table 3-3 for significance levels).

Table 3-3: Significance levels from the Mann Whitney U test investigating differences between group performances.

	Verbal Immediate		**Verbal Delayed**		**Visual Immediate**		**Visual delayed**	
Contrast	*AS 1*	*AS2*	*AS1*	*AS2*	*AS1*	*AS2*	*AS1*	*AS2*
Right vs Left	1	0.66	0.76	1	0.43	1	0.79	0.19

To investigate changes in memory performance from AS1 to AS2 over time a series of Wilcoxon Signed Ranks tests were conducted within groups. These revealed the right group's visual delayed performance significantly increased between AS1 and AS2 ($p = 0.043$). Otherwise, there were no significant differences between any other memory estimates from AS1 to AS2 (see Table 3-4 for significance levels). Likewise, the left group showed no significant changes in their memory performance from AS1 to AS2 (see Table 3-4 for p values).

Table 3-4: Significance levels from the Wilcoxon Signed Ranks test investigating differences within groups from AS1 to AS2.

Side	Verbal Immediate AS1 vs AS2 (p value)	Verbal Delayed AS1 vs AS2 (p value)	Visual Immediate AS1 vs AS2 (p value)	Visual delayed AS1 vs AS2 (p value)
Right	0.786	0.752	0.249	0.043
Left	0.28	0.72	0.47	0.46

3.1.4. Language

The only substantial group of RS individuals to have two pre-surgery language assessment were 6 left RS individuals. Hence, only the average receptive and expressive language indices from the CELF-IV^{UK} were computed at AS1 and AS2 (see Figure 3-9). The language data from AS1 did not fulfil parametric assumptions (kurtois > 2.7) and therefore non-parametric explorative analyses were conducted. A Mann Whitney U test suggested expressive language scores at AS1 were significantly lower than receptive language scores ($p = 0.025$). However, there were no significant differences between the receptive and expressive language scores at AS2 ($p = 0.21$). From AS1 to AS2 a Wilcoxon Signed Ranks test showed no significant change occurred from AS1 to AS2 in the either the receptive ($p = 0.67$) or expressive language ($p = 0.48$) scores for this left RS group.

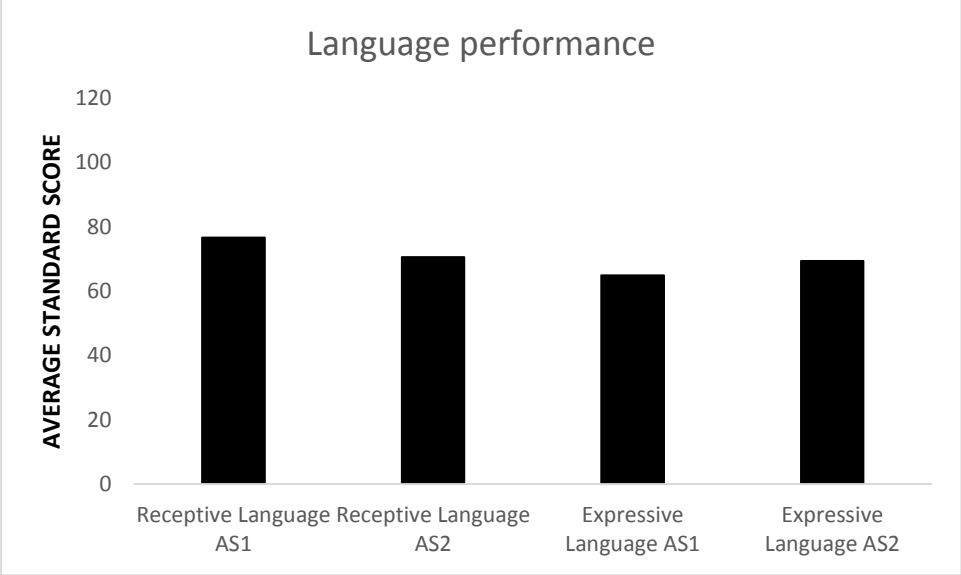

Figure 3-9: The language pre-surgery trajectory at AS1 and AS2 for the left RS group.

3.1.5. Multiple regression for medical variables

A standard multiple regression was carried out to look at the effect of two specific medical variables—AEDs and seizure frequency—on the change in the VCI and PRI scores from AS1 to AS2. The change in VCI or PRI was the dependent variable and the AEDs and seizure frequency were the independent variables. For the change in VCI these two variables did not account for a significant amount of variance (R^2 = 0.17, adjusted R^2 = 0.87; (F (2, 20) = 2.05, p = 0.15)). However, the partial regression coefficients showed the number of AEDs had a trend towards a significant unique contribution to the change in VCI from AS1 to AS2 (B = 0.007, Beta = 0.44, (t (20) = 1.9, p = 0.067)). Seizure frequency, on the other hand, was not independently associated with change in VCI (t (20) = 0.18, p = 0.86).

The same multiple regression was conducted for the change in PRI as the dependent variable. This showed that neither independent variable accounted for a significant amount of change in the PRI (R^2= 0.46, R^2adjusted = -0.049, F (2, 20) = 0.48, p = 0.62). Likewise, the partial regression coefficients showed that neither medical variable had a significant unique contribution to the change in PRI (AED = t (20) = 0.52, p = 0.61; Seizure frequency = t (20) =

0.71, p = 0.48).

3.2. **Cognitive trajectory pre- to post-op**

3.2.1. Intellect

3.2.1.1. Descriptive analyses

Another major aim was to investigate the cognitive trajectory of RS individuals pre- and post-FH. Again the average IQ scores were calculated for the left and right groups at 2-yearly intervals in those who had cognitive assessment before and after FH (Figure 3-10 and Figure 3-11). In these average trajectories 0 denotes surgery. These figures show that in both groups all IQ indices decline from the final pre-operative assessment to the first post-operative assessment. Post-operatively, the same differential pattern of VCI and PRI ability was observed as in the pre-surgical trajectory, with the left group having a poorer VCI in comparison to their PRI and vice versa. This pattern is seen to be maintained up to four years post-op. Both left and right groups' WMI and PSI scores appear to decline at similar rates pre-op to post-op. This trajectory should also be viewed with some caution due to low numbers of individuals who completed the WMI and PSI (see Table 2-3).

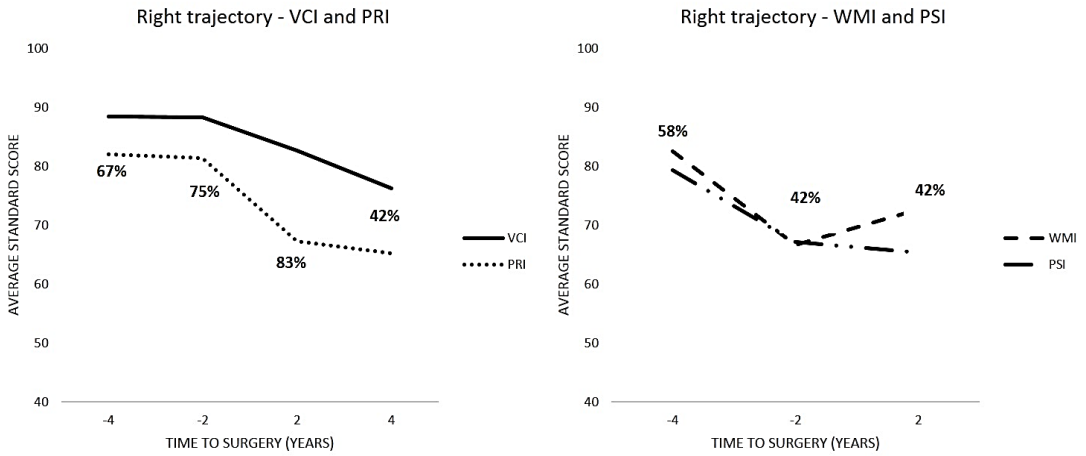

Figure 3-10: The right RS group's pre-to post-op trajectory averaged every two years for their VCI, PRI, WMI and PSI scores pre- and post-op (0 represents date of surgery). The proportion of the sample that contributed to each point is represented as a percentage. Note that if less than 15% of the sample contributed towards a point it was excluded.

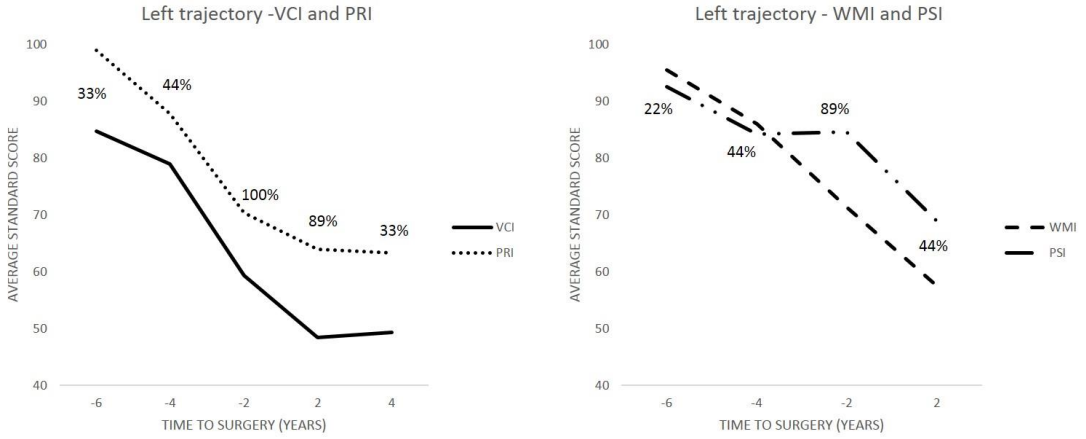

Figure 3-11: The left RS group's pre-to post-op trajectory averaged every two years for their VCI, PRI, WMI and PSI scores pre- and post-op (0 represents date of surgery). The proportion of the sample that contributed to each point is represented as a percentage. Note that if less than 15% of the sample contributed towards a point it was excluded.

3.2.1.2. Parametric analyses

For the pre- to post-op assessment the left and right RS groups again did not differ in terms of

age at seizure onset nor age at surgery (all $p > 0.05$).

To investigate the effect of group and assessment on VCI and PRI performance a repeated measures ANOVA was conducted. Right and left RS groups ('side') were compared on their VCI and PRI index scores ('test') at the pre- and post-op assessments ('time'). The dependent variable was their VCI and PRI scores at the pre- or post-operative assessment. This revealed a significant main effect of time ($F(1, 19) = 11.88$, $p = 0.003$), indicating that there was a decline in both the left and right groups' VCI and PRI scores from the pre- to the post-op (Figure 3-12). There was also a significant interaction of test and side ($F(1,19) = 21.71$, $p = 0.000$), indicating the left RS group's VCI performance is significantly below the right RS group's at both assessments. There was a trend towards a significant interaction between time by test by side ($F(1, 19) = 3.32$, $p = 0.08$) suggestive of a specific decline that occurred in the left group over time in the VCI scores, and in both the groups in the PRI scores. There was no significant main effect of time ($F(1, 19) = 0.2$, $p = 0.66$), nor an interaction between time and side ($F(1, 19) = 1.2$, $p = 0.29$) and time by side ($F(1, 19) = 0.23$, $p = 0.63$).

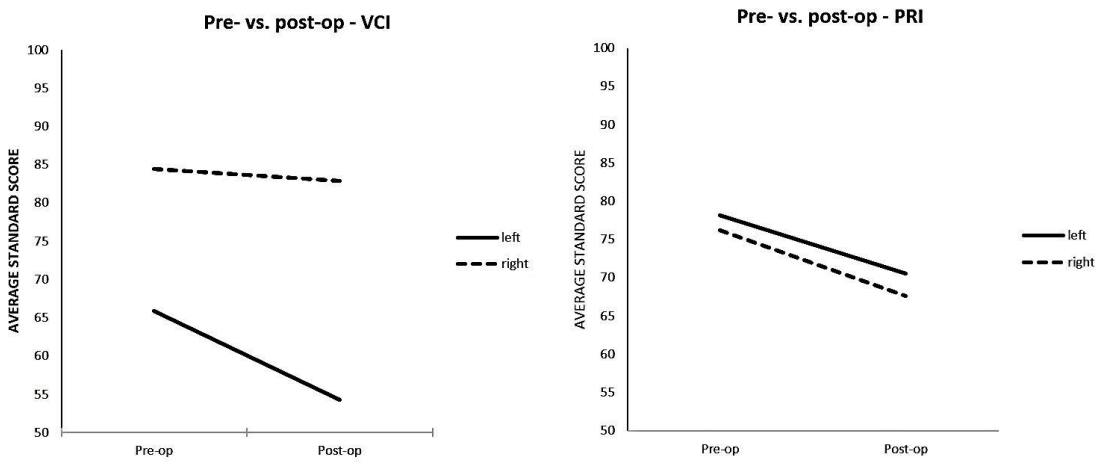

Figure 3-12: The VCI and PRI pre- to post-op trajectory for the left and right RS groups.

Post-hoc analyses were conducted to look at group differences in performance pre- and post-op. For the VCI two independent t-tests compared group performance at pre- and

post-op assessment. These indicated the left group performs significantly worse on the VCI than the right at both assessments (pre-op: t (19) = -2.67, p = 0.015; post-op: t (19) = -5.28, p = 0.00). For the PRI performance two independent t-tests revealed there was no significant difference between the groups' performance at either pre- or post-op (pre-op: t (19) = 0.51, p = 0.71; post-op: t (19) = 0.62).

Within-group differences were explored using four paired t-tests. For the left group this showed a significant decline in VCI and PRI scores from pre- to post-FH (VCI: t (8) = 2.83, p = 0.022; PRI: t (8) = 3.1, p = 0.015). For the right group there was a trend towards a decline in PRI scores (t (11) = 1.98, p = 0.072) but not for the VCI scores (t (11) = 0.48, p = 0.64).

3.2.1.3. Non-parametric analyses

For the WMI and PSI scores non-parametric analyses were conducted due to the small group sizes (see Table 2-3). To investigate group differences in WMI and PSI performances at pre- and post-op assessments four Mann Whitney U tests were conducted between groups. They revealed the left group's WMI performance was significantly poorer than the right's at the post-op assessment (p = 0.009; Figure 3-13). Otherwise, there were no significant differences between the groups' performances for WMI and PSI at the pre-op assessment (p = 0.83; PSI: p = 0.43), nor the PSI at the post-op assessment (p = 0.33; Figure 3-13).

To investigate possible changes within groups from pre- to post-op assessment, four Wilcoxon Signed Ranked tests were conducted. These showed the left group significantly declined in WMI and PSI performance from pre- to post-op assessment (WMI: p = 0.043; PSI: p = 0.043), but the right group did not (WMI: p = 0.91; PSI: p = 0.34).

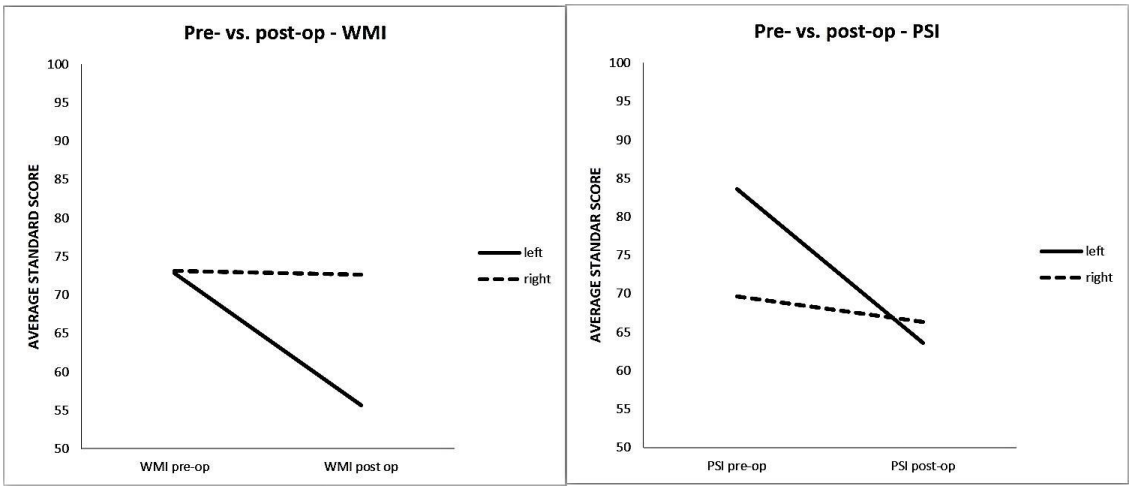

Figure 3-13: The WMI and PSI pre-to post-op trajectory for the left and right RS groups.

3.2.2. Academic attainments

For the pre- to post-op assessment only a small number of individuals had academic attainments assessed (see Table 2-3). Due to these low sample sizes the trajectory was not plotted over time. In addition, the numbers in the left spelling group dropped so low (N = 2) that they were not included in the statistical analyses below. The academic attainment scores between groups did not fulfil parametric assumptions (right group numerical operations post-op kurtosis = 4.1, $p > 0.001$) and so non-parametric explorative analyses were conducted.

3.2.2.1. Non-parametric analyses

To investigate differences between the groups' reading and numerical operations performance at the pre- and post-op assessments four Mann-Whitney U tests were conducted. These revealed that the left group had a trend towards a significantly lower reading score at the pre- ($p = 0.1$) and the post-op ($p = 0.067$) assessments in comparison to the right group. There were no significant differences between the two groups' performances in the numerical operations at pre- ($p = 0.79$) or post-op ($p = 0.19$; see Figure 3-14).

To investigate the change within groups from the pre- to post-op assessment a series of Wilcoxon Signed Rank tests were conducted. In the left group there was a trend towards a

significant decline in their reading and numerical operations scores from pre- to post-op (reading: p = 0.1; numerical operations: p = 0.06). For the right group there was a trend towards a significant decline for the reading scores from the pre- to the post-op assessment (p = 0.1), but not for the numerical operations (p = 0.14; Figure 3-14). For the right group's spelling score there was no significant decline from pre- to post-op (p = 0.43; Figure 3-15).

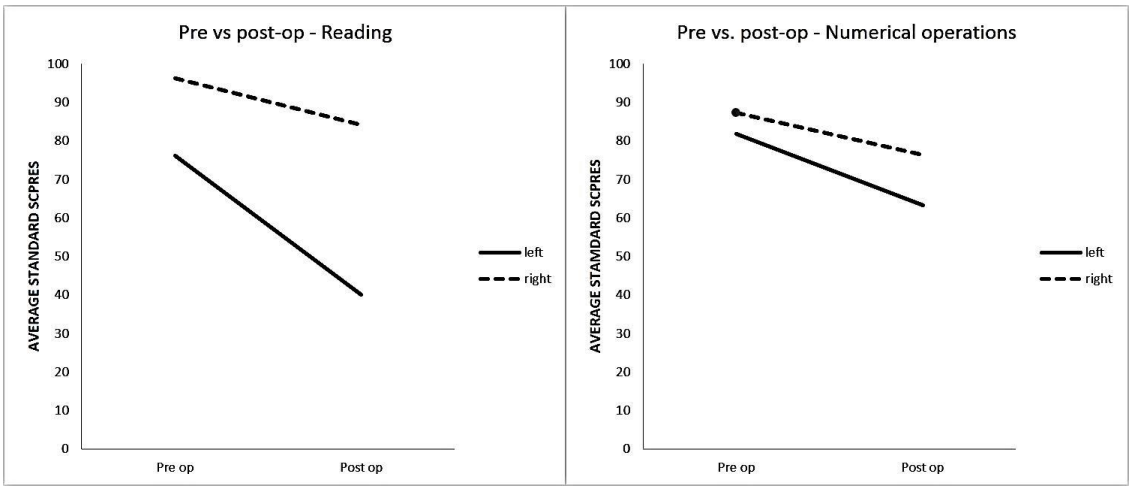

Figure 3-14: The reading and numerical operations pre-to post-op trajectory for the left and right RS groups.

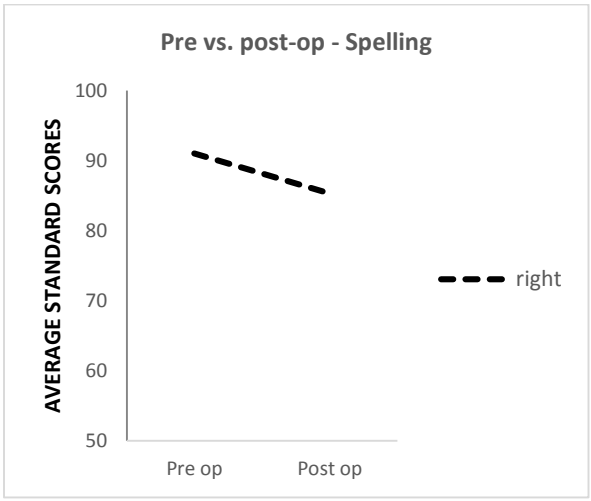

Figure 3-15: The spelling pre-to post-op trajectory for the right RS group.

3.2.3. Memory

A very small proportion of our sample had completed memory assessments before and after surgery (see Table 2-3). The only substantial group who undertook pre- and post-op assessment (an estimate of verbal immediate memory) was the right group (n=7) and so only this group was investigated statistically. To gauge some idea of the pattern of memory performance in each group verbal and visual immediate and delayed scores were plotted (Figure 3-16). This graph indicates no obvious pattern of change in memory estimates in either group from pre- to post-op. This is may be due to the small sample size.

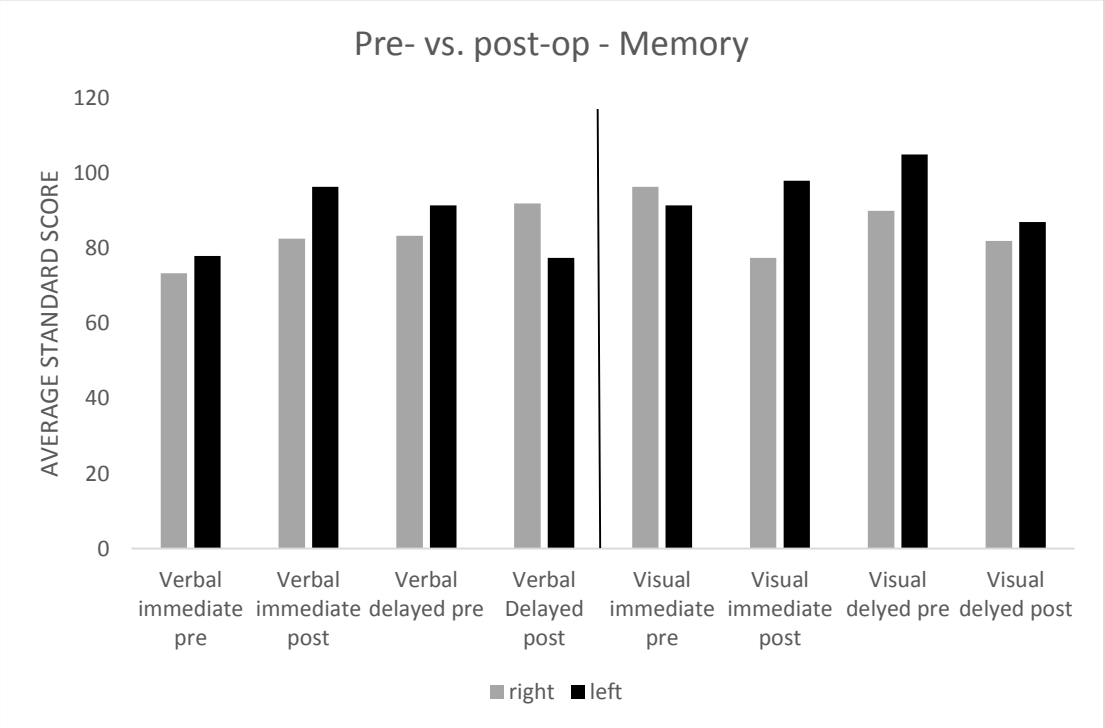

Figure 3-16: The memory pre-to post-op trajectory for the left and right RS groups.

The right group's pre- to post-op verbal immediate performance was compared using a Wilcoxon Signed Rank test. This analysis revealed no significant change in the immediate memory performance from pre- to post-op ($p = 0.31$).

3.2.4. Multiple regression for medical factors

Multiple regression analyses were conducted to determine the effect of seizure frequency and AEDs on the change in VCI and PRI from pre-op to post-op assessments. For the change in VCI neither medical variable accounted for the variance of change in VCI (R^2 = 0.048, adjusted R^2 = -0.064; (F (2, 18) = 0.48 p = 0.66)). The partial regression coefficients showed neither AEDs nor seizure frequency had a unique contribution to change in VCI score from pre- to post-op assessment (AED: t (20) = -0.65, p = 0.53; Seizure frequency: t (20) = 0.82, p = 0.42).

For the PRI change neither medical factor accounted for a significant amount of variance from pre- to post-op assessment (R^2= 0.17, adjusted R^2 = 0.067; F (2, 18) = 1.68, p = 0.22). However, the partial regression coefficient showed a trend that number of AEDs made a unique contribution towards the PRI change (AED t (20) = 1.81, p = 0.08); however, this was not the case for seizure frequency (t (20) = -0.79, p = 0.44).

3.3. **Neuroimaging**

3.3.1. Grey matter VBM analyses

One of the major aims was to determine the pattern of brain atrophy over time in RS individuals prior to surgery, using VBM, a fully automated technique for looking at whole brain grey matter. The contrast 'scan 1-scan 2' (i.e., scan 1 greater than scan 2) revealed a significant decrease in grey matter in the *unaffected* hemisphere in a number of regions including: the frontal lobe (uncorrected p = 0.00, x =102, z = 181, y = 66), insular cortex (uncorrected p = 0.00, x= 126, y = 117, z = 76) temporal lobe (uncorrected p = 0.00, x = 134, y = 126, z = 40) and retrosplenial cortex (corrected p = 0.001 x = 103, y = 58, z =75; Figure 3-17). In the affected hemisphere the only observable decreases in grey matter were noted in the retrosplenial cortex (uncorrected p = 0.000, x = 103, y= 58, z =-75). The contrast 'scan 2-scan 1' revealed no significant clusters of change indicative that neither hemisphere increased in grey matter

between scan 1 and 2.

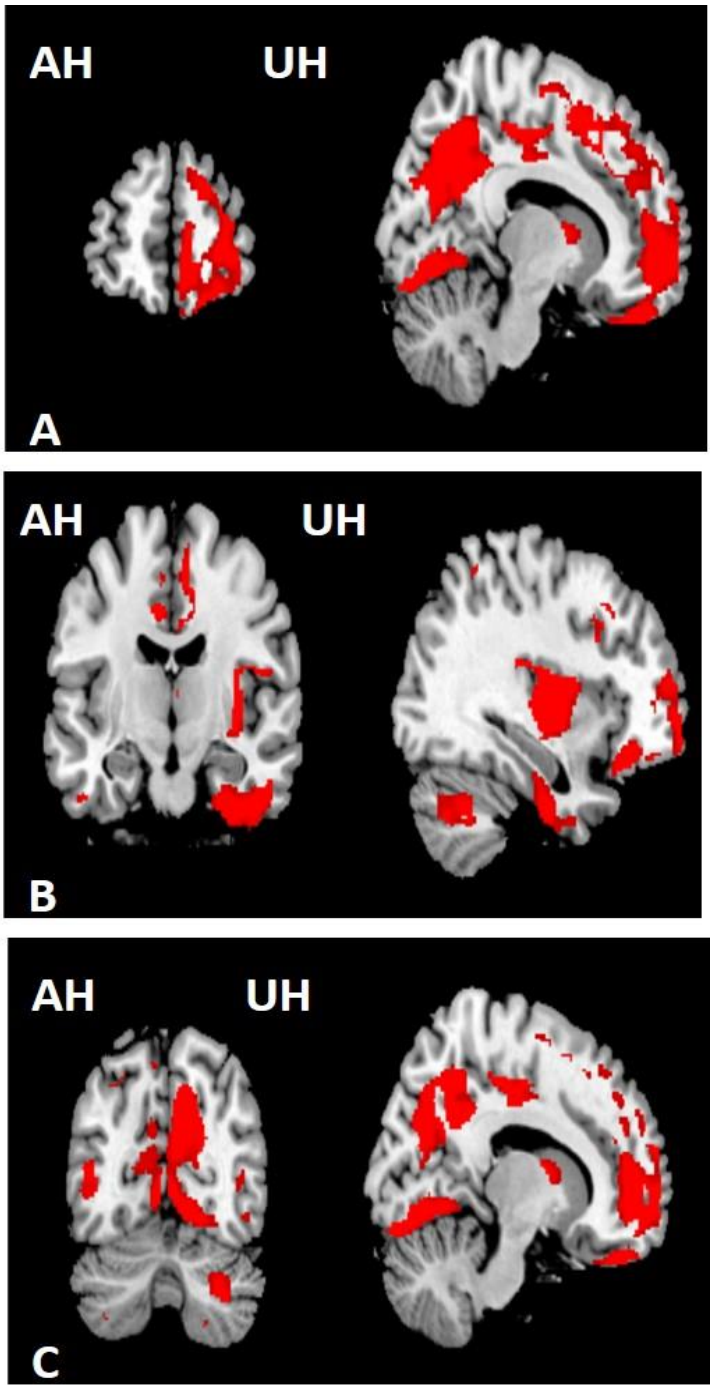

Figure 3-17: Visualisation of the grey matter VBM contrast 'scan 1-scan 2' showing significant decline in the grey matter of the unaffected side in the (A) frontal lobe, (B) insula and temporal lobe and (C) retrosplenial cortex in the unaffected side and affected side; UH = unaffected hemisphere, AH = affected hemisphere.

These VBM findings were confirmed by creating a mean image of all 18 grey matter brains at scan 1 and scan 2 and subtracting these from one another. This subtraction image, in which lighter colours indicate a decrease in grey matter, again revealed a decrease in grey matter that is observable in the temporal and insular regions of the unaffected hemisphere (Figure 3-18).

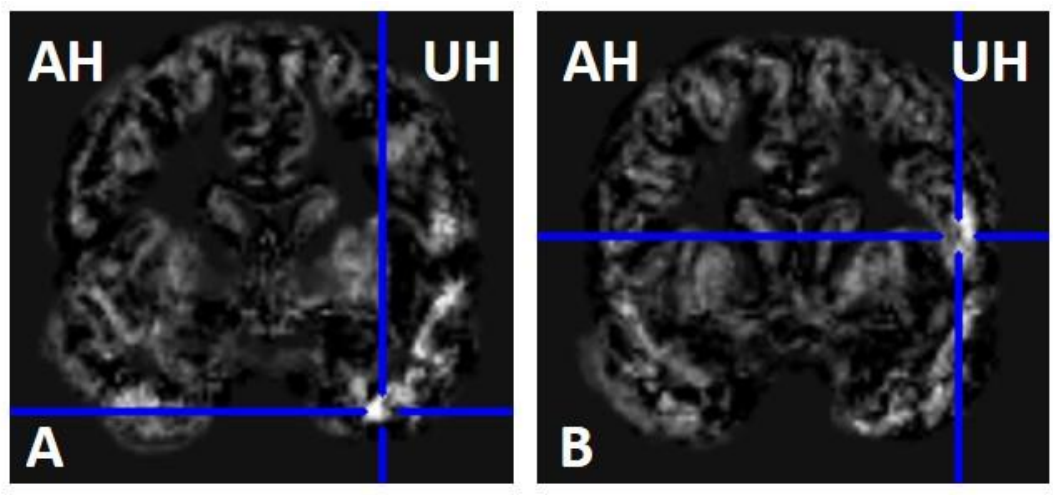

Figure 3-18: Subtraction images of mean grey matter images scan 1-scan 2. Brighter colours indicate a reduction in grey matter. A decrease of grey matter is seen in the temporal pole (A) and the insula (B) of the unaffected hemisphere (Note- All affected hemispheres are flipped to the left hemisphere); UH = unaffected hemisphere, AH = affected hemisphere.

3.3.2. White matter VBM analyses

For the white matter the contrast 'scan 1 - scan 2' revealed a significant decrease in the white matter of the anterior portion of the genu of the corpus callosum in the "unaffected" hemisphere (uncorrected p = 0.00, x = 104, y = 151 , z = 72; Figure 3-19). This white matter tract projects from the frontal regions that were found to have atrophied in our grey matter analysis above.

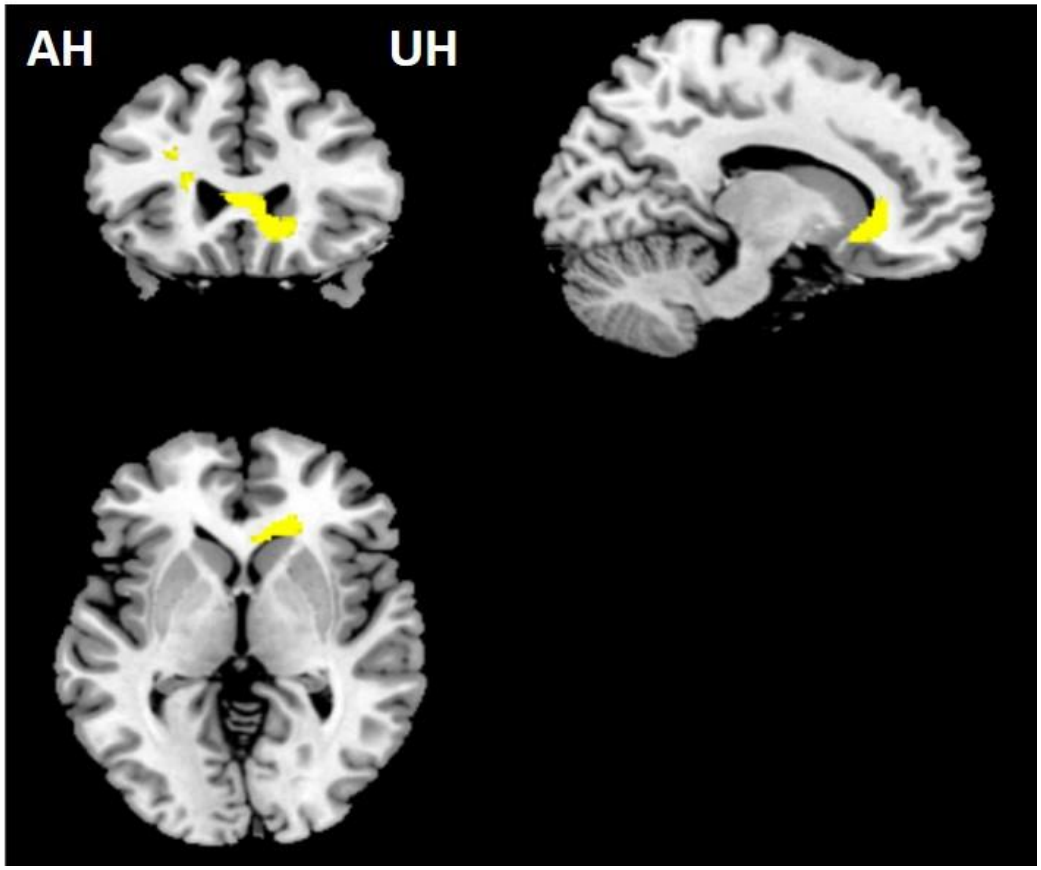

Figure 3-19: White matter VBM analysis 'scan 1-scan 2' indicating a significant decline in the white matter of the genu of the corpus callosum in the unaffected side; UH = unaffected hemisphere, AH = affected hemisphere.

The contrast 'scan 2-scan 1' showed a number of significant clusters suggestive of an increase in white matter in the "unaffected" hemisphere between scans 1 and 2. However, inspection of these clusters revealed they are in the same or surrounding the regions of grey matter atrophy between scans 1 and scan 2 (see Figure 3-20 for these contrasts visualised together). This suggests that these clusters do not represent an increase in white matter between scan 1 and 2, but that at scan 2 the atrophying grey matter is erroneously classified by VBM as white matter. Difficulties in classification of white matter in VBM are often experienced and will be discussed in Chapter 4.

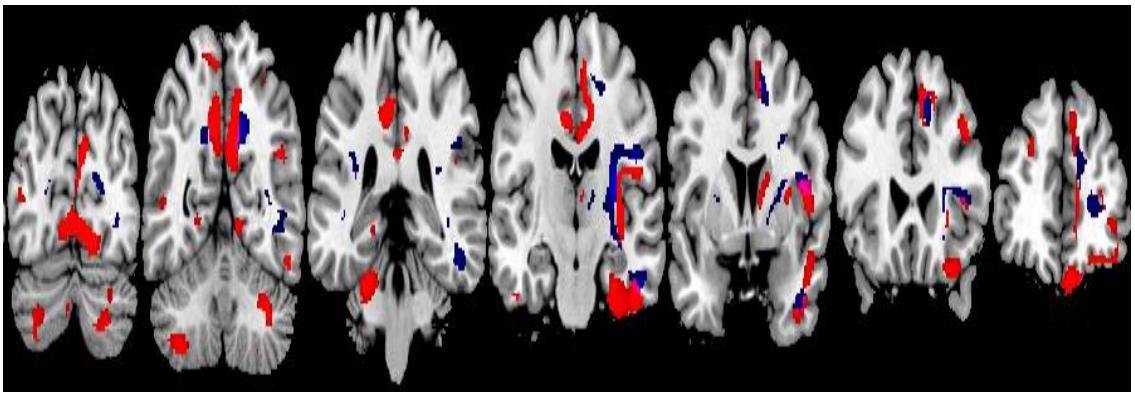

Figure 3-20: Coronal cross sections throughout the brain. Clusters from the grey matter contrast 'scan 1-scan 2' are in red and the white matter contrast 'scan 2-scan 1' are in blue. These clusters are seen to be often overlapping or in the same region.

3.3.3. Relationship between grey and white matter and cognition

To investigate if the change in the 18 individuals with MRI scans VCI or PRI scores were related to cortical grey and white matter changes a series of correlations were conducted. Pearson's correlations between the VCI and PRI change scores (nearest scan 2 assessment – nearest scan 1 assessment) and the change in cortex in specific brain regions from scan 1 to scan 2 ((scan 2 grey + white matter) – (scan 1 grey + white matter); Table 3-5) were conducted.

*Table 3-5: Pearson's correlations showing the relationship between the VCI and PRI change and the change in grey and white matter for specific brain regions from scan 1 to scan 2. All df = 17. UH=unaffected hemisphere, AH=affected hemisphere, *= significant at the p=0.05 level.*

	VCI change		**PRI change**	
	R	p	R	p
Whole brain	0.12	0.33	0.35	0.08
AH	0.17	0.25	0.34	0.089
UH	0.2	0.22	0.26	0.16
Whole Frontal	0.79	0.38	0.35	0.084
AH Frontal	0.2	0.22	0.35	0.086
UH Frontal lobe	0.22	0.19	0.18	0.25
Whole Temporal	0.19	0.24	0.1	0.35
AH Temporal	0.76	0.38	0.265	0.15
UH Temporal	0.24	0.18	-0.05	0.41
Whole Parietal	0.17	0.26	0.43	0.043*
AH Parietal	0.22	0.2	0.4	0.06
UH parietal	0.063	0.4	0.41	0.05*

Whole occipital	0.18	0.24	0.40	0.05*
AH occipital	0.22	0.2	0.4	0.05*
UH occipital	0.12	0.32	0.37	0.07

A significant relationship was found between the change in PRI score and the grey and white matter change of the whole (i.e., both hemispheres) parietal and occipital lobes (see Table 3-5). These findings were supported by a significant or trend towards a significant relationship between the change in PRI and the change in the affected and unaffected hemispheres of the parietal and occipital lobes. These correlations indicate a decline in both hemispheres in these regions is associated with a decline in the PRI performance over time. Furthermore, a trend towards a significant relationship was found between PRI change and the whole brain and the whole frontal grey and white matter changes. This suggests both affected and unaffected grey and white matter decline contribute to change in the PRI scores. Interestingly, there was no significant relationship between the VCI change and the change in any masks of interest (see Table 3-5).

Chapter 4 - Discussion

4.1. Introduction

The present thesis looked to characterise the cognitive and brain changes that occurred pre-surgery and pre-and post FH in individuals with RS. More specifically, the neuropsychological performance of individuals with RS was explored at time points before and after surgery using standardised psychometric measures of IQ, academic achievement, language and memory. Changes within the left and right RS groups were investigated as well as any significant differences between them that occurred over time both pre-surgery and pre- and post-FH. It had been a major aim to look for associations between medical variables and cognitive change over time, however, due to a smaller than expected sample size only an explorative multiple regression looking at seizure frequency and AEDs' effects on IQ was possible.

This study was the first to use fully automated VBM analysis to investigate grey and white matter changes in RS individuals before surgery. The possible relationship between these brain changes and cognitive decline was then explored through extracting grey and white matter values from regions of interest within the brain and comparing them to cognitive change through correlational analyses.

This thesis expanded on previous research in a number of crucial ways. First, it interrogated the trajectory of cognition at time points *before* neurosurgery and looked at IQ in more detail to allow the differing VCI, PRI, WMI and PSI IQ changes to be examined. Second, the effect of important medical factors, such as AEDs and seizure frequency, on cognitive abilities before and after surgery was explored. Third, the follow up time post-surgery was around 1-2 years and thus timing of assessment was not a possible confounding factor (as has been the case in previous studies; Pulsifer et al., 2004).

A summary of the main findings is presented and discussed below. All results pertain to results of parametric and non-parametric statistical analyses. All results discussed were statistically significant unless stated. The limitations are then acknowledged and future research is discussed. Finally, the findings' implications for clinical practice are discussed, in particular with regard to medical management.

4.2. **Cognitive trajectory pre-surgery**

4.2.1. Intellect

This study looked to investigate the cognitive trajectory of RS individuals pre-surgery (Question 1a). It was also interested to see if there were any significant differences between the cognitive performance of the left and right RS individuals pre-surgery (Question 2a). In regard to Question 1a, pre-surgery we found significant changes over time in right and left RS groups' intellectual functioning. In both groups VCI, WMI and PSI performance declined significantly between two assessments prior to surgery; however, the decline in PRI, although observable, did not reach significance at the post-hoc level in either group.

In regard to Question 2a, some similarities and differences between groups were also observed in IQ performance. From AS1 to AS2 the groups did not differ in their WMI and PSI abilities and the decline performance in these abilities pre-surgery appeared similar in all RS individuals. However, an interesting dissociable pattern of performance was hinted at between the groups' VCI and PRI performances. Findings from an ANOVA suggested the right group's PRI performance was poorer than the left group at AS1 and AS2, whereas the left group's VCI was poorer than the right. However, although this pattern was suggested by a significant interaction between group and test at the ANOVA level, post-hoc the difference between the groups' VCI and PRI performances at each assessment failed to reach significance. This may be due to issues with a small sample size and large spread of scores in the data. However, the

groups were checked for outliers and although there was a wide spread in each group no individual score was two standard deviations from the mean, permitting exclusion.

No previous investigation has looked at the changes in intellect at multiple time points before surgery in those with RS. Our study, which indicates a decline in most intellectual composites in both RS groups prior to surgery (apart from PRI which failed to reach significance), therefore importantly adds to the literature and supports clinical observation (Varadkar et al., 2014).

The left side of the brain is typically thought to be lateralised for language (Geschwind, 1970), whereas the right hemisphere is more involved in non-verbal visuo-spatial processing, problem solving and attention (Reeves et al., 2008). This study's findings may be concordant with this idea and suggested those with a disease causing progressive atrophy of the left hemisphere experience difficulties in tasks heavily reliant on verbal/language abilities over and above deficits experienced in non-verbal problem solving. By contrast, those with progressive right atrophy due to RS experience difficulties in tests that rely heavily on spatial and object perception, organisation and problem solving. Of note, based on literature that suggests 96% of those who are right handed and 90% of those who are left handed are left hemisphere language dominant (Knecht et al., 2000), all individuals in our study were presumed to be left language dominant; however, difficulties with this will be discussed in the Limitations section to follow.

As mentioned, working memory performance did not differ between groups. In the Wechsler intelligence tests the working memory subtests are in the verbal domain, therefore, it is somewhat surprising that both groups' working memory abilities were equally affected pre-surgery. However, a recent meta-analysis of 200 fMRI studies of normal subjects conducting verbal working memory tasks showed a bilateral network of activation in the frontal and parietal lobe (Rottschy et al., 2013). Hence, it is possible that those who were

typically developing and then began to experience atrophy to one hemisphere of the brain (as in RS) may experience deficits in verbal working memory.

Processing speed subtests rely heavily on the motor abilities of the dominant hand (typically right). It may have been predicted that the left RS group who may have begun to experience hemiparesis in their right dominant hand would have had a poorer performance on the PSI than the right group. However, the PSI subtests are likely to rely heavily on visuospatial and attentional functions (Flanagan & Kaufman, 2009) which may also have been more specifically affected in the right RS group (Reeves et al., 2008), leading to deficits in the PSI in both RS groups.

Few investigations have explored the cognitive trajectories of those with whole hemisphere aetiologies that cause epilepsy. A previous investigation showed those with cortical dysplasia of the whole left and right hemisphere had difficulties in verbal IQ and non-verbal IQ respectively (Klein et al., 2000). The only previous large investigation of individuals with RS conducted one assessment pre-surgically (Pulsifer et al., 2004) and found no significant differences between left and right RS groups' Full Scale IQ. However, Pulsifer and colleagues (2004) failed to investigate the contributions of intellect indices (VCI, PRI, WMI and PSI) on their FSIQ performance as in this investigation. Our study, therefore, expands on Pulsifer and colleagues' (2004) results and suggests there may be important differences in the intellectual performance of the left and right RS groups which may have previously been overlooked.

There is a paucity of data looking at the neuropsychological profile of those with gross damage to their right hemisphere. Our study is the first to investigate a group of right RS individuals and shows that they may have some specific difficulties in non-verbal intellectual abilities and relatively intact verbal intellectual abilities. This builds on previous evidence from a single case study that indicated an individual with gross right sided pathology had deficits in non-verbal IQ and spatial perception, but better preserved verbal IQ (Chiricozzi et al., 2005).

4.2.2. Medical Variables

Another aim of this study was to explore the impact of the medical variables of seizure frequency and number of AEDs on the change in VCI and PRI pre-surgery (Question 3a). Due to a smaller than expected sample size an explorative multiple regression analysis was conducted with only these two variables of interest. These variables were picked as evidence suggests these are the most likely to impact cognitive in those with epilepsy (Hermann et al., 2010). Our findings show a trend towards significance that the number of AEDs was a negative predictor of VCI decline from AS1 to AS2 but not of change in PRI. There is also a possibility that this indirectly indicates those with more severe epileptic disease, who are often prescribed more AEDs, have poorer cognitive abilities. This result, although tentative, supports previous findings that suggest the number of AEDs negatively predicts decline in IQ scores in those with intractable epilepsy (Skirrow et al., 2011).

On the other hand, seizure frequency was not found to be predictive of change in VCI or PRI from AS1 to AS2. This is surprising considering previous research that showed adults with intractable epilepsies' cognitive decline was predicted by frequency of seizures (Thompson & Duncan, 2005). However, investigation into the impact of seizure frequency in children's cognition has suggested that seizures may not have a negative impact on cognitive abilities, and at seizure onset intellectual abilities lag behind normal children (Rathouz et al., 2014). The current study's failure to find that seizure frequency predicts VCI or PRI change may therefore support this idea that seizures do not have a deleterious impact on cognition in childhood. However, the absence of a significant finding may also be due to lack of power (i.e., a type 2 error) and so this suggestion is speculative and requires further investigation.

4.2.3. Academic attainments

The trajectory of academic attainments pre-surgery followed a similar pattern as intellect,

although functions appeared to be better preserved in both groups. With regards to Question 1a, a significant decline in reading abilities was observed in the left group from AS1 to AS2 and there was a trend towards a significant decline in the right group. A trend towards a decline between AS1 and AS2 was also seen in the numerical abilities and spelling in both groups, but this failed to reach significance.

Investigating the differences between groups showed the left group had significant weaknesses in reading in comparison to the right group at both assessments pre-surgery. In addition, the left group also had a significantly impaired spelling performance at AS2 in comparison to the right group pre-surgery. These findings add to the notion that the left RS individuals experience particular deficits in verbally-mediated abilities pre-surgery and this extends to the academic skills of reading and spelling. The right group, in comparison, had relatively intact reading and spelling abilities initially but these did decline over time.

Differences between the groups' numerical operations trajectories failed to reach significance. Inspection of the numerical operations performances showed the left group were already performing in the low range by AS1 and then they remained at this performance level at AS2. The right group, however, experienced a decline in numerical operations performance from AS1 to AS2 from the low average to borderline ranges, and there was a trend towards significance that they performed significantly better at AS1 in comparison to the left group. Both groups therefore seem to experience difficulties with numerical operations. This is in line with the view that both hemispheres of the brain support successful arithmetic abilities (Dehaene, Molko, Cohen, & Wilson, 2004). Indeed, numerical ability is supported by activation in the intraparietal and prefrontal cortex of the left and right hemispheres in both adults and children (Dehaene et al., 2004).

4.2.4. Memory and language

In this study a small number of right and left RS individuals undertook memory and language testing pre-surgery. Due to the small numbers, no distinct patterns could be observed over time or between groups. Problems with small samples and conducting long psychometric assessments in individuals with rare and disabling diseases will be discussed in Limitations.

4.3. **Cognitive trajectory pre-to post-op**

4.3.1. Intellect

This study investigated the cognitive trajectory of RS individuals pre- to post-op (Question 1b). Our findings suggest that after FH those with left RS had particularly poor intellectual outcomes and they experienced a significant decline in all four IQ indices (VCI, PRI, WMI and PSI). Those with right RS, on the other hand, only experienced a trend towards a significant decline in their PRI scores and remained better preserved in all other intellectual abilities post-op. This finding is in direct contrast to Pulsifer and colleagues (2004) who found no significant decline in Full Scale IQ pre- to post-op in either RS group. However, a number of differences between our studies may explain this differing result. As already mentioned the time to post-op assessment between our studies was significantly different; Pulsifer and colleagues (2004) post-op assessments were conducted from 1-26 years after surgery, whereas ours were conducted 0.6-2 years post-operatively. It may be possible, therefore, that our sample indicates there is a decline in most IQ indices in the first few years after surgery, whereas Pulsifer and colleagues' (2004) results suggest IQ can improve to pre-surgical levels after an unknown period of time. This suggestion is in line with previous investigations that have shown that only 8 years after epilepsy surgery cognitive recovery and improvement is seen in epileptic individuals (Skirrow et al., 2011). Alternatively, there may be other important differences between our samples, such as timing to surgery, seizure frequency or epilepsy duration, which

may have an important impact on cognition in each group. These medical data are not reported by Pulsifer and colleagues (2004) and so no formal comparison can be made.

This study also examined the differences in group performance at the pre- and post-op assessment (Question 2b). In between-groups analyses, the left RS individuals had specific weaknesses in intelligence indices that required language, with a significantly weaker VCI performance at pre- and post-op, and had a poorer WMI at post-op when compared to the right group. There were no other significant differences between groups. These findings suggest those with progressive atrophy and then functional disconnection of their left language-dominant hemisphere experience significant effects on intellectual tasks requiring language and verbal abilities. Previous pre- to post-operative studies of those with RS affecting their left hemisphere have found impairments in expressive language post-FH (Boatman et al., 1999; Pulsifer et al., 2004). Our results, therefore, extend these findings and suggest that intellectual tests requiring language (VCI and WMI) are also significantly affected by the disconnection of the presumed language-dominant hemisphere.

The trajectory of the PRI performance from the pre- to post-op assessment declined in both groups (although this was a trend for the right group) and there was no significant difference between their performances. Comparing the trajectories across both pre-surgery and pre- to post-op analyses suggests the right group remained on a similar trajectory in their PRI performance across time and slowly declined from the low average range (AS1) to the borderline range (post-op). The left group, however, despite showing relatively preserved PRI in the pre-operative trajectory, experienced a marked decline in their PRI from the pre- to post-op assessment, moving from the average range at AS1 to the borderline range post-op. It therefore seems that the disconnection of the language-dominant hemisphere leads to particular difficulties in all areas of intellectual functioning, even when these do not directly require language.

The explanation for why left FH causes decline in all areas of intellectual function, even when these do not require language, is unknown. Previous investigations have shown participants with left hemisphere damage have deficits on both verbal and non-verbal spatial reasoning tasks which cannot be explained by difficulties in aphasia alone (Baldo et al., 2005; Langdon & Warrington, 2000). It may be that expressive and receptive language difficulties experienced by those with left hemisphere damage (Pulsifer et al., 2004) negatively impacts on an individual's ability to use inner speech or covert language to support on-line problem solving which may negatively impact all areas of cognition (Baldo et al., 2005). Alternatively, receptive language difficulties may lead to problems understanding new tasks or concepts which may have a knock-on effect on left RS abilities to respond to either verbal or non-verbal stimuli.

4.3.2. Medical Variables

An explorative multiple regression suggested neither total number of AEDs nor seizure frequency was predictive of the change in VCI or PRI from the pre- to post-op assessments. This suggests that these medical variables do not have a significant impact on the decline in IQ scores after FH. Considering the above findings it may be that the disconnection of one hemisphere of the brain through FH has a higher impact on IQ performance than these medical variables. However, it is also possible this finding is a false negative due to a small sample size and this will be discussed in the Limitations section.

4.3.3. Academic attainments

Due to small sample size non-parametric analyses were conducted on the academic attainment scores from pre- to post-op. This yielded a number of trends towards significance but no significant findings. In regards to Question 1b a number of trends suggested there was a decline in reading and numerical operations scores in the left group and in reading alone in

the right group. There were no other declines in any other academic attainments in the groups. Spelling was not measured in the left group, possibly due to left RS individuals' severe impairments limiting their ability to engage in a written spelling test at the post-op stage (see Limitations for further discussion).

In regards to differences between groups (Question 2b) there was a trend towards the left group performing significantly worse on the reading test at both pre- and post-op assessment in comparison to the right. This is in line with the findings pre-surgery and suggests that the left group's particular weakness in verbal tasks post-FH also extends to reading abilities. No difference between the groups' abilities in numerical operations was found. This is in line with previous research that has suggested that mathematical abilities are supported by both hemispheres of the brain (Dehaene et al., 2004) and it follows that both left and right RS individuals after FH are susceptible to deficits in these areas.

4.3.4. Language and Memory

No language assessments were carried out in either group pre- to post-FH and so this study was not able to explore this. For the memory assessments, no significant or observable change in performance was seen from pre- to post-op in either group. This may be due to small numbers of memory assessment overall (total N = 7; see Limitations).

4.4. **Neuroimaging**

4.4.1. Grey matter VBM analyses

This study investigated if VBM analyses could detect change in grey and white matter in RS individuals at two time points pre-surgery (Question 4). Our findings revealed for the first time that pre-surgically those with RS experience a significant atrophy of the grey matter in regions of the unaffected hemisphere, and to a lesser extent the affected hemisphere. More

specifically, we showed the unaffected hemisphere retrosplenial cortex (i.e., a region in the parietal lobe), temporal lobe, insula and prefrontal cortex experienced grey mater atrophy prior to surgery. RS is classically characterized as a disease of one hemisphere of the brain (Bien et al., 2005). This has been corroborated by numerous radiological and MRI investigations that have shown the affected hemisphere experiences the most significant decline, whilst the unaffected hemisphere changes are small and often in only a proportion of those with RS (Larionov et al., 2005; Wagner et al., 2012).

Our results seem to contradict this notion; however, important differences in the timing of our scans in comparison to prior investigations may explain the contrasting results found. This study's scans were conducted on average approximately 3.5 years after seizure onset (scan 1) to 6.8 years (scan 2). This is much later in the RS disease course than Wagner and colleagues (2012) who investigated grey matter change from on average around 0.7 years to 3 years post-onset of RS. This investigation, therefore, is looking at the brain changes in RS after 3 years and suggests that later in the disease progression the unaffected hemisphere experiences significant grey matter atrophy in regions across the whole hemisphere including the frontal, temporal, parietal and occipital lobes and cerebellum.

At this later time point the affected hemisphere seems to undergo more subtle grey matter atrophy with some small areas of decline in the retrosplenial cortex, occipital and temporal lobe. This finding may reflect the fact that our sample's affected hemisphere's grey matter has already atrophied in the 3 years post-RS onset and prior to scan 1 and so has little capacity to decline further. Previous investigations would support this notion of a catastrophic and significant decline in the affected hemisphere's grey matter in the first 2 years of disease course (Bien et al., 2005; Wagner et al., 2012). Importantly, however, due to the lack of scans conducted in the first 3 years after onset this possibility could not be verified. Issues around lack of scans across the whole disease course will be discussed in the Limitation section below.

Our findings that the unaffected hemisphere significantly declines in grey matter prior to surgery may also help explain some of our cognitive findings above. In particular, atrophy in the unaffected hemisphere may underpin the particular deficits found post-op that are not predicted by affected hemisphere damage. This was most pertinent for the left group, who, after FH, experienced significant declines in all areas of intellectual functioning. It is possible that difficulties in all psychometric tests post-op were underpinned by a significantly damaged unaffected hemisphere, which was unable to support normal functioning post-FH. This suggestion is speculative and future investigations will be important to determine if there is a causal link between the damaged unaffected hemisphere and deficits observed post-op.

4.4.2. White matter VBM analyses

A significant decline was found in the white matter of the genu (front) of the corpus callosum running between the affected and unaffected hemispheres from scan 1 to 2. The corpus callosum is the major collosal fiber of the brain which connects the two cerebral hemispheres and the genu portion specifically connects the prefrontal and frontal regions (Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2003). In this study it is notable that a white matter tract which connects the right and left frontal lobes was seen to decline in integrity. It is plausible that this tract may be an important connection to explore when investigating the influence the affected hemisphere has on the unaffected hemisphere (see Future Directions below).

This study found significant increases in the white matter of the unaffected hemisphere of the brain from scan 1 to scan 2. Careful examination of these findings however suggested that areas of "increase" in white matter were in the same location or immediately next to the regions of grey matter decline found above. Utilizing VBM to investigate white matter is controversial due to difficulties in VBM's ability to successfully segment white from and grey matter, particularly when there are areas of neuronal death (Eggert, Sommer, Jansen, Kircher, & Konrad, 2012; Whitwell, 2009). Indeed, diffusion tensor imaging (DTI) is a more

powerful and reliable method for investigating the white matter integrity of the brain (Beaulieu, 2002). This study, however, did not have access to diffusion weighted scans as these are not normally carried out in clinical practice.

VBM analysis first estimates the likelihood of each voxel being grey, white matter or cerebral spinal fluid and then compares each voxel between scans to see if there is a significant difference between them (Ashburner & Friston, 2000). To circumvent difficulties around VBM misattributing voxels to white matter which are in fact brain lesions, some studies have a high threshold (i.e., 0.8) so that only voxels with a very high probability of being white matter are included in analyses. This investigation had a threshold of 0.2 which is regularly used in VBM studies of brain damage (Coan et al., 2009), but, problematically, leads to a number of likely false positives. Whilst a high threshold could have been applied in the present study, it is likely this would have led to false negatives and the failure to find the significant decline in white matter in the genu of corpus callosum above. The need for imaging data, such as DTI, that can reliably explore the white matter integrity in this sample will be discussed in Future directions below.

4.4.3. Relationship between grey and white matter and cognition

Finally, this study investigated if the neurobiological correlates of neuropsychological decline (VCI and PRI) could be determined at the whole brain and within regions of interest pre-surgery (Question 5). The results are the first to elucidate the region of the brain change that may underlie the decline in perceptual reasoning seen in those with RS. A significant relationship was found between the decline in perceptual reasoning performance and the atrophy of the grey and white matter of the bilateral parietal and occipital lobes. There was also a suggestion that the decline of the grey and white matter of the frontal lobe may be related to the change in perceptual reasoning scores, but this failed to reach significance possibly due to our sample size and lack of statistical power. The VBM analysis described above

showed that regions within the bilateral parietal and unaffected occipital lobes were regions of particularly significant atrophy over time in our sample. It seems consistent then that this significant brain atrophy may have knock on effects to cognitive functions of these brain regions.

These findings may be able to explain cognitive trajectory findings found in our larger group. Pre-surgery both groups experienced difficulties with perceptual reasoning tasks. It is possible then that the atrophy of the bilateral grey and white matter of the parietal and occipital lobes underpinned this decline. This would be concordant with previous evidence that bilateral regions of the parietal lobe, prefrontal cortex and the junction of the occipital-temporal cortex crucially support novel problem solving perceptual reasoning tasks (Eslinger et al., 2009). Progressive atrophy of both sides of the brain and their relationship to perceptual reasoning abilities may also elucidate the deficits observed in the PRI in both groups post-op. Indeed, it may be that after disconnection of the affected hemisphere this leaves the remaining damaged parietal and occipital lobe unable to support successful perceptual reasoning skills (see Future directions).

This study did not find a relationship between the change in verbal comprehension and any brain regions over time. This is surprising considering that previous evidence suggests the frontal and temporal regions of the language dominant hemisphere crucially support language comprehension (Binder et al., 1996; Dronkers et al., 2004). It may be that methodological steps carried out for the VBM analyses could explain our lack of significant results. The right RS group's brains were flipped so that affected and unaffected hemispheres were on the same side. This ensured higher statistical power for the VBM analyses. However, this meant that the language dominant and non-dominant hemispheres were mixed to make one "affected" hemisphere. Based on the evidence above it would be predicted that verbal comprehension is supported by the frontotemporal network of the language dominant side

(Warburton et al., 1999). By placing the language dominant and non-dominant sides into the same space it is therefore likely that any relationship between verbal comprehension and the atrophy of the language dominant hemisphere is being weakened by the 9 non-dominant hemispheres included. The current investigation's inability to conduct correlations within the groups of left and right (presumed language dominant and non-language dominant) cases is problematic and was due to sample sizes; this will be discussed in the Limitations section below.

4.5. **Limitations**

The major limitation of this study was that the sample size was smaller than expected and so a number of our analyses were underpowered. This was particularly seen in some of our post-hoc analyses that failed to reach significance, despite the ANOVA indicating significant differences between groups. In addition, a smaller than expected sample size meant that our multiple regression analyses were likely to be underpowered and only 2 explorative medical variables' impacts on cognition could be explored. Whilst an increase in sample size would have been desirable, RS is an extremely rare disorder and so large numbers of these individuals do not exist to study. This study is currently the second largest (after Pulsifer et al., 2004) to investigate a group of individuals with RS. What is more, our sample size was almost exactly the same as many of Pulsifer and colleagues' (2004) for a number of group analyses. GOSH is a tertiary service and sees all children diagnosed with RS in the UK. Hence, it is unlikely this study suffered from being a clinical evaluation and it is unlikely that gaining ethics and conducting recruitment of RS participants outside GOSH would have led to any significant increase in our sample size.

Although, a lack of power was the primary statistical difficulty in this study, it is also possible that by conducting multiple statistical analyses a type 1 error was committed. To

protect against false positives bonferroni correction of p values could have been conducted, however, this would have likely led to further false negatives. Balancing the need to protect against type 1 and type 2 error is an ongoing difficulty in psychological research, especially in studies when sample sizes are small.

As our study was a clinical evaluation assessments were conducted for clinical practice and not experimental reasons. This meant there were large differences in the number of psychometric assessments of intellect, academic attainments, memory and language conducted on RS individuals. There were particularly low numbers of memory and language testing which may explain the lack of pattern in results observed. Memory and language testing (CMS and CELF-IV^{UK}) in particular are long and effortful tests. Neuropsychological testing of those with RS can be particularly difficult due to frequent seizures, fatigue due to RS processes, hemiplegia and hemianopia. In addition, those with left RS have particular difficulties with language both pre- and post-op. These challenges in cognitive testing of RS individuals may explain the dearth of memory and language assessments and it may be that under these difficult circumstances estimation of intellect and academic attainments were prioritised. Language and spelling were most noticeably not conducted post-op in left RS cases. This may be because individuals were no longer able to spell or to speak without great effort. This reflects inherent difficulties in gaining measures of individuals' cognitive abilities when they are performing within the exceptionally low range.

In terms of the neuroimaging component of this study it would have been beneficial for scans to be available from the onset of RS disease process. This would have allowed the pattern of atrophy over time in the brain to be determined. This may have shown the affected hemisphere followed by the unaffected hemisphere (as we observed) atrophying over time. As GOSH is a tertiary service, however, most RS individuals will only receive treatment at this hospital after experiencing seizures for a number of years. Hence, no scans were available

before the 3 years post-onset of seizures. In the future, it will be important for the brain atrophy of those with RS to be fully characterised over time (see Future directions) with a proactive approach to scanning seen.

Finally, this study presumed that in all RS individuals' language abilities were lateralised to their left hemisphere. Previous research suggests that in those who experience normal development this is likely to be the case (Knecht et al., 2000). However, it is possible that atypical lateralisation or reorganisation may have occurred in this sample that may have impacted our results in some unknown way. To have been able to determine each individual's language lateralisation an expressive and receptive language fMRI would have been needed for each RS individual. Due to the clinical evaluation nature of the project, as well as its scale, it was not practically possible for this to occur. In addition, a number of our sample were historical patients at GOSH and so would now be adults under a different hospital's care. The complexity of language lateralisation in those with progressive atrophy of the brain, especially when it effects the language dominant side, is in the early stages of being understood (Liégeois, Connelly, et al., 2008; Liégeois, Cross, Polkey, Harkness, & Vargha-Khadem, 2008). Future investigations will need to continue to disseminate the effect of lateralisation on cognition before and after FH.

4.6. **Future directions**

This study went some way to characterise the cognitive trajectory of those with RS at multiple time points before and after FH. In the future, it will be important that continued efforts are made to fully characterise their cognitive trajectory in this tragic and disabling neurological disease. To help increase our knowledge of the impact of RS on cognitive functions beyond intellect and academic attainments, shortened neuropsychological assessment protocols including a number of different cognitive domains, such as memory and language, could be

adopted. It would also be beneficial, when possible, to conduct tests that allow the estimation of functions that may be catastrophically affected by RS like language and spelling, which currently are not consistently measured.

An increased sample size of RS individuals who have psychometric assessment over time would increase statistical power and this may allow further dissemination of RS individuals' cognitive trajectory. In addition, a larger sample size would allow the possible impact of further medical variables on cognition to be investigated.

This investigation only had the scope to examine cognitive trajectory up to around one year post-FH. In the future it will be important to longitudinally follow those with RS into adulthood to determine the possible effects different treatment options (including FH, AEDs and immunosuppression) have on the long-term cognitive functional outcomes of RS. Recent studies have suggested through long-term follow-up that those with hippocampal sclerosis who undergo epilepsy surgery do improve in their intellectual abilities, but only after 8 years post-op (Skirrow et al., 2011). It would be an intriguing prospect to determine if this were also the case with RS and if so, by what means recovery and possible brain reorganisation takes place.

This study was the first to find that the unaffected hemisphere of the brain in RS atrophies over time and that bilateral atrophy of the parietal and occipital lobes may be linked to weaknesses in perceptual reasoning skills. Further understanding of this potentially important finding is needed through regular longitudinal neuroimaging of RS individuals before and after FH. Structural MRI scanning and diffusion weighted imaging could be conducted as closely as possible to disease onset and regularly throughout the disease progression to allow the grey and white matter changes in those with RS to be determined over time. An initial language fMRI could also be completed so that language lateralisation of each RS individual could be determined. Proximal to the scans a neuropsychological

assessment could be conducted to allow further investigation of the relationship between cognitive change and its neural correlates.

These regular neuroimaging and neuropsychological investigations could importantly allow the impact of different medical variables, in particular, timing to surgery, and its impact on brain integrity and cognitive outcome, to be determined. Eventually, it would be important to determine the mechanism by which the unaffected hemisphere may be damaged. It may be that seizure activity propagates from the affected hemisphere into the unaffected hemisphere which might lead to damage of the unaffected hemisphere (Hartman & Cross, 2014). On the other hand, it may be that left to progress naturally RS is in fact a bilateral disease process that preferentially affects one side of the brain initially, but that then causes more subtle atrophy and inflammation of the other hemisphere. The results of these studies may have important implications for the medical treatment of RS individuals.

The longitudinal cognitive and neuroimaging studies described would highly benefit from being conducted across multiple centres around the world to include as many RS individuals as possible. Worldwide cooperation and data sharing is vital and common in extremely rare and neurological conditions (e.g., http://genfi.org.uk/). Indeed, the creation of consortia of researchers allows for faster and more thorough research to be conducted and the quicker development of therapeutic treatments. In the future, initial contact with the Rasmussen Encephalitis Children's Project (http://www.rechildrens.org/) and John Hopkins University in the USA may be an important step to start to set up a consortium to allow cognitive and neuroimaging data sharing of those with RS around the world.

4.7. **Clinical implications**

The neuroimaging finding of this study in particular may have important implications for clinical care and management of those with RS. The VBM results may suggest that a longer

disease course in RS could be potentially harmful to the unaffected hemisphere, which may in turn have significant negative consequences for an individual's cognitive functioning. These findings may be the first clue as to why outcomes after FH are variable and often difficult to predict. It will be important to explore the possibility that damage to the unaffected hemisphere may lead to poorer outcomes both before and after surgery through the longitudinal studies described above. Results of these longitudinal investigations may indicate the need for quicker decision-making around the FH and shorter waiting times to surgery. This idea echoes a recent review that suggested that waiting until motor and cognitive abilities have declined before offering FH may not be advisable (Hartman & Cross, 2014). However, these authors concluded there was not currently sufficient evidence to determine the ideal timing of FH in RS (Hartman & Cross, 2014). It is hoped that a better understanding of RS, its expected outcomes, and important variables that may impact outcome will empower those with RS, their families, and the professionals who care for them to make proactive decisions about their medical care and future. Decisions around timing of FH are taken by individuals with RS, their families and their medical teams jointly. Increasing knowledge into the impacts of a long RS disease course and its effect on the unaffected hemisphere may potentially help all stake holders to take better informed difficult decisions around the timing of FH.

This study characterised the trajectory of RS before and after FH and showed for the first time that there are specific differences in performance between groups at different time points. This knowledge could help Clinical Neuropsychologists make more informed decisions around psychometric assessment and rehabilitation strategies that will most benefit the RS individual, considering their particular disease progression. For example, those with left RS who are moving towards FH could be taught alternate means of communication, such as sign language, so that post-op they have way of communicating before intensive speech and language therapy. The knowledge that those with left RS have weaknesses in all areas of IQ

and academic attainments post-op may also help clinicians to make recommendations around their return to education after surgery and the intensive supports that may be needed.

By further elucidating the outcomes of those with RS this study may also support medical professionals to counsel families as to the expected trajectory for their children affected by RS at the time of diagnosis. Research into other paediatric disorders has suggested poor information at the time of diagnosis or indeed withheld diagnoses can lead to an increased prevalence of depression, isolation and fear for what the future will hold (Sutton et al., 2006). In this way it may be that a greater understanding of a disease, especially when it is rare and life changing, may be an important first step for those affected by RS in the process towards psychological adjustment (Titman & Edwards, 2010). To this end, to ensure that this study's findings are disseminated as widely as possible the guides to RS for teenagers and schools already written will be updated with the findings of the cognitive results of this study. These will be given to those affected by RS when appropriate and sent with neuropsychological reports to schools and other medical professionals to help aid understanding of the RS disease and its expected outcomes. It is highly important that those supporting an RS individual have a good appreciation and understanding of the complex and difficult changes the RS young person goes through (e.g., hemiplegia, hemianopia, cognitive changes, EPC) which are way beyond the observable symptoms of epilepsy. It is hoped that this understanding of the devastating symptoms and disease course of RS will lead to improved care and support in the community for those affected by RS and their families.

4.8. **Conclusion**

This study explored the cognitive trajectory and brain changes at time points before and after surgery in those with RS, a rare neurological disease. Most significantly, our VBM findings showed for the first time that in a subset of our RS participants, specific regions in the

unaffected hemispheres atrophied from around 3 to 6 years post-onset of seizures. Atrophy over time within the parietal and occipital lobes was also seen to be associated with a decline in PRI, which indicates the atrophy of the affected and unaffected hemispheres may have negative impacts on cognitive outcome. This finding builds significantly on previous research (Larionov et al., 2005; Wagner et al., 2012) and may have important implications in regards to the timing of FH. These results will therefore be disseminated in a timely manner.

This study also characterised the cognitive trajectory of RS pre-surgery and pre- and post-op. Some of our findings failed to reach significance, in particular two multiple regression analyses that aimed to explore the impact of medical variables on cognition and post-hoc analyses. Pre-surgery results indicated that both left and right individuals declined in IQ and academic attainment performance over time. There were also some observable differences in group performance and those with left RS were weaker on tasks requiring verbal faculties, whereas the right group had more difficulties with non-verbal perceptual reasoning tasks. The cognitive trajectory pre- to post-op showed those with left RS declined in all IQ abilities post-FH, which was not the case for right RS individuals. In addition, left RS young people were significantly weaker on tasks that required language (VCI and WMI) in comparison to right RS. These findings expand on previous research (Pulsifer et al., 2004) and suggest for the first time that those with left RS have particularly poor outcomes after FH. Future longitudinal research is needed to further understand the cognitive trajectory, brain changes and the links between them in those with RS at multiple time points before and after surgery.

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Appendix

Appendix 1

Dear Sarah

RE: [The Trajectory of Children with Rasmussen's Syndrome]

Thank you for your email seeking additional clarity on whether your project should be classified as research requiring NHS Research Ethics Committee (REC) review.

Based on the information you have provided, our advice is that the project is not considered to be research and does not require review by an NHS Research Ethics Committee.

In giving this advice, we add….

If these assessments are part of routine care, then such analysis could be seen as service evaluation and hence wouldn't require REC review.

This advice is in line with:

- The harmonised UK-wide edition of the Governance Arrangements for Research Ethics Committees (GAfREC), which came into effect on 01 September 2011;
- The Health Research Authority (HRA) decision tools for determining whether a project is research and whether NHS REC review is required;
- The National Research Ethics Service (NRES) leaflet, *Defining Research* and the algorithm *Does my project require review by a Research Ethics Committee?*.

This response should not be interpreted as giving a form of ethical approval or any endorsement to your project. However, it may be provided to a journal or other body as evidence if required.

You should also be aware that:

- All types of study involving human participants should be conducted in accordance with basic ethical principles, such as informed consent and respect for the confidentiality of participants. Also, in processing identifiable data there are legal requirements under the Data Protection Act 2000. When undertaking an audit or service/therapy evaluation, the investigator and his/her team are responsible for considering the ethics of their project with advice from within their organisation.
- This response only covers whether your project is classified as research and whether it requires review by an NHS REC. You are strongly advised to consider other approvals that may be required for your project.

Regards

Queries Line

REF 04/57

The Queries Line is an email-based service that provides advice from HRA senior management, including operations managers based in our regional offices throughout England. Providing your query in an email helps us to quickly direct your enquiry to the most appropriate member of our team who can provide you with an accurate

written response. It also enables us to monitor the quality and timeliness of the advice given by the HRA to ensure we can give you the best service possible, as well as use queries to continue to improve and to develop our processes.

Please note:

- If you have been asked to follow a particular course of action by a REC as part of a provisional or favourable opinion with conditions, then the REC requirements are mandatory to the opinion, unless specifically revised by that REC.
- Should you wish to query the REC requirements, this should either be through contacting the REC direct or, alternatively, the relevant local operational manager (details available from the HRA website http://www.hra.nhs.uk/contact-us/).

Queries Line

Health Research Authority

Ground Floor, Skipton House, 80 London Road, London SE1 6LH

Email: nres.queries@nhs.net | www.hra.nhs.uk and www.nres.nhs.uk

Streamline your research application process with IRAS (Integrated Research Application System)

Help save paper - do you need to print this email?

Appendix 2

Dear Sarah,

Re: The Cognitive Trajectory of Children with Rasmussen Syndrome

Please accept this as confirmation that your project has been registered as a **Service Evaluation** with the Clinical Audit Department and does not require approval from a local research ethics committee.

It is expected that all Clinical Audit is undertaken in line with the Trust Clinical Audit Policy.

1. All **Service Evaluation** Projects should be completed and of value to the service.

2. You will be required to advise us of progress with your audit at the time the project is estimated to be completed. The estimated completion date for your project is **October 2015**. We will send a request for information on this project at the end of that month and will ask for a summary of your work.

3. Changes should be planned where standards for care are not met and there is a real scope for improvement of care or practice, a re-audit may also be necessary.

You are responsible for ensuring that patient information and confidentiality is maintained as part of the project. Information which could identify patients should not be shared outside

of the Trust. If you are involving patients/carers directly in your work then it is important that participants have the opportunity to refuse from participating in your project. You may need to consider whether consent is required.

Should you require access to medical records it is recommended that you note your audit registration number which is **1443.** Please contact Sue Hewitt ext. 5609, to request case notes which are in the library .It is recommended you check the location of the notes on PIMs before contacting Medical Records to avoid delays

In the meantime, please do not hesitate to contact me for advice or support for your project.

We may be able to help you with the following:

•advice and assistance on planning the audit , selection of methodology, and ensuring that audit standards are appropriate for the aim of the project.

•assistance with the design of data collection tools to help measure against standards. We can help you by designing electronic tools to make it easier for you to collect reliable data on computer or mobile device.

•advice on sources of data which may exist within the Trust

•we can assist with data analysis and presenting work to a high standard.

Information sharing about Clinical Audit

Further information summarising currently registered projects and the results of completed projects can be found by clicking on the on the Clinical Audit dashboard page.

http://qst/dashboards/

or on the Clinical Audit intranet page

Good luck with your project, and please get in touch if you require our help

Kind regards

Lucy Kemp

Clinical Audit Assistant

Quality & Safety

Tel 0207 405 9200 **ext 5176**

Great Ormond Street Hospital for Children NHS Foundation Trust

Room A6002, level 6, Paul O'Gorman Building,

Great Ormond Street, London, WC1N 3JH

Clinical audit information for staff

Appendix 3

Dear Sarah,

As REC has deemed this service evaluation, this project will not require registering with R&D - however you do have to register your project with Andrew Pearson whom I have copied in on this email.

Kind Regards,

Manju

Manju Agarwal

Research Management and Governance Officer

Phone: +44 (0) 207 905 2845 | Fax: +44 (0) 207 905 2201 | Email Manju.Agarwal@gosh.nhs.uk

Appendix 4

Application Details:	View the form click here Revise the form click here
Applicant Name:	**Sarah Rudebeck**
Application title:	**The Cognitive Trajectory of Children with Rasmussen Syndrome**
Comments:	Approved. Reviewer comments below. It looks as though the applicant has carefully explored the potential ethical considerations, and has sought the necessary assurances from NRES enquiries and from the Clinical Audit Department at GOSH that the proposed project falls within the definition of a clinical evaluation. As long as Trust guidelines concerning data protection and clinical standards are followed, I have no additional comments.

Appendix 5

Great Ormond Street Hospital for Children NHS Trust

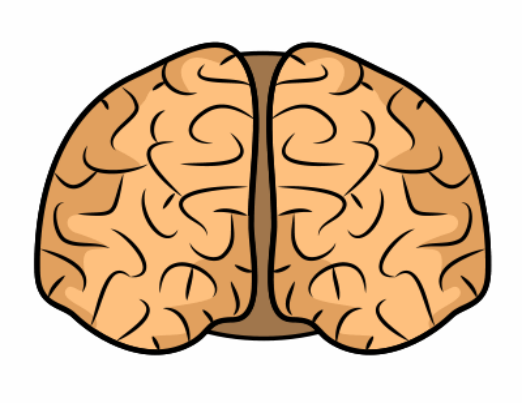
Great Ormond Street
London WC1N 3JH

Tel: 020 7405 9200

Rasmussen Syndrome

This guide is to help explain Rasmussen Syndrome (RS) which is sometimes also called Rasmussen encephalitis. The brain and RS are complicated things and sometimes Doctors and other health professionals use long and complicated words that might make it a bit tricky to understand what they say. We hope this guide will make it easier to understand RS and help you make decisions about your treatment.

The Brain



The brain is made up of two halves - these are called hemispheres. Each half is made up of thousands of brain cells. Whilst the hemispheres are in charge of lots of different functions in our body, each hemisphere controls the movement, sensation and vision for the ***opposite*** side of your body. This means your right brain

hemisphere is in charge of the left hand side of your body and the left hemisphere is in charge of the right.

Rasmussen syndrome

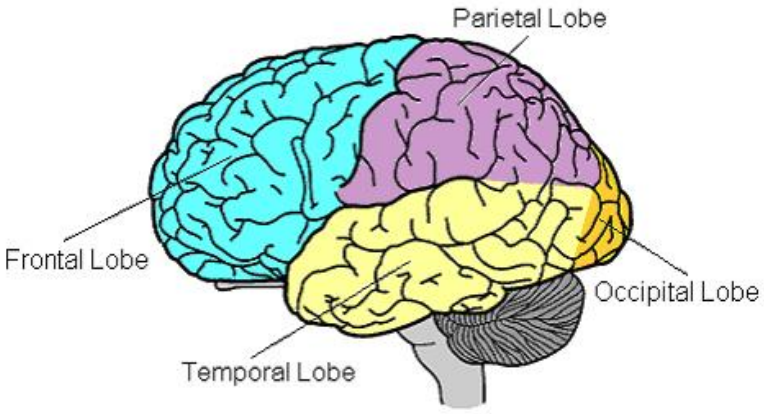
In Rasmussen syndrome the brain cells in one hemisphere become swollen and inflamed. Right now researchers are trying to understand why this happens. It might be what is known as an "auto immune response" in which your own antibodies attack the brain cells, but we still do not know the cause. Researchers are working hard to work out the cause of Rasmussen syndrome so better treatments can be found.

Who gets Rasmussen syndrome?

Children from the age of 3-11 years old are the people most likely to get RS, but sometimes adults have it too.

What are the symptoms?

When brain cells are damaged they can malfunction and this causes seizures. Seizures can range from ones where you can't control your body and move your arms and legs (generalised tonic-clonic), to being sick (yup that can be a seizure too). Seizures can often be really frightening for the person experiencing them. The number of seizures a person with RS will have is different for each person. For some people they will happen a few times a year and for others they will have them all the time. When seizures happen all the time this is called "epilepsia partialis continua".



The parts of the brain that are most affected by RS are the frontal lobe (at the front) and temporal lobe (at the side). At the back of the frontal lobe in each hemisphere there is the control center for movement. When the nerve cells in this area become damaged people with RS can experience jerking in the arm and/or leg on the opposite side of their body. Over time as this center is affected more and more weakness on the side of the body happens. This weakness on one side of your body is also called 'hemiparesis' or 'hemiplegia'.

The brain also controls our ability to remember things, learn, reason and understand what we read and speak. These abilities are not affected in everyone with RS and the pattern of change will be different for everyone. For example, some people with RS might find maths harder, whereas others might start to forget things more often.

Sometimes people with the left hemisphere of their brain affected by RS can find it harder to think of words and speak. This is because the language center of the brain is normally in the left hemisphere. It can be really upsetting and frustrating to find it difficult to speak and do things at school that used to be easy. Remember to talk to those who you are close to, like your Mum and Dad, friend, Doctor or Psychologist if you feel sad or down.

Diagnosing RS

Your Doctor will do a number of different tests to try and work out if you have RS. This will often include an EEG (when electrodes are stuck on your head), MRI scan (where you might go in a big scanner that makes a

lot of noise) and sometimes neuropsychological testing where you will do games and puzzels to see how you are doing in your learning. One thing that doctors will look out for is a change in your brain scans over time. There is no single blood tests that can be done to diagnose RS and your Neurologist will make the diagnosis based on all the different scans and assessments you have.

Common Treatments at GOSH

Medications

Your Neurologists will try and reduce the number of seizures you are having by giving you anti-epileptic drugs. Commonly used epilepsy medicines include carbamazepine, levetiracetam, topiramate and clobazam. Another medicine people are often prescribed are medicines to suppress or alter the immune system. These have to be given in hospital once a month so that the Doctors and Nurses can keep an eye on how you are doing.

Surgery

For some people with RS the best treatment option is for the whole of one side of the brain to be disconnected – this is called a hemispherectomy or hemispherotomy. Scientists have shown having this procedure offers the best chance of reducing seizures. In the UK it is normally only carried out when you already have problems moving one side of your body, lots of seizures and are finding learning difficult. This is because after the hemispherectomy you will have permanent weakness on the side of your body opposite to the hemisphere disconnected. Other things that might change are your ability to speak (especially if your left hemisphere is disconnected) and some people notice it's harder remember things, write fast, concentrate and do maths - but this is different for everyone. We are currently doing research to try and work out what changes occur in peoples learning ability after hemispherectomy.

It is a big decision to have a hemispherectomy and you and your family will talk to your Neurologist and Surgeon about the decision lots of times.

They will help you think about all the pro's and con's and explain things in more detail than this guide. Remember that Doctors love questions so ask them anything you want to know or do not understand. Sometimes it's hard to remember all the questions you have so try writing down any you can think of when you are at home. Then impress the Doctor by getting out your list in your consultation and asking your questions.

Rehab after hemispherectomy

If you and your Doctors decide for you to have a hemispherectomy afterwards you will have 3 months rehabilitation normally in a special center near your house. At this center there is a big team of Doctors, Nurses, Psychologists, Physiotherapists, Speech and Language therapists and Occupational therapist who will work with you for a number of month. They will make sure you recover from surgery. The Physiotherapist will work with you to help you move your effected side that you will have permanent weakness in. Normally people can regain the movement of the big muscles in their leg and arms but not the small muscles like the hand. You will have to work hard though and do all you exercises every day they set you! The speech therapists will help you try to speak again if you are having problems with that, whilst the occupational therapist will make sure the right changes are made to your home and school so you can move around OK.

Recovering from surgery like this can take many months and sometimes can leave people feeling frustrated and upset. Make sure you get lots of support and hugs from you friends and family and talk to the Psychologist in the team if you feel down. They can give you some tips and ideas about how to feel better or sometimes they can just listen and be there for you. Psychologists are good talkers and listeners.

Outlook after surgery

Everyone with RS has different outcomes after surgery. Some people will go on to University and into jobs whereas other people find things a little more tricky to do. Whatever your outcome you will still be able to lead a fulfilling life you will just need a little more help and support. Here is what Brandi Binder says who had RS and hemipsherectomy at the age of 5 years: ”Even though I have only half of my brain, I am still a whole person”.

For more information on Brandi who is an artist and speaker see (www.brandibinder.com).

Further help, information and supports:

www. rechildrens.org – a foundation set up by a family dealing with RS. They organise research, fundraising and supports.

http://hemifoundation.homestead.com/rasmussen.html - information and support for those who have had a hemispherectomy.

https://www.epilepsy.org.uk/info/syndromes/rasmussen-syndrome - information and support about seizures and RS.

www.brandibinder.com – Blog and website of a RS induvidual who had a hemispherectomy 17 years ago and now is an artist and speaker.

http://www.cafamily.org.uk/medical-information/conditions/r/rasmussen-encephalitis/ - how to get in contact with other families and people experiencing RS.

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Rasmussen syndrome - a guide for schools

This guide is to help explain Rasmussen Syndrome (RS) which is sometimes also known as Rasmussen encephalitis. This is a rare and complex neurological disorder that can affect all elements of a child's life including their motor abilities, self-care, vision, speech and learning levels. We hope this guide will make it easier for those supporting a child or adolescent with a diagnosis of RS appropriately.

What is Rasmussen syndrome?

In Rasmussen syndrome is a progressive neurological disorder in which the brain cells in one hemisphere of the brain become swollen and inflamed. This inflammation causes damage to this side of the brain and it slowly will begin to atrophy or shrink. The cause of Rasmussen syndrome it is not known but currently research suggests it's an "auto immune response" in which your own antibodies attack the brain cells.

Rasmussen syndrome is typically diagnosed when one side of the bran is seen be shrinking on an MRI scan, frequent seizures cannot be controlled by medication and changes are observed in a child's learning and cognition. There is no single test that can be done to diagnose Rasmussen syndrome and there is no cure for the underlying cause as this is still unknown.

Who gets Rasmussen Syndrome?

Children from the age of 3-11 years old are the people most likely to be diagnosed with Rasmussen syndrome. It is very rare with around 2 new cases being diagnosed in the UK a year.

What are the symptoms?

1. **Seizures** - When brain cells are damaged they can malfunction and this causes seizures. Children with Rasmussen syndrome typically have generalized and focal seizures. For more information about seizures please see (https://www.epilepsy.org.uk/info/seizures-explained). In Rasmussen syndrome some children also experiences "epilepsia partialis continua" which is when a child experience motor seizures in either their hand, arm, leg, foot or face. These can occur for a few seconds of minutes and normally occur over days or weeks. Seizures are very hard to control in Rasmussen syndrome using typical anti-epileptic medications.

2. **Hemiparesis and hemiplegia** - The parts of the brain that are most affected by RS are the frontal lobe (at the front) and temporal lobe (at the side). At the back of the frontal lobe in each hemisphere there is the control center for movement. When the nerve cells in this area become damaged people with RS can experience jerking in the arm and/or leg on the opposite side of their body. Over time as this center is affected more and more weakness on the side of the body happens. This weakness on one side of your body is also called 'hemiparesis' or 'hemiplegia'. Hemiparesis will often mean that a child will need supports to get around such as a wheelchair or splints for their arms or legs, as one of their sides weakened and in extreme cases paralyzed.

3. **Learning and cognition** –the pattern of learning and cognition change is different in all individuals with Rasmussen syndrome. Most commonly we see a pattern in which those with RS will progressively loose cognitive abilities, in particular verbal and non-verbal intelligence, processing speed, memory and visual perception. This will affect all level of their academic ability and they will likely go from a child with normal abilities to having abilities in the low average and low range. In those with RS affecting their left hemisphere they are likely to experience problems with speech and language. They may have problems comprehending speech or expressing themselves with frequent word finding difficulties. Alternatively they may have issues with the motor movements needed to produce speech sounds. Those with right hemisphere RS will commonly experience problems with non-verbal intellectual tasks such as, maths and science and problem solving. Research is currently trying to understand better what happens to RS individual's cognitive abilities over the syndromes progression.

4. **Behavior and Emotions** – some people with RS will start to have more difficulties with concentration, attention and getting along with others. This may be because their frontal lobe is becoming increasingly swollen and inflamed and this is the area of the brain that controls impulsivity, theory of mind and attention. In addition, anyone who is experiencing a life changing disorder will need help and support to adapt to the changes occurring to their body, brains and functioning. Feelings of frustration, depression, anger and anxiety can be common in those with RS at different points as the syndrome progresses.

Common Treatments

Medications

The number of seizures will try to be reduced by giving the young person anti-epileptic drugs. Commonly used epilepsy medicines include carbamazepine, levetiracetam, topiramate and clobazam. Another medicine people are often prescribed are medicines to suppress or alter the immune system this is called intravenous immunoglobulin but is often called IVIG for short hand. These have to be given in hospital once a month.

Surgery

For some people with RS the best treatment option is for the whole of one side of the brain to be disconnected – this is called a hemispherectomy or hemispherotomy. Scientists have shown having this procedure offers the best chance of reducing seizures. In the UK it is normally only carried out when the RS individual already have problems moving one side of your body, lots of seizures and are finding learning difficult. This is because after the hemispherectomy the RS individual will have permanent weakness on the side of your body opposite to the hemisphere disconnected. Other likely consequences of the surgery are on speech and language (especially if the left hemisphere is disconnected) and cognitive ability is expected to remain the same but not necessarily improve. Research is currently being undertaken at GOSH to try and work out what changes occur in peoples learning ability after hemispherectomy.

What can we do to help at school?

Seizures

It is important that at your school a there is a seizure plan that is designed with the affected child and family and local epilepsy nurse. A trained first aider will need to know what to do if a seizure occurs and how to give emergency medication if it is prescribed. Your local epilepsy nurse can do a visit to run through a plan with you and your young person. They can also advise on extra supervisions needed during certain activities like swimming and games. Often after someone has a seizure they experience tiredness and need a place to rest. Ideally this should be provided at school so that they can rest and recover and rejoin lessons when they feel better. This will also minimize the amount of school missed.

Hemiparesis

To aid those to move around with hemiparesis special modifications may need to be made to the school to make areas wheelchair accessible. Specialist advice should be sort from an Occupational Therapist in the local disable children's social work team or hospital in which their care is under. A safe route in an event of a fire alarm should also be thought through carefully planned for the young person.

Learning

Those with RS will typically be cognitively assessed at GOSH or a nearby hospital yearly so that the changes in their learning ability can be monitored. It is important that any recommendations to aid changing learning abilities are quickly put in to place so they can achieve the best outcome possible. These may include:

- Applying for a state of special educational needs
- 1-to-1 support or small group teaching
- Specific teaching modifications to taking into account changing cognitive function
- Reducing the number of GCSE's and A-Levels taken

- Help and support them catch up on worked missed after a time of absence due to sickness.

- For specialist advice and consultation on how to best support someone's learning with RS please feel free to contact the Neuropsychology Team at GOSH (tel: 020 7829 8679 ext 0146).

Behaviour and Emotions

It is important that a young person with RS mood and behavior are monitored closely at school. People with RS often become left out and bullied by their peers due to their perceived difference such as epilepsy, learning disability and motor problems. Those in their class should be actively taught about RS and encouraged to be supportive towards the RS individual whilst not treating them as different or special. Any bullying should also be dealt with quickly by head of years/SENCO to ensure that this does not further negatively impact the RS child who is already dealing with high number of difficult and upsetting circumstances. If it is perceived to be helpful the RS individual may benefit from attending a school counselor or CAMHS service to have someone to talk to and make sense of their diagnosis. For specialist support and consultation on how to support someone's behavior and emotional health with RS please contact Pediatric Psychology at GOSH (tel: 020 7829 8679).

Further help, information and supports:

www. rechildrens.org – a foundation set up by a family dealing with RS. They organise research, fundraising and supports.

http://hemifoundation.homestead.com/rasmussen.html - information and support for those who have had a hemispherectomy.

https://www.epilepsy.org.uk/info/syndromes/rasmussen-syndrome - information and support about seizures and RS.

www.brandibinder.com – Blog and website of a RS induvidual who had a hemispherectomy 17 years ago and now is an artist and speaker.

http://www.cafamily.org.uk/medical-information/conditions/r/rasmussen-encephalitis/ - how to get in contact with other families and people experiencing RS.