Some long-term outcomes of visual dysfunction arising from vigabatrin ocular toxicity

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Doctor of Philosophy, 2014
Abstract

The purpose of this thesis was to assess long-term outcomes of the visual dysfunction arising from the ocular toxicity associated with the anti-epileptic drug vigabatrin (VGB).

The risk of vigabatrin-associated visual field loss (VAVFL) with increasing exposure to VGB was modelled from retrospectively collected data from a cohort of 147 individuals (median exposure 7.9 years; IQR 3.6, 11.0). The modelled frequency of VAVFL increased with increasing exposure and plateaued at 75-80% after approximately 6 years duration and 5kg cumulative dose.

The relationship between the numbers of retinal ganglion cell soma and axons, derived by standard automated perimetry and time-domain optical coherence tomography (TDOCT), respectively, was evaluated in 24 individuals with VAVFL and in 16 exposed to vigabatrin but with normal fields (VGBN). A strong linear association was present between the two outcomes, which was suggestive of an optic neuropathy, and was similar to the association for a control group of 18 individuals with open angle glaucoma.

A follow-up visual field, after a median interval of 7.0 years (IQR 6.5, 7.6) was determined in 19 individuals with VAVFL and in 8 with VGBN, after a median withdrawal from VGB of 7.1 years (IQR 5.4, 8.4). No consistent trend was noted for either a deterioration or improvement in the field.

A follow-up scan of the peripapillary retinal nerve fibre layer (RNFL) thickness, by TDOCT, after a median interval of 6.5 years (IQR 5.8, 6.9) was obtained in 13 individuals with VAVFL and in 4 with VGBN, after a median withdrawal from VGB of 8.0 years (IQR 5.3, 10.2). No consistent trend was noted for either a deterioration or improvement of the RNFL thickness.

The macular thickness was evaluated by TDOCT in 32 individuals with VAVFL and in 14 with VGBN. No difference in thickness was noted between the two groups.

In conclusion, the prevalence of VAVFL, arising from the longer-term exposure to the drug, was substantially greater than previously recognized. The strong association between structural and functional outcomes, considered in terms of numbers of ganglion cell soma and axons, respectively, indicated that vigabatrin toxicity causes an optic neuropathy. Within the limits of the cohorts studied and the investigative methods employed, there was no evidence for either recovery or worsening of either structural or functional abnormality following long-term withdrawal from vigabatrin. Clinicians and patients should be alerted to the presence of the above findings.
For My Parents
Acknowledgements

I would like to express my sincere gratitude to my wife, Zahra Almualem, who has supported me, endured the difficulties throughout, and has looked after myself and my children.

I am also grateful to my primary supervisor, Prof John Wild, who made sure that I was fully equipped with the knowledge and skills for my studies as well as for the future research. I would also like to thank my secondary supervisor, Prof Philip Smith, for kindly allowing me to examine his patients.

I am also grateful to Prof David Fone, to Prof Robert Newcombe, to Dr Charlotte Lawthom and to Mr Gareth Lewis for their collaboration in the work described in Chapter Three.

My thanks also go to Belinda Colton, Senior Medical Photographer in the Cardiff Eye Unit at the University Hospital of Wales, for undertaking the OCT scans; to the Epilepsy Specialist Nurses, Vicki Myson and Malissa Pierri, at the Alan Richens Unit, University Hospital of Wales; and to the patients attending the Alan Richens Unit who participated in the various studies.

My colleagues, Khoulod Alshaghroud, Aris Chandrinos, and Elaine Malissova, have given me their friendship and, therefore, a conducive working environment.

My family at home in Saudi Arabia have always encouraged and supported me. I wish to reserve a special place in these Acknowledgements for my beloved father who died during my studies, on 8th of January, 2013. I thank him for his enthusiastic and positive support and for always encouraging me. I also wish to thank my mother for her continual supplications to Allah for guidance in my studies.
DECLARATION

This work has not previously been accepted in substance for any degree and is not concurrently submitted in candidature for any degree.

Signed ........................................ (Candidate) Date 14.10.2014

STATEMENT 1

This thesis is being submitted in partial fulfilment of the requirements for the degree of PhD

Signed ........................................ (Candidate) Date 14.10.2014

STATEMENT 2

This thesis is the result of my own independent work/investigation, except where otherwise stated. Other sources are acknowledged by explicit references.

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<td>AED</td>
<td>Anti-epileptic drug</td>
</tr>
<tr>
<td>CPMP</td>
<td>Committee for Proprietary Medicinal Products</td>
</tr>
<tr>
<td>EMEA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EOG</td>
<td>Electrooculogram</td>
</tr>
<tr>
<td>ERG</td>
<td>Electroretinogram</td>
</tr>
<tr>
<td>ETDRS</td>
<td>Early Treatment of Diabetic Retinopathy Study</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>ISCEV</td>
<td>International Society for Clinical Electrophysiology of Vision</td>
</tr>
<tr>
<td>OAG</td>
<td>Open angle glaucoma</td>
</tr>
<tr>
<td>OCT</td>
<td>Optical coherence tomography</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>REMS</td>
<td>Risk Evaluation and Mitigation Strategy</td>
</tr>
<tr>
<td>SAP</td>
<td>Standard automated perimetry</td>
</tr>
<tr>
<td>SHARE</td>
<td>Support, Help, and Resources for Epilepsy</td>
</tr>
<tr>
<td>VEP</td>
<td>Visual evoked potential</td>
</tr>
<tr>
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and the denominator indicates the number of locations exhibiting abnormality at the
given probability value, at the baseline examination. An identical analysis for the outer
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number of locations exhibiting identical probability values at the two examinations. The
number of locations exhibiting an improvement, by the number of probability levels, at
the follow-up examination is shown to the left of the vertical shading and the number of
locations exhibiting a deterioration, by the number of probability levels, is shown to the
right of the vertical shading. The numerator indicates the number of locations exhibiting
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number of locations exhibiting identical probability values at the two examinations. The
number of locations exhibiting an improvement, by two or by three or more probability
levels, respectively, at the follow-up examination is shown to the left of the vertical
shading and the number of locations exhibiting a deterioration, by two or by three or more probability levels, respectively, is shown to the right of the vertical shading. The numerator indicates the number of locations exhibiting normality, and the denominator indicates the number of locations exhibiting abnormality at the given probability value, at the baseline examination. An identical analysis for the outer two annuli (1st or 2nd) of stimulus locations (as indicated in Table 6-13), by three or more probability levels, at the follow-up examination is shown to the left (improvement) and right (deterioration) of the vertical shading. *indicates an individual considered by clinical evaluation to exhibit progressive visual field loss in both eyes. .........................................................192

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respectively, at the follow-up examination is shown to the left of the vertical shading and the number of locations exhibiting a deterioration, by two or more probability levels, respectively, is shown to the right of the vertical shading. The numerator indicates the number of locations exhibiting normality, and the denominator indicates the number of locations exhibiting abnormality at the given probability value, at the baseline examination.

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Chapter 1. **Epilepsy and vigabatrin**

### 1.1 Epilepsy

Epilepsy is a diverse collection of clinical syndromes with a common characteristic of seizures as a consequence of abnormal synchronization and amplification of neural firing in electrical unstable areas of the brain (Tobias, Brodie and Brodie, 1994). The prevalence of epilepsy is between 5-10 cases per 1000; (Beghi, 2004; Wheless, Ramsay and Collins, 2007). According to the National Health Service, approximately 456,000 people in the UK are affected by epilepsy (Medicinnet, 2013). The incidence of epilepsy in the United States and Europe is between 20 to 70 cases per 100,000 per year (Tobias et al., 1994; Brodie et al., 1997; Hesdorffer et al., 2011).

The prevalence of epilepsy varies with age and gender. The prevalence decreases from early childhood to early adulthood and then steadily increases with increasing age. The prevalence is slightly higher in males than in females (Hauser, Annegers and Kurland, 1993; Faught et al., 2012).

### 1.2 Mortality of epilepsy

The risk of death for an individual with epilepsy is greater compared to that for the general population. The overall sudden unexpected death in epilepsy (SUDEP) is 0.9-
2.3 per 1000 person years (Hart, 2012). However, a causal relationship between antiepileptic drug therapy (AED) and death cannot be excluded (Ackers et al., 2011).

1.3 Classification of epilepsy

The most commonly used systems over the last decade for the classification of epilepsy have been those developed under the auspices of the International League Against Epilepsy (ILAE), namely, the International Classification of Epileptic Seizures (1981) (Berg et al., 2010; Berg and Millichap, 2013) and the International Classification of Epilepsies, Epileptic Syndromes and Related Seizure Disorders (1989). However, these classifications are gradually being superseded by a revised terminology and schema for the organization of seizures and epilepsies proposed by the ILAE Commission on Classification and Terminology in 2010 (Berg et al., 2010). Even so, the latter approach is the subject of on-going discussion (Byung-In, 2013).

The ILAE Classification of 1981 and 1989 divided epilepsy into three types: Partial seizures, Generalized seizures, and Unclassified seizures. Partial seizures were those which began locally and were divided into three subtypes: Simple partial seizures, Complex partial seizures, and Partial seizures with secondary generalisation. Generalized seizures were divided into six subgroups: Absence seizures, Myoclonic seizures, Clonic seizures, Tonic seizures, Tonic-Clonic seizures and Atonic seizures.

A comparison of the 1981 and 1989 ILAE classifications with the ILEA proposal of 2010 is reproduced from Berg and Scheffer (2011) as Table 1-1.
<table>
<thead>
<tr>
<th>Old terminology and concepts</th>
<th>Recommended new terminology and concepts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal and generalized</td>
<td></td>
</tr>
<tr>
<td>For seizures</td>
<td></td>
</tr>
<tr>
<td>Focal (previously “partial”): the first clinical and electroencephalographic changes indicate initial activation of a system of neurons limited to a part of one cerebral hemisphere</td>
<td>Focal seizures are conceptualized as originating at some point within networks limited to one cerebral hemisphere</td>
</tr>
<tr>
<td>Generalized: the first clinical changes indicate initial involvement of both hemispheres</td>
<td>Generalized seizures are conceptualized as originating at some point within and rapidly engaging bilaterally distributed networks</td>
</tr>
<tr>
<td>For epilepsies</td>
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</tr>
<tr>
<td>Localization-related (focal, partial): epilepsies with focal seizures Generalized: epilepsies with generalized seizures</td>
<td>These terms were abandoned as overarching categories for classifying epilepsies, per se, as many syndromes include both seizure types; they may still apply in some but not all instances.</td>
</tr>
<tr>
<td>Aetiology</td>
<td></td>
</tr>
<tr>
<td>Idiopathic: there is no underlying cause other than a possible hereditary predisposition. Symptomatic: the epilepsy is the consequence of a known or suspected disorder of the central nervous system Cryptogenic: this refers to a disorder whose cause is hidden or occult. Cryptogenic epilepsies are presumed to be symptomatic</td>
<td>Genetic: the epilepsy is, as best as understood, the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder. This attribution must be supported by specific forms of evidence. Structural/metabolic: there is a distinct other structural or metabolic condition or disease that has been demonstrated to be associated with a substantially increased risk of developing epilepsy. These disorders may be of acquired or genetic origin. When of genetic origin, there is a separate disorder interposed between the gene defect and the epilepsy unknown:</td>
</tr>
</tbody>
</table>
Old terminology and concepts | Recommended new terminology and concepts
--- | ---
the nature of the underlying cause is unknown; it may have a fundamental genetic basis (e.g., a previously unrecognized channelopathy) or it may be the consequence of an unrecognized structural or metabolic disorder not yet identified

Focal seizure types

| Complex partial: with impairment of consciousness. Simple partial: consciousness not impaired. Secondarily generalized (note: this was not the terminology used in the 1981 document but has come into common use) | No specific classification is recommended. Seizures should be described accurately according to their semiologic features without trying to fit them into artificial categories |

Organizational structure for epilepsies

| Hierarchically organized by localization-related, generalized, and undetermined. Within those groups, by aetiology (idiopathic, symptomatic, cryptogenic) | No specific organization is proposed. Instead a flexible approach depending on needs is advocated |

Table 1-1: The major changes between the ILAE 1981 and 1989 Classification and Terminology (left hand column) and the ILAE Terminology and Concepts proposed in 2010 (right hand column) (Berg and Scheffer, 2011).

1.4 Vigabatrin

Vigabatrin (VGB) was first synthesized in 1974 as an analogue of gamma-aminobutyric acid (GABA) (Sankar and Derdiarian, 1998). The latter is the main inhibitory neurotransmitter in the central nervous system. The mechanism of action of vigabatrin is thought to occur through the selective, non-competitive and irreversible inhibition of GABA transaminase, the enzyme which catalyses GABA, thereby increasing whole
brain pre-synaptic GABA levels (Lawden, 2006; Willmore et al., 2009). In the rat retina, vigabatrin is accumulated in higher concentrations than in the cortex and is associated with an accumulation of retinal GABA (Sills et al., 2001).

Vigabatrin (Sabril) was introduced in 1989 as add-on therapy for adults with drug-resistant partial epilepsy (Best and Acheson, 2005) and as mono-therapy for infantile spasms (IS) (Chiron et al., 1990). By 2006, vigabatrin was available in at least 85 countries (Wild et al., 2006). Vigabatrin was approved in 2009 by the United States Food and Drugs Administration (FDA) as add-on therapy for adults who have responded inadequately to alternative anti-epileptic drugs (AEDs) and in whom the potential benefits of the drug outweigh the risk of the visual field loss, and as mono-therapy for children, of one month to two years of age, with IS.

1.4.1 Efficacy of vigabatrin in adults

The most recent Cochrane Review of the efficacy of vigabatrin, when used as add-on therapy for adults with drug resistant partial epilepsy, is based upon 11 short-term, randomised, placebo-controlled trials covering doses of between 1000mg and 6000mg and comprises 982 observations on 747 individuals (Hemming et al., 2013). Individuals treated with vigabatrin were significantly more likely to obtain a 50% or greater reduction in seizure frequency compared with those treated with placebo (Risk Ratio [RR] 2.58, 95% CI 1.87 to 3.57). Those treated with vigabatrin were also significantly more likely to have treatment withdrawn (RR 2.49, 95% CI 1.05 to 5.88), and were more likely to experience fatigue or drowsiness. Some evidence of small study effect bias was present, with smaller studies tending to report greater estimates of the RR than larger studies. The RR for a 50% reduction in seizure frequency may, therefore, be less than that obtained with a meta-analysis of all available studies.
1.4.2 Efficacy of vigabatrin in Infantile Spasms (IS)

Infantile spasms is a rare syndrome that includes a peculiar type of seizure, a high risk of psychomotor retardation and, usually, a characteristic pattern to the electroencephalogram (EEG) known as hypsarrhythmia (Mackay et al., 2004). IS can be associated with cerebral palsy, Down syndrome, tuberous sclerosis, and neuronal migration disorders (Hancock, Osborne and Edwards, 2013). The prevalence of IS is 0.16 to 0.42 per 1000 live births (Hancock, Osborne and Edwards, 2013).

The most recent Cochrane Review of the efficacy of treatment for IS is based upon 18 randomised controlled trials and comprises 916 individuals and covers a range of 12 different pharmaceutical agents (Hancock, Osborne and Edwards, 2013). Sixteen of the 18 studies each contained less than 100 individuals. The majority of the studies exhibited poor methodology and there was insufficient evidence to recommend vigabatrin as a treatment for IS.

1.5 Vigabatrin-associated visual field loss

1.5.1 Historical Perspective

In 1997, a case series, in the British Medical Journal, of three individuals linked the presence of visual field loss to the use of vigabatrin (Eke., et al 1997). The individuals had been exposed to 2.3kg, 3.5kg and 4.1kg of vigabatrin over 37, 28, and 38 months, respectively, and all presented with normal visual acuities but were symptomatic for their field loss which manifested as a ‘concentric’ constriction. Two of the three individuals exhibited bilateral optic nerve head pallor. All three exhibited abnormalities of the Arden Index (the ratio between the light and dark potentials) of the
electrooculogram (EOG) (Arden, Barrada et al., 1962) and of the oscillatory potentials of the electroretinogram (ERG) but had normal visually evoked potentials to flash and to pattern stimuli.

A number of additional case reports were subsequently published shortly afterwards as Letters to the Editor of the British Medical Journal (Blackwell, Hayllar and Kelly, 1997; Brodie et al., 1997; Wilson and Brodie, 1997; Wong, Mawer and Sander, 1997). The association of vigabatrin with visual field loss was confirmed in the ensuing two years (Krauss, Johnson and Miller, 1998; Rao et al., 1998; Arndt et al., 1999; Daneshvar et al., 1999; Kalviainen et al., 1999; Lawden et al., 1999; Miller et al., 1999; Wild et al., 1999a; Wohlrab et al., 1999) and over the following decade and beyond.

In the historical context, the findings of Kälviäinen and colleagues in 1999 were unique and particularly important in that they referred to adults exclusively treated with vigabatrin as monotherapy; thereby excluding the possibility of other AEDs in the aetiology of the field loss. Similarly, the study of Wild and colleagues in 1999 was the first to report the absence of field loss, other than that attributable to a known aetiology, in a substantial number of individuals with epilepsy who had never been treated with vigabatrin; thereby adding further evidence to the hypothesis that vigabatrin, alone, was associated with visual field loss.

A retinal location for the toxicity associated with vigabatrin was supported by the findings from a case series of 4 individuals in whom the oscillatory potentials were absent (Krauss et al., 1998).
The three individuals described by Eke and colleagues (1997) subsequently formed part of a larger case series of eight individuals (Harding et al., 2000c) and had undergone more detailed visual field and visual electrophysiological examination. On withdrawal of vigabatrin, the Arden index of these three individuals returned to the normal range, indicating a metabolic effect of vigabatrin on the retinal pigment epithelium but the visual field loss remained (Harding et al., 2000c). The 30Hz b-wave exhibited a reduction in latency in five of the six eyes and the OP1 and OP2 latencies and amplitudes were all abnormal (Harding et al., 2000b). The results from the remaining ERG responses defined by the International Society for Clinical Electrophysiology of Vision (ISCEV) standards were normal as were the Flash and Pattern visual evoked potentials (VEPs).

As of December 2013, there are approximately 200 publications which discuss vigabatrin-associated visual field loss in the MEDLINE (1998-2013), SCOPUS (1998-2013) and CINAHL (1998-2013) databases.
<table>
<thead>
<tr>
<th>Study ID</th>
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<th>Type of test</th>
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<th>Mean cumulative dose (g)</th>
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<tr>
<td>43</td>
<td>Wild et al., (2009)</td>
<td>A&amp;C</td>
<td>L</td>
<td>210</td>
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<td>BOTH</td>
<td>2.9</td>
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<td>44</td>
<td>Sergott et al., (2010)</td>
<td>C/L</td>
<td>83</td>
<td>NA</td>
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<td>BOTH</td>
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A, Adult population; C, Child population; L, Longitudinal study; CS, Cross-sectional study; S, Static perimetry; K, Kinetic perimetry; BOTH, Static and Kinetic perimetry; ERG, Electoretinogram; NA, Not applicable, VAVFL, vigabatrin-associated visual field loss.

Table 1-2: The frequency of vigabatrin-associated visual field loss. The studies highlighted in bold indicate those containing individuals with five or more years of exposure to vigabatrin.

### 1.5.2 The Frequency of vigabatrin-associated visual field loss

The various estimates of the frequency of vigabatrin-associated visual field loss are summarised, by study, in Table 1-2. Aside from the issues associated with the representative nature of a given cohort, the determination of the prevalence of vigabatrin-associated visual field loss is influenced by the sensitivity and specificity of the perimetric technique to identify the vigabatrin-associated visual field loss, by the ability of the individual to produce a reliable result, and by the experience of the clinician to interpret, correctly, the result from the examination. In addition, it should also be noted that approximately 20% to 25% of adult individuals exposed to vigabatrin are unable to perform perimetry reliably (Harding et al., 2000c).
The frequency of vigabatrin-associated visual field loss ranges from 6% (Gaily, Jonsson and Lappi, 2009) to 93% (Clayton et al., 2013). A pooled analysis of 335 individuals, from all available studies at the time, yielded a frequency estimate of 32% (95% CI 28, 36%) (EMEA, 1999). However, the only systematic review of the prevalence of vigabatrin-associated visual field loss, which is based upon 32 studies and includes 1,678 individuals exposed to vigabatrin and 406 controls, found that the median for visual field loss was 45% [interquartile range (IQR) 33–60] (Maguire et al., 2010). For a mean cumulative dose of 1000g of vigabatrin, the estimated proportion with field loss was 34%, compared to 53% for those receiving a cumulative dose of 5000g. For the nine studies reporting vigabatrin-associated visual field loss, specifically, the median value for vigabatrin-associated visual field loss was 31% (IQR 21–52) and the median value of field loss attributed to other causes was 10% (IQR 5–13). Adults yielded a higher median proportion with visual field loss than children [55% (IQR 40, 63) compared to 33% (IQR 22, 56)]. The studies described within the systematic review were based upon relatively short-term exposures to vigabatrin (mean duration 3.9 years; standard deviation [SD] 1.5; mean cumulative dose 3.5 kg; SD 1.5 kg).

The lower prevalence of vigabatrin-associated visual field loss in children may simply arise from an under reporting due to an inability to perform perimetry under the age of approximately 9 to 10 years. To overcome this latter problem, a field-specific VEP was developed which utilised a central stimulus (0° to 5° radius) and a peripheral stimulus (30° to 60° radius) (Harding et al., 2000c). Both stimuli consisted of black and white checks which increased in size with eccentricity. The checks reversed at different rates, allowing separate central and peripheral responses to be recorded. In a limited case series of 12 children, the field-specific VEP identified 3 of 4 abnormal visual fields, and 7 of 8 normal fields, designated by perimetry (Harding et al., 2000c). Alternatively,
aspects of the full field ERG can be utilised, such as the outcome to the 30Hz flicker (Harding, Robertson and Holliday, 2000a).

Although it is possible that the prevalence of vigabatrin-associated visual field loss may be lower in children, there is no evidence of vigabatrin toxicity in children exposed to vigabatrin in utero (Sorri et al., 2005; Lawthom, Smith and Wild, 2008).

### 1.5.3 Characteristics of vigabatrin-associated visual field loss

The visual field loss associated with vigabatrin is, typically, a bilateral and clinically symmetrical, ‘concentric’ constriction of the peripheral field which is generally more pronounced nasally than temporally, both in terms of area and depth, and which, in almost all cases, encroaches upon at least the nasal region of the central field (i.e. out to a radius of 27º from fixation) (Wild et al., 2009). By static perimetry, using Goldmann stimulus size III, the field loss manifests as a steep sided bi-nasal annulus extending to varying degrees, vertically across the horizontal midline and also centripetally. In severe manifestations, the defect by static perimetry manifests as a concentric constriction to within approximately 15º from fixation (Wild et al., 2009).

The nasal to temporal asymmetry in the magnitude of the field loss is less apparent by kinetic perimetry (Lawden, 2006).

The frequency of vigabatrin-associated visual field loss is higher with static threshold perimetry of the central field and suprathreshold perimetry of the peripheral field compared to that with kinetic perimetry of both the central and peripheral field (Odds Ratio [OR] 2.32; CI 1.33, 4.16) or the peripheral field only (OR 2.86; CI 0.30, 25.0) (Wild et al., 2009). Equally, the results from the systematic review of Maguire et al.,
(2010) indicated that the median proportion of field loss was higher for a combination of static and kinetic perimetry (55% IQR 37, 60) compared either to static perimetry, alone, (50%; IQR 30, 62) or to kinetic perimetry, alone, (42% IQR 33, 64).

The degree of symmetry of vigabatrin-associated visual field loss was used by Conway, Cubbidge and Hosking, (2008) to develop a Vigabatrin Severity index and a Defect Symmetry Index.

The visual field loss associated with vigabatrin is initially asymptomatic (Eke et al., 1997; Lawden et al., 1999; Wild et al., 1999a). The visual acuity is normal, or near normal, and the relative sparing of the temporal field in one eye compensates for the predominantly nasal defect in the contralateral eye (Wild et al., 1999a). Field loss becomes symptomatic as the temporal field becomes increasingly affected, i.e., as the field loss becomes a bilateral concentric constriction within approximately 15° eccentricity.

1.5.4 Risk factors for vigabatrin-associated visual field loss

1.5.4.1 Gender

Male preponderance is generally considered to be the major risk factor for vigabatrin-associated visual field loss (Wild et al., 1999a; Hardus et al., 2000b; Hardus et al., 2000c; Kalviainen and Nousiainen, 2001; Newman, Tocher and Acheson, 2002; Wild et al., 2009). The risk of vigabatrin-associated visual field loss is 2 to 2.5 times greater for males (OR 2.1, 95% CI 1.20, 4.6%) (Wild et al., 1999a). However, most smaller scale studies have failed to show such an association (Manuchehri et al., 2000; Comaish et al., 2002; Gonzalez et al., 2009) and, therefore, the lack of an association is reflected in the results of the systematic review of (Maguire et al., 2010).
1.5.4.2 Age

Although many studies have not specifically addressed the issue of age, the frequency of vigabatrin-associated visual field loss is considered to be lower in children than in adults. As was discussed earlier, the systematic review of Maguire et al., (2010), for example, found the median proportion of adults with field loss of all types was 55% (IQR 40, 63) compared to that for children of 33% (IQR 40, 63). As was also discussed earlier, the lower frequency of vigabatrin-associated visual field loss in children is most likely to reflect the difficulties in obtaining a reliable result from the visual field examination.

1.5.4.3 Smoking

Smoking exhibits borderline significance as a risk factor for developing vigabatrin-associated visual field loss (Wild et al., 1999a; Kalviainen and Nousiainen, 2001).

1.5.4.4 Cumulative dose of vigabatrin

The association of larger cumulative doses of vigabatrin with a higher frequency of cases of vigabatrin-associated visual field loss is equivocal. However, as discussed previously, the systematic review of Maguire et al., (2010) found a prevalence of 34% with visual field loss (of all types) for a mean cumulative dose of 1000g compared to 53% for a mean cumulative dose of 5000g. However, in a study not included in the systematic review, the prevalence of vigabatrin associated visual field loss was 4% (2 of 51 individuals) for cumulative doses of less than 1000g and 71% (10 of 14 individuals) for cumulative doses of greater than 3000g (Malmgren, Ben-Menachem and Erisén, 2001). The latter study was unusual in that the cohort comprised a relatively large number of individuals who had low cumulative doses of vigabatrin but the composition
highlighted the clear distinction between low and higher cumulative doses of vigabatrin in the evolution of vigabatrin-associated visual field loss. Similar findings were reported by Lawden et al., (1999); the mean cumulative dose for those without vigabatrin-associated visual field loss was 1.7kg compared to 4.4kg for those with vigabatrin-associated visual field loss.

Interestingly, in the largest study to date and which involved 734 individuals of whom 421 were exposed to vigabatrin and based upon the 524 individuals who were able to undertake a visual field examination reliably (386 exposed to vigabatrin and 138 exposed to other AEDs), the presence of vigabatrin-associated visual field loss was associated with mean daily dose of vigabatrin (OR 26.4; 95% CI 2.4, 291.7) (Wild et al., 2009). Other studies have reported that cumulative vigabatrin exposure is positively correlated with the prevalence of vigabatrin-associated visual field loss (Manuchehri, 2000; Hardus et al., 2001b; Malmgren et al., 2001) and with the severity of the field loss (Manuchehri, 2000; Hardus et al., 2001b; Frisen, 2004). Alternatively, increasing cumulative dose of vigabatrin has not been found to be associated with a higher frequency of vigabatrin-associated visual field loss (Kalviainen et al., 1999; Newman et al., 2002; Nicolson et al., 2002; Kinirons et al., 2006).

1.5.4.5 Duration of vigabatrin therapy

The association of longer durations of vigabatrin therapy with a higher frequency of vigabatrin-associated visual field loss is also equivocal. The systematic review of Maguire et al., (2010) failed to find any association between duration of vigabatrin therapy and the presence of visual field loss. The studies were based upon relatively short-term exposures to vigabatrin (mean duration 3.9 years; standard deviation [SD] 1.5; mean cumulative dose 3.5 kg; SD 1.5).
However, the study by Wild and colleagues in 2009, which is described in above, found that the frequency of vigabatrin-attributed visual field loss increased substantially with increase in the duration of vigabatrin therapy (OR 15.2; 95% CI 4.4 to 51.7). Such findings are in accord with those of (Lawden et al., 1999; Hardus et al., 2001b; Malmgren et al., 2001; Toggweiler and Wieser, 2001; Schmitz et al., 2002).

Individual cases of vigabatrin associated visual field loss have been reported after 6 weeks (Schmitz, 1999), and 6 months (cumulative dose 365g) (Kiratli and Türkçüoğlu, 2001) of vigabatrin. However, the field loss (confirmed as that attributable to vigabatrin toxicity) was only illustrated for the individual described in the latter study.

1.5.5 Cumulative dose/duration of vigabatrin and the severity of vigabatrin-associated visual field loss

The association between cumulative dose and/or duration of vigabatrin therapy and the severity of vigabatrin-associated visual field loss has received relatively little attention. Most studies have utilised inappropriate perimetric methodology to determine the full range of the depth of the field loss, i.e., examination with two-zone age-corrected suprathreshold perimetry (Manuchehri, 2000), with the Esterman Test (Hardus et al., 2001ab) with the II4e and V4e (Frisen, 2004) with the I4e (Newman et al., 2002) or with the V4e isopter (Hardus et al., 2001ab; Malmgren et al., 2001). However, the latter study found modest relationships, accounting for 25% to 45% of the variance, between the extent of the V4e isopter and mean daily dose, cumulative dose and duration of vigabatrin, respectively, in a cohort of 92 individuals with a maximum cumulative dose approaching 7 to 8kg (Hardus et al., 2001ab). A similar level of association was found by Frisen, (2004) for 10 individuals (with a maximum cumulative dose of approximately 4kg) for the extents of the nasal (R²=0.29) and temporal (R²=0.53) II2e
isopters and the cumulative dose of vigabatrin. In the same study, however, the association for the outcome of Rarebit perimetry was higher (R²=0.85 and R²=0.68, respectively). Rarebit perimetry uses short (200msec) presentations of pairs of light spots (with a diameter equal to one-half of the normal minimum angle of resolution) presented against a dark background. The two spots are separated by 4º. The observer is required to indicate the number of spots seen (0-2) on each presentation. The visual field is sampled in 5º circular test areas.

A more modest correlation may be present between cumulative dosage and the mean radial degree for the I4e isopter (Clayton et al., 2011) or there may be no correlation at all between either cumulative dosage or duration of treatment and radial extent of the I4e isopter (r²=0.04 and r²=0.04, respectively) (Newman et al., 2002).

Interestingly, the two indices based upon the between-eye symmetry of vigabatrin-associated visual field loss, the Vigabatrin Severity Index and the Defect Symmetry Index developed by Conway et al., (2008) each correlated with the maximum dose.

1.5.6 The evolution of vigabatrin-associated visual field loss following withdrawal of vigabatrin

There are relatively few studies which have evaluated the subsequent outcome of vigabatrin-associated visual field loss following withdrawal from vigabatrin and those studies which have been undertaken have involved relatively few individuals over relatively short follow-up periods. The definition, and severity, of vigabatrin-associated visual field loss are not stated; the sensitivity and specificity of the perimetric technique for the detection of change in the visual field, and the definition of change in the field loss varies, between the various studies. Nevertheless, it would appear that vigabatrin-
attributed visual field loss remains stable following withdrawal from vigabatrin (i.e., it neither worsens nor improves) over follow-up periods of up to 9 months (Johnson et al., 2000); 18 months (Newman et al., 2002); more than 24 months (Hardus et al., 2000a; Hardus et al., 2000b); 38 months (Nousiainen, Mantyjarvi and Kalviainen, 2001); 4 years (Hardus et al., 2003) and 4–6 years (Kjellström et al., 2008).

It should be noted, however, that a number of studies have suggested that the visual field improves following withdrawal of vigabatrin (Krakow et al., 2000; Vanhatalo et al., 2001). The majority of these reports involve case studies of children (Krakow et al., 2000; Krämer, Ried and Landau, 2000) and it has been speculated that children are more able to repair the retinal damage arising from vigabatrin toxicity. A more plausible explanation for the improvement in the visual field is the perimetric learning effect, whereby the differential light sensitivity improves over the initial visual field examinations, and which would be expected as the child becomes older and more capable of performing perimetry. Indeed, the baseline visual field ‘defect’ of a 10 year old girl exposed to vigabatrin, illustrated by Versino and Veggiotti, (1999) is clearly that attributable to the perimetric fatigue effect.

1.5.7 The evolution of the normal visual field following withdrawal of vigabatrin

The outcome of the normal visual field following withdrawal of vigabatrin has not been studied. Therefore, the potential for, and the time period of, any vigabatrin toxicity following withdrawal of the drug is unknown.
1.5.8 The evolution of vigabatrin-associated visual field loss with continued exposure to vigabatrin

It is generally accepted that, once established, vigabatrin-associated visual field loss is stable and does not progress with continued usage of vigabatrin at least over the short-term, i.e., 11 months (Lawden et al., 1999); 12 months (Paul et al., 2001); 18 months (Graniewski-Wijnands and van der Torren, 2002); 24 months (Schmidt et al., 2002); 38 months (Nousiainen et al., 2001); 43 months (Best and Acheson, 2005) or between 18 and 66 months (Kinirons et al., 2006) Table 1-2. Nevertheless, the sensitivity and specificity of the perimetric technique for the detection of a progressive worsening of vigabatrin-associated visual field loss, and the definition of a worsening of the field loss, together with the severity of the field loss again varies between studies.

A single case report, published after the start of the research for this thesis, described a significant worsening of vigabatrin-associated visual field loss, in terms of the extent (mean radial degrees) of the I4e isopter over ten years of treatment with vigabatrin (Clayton et al., 2010). A subsequent publication from the same group evaluated the visual fields of 14 individuals (including the individual from the earlier publication) from the baseline visual field (which had been undertaken, on average, 5 years after the commencement of vigabatrin) over a follow-up ranging from 104 to 144 months (Clayton et al., 2013). Visual field progression for the I4e isopter was present in six individuals; however, in 5 of these 6 individuals, progression was from a normal field to vigabatrin-associated visual field loss.
1.5.9 The evolution of the normal field with continued exposure to vigabatrin

With the exception of the study by Clayton et al., (2013), the outcome of the normal visual field with continuation of longer-term vigabatrin treatment has not been studied. Therefore, the potential for, and the time period of, any vigabatrin dysfunction remains unknown.

1.5.10 Electrophysiological abnormalities associated with vigabatrin

1.5.10.1 Electroretinography

The outcome of electroretinography (ERG) in individuals exposed to vigabatrin is equivocal and no consistent association has been established between any of the ERG abnormalities and vigabatrin-associated visual field loss. Initially, the whole-field ERG was thought to be normal in individuals with vigabatrin-associated visual field loss (Blackwell et al., 1997; Harding, 1997; Lawden et al., 1999).

1.5.10.1.1 Photopic b-wave

Subsequently, a reduction in the adult photopic b-wave amplitude was found to be present with vigabatrin monotherapy (Coupland et al., 2001), with vigabatrin therapy and current or previous exposure to other AEDs (Miller et al., 1999; Coupland et al., 2001; Comaish et al., 2002) and in individuals withdrawn from vigabatrin with current or previous exposure to other AEDs (Coupland et al., 2001; Graniewski-Wijnands and van der Torren, 2002; van der Torren et al, 2002). Surprisingly, the association of these findings to the presence of vigabatrin-associated visual field loss was not reported in two (Coupland et al., 2001; Graniewski-Wijnands and; van der Torren et al., 2002) of these studies. However, Miller et al., (1999) found a positive correlation (the magnitude
of which was unspecified) between the amplitude of the photopic b-wave and the extent of the visual field to an unspecified isopter. In a separate study of 32 individuals receiving vigabatrin as monotherapy, 13 exhibited vigabatrin-associated visual field loss; three of the 13 exhibited severe field loss and all manifested a reduced photopic b-wave amplitude (Kalviainen et al., 1999). Similarly, (Hardus et al., 2001a) reported a decreased photopic b-wave amplitude to be present with more extensive vigabatrin-associated visual field loss. Conversely, the photopic b-wave can seemingly be unaffected by current vigabatrin therapy even in cases of severe vigabatrin-associated visual field loss (Arndt et al., 1999). Interestingly, Harding et al., (2000b) found that, in those with severe vigabatrin-associated visual field loss, the photopic b-wave amplitude was significantly smaller (p<0.05) for those withdrawn from vigabatrin, and currently being treated with carbamazepine, compared to those receiving vigabatrin. This latter outcome, was consistent that the finding that the photopic b-wave amplitude is reduced in adult individuals with epilepsy receiving carbamazepine who had never been exposed to vigabatrin (Harding et al., 2000a; Harding et al., 2000b). A deterioration in the photopic b-wave amplitude has been used as a measure for monitoring the progression of vigabatrin dysfunction (Cohen et al., 2000). Eleven of 14 individuals (78%) with vigabatrin-associated visual field loss showed progressive reduction of the photopic b-wave amplitude; however, the specificity was poor in that 23 of 46 individuals without vigabatrin-associated visual field loss also manifested such changes.

In infants (median age 7.6 months; range 1.5 to 24 months), the photopic b-wave amplitude has been shown to initially increase (p = 0.04) after 6 months and then to decrease by 18 months (Morong et al., 2003) either with vigabatrin monotherapy or with vigabatrin multitherapy (Westall et al., 2003).
Occasional reports suggest that an increase in the implicit time of the photopic b-wave can be associated with vigabatrin-associated visual field loss (Besch et al., 2002). However; the implicit time of the photopic b-wave is also increased with short duration vigabatrin therapy in normal individuals and indicates a metabolic effect resulting from an increase in GABA (Harding et al., 1998a). It can also be present in some individuals exposed to vigabatrin with normal fields (Jensen et al., 2002).

1.5.10.1.2 Scotopic b-wave

Several studies have found a reduction in the amplitude of the scotopic b-wave in association with a reduction in the amplitude of the photopic b-wave (Kalviainen et al., 1999; Miller et al., 1999; Coupland et al., 2001; Hardus et al., 2001a; Comaish et al., 2002). The reduction in the amplitude of the scotopic b-wave is present in individuals receiving vigabatrin monotherapy (Kalviainen et al., 1999; Coupland et al., 2001) in individuals receiving vigabatrin monotherapy with severe vigabatrin-associated visual field loss; in individuals receiving vigabatrin therapy and current or previous exposure to other AEDs (Coupland et al., 2001) with either normal fields (Jensen et al., 2002) or with vigabatrin-associated visual field loss (Daneshvar et al., 1999; Miller et al., 1999; Hardus et al., 2001a; Comaish et al., 2002; Jensen et al., 2002); and in individuals withdrawn from vigabatrin with current or previous exposure to other AEDs (Coupland et al., 2001). Interestingly, Graniewski-Wijnands and van der Torren (2002) found that six of nine individuals exhibited abnormalities of the scotopic b-wave amplitude and implicit time immediately prior to withdrawal of vigabatrin and that, following withdrawal, the appearance returned to the normal range in 4 of the 6 individuals. However, the proportion of these 6 individuals with vigabatrin-associated visual field loss was not given. Conversely, other groups have found no abnormality of either the
scotopic b-wave amplitude or implicit time with exposure to vigabatrin (Arndt et al., 1999; Harding et al., 2000b).

1.5.10.1.3 30 Hz flicker

The 30 Hz flicker ERG is considered to be the most effective electrophysiological technique for the detection of vigabatrin-associated visual field loss: a reduced 30Hz flicker b-wave amplitude predicted vigabatrin-associated visual field loss with 100% sensitivity at a specificity of 75% (Harding et al., 2000b). An abnormal 30Hz flicker amplitude and an abnormal implicit time has also been shown to be present with vigabatrin-associated visual field loss (McDonagh et al., 2003). In addition, a reduction in the 30Hz flicker b-wave amplitude correlates (r = 0.64, and r = 0.72) with the degree of visual field constriction by kinetic perimetry (Miller et al., 1999). Conversely, no correlation has been found between either 30Hz flicker implicit time (r=0.22) or amplitude (r=0.21) and cumulative dose of vigabatrin (McDonagh et al., 2003). The reduction in the 30Hz flicker b-wave amplitude has been found in a modest number of individuals receiving, variously, vigabatrin monotherapy; vigabatrin therapy and current or previous exposure to other AEDs; and previous vigabatrin with current or previous exposure to other AEDs (Coupland et al., 2001). Interestingly, in a case series of eight individuals, vigabatrin-associated visual field loss and abnormal 30Hz flicker b-wave amplitude, present whilst receiving vigabatrin therapy, were still present in all eight individuals at follow-up 4–6 years after discontinuation of vigabatrin (Kjellström et al., 2008). Conversely, in a separate study of vigabatrin-associated visual field loss, at 100% sensitivity, Cohen et al., (2000) was only able to demonstrate a specificity of 50% for the 30Hz flicker b-wave amplitude.
In children, the 30Hz flicker amplitude declines between 6 months and 1 year of vigabatrin treatment (Westall et al., 2003). Indeed, the 30 Hz flicker cone b-wave amplitude was abnormal in each of seven children with vigabatrin-associated visual field loss and normal in each of five children with normal fields (Ponjavic and Andréasson, 2001). Conversely, an abnormal 30Hz flicker amplitude occurred infrequently in 114 paediatric individuals (median age at test 22.9 months; range 2.4 to 266.1; and median duration of vigabatrin (9.7 months; range 0.3 to 140.7) (Moskowitz et al., 2012). In a subset of 39 children who underwent perimetry, there was no significant association between visual field loss and any ERG parameter (Moskowitz et al., 2012).

1.5.10.4 Photopic and Scotopic a-waves

Normal photopic and scotopic a-waves are present with vigabatrin monotherapy (Coupland et al., 2001), with vigabatrin therapy and current or previous exposure to other AEDs (Coupland et al., 2001) and in individuals withdrawn from vigabatrin with current or previous exposure to other AEDs (Coupland et al., 2001). However, individuals receiving vigabatrin monotherapy with severe visual field loss exhibit a reduced photopic and scotopic a-wave amplitude (Kalviainen et al., 1999). Indeed, a reduction in the photopic a-wave amplitude can be found in some individuals with vigabatrin-associated visual field loss (Jensen et al., 2002). However, in individuals with severe vigabatrin-associated visual field loss, the implicit time of the scotopic a-wave is prolonged in those receiving vigabatrin compared to those withdrawn from the drug (Harding et al., 2000c). This latter finding suggests that scotopic a-wave implicit time is more related to current vigabatrin therapy than to the presence of the field loss. Increases in the implicit times of either the scotopic or photopic a-waves are also present in individuals currently treated with vigabatrin irrespective of the presence of
vigabatrin-associated visual field loss (Miller et al., 1999). Interestingly, Harding et al., (2000c) also found that the photopic a-wave latency increased with increasing severity of the visual field defect. Conversely, the photopic and scotopic a-waves (Arndt et al., 1999; Daneshvar et al., 1999) or the photopic a-wave (Comaish et al., 2002) are also normal in individuals exposed to vigabatrin irrespective of the presence of vigabatrin-associated visual field loss.

In children, the amplitude and implicit time of the a-wave for the combined rod-cone response have been found to be abnormal (Kjellstrom, Andreasson and Ponjavic, 2011). Similarly, the amplitude of the a-wave for the combined rod-cone response is abnormal in adults with vigabatrin-associated visual field loss (Kjellstrom, Andreasson and Ponjavic, 2013).

1.5.10.1.5 Oscillatory potentials

Reduced photopic oscillatory potentials were found in all four individuals in the case series describing the electrophysiological characteristics of vigabatrin-associated dysfunction (Krauss et al., 1998). Reduced amplitudes of the photopic oscillatory potentials were also present in all 32 individuals who were currently receiving vigabatrin, irrespective of the status of the visual field (Miller et al., 1999). Indeed, similar frequencies of abnormality of the summed amplitude of the photopic oscillatory potentials were found in those treated with vigabatrin monotherapy, those treated with vigabatrin multitherapy and those withdrawn from vigabatrin, respectively; although the relationship to the presence of vigabatrin-associated visual field loss was not stated (Coupland et al., 2001). However, in the case series of 18 individuals receiving vigabatrin described by Arndt et al., (1999) the oscillatory potentials were absent in all five individuals with severe loss but were also present in 4 of 7 individuals with mild
loss and absent in 2 of 7 individuals with normal visual fields. Similarly, in the case series of individuals receiving vigabatrin monotherapy described by Kalviainen et al., (1999), the oscillatory potentials were absent in all three individuals with severe loss and in 6 of the 10 individuals with mild loss. However, Harding et al., (2000b) found that the latency of the second oscillatory potential was prolonged in current compared to previous vigabatrin users, all with advanced visual field loss, suggesting that the increase was more related to current vigabatrin use than to the presence of the visual field loss. The association between abnormality of the oscillatory potentials and vigabatrin-associated visual field loss, particularly in those with advanced loss, was also reported by Besch et al., (2002) and by Comaish et al., (2002). The latter group found a strong correlation (r = 0.83) between the averaged amplitude for the first three oscillatory potentials and the area of the remaining field. A correlation has also been found between the implicit time of the second and third oscillatory potentials and the presence of vigabatrin-associated visual field loss (van der Torren et al., 2002). However, whilst the latency of the first oscillatory potential is associated with severe vigabatrin-associated visual field loss the second oscillatory appears to be affected by the presence of current vigabatrin therapy (Harding et al., 2000c). However, the reduction in the amplitude of the first and of the second oscillatory potentials remained in all 8 individuals with vigabatrin-associated visual field loss 4–6 years after withdrawal of vigabatrin (Kjellstrom et al., 2013). Conversely, the oscillatory potentials were normal in all 9 individuals with vigabatrin-associated visual field loss in the case series of (Daneshvar et al., 1999).

In infants, the early oscillatory potentials showed a significant reduction after 6 months and remained as such for the duration of treatment (Westall et al., 2003).
1.5.10.2 Multi-Focal Electroretinogram (mfERG)

Relatively few studies have utilised the mfERG to investigate vigabatrin-associated dysfunction and the results are equivocal. In a case presentation of an individual with vigabatrin-associated visual field loss, the second oscillatory potential of the full field ERG was abnormal and the mfERG normal (Ruether et al., 1998). However, in four individuals with vigabatrin-associated visual field loss, two from each of two separate case series, a marked overall reduction in amplitude of the mfERG was present peripherally which correlated with the appearance of the visual field; the implicit times were normal (Mackenzie and Klistorner, 1998; Lawden et al., 1999). A subsequent case history described the outcome of the wide-field (90°) mfERG in an individual with vigabatrin-associated visual field loss (McDonagh et al., 2003). Normal retinal function was recorded in the central 40° of both eyes; however, a delay in implicit time occurred with increase in eccentricity together with a marked reduction in peripheral b-wave amplitudes. Nevertheless, in another study, a reduced amplitude was only found in 12 of 20 individuals exposed to vigabatrin; however, the mfERG oscillatory potentials were delayed in all 18 individuals with vigabatrin-associated visual field loss (Besch et al., 2002).

In a case series of 12 children exposed to vigabatrin, 7 of whom exhibited vigabatrin-associated visual field loss, 6 had a reduced amplitude of the peripheral mfERG although there was little correlation with the visual field loss (Ponjavic and Andréasson, 2001).

The wide-field mfERG exhibits a reduced peripheral amplitude and an increased implicit time compared to the central amplitude response in individuals with vigabatrin-associated visual field loss (McDonagh et al., 2003). Of the 32 individuals exposed to
vigabatrin, all 19 with vigabatrin-associated visual field loss were identified whilst 2 of the 13 individuals with a normal field were classified as abnormal, i.e., 100% sensitivity and 86% specificity. However, of the 21 individuals who had never received vigabatrin all 21 exhibited a normal field but, of these, 8 manifested a reduction of the peripheral amplitude mfERG.

A later, and more extensive, study, from the same centre (Gonzalez et al., 2009), comprised 56 individuals currently treated with vigabatrin (Group 1), 49 previously treated with vigabatrin (Group 2), 46 with no previous exposure to vigabatrin but receiving GABAergic anti-epileptic drugs (Group 3) and 53 individuals treated with non-GABA-ergic anti-epileptic drugs but with no prior exposure to any GABAergic drug (Group 4). Bilateral visual field constriction was present in 59% of individuals in Group 1, in 43% of individuals in Group 2, in 24% of individuals with no exposure to vigabatrin (Groups 3 and 4). Wide-field mfERG abnormalities were present in 48% of individuals in Group 1 and in 22% of individuals in Group 2. A total of 21 vigabatrin exposed individuals (current and previous) exhibited visual field loss in the presence of a normal mfERG whereas only 3 vigabatrin exposed individuals manifesting a normal visual field exhibited an abnormal mfERG. However, the results of the full-field ERG were equivocal. Bilateral reductions in the amplitude of rod, oscillatory potential, cone a-wave, cone b-wave, and 30Hz flicker responses were noted in individuals with visual field loss compared to those without. However, such reductions were also present in individuals in Group 3 i.e., those with no previous exposure to vigabatrin but receiving GABAergic anti-epileptic drugs. Notably, the reduction in the amplitude of the photopic b-wave correlated with the presence of wide-field mfERG abnormalities for individuals in Group 1.
Interestingly, Kjellstrom et al., (2013) found significant positive correlations, in 12 individuals with vigabatrin-associated visual field loss and previously exposed to vigabatrin, between the total averaged retinal nerve fibre layer thickness derived by optical coherence tomography (see Section 1.5.12) and the amplitudes of the b-waves of the combined rod-cone response (rho r = +0.60; p = 0.04), and the 30Hz flicker response (rho r = +0.64; p = 0.026). These correlations were maintained for the retinal nerve fibre layer thickness of the superior quadrant and of the inferior quadrant and the b-wave amplitude of the combined rod-cone response (superior: rho = +0.66; p = 0.019; inferior: rho = +0.73; p = 0.007) and for the 30Hz flicker response (superior: rho = +0.73; p = 0.007, inferior: rho = +0.75; p = 0.005). No correlations were present for the retinal nerve fibre layer thickness of the temporal quadrant and any of the ERG outcomes.

1.5.10.3 Electrooculogram (EOG)

Two out of the 3 individuals in the original case series of (Eke et al., 1997) exhibited an abnormal Arden Index of the EOG; however, following withdrawal of vigabatrin, the Arden Index returned to the normal range in both individuals (Harding, 1997).

The link between an abnormal EOG and vigabatrin-associated visual field loss, in current vigabatrin users, was also reported by others; however, in these studies, individuals with normal visual fields also had an abnormal EOG (Arndt et al., 1999; Daneshvar et al., 1999; Lawden et al., 1999; van der Torren et al., 2002). In the study by Lawden et al., (1999), the Arden Index was abnormal in all individuals who were currently receiving vigabatrin but was reversible upon withdrawal of the drug; the improvement in the Arden index, where present, was unrelated to the severity of the vigabatrin-associated visual field loss.
The improvement in the Arden Index, and/or the lower frequency of abnormality, following withdrawal of vigabatrin has since been confirmed by others (Harding et al., 1998b; Coupland et al., 2001; Comaish et al., 2002; Graniewski-Wijnands and van der Torren, 2002). Furthermore, the Arden Index has been shown to be reduced in young normal individuals at nine days of exposure to vigabatrin without any alteration to the visual field (Harding et al., 1998a). Collectively, the results from these various studies indicate a metabolic effect of vigabatrin on the retinal pigment epithelium and/or the retinal pigment epithelial-outer segment complex.

1.5.10.4 Visual Evoked Potential

The majority of studies have found a normal visually evoked potential (VEP) in adults (Liegeois-Chauvel et al., 1989; Eke et al., 1997; Mauguiere et al., 1997; Wilson and Brodie, 1997; Ruether et al., 1998; Lawden et al., 1999) and in children with vigabatrin-attributed visual field loss (Uldall et al., 1995).

However, an abnormal VEP has been found in 22% of 32 individuals exposed to vigabatrin (Miller et al., 1999). A similar prevalence (30%) has also been found in adults, the majority of whom exhibited advanced vigabatrin-associated visual field loss (Daneshvar et al., 1999) and also in children (33%) (Gross-Tsur et al., 2000). The reduction in the VEP reflects the central dominance of the traditional summed VEP responses and it can be postulated that mfVEP technology may identify vigabatrin toxicity more peripherally (Lawthom, Smith and Wild, 2009).
1.5.11 Fundal abnormalities and vigabatrin-associated visual field loss

The fundal abnormalities, visible by ophthalmoscopy, in individuals with vigabatrin-associated visual field loss, if present, are subtle and include retinal nerve fibre layer (RNFL) attenuation (Miller et al., 1999; Frisen and Malmgren, 2003; Buncic et al., 2004) ‘inverse’ or nasal, optic nerve head atrophy, i.e. that sparing the temporal sector which contains the papillomacular bundle (Frisen and Malmgren, 2003; Buncic et al., 2004); an abnormal macular reflex (Krauss et al., 1998; Buncic et al., 2004); epi-retinal membrane formation (Krauss et al., 1998); peripheral vessel irregularity (Krauss et al., 1998; Wild et al., 1999a) and peripheral pigmentary disturbances (Lawden et al., 1999; Wild et al., 1999a). However, the various fundal abnormalities are not sufficiently common, or consistent, to make a diagnosis of vigabatrin toxicity, based upon the ophthalmoscopic appearance, alone (Lawden, 2006). The optic nerve head atrophy is a late presentation of vigabatrin-associated visual field loss.

1.5.12 Digital Imaging of the retinal nerve fibre layer

The imaging of an attenuated peripapillary retinal nerve fibre layer in an individual with vigabatrin-associated visual field loss was first described by Viestenz, Viestenz and Mardin (2003) using both scanning laser ophthalmoscopy (Heidelberg Retinal Tomography) and nerve fibre layer polarimetry (Retinal Nerve Fibre Layer Analyzer GDx). The case history described a 70-year-old male exposed to a cumulative dose 3.7kg of vigabatrin who exhibited bilateral moderate visual field loss, optic disc pallor, reduced photopic and scotopic b-wave amplitudes and delayed VEPs.

The use of optical coherence tomography (OCT) to image the retinal nerve fibre layer in an individual with vigabatrin-associated visual field loss was first described by Choi
and Kim, (2004). In a landmark case description, an 18 year old male with a cumulative dose of approximately 6.0 kg vigabatrin over seven and a half years manifested the typical bilateral nasal annular defect present with vigabatrin-associated visual field loss. The peripapillary retinal nerve fibre layer thickness by OCT was attenuated in all quadrants except for the temporal quadrant in both eyes and the inferior quadrant in the right eye. The preservation of the temporal quadrant, i.e., that which contains the papillomacular bundle was compatible with the inverse optic atrophy (i.e., that sparing the temporal region of the optic nerve head) independently described by Frisen and Malmgren, (2003) and Buncic et al., (2004). In the following year, the results from a case series of 8 individuals confirmed the presence of an attenuated retinal nerve fibre layer in individuals with vigabatrin-associated visual field loss (Rebolleda et al., 2005). Twelve eyes had abnormal visual fields, and 4 eyes showed normal electrophysiology and normal visual fields. The peripapillary retinal nerve fibre layer thickness was attenuated in at least one quadrant in 12 eyes (75%), and in at least two quadrants in 9 eyes (56.3%). The most frequently attenuated quadrants were the nasal and superior (83%), and inferior (41.7%). The temporal quadrant peripapillary retinal nerve fibre layer thickness was normal in all eyes despite the inclusion of cases of very advanced (sic) visual field loss. The characteristics of the attenuation and the preservation of the temporal quadrant peripapillary retinal nerve fibre layer thickness was in accord with that of Choi and Kim, (2004) and entirely compatible with the concept of inverse optic atrophy (Frisen and Malmgren, 2003; Buncic et al., 2004).

In a case-controlled study (Wild et al., 2006), which was accepted for publication prior to publication of the commentary by Rebolleda et al., (2005), and which used an OCT scan based upon the vertical diameter of the optic nerve head, an attenuated total peripapillary retinal nerve fibre layer thickness was found in all 13 adults with
vigabatrin-associated visual field loss. Of the 8 individuals who were exposed to vigabatrin but who manifested normal fields, 3 exhibited an attenuated total peripapillary retinal nerve fibre layer thickness. All but two of the 14 individuals who had been exposed to carbamazepine monotherapy (a non-GABAergic anti-epileptic drug) and all 7 of the individuals treated with sodium valproate monotherapy (a mildly GABAergic anti-epileptic drug) exhibited a total peripapillary retinal nerve fibre layer thickness within the normal range. Subsequent studies have confirmed that lack of peripapillary retinal nerve fibre layer thinning in individuals exposed to other anti-epileptic drugs (Lawthom et al., 2009; Akçakaya et al., 2010; Clayton et al., 2011; Moseng et al., 2011; Clayton et al., 2012).

The characteristic pattern of peripapillary retinal nerve fibre layer attenuation unique to vigabatrin-attributed toxicity, namely superior and/or inferior quadrant thinning, either with or without nasal quadrant thinning and a normal temporal quadrant thickness was subsequently confirmed in other cohorts (Lawthom et al., 2009; Akçakaya et al., 2010; Moseng et al., 2011; Clayton et al., 2012; Kjellstrom et al., 2013).

Apart from the initial case report by Viestenz et al., (2003), imaging of the retinal nerve fibre layer in individuals exposed to vigabatrin by scanning laser ophthalmoscopy and by nerve fibre layer polarimetry has received little attention. However, the results from the case series of 8 individuals with vigabatrin-associated visual field loss (mean cumulative dose of vigabatrin 5.4 kg; mean duration 81 months) described by Durnian and Clearkin, (2008) were compatible with those derived by OCT. All eight individuals had a significantly reduced peripapillary retinal nerve fibre layer (mean TSNIT=36.5μm), particularly superiorly (mean 42.7μm), and inferiorly (mean 39.2μm), i.e., an attenuation of the long nerve fibres, which was consistent with the nasal
predominance of the field loss. Conversely, in their case control study described above, Wild et al., (2006) found that scanning laser ophthalmoscopy exhibited a poorer sensitivity (77%) compared to OCT for the detection of vigabatrin-associated visual field loss.

1.5.13 The renaissance of vigabatrin?

1.5.13.1 Epilepsy

As was discussed in Section 1.4, vigabatrin gained approval from the US Food and Drug Administration (FDA) in August 2009 as monotherapy for individuals from 1 month to 2 years of age with IS, and as adjunctive therapy for adults with refractory complex partial seizures whose seizures have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision field loss (Pellock et al., 2011).

The FDA approval of vigabatrin was accompanied by the implementation of a Risk Evaluation and Mitigation Strategy (REMS) which is a programme designed to reduce the risk of vigabatrin-associated visual field loss whilst, at the same time, providing risk–benefit analyses for appropriate individual populations The programme is a administered through the Support, Help, and Resources for Epilepsy (SHARE) scheme administered by the Marketing Authorisation Holder for vigabatrin in the USA, Lundbeck Inc (Pellock et al., 2011). The REMS programme included the establishment of a registry of individuals in the USA treated with vigabatrin, and which is mandatory for prescribers and individuals, to assess the incidence, prevalence, time to onset, progression, and severity of vision loss (Pellock et al., 2011). As part of the Registry, benefit–risk assessments are required early in the course of vigabatrin therapy:
ophthalmological assessments, including visual acuity and perimetry and/ or optical coherence tomography, are required at baseline (≤4 weeks after therapy initiation), every 3 months during therapy, and at 3 to 6 months after discontinuation (Sergott, 2010; Sergott et al., 2010; Pellock et al., 2011).

Following the approval by the FDA, numerous medical-marketing papers, sponsored by the Marketing Authorisation Holder for vigabatrin in the USA, have been published, in a Supplement to Acta Neurologica Scandanavica (Ben-Menachem, 2011; Ben-Menachem and Sander, 2011; Carmant, 2011; Faught, 2011; Pellock, 2011; Pellock et al., 2011; Plant and Sergott, 2011; Walker and Kalviainen, 2011), but also elsewhere (Sergott, 2010; Sergott et al., 2010; Sergott, Foroozan and Pellock, 2012a).

1.5.13.2 Substance abuse

Vigabatrin has recently received Fast Track designation from the FDA for the treatment of cocaine and/ or methamphetamine dependence (Buddy, 2008). Fast Track is a process designed to facilitate the development, i.e. to expedite the review of drugs to treat serious conditions and fill an unmet medical need (FDA, 2014).

GABA suppresses both the firing rate and the amount of dopamine released in the brain. As was discussed in Section 1.4, vigabatrin is thought to selectively, non-competitively and irreversibly, inhibit GABA transaminase, the enzyme which catalyses the breakdown (catabolism) of GABA, thereby increasing whole brain pre-synaptic GABA levels. As a consequence, vigabatrin has been trialled in two open-label studies (Brodie, Figueroa and Dewey, 2003; Brodie et al., 2005) and two double-blind placebo-controlled studies (Brodie et al., 2009; Somoza et al., 2013) for the treatment of cocaine dependence. The efficacy of vigabatrin to induce abstinence is beyond the
scope of this review. The treatment regime for the study by Brodie et al., (2009) involved a cumulative dose of 131.5g over 9 weeks and that of Berezina et al., (2012) and of Somoza et al., (2013) involved escalation of vigabatrin to a maximum of 3g of vigabatrin per day after two weeks, which was maintained for nine weeks, and tapered to zero at week 12, i.e. a total dose of 218g.

No cases of vigabatrin-associated visual field loss have been reported in safety studies at either the lower (Fechtner et al., 2006) or higher level (Berezina et al., 2012; Somoza et al., 2013) of dosing. However, the peripheral field (HFA Program 60-4) was utilized in these studies. The definition of visual field change was defined either as a change in the Mean Sensitivity by 2SDs of that obtained for the study cohort at baseline in one or more quadrants (Fechtner et al., 2006) or, rather liberally, as a reduction in sensitivity either of ≥15dB at each of 5 or more stimulus locations or of ≥33% in one or more of the three peripheral annuli (Berezina et al., 2012). Interestingly, no definition for the change in the visual field was described by Somoza et al., (2013) whilst the definition for change in any wave form of the ERG was defined as a ≥50% reduction in amplitude or as a ≥50% increase in implicit time, or both.

1.5.13.3 Migraine Prophylaxis

Vigabatrin has been trialled as a prophylactic therapy for migraine. However, the latest Cochrane review finds that vigabatrin is no better than a placebo in reducing headache frequency per 28 day period during treatment (Linde et al., 2013).

1.5.13.4 Other uses

GABA-ergic mechanisms are important in the development and maintenance of alcohol dependence. However, the efficacy, safety and tolerability of vigabatrin for the
treatment of alcohol withdrawal syndrome needs further study (Caputo and Bernardi, 2010). Vigabatrin may also suppress the craving for nicotine (Wickelgren, 1998).

Vigabatrin has been shown to be a candidate for cerebral microdialysis in individuals with severe head injury (Carpenter et al., 2012). Vigabatrin and GABA levels increased more in abnormal brain than in sites further from the lesion(s) (Sergott et al., 2010).

It has been speculated that a deficiency of the amino acid taurine is associated with vigabatrin ocular toxicity (Jammoul et al., 2009).

In the mammalian retina, taurine is the most abundant amino acid during both development and adulthood (Macaione et al., 1974). The concentration in adults is higher compared to other parts of the eye and to the brain and to all other organs in all species examined (Pasantes-Morales and Cruz 1985). Within the retina the concentration is highest in the photoreceptors (Huxtable, 1989) and in the outer nuclear layer (Pasantes-Morales et al., 1972). The physiological concentrations of taurine cannot occur from endogenous synthesis, alone, and must occur from exogenous synthesis of food. Uncooked meat and seafood (Zhao, 1994) and milk and eggs (Hayes and Sturman, 1981) are major sources of taurine. Dietary taurine uptake is dependent upon transportation across the intestinal barrier to the blood. In human, two intestinal transport mechanisms mediate the transport of taurine: a high affinity, low capacity $\text{NA}^+$ and $\text{Cl}^-$ dependent transporter (Tau-T) and a low-affinity transport for amino acids (Anderson et al., 2009). The latter represents the major uptake for taurine. The topographical distribution of Tau-T within the mammalian retina suggests that dietary taurine in the plasma is taken up by the retinal pigment epithelium and the outer retina.
to supply the photoreceptors and by the capillary endothelium in the inner retina to supply the ganglion cells (Vinnakota et al., 1997).

The role of taurine, particularly in the retina is unclear. Taurine is considered to be an anti-oxidant (Froger et al., 2014). It is also a mediator of cellular Ca\(^{2+}\) influx and may be cytoprotective by preventing excitotoxicity due to excess glutamate release and glutamate receptor activation (El Idrissi and Trenkner, 1999) particularly in NMDA-exposed retinal ganglion cells. Taurine is considered to be an agonist of all the GABA receptors (Albrecht and Schousboe, 2005; Jones and Palmer, 2009) although there is no clear evidence of GABA\(_B\) activation (Froger et al., 2013). It may also activate the strychnine-sensitive glycine ionotropic receptors in retinal ganglion cells (Bulley and Shen, 2010) and in cones (Balse et al., 2006) and be responsible for 5HT receptor activation in ganglion cells (Bulley et al., 2013).

Dietary deprivation of taurine, as expressed by depletions both in plasma and in retinal concentrations, in cat (Hayes et al., 1975; Aguirre, 1978), in infant primate (Imaki et al., 1998) and in children and adult humans (Ament et al., 1986; Milea et al., 2000) leads to extensive photoreceptor degeneration. Taurine depletion, with the consequent photoreceptor degeneration, can also be induced by pharmacological agents such as guanidoethane and B-alanine which can be used to block Tau-T activity and therefore decrease the synthesis of exogenous taurine and subsequent uptake (Lake et al., 1988; Pasantes Morales et al., 1983). Guanidoethane treated mice also exhibit ganglion cells loss which was initially considered to be secondary to the photoreceptor degeneration as with retinitis pigmentosa (Lake and Malik et al., 1988; Imaki et al., 1998) but is now considered to occur concomitantly with the photoreceptor degeneration (Gaucher et al., 2012). Similarly, taurine depletion induced in knockout mice by disruption of the gene
encoding Tau-T leads to photoreceptor degeneration (Heller-Stilb et al., 2002; Rascher, Servos et al., 2004).

Vigabatrin exposed rats exhibit depleted plasma levels of taurine compared to controls and the extent of the taurine depletion negatively correlates with the photopic ERG amplitudes and with cone density (Jammoul et al., 2009). In the same study, vigabatrin-treated rats who received taurine supplementation via drinking water exhibited higher plasma taurine levels, a greater cone density and greater photopic ERG amplitudes than those vigabatrin exposed rats who did not receive supplementation. However, these measures were lower than untreated rats indicating that taurine may have a cytoprotective role in vigabatrin toxicity.

Clearly, the role of taurine depletion in the development of vigabatrin ocular toxicity in human requires investigation.

1.6 Summary

Vigabatrin is a well-tolerated anti-epileptic drug which is used as add-on therapy for adults with drug-resistant partial epilepsy and as monotherapy for infantile spasms.

Vigabatrin causes retinal toxicity which results in vigabatrin-associated visual field loss; a bilateral and clinically symmetrical, ‘concentric’ constriction of the field which is generally more pronounced nasally than temporally, particularly within the central field.
The frequency of vigabatrin-associated visual field loss varies from 6% for exposures up to 1.75 years to 93% for exposures up to 10 years with an ‘accepted’ frequency of between 30% and 40%. However, the frequency for longer-term exposures, such as the latter, remains to be confirmed. The frequency in children is thought to be lower than in adults. The frequency of vigabatrin-associated visual field loss is higher with standard automated perimetry than with kinetic perimetry.

Male gender is a risk factor for vigabatrin-associated visual field loss. The association between duration and cumulative dose of vigabatrin-associated visual field loss is equivocal.

No consistent association has been established between abnormality of the various ERGs and the presence of vigabatrin-associated visual field loss. The 30Hz flicker exhibits the strongest association with the presence of vigabatrin-associated visual field loss. An abnormality of the photopic oscillatory potentials may be associated with a metabolic effect of vigabatrin. The Arden Index of the EOG is also associated with the use of vigabatrin.

The fundal signs of vigabatrin toxicity using ophthalmoscopy are subtle but include retinal nerve fibre layer thinning and an associated inverse optic atrophy. The retinal nerve fibre layer thinning is also present by optical coherence tomography.

The progressive nature of vigabatrin-associated visual field loss with continued therapy, or following withdrawal of the drug, are both equivocal. Given the extent of the structural abnormality of the retinal nerve fibre layer, recovery of visual function is unlikely.
Chapter 2. **Rationale for the Research**

2.1 **Introduction**

The work described in this thesis is a natural consequence of the previous work undertaken on vigabatrin ocular toxicity at Aston University, Birmingham, and, subsequently, in the Cardiff School of Optometry and Vision Sciences, Cardiff University.

The initial work undertaken by Professor Wild and colleagues at Aston University had contributed to the understanding of the prevalence of the visual field loss associated with vigabatrin (Lawden et al., 1999; Wild et al., 1999a); had described the characteristics of the visual field loss associated with vigabatrin, namely the bilateral, clinically symmetrical, concentric constriction which was more marked nasally than temporally (Wild et al., 1999a); and had identified the visual electrophysiological abnormalities associated with vigabatrin (Harding et al., 2000b; Harding et al., 2000c).

The subsequent phases of the work undertaken by Professor Wild and colleagues at Cardiff University had concentrated on developing an objective technique for the detection of vigabatrin-associated visual field loss using either visual electrophysiology (Harding et al., 2002) or ocular imaging of the retinal nerve fibre layer (Wild et al., 2006; Lawthom et al., 2009); and establishing more accurate estimates of the prevalence of vigabatrin associated visual field loss either through an observational
study of the largest, to date, cohort exposed to vigabatrin (Wild et al., 2007; Wild et al., 2009) or by systematic review (Maguire et al., 2010).

It can be seen from the literature review in Chapter One that, at the commencement of this thesis in 2009, the estimates of the prevalence of vigabatrin-associated visual field loss varied widely but were taken to be ‘in the region’ of 30-40%. The validity of this clinical approximation, in individuals with exposures of up to approximately four years, was subsequently confirmed by Maguire et al., (2010). It was also accepted in the literature that the field loss was both irreversible (Johnson et al., 2000; Newman, Tocher and Acheson, 2002; Hardus et al., 2000a; Hardus et al., 2000b; Nousiainen, Mantyjarvi and Kalviainen, 2001; Hardus et al., 2003; Kjellström et al., 2008) and also non-progressive upon withdrawal of vigabatrin (Lawden et al., 1999; Paul et al., 2001; Graniewski-Wijnands and van der Torren, 2002; Nousiainen et al., 2001; Schmidt et al., 2002; Best and Acheson, 2005; Kinirons et al., 2006) over a maximum period ranging from 4 to 6 years following withdrawal of vigabatrin (Kjellström et al 2008).

The literature on the outcome of visual electrophysiology was equivocal. It was generally accepted that the abnormalities of the electrooculogram which reversed on withdrawal of the drug (Harding et al., 1998a; Harding et al., 1998b; Coupland et al., 2001; Comaish et al., 2002; Graniewski-Wijnands and van der Torren, 2002) were indicative of a metabolic effect of vigabatrin and that the abnormalities in the electroretinagram were indicative of a retinal location for vigabatrin toxicity which was most likely attributable to a cone pathway abnormality (Harding et al., 2000c).

The literature on the fundal appearance associated with vigabatrin toxicity was limited. However, two separate and independent studies had noted the presence of an ‘inverse’
optic atrophy (Buncic et al., 2004) or ‘C-shaped or ‘temporal sparing’ optic atrophy (Frisen and Malmgren, 2003) which was associated with vigabatrin-associated visual field loss. In addition, attenuation of the retinal nerve fibre layer had, initially, also been observed by fundoscopy (Miller et al., 1999; Frisen and Malmgren, 2003; (Buncic et al., 2004) and, subsequently, by optical coherence tomography (Viestenz, Viestenz and Mardin, 2003). A single study had noted the presence of an abnormal macular appearance in some cases of vigabatrin-associated visual field loss (Krauss et al 2003).

The risk factors for vigabatrin-associated visual field loss were generally considered to be male gender (Wild et al., 1999a; Hardus et al., 2000b; Hardus et al., 2000c; Kalviainen and Nousiainen, 2001; Newman et al., 2002; Wild et al., 2009) and, as would be expected, either cumulative dose (Malmgren et al., 2001; Lawden et al., 1999) or duration (Lawden et al., 1999; Hardus et al., 2001b; Malmgren et al., 2001; Toggweiler and Wieser, 2001; Schmitz et al., 2002) of vigabatrin or mean daily dose of vigabatrin (Lawden et al., 1999; Hardus et al., 2001b).

Clearly, a number of clinically important issues concerning vigabatrin toxicity were unknown. In particular, the prevalence of vigabatrin-associated visual field loss arising from longer-term usage of the drug was not known. Equally, the relation between the structural and/ or functional outcome measures at any given time point was also unknown. Moreover, the nature of any progression (i.e. a worsening) in the structural and/ or functional outcome measures of vigabatrin toxicity for those either remaining on, or withdrawn from, the drug were also unknown.
2.2 Primary Aims of the Study

The Primary aims of the work contained in this thesis were to:

Model the risk (frequency), by means of a cross-sectional approach, of vigabatrin-associated visual field loss, in terms of cumulative dose and duration of vigabatrin, with particular reference to long-term usage of vigabatrin.

Determine the relationship between the structural (i.e. retinal nerve fibre layer thickness) and functional (visual field severity) outcomes, evaluated in terms of retinal ganglion cell count, arising from vigabatrin toxicity.

Evaluate any progressive nature (i.e. a worsening) of the functional and of the structural outcome measures in individuals withdrawn from vigabatrin and in those with continuing exposure to the drug.

Investigate any difference in macular thickness between those with vigabatrin-associated visual field loss and those exposed to vigabatrin but with normal fields.

2.3 Clinical Studies and Outcomes

The various studies described in this thesis were based upon individuals recruited from the Alan Richens Unit, Welsh Epilepsy Centre, University Hospital of Wales. The appropriate data sets had either been collected previously and were used retrospectively or were collected prospectively. All participants conformed to rigid inclusion/exclusion criteria. The study protocols were considered by the National Institute for Social Care
and Health Research to lie within the category of clinical audit and, as such, placed the work outside of the remit of the National Health Service Research and Ethics Committees (Scott, 2009).

The experimental work was divided into five separate studies.

2.4 Modelling the risk of visual field loss arising from long-term exposure to vigabatrin

The study, described in Chapter 3, involved modelling, from the cross-sectional evidence, the risk of visual field loss arising from the long-term usage of vigabatrin. The study was a retrospective cohort study of 147 individuals treated with vigabatrin for refractory complex partial (focal) seizures. The median duration of vigabatrin exposure was 7.9 years (IQR 3.6 to 11.0; range 0.2 to 16.1 years). Eighty-seven individuals exhibited vigabatrin-associated visual field loss. The modelling was undertaken jointly by an epidemiologist, Professor David Fone, Epidemiologist, and by Professor Robert Newcombe, Medical Statistician, both of whom were from the Institute of Public Health at Cardiff University. Standard and plateau univariate logistic regression techniques were explored. The plateau model for duration and for cumulative dose exhibited a better fit than the standard model. The study was published in the academic journal CNS Drugs (Appendix).
2.5 The structure-function relationship in vigabatrin toxicity

The study described in Chapter 4 explored the relationship between the structural outcome (i.e. the extent of the retinal nerve fibre layer attenuation derived by optical coherence tomography) and the functional outcome (i.e. the visual field derived by threshold perimetry) in terms of the remaining retinal ganglions cells calculated by each technique based upon the model developed by (Harwerth et al., 2010). Such an approach, i.e., in terms of remaining ganglion cells, converts the logarithmic scale used in perimetry to a linear scale, thereby simplifying the type of potential relationship with a linear structural outcome, and is also more appropriate for quantifying residual function. The study was undertaken on 40 individuals treated with vigabatrin for refractory complex partial (focal) seizures of whom 24 had vigabatrin-associated visual field loss. A group of 22 normal individuals and a group of 18 individuals with open angle glaucoma were used as controls.

2.6 Long-term follow-up of vigabatrin-associated visual field loss

The literature suggests that vigabatrin-associated visual field loss neither reverses nor progresses over a maximum period ranging from 4 to 6 years following withdrawal of vigabatrin (Kjellström et al., 2008). The study described in Chapter 5 evaluated the longer-term follow-up of the visual field in 27 individuals exposed to vigabatrin. Nineteen of the 27 individuals had vigabatrin-associated visual field loss; of these, 13 were receiving vigabatrin at the time of their initial visual field examination and the remaining six had been withdrawn from vigabatrin prior to their initial examination. Of 8 individuals with normal fields, 6 had been withdrawn from vigabatrin prior to the
initial visual field examination. The median interval between the two visual field examinations was 7.02 years (IQR 6.49, 7.61). All individuals had withdrawn from vigabatrin prior to the second visual field examinations.

2.7 The long-term follow-up of vigabatrin-associated retinal nerve fibre layer thinning

To date, there have been no studies evaluating the status of the retinal nerve fibre layer thickness following withdrawal of vigabatrin. The study described in Chapter 6 evaluated the long-term follow-up of the retinal nerve layer thickness in 17 individuals exposed to vigabatrin. Thirteen of the 17 individuals had vigabatrin-associated visual field loss. Of these, 11 were receiving vigabatrin at the time of the initial optical coherence tomography examination and two had been withdrawn from vigabatrin prior to the initial examination. Of the four individuals with normal fields, all 4 had been withdrawn from vigabatrin prior to the initial optical coherence tomography examination. The median interval between the two optical coherence tomography examinations was 6.5 years (IQR 5.8, 6.9).

2.8 The macular thickness in individuals exposed to vigabatrin

Epiretinal membrane formation and either an irregular sheen or abnormal pigmentation at the macular have been found in some individuals with vigabatrin ocular toxicity (Krauss et al., 2003). The study described in Chapter 7 evaluated the macular thickness, determined by time-domain optical coherence tomography, in 62 individuals exposed to vigabatrin, of whom 45 exhibited vigabatrin-associated visual field loss.
2.9 Logistics

The visual field and optical coherence tomographic examinations for the studies described in Chapters 4, 5, 6 and 7 were undertaken during normal clinic hours in the Welsh Epilepsy Clinic and in the Cardiff Eye Unit, respectively, and were, therefore, dependent upon the goodwill of the study participants, and of individuals and staff, alike. The visual field examinations were undertaken by the Author and the optical coherence tomographic examinations by a Senior Medical Photographer, Ms Belinda Colton, who was experienced in the technique. The concomitant ophthalmological and neurological examinations were undertaken as part of the routine clinical care of the given individual.

In total, a maximum of 147 individuals with refractory partial (focal) epilepsy who were exposed to vigabatrin and who had yielded reliable fields were involved in the study described in Chapter 3. A total of 72 individuals were examined by the Author during the development of this thesis. Of these 72 individuals, 9 yielded unreliable outcomes to the visual field examination. The remaining 63 individuals took part in at least one of the studies described in Chapters 4, 5, 6 and 7.

The Author was responsible to Professor John Wild, as supervisor, for the compilation, and the quality control, of the data files.
Chapter 3. Modelling the risk of visual field loss arising from the long-term exposure to vigabatrin: a cross-sectional approach

3.1 Introduction

It was shown in Chapter One that, although the estimate of the frequency of vigabatrin-associated visual field loss ranges from 6% (Gaily, Jonsson and Lappi, 2009) to 93% (Clayton et al., 2013), the frequency is generally considered to be approximately 32% (95% CI 28, 36%) (EMEA, 1999) and is based upon the visual fields of 335 individuals submitted to the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Agency in 1999 by the Marketing Authorisation Holder (EMEA, 1999). The cumulative incidence of vigabatrin-associated visual field loss, derived from the cross-sectional data, and modelled for the time to onset, rather than the time to detection, of the field loss, increased rapidly in the first two years of treatment and then stabilised at three years of exposure (EMEA, 1999). The corresponding model for cumulative dose increased steeply within the first 2kg of intake and reached a plateau after 3kg. However, the models were limited by the lack of treatment durations in excess of 5-6 years and the CPMP noted that there was no reliable evidence to indicate that the risk of developing vigabatrin-associated visual field loss lessened after three years of treatment (EMEA, 1999).

It was also shown in Chapter One that a reliable estimate of the prevalence of vigabatrin-associated visual field loss could also be gained from the systematic review
by Maguire et al., (2010) of 32 observational studies of individuals exposed to vigabatrin. This review generated a median of 45% (IQR 33 to 60) for the proportion of individuals with field loss. For a mean cumulative dose of 1kg of vigabatrin, the estimated proportion with field loss was 34% compared to 53% for 5kg. However, only nine studies specifically reported vigabatrin-associated visual field loss as opposed to field loss, in general. The median for vigabatrin-associated visual field loss was 31% (IQR 21 to 52) and that for field loss attributable to other causes 10% (IQR 5 to 13). The studies were also based upon relatively short-term exposures to vigabatrin (mean duration 3.9 years; standard deviation [SD] 1.5; mean cumulative dose 3.5kg; SD 1.5) (Maguire et al., 2010).

The longer-term safety profile of vigabatrin in relation to the associated visual field loss is unknown. It is, therefore, essential to determine the rate and magnitude of any increase in the frequency of vigabatrin-associated visual field loss arising from longer-term usage.

### 3.2 Aim

The purpose of the study was to assess the risk (frequency) of vigabatrin-associated visual field loss, in terms of duration and cumulative dose of vigabatrin, with particular reference to long-term usage of vigabatrin in individuals with refractory complex partial (focal) seizures.
3.3 Methods

3.3.1 Cohort

The study was a retrospective cohort study. The cohort was derived from the case notes of individuals attending the Alan Richens Unit Welsh Epilepsy Centre, University Hospital of Wales, Cardiff, UK, who had been treated with vigabatrin for refractory complex partial (focal) seizures. It comprised 147 unselected consecutive individuals (80 females, 67 males) who had all yielded a reliable outcome to an identical and robust perimetric protocol and for whom a full anti-epileptic drug history was available. All individuals had undergone an ophthalmological examination and 145 individuals had met predefined inclusion criteria in each eye; namely, a distance refractive error of less than or equal to 5 dioptres mean sphere and less than 2.5 dioptres cylinder; a visual acuity of 20/30 or better in each eye; normal pupil reactions; an intraocular pressure of $\leq 21$mmHg; open angles; crystalline lens integrity defined by LOCS III (Chylack et al., 1993) as less than, or equal to, nuclear opalescence grade 2 and nuclear colour grade 2, cortical cataract less than or equal to grade C1 and posterior subcapsular cataract less than C1; no optic nerve head or fundal abnormalities characteristic of a known disease other than vigabatrin toxicity; no previous ocular surgery or trauma; no visual field loss other than that attributable either to vigabatrin toxicity or to cortical lesions; no topical ocular therapy other than ocular lubricants; no systemic medication known to affect the visual field other than vigabatrin; no history of diabetes mellitus and no family history of glaucoma. The remaining two individuals had bilateral open-angle glaucoma and unilateral central serous retinopathy, respectively. However, in the first individual, the vigabatrin-associated visual field loss could be clearly distinguished from the
glaucomatous field loss and in the second individual, the vigabatrin-associated visual field loss was clearly evident in the contralateral eye.

Of the 147 individuals, 124 were under the care of the Welsh Epilepsy Unit and 23 had been referred from other hospitals for perimetry. Almost all the individuals had received vigabatrin in tablet formulation.

Of the 147 individuals, 137 had commenced treatment with vigabatrin between 1989, the year of its licensing, and 1997 inclusive, the year of the first publication linking vigabatrin to visual field loss. A further 4 individuals had begun treatment prior to 1989 on an off-label compassionate basis. Of the remaining 6 individuals, 4 had begun treatment in 1998 and one each in 1999 and 2000, respectively. Fifty eight of the 147 individuals (39.4%) had commenced vigabatrin between 1986 and the end of 1991.

3.3.2 Visual field examination

A systematic programme of visual field examination of individuals exposed to vigabatrin had been initiated in the Welsh Epilepsy Unit from 2000 onwards as a consequence of the then emerging consensus on the association of vigabatrin with visual field loss (Eke et al., 1997; Kalviainen et al., 1999; Miller et al., 1999; Wild et al., 1999a). All individuals had been/ were withdrawn from vigabatrin, as a safety measure, either prior to, or immediately following, the visual field examination.

Examination of the full field had been undertaken with three-zone age-corrected suprathreshold (Humphrey Field Analyzer 750 Full Field 135 Screening Test with Goldmann stimulus size III). For the assessment of the central field, each individual wore their distance correction in trial lens form together with the appropriate near
correction for the viewing distance of the perimeter bowl, where necessary. Individuals with visual field results deemed to be abnormal, or to be suspicious of abnormality, had then undergone threshold static perimetry of the central field on a separate occasion (HFA Program 30-2: Goldmann stimulus size III and the FASTPAC algorithm).

Each individual had received extensive instruction and practice on the requirements of the given visual field examination. Rest periods of one minute had been given after a maximum of three minutes of perimetry, during which time the individual had been required to continue looking into the bowl of the perimeter. A rest period of 10 to 15 minutes, in the waiting area of the clinic, had taken place between the examinations of the two eyes. Visual field examinations which had yielded greater than 15% incorrect responses to the false-positive and/ or greater than 20% incorrect responses to the fixation loss catch trials and/ or poor quality outcomes to the gaze tracking had been repeated on a separate occasion. Individuals who had manifested such an outcome to the repeat examination were not included in the cohort. A similar approach was adopted for incorrect responses to the false-negative catch trials: the repeat criterion was greater than 30% incorrect responses but the tolerance widened with increase in severity of the field loss (Bengtsson and Heijl, 2000). Any examination deemed to have initially yielded an equivocal diagnostic outcome, including an apparent learning effect, had also been repeated on a subsequent occasion.

The visual fields of the 147 individuals were reviewed, masked to anti-epileptic drug history, by Dr Charlotte Lawthem, Consultant Neurologist, Mr Gareth Lewis, Specialist Registrar in Ophthalmology, and Professor John Wild. The visual fields from 15 individuals with epilepsy who had never been treated with vigabatrin were randomly interposed within the series of visual fields for review. These visual fields all exhibited
a normal appearance and were included such that the reviewers were aware that not all the visual fields for review emanated from patients exposed to vigabatrin. The definition of vigabatrin-associated visual field loss followed that previously described, namely, a bilateral clinically symmetrical, ‘concentric’ constriction of the peripheral field which, by static perimetry using Goldmann stimulus size III, is generally more pronounced nasally than temporally (Wild et al., 2009) and which, in almost all cases, encroaches upon at least the nasal region of the central field (i.e. out to a radius of 27º from fixation) (Wild et al., 2009). In severe manifestations, the defect by static perimetry manifests as a concentric constriction to within approximately 15º from fixation (Wild et al., 2009). The vigabatrin-associated visual field loss was required to exhibit a consistent appearance between suprathreshold and threshold perimetry. The perimetric algorithms, and the definition of vigabatrin-associated visual field loss, were those approved by the Committee for Proprietary Medicinal Products (CPMP) for the investigation of the association between vigabatrin and visual field loss (Wild et al., 2009). Illustrations of typical vigabatrin-associated visual field loss are given in Wild et al (1999).

The severity of the vigabatrin-associated visual field loss was expressed, objectively, in terms of the Mean Deviation (MD) visual field index, averaged across the two eyes. The MD is the weighted mean of the difference, across each stimulus location within the central field, between the measured value of sensitivity and the age-corrected normal value (Heijl, Lindgren and Olsson, 1987b). It enables a continuous (ratio) scale of measurement, is used universally in the clinical and in the research setting, and, in the context of the current study, expresses the extent of the vigabatrin-associated visual field loss within the functionally important central field. Individuals with concomitant field loss were omitted from this sub-analysis.
3.3.3 Statistical analysis

Gender; age at the time of the visual field examination; age at onset of epilepsy; age at onset of treatment with vigabatrin; duration and cumulative dose of vigabatrin at the time of the visual field examination; and anti-epileptic drugs used prior to, and concurrently with, vigabatrin were each evaluated as explanatory variables. The extent of GABA-ergic activity of each of the other anti-epileptic drugs was expressed, on a four point scale, in descending order of empirically assigned magnitude. Tiagabine was graded as level 1; the benzodiazepines as level 2; valproate, phenobarbital and primodone as level 3; and the remainder as level 4 (Wild et al., 2009).

The characteristics of the cohort were described with descriptive statistics. Independent t-tests for continuously distributed variables, and chi-square tests for categorical variables, were used to assess univariate associations between vigabatrin-associated visual field loss and the duration and the dose of vigabatrin and between vigabatrin-associated visual field loss and each of the other explanatory variables. Statistical analysis was undertaken using SPSS Statistics 20 (IBM Corporation, Armonk, NY).

A confidence interval for the relative risk of vigabatrin-associated visual field loss by gender was calculated by the score method (Miettinen and Nurminen, 1985).

The degree of associations between duration and cumulative dose of vigabatrin and the severity of vigabatrin-associated visual field loss was characterised by the Spearman rank correlation, \( r_s \).
3.3.4 Modelling

The increase in the risk (frequency) of individuals with vigabatrin-associated visual field loss (p) with increasing exposure to vigabatrin (x) was evaluated by logistic regression. In addition to the standard logistic regression model, a plateau model was utilised:

\[
p = \frac{k}{1 + \exp(-\alpha - \beta x)}
\]

where k denotes a plateau value lower than 1 (100%), and where \( \alpha \) and \( \beta \) are intercept and slope parameters, respectively. For the plateau model, the risk of vigabatrin-associated visual field loss at the highest exposures approaches k, not 1, whereas for the standard regression model, \( k \equiv 1 \). The standard and plateau models were fitted by maximum likelihood with profile likelihood CIs for the parameters. Comparisons between the standard and plateau models were performed by referring the difference in deviance to the Chi-square distribution. The two models were each applied separately for duration and for cumulative dose. Models of these two exposure variables, considered together, were also evaluated.

3.4 Results

3.4.1 Demographics of the cohort.

The age at visual field examination (Table 3-1) ranged from 12.6 to 75.9 years with a mean of 40.3 years (SD 13.7), median 39.6, (IQR 30.4 to 50.6); females 40.5 years (SD 13.4, median 40.1, IQR 30.5 to 50.7), males 40.0 years (SD 14.2, median 38.8, IQR 30.4 to 50.6).
<table>
<thead>
<tr>
<th>Age</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>All individuals</td>
<td>40.3 (13.7)</td>
<td>39.6 (30.4, 50.6)</td>
<td>12.6</td>
<td>75.9</td>
</tr>
<tr>
<td>Male</td>
<td>40.0 (14.2)</td>
<td>38.8 (30.4, 50.6)</td>
<td>16.1</td>
<td>75.9</td>
</tr>
<tr>
<td>Female</td>
<td>40.5 (13.4)</td>
<td>40.1 (30.5, 50.7)</td>
<td>12.6</td>
<td>66.5</td>
</tr>
</tbody>
</table>

Table 3-1: The summary statistics for the distribution of age amongst the 147 individuals in the study and for the distribution of age by gender.

Overall, 87 individuals (59%) exhibited vigabatrin-associated visual field loss; 44 / 67 (66%) were males and 43 / 80 (54%) females (relative risk 1.22, 95% CI 0.93 to 1.61, p = 0.14).

<table>
<thead>
<tr>
<th>Gender</th>
<th>Status</th>
<th>VAVFL (%)</th>
<th>Vigabatrin exposed with normal field (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td>44 (51%)</td>
<td>23 (39%)</td>
<td>67</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>43 (49%)</td>
<td>37 (61%)</td>
<td>80</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>87 (59%)</td>
<td>60 (41%)</td>
<td>147</td>
</tr>
</tbody>
</table>

Table 3-2: The frequency of vigabatrin-associated visual field loss (VAVFL) by gender.

Eleven individuals exhibited superior homonymous quadrantanopia secondary to neurosurgery for seizure control; of these, seven exhibited vigabatrin-associated visual field loss. Twelve others had homonymous hemianopia or quadrantanopia secondary to other causes; of these, eight had vigabatrin-associated visual field loss. No cases of field loss were designated in any of the visual fields from the 15 individuals with epilepsy who had never received vigabatrin.

3.4.2 Evaluation of the explanatory variables for vigabatrin-associated visual field loss

Individuals exhibiting vigabatrin-associated visual field loss were slightly older at the onset of epilepsy and at the time of perimetry, but younger at the onset of treatment.
with vigabatrin, than those without vigabatrin-associated visual field loss (Table 3-3); however, the differences in the mean ages were not statistically significant (1.4 years, 95% CI -2.9 to 5.8; 0.2 years, 95% CI -4.3 to 4.7; and -3.4 years, 95% CI –8.0 to 1.1, respectively).

The mean duration of vigabatrin therapy, 7.4 years (SD 4.1, median 7.9, range 0.2 to 16.1 years, IQR 3.6 to 11.0), was not significantly different for gender: females 7.2 years (SD 4.2) and males 7.6 years (SD 4.0); difference between means 0.5 years (95% CI -0.9 to 1.8). Similarly, the mean cumulative dose, 6.4 kg (SD 4.6, median 5.8, range 0.2 to 19.8, IQR 2.5 to 8.7), was not significantly different for gender: females 6.0 kg (SD 4.5) and males 6.8 kg (SD 4.8); difference between means 0.8 kg (95% CI -0.8 to 2.3).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of VGB (yr)</td>
<td>7.4 (4.1)</td>
<td>7.9 (3.6, 11.0)</td>
<td>0.2</td>
<td>16.1</td>
</tr>
<tr>
<td>Cumulative dose of VGB at follow-up (kg)</td>
<td>6.4 (4.6)</td>
<td>5.8 (2.5, 8.7)</td>
<td>0.2</td>
<td>19.8</td>
</tr>
</tbody>
</table>

Table 3-3: The summary statistics for the distribution of duration of vigabatrin therapy and the distribution of cumulative dose of vigabatrin amongst the 147 individuals in the study.

The duration and cumulative dose of vigabatrin therapy were highly correlated ($r_s = +0.86$, p<0.001) (Figure 3-1).

The mean duration and mean cumulative dose of vigabatrin therapy (Table 3-4) for those with vigabatrin-associated visual field loss was 8.9 years (SD 3.1) and 8.0 kg (SD 4.4), respectively, compared to 5.2 years (SD 4.3) and 4.0 kg (SD 3.9) for those without
vigabatrin-associated visual field loss (difference between means 3.7 years, [95% CI: 2.5, 4.9] and 4.0 kg, [95% CI: 2.6, 5.5]).

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAVFL</td>
<td>8.9 (3.2)</td>
<td>9.24 (6.8, 11.7)</td>
<td>0.2</td>
<td>15.3</td>
</tr>
<tr>
<td>Normal field</td>
<td>5.3 (3.9)</td>
<td>4.0 (1.4, 9.1)</td>
<td>0.3</td>
<td>16.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cumulative dose of vigabatrin (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAVFL</td>
<td>8.0 (4.4)</td>
</tr>
<tr>
<td>Normal field</td>
<td>4.0 (4.0)</td>
</tr>
</tbody>
</table>

Table 3-4: The summary statistics for the distribution of duration of vigabatrin therapy (top) and of cumulative dose of vigabatrin (bottom) by presence or absence of vigabatrin-associated visual field loss (VAVFL).

Vigabatrin-associated visual field loss was not significantly associated with the level of GABAergic activity of other anti-epileptic drugs taken either before, or concurrently with, vigabatrin.

The summary statistics of the Mean Deviation visual field index (Table 3-5) for those with vigabatrin-associated visual field loss (excluding those with other concomitant field loss) were mean -8.12dB (SD 4.9); median -6.5dB (IQR -4.26 to -10.5; range -0.8 to -29.0dB). The corresponding summary statistics for the MD for those without vigabatrin-associated visual field loss (excluding those with other concomitant field loss) were mean -1.5dB (SD 1.7); median-1.5dB (IQR -0.06 to -2.6; range -4.8 -1.4dB).
Figure 3-1: The scatter plot of cumulative dose of vigabatrin (kg) against duration of vigabatrin therapy (yr) for the individuals with (filled symbols) and without (open symbols) vigabatrin-associated visual field loss.

Table 3-5: The summary statistics for the Mean Deviation visual field index, averaged between the two eyes, by the presence or absence of vigabatrin-associated visual field loss (VAVFL).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAVFL</td>
<td>-8.12 (4.9)</td>
<td>-6.5 (-4.3, -10.5)</td>
<td>-0.8</td>
<td>-29.0</td>
</tr>
<tr>
<td>Normal field</td>
<td>-1.5 (1.7)</td>
<td>-1.5 (-2.6, -0.06)</td>
<td>1.4</td>
<td>-4.8</td>
</tr>
</tbody>
</table>
No evidence was found for an association between the severity of the vigabatrin-associated visual field loss, as expressed by the MD, and either duration ($r_s +0.22$, 95% CI -0.03 to +0.45) or cumulative dose of vigabatrin ($r_s +0.02$, 95% CI -0.24 to +0.28). Severe vigabatrin-associated visual field loss was noted even at very low exposures. Three outlier individuals exhibited severe vigabatrin-associated visual field loss of more than two SDs from an assumed linear fitted line of best fit, which was associated with durations of 3, 6 and 13 years and cumulative doses of 3, 7, and 19 kg, respectively.

3.4.3 The risk (frequency) of vigabatrin-associated visual field loss with increasing exposure to vigabatrin

The outcome of the visual field examination by decile group of exposure, by current or previous vigabatrin therapy at the time of the visual examination, and by severity of the vigabatrin-associated visual field loss, expressed in terms of the MD averaged between the two eyes, is given in Table 3-6 for duration of vigabatrin therapy and in Table 3-7 for cumulative dose of vigabatrin.

The risk (frequency), derived by the plateau model, of developing vigabatrin-associated visual field loss according to duration (Figure 3-2) top and to cumulative dose (Figure 3-2) bottom of vigabatrin was expressed as the proportion of individuals with vigabatrin-associated visual field loss, by decile group of exposure to vigabatrin, plotted against the median exposure for the corresponding decile group. The relevant parameter estimates are given in Table 3-8. The plateau, towards which the frequency of vigabatrin-associated visual field loss increased with increasing exposure, was 76% (95% CI 67 to 85) beyond approximately six years duration and 79% (95% CI 70 to 87) after approximately 5 kg cumulative dose.
In comparison to the plateau model, the standard model with $k \equiv 100\%$ was a highly significantly poorer fit to the data ($\chi^2 = 12.75$ for duration, $\chi^2 = 18.93$ for cumulative dose, both $p<0.001$). The standard model failed to express the very steep rise in the proportion of individuals with vigabatrin-associated visual field loss between exposures of approximately 2 and 6 kg. It fitted a proportion of 20 - 25% at zero exposure, which rose to over 90% for the highest exposures in the cohort; both these modelled proportions were much higher than the observed proportions. The observed proportion at minimal exposure in the plateau model was very low, but not zero: one individual had developed vigabatrin-associated visual field loss after taking 0.189 kg of vigabatrin over 9 weeks. A model which incorporated a plateau and constrained the proportion to be zero at zero exposure was a slightly poorer fit than the unconstrained plateau model.

The modelled frequency of individuals with vigabatrin-associated visual field loss assumes that the field loss in those who had discontinued vigabatrin prior to the visual field examination was not reversible (Johnson et al., 2000; Nousiainen et al., 2001; Newman et al., 2002). Seventy-one (48%) individuals were receiving vigabatrin at the time of the visual field examination. Visual field loss was marginally significantly more common in these latter individuals (48 / 71, 68%) than in those who had discontinued treatment (39 / 76, 51%; $p = 0.045$). However, the individuals who were currently receiving vigabatrin had significantly longer durations of use (mean 8.6 years compared to 6.2 years, $p < 0.001$) and significantly greater cumulative doses (mean 7.3kg compared to 5.5kg, $p = 0.017$) compared to those who were not. The incorporation of an additional term in the plateau model for current vigabatrin therapy did not give an appreciably better fit ($\chi^2 = 0.46$, $p = 0.50$ for duration; $\chi^2 = 0.04$, $p = 0.84$ for cumulative dose).
<table>
<thead>
<tr>
<th>Decile</th>
<th>Number of individuals</th>
<th>Duration of vigabatrin therapy</th>
<th>Vigabatrin therapeutic status at the perimetric examination and corresponding visual field outcome</th>
<th>Severity of vigabatrin-associated visual field loss (MD [dB])&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Min.</td>
<td>Max.</td>
<td>Mean</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>0.2</td>
<td>1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>1.3</td>
<td>2.8</td>
<td>2.0</td>
</tr>
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<td>3</td>
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<td>15</td>
<td>11.6</td>
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<td>12.0</td>
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<tr>
<td>10</td>
<td>14</td>
<td>12.4</td>
<td>16.1</td>
<td>13.4</td>
</tr>
</tbody>
</table>

Table 3-6: The summary statistics for duration of vigabatrin therapy for each decile group by vigabatrin therapeutic status, visual field outcome and severity of the vigabatrin-associated visual field loss (VAVFL). <sup>1</sup>The severity of the vigabatrin-associated visual field loss is expressed in terms of the visual field index, Mean Deviation (MD), averaged between the two eyes. An increasingly negative MD represents a worsening of the visual field. Note individuals with concomitant visual field loss are excluded from the distributions of the MD.
Table 3-7: The summary statistics for cumulative dose of vigabatrin therapy (kg) for each decile group by vigabatrin therapeutic status, visual field outcome and severity of the vigabatrin-attributed visual field loss (VAVFL). ¹The severity of the vigabatrin-associated visual field loss is expressed in terms of the visual field index, Mean Deviation (MD), averaged between the two eyes. An increasingly negative MD represents a worsening of the visual field. Note individuals with concomitant visual field loss are excluded from the distributions of the MD.

<table>
<thead>
<tr>
<th>Decile</th>
<th>Number of individuals</th>
<th>Cumulative dose of vigabatrin (kg)</th>
<th>Vigabatrin therapeutic status at the perimetric examination and corresponding visual field outcome</th>
<th>Severity of vigabatrin-attributed visual field loss (MD [dB])¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Min.</td>
<td>Max.</td>
<td>Mean</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>0.1</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
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<td>1.0</td>
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</tr>
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<td>1.5</td>
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<td>2.5</td>
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<td>3.9</td>
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Figure 3-2: The risk of developing vigabatrin-associated visual field loss according to duration (top) and cumulative dose (bottom) of vigabatrin. In each panel, the 10 symbols each represent decibel groups defined by the relevant exposure, and show the proportions of individuals in each exposure group with vigabatrin-associated visual field loss, plotted against the median exposure for the group. The smooth curves are fitted by a logistic regression model incorporating a plateau. The middle curve shows the estimated cumulative risk of vigabatrin-associated visual field loss at each exposure. The lower and upper curves represent the 95% confidence interval.
Table 3-8: Parameter estimates for the plateau logistic regression models for the risk (frequency) of developing vigabatrin-associated visual field loss by duration and by cumulative dose of vigabatrin. The plateau parameter, k, may be regarded as the proportion of the caseload of individuals treated with vigabatrin who would develop vigabatrin-associated visual field loss following a high degree of exposure to the drug. 95% confidence limits are shown for the plateau k, for the slope parameter β and the corresponding odds ratio, $e^\beta$, representing the increase in the odds of developing vigabatrin-associated visual field loss for an additional unit of exposure among those susceptible to developing it.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model by duration (years)</th>
<th>Model by cumulative dose (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept $\alpha$</td>
<td>-3.28</td>
<td>-3.36</td>
</tr>
<tr>
<td>Slope $\beta$</td>
<td>0.98 (0.48 to 2.38)</td>
<td>1.29 (0.71 to 2.28)</td>
</tr>
<tr>
<td>Odds ratio per unit exposure, $e^{\beta}$</td>
<td>2.67 (1.61 to 10.79)</td>
<td>3.63 (2.03 to 9.74)</td>
</tr>
<tr>
<td>Plateau $k$</td>
<td>0.76 (0.67 to 0.85)</td>
<td>0.79 (0.70 to 0.87)</td>
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3.5 Discussion

The current study describes the risk (frequency) of vigabatrin-associated visual field loss at higher exposures to vigabatrin than previously evaluated: over half the individuals (85 / 147; 58%) had received vigabatrin for more than 7 years and almost one third (31%) for more than 10 years. The two novel plateau models indicate that the frequency of vigabatrin-associated visual field loss, compiled from the cross-sectional evidence, rises steeply up to approximately 6 years or 5kg cumulative dose, then levels out at a plateau of between 75-80%. The plateau is substantially higher than frequencies at lower exposures to vigabatrin (EMEA, 1999; Wild et al., 2009; Maguire et al., 2010) yet it is firmly well below 100%.

Duration and cumulative dose of vigabatrin were highly correlated, and exhibited similar patterns of increasing frequency of vigabatrin-associated visual field loss with
increasing exposure. A plateau model incorporating duration and dose, together, described the data significantly better than the model by duration, alone \((\chi^2 = 9.02, p = 0.003)\) but not appreciably better than the model by cumulative dose, alone \((\chi^2 = 0.09, p = 0.77)\). This suggests that the risk of developing vigabatrin-associated visual field loss is determined by cumulative dose rather than by duration. It can also be seen from Figure 3-1 that, for any given duration (i.e. for any vertical slice), the data points representing individuals with vigabatrin-associated visual field loss tend to lie above (i.e. at greater cumulative doses) than those points representing individuals with no vigabatrin-associated visual field loss. Conversely, for any horizontal slice, there is no apparent tendency for the data points representing individuals with vigabatrin-associated visual field loss to lie to the right (i.e. at greater durations) of those points representing individuals with no vigabatrin-associated visual field loss. The greater influence of cumulative dose compared to duration is also consistent with that of the only systematic review of vigabatrin-associated visual field loss (Maguire et al., 2010).

The main limitation of the study is that the estimate of the increase in the frequency of vigabatrin-associated visual field loss with increased expose to vigabatrin was based upon a cross-sectional evaluation of the effects of duration and of cumulative dose. Ethical considerations of the potential risk for vigabatrin-associated visual field loss with continuing exposure to vigabatrin prevent a formal prospective longitudinal clinical trial over an equivalent time period. Even for such a study, the precision of the estimate of the increase in frequency would be dependent upon the number of, and interval between, the perimetric examinations. In the USA, approval for vigabatrin was conditional upon implementation of a Risk Evaluation and Mitigation Strategy (REMS) which is currently administered via the USA Marketing Authorisation Holder’s
programme (Pellock et al., 2011; SHARE, 2013). As part of this programme, the outcomes from ophthalmological testing of all individuals treated with vigabatrin in the USA are mandatorily collated in a registry. Analysis of the registry could eventually provide some longitudinal perspective as to the increase in the frequency of vigabatrin-associated visual field loss with increased exposure to vigabatrin. However, the registry will be only be analysed for the first six years and the outcome will not approach the level of evidence from prospective clinical trial data (Pellock et al., 2011). The most recent analysis of the registry, at three years, has yielded little in regard to the frequency of vigabatrin-associated visual field loss. The registry comprised 4292 individuals: of these, 62% had infantile spasms; 55% of all individuals had discontinued vigabatrin; and only 7% had undergone a visual field examination at baseline (Sergott et al., 2012a). A current, small-scale, prospective study, over one year, of approximately 80 adult individuals, de novo to vigabatrin and undergoing regular perimetry and optical coherence tomography, of whom it is estimated 20 will complete the study, may provide some evidence as to the short-term onset of vigabatrin-associated visual field loss (Sergott, Laxter and Torri, 2012b).

In the current study, the modelled frequency of individuals with vigabatrin-associated visual field loss at 3 years of exposure, 31.7%, is identical to that, submitted to the CPMP, for an equivalent exposure (EMEA, 1999). The latter estimate was based upon the modelled time to onset of the field loss whilst that of the current study was derived from the time to detection of the field loss. The modelled frequency is also in agreement with the median frequency of 31% derived by the systematic review for a similar exposure (Maguire et al., 2010).
Vigabatrin-associated visual field loss is largely initially asymptomatic unless the field loss is concentric within the central field (Lawden et al., 1999; Miller et al., 1999; Coupland et al., 2001). The visual acuity remains normal or near-normal and, in less severe cases, the predominantly nasal loss in the ipsilateral eye is compensated by the relatively well-preserved temporal field in the contralateral eye (Wild et al., 1999a). As a consequence of the asymptomatic nature, it is likely that, for most individuals, the time to detection will have preceded the time to self-referral on the basis of symptoms.

The marked difference in the distributions of the Mean Deviation visual field index between the two cohorts (i.e. those with, and those without, vigabatrin-associated visual field loss) clearly indicates the high sensitivity and high specificity both of the perimetric protocol and of the definition of vigabatrin-associated visual field loss.

The established literature on vigabatrin-associated visual field loss, evidenced by the outcome of the systematic review (Maguire et al., 2010), is contrary to the findings of Sergott et al., (2010), the latter were derived from a subset of the cohort described by Wild et al., (2009). Based upon an evaluation of the outcome of kinetic perimetry in terms of the angular extent of the V4e or IVe isopter along the temporal meridian, and an empirical definition for normality (Sergott et al., 2010) the approach yielded poor sensitivity (72% of those exposed to vigabatrin, exhibited field loss) and poor specificity (45% of those with no exposure to vigabatrin, exhibited field loss) when compared to the outcome in the same cohort based upon the CPMP accepted protocol and classification system of static perimetry (Wild et al 2009). The extremities of the temporal field exhibit the largest between- and within-individual variability in response to kinetic perimetry and is the least affected by vigabatrin-associated visual field loss. The efficient detection of visual field loss by good quality kinetic perimetry can only be
undertaken in terms of a comparison of the shape and extent of a number of isopters across all meridians. The guidelines provided by the Marketing Authorisation Holders of vigabatrin outside of the USA stipulate that, when undertaken, kinetic perimetry of individuals exposed to vigabatrin should examine the III4e, I4e and I2e or I1e isopters. However, Wild et al., (2009) also showed that, in the full data set, vigabatrin-associated visual field loss was more frequently detected with static than with kinetic perimetry (OR, maximum, 3.3; 95% CI: 0.8 to 13.5) at a specificity of 99.2%. Sergott et al., (2010) also failed to undertake any quality control of the data subset: the output from many of the visual field examinations by kinetic perimetry had been of such poor quality that Wild et al., (2009) had introduced a protocol amendment which had replaced the technique, wherever possible, with static perimetry.

The severity of the vigabatrin-associated visual field loss, as expressed by the Mean Deviation visual field index, was not significantly associated with either the duration or the cumulative dose of vigabatrin. Clearly, the absence of a correlation between the Mean Deviation and either the cumulative dose, or the duration, of vigabatrin cannot be explained by any restriction in the range of severity of the vigabatrin-associated visual field loss. The absence of any correlation is in agreement with some shorter-term exposure studies (Nousiainen et al., 2001; Kinirons et al., 2006) but not with others (Hardus et al., 2000b; Koller et al., 2001) and is consistent with the concept of an idiosyncratic drug reaction.

The lack of an association of vigabatrin-associated visual field loss with any other antiepileptic drug either prior to, or concurrently with, vigabatrin is consistent with most studies. The absence of any association may arise from the insufficient number of cases with vigabatrin-associated visual field loss to accommodate the multiplicity of
therapeutic combinations. However, sodium valproate has been implicated with more severe vigabatrin-associated visual field loss (Arndt et al., 2002).

Vigabatrin-associated visual field loss is considered by some to be, principally, a defect of the peripheral field (Frisen and Malmgren, 2003), i.e., that beyond a radius of 27º from fixation. However, all but one of the individuals manifested vigabatrin-associated visual field loss within the central field. Such a finding underlines the importance of threshold perimetry of the central field out to 27º eccentricity, in conjunction with three-zone age-corrected suprathreshold static perimetry of the peripheral field, for delineating vigabatrin-associated visual field loss and which, together with a robust definition of vigabatrin-associated visual field loss based upon abnormality exhibiting at least nasal encroachment within the central field, would reduce false-positive outcomes such as those clearly evident in the illustrations of Gonzalez et al., (2009).

The visual field examination of individuals receiving vigabatrin can often be inconclusive due to the inherent cognitive demands. The frequent requirement for one or more confirmatory repeat examinations further increases the cost of management of such individuals. However, even after repeated examinations, the results often remain equivocal. In the compilation of this cohort of 147 individuals, a further 20 competent adult individuals (12%) had been unable to produce a reliable result. This figure compares with estimates of approximately 25% in similar individuals (Wild et al., 2006; Wild et al., 2009). However, assessment of the retinal nerve fibre layer thickness by optical coherence tomography shows promise either as an alternative, or as an adjunct, to perimetry (Wild et al., 2006; Clayton et al., 2011; Clayton et al., 2012) and is acceptable for REMS in individuals who are unable to undertake perimetry (Pellock et al., 2011).
The earliest onset of vigabatrin-associated visual field loss (0.189kg over a treatment period of 8 weeks) is compatible with onsets of between 4 (Malmgren et al., 2001) and 6 months (Kiratli and Türkçüoğlu, 2001). The obvious rapid manifestation of vigabatrin-associated visual field loss in some individuals; the continued increase in the frequency of vigabatrin-associated visual field loss up to six years of exposure, reported here; and the potential for longer-term worsening of existing vigabatrin-associated visual field loss (Clayton et al., 2010; Clayton et al., 2013) is compatible with the REMS stipulation for perimetry at baseline and at a minimum of three monthly intervals (Pellock et al., 2011) throughout the treatment period and within 3 to six months following withdrawal. These requirements are more stringent than others; which advocate a baseline examination followed by six-monthly examinations either for the entire treatment period (Aventis, 2010) or for the first five years of exposure followed by yearly examinations for those without vigabatrin-associated visual field loss (Hawker and Astbury, 2008). Based upon the results of the current study, these latter two recommendations should be brought into line with those of REMS. The resultant increased economic cost for the provision of the ensuing additional visual investigations will need to be considered in the use of vigabatrin outside of the USA.

GABA elevation dampens the increase in brain dopamine responsible for drug ‘highs’ (Gerasimov et al., 2001) and a maximum cumulative dose of vigabatrin of between 0.137kg (Fechtner et al., 2006) and 0.218kg (Berezina et al., 2012) over 9 to 12 weeks, respectively, has been proposed as anti-addiction therapy for misuse of stimulant drugs. The early onset case of vigabatrin-associated visual field loss in the current study was associated with a cumulative dose of 0.189kg.
Vigabatrin can induce clinically profound bilateral peripheral visual field loss which encroaches into the central field, to varying degrees, as evidenced by the range of the MD index encountered in the study (Table 3-6). There are no staging systems for vigabatrin-associated visual field loss in terms of the Mean Deviation; a recent study of individuals with glaucomatous visual field loss designated Mean Deviation of better than -6.00dB as mild, of between -6.00dB and -12.00dB as moderate and worse than -12.00dB as severe (Pillai et al., 2013). From an ophthalmological perspective, any vigabatrin-associated visual field loss is unacceptable, regardless of severity, and is a major concern when superimposed upon existing loss e.g., that from cortical involvement. Even if such individuals are excluded from treatment with vigabatrin, a proportion of those who are treated and who develop vigabatrin-associated visual field loss will go on to develop field loss secondary to conditions concomitant with aging such as open angle glaucoma and/ or macular degeneration. From a neurological perspective, where the goal is a reduction in seizure frequency, the vigabatrin-associated visual field loss may be of secondary concern; however, it should be noted that most individuals are initially asymptomatic but can subsequently attribute difficulties in particular activities of daily living to their vigabatrin-associated visual field loss. The psychological and sociological ramifications of the vigabatrin-associated visual field loss should also not be underestimated. For example, one individual in the cohort was dismissed from his employment as a result of vigabatrin-associated visual field loss, subsequently required a guide dog and enlisted on a course of visual rehabilitation at a college for individuals with severe sight impairment.
3.6 Conclusion

The increasing frequency of vigabatrin-associated visual field loss with long-term exposure to vigabatrin substantially increases the risk-benefit for visual field loss and, with the requirement for an increased number of perimetric and/ or optical coherence tomographic examinations, the cost-benefit for therapy. Clinicians, individuals and carers should be aware of these findings to enable an informed choice as to the benefit of vigabatrin.
Chapter 4. Topographical variation in the retinal ganglion cell structural and functional association in vigabatrin toxicity

4.1 Introduction

The association between the extent of the exposure to vigabatrin and the severity of vigabatrin-associated visual field loss is equivocal. Most studies have utilised a perimetric methodology, and/or analysis, inappropriate for describing the full topographical extent of the field loss, e.g., the Esterman test (Hardus et al., 2001a;b), Two Zone age-corrected suprathreshold perimetry (Manuchehri et al., 2000), or the radial extent of a given isopter (Best and Acheson, 2005). Other studies involving threshold perimetry, which expresses the full topographical extent of the field loss, have used outcomes based upon the logarithmic (dB) representation of perimetric sensitivity (Conway, Cubtridge and Hosking, 2008; Wild et al., 2013). This latter measure generates a curvilinear association, if present, with a variable, such as drug exposure, considered on a linear scale. A curvilinear association can be more difficult to recognize than a linear trend when excessive variability is associated with the measurement of one or both variables.

The association between the extent of the retinal nerve fibre layer thickness and the severity of the vigabatrin-associated visual field loss has received relatively little attention. The reduction in thickness exhibits a weak linear association with the reduction in the extent of the I4e isopter, expressed either linearly in mean radial...
degrees (Clayton et al., 2011) or qualitatively (Clayton et al., 2012) and a weak exponential association with the reduction in the Mean Sensitivity of the central field (a measure based upon the logarithmic representation of sensitivity) derived by threshold perimetry (Wild et al., 2006). However, these studies failed to account for the presence of the non-axonal component of reflectance in the retinal nerve fibre layer, i.e., that arising from glial cells and blood vessels etc, which remains in advanced disease, and which results in a floor effect of approximately 35-55μm (Sihota et al., 2006). The presence of a floor effect will both hinder the identification, and diminish the strength, of any association between the retinal nerve fibre layer thickness and a given variable. In addition, the studies also failed to evaluate the influence on any association of the topographic/ regional variation in the distribution of the ganglion cell axons. As a consequence, the extent to which vigabatrin-associated visual field loss is influenced by retinal ganglion cell soma and/ or axonal dysfunction remains unknown.

A linear association between the retinal nerve fibre layer thickness and the severity of the visual field loss derived by threshold perimetry, when expressed on a linear scale, can be successfully modelled in diseases involving/ implicating the retinal ganglion cells, e.g., glaucoma (Hood et al., 2007; Hood and Kardon, 2007), ischaemic optic neuropathy (Hood et al., 2008) and optic neuritis (Cheung et al., 2008). In addition, two models have been proposed which, respectively, enable calculation, at each stimulus location, of the number of residual retinal ganglion cells based upon the outcome of standard automated perimetry and the number of residual retinal ganglion cell axons based upon the outcome of Time-domain optical coherence tomography (Harwerth et al., 2010). These models were developed from experimental glaucoma induced in primate and were subsequently refined for clinical use in human. The models generate
clinically similar/identical numbers of residual ganglion cells in open angle glaucoma (Medeiros et al., 2012a; Medeiros et al., 2012b).

Given the apparent involvement of the retinal ganglion cells in the pathogenesis of vigabatrin-associated visual field loss, either as a primary or as a secondary process, it would seem appropriate to investigate the structural and functional association, expressed on linear scales in terms of residual ganglion cell characteristics. By these means, the extent to which the characteristic pattern of vigabatrin-associated visual field loss is influenced by retinal ganglion cell soma and/or axonal dysfunction can be further investigated.

4.2 Aim

The aim of the study was to determine, as a function of retinal location, the association between the number of residual ganglion cell soma derived by standard automated perimetry and the number of residual ganglion cell axons derived by Time-domain optical coherence tomography in individuals with vigabatrin-associated visual field loss and in individuals previously exposed to vigabatrin but with normal fields.

4.3 Methods

The study utilised a prospective cross-sectional design.
4.3.1 Cohort

The primary cohort comprised 40 individuals consecutively presenting to the Alan Richens Unit of the Welsh Epilepsy Centre, University Hospital of Wales, Cardiff, UK, who had previously been treated with vigabatrin for refractory complex partial (focal) seizures, who conformed to pre-defined inclusion criteria, and who had volunteered to take part in the study. The 40 individuals had been exposed to a variety of AEDs prior to treatment with vigabatrin. None of the individuals had received tiagabine which was considered to exhibit a level one category of GABAergic activity when expressed on a 4-point scale in descending order of empirically assigned magnitude (Chapter 3). One individual had received clobazam and 15 had received sodium valproate (levels 2 and 3 GABAergic activity, respectively).

The secondary cohorts, used for control purposes, comprised 18 individuals with open angle glaucoma and 22 normal individuals. The individuals with open angle glaucoma were consecutively presenting individuals to the Glaucoma Clinics of the Cardiff Eye Unit, University Hospital of Wales, Cardiff, UK who had participated in a previous study which had employed an identical methodology. The normal individuals had participated in the same previous study and were consecutive volunteers recruited from those attending the Cardiff University Eye Clinic. All conformed to inclusion criteria identical to that of the cohort exposed to vigabatrin with the exception that none were epileptic and those with open angle glaucoma exhibited glaucomatous optic neuropathy, glaucomatous visual field loss and a medically treated intraocular pressure of $\leq 21$mmHg.
4.3.2 Perimetry

The individuals exposed to vigabatrin underwent standard automated perimetry in each eye using Program 30-2, Goldmann size III, and the FASTPAC algorithm of the Humphrey Field Analyser 750 (software revision 12.6/14.0) (Carl Zeiss, Meditec, Dublin, CA). They were all experienced in standard automated perimetry having previously undergone Program 30-2 and the FASTPAC algorithm, reliably, on at least two previous occasions. In addition, they had also undergone Three Zone suprathreshold perimetry of the central and peripheral field using the Full Field 135 Point Screening Test of the Humphrey Field Analyzer. The field of the right eye was examined before that of the left eye.

The individuals with open angle glaucoma and the normal individuals all underwent standard automated perimetry in each eye using Program 24-2, Goldmann size III, and the SITA Standard algorithm of the Humphrey Field Analyser 750 (software revision 12.6/12.6). The individuals with open angle glaucoma were experienced in standard automated perimetry having undergone Program 24-2 and either the SITA Fast or the SITA Standard algorithms on at least three previous occasions. Most of the normal individuals had previously undergone standard automated perimetry as part of their routine clinical care.

All individuals from all cohorts wore their refractive correction appropriate for the viewing distance of the perimeter. The field of the right eye was examined before that of the left eye. Rest periods of one minute were given to the individuals in each cohort after a maximum of three minutes of perimetry during which time each individual was required to continue looking into the bowl of the perimeter. A further rest period, ranging from 10 minutes to 30 minutes depending upon the individual, was given.
between the examination of the two eyes. Visual field examinations which had yielded
greater than 15% incorrect responses to the false-positive and/ or greater than 20%
incorrect responses to the fixation loss catch trials and/ or poor quality outcomes to the
gaze tracking were repeated on a separate occasion. Two individuals with vigabatrin-
associated visual field loss who had manifested such an outcome to the repeat
examination were not included in the cohort. A similar approach was adopted for
incorrect responses to the false-negative catch trials: the repeat criterion was greater
than 30% incorrect responses but the tolerance widened with increase in severity of the
field loss (Bengtsson and Heijl, 2000).

The visual field examination of the individuals exposed to vigabatrin was undertaken by
the Author and that of the individuals with open-angle glaucoma and the normal
individuals by an experienced technician.

The fields of each individual were reviewed at the end of the study, masked to the given
cohort, in random sequence by Professor John Wild who is highly experienced in
interpreting the visual fields derived by automated perimetry in individuals exposed to
vigabatrin and also in individuals with glaucoma.

4.3.3 Optical Coherence Tomography

Following perimetry, all individuals underwent measurement of the peripapillary retinal
nerve fibre layer using the standard 3.4 Scan protocol of the Time-domain StratusOCT
(Software Version 3.0) (Carl Zeiss, Meditec, Dublin, CA). The pupil was dilated, if
necessary, with one drop of 0.5% tropicamide and one drop of 2.5% phenylephrine
hydrochloride. Individuals were instructed to fixate the external fixation target which
was suitably positioned by the operator to ensure optimum centration of the scan on the
optic nerve head. The polarization and Z-axis offset were optimised to gain maximum reflection of the signal. Between three and six images were retained for each individual. All retained images were free from blink or movement artefacts and had a signal to noise ratio of ≥ 33dB. All images were acquired by a senior medical photographer, Ms Belinda Colton, who is highly experienced in optical coherence tomography. The image possessing the most optimal placement of the scan centre, compatible with the maximum signal to noise ratio, was then selected for each individual by the Author and by Professor John Wild independently of each other and masked to the visual field status. Both the Author and Professor Wild are experienced in the interpretation of optical coherence tomography. In cases of discordance between the two assessors for any given individual, a consensus was subsequently reached.

4.3.4 Ganglion cell calculation

The differential light sensitivity, in dB, at each stimulus location corresponding to the Program 24-2 stimulus configuration was extracted from the Single Field Analysis print-out for each individual; and entered into an Excel 2007 spreadsheet. Similarly, the global, quadrant and sector retinal nerve fibre layer thicknesses, automatically calculated by the StatusOCT analysis software, were separately extracted from the print-out of the selected image of each individual and entered into the spreadsheet.

4.3.4.1 Calculation of ganglion cell soma quantity from standard automated perimetry

The ganglion cell soma quantity for standard automated perimetry was calculated for each stimulus location of the Program 24-2 grid using the equations of (Harwerth et al., 2010):
\[ m = [0.054 \times (ecc \times 1.32)] + 0.9 \] (1)

\[ b = [-1.5 \times (ecc \times 1.32)] - 14.8 \] (2)

\[ gl = \frac{((s - 1) - b)}{m} + 4.7 \] (3)

and

\[ gc_{sap} = \Sigma 10^A (gl \times 0.1) \] (4)

where \( m \) and \( b \) represent the slope and intercept, respectively, of the linear function of ganglion cell density by differential light sensitivity at the given eccentricity (ecc); and where the ganglion cell density (gl), defined as the number of somas per \( mm^2 \) of retina, and the differential light sensitivity (s) are both expressed in dBs; and where \( gc_{sap} \) is the total number of retinal ganglion cells across the given number of stimulus locations.

The constant, -1, in Equation (3) accounts for the approximate 1dB higher sensitivity of the SITA Standard algorithm compared to the Full Threshold algorithm (Bengtsson and Heijl, 1998; Wild et al., 1999b; Wild et al., 1999c) and was used for the calculation of the ganglion cell quantity for the individuals with open angle glaucoma. The constant was omitted for the calculation of the ganglion cell soma quantity for the individuals exposed to vigabatrin since the differential light sensitivities obtained with the Full Threshold and FASTPAC algorithms are clinically identical (Wild et al., 1999b; Wild et al., 1999c). The constant 4.7 in Equation (3) converts retinal ganglion cell soma density to the total number of retinal ganglion cell somas at the given stimulus location based upon the 6° square stimulus grid of Program 24-2.

The ganglion cell soma quantities derived by standard automated perimetry at each stimulus location were then summed, as appropriate, to give the separate global, quadrant and sector totals corresponding to that of the StratusOCT, based upon the
topographical map of Wirtschafter et al., (1982) and as described by Garway-Heath et al., (2000) (Figure 4-1) which relates the axons of the retinal ganglion cells sub-serving the given perimetric stimulus location to their entry point at the optic nerve head.
Figure 4-1: The sectors of the optic nerve head, for the right eye, after Wirtschafter et al., (1982) and as described by Garway-Heath et al., (2000) (Top) and the stimulus locations of the visual field (Program 24-2) for the right eye corresponding to the given sectors of the optic nerve head (Bottom). The black shading indicates the blind spot.
4.3.4.2 Calculation of ganglion cell axon quantity from optical coherence tomography

The ganglion cell axon quantity derived by optical coherence tomography was calculated for the optic nerve head, as a whole, and for each of the quadrants and the sectors derived by the StratusOCT using the additional equations of Harwerth et al., (2010) developed with the StratusOCT:

\[ d = (-0.007 \times \text{age}) + 1.4 \]
\[ a = \text{mh} \times \text{px} \times 21.2 \times d \]
\[ c = (-0.26 \times \text{MD}) + 0.12 \]

and

\[ ax_{oc} = 10 \wedge [(\log a) \times 10] - c \]

where \( d \) is the axonal density, i.e. the number of axons per \( \mu m^2 \); age is in years, \( a \) is the number of axons for a section of the retinal nerve fibre layer scan with a mean height (mh) in \( \mu m \) over px number of pixels; 21.2 is the length per pixel in \( \mu m \) for the 10.87 mm scan length of the standard retinal nerve fibre layer (3.4) Scan protocol of the StratusOCT; \( c \) is a correction factor in dBs for the non-axonal component of the measured retinal nerve fibre layer thickness at the given stage of the disease, expressed by the un-weighted Mean Deviation (MD) index for the given visual field sector; and \( ax_{oc} \) is the age-corrected and non-axonal component-corrected total number of retinal ganglion cell axons in the given sector of the peripapillary retinal nerve fibre layer.
4.3.5 Statistical Analysis

The characteristics of the cohort were described with descriptive statistics using independent t-tests for continuously distributed variables, and the chi-square tests or Fisher’s exact tests for categorical variables.

The degree of association between duration and cumulative dose of vigabatrin was characterised by the Pearson correlation coefficient, $r$.

The degree of association between residual ganglion cell soma quantity derived by standard automated perimetry and residual ganglion cell axon quantity derived by optical coherence tomography was illustrated by the use of separate scatter graphs for the entire scan, for each of the four quadrants and for each of the 12 sectors.

The degree of association between the residual ganglion cell soma quantity derived by standard automated perimetry and the duration of vigabatrin therapy and between the residual ganglion cell axon quantity derived by optical coherence tomography and the duration of vigabatrin therapy was characterised by the Spearman rank correlation, $r_s$. 
4.4 Results

4.4.1 Demographics of the cohort exposed to vigabatrin

The demographic characteristics of the cohort exposed to vigabatrin are shown in Table 4-1.

The cohort contained a greater number of females than males ($\chi^2 = 6.4; p<0.011$). The males were slightly older than the females at the time of the study; however, the differences in the mean ages were not statistically significant (difference between means 1.7 years 95% CI -9.75 to 13.13; p=0.762).

Twenty-four of the 40 individuals exhibited vigabatrin-associated visual field loss. The individuals with vigabatrin-associated visual field loss were slightly older at the time of the study than those exposed to vigabatrin but with normal fields; however, the difference in the mean ages was not statistically significant (difference between means 1.6 years, 95% CI -9.7 to 6.5; p=0.690).

The between-gender difference in the proportion with vigabatrin-associated visual field loss, 8 out of 12 males and 16 out of 28 females, was not statistically significant (p=0.729).

The exposure to vigabatrin for the individuals with vigabatrin-associated visual field loss, 8.9kg (SD 4.3) cumulative dose and 10.3 years (SD 3.5) duration, respectively, was statistically significantly greater than that for the individuals with normal fields, 3.9kg (SD 4.5) and 5.4 years (SD 4.9), (difference between means 4.93kg, 95% CI 2.05 to 7.81, p<0.001; and 4.10 years, 95% CI 1.53 to 6.68; p<0.003).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Visual field outcome</th>
<th>Normal</th>
<th>VAVFL</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of individuals</td>
<td></td>
<td>16</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Male</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>Mean (SD)</td>
<td>42.6 (11.6)</td>
<td>44.2 (12.8)</td>
<td>43.5 (12.2)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>43.5 (32.7, 48.5)</td>
<td>44.5 (35.7, 54.2)</td>
<td>44.5 (35.0, 51.2)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>19.6 – 65.5</td>
<td>22.8 – 68.6</td>
<td>19.6 – 68.6</td>
</tr>
<tr>
<td>Cumulative dose of vigabatrin (kg)</td>
<td>Mean (SD)</td>
<td>3.9 (4.5)</td>
<td>8.9 (4.3)</td>
<td>7.0 (5.0)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>1.5 (1.0, 6.0)</td>
<td>8.5 (6.1, 12.7)</td>
<td>6.7 (2.2, 11.6)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.27 – 14.2</td>
<td>2.14 – 18.9</td>
<td>0.27 – 18.9</td>
</tr>
<tr>
<td>Duration of vigabatrin (yrs)</td>
<td>Mean (SD)</td>
<td>7.3 (5.8)</td>
<td>10.3 (3.5)</td>
<td>9.1 (4.7)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>5.5 (2.0, 13.5)</td>
<td>10.2 (7.0, 12.9)</td>
<td>9.2 (5.5, 12.9)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.04 – 18.2</td>
<td>4.8 – 17.9</td>
<td>0.04 – 18.2</td>
</tr>
<tr>
<td>Interval from withdrawal of vigabatrin (yrs)</td>
<td>Mean (SD)</td>
<td>9.3 (4.5)</td>
<td>6.7 (3.5)</td>
<td>7.7 (4.1)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>9.0 (5.9, 11.9)</td>
<td>7.1 (5.1, 8.9)</td>
<td>7.8 (5.2, 10.7)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>2.0-17.4</td>
<td>1.8-12.57</td>
<td>1.8-17.4</td>
</tr>
<tr>
<td>MD average of both eyes (dB)</td>
<td>Mean (SD)</td>
<td>-2.0 (2.4)</td>
<td>-7.8 (5.1)</td>
<td>-5.3 (5.1)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>-1.05 (-3.7, -0.09)</td>
<td>-5.9 (-12.8, -4.1)</td>
<td>-4.2 (-8.6, -1.4)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>-5.6 – 0.46</td>
<td>-21.5 – (-0.80)</td>
<td>-21.5 – (-0.46)</td>
</tr>
<tr>
<td>PSD averaged of both eyes (dB)</td>
<td>Mean (SD)</td>
<td>2.56 (0.8)</td>
<td>7.7 (3.5)</td>
<td>5.6 (3.7)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>2.2 (2.0, 3.0)</td>
<td>7.8 (4.5, 11.2)</td>
<td>4.4 (2.4, 8.5)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>1.77 – 5.1</td>
<td>2.4 – 13.49</td>
<td>1.77 – 13.49</td>
</tr>
</tbody>
</table>

Table 4-1: The summary statistics, mean, standard deviation (SD) median, interquartile range (IQR) and range, for the demographic characteristics of the 40 individuals exposed to vigabatrin by visual field outcome (VAVFL indicates vigabatrin-associated visual field loss. MD indicates Mean Deviation, PSD indicates Pattern Standard Deviation).

The two parameters describing the severity of the visual field loss, the Mean Deviation and the Pattern Standard Deviation, each averaged across the two eyes, were each statistically significantly worse for the individuals with vigabatrin-associated visual field loss -7.8dB (SD 5.1) and 7.7dB (SD 3.5) compared to the individuals with normal fields, -2.0dB (SD 2.4) and 2.56dB (SD 0.8), (difference between means -5.70dB 95% CI -2.83 to -8.56; p<0.001; and 5.15 95% CI 3.31 to 7.00 (p<0.001), respectively.

The duration and cumulative dose of vigabatrin therapy were highly correlated ($r_s = 0.69; p<0.001$).
4.4.2 Demographics of the cohort with open angle glaucoma

The demographic characteristics of the cohort with open angle glaucoma and of the cohort of normal individuals are shown in Table 4-2.

The field loss of the individuals with open angle glaucoma was predominantly focal.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Open angle glaucoma</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10</td>
</tr>
<tr>
<td>Age at enrolment</td>
<td>Mean (SD)</td>
<td>68.9 (9.0)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>68.4 (62.3, 77.2)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>54.2-84.4</td>
</tr>
<tr>
<td>Designated Eye</td>
<td>Average of both eyes</td>
<td></td>
</tr>
<tr>
<td>Mean Deviation (dB)</td>
<td>Mean (SD)</td>
<td>-3.0 (4.5)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>-1.5 (-0.23, -4.5)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>-18.23 – -0.66</td>
</tr>
<tr>
<td>Pattern Standard Deviation (dB)</td>
<td>Mean (SD)</td>
<td>4.32 (3.0)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>2.82 (2.24, 6.67)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>1.64 – 13.3</td>
</tr>
</tbody>
</table>

Table 4-2: The summary statistics, mean, standard deviation (SD) median, interquartile range (IQR) and range, for the demographic characteristics of the 18 individuals with open angle glaucoma and of the 22 normal individuals (MD indicates Mean Deviation, and PSD indicates Pattern Standard Deviation). Note the MD and PSD are given for the designated eye of the individuals with open angle glaucoma.

4.4.3 Demographics of the cohort of normal individuals

The demographic characteristics of the cohort of normal individuals are shown in Table 4-2.

4.4.4 Retinal ganglion cell structural and functional association

The summary statistics for the estimated number of ganglion cell soma and axons for the individuals exposed to vigabatrin with normal fields are given in Table 4-3 for the right eye and in Table 4-4 for the left eye. The corresponding data for the individuals
with vigabatrin-associated visual field loss are given in Table 4-5 and Table 4-6; for the designated eye of the individuals with open angle glaucoma in Table 4-7 and the normal individuals in Table 4-8 and Table 4-9.

### 4.4.5 Global Evaluation

The associations between the number of remaining ganglion cell soma derived from perimetry and the number of remaining ganglion cell axons derived from the complete circular OCT scan for each eye of the individuals exposed to vigabatrin are represented as separate scatter plots in Figure 4-2.

The corresponding associations for each eye of the individuals with open angle glaucoma and for each eye of the normal individuals are shown together in Figure 4-3 and for the designated eye of the individuals with open angle glaucoma in Figure 4-4.

The association for those exposed to vigabatrin superimposed upon that for the designated eye of those with open angle glaucoma is shown in Figure 4-5.

The association for those exposed to vigabatrin superimposed upon that for the designated eye of those open angle glaucoma and upon that for the normal individuals is shown in Figure 4-6.
<table>
<thead>
<tr>
<th>Right Eye</th>
<th>Global</th>
<th>Quandrant</th>
<th>Sector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inferior</td>
<td>Superior</td>
</tr>
<tr>
<td>Mean</td>
<td>1,185,347</td>
<td>435,222</td>
<td>348,591</td>
</tr>
<tr>
<td>SD</td>
<td>259,500</td>
<td>95,953</td>
<td>75,393</td>
</tr>
<tr>
<td>Median</td>
<td>1,216,382</td>
<td>452,074</td>
<td>338,741</td>
</tr>
<tr>
<td>Q1</td>
<td>933,768</td>
<td>376,545</td>
<td>292,298</td>
</tr>
<tr>
<td>Q3</td>
<td>1,327,246</td>
<td>490,690</td>
<td>413,618</td>
</tr>
<tr>
<td>Minimum</td>
<td>786,446</td>
<td>242,744</td>
<td>240,370</td>
</tr>
<tr>
<td>Maximum</td>
<td>1,609,421</td>
<td>581,029</td>
<td>466,731</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Left Eye</th>
<th>Global</th>
<th>Quandrant</th>
<th>Sector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inferior</td>
<td>Superior</td>
</tr>
<tr>
<td>Mean</td>
<td>1,241,236</td>
<td>525,956</td>
<td>471,129</td>
</tr>
<tr>
<td>SD</td>
<td>292,047</td>
<td>143,388</td>
<td>108,841</td>
</tr>
<tr>
<td>Median</td>
<td>1,201,933</td>
<td>522,368</td>
<td>451,325</td>
</tr>
<tr>
<td>Q1</td>
<td>1,052,449</td>
<td>439,370</td>
<td>384,665</td>
</tr>
<tr>
<td>Q3</td>
<td>1,448,700</td>
<td>645,300</td>
<td>503,614</td>
</tr>
<tr>
<td>Minimum</td>
<td>754,597</td>
<td>314,042</td>
<td>324,231</td>
</tr>
<tr>
<td>Maximum</td>
<td>1,807,690</td>
<td>799,189</td>
<td>697,033</td>
</tr>
</tbody>
</table>

Table 4-3: The summary statistics, by quadrant, for the estimated number of retinal ganglion cell soma (top) and axons (bottom) in the right eye for the individuals exposed to vigabatrin with normal fields.

<table>
<thead>
<tr>
<th>Left Eye</th>
<th>Global</th>
<th>Quandrant</th>
<th>Sector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inferior</td>
<td>Superior</td>
</tr>
<tr>
<td>Mean</td>
<td>853,351</td>
<td>257,204</td>
<td>264,553</td>
</tr>
<tr>
<td>SD</td>
<td>194,144</td>
<td>64,138</td>
<td>68,831</td>
</tr>
<tr>
<td>Median</td>
<td>873,801</td>
<td>275,628</td>
<td>263,444</td>
</tr>
<tr>
<td>Q1</td>
<td>761,931</td>
<td>241,258</td>
<td>230,230</td>
</tr>
<tr>
<td>Q3</td>
<td>959,108</td>
<td>306,308</td>
<td>282,955</td>
</tr>
<tr>
<td>Minimum</td>
<td>463,541</td>
<td>109,039</td>
<td>140,414</td>
</tr>
<tr>
<td>Maximum</td>
<td>1,231,153</td>
<td>328,896</td>
<td>462,120</td>
</tr>
</tbody>
</table>

Table 4-4: The summary statistics, by quadrant and by Sectors 6 and 11, for the estimated number of retinal ganglion cell soma (top) and axons (bottom) in the left eye for the individuals exposed to vigabatrin with normal fields.
<table>
<thead>
<tr>
<th>Right Eye</th>
<th>Global</th>
<th>Quadrant</th>
<th>Sector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inferior</td>
<td>Superior</td>
</tr>
<tr>
<td>Mean</td>
<td>983,085</td>
<td>331,694</td>
<td>279,383</td>
</tr>
<tr>
<td>SD</td>
<td>318,821</td>
<td>108,855</td>
<td>85,560</td>
</tr>
<tr>
<td>Median</td>
<td>931,774</td>
<td>304,882</td>
<td>267,717</td>
</tr>
<tr>
<td>Q1</td>
<td>799,195</td>
<td>256,384</td>
<td>228,821</td>
</tr>
<tr>
<td>Q3</td>
<td>1,182,282</td>
<td>434,945</td>
<td>334,730</td>
</tr>
<tr>
<td>Minimum</td>
<td>437,420</td>
<td>156,650</td>
<td>112,860</td>
</tr>
<tr>
<td>Maximum</td>
<td>1,607,984</td>
<td>518,089</td>
<td>452,971</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Left Eye</th>
<th>Global</th>
<th>Quadrant</th>
<th>Sector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inferior</td>
<td>Superior</td>
</tr>
<tr>
<td>Mean</td>
<td>918,761</td>
<td>379,702</td>
<td>340,889</td>
</tr>
<tr>
<td>SD</td>
<td>321,504</td>
<td>154,963</td>
<td>130,496</td>
</tr>
<tr>
<td>Median</td>
<td>967,825</td>
<td>421,418</td>
<td>329,642</td>
</tr>
<tr>
<td>Q1</td>
<td>702,269</td>
<td>274,441</td>
<td>273,090</td>
</tr>
<tr>
<td>Q3</td>
<td>1,114,201</td>
<td>474,377</td>
<td>422,894</td>
</tr>
<tr>
<td>Minimum</td>
<td>280,974</td>
<td>89,495</td>
<td>71,787</td>
</tr>
<tr>
<td>Maximum</td>
<td>1,583,883</td>
<td>651,783</td>
<td>625,578</td>
</tr>
</tbody>
</table>

Table 4-5: The summary statistics, by quadrant and by Sectors 6 and 11, for the estimated number of retinal ganglion cell soma (top) and axons (bottom) in the right eye for the individuals with vigabatrin-associated visual field loss.

<table>
<thead>
<tr>
<th>Left Eye</th>
<th>Global</th>
<th>Quadrant</th>
<th>Sector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inferior</td>
<td>Superior</td>
</tr>
<tr>
<td>Mean</td>
<td>518,443</td>
<td>148,817</td>
<td>136,573</td>
</tr>
<tr>
<td>SD</td>
<td>191,365</td>
<td>76,390</td>
<td>61,604</td>
</tr>
<tr>
<td>Median</td>
<td>486,948</td>
<td>139,786</td>
<td>123,701</td>
</tr>
<tr>
<td>Q1</td>
<td>388,325</td>
<td>89,524</td>
<td>93,242</td>
</tr>
<tr>
<td>Q3</td>
<td>642,669</td>
<td>198,193</td>
<td>187,668</td>
</tr>
<tr>
<td>Minimum</td>
<td>125,317</td>
<td>33,731</td>
<td>26,674</td>
</tr>
<tr>
<td>Maximum</td>
<td>900,333</td>
<td>311,928</td>
<td>236,787</td>
</tr>
</tbody>
</table>

Table 4-6: The summary statistics, by quadrant and by Sectors 6 and 11, for the estimated number of retinal ganglion cell soma (top) and axons (bottom) in the left eye for the individuals with vigabatrin-associated visual field loss.
<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th>Quadrant</th>
<th>Sector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Superior</td>
<td>Nasal</td>
</tr>
<tr>
<td>Mean</td>
<td>903,005</td>
<td>349,427</td>
<td>294,164</td>
</tr>
<tr>
<td>SD</td>
<td>319,977</td>
<td>140,403</td>
<td>100,782</td>
</tr>
<tr>
<td>Median</td>
<td>904,361</td>
<td>362,312</td>
<td>307,361</td>
</tr>
<tr>
<td>Q1</td>
<td>735,405</td>
<td>272,087</td>
<td>224,753</td>
</tr>
<tr>
<td>Q3</td>
<td>1,190,853</td>
<td>476,674</td>
<td>377,965</td>
</tr>
<tr>
<td>Minimum</td>
<td>270,534</td>
<td>50,785</td>
<td>85,506</td>
</tr>
<tr>
<td>Maximum</td>
<td>1,417,993</td>
<td>564,935</td>
<td>443,844</td>
</tr>
</tbody>
</table>

Table 4-7: The summary statistics, by quadrant and by Sectors 6 and 11, for the estimated number of retinal ganglion cell soma (top) and axons (bottom) in the designated eye for the individuals with visual field loss due to open angle glaucoma.
### Right Eye

<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th>Quadrant</th>
<th>Sector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inferior</td>
<td>Superior</td>
</tr>
<tr>
<td>Mean</td>
<td>1,200,214</td>
<td>431,557</td>
<td>364,385</td>
</tr>
<tr>
<td>SD</td>
<td>242,343</td>
<td>95,716</td>
<td>65,256</td>
</tr>
<tr>
<td>Median</td>
<td>1,211,778</td>
<td>428,297</td>
<td>370,036</td>
</tr>
<tr>
<td>Q1</td>
<td>1,057,920</td>
<td>383,080</td>
<td>331,873</td>
</tr>
<tr>
<td>Q3</td>
<td>1,380,619</td>
<td>500,823</td>
<td>407,954</td>
</tr>
<tr>
<td>Minimum</td>
<td>626,949</td>
<td>226,512</td>
<td>212,160</td>
</tr>
<tr>
<td>Maximum</td>
<td>1,616,910</td>
<td>623,124</td>
<td>476,069</td>
</tr>
</tbody>
</table>

### Left Eye

<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th>Quadrant</th>
<th>Sector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inferior</td>
<td>Superior</td>
</tr>
<tr>
<td>Mean</td>
<td>1,115,065</td>
<td>427,240</td>
<td>362,908</td>
</tr>
<tr>
<td>SD</td>
<td>201,723</td>
<td>78,223</td>
<td>81,679</td>
</tr>
<tr>
<td>Median</td>
<td>1,160,026</td>
<td>444,259</td>
<td>360,149</td>
</tr>
<tr>
<td>Q1</td>
<td>1,039,610</td>
<td>373,225</td>
<td>317,534</td>
</tr>
<tr>
<td>Q3</td>
<td>1,281,988</td>
<td>479,948</td>
<td>394,558</td>
</tr>
<tr>
<td>Minimum</td>
<td>406,095</td>
<td>292,951</td>
<td>246,393</td>
</tr>
<tr>
<td>Maximum</td>
<td>1,491,837</td>
<td>559,568</td>
<td>508,884</td>
</tr>
</tbody>
</table>

#### Table 4-8: The summary statistics, by quadrant and by Sectors 6 and 11, for the estimated number of retinal ganglion cell soma (top) and axons (bottom) in the right eye for the normal individuals.

### Left Eye

<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th>Quadrant</th>
<th>Sector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inferior</td>
<td>Superior</td>
</tr>
<tr>
<td>Mean</td>
<td>965,857</td>
<td>295,886</td>
<td>291,508</td>
</tr>
<tr>
<td>SD</td>
<td>186,248</td>
<td>63,681</td>
<td>94,656</td>
</tr>
<tr>
<td>Median</td>
<td>915,176</td>
<td>282,517</td>
<td>288,573</td>
</tr>
<tr>
<td>Q1</td>
<td>829,139</td>
<td>257,995</td>
<td>250,096</td>
</tr>
<tr>
<td>Q3</td>
<td>1,070,439</td>
<td>349,272</td>
<td>339,358</td>
</tr>
<tr>
<td>Minimum</td>
<td>702,248</td>
<td>193,297</td>
<td>32,435</td>
</tr>
<tr>
<td>Maximum</td>
<td>1,350,330</td>
<td>439,406</td>
<td>477,670</td>
</tr>
</tbody>
</table>

#### Table 4-9: The summary statistics, by quadrant and by Sectors 6 and 11, for the estimated number of retinal ganglion cell soma (top) and axons (bottom) in the left eye for the normal individuals.
Figure 4-2: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) for the right (left column) and left (right column) eyes of the individuals exposed to vigabatrin. Filled circles represent individuals with vigabatrin-associated visual field loss and open squares represent individuals exposed to vigabatrin but with normal visual fields. The line of unity is given for comparison.
Figure 4-3: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) for the right (left column) and left (right column) eyes of the individuals with open angle glaucoma. Filled circles represent individuals with bilateral glaucomatous visual field loss; filled triangles, individuals with glaucomatous field loss in the represented eye; open triangles, individuals with glaucomatous field loss in the fellow eye; and open circles normal individuals. The line of unity is given for comparison.
Figure 4-4: Scatter plot illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) for the designated eye of the individuals with open angle glaucoma. The line of unity is given for comparison.
Figure 4-5: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) for the right (left column) and left (right column) eyes of the individuals exposed to vigabatrin and for the designated eye of the individuals with open angle glaucoma. Filled circles represent individuals with vigabatrin-associated visual field loss; open squares represent individuals exposed to vigabatrin but with normal visual fields; and filled triangles represent individuals with open angle glaucoma in the designated eye. The line of unity is given for comparison.
Figure 4-6: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) for the right (left column) and left (right column) eyes of the individuals exposed to vigabatrin and for the designated eye of the individuals with open angle glaucoma. Filled circles represent individuals with vigabatrin-associated visual field loss; open squares represent individuals exposed to vigabatrin but with normal visual fields; filled triangles represent individuals with open angle glaucoma and open circles represent normal individuals. The line of unity is given for comparison.
4.4.5.1 Quadrant Evaluation

The summary characteristics, by quadrant and by sector, for the number of remaining ganglion cell axons and the corresponding remaining number of retinal ganglion cell soma for each eye of the individuals exposed to vigabatrin but with normal fields and for the individuals with vigabatrin-associated visual fields loss are given in Table 4-3 to Table 4-4, respectively.

The associations for each eye of the individuals exposed to vigabatrin for the superior and inferior quadrants are given in Figure 4-7 and for the nasal and temporal quadrants in Figure 4-8.

Similarly, the association for each eye of the individuals with open angle glaucoma and for each eye of the normal individuals, for the superior and inferior quadrants and for the nasal and temporal are given in Figure 4-9 and Figure 4-10, respectively. The association for the designated eye of the individuals with open angle glaucoma for the superior and inferior quadrants and for the nasal and temporal quadrants are given in Figure 4-11 and Figure 4-12, respectively.

The associations, for each eye, of the individuals exposed to vigabatrin, combined with the designated eye of the individuals with open angle glaucoma and the normal individuals are given for the superior and inferior quadrants and for the nasal and temporal quadrants in Figure 4-13 and Figure 4-14, respectively.
Figure 4-7: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by Time-domain optical coherence tomography (OCT) (axons) for the superior (top) and inferior (bottom) quadrants for the right (left column) and left (right column) eyes of the individuals exposed to vigabatrin. Filled circles indicate individuals with vigabatrin-associated visual field loss and open squares indicate individuals exposed to vigabatrin but with normal visual fields. The line of unity is given for comparison. Note the scaling of the axes is different to that in Figure 4-2.
Figure 4-8: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by Time-domain optical coherence tomography (OCT) (axons) for the nasal (top) and temporal (bottom) quadrants for the right (left column) and left (right column) eyes of the individuals exposed to vigabatrin. Filled circles indicate individuals with vigabatrin-associated visual field loss and open squares indicate individuals exposed to vigabatrin but with normal visual fields. The line of unity is given for comparison. Note the scaling of the axes is different to that in Figure 4-2 to Figure 4-6.
Figure 4-9: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by Time-domain optical coherence tomography (OCT) (axons) for the superior (top) and inferior (bottom) quadrants for the right (left column) and left (right column) eyes of the individuals with open angle glaucoma and of the normal individuals. Filled circles represent individuals with bi-lateral glaucomatous visual field loss; filled triangles, individuals with glaucomatous field loss in the given eye; open triangles, individuals with glaucomatous field loss in the fellow eye; and open circles, normal individuals. The line of unity is given for comparison.
Figure 4-10: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by Time-domain optical coherence tomography (OCT) (axons) for the nasal (top) and temporal (bottom) quadrants for the right (left column) and left (right column) eyes of the individuals with open angle glaucoma and of the normal individuals. Filled circles represent individuals with bi-lateral glaucomatous visual field loss; filled triangles, individuals with glaucomatous field loss in the given eye; open triangles, individuals with glaucomatous field loss in the fellow eye; and open circles, normal individuals. The line of unity is given for comparison.
Figure 4-11: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by Time-domain optical coherence tomography (OCT) (axons) for the superior (top) and inferior (bottom) quadrants of the designated eye of the individuals with open angle glaucoma. The line of unity is given for comparison. Note the scaling of the axes is different to that in Figure 4-2 to Figure 4-6.
Figure 4-12: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by Time-domain optical coherence tomography (OCT) (axons) for the nasal (top) and temporal (bottom) quadrants of the designated eye of the individuals with open angle glaucoma. The line of unity is given for comparison. Note the scaling of the axes is different to that in Figure 4-2 to Figure 4-6.
Figure 4-13: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by Time-domain optical coherence tomography (OCT) (axons) for the superior (top) and inferior (bottom) quadrants of the right (left column) and left (right column) eyes of the individuals exposed to vigabatrin and of the designated eye of the individuals with open angle glaucoma. Filled circles represent individuals with vigabatrin-associated visual field loss; open squares represent individuals exposed to vigabatrin but with normal visual fields; filled triangles represent individuals with open angle glaucoma, and open circles represent normal individuals. The line of unity is given for comparison. Note the scaling of the axes is different to that in Figure 4-2 to Figure 4-6.
Figure 4-14: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by Time-domain optical coherence tomography (OCT) (axons) for the nasal (top) and temporal (bottom) quadrants of the right (left column) and left (right column) eyes of the individuals exposed to vigabatrin and of the designated eye of the individuals with open angle glaucoma. Filled circles represent individuals with vigabatrin-associated visual field loss; open squares represent individuals exposed to vigabatrin but with normal visual fields; filled triangles represent individuals with open angle glaucoma; and open circles normal individuals. The line of unity is given for comparison. Note the scaling of the axes is different to that in Figure 4-2 to Figure 4-6.
4.4.5.2 Sector Evaluation

The associations for each eye of the individuals exposed to vigabatrin by each of the 8 sectors are given in Figure 4-15 to Figure 4-18, inclusive and for each eye of the individuals with open angle glaucoma of the normal individuals in Figures 4-19 to Figures 4-22. The combined data set for Sectors 6 and 11 are given in Figure 4-23 and Figure 4-24.
Figure 4-15: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) for Sectors 7 (top) and 10 (bottom) of the right (left column) and left (right column) eyes of the individuals exposed to vigabatrin. Filled circles represent individuals with vigabatrin-associated visual field loss and open squares represent individuals exposed to vigabatrin but with normal visual fields. The line of unity is given for comparison.
Figure 4-16: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) for Sectors 6 (top) and 11 (bottom) of the right (left column) and left (right column) eyes of the individuals exposed to vigabatrin. Filled circles represent individuals with vigabatrin-associated visual field loss and open squares represent individuals exposed to vigabatrin but with normal visual fields. The line of unity is given for comparison.
Figure 4-17: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) for Sectors 4 and 5 (top) and Sectors 12 and 13 (bottom) of the right (left column) and left (right column) eyes of the individuals exposed to vigabatrin. Filled circles represent individuals with vigabatrin-associated visual field loss and open squares represent individuals exposed to vigabatrin but with normal visual fields. The line of unity is given for comparison.
Figure 4-18: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) for Sectors 1 and 14 of the right (left column) and left (right column) eyes of the individuals exposed to vigabatrin. Filled circles represent individuals with vigabatrin-associated visual field loss and open squares represent individuals exposed to vigabatrin but with normal visual fields. The line of unity is given for comparison. Filled circles represent individuals with vigabatrin-associated visual field loss; open squares represent individuals exposed to vigabatrin but with normal visual fields; filled triangles represent individuals with open angle glaucoma; and open circles normal individuals.
Figure 4-19: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) for Sectors 7 and 10 of the right (left column) and left (right column) eyes of the individuals with open angle glaucoma and of the normal individuals. Filled circles represent individuals with bi-lateral glaucomatous visual field loss; filled triangles, individuals with glaucomatous field loss in the given eye; open triangles, individuals with glaucomatous field loss in the fellow eye; and open circles represent normal individuals. The line of unity is given for comparison.
Figure 4-20: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) for Sectors 6 and 11 of the right (left column) and left (right column) eyes of the individuals with open angle glaucoma and of the normal individuals. Filled circles represent individuals with bi-lateral glaucomatous visual field loss; filled triangles, individuals with glaucomatous field loss in the given eye; open triangles, individuals with glaucomatous field loss in the fellow eye; and open circles represent normal individuals. The line of unity is given for comparison.
Figure 4-21: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) (top) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) (bottom) for Sectors 4 and 5 and 12 and 13 of the right (left column) and left (right column) eyes of the individuals with open angle glaucoma and of the normal individuals. Filled circles represent individuals with bilateral glaucomatous visual field loss; filled triangles, individuals with glaucomatous field loss in the given eye; open triangles, individuals with glaucomatous field loss in the fellow eye; and open circles represent normal individuals. The line of unity is given for comparison.
Figure 4-22: Scatter plots illustrating the association between the estimated number of remaining retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) (top) and that derived by the circular scan of Time-domain optical coherence tomography (OCT) (axons) (bottom) for Sectors 1 and 14 of the right (left column) and left (right column) eyes of the individuals with open angle glaucoma and of the normal individuals. Filled circles represent individuals with bi-lateral glaucomatous visual field loss; filled triangles, individuals with glaucomatous field loss in the given eye; open triangles, individuals with glaucomatous field loss in the fellow eye; and open circles represent normal individuals. The line of unity is given for comparison.
Figure 4-23: Scatter plots illustrating the association between the estimated number of retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by Time-domain optical coherence tomography (OCT) (axons) for Sectors 6 and 11 of the right (left side) and left (right side) eyes. Filled circles indicate individuals with vigabatrin-associated visual field loss, open squares indicate individuals exposed to vigabatrin but with normal visual fields and filled triangle indicate open angle glaucoma individuals, and open circles represent normal individuals. The line of unity is given for comparison. Note the scale is different from Figure 4-1.
Figure 4-24: Scatter plots illustrating the association between the estimated number of retinal ganglion cells derived from standard automated perimetry (SAP) (cell soma) and that derived by Time-domain optical coherence tomography (OCT) (axons) for Sectors 6 and 11 of the right (left side) and left (right side) eyes. Filled circles indicate individuals with vigabatrin-associated visual field loss, open squares represent individuals exposed to vigabatrin but with normal visual fields and Filled triangle represent open angle glaucoma individuals. The line of unity is given for comparison. Note the scale is different from Figure 4-1.
The estimated number of remaining retinal ganglion cells derived by standard automated perimetry (cell soma) and by the complete circular scan of Time-domain optical coherence tomography (axons) against the duration of vigabatrin are given in Figure 4-25. The corresponding associations for the superior and inferior quadrants are given in Figure 4-26 and Figure 4-27 respectively, and for Sectors 11 and 6 are given in Figure 4-28 and Figure 4-29, respectively.
Figure 4-25: The estimated number of remaining retinal ganglion cells derived by standard automated perimetry (cell soma) (top) and by the circular scan of Time-domain optical coherence tomography (axons) (bottom) against the duration of exposure to vigabatrin for the right eye (left column) and the left eye (right column) eyes of the individuals exposed to vigabatrin against. Filled circles represent individuals with vigabatrin-associated visual field loss and open squares represent individuals exposed to vigabatrin but with normal visual fields. VGB represents vigabatrin.
Figure 4-26: The estimated number of remaining retinal ganglion cells derived by standard automated perimetry (cell soma) (top) and from the superior quadrant of the circular scan of Time-domain optical coherence tomography (axons) (bottom) against the duration of exposure to vigabatrin for the right eye (left column) and the left eye (right column) eyes of the individuals exposed to vigabatrin against. Filled circles represent individuals with vigabatrin-associated visual field loss and open squares represent individuals exposed to vigabatrin but with normal visual fields. VGB represents vigabatrin.
Figure 4-27: The estimated number of remaining retinal ganglion cells derived by standard automated perimetry (cell soma) (top) and from the inferior quadrant of the circular scan of Time-domain optical coherence tomography (axons) (bottom) against the duration of exposure to vigabatrin for the right eye (left column) and the left eye (right column) eyes of the individuals exposed to vigabatrin against. Filled circles represent individuals with vigabatrin-associated visual field loss and open squares represent individuals exposed to vigabatrin but with normal visual fields. VGB represents vigabatrin.
Figure 4-28: The estimated number of remaining retinal ganglion cells derived by standard automated perimetry (cell soma) (top) and from Sector Six of the circular scan of Time-domain optical coherence tomography (axons) (bottom) against the duration of exposure to vigabatrin for the right eye (left column) and the left eye (right column) eyes of the individuals exposed to vigabatrin against. Filled circles represent individuals with vigabatrin-associated visual field loss and open squares represent individuals exposed to vigabatrin but with normal visual fields. VGB represents vigabatrin.
Figure 4-29: The estimated number of remaining retinal ganglion cells derived by standard automated perimetry (cell soma) (top) and from Sector Eleven of the circular scan of Time-domain optical coherence tomography (axons) (bottom) against the duration of exposure to vigabatrin for the right eye (left column) and the left eye (right column) eyes of the individuals exposed to vigabatrin against. Filled circles represent individuals with vigabatrin-associated visual field loss and open squares represent individuals exposed to vigabatrin but with normal visual fields. VGB represents vigabatrin.
4.5 Discussion

The results demonstrate a strong linear association between the number of residual retinal ganglion cell soma derived from standard automated perimetry and the number of residual retinal ganglion cell axons derived by Time-domain optical coherence tomography. This strong association is compatible with that found in other optic neuropathies including open angle glaucoma (Hood et al., 2007; Hood and Kardon, 2007; Medeiros et al., 2012a; Medeiros et al., 2012b) and ischaemic optic neuropathy (Hood et al., 2008) and would suggest that vigabatrin toxicity causes an optic neuropathy. However, it not known whether the vigabatrin-associated optic neuropathy is of a primary or of a secondary origin.

The degree of association is remarkable given that the data was obtained from individuals with severe epilepsy, many of whom had related cognitive difficulties. It is also remarkable given the considerable between-subject variation in the topography of the retinal nerve fibre layer at the entry to the optic nerve head (Strouthidis et al., 2006; Ferreras et al., 2008).

The associations for the global, inferior and, superior quadrants are linear in each eye both for those with vigabatrin-associated visual field loss and for those exposed to vigabatrin but a with normal field; however, the trends lie above the line of unity. In general, the data points for those exposed to vigabatrin but with normal fields, and those of the normal individuals, lie closer to the line of unity than those for the individuals with vigabatrin-associated visual field loss and for the individuals with open angle glaucoma (Figure 4-6).
A linear association is also present both for the nasal and the temporal quadrants. The trend for the nasal quadrant lies considerably below the line of unity. This trend can be explained by an under sampling of the perimetric stimulus locations within this region. The under-sampling of the stimulus locations in the nasal quadrant results in an overlap of apparent residual ganglion cell soma between those with and without vigabatrin-associated visual field loss. This overlap is attributable to the fact that the nasal quadrant of the optic nerve head represents the temporal visual field which is the least affected in vigabatrin-associated visual field loss. The trend for the temporal quadrant lies considerably above the line of unity. This trend can be explained by an under sampling of the perimetric stimulus locations within the region but also by the fact that the temporal quadrant contains the papillomacular bundle, the visual field of which is seemingly only affected in severe cases of vigabatrin toxicity. The nasal and temporal quadrants contain 5 and 3 stimulus locations, respectively, compared to the 23 and 21 stimulus locations, for the superior and inferior quadrants respectively.

Similarly, the associations for each of the optic nerve head sectors are linear but the numbers of calculated residual ganglion cell soma are markedly influenced by the number of available perimetric stimulus locations and this disparity interacts with the topographical characteristics of the toxicity. Clearly, one approach, in any future study, would be to increase the number of stimulus locations within the nasal and temporal quadrants and within each of the under-sampled sectors. However, such an approach would not overcome the lack of stimulus locations beyond the grid utilised by Program 24-2, i.e., that for the peripheral field. Indeed, the formulae for calculating residual retinal ganglion cell soma, developed by Harwerth and colleagues (Harwerth et al 2010; Medeiros et al., 2012a; Medeiros et al., 2012b; Tatham et al., 2013) should be extended to include more peripheral stimulus locations. However, the accuracy of the calculation
of the more peripheral ganglion cell soma would be influenced by the increased within- and between-subject variability associated with the estimation of threshold which increases with increase in eccentricity and which is well established in clinical perimetry (Heijl et al., 1987a). Interestingly, a novel stimulus configuration has been proposed by Garway-Heath and colleagues (Asaoka et al., 2012) which utilised four stimulus locations for each of the 12 sectors of the optic nerve head and which contained proportionately more stimulus locations in the nasal sectors and in the papillomacular region compared to the grid of Program 24-2. Such stimulus locations exhibited higher structure-function correlations than those derived with Program 24-2. However, the utility of this novel stimulus grid will be limited until an accompanying date base of age-corrected normal values of sensitivity can be offered by the manufacture together with the accompanying statistical analysis package.

The greater number of residual ganglion cell soma, compared to the number of residual ganglion cell axons, in the individuals exposed to vigabatrin, in those regions with an adequate sampling of stimulus locations, may also arise from a lack of consideration of normal age-related changes. The number of residual ganglion cell soma is calculated from the measured differential sensitivity without any correction for age (Harwerth et al., 2010). It is well accepted that sensitivity declines with increase in age (Jaffe, Alvarado and Juster, 1986; Heijl et al., 1987a). Consequently, the number of residual ganglion cell soma will decrease with increase in age. The younger age of the individuals exposed to vigabatrin compared to that of those with open-angle glaucoma, in whom the formulae were developed, may account for some of the discrepancy between the retinal ganglion cell soma and axon counts. In contrast, the formula for the calculation of ganglion cell axons does compensate for the effect of age (Harwerth et al., 2010). The traditional perimetric approach for overcoming the effect of age is to
compare the measured sensitivity at any given location with that of corresponding age-corrected normal value of sensitivity. Such a comparison is displayed, with the Humphrey Field Analyzer, in terms of the Total Deviation map. Notwithstanding such an approach, it is still not possible to differentiate between a normal reduction in sensitivity due to a loss of clarity of the ocular media from that due to normal ‘neural’ changes. Several studies have attempted to correlate the reduction in the differential light sensitivity with the increased absorption and/or increased forward intra-ocular light scatter arising from a loss of clarity of the ocular media (Wood, Wild and Crews, 1987; Dengler-Harles et al., 1990; Moss, Wild and Whitaker, 1995) but with varying success. Furthermore, the use of the Total Deviation map compares the measured sensitivity with the ‘average’ normal sensitivity: the ‘average’ value declines with increase in age but may not be linear as currently computed (Bengtsson et al., 1997; Artes et al., 2005).

Quantification of the trend line in terms of the slope and intercept using univariate regression was not undertaken since neither the residual ganglion cell soma nor the residual ganglion cell axons could be considered to be the dependent variable and each exhibit measurement errors of different magnitude. Univariate regression analysis using the least squares techniques can only be undertaken with a pre-defined dependent variable which does not exhibit a measurement error. Previous studies have considered structure to be the independent variable and function to be the dependent variable (Harwerth et al., 2007; Racette et al., 2007) and the validity of this approach has been debated (Marin-Franch et al., 2013; Redmond et al., 2013b). Alternative techniques such as Passing-Bablock regression (Passing and Bablock 1983) which has been used in other studies of the structure-function relationship (Redmond et al., 2013a) have also been debated (Marin-Franch et al., 2013; Redmond et al., 2013b). Indeed, the gradient
of a linear fit can change by factor of 10 for the same structure-function data depending
upon the type of regression applied (Marin-Franch et al., 2013).

Assuming a one-to-one relationship between a ganglion cell soma and a ganglion cell
axon, alternative techniques such as that proposed by Bland and Altmann (1995),
whereby the difference in the magnitude between the two variables are plotted against
the mean of the two magnitudes, could have been used; however, the potential linearity
of the association is more easily recognisable by the comparison with a series of linear
trend lines. In the current study, a linear trend line of unity constrained to pass through
the origin, was adopted for the comparison.

Evaluation of the number of retinal ganglion cells is receiving considerable attention in
open angle glaucoma. For example, the relationship between the estimated retinal
ganglion cell count and the cup-to-disc ratio suggests that assessment of change in the
ratio is an insensitive method for evaluating progressive damage in glaucoma as a small
change in the ratio can be associated with a large loss of ganglion cells particularly in
large cup-to-disc ratios (Tatham et al., 2013b). The combination of retinal ganglion cell
counts from both structural and functional assessments also identifies progressive
glaucomatous loss earlier than conventional measures of either structure, alone, or
function, alone (Meira-Freitas et al., 2014). It can be anticipated, therefore, that a
combined estimate of the retinal ganglion cells will provide a more sensitive tool in the
evaluation of individuals receiving vigabatrin.

Given the clear implication of the retinal ganglion cells in vigabatrin toxicity, it is
perhaps surprising that the pattern electroretinogram (PERG) does not identify the
dysfunction. However, the PERG (in contrast to the flash ERG) is a local response and
reflects the integrity of the optics, photoreceptors, bipolar cells and retinal ganglion cells (Bach et al., 2013). The standard stimulus field for clinical pattern electroretinography, recommended by the International Society for Clinical Electrophysiology for Vision is 15° (±3°) which lies within the region of the visual field which is normal even in those with severe vigabatrin-associated visual field loss. A larger stimulus field, such as 30°, is also recommended but this, at best, would only identify those with severe vigabatrin-associated visual field loss.

It also can be seen from Figure 4-1 to Figure 4-6 that a combined structure and function measure is able to differentiate individuals with vigabatrin-associated visual field loss from those exposed to vigabatrin with a normal visual field. Similarly, as would be expected from other studies (Medeiros et al., 2012a; Medeiros et al., 2012b) the combination is also able to distinguish individuals with open angle glaucoma from normal individuals. The presence of outliers within each grouping, and, therefore, the magnitude of the sensitivity and specificity, are not merely due to the presence of variability associated with given measurement but is also dependent upon the correct clinician-based diagnosis. As mentioned above, the estimation of ganglion cells from perimetry is based upon the absolute measure of sensitivity, i.e., the height of the visual field, which, itself, is influenced by optical as well as neural factors e.g., forward intraocular light scatter arising from cataract.

In addition, it should never be forgotten that the visual field examination is a subjective test. Close inspection of the data sets suggest that, in general, individuals exposed to vigabatrin performed ‘better’ in the second eye examined, most likely due to a refreshment of the perimetric experience, and that individuals with open angle glaucoma and normal individuals performed ‘worse’ in the second eye examined most likely due
to the perimetric fatigue effect. Indeed, normal individuals do not always produce perimetrically normal results.

As might be expected from the findings of the previous chapter, Chapter Three, the individuals with vigabatrin associated visual field loss had longer exposures and higher cumulative doses than those with a normal field (mean cumulative dose 8.9kg [SD 4.3] compared to 3.9kg [4.5]; and 10.3 years [3.5] compared to 7.3 years [5.8]). A weak negative association was present between the residual ganglion cell axons derived by optical coherence tomography and the duration of exposure to vigabatrin Figure 4-25 to Figure 4-29 both for those with vigabatrin-associated visual field loss and, surprisingly, for those exposed to vigabatrin but with normal fields. No association was present between ganglion cell soma derived from standard automated perimetry and duration of exposure to vigabatrin.

As stated previously, the strong topographical association, in general, between the residual ganglion cells counts derived from standard automated perimetry and from optical coherence tomography suggests that a combined outcome measure would be of use in the management of individuals exposed to vigabatrin. One approach is to overlay the Pattern Deviation probability map of the visual field with that of the probability map from optical coherence tomography arranged according to the axonal configuration of the optic nerve head such as that described by Wirtschafter et al (1982) and used throughout the study. The combined probability maps are illustrated in the Appendix at the end of this Chapter. The maps for the visual field were based upon the Pattern Deviation analysis, i.e. that reflecting localised abnormality, whilst those for optical coherence where based upon overall loss. It can be envisaged that at some point in the
future, resolution permitting, the retinal nerve fibre probability analysis will be divided into overall loss and localised loss commensurate with that for periemetry.

Optical coherence tomography was undertaken using the Time-domain StratusOCT. The time for image capture for the StratusOCT is slower than that of its successor, the Spectral-domain Cirrus OCT, manufactured by the same company. The Cirrus OCT, acquires data approximately 70 times faster and with better resolution (5μm compared to 8–10μm axial resolution) (Jeoung et al., 2010). The faster acquisition, together with automated compensation for misalignment, of Spectral-domain optical coherence tomography should reduce the variability associated with the acquisition of the given scan. Despite careful selection of each scan, 11 of the 24 individuals with vigabatrin-associated visual field loss, and 8 of the 17 individuals exposed to vigabatrin but with normal fields, exhibited disparities in the probability level between the two vertical hemifields due to scan misalignment.

In summary, vigabatrin toxicity is associated with retinal ganglion cell axonal and/ or soma loss; however, it is not known whether the optic neuropathy occurs as a result of the direct or the indirect action of the toxicity. The use of a combined structural and functional assessment based upon estimations of residual retinal ganglion cells calculated from optical coherence tomography and from standard automated perimetry may provide a more sensitive tool for detecting and monitoring vigabatrin toxicity.
Chapter 5. The outcome of the visual field following long-term withdrawal of vigabatrin

5.1 Introduction

It was shown in Chapter One that the visual field seemingly remains stable, in those individuals with vigabatrin-associated visual field loss, and also in those with normal visual fields, who have withdrawn from vigabatrin for periods of up to 9 months (Johnson et al., 2000), 18 months (Newman et al., 2002), 24 months (Hardus et al 2000a;b), 38 months (Nousiainen et al 2001), 4 years (Hardus et al 2003 and between 4 and 6 years (Kjellström et al 2008). However, the outcome of the visual field examination following longer-term withdrawal from vigabatrin has not received any attention and, therefore, it is not known as to whether the vigabatrin-associated visual field loss remains stable or exhibits a capacity either for further deterioration or, less likely, for improvement.

Similarly, it was also shown in Chapter One that the visual field of those with vigabatrin-associated visual field loss who continue on treatment with vigabatrin remains stable over follow-up periods of 11 months (Lawden et al 1999), 12 months (Paul et al 2001), 18 months (Graiewski-Wijnands and van der Torron 2002), 24 months (Schmidt et al 2002), between 4 and 38 months (Nousiainen et al 2001), between 18 and 43 months (Best and Acheson 2005), between 18 and 66 months (Kinirons et al 2006) and between 4 and 72 months (Johnson et al., 2000; Newman et al., 2002; Kjellström et al., 2008). However, the longer-term status of vigabatrin-associated visual field loss in
those individuals continuing on vigabatrin and also of those with normal visual fields who remain on vigabatrin has received little attention. The one report evaluating the outcome of long-term vigabatrin therapy was published during the compilation of this thesis (Clayton et al., 2013). Fourteen individuals treated with vigabatrin (including the individual described in the case report by (Clayton et al., 2010) initially underwent kinetic perimetry after a mean duration of 65 months (mean cumulative dose 4.7kg) and were subsequently followed for a mean period of 128 months whilst remaining on the drug (final cumulative dose 11.6kg). Thirteen of the 14 individuals exhibited a reduction in the extent of the I4e isopter which, itself, was correlated with increasing cumulative dose.

In the data set described in Chapter Three, all individuals had withdrawn from vigabatrin either following, or immediately after, the initial visual field examination. Such an outcome provided an opportunity, by means of introducing a further visual field examination, to determine the status of the visual field following long-term withdrawal from vigabatrin.

5.2 Aim

The aim of the study was to determine, by the addition of a long-term follow-up visual field examination in individuals withdrawn from vigabatrin, the capacity for deterioration or for improvement in those with vigabatrin-associated visual field loss or for a deterioration in those with previously normal fields. The outcome was to be evaluated in relation to two aspects: the interval between the baseline and follow-up visual field examinations and the severity of the baseline visual field loss. If either a
worsening or an improvement in the fields was found, the extent of the alteration would be investigated with respect to the time since withdrawal from vigabatrin and to the duration and cumulative dose of vigabatrin.

5.3 Methods

5.3.1 Cohort

The study was a prospective cohort study. The case series comprised 42 individuals with epilepsy who had attended the Alan Richens Unit, Welsh Epilepsy Centre at the University Hospital of Wales, Cardiff, who had a history of treatment with vigabatrin and who had previously undergone visual field examination using the standard protocol described in Chapter Three. All individuals had volunteered to undertake the follow-up visual field examination.

5.3.2 Visual field examination

Each individual was re-examined with Program 30-2 and the FASTPAC strategy of the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA) in an identical manner to that described in Chapter 4. Each individual wore the distance refraction corrected, where necessary, for the viewing distance of the perimeter bowl. The field of the right eye was always examined before that of the left eye. A rest period of between approximately 30 seconds and two minutes was given approximately every three minutes for any given individual. A further rest period of between 10 to 30 minutes depending upon the individual was given between the examinations of each eye.
Fixation was monitored using the gaze tracker and the Heijl-Krakau blind spot technique. Reliability was also monitored in terms of the number of incorrect responses to the false-positive and the false-negative catch trials in an identical manner to that used in Chapter Four. Visual field examinations which had yielded greater than 15% incorrect responses to the false-positive and/ or greater than 20% incorrect responses to the fixation loss catch trials and/ or poor quality outcomes to the gaze tracking were repeated on a separate occasion. A similar approach was adopted for incorrect responses to the false-negative catch trials: the repeat criterion was greater than 30% incorrect responses but the tolerance widened with increase in severity of the field loss (Bengtsson and Heijl, 2000).

5.3.3 Statistical Analysis

The difference in the outcome of the visual field between the follow-up and baseline examinations in relation to the interval between the respective examinations was evaluated by scattergraph in terms of the visual field indices Mean Deviation and Corrected Pattern Standard Deviation.

The difference in the outcome of the visual field between the follow-up and baseline examinations in relation to the severity of the field loss at the baseline examination was evaluated in two ways. Firstly, in terms of the visual field indices Mean Deviation and Corrected Pattern Standard Deviation using the technique of Bland and Altman (Bland and Altman, 1995) whereby the difference in the given index between the two examinations was plotted against that of the mean of the two indices and the outcome described in terms of the Mean and ±2SD of the differences. Secondly, and in tabular format, in terms of the Pattern Deviation probability values.
5.4 Results

5.4.1 Cohort

Of the 42 individuals, 15 were excluded from the analysis on the basis of the appearance of the visual field recorded at the follow-up examination. Of these 15 individuals, one was excluded due to the emergence of repeatable visual field loss of differing appearance between the two eyes but of unknown aetiology; five due to a fatiguing artefact present in the fields from one or both eyes; three due to grossly unreliable visual fields; and six due to end-stage visual field loss and the accompanying gross unreliability.

The distribution of the remaining 27 individuals by vigabatrin treatment and by visual field outcome at the baseline examination is given in Table 5-1.

<table>
<thead>
<tr>
<th>Vigabatrin therapy</th>
<th>Normal fields</th>
<th>VAVFL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawn</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>On-going</td>
<td>2</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>19</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 5-1: The number of individuals by vigabatrin treatment and visual field outcome at the baseline examination. VAVFL indicates vigabatrin-associated visual field loss.

The age of the 27 individuals at the follow-up visual field examination ranged from 26.2 to 72.5 years (mean 50.9 years SD 13.9; median 54.7 years IQR 40.7, 60.2). The interval between the follow-up and the baseline examination ranged from 5.5 to 8.6
years (mean 7.0, SD 0.8 years; median 7.0 years IQR 6.5, 7.6). The biographical characteristics, at the time of follow-up, are shown in Table 5-2.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of VGB (yr)</td>
<td>9.4 (3.7)</td>
<td>11.1 (6.0, 12.1)</td>
<td>1.16</td>
<td>18.2</td>
</tr>
<tr>
<td>Cumulative dose of VGB at follow-up (kg)</td>
<td>8.7 (4.8)</td>
<td>8.4 (5.2, 12.7)</td>
<td>0.69</td>
<td>19.0</td>
</tr>
<tr>
<td>Daily dose (g)</td>
<td>2.5 (0.9)</td>
<td>2.1 (1.8, 3.2)</td>
<td>1.41</td>
<td>4.04</td>
</tr>
<tr>
<td>Interval between onset of VGB and baseline perimetry (yr)</td>
<td>10.2 (3.2)</td>
<td>11.6 (8.8, 12.2)</td>
<td>0.9</td>
<td>14.4</td>
</tr>
<tr>
<td>Interval between perimetry (yr)</td>
<td>7.0 (0.8)</td>
<td>7.0 (6.5, 7.6)</td>
<td>5.5</td>
<td>8.6</td>
</tr>
<tr>
<td>Age at baseline (yr)</td>
<td>43.9 (13.9)</td>
<td>48.7 (33.7, 53.6)</td>
<td>17.81</td>
<td>65.4</td>
</tr>
<tr>
<td>Age at follow-up (yr)</td>
<td>50.9 (13.9)</td>
<td>54.7 (40.7, 60.2)</td>
<td>26.2</td>
<td>72.5</td>
</tr>
<tr>
<td>Interval between withdrawal of VGB and follow-up perimetry (yr)</td>
<td>7.1 (3.4)</td>
<td>7.1 (5.4, 8.4)</td>
<td>0.89</td>
<td>16.2</td>
</tr>
</tbody>
</table>

Table 5-2: The summary statistics of the biographical characteristics, at the time of follow-up, for the 27 individuals.

Nineteen of the 27 individuals (12 males, 63% and 7 females, 37%) had exhibited vigabatrin-associated visual field loss at the initial examination. Of these 19 individuals, 6 had discontinued vigabatrin prior to the baseline examination.

The duration of vigabatrin exposure, and the magnitude of the cumulative dose of vigabatrin, at the follow-up examination for the 19 individuals with vigabatrin-associated visual field loss ranged from 4.0 to 17.0 years (mean 10.8 years, SD 3.2; median 11.1 years IQR 9.7, 12.8) and from 2.2 to 19.0 kg cumulative dose (mean 9.9 kg SD 4.5; median 8.7 kg, IQR 6.4, 7.7), respectively. The biographical characteristics, at the time of follow-up, are shown in Table 5-1 to Table 5-5. Four of the 19 individuals
exhibited homonymous quadrantic loss at both the follow-up and the baseline examinations in addition to vigabatrin-associated visual field loss. A fifth individual exhibited homonymous quadrantic loss at the follow-up examination as a result of neurosurgery undertaken during the interval between the two visual field examinations. In these latter five cases, the visual fields were evaluated in terms the remaining three quadrants. The remaining 8 of the 27 individuals had manifested normal visual fields at the baseline examination. Of these 8 individuals, 6 had discontinued vigabatrin prior to the baseline examination. None of these 8 individuals manifested any quadrantic or hemianopic loss.

In clinical terms, no individual ‘converted’ from manifesting normal fields at the baseline examination to vigabatrin-associated visual field loss at the follow-up examination.

The duration of vigabatrin exposure, and the magnitude of the cumulative dose of vigabatrin, at the follow-up examination for the 8 individuals with normal visual fields ranged from 1.16 to 13.60 years (mean 8.2 years, SD 5.9; median 6.9 years, IQR 2.8, 13.0), and from 0.69 to 14.22kg (mean 6.11kg SD 4.9; median 4.37kg IQR 1.92, 10.74). The biographical characteristics, at the time of follow-up, are shown in Table 5-5 to Table 5-8.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of vigabatrin (yr)</td>
<td>10.8 (3.2)</td>
<td>11.1 (9.7, 12.8)</td>
<td>4.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Cumulative dose of vigabatrin at follow-up (kg)</td>
<td>9.9 (4.5)</td>
<td>8.7 (6.4, 7.7)</td>
<td>2.2</td>
<td>19.0</td>
</tr>
<tr>
<td>Daily dose (g)</td>
<td>2.7 (0.9)</td>
<td>2.8 (1.8, 3.7)</td>
<td>1.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Interval between onset of vigabatrin and baseline perimetry (yr)</td>
<td>9.9 (3.4)</td>
<td>11.6 (9.4, 12.1)</td>
<td>0.9</td>
<td>12.9</td>
</tr>
<tr>
<td>Interval between perimetry (yr)</td>
<td>7.3 (0.8)</td>
<td>7.4 (6.5, 7.7)</td>
<td>5.8</td>
<td>8.6</td>
</tr>
<tr>
<td>Age at baseline (yr)</td>
<td>42.9 (15.2)</td>
<td>49.3 (24.9, 53.6)</td>
<td>17.8</td>
<td>65.4</td>
</tr>
<tr>
<td>Age at follow-up (yr)</td>
<td>50.3 (15.2)</td>
<td>57.0 (32.7, 61.5)</td>
<td>26.2</td>
<td>72.5</td>
</tr>
<tr>
<td>Interval between withdrawal of vigabatrin and follow-up perimetry (yr)</td>
<td>6.2 (2.4)</td>
<td>6.9 (5.3, 7.2)</td>
<td>0.86</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Table 5-3: Summary statistics of the individual characteristics, at the time of follow-up, for the 19 individuals with vigabatrin-associated visual field loss.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of vigabatrin (yr)</td>
<td>7.91 (3.5)</td>
<td>7.3 (4.6, 12.0)</td>
<td>4.0</td>
<td>12.1</td>
</tr>
<tr>
<td>Cumulative dose of vigabatrin at follow-up (kg)</td>
<td>9.11 (2.2)</td>
<td>8.8 (5.22, 13.4)</td>
<td>2.2</td>
<td>16.1</td>
</tr>
<tr>
<td>Daily dose (g)</td>
<td>2.8 (1.0)</td>
<td>3.03 (1.7, 3.7)</td>
<td>1.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Interval between onset of vigabatrin and baseline perimetry (yr)</td>
<td>9.9 (2.8)</td>
<td>10.9 (7.0, 12.3)</td>
<td>5.9</td>
<td>12.6</td>
</tr>
<tr>
<td>Interval between perimetry (yr)</td>
<td>7.3 (0.8)</td>
<td>7.4 (6.5, 7.7)</td>
<td>5.8</td>
<td>8.6</td>
</tr>
<tr>
<td>Age at baseline (yr)</td>
<td>42.9 (15.2)</td>
<td>49.3 (1.7, 3.7)</td>
<td>17.8</td>
<td>65.4</td>
</tr>
<tr>
<td>Age at follow-up (yr)</td>
<td>50.4 (15.1)</td>
<td>57.0 (32.7, 61.5)</td>
<td>26.2</td>
<td>72.5</td>
</tr>
<tr>
<td>Interval between withdrawal of vigabatrin and follow-up perimetry (yr)</td>
<td>7.8 (1.9)</td>
<td>7.7 (6.5, 9.1)</td>
<td>5.3</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Table 5-4: The summary statistics of the individual characteristics, at the time of follow-up, for the 6 individuals with vigabatrin-associated visual field loss who were withdrawn from vigabatrin prior to the baseline examination.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of vigabatrin (yr)</td>
<td>10.7 (2.4)</td>
<td>11.1 (10.2, 12.1)</td>
<td>3.50</td>
<td>12.8</td>
</tr>
<tr>
<td>Cumulative dose of vigabatrin at follow-up (kg)</td>
<td>10.2 (4.4)</td>
<td>8.7 (6.9, 12.9)</td>
<td>2.52</td>
<td>19.0</td>
</tr>
<tr>
<td>Daily dose (g)</td>
<td>2.7 (0.9)</td>
<td>2.0 (1.9, 3.6)</td>
<td>1.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Interval between onset of vigabatrin and baseline perimetry (yr)</td>
<td>9.9 (3.8)</td>
<td>11.6 (9.8, 12.0)</td>
<td>0.9</td>
<td>12.9</td>
</tr>
<tr>
<td>Interval between perimetry (yr)</td>
<td>7.3 (0.8)</td>
<td>7.4 (6.5, 7.7)</td>
<td>5.8</td>
<td>8.6</td>
</tr>
<tr>
<td>Age at baseline (yr)</td>
<td>42.9 (15.2)</td>
<td>49.3 (24.9, 53.6)</td>
<td>17.8</td>
<td>65.4</td>
</tr>
<tr>
<td>Age at follow-up (yr)</td>
<td>50.3 (15.1)</td>
<td>57.0 (32.7, 61.5)</td>
<td>26.2</td>
<td>72.5</td>
</tr>
<tr>
<td>Interval between withdrawal of vigabatrin and follow-up perimetry (yr)</td>
<td>5.5 (2.3)</td>
<td>6.0 (4.7, 7.1)</td>
<td>0.86</td>
<td>9.3</td>
</tr>
</tbody>
</table>

Table 5-5: The summary statistics of the individual characteristics, at the time of follow-up, for the 13 individuals with vigabatrin-associated visual field loss who were withdrawn from vigabatrin between the initial and the follow-up visual field examinations.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of vigabatrin (yr)</td>
<td>8.2 (5.9)</td>
<td>6.9 (2.8, 13.0)</td>
<td>1.1</td>
<td>18.2</td>
</tr>
<tr>
<td>Cumulative dose of vigabatrin at follow-up (kg)</td>
<td>6.11 (4.9)</td>
<td>4.37 (1.9, 10.7)</td>
<td>0.7</td>
<td>14.2</td>
</tr>
<tr>
<td>Daily dose (g)</td>
<td>2.02 (0.5)</td>
<td>1.95 (1.7, 2.4)</td>
<td>1.4</td>
<td>2.9</td>
</tr>
<tr>
<td>Interval between onset of vigabatrin and baseline perimetry (yr)</td>
<td>11.0 (2.6)</td>
<td>11.8 (8.1, 13.3)</td>
<td>7.3</td>
<td>14.4</td>
</tr>
<tr>
<td>Interval between perimetry (yr)</td>
<td>6.32 (0.6)</td>
<td>6.23 (5.7, 6.8)</td>
<td>5.5</td>
<td>7.3</td>
</tr>
<tr>
<td>Age at baseline (yr)</td>
<td>46.3 (10.2)</td>
<td>46.26 (1.7, 2.4)</td>
<td>28.5</td>
<td>62.4</td>
</tr>
<tr>
<td>Age at follow-up (yr)</td>
<td>52.6 (10.2)</td>
<td>53.27 (1.7, 2.4)</td>
<td>35.4</td>
<td>68.9</td>
</tr>
<tr>
<td>Interval between withdrawal of vigabatrin and follow-up perimetry (yr)</td>
<td>8.9 (4.5)</td>
<td>8.4 (6.4, 11.9)</td>
<td>1.0</td>
<td>16.2</td>
</tr>
</tbody>
</table>

Table 5-6: Summary statistics of the individual characteristics, at the time of follow-up, for the 8 individuals with normal visual fields.
### Table 5-7: The summary statistics of the individual characteristics, at the time of follow-up, for the 6 individuals with normal fields who were withdrawn from vigabatrin prior to the baseline examination.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of vigabatrin (yr)</td>
<td>5.8 (4.0)</td>
<td>5.7 (1.7, 9.0)</td>
<td>1.2</td>
<td>12.0</td>
</tr>
<tr>
<td>Cumulative dose of vigabatrin at follow-up (kg)</td>
<td>4.2 (3.8)</td>
<td>3.3 (1.3, 6.7)</td>
<td>0.7</td>
<td>11.2</td>
</tr>
<tr>
<td>Daily dose (g)</td>
<td>1.9 (0.4)</td>
<td>1.8 (1.6, 2.2)</td>
<td>1.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Interval between onset of vigabatrin and baseline perimetry (yr)</td>
<td>10.3 (2.7)</td>
<td>10.2 (7.7, 12.6)</td>
<td>7.3</td>
<td>14.4</td>
</tr>
<tr>
<td>Interval between perimetry (yr)</td>
<td>6.3 (0.6)</td>
<td>6.2 (5.9, 6.8)</td>
<td>5.5</td>
<td>7.3</td>
</tr>
<tr>
<td>Age at baseline (yr)</td>
<td>46.3 (10.3)</td>
<td>46.3 (1.6, 2.2)</td>
<td>28.5</td>
<td>62.4</td>
</tr>
<tr>
<td>Age at follow-up (yr)</td>
<td>52.6 (10.2)</td>
<td>53.3 (45.9, 59.5)</td>
<td>35.4</td>
<td>68.9</td>
</tr>
<tr>
<td>Interval between withdrawal of vigabatrin and follow-up perimetry (yr)</td>
<td>10.8 (3.1)</td>
<td>10.2 (8.2, 13.0)</td>
<td>8.2</td>
<td>16.2</td>
</tr>
</tbody>
</table>
### Table 5-8: The summary of the individual characteristics, at the time of follow-up, for the 2 individuals with normal visual fields who were withdrawn from vigabatrin between the initial and the follow-up visual field examinations.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Individual 1</th>
<th>Individual 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of vigabatrin (yr)</td>
<td>13.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Cumulative dose of vigabatrin at follow-up (kg)</td>
<td>14.2</td>
<td>9.5</td>
</tr>
<tr>
<td>Daily dose (g)</td>
<td>2.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Interval between onset of vigabatrin and baseline perimetry (yr)</td>
<td>13.6</td>
<td>12.7</td>
</tr>
<tr>
<td>Interval between perimetry (yr)</td>
<td>6.9</td>
<td>6.6</td>
</tr>
<tr>
<td>Age at baseline (yr)</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>Age at follow-up (yr)</td>
<td>35</td>
<td>45</td>
</tr>
<tr>
<td>Interval between withdrawal of vigabatrin and follow-up perimetry (yr)</td>
<td>1.0</td>
<td>5.9</td>
</tr>
</tbody>
</table>

All 15 individuals (two with normal fields and 13 with vigabatrin-associated visual field loss) who were receiving vigabatrin at the time of the baseline examination had been withdrawn from vigabatrin by the time of the follow-up examination.

### 5.4.2 Interval between the follow-up and baseline examinations

#### 5.4.2.1 Mean Deviation

The difference in the Mean Deviation between the follow-up and the baseline examinations, averaged across the fields of the two eyes for an individual, against the interval between the two examinations, for the 19 individuals with vigabatrin-associated visual field loss is illustrated in Figure 5-1.
The corresponding plots for the field of the right eye and of the left eye are given in Figure 5-2 and Figure 5-3.

Figure 5-1: The difference in the Mean Deviation (MD), averaged across the two eyes for an individual, between the follow-up and the baseline examinations against the interval between the two examinations for the 6 individuals with vigabatrin-associated visual field loss withdrawn from vigabatrin prior to the baseline examination (filled symbols) and for the 13 individuals with vigabatrin-associated visual field loss receiving vigabatrin at the time of the baseline examination (open symbols).
Figure 5-2: The difference in Mean Deviation (MD), for the right eye of an individual, between the follow-up and the baseline examinations against the interval between the two examinations for the 6 individuals with vigabatrin-associated visual field loss withdrawn from vigabatrin prior to the baseline examination (filled symbols) and for the 13 individuals with vigabatrin associated visual field loss receiving vigabatrin at the time of the baseline examination (open symbols).
Figure 5-3: The difference in Mean Deviation (MD), for the left eye of an individual, between the follow-up and the baseline examinations against the interval between the two examinations for the 6 individuals with vigabatrin-associated visual field loss withdrawn from vigabatrin prior to the baseline examination (filled symbols) and for the 13 individuals with vigabatrin associated visual field loss receiving vigabatrin at the time of the baseline examination (open symbols).

The difference in the MD between the follow-up and the baseline examinations, averaged across the fields of the two eyes for each individual, was independent of the interval between the two examinations for the 27 individuals ($R^2 = 0.001$). Similarly, the differences in the MD for the right eye and for the left eye were also each
independent of the interval between the two examinations ($R^2 = 0.003$ and $R^2 = 0.0$, respectively) (Table 5-9).

No relationship was present between the change in the respective MDs from the baseline to the follow-up examination and the corresponding interval between the two visual field examinations for those with vigabatrin-associated visual field loss, regardless of whether the individuals were receiving ($R^2 = 0.01$, $R^2 = 0.08$, and $R^2 = 0.02$, respectively), or had been withdrawn from, vigabatrin ($R^2 = 0.05$, $R^2 = 0.12$, and $R^2 = 0.00$, respectively) (Table 5-9).

The difference in the MD at the follow-up examination, averaged across the fields of the two eyes for an individual, against that at the baseline examination for the 8 individuals with normal fields is illustrated in Figure 5-4. The corresponding plots for the field of the right eye and of the left eye are given in Figure 5-5 and Figure 5-6.

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<th>Left eye MD</th>
</tr>
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<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Off drug (VAVFL)</td>
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<td>0.12</td>
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</tr>
<tr>
<td>On drug (VAVFL)</td>
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<td>0.08</td>
<td>0.02</td>
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<tr>
<td>All (Normal field)</td>
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<td>0.00</td>
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</tr>
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<td>-</td>
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*Table 5-9: The Coefficients of Determination, ($R^2$) for the change in the Mean Deviation (MD) between the follow-up and the baseline examinations against the interval between the two examinations.*
Figure 5-4: The difference in the Mean Deviation (MD), averaged across the two eyes for an individual, between the follow-up and the baseline examinations against the interval between the two examinations for the 6 individuals with a normal field withdrawn from vigabatrin prior to the baseline examination (filled symbols) and for the 2 individuals with a normal field receiving vigabatrin at the time of the baseline examination (open symbols).
Figure 5-5: The difference in the Mean Deviation (MD), for the right eye between the follow-up and the baseline examinations against the interval between the two examinations for the 6 individuals with normal field withdrawn from vigabatrin prior to the baseline examination (filled symbols) and for the 2 individuals with a normal field receiving vigabatrin at the time of the baseline examination (open symbols).
Figure 5-6: The difference in the Mean Deviation (MD), for the left eye between the follow-up and baseline examinations against the interval between the two examinations for the 6 individuals with a normal field withdrawn from vigabatrin prior to the baseline examination (filled symbols) and for the 2 individuals with a normal field receiving vigabatrin at the time of the baseline examination (open symbols).
The magnitudes of the Coefficients of Determination were similar, within the remit of the limited numbers of individuals, to those for the 6 individuals with normal fields (Table 5-9) who had been withdrawn from vigabatrin prior to the first examination and who would not, normally, be expected to exhibit any such relationship.

5.4.2.2 Corrected Pattern Standard Deviation

The difference in the mean Corrected Pattern Standard Deviation (CPSD) between the follow-up and the baseline examinations, averaged across the fields of the two eyes for each individual, against the interval between the two examinations, for the 19 individuals with vigabatrin-associated visual field loss is illustrated in Figure 5-7. The corresponding plots for the field of the right eye and of the left eye are given in Figure 5-8 and Figure 5-9.
Figure 5-7: The difference in the Corrected Pattern Standard Deviation (CPSD), averaged across the two eyes for an individual, between the follow-up and the baseline examinations against the interval between the two examinations for the 6 individuals with vigabatrin associated visual field loss withdrawn from vigabatrin prior to the baseline examination (filled symbols) and for the 13 individuals with vigabatrin associated visual field loss receiving vigabatrin at the time of the baseline examination (open symbols).
Figure 5-8: The difference in the Corrected Pattern Standard Deviation (CPSD), for the right eye, between the follow-up and the baseline examinations against the interval between the two examinations for the 6 individuals with vigabatrin associated visual field loss withdrawn from vigabatrin prior to the baseline examination (filled symbols) and for the 13 individuals with vigabatrin associated visual field loss receiving vigabatrin at the time of the baseline examination (open symbols).
Figure 5.9: The difference in the Corrected Pattern Standard Deviation (CPSD), for the left eye, between the follow-up and the baseline examinations against the interval between the two examinations for the 6 individuals with vigabatrin associated visual field loss withdrawn from vigabatrin prior to the baseline examination (filled symbols) and for the 13 individuals with vigabatrin associated visual field loss receiving vigabatrin at the time of the baseline examination (open symbols).
Figure 5-10: The difference in the Corrected Pattern Standard Deviation (CPSD), averaged across the two eyes for an individual, between the follow-up and the baseline examinations against the interval between the two examinations for the 6 individuals with a normal field withdrawn from vigabatrin prior to the baseline examination (filled symbols) and for the 2 individuals with a normal field receiving vigabatrin at the time of the baseline examination (open symbols).
Figure 5-11: The difference in the Corrected Pattern Standard Deviation (CPSD), for the right eye between the follow-up and the baseline examinations against the interval between the two examinations for the 6 individuals with a normal field withdrawn from vigabatrin prior to the baseline examination (filled symbols) and for the 2 individuals with normal field receiving vigabatrin at the time of the baseline examination (open symbols).
Figure 5-12: The difference in the Corrected Pattern Standard Deviation (CPSD), for the left eye between the follow-up and the baseline examinations against the interval between the two examinations for the 6 individuals with a normal field withdrawn from vigabatrin prior to the baseline examination (filled symbols) and for the 2 individuals with normal field receiving vigabatrin at the time of the baseline examination (open symbols).
No relationship was present between the change in the Corrected Pattern Standard Deviation between the follow-up and the baseline examinations and the interval between the visual field examinations for those with vigabatrin-associated visual field loss regardless of whether the individuals were receiving ($R^2 = 0.00$, $R^2 = 0.29$, and $R^2 = 0.27$, respectively), or had been withdrawn from, vigabatrin ($R^2 = 0.01$, $R^2 = 0.00$, and $R^2 = 0.04$, respectively), (Table 5-10).

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<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>Off drug (VAVFL)</td>
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<td>0.00</td>
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</tr>
<tr>
<td>On drug (VAVFL)</td>
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</tr>
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<td>All (Normal field)</td>
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<td>-</td>
<td></td>
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</tr>
</tbody>
</table>

Table 5-10: The Coefficients of Determination, ($R^2$) for the change in the Corrected Pattern Standard Deviation (CPSD) between the follow-up and the baseline examinations against the interval between the two examinations.

The magnitudes of the Coefficients of Determination were similar, within the remit of the limited numbers of individuals, to the 6 with normal fields (Table 5-10) who had been withdrawn from vigabatrin prior to the first examination and who would not, normally, be expected to exhibit any such relationship.
5.5 Severity of vigabatrin-associated visual field loss

5.5.1 Mean Deviation

As a consequence of the lack of a relationship between the change in the MD and the interval between examinations, the influence of the severity of the field loss was considered in terms of the absolute difference between examinations irrespective of the interval between examinations. The Mean Deviation at the follow-up examination, averaged across the fields of the two eyes for an individual, against that at the baseline examination for those with vigabatrin associated visual field loss is illustrated in Figure 5-13.

The corresponding plots for the field of the right eye and of the left eye are given in Figure 5-14 and Figure 5-15.

The Mean ±2SD of the difference in the Mean Deviation, averaged across the fields of the two eyes for an individual, between the follow-up and the baseline examinations, against that of the mean of the two examinations for the two eyes, for the 19 individuals with vigabatrin associated visual field loss, is given in Figure 5-16.

The corresponding plots for the field of the right eye and of the left eye are given in Figure 5-17 and Figure 5-18.
Figure 5-13: The mean of the Mean Deviation (MD) between the two eyes at the follow-up examination against that at the baseline examination for the 19 individuals with vigabatrin-associated visual field loss. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination.
Figure 5-14: The Mean Deviation (MD) for the right eye at the follow-up examination against that at the baseline examination for the 19 individuals with vigabatrin associated visual field loss. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination.
Figure 5-15: The Mean Deviation (MD) for the left eye at the follow-up examination against that at the baseline examination for the 19 individuals with vigabatrin associated visual field loss. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination.
Figure 5-16: The difference in the Mean Deviation (MD), averaged across the fields of the two eyes for an individual, between the follow-up examination and the baseline examination against the mean of these examinations for the 19 individuals with vigabatrin associated visual field loss. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean. The corresponding values for the 8 individuals with normal fields are illustrated in red (however, for clarity, the data points have been omitted).
Figure 5.17: The difference in the Mean Deviation (MD), for the right eye, between the follow-up examination and the baseline examination against the mean of these examinations for the 19 individuals with vigabatrin associated visual field loss. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. The solid black line represents the mean of the differences and the dotted black lines ± 2SD of the mean. The corresponding values for the 8 individuals with normal fields are illustrated in red (however, for clarity, the data points have been omitted).
Figure 5-18: The difference in the Mean Deviation (MD), for the left eye, between the follow-up examination and the baseline examination against the mean of these examinations for the 19 individuals with vigabatrin associated visual field loss. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean. The corresponding values for the 8 individuals with normal fields are illustrated in red (however, for clarity, the data points have been omitted).
The Mean Deviation at the follow-up examination, averaged across the fields of the two eyes for an individual, against that at the baseline examination for the 8 individuals with a normal field is illustrated in Figure 5-19.

The corresponding plots for the field of the right eye and of the left eye are given in Figure 5-20 and Figure 5-21, respectively.

Figure 5-19: The mean of the Mean Deviation (MD) between the two eyes at the follow-up examination against that at the baseline examination for the 8 individuals with normal fields. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. Note the difference in scaling of both the abscissa and the ordinate compared to Figure 5-13.
Figure 5-20: The Mean Deviation (MD) for the right eye at the follow-up examination against that at the baseline examination for the 8 individuals with normal fields. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. Note the difference in scaling of both the abscissa and the ordinate compared to figure 5-13.
Figure 5-21: The Mean Deviation (MD) for the left eye at the follow-up examination against that at the baseline examination for the 8 individuals with normal fields. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. Note the difference in scaling of both the abscissa and the ordinate compared to figure 5-13.
The Mean ±2SD of the difference in the Mean Deviation, averaged across the fields of the two eyes for an individual, between the follow-up and the baseline examinations, against that of the mean of the two examinations for the two eyes, for the 8 individuals with normal fields, is given in Figure 5-22. The corresponding plots for the field of the right eye and of the left eye are given in Figure 5-23 and Figure 5-24, respectively.

Figure 5-22: The difference in Mean Deviation (MD), averaged across the fields of the two eyes for an individual, between the follow-up examination and the baseline examination against the mean of these examinations for the 8 individuals with normal fields. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean.
Figure 5-23: The difference in Mean Deviation (MD) for the right eye between the follow-up examination and the baseline examination against the mean of these examinations for the 8 individuals with normal fields. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean.
Figure 5-24: The difference in Mean Deviation (MD) for the left eye between the follow-up examination and the baseline examination against the mean of these examinations for the 8 individuals with normal fields. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean.
5.5.2 Corrected Pattern Standard Deviation

As a consequence of the lack of a relationship between the change in the CPSD and the interval between examinations, the CPSD was also subsequently considered in terms of the absolute difference between examinations irrespective of the interval between examinations. The Corrected Pattern Standard Deviation at the follow-up examination, averaged across the fields of the two eyes for an individual, against that at the baseline examination for the two eyes, for the 19 individuals with vigabatrin associated visual field loss is illustrated in Figure 5.25. The corresponding plots for the field of the right eye and of the left eye are given in Figure 5.26 and Figure 5.27, respectively.
Figure 5-25: The mean of the Corrected Pattern Standard Deviation (dB) between the two eyes at the follow-up examination against that at the baseline examination for the 19 individuals with vigabatrin associated visual field loss. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination.
Figure 5-26: The Corrected Pattern Standard Deviation (CPSD) for the right eye at the follow-up examination against that at the baseline examination for the 19 individuals with vigabatrin associated visual field loss. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination.
Figure 5-27: The Corrected Pattern Standard Deviation (CPSD) for the left eye at the follow-up examination against that at the baseline examination for the 19 individuals with vigabatrin associated visual field loss. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination.
The Mean ±2SD of the difference in the Corrected Pattern Standard Deviation, averaged across the fields of the two eyes for an individual, between the follow-up and the baseline examinations, against that of the mean of the two examinations for the two eyes, for the 19 individuals with vigabatrin associated visual field loss, is given in Figure 5-28. The corresponding plots for the field of the right eye and of the left eye are given in Figure 5-29 and Figure 5-30, respectively.
Figure 5-28: The difference in the Corrected Pattern Standard Deviation (CPSD), averaged across the fields of the two eyes for an individual, between the follow-up examination and the baseline examination against the mean of these examinations for the 19 individuals with vigabatrin associated visual field loss. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean. The corresponding values for the 8 individuals with normal fields are illustrated in red (however, for clarity, the data points have been omitted).
Figure 5-29: The difference in the Corrected Pattern Standard Deviation (CPSD), for the right eye, between the follow-up examination and the baseline examination against the mean of these examinations for the 19 individuals with vigabatrin associated visual field loss. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. The solid lack line represents the mean of the differences and the dotted black lines +/- 2SD of the mean. The corresponding values for the 8 individuals with normal fields are illustrated in red (however, for clarity, the data points have been omitted).
Figure 5-30: The difference in the Corrected Pattern Standard Deviation (CPSD), for the left eye, between the follow-up examination and the baseline examination against the mean of these examinations for the 19 individuals with vigabatrin associated visual field loss. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. The solid lack line represents the mean of the differences and the dotted black lines +/- 2SD of the mean. The corresponding values for the 8 individuals with normal fields are illustrated in red (however, for clarity, the data points have been omitted).
Figure 5-31: The difference in the Corrected Pattern Standard Deviation (CPSD), averaged across the fields of the two eyes for an individual, between the follow-up examination and the baseline examination against the mean of these examinations for the 8 individuals with normal fields. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean.
Figure 5-32: The difference in Corrected Pattern Standard Deviation for the right eye, between the follow-up examination and the baseline examination against the Mean of these examinations for the 8 individuals with normal fields. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean.
Figure 5-33: The difference in Corrected Pattern Standard Deviation for the left eye, between the follow-up examination and the baseline examination against the Mean of these examinations for the 8 individuals with normal fields. Open symbols represent those individuals receiving vigabatrin at the baseline examination and the filled symbols those withdrawn from vigabatrin prior to the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean.
5.5.3 Pattern Deviation Probability value

The difference for each individual in the magnitudes of the Pattern Deviation probability value, across all stimulus locations, between the follow-up and baseline examinations for those with vigabatrin associated visual field loss is shown in Table 5-13 and Table 5-14 for the 6 individuals receiving vigabatrin at the baseline examination and in Table 5-11 and Table 5-12 for the 13 individuals withdrawn from vigabatrin prior to the baseline examination. The vertical shading in each table indicates the number of stimulus locations exhibiting identical probability values at the two examinations. The number of locations exhibiting an improvement, by the number of probability levels, at the follow-up examination is shown to the left of the shading and the number of locations exhibiting a deterioration, by the number of probability levels, is shown to the right of the shading. The numerator indicates the number of locations exhibiting normality, and the denominator indicates the number of locations exhibiting abnormality at the given probability value, at the baseline examination. A reduction of the data, in terms of the number of locations exhibiting either an improvement or a deterioration over two and up to three or more probability levels is shown in Table 5-11 to Table 5-18, respectively. The latter Tables also include the number of locations in the extreme outer annulus (1st) and in the immediate inner annulus (2nd) (Figure 5-34) exhibiting either an improvement or a deterioration by three or more probability levels.
Figure 5-34: The stimulus locations in the outer (filled rectangles) and inner (open rectangles) annuli used in the analysis of the change in the Pattern Deviation Probability values between the follow-up and baseline examinations.
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Table 5-11: The difference for each individual in the magnitudes of the Pattern Deviation probability value, across all stimulus locations, between the follow-up and the baseline examination for the 6 individuals with vigabatrin associated visual field loss and withdrawn from vigabatrin prior to the baseline examination. The shading indicates the number of locations exhibiting identical probability values at the two examinations. The number of locations exhibiting an improvement, by the number of probability levels, at the follow-up examination is shown to the left of the vertical shading and the number of locations exhibiting a deterioration, by the number of probability levels, is shown to the right of the vertical shading. The numerator indicates the number of locations exhibiting normality, and the denominator indicates the number of locations exhibiting abnormality, at the given probability value, at the baseline examination. *indicates an individual considered by clinical evaluation to exhibit progressive visual field loss in both eyes.
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<td>0/2</td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>Severe*</td>
<td>1/0</td>
<td>1/0</td>
<td>0/4</td>
<td>0/2</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0</td>
<td>0/0</td>
<td>0/2</td>
<td>0/0</td>
</tr>
<tr>
<td>6</td>
<td>R</td>
<td>Mild</td>
<td>1/0</td>
<td>2/0</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0</td>
<td>0/0</td>
<td>0/3</td>
<td>0/0</td>
</tr>
</tbody>
</table>

Table 5-12: The difference for each individual in the magnitudes of the Pattern Deviation probability value, across all stimulus locations, between the follow-up and the baseline the examination for the 6 individuals with vigabatrin associated visual field loss and withdrawn from vigabatrin prior to the baseline examination. The shading indicates the number of locations exhibiting identical probability values at the two examinations. The number of locations exhibiting an improvement, by two or by three or more probability levels, respectively, at the follow-up examination is shown to the left of the vertical shading and the number of locations exhibiting a deterioration, by two or by three or more probability levels, respectively, is shown to the right of the vertical shading. The numerator indicates the number of locations exhibiting normality, and the denominator indicates the number of locations exhibiting abnormality at the given probability value, at the baseline examination. An identical analysis for the outer two annuli (1\textsuperscript{st} or 2\textsuperscript{nd}) of stimulus locations, by three or more probability levels, at the follow-up examination is shown to the left (improvement) and right (deterioration) of the vertical shading. *indicates an individual considered by clinical evaluation to exhibit progressive visual field loss in both eyes.
<table>
<thead>
<tr>
<th>No</th>
<th>Eye</th>
<th>Visual Field Grade</th>
<th>Improvement ▲ Number of Probability Levels</th>
<th>Deterioration ▼ Number of Probability Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R</td>
<td>Severe</td>
<td>0/1 0/1 0/3 0/7 35/15 2/1 0/0 1/9 0/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/1 0/3 0/2 0/9 25/12 1/10 3/4 3/2 0/0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>Severe*</td>
<td>0/5 0/5 0/4 0/7 18/27 1/1 2/1 0/0 6/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/4 0/3 0/0 0/5 25/32 0/2 0/1 0/0 1/0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>Severe</td>
<td>0/2 0/4 0/7 0/8 18/18 2/3 3/3 1/3 3/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
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<td></td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>Severe</td>
<td>0/2 0/2 0/3 0/5 21/37 2/1 1/0 0/1 1/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0 0/6 0/4 0/1 21/27 2/6 0/8 0/0 1/0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>Severe*</td>
<td>0/1 0/2 0/0 0/3 28/21 2/7 2/6 0/2 3/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0 0/3 0/0 0/2 25/9 4/5 5/3 3/0 14/0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>R</td>
<td>Severe*</td>
<td>0/0 0/0 0/1 0/2 18/22 2/9 4/3 3/7 5/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0 0/0 0/2 0/2 27/30 2/4 1/3 1/3 1/0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>R</td>
<td>Mild</td>
<td>0/0 0/2 0/4 0/7 55/3 2/1 0/0 0/0 2/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td>R</td>
<td>Severe</td>
<td>0/4 0/0 0/4 0/4 42/10 2/3 1/2 0/2 2/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/2 0/4 0/2 0/3 39/10 4/3 4/2 1/0 2/0</td>
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</tr>
<tr>
<td>9</td>
<td>R</td>
<td>Moderate</td>
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</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>R</td>
<td>Mild</td>
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<td></td>
</tr>
<tr>
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<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
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<td></td>
</tr>
<tr>
<td>12</td>
<td>R</td>
<td>Severe*</td>
<td>0/0 0/0 0/0 0/5 21/10 2/5 7/5 3/4 14/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/1 0/0 0/3 0/5 27/8 2/3 2/10 1/4 10/0</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>R</td>
<td>Severe*</td>
<td>0/0 0/0 0/0 0/2 37/22 3/5 7/3 0/4 3/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0 0/0 0/0 0/3 37/17 1/6 4/1 1/4 2/0</td>
<td></td>
</tr>
</tbody>
</table>

Table 5-13: The difference for each individual in the magnitudes of the Pattern Deviation probability value, across all stimulus locations, between the follow-up and the baseline the examination for the 13 individuals with vigabatrin associated visual field loss receiving vigabatrin at the baseline examination. The shading indicates the number of locations exhibiting identical probability values at the two examinations. The number of locations exhibiting an improvement, by the number of probability levels, at the follow-up examination is shown to the left of the vertical shading and the number of locations exhibiting a deterioration, by the number of probability levels, is shown to the right of the vertical shading. The numerator indicates the number of locations exhibiting normality, and the denominator indicates the number of locations exhibiting abnormality at the given probability value, at the baseline examination. *indicates an individual considered by clinical evaluation to exhibit progressive visual field loss in both eyes.
<table>
<thead>
<tr>
<th>No</th>
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<th>Visual Field Grade</th>
<th>Annulus ≥3</th>
<th>Improvement ▲</th>
<th>Deterioration ▼</th>
<th>Annulus ≥3</th>
</tr>
</thead>
<tbody>
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<td>Severe</td>
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<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>Severe*</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>Severe</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
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<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>Severe</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
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<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>Severe*</td>
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<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>6</td>
<td>R</td>
<td>Severe*</td>
<td>1/1</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>7</td>
<td>R</td>
<td>Mild</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
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<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>8</td>
<td>R</td>
<td>Severe</td>
<td>2/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>9</td>
<td>R</td>
<td>Moderate</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
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<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>10</td>
<td>R</td>
<td>Mild</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
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<td>L</td>
<td></td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>11</td>
<td>R</td>
<td>Severe</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>12</td>
<td>R</td>
<td>Severe*</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>13</td>
<td>R</td>
<td>Severe*</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td></td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>

Table 5-14: The difference for each individual in the magnitudes of the Pattern Deviation probability value, across all stimulus locations, between the follow-up and the baseline the examination for the 13 individuals with vigabatrin associated visual field loss receiving vigabatrin at the baseline examination. The shading indicates the number of locations exhibiting identical probability values at the two examinations. The number of locations exhibiting an improvement, by two or by three or more probability levels, respectively, at the follow-up examination is shown to the left of the vertical shading and the number of locations exhibiting a deterioration, by two or by three or more probability levels, respectively, is shown to the right of the vertical shading. The numerator indicates the number of locations exhibiting normality, and the denominator indicates the number of locations exhibiting abnormality at the given probability value, at the baseline examination. An identical analysis for the outer two annuli (1st or 2nd) of stimulus locations (as indicated in Table 6-13), by three or more probability levels, at the follow-up examination is shown to the left (improvement) and right (deterioration) of the vertical shading. *indicates an individual considered by clinical evaluation to exhibit progressive visual field loss in both eyes.
The difference for each individual in the magnitudes of the Pattern Deviation probability levels, across all stimulus locations, between the follow-up and the baseline examination for the 6 individuals with normal visual fields and withdrawn from vigabatrin prior to the baseline examination is shown in Table 5-15 and Table 5-16.

Table 5-15: The difference for each individual in the magnitudes of the Pattern Deviation probability value, across all stimulus locations, between the follow-up and the baseline examination for the 6 individuals with normal visual fields and withdrawn from vigabatrin prior to the baseline examination. The shading indicates the number of locations exhibiting identical probability values at the two examinations. The number of locations exhibiting an improvement, by the number of probability levels, at the follow-up examination is shown to the left of the vertical shading and the number of locations exhibiting a deterioration, by the number of probability levels, is shown to the right of the vertical shading. The numerator indicates the number of locations exhibiting normality, and the denominator indicates the number of locations exhibiting abnormality at the given probability value, at the baseline examination.
<table>
<thead>
<tr>
<th>No</th>
<th>Eye</th>
<th>Improvement ▲ ≥2</th>
<th>Same ±1</th>
<th>Deterioration ▼ ≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R</td>
<td>0/0</td>
<td>72/1</td>
<td>2/1</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0/0</td>
<td>64/8</td>
<td>4/0</td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>0/1</td>
<td>70/3</td>
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</tr>
<tr>
<td></td>
<td>L</td>
<td>0/2</td>
<td>71/3</td>
<td>0/0</td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>0/0</td>
<td>75/1</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0/0</td>
<td>73/3</td>
<td>0/0</td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>0/1</td>
<td>68/4</td>
<td>2/1</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0/0</td>
<td>73/1</td>
<td>2/0</td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>0/0</td>
<td>72/4</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0/3</td>
<td>68/4</td>
<td>1/0</td>
</tr>
<tr>
<td>6</td>
<td>R</td>
<td>0/0</td>
<td>75/1</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0/0</td>
<td>74/2</td>
<td>0/0</td>
</tr>
</tbody>
</table>

Table 5-16: The difference for each individual in the magnitudes of the Pattern Deviation probability value, across all stimulus locations, between the follow-up and the baseline examination for the 6 individuals with normal visual fields and withdrawn from vigabatrin prior to the baseline examination. The shading indicates the number of locations exhibiting identical probability values at the two examinations. The number of locations exhibiting an improvement, by two or more probability levels, respectively, at the follow-up examination is shown to the left of the vertical shading and the number of locations exhibiting a deterioration, by two or more probability levels, respectively, is shown to the right of the vertical shading. The numerator indicates the number of locations exhibiting normality, and the denominator indicates the number of locations exhibiting abnormality at the given probability value, at the baseline examination.

The difference for each individual in the magnitudes of the Pattern Deviation probability value, across all stimulus locations, between the follow-up and the baseline examination for the two individuals with normal fields and receiving vigabatrin at the baseline examination is shown in Table 5-17 and Table 5-18.
Table 5-17: The difference for each individual in the magnitudes of the Pattern Deviation probability value, across all stimulus locations, between the follow-up and the baseline examination for the 2 individuals with normal visual fields and receiving vigabatrin at the baseline examination. The shading indicates the number of locations exhibiting identical probability values at the two examinations. The number of locations exhibiting an improvement, by two or more probability levels, respectively, at the follow-up examination is shown to the left of the vertical shading and the number of locations exhibiting a deterioration, by two or more probability levels, respectively, is shown to the right of the vertical shading. The numerator indicates the number of locations exhibiting normality, and the denominator indicates the number of locations exhibiting abnormality at the given probability value, at the baseline examination.

<table>
<thead>
<tr>
<th>No</th>
<th>Eye</th>
<th>Improvement ▲ Number of Probability Levels</th>
<th>Deterioration▼ Number of Probability Levels</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td>Same</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
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<td>0/2</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0/2</td>
<td>0/0</td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>0/0</td>
<td>0/2</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>

Table 5-18: The difference for each individual in the magnitudes of the Pattern Deviation probability value, across all stimulus locations, between the follow-up and the baseline examination for the two individuals with normal fields and receiving vigabatrin at the baseline examination. The shading indicates the number of locations exhibiting identical probability values at the two examinations. The number of locations exhibiting the given improvement in the probability level at the follow-up examination is shown to the left of the shading and the number of locations exhibiting the given deterioration to the right of the shading. The numerator indicates the number of locations exhibiting normality, and the denominator indicates the number of locations exhibiting abnormality at the given probability value, at the baseline examination.

<table>
<thead>
<tr>
<th>No</th>
<th>Eye</th>
<th>Improvement ▲ Number of Probability Levels</th>
<th>Deterioration▼ Number of Probability Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Same ±1</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>R</td>
<td>0/3</td>
<td>0/4</td>
</tr>
<tr>
<td></td>
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<tr>
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<td>L</td>
<td>0/0</td>
<td>0/2</td>
</tr>
</tbody>
</table>
5.6 Discussion

The outcome of any study of visual field progression is influenced by the number of visual field examinations within the given time period and by the length of the time period, itself (Casas-Llera et al., 2009). Clearly, the conclusions that can be obtained from a time period which involves only two visual field examinations are limited due to the inherent within- and between-examination variability arising from the subjective nature of the examination, itself.

If no alteration occurred in the visual field between the two examinations, the outcomes would be identical. However, given the between-examination variability inherent in perimetry, and given that only two examinations were undertaken for each individual, it could be hypothesized that, if ‘no change’ was present across the case series, one half of individuals would exhibit an apparent deterioration between the two examinations and one half would exhibit an apparent improvement at the follow-up examination. Clearly, either a ‘true’ deterioration or a ‘true’ improvement would be indicated by a greater proportion of individuals exhibiting the particular trend/ direction.

Clearly, no recovery of the visual field to normality, or near normality, was uniformly manifest across all individuals with vigabatrin-associated visual field loss in the case series. Such an outcome would be unlikely given the catastrophic retinal damage associated with vigabatrin associated visual field loss, albeit in one individual, at post-mortem (Ravindran et al., 2001) and with the mounting evidence for retinal nerve fibre layer thinning, identifiable by optical coherence tomography, associated with vigabatrin toxicity and with vigabatrin-associated visual field loss (Lawthom et al., 2009; Clayton et al., 2011).
The difference in the Mean Deviation and in the Corrected Pattern Standard Deviation between the follow-up and the baseline examinations for those with vigabatrin-associated visual field loss was considered in the context of the magnitude of two SDs of the distribution of the mean of the corresponding difference for the 8 individuals with normal fields. Given that the between-examination variability should be greater for those with vigabatrin-associated visual field loss, it was remarkable to note that 12 of the 19 individuals with vigabatrin-associated visual field loss exhibited a difference in the Mean Deviation which lay within two SDs of the corresponding distribution for the individuals with normal fields. Of the remaining 7 individuals, 4 exhibited an apparent deterioration and 3 an apparent improvement.

The visual field loss associated with vigabatrin is absolute, or near absolute, for the Goldmann size III stimulus used in static perimetry and is also characterised by a steep border. The inherent variability in perimetry exhibits a minimum at normal levels of sensitivity but increases to a maximum at a measured sensitivity, for the Humphrey Field Analyzer, of approximately 15-19dB (Wall, Kutzko and Chauhan, 1997; Gardiner et al., 2014) after which it declines as the measured sensitivity approaches zero.

The study shows that there is no clinical significant reversibility of vigabatrin-associated visual field loss in individuals who had withdrawn from the drug between 0.86 and 11.1 years prior to the follow-up examination. This finding provides further evidence that vigabatrin-associated visual field loss is not reversible after discontinuation of the drug.
5.7 Conclusion

Within the limited number of individuals in, and the duration of follow-up of, the study, it is clear that, following long-term withdrawal from the drug, vigabatrin-associated visual field loss does not recover and that individuals exposed to the drug with normal fields do not subsequently manifest field loss.
Chapter 6. The outcome of the retinal nerve fibre layer following long-term withdrawal of vigabatrin

6.1 Previous work

It was shown in Chapter 5 that no consistent trend was present either for an improvement or for a deterioration in the visual field, for those with vigabatrin-associated visual field loss and for those exposed to vigabatrin with a normal field, who had been withdrawn from vigabatrin for a period of up to 11 years. However, only two visual field examinations had been undertaken per individual. The outcome of the visual field examination is affected by within- and between-visit variability associated with the threshold estimate and it is possible that these factors could have masked any trend. Optical coherence tomography also exhibits within- and between-examination variability but is an objective test. However, it is not known whether the peripapillary nerve fibre layer thickness remains stable or exhibits a capacity either for further deterioration or for improvement following long-term withdrawal from vigabatrin.

6.2 Aim

The aim of the study was to determine the long-term outcome of the peripapillary retinal nerve fibre layer thickness in individuals withdrawn from vigabatrin with particular reference either for further deterioration or for improvement in those with an attenuated thickness or for a deterioration in those with a previously normal thickness.
The outcome for the study was to be evaluated in terms of two aspects: the interval between the retinal nerve fibre layer examinations and the thickness of the retinal nerve fibre layer at the initial assessment. If either a worsening or an improvement in the retinal nerve fibre layer thickness was found, the extent of the alteration would be investigated with respect to the time since withdrawal from vigabatrin and to the duration and cumulative dose of vigabatrin.

6.3 Methods

6.3.1 Cohort

The study was a prospective cohort study. The cohort comprised 17 consecutively presenting individuals with refractory complex partial (focal) seizures who were attending the Alan Richens Unit, Welsh Epilepsy Centre, University Hospital of Wales, Cardiff. Each individual had been exposed to vigabatrin, had previously undergone measurement of the retinal nerve fibre layer thickness by Time-domain optical coherence tomography and had volunteered to take part in the follow-up study. No individuals manifested concomitant visual field loss of any type.

6.3.2 Optical Coherence Tomography

All individuals underwent measurement of the peripapillary retinal nerve fibre layer in the right eye, only, using an identical protocol to that undertaken at the initial examination; namely, the standard 3.4 Scan protocol of the StratusOCT (Software Version 3.0) (Carl Zeiss, Meditec, Dublin, CA). The procedures were as described in Chapter 4.
6.3.3 Visual field examination

Each individual was re-examined with Program 30-2 and the FASTPAC strategy of the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA) in an identical manner to that described in Chapters 4 and 5.

6.3.4 Statistical Analysis

Global and quadrants retinal nerve fibre layer thicknesses, automatically calculated for each scan using the commercially available StatusOCT analysis software (Version 3.0), were extracted from the print-out for each individual and inputted into an Excel spreadsheet.

6.4 Results

The age of the 17 individuals at the follow-up examination ranged from 30.0 to 68.9 years (mean 52.5 years SD 9.9; median 54.4 years; IQR 45.1, 58.6).

The interval between the baseline and follow-up examination ranged from 2.8 to 7.4 years (mean 6.1 years, SD 1.3; median 6.5 years IQR 5.8, 6.9).

Thirteen of the 17 individuals (6 males; 46 % and 7 females; 54%) had exhibited vigabatrin-associated visual field loss and corresponding retinal nerve fibre layer thinning at the baseline examination Table 6-1. Of these 13 individuals, 11 had withdrawn from vigabatrin prior to the baseline examination and 2 were receiving vigabatrin at the baseline examination. All 13 individuals had withdrawn from vigabatrin by the time of the follow-up examination.
The remaining 4 individuals, all with a normal visual field and a normal retinal nerve fibre layer thickness, had withdrawn from vigabatrin prior to the baseline examination Table 6-3.

The 17 individuals by gender and by visual field outcome at the baseline examination are given in Table 6.1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Visual Field Outcome</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>VAVFL</td>
<td>Total</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>13</td>
<td>17</td>
</tr>
</tbody>
</table>

**Table 6-1**: The 17 individuals by gender and by visual field outcome at the baseline examination. VAVFL indicates vigabatrin-associated visual field loss.

The duration of vigabatrin exposure for the 13 individuals with vigabatrin-associated visual field loss ranged from 1.9 to 17.0 years with a mean (SD) of 10.7 years (4.3). The cumulative dose ranged from 2.1 to 12.83kg with a mean (SD) of 8.0kg (3.5) (Table 6-2).
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of vigabatrin (yr)</td>
<td>10.7 (4.3)</td>
<td>12.0 (7.8, 12.8)</td>
<td>1.9</td>
<td>17.0</td>
</tr>
<tr>
<td>Cumulative dose of vigabatrin at follow-up (kg)</td>
<td>8.0 (3.5)</td>
<td>7.4 (5.6, 11.7)</td>
<td>2.1</td>
<td>12.8</td>
</tr>
<tr>
<td>Daily dose (g)</td>
<td>2.1 (0.7)</td>
<td>1.8 (1.5, 2.8)</td>
<td>1.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Interval between onset of vigabatrin and baseline OCT (yr)</td>
<td>13.2 (2.7)</td>
<td>13.1 (11.1, 15.6)</td>
<td>8.4</td>
<td>17.5</td>
</tr>
<tr>
<td>Interval between OCT (yr)</td>
<td>6.1 (1.4)</td>
<td>6.5 (5.7, 7.2)</td>
<td>2.7</td>
<td>7.4</td>
</tr>
<tr>
<td>Age at baseline (yr)</td>
<td>44.9 (9.8)</td>
<td>45.8 (39.3, 51.2)</td>
<td>23.0</td>
<td>61.0</td>
</tr>
<tr>
<td>Age at follow-up (yr)</td>
<td>50.5 (9.8)</td>
<td>50.9 (42.1, 55.7)</td>
<td>29.9</td>
<td>67.2</td>
</tr>
<tr>
<td>Interval between withdrawal of vigabatrin and follow-up OCT (yr)</td>
<td>6.6 (3.9)</td>
<td>7.0 (4.9, 8.9)</td>
<td>3.3</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Table 6-2: The summary statistics of the demographic information for the 13 individuals with vigabatrin-associated visual field loss and corresponding attenuation of the peripapillary retinal nerve fibre layer thickness at the follow-up examination.
The duration of vigabatrin exposure for the 4 individuals with normal fields ranged from 2.0 to 12.0 years with a mean (SD) of 6.9 years (4.2). The cumulative dose ranged from 1.5 to 11.1kg with a mean (SD) of 5.3kg (4.1) (Table 6-3).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of vigabatrin (yr)</td>
<td>6.9 (4.2)</td>
<td>6.7 (2.8, 11.0)</td>
<td>2.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Cumulative dose of vigabatrin at follow-up (kg)</td>
<td>5.3 (4.1)</td>
<td>4.3 (2.0, 9.7)</td>
<td>1.5</td>
<td>11.1</td>
</tr>
<tr>
<td>Daily dose (g)</td>
<td>2.0 (0.3)</td>
<td>1.9 (1.8, 2.4)</td>
<td>1.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Interval between onset of vigabatrin and baseline OCT (yr)</td>
<td>12.9 (3.4)</td>
<td>12.4 (10.0, 16.4)</td>
<td>9.2</td>
<td>17.7</td>
</tr>
<tr>
<td>Interval between OCT (yr)</td>
<td>6.0 (0.3)</td>
<td>5.9 (5.8, 6.4)</td>
<td>5.8</td>
<td>6.5</td>
</tr>
<tr>
<td>Age at baseline (yr)</td>
<td>55.2 (8.0)</td>
<td>53.9 (48.1, 63.4)</td>
<td>46.8</td>
<td>65.9</td>
</tr>
<tr>
<td>Age at follow-up (yr)</td>
<td>58.8 (7.5)</td>
<td>57.3 (52.5, 6.7)</td>
<td>51.9</td>
<td>68.9</td>
</tr>
<tr>
<td>Interval between withdrawal of vigabatrin and follow-up OCT (yr)</td>
<td>10.0 (2.2)</td>
<td>9.9 (8.0, 11.9)</td>
<td>8.0</td>
<td>12.0</td>
</tr>
</tbody>
</table>

Table 6-3: The summary statistics of the demographic information for the 4 individuals with a normal visual field at the follow-up examination.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of vigabatrin (yr)</td>
<td>9.7 (4.5)</td>
<td>11.0 (6.6, 12.5)</td>
<td>1.9</td>
<td>17.0</td>
</tr>
<tr>
<td>Cumulative dose of vigabatrin at follow-up (kg)</td>
<td>7.4 (3.7)</td>
<td>6.5 (4.3, 11.4)</td>
<td>1.5</td>
<td>12.8</td>
</tr>
<tr>
<td>Daily dose (g)</td>
<td>2.1 (0.6)</td>
<td>1.9 (1.5, 2.7)</td>
<td>1.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Interval between onset of vigabatrin and baseline OCT (yr)</td>
<td>13.1 (2.8)</td>
<td>12.8 (11.1, 15.6)</td>
<td>8.4</td>
<td>17.7</td>
</tr>
<tr>
<td>Interval between OCT (yr)</td>
<td>6.1 (1.3)</td>
<td>6.5 (5.8, 6.9)</td>
<td>2.8</td>
<td>7.4</td>
</tr>
<tr>
<td>Age at baseline (yr)</td>
<td>48.0 (10.0)</td>
<td>51.4 (40.9, 53.2)</td>
<td>23.5</td>
<td>65.9</td>
</tr>
<tr>
<td>Age at follow-up (yr)</td>
<td>52.5 (9.9)</td>
<td>54.4 (45.1, 58.6)</td>
<td>29.9</td>
<td>68.9</td>
</tr>
<tr>
<td>Age at onset of vigabatrin therapy (yr)</td>
<td>11.3 (2.1)</td>
<td>12.1 (9.4, 12.6)</td>
<td>7.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Interval between withdrawal of vigabatrin and follow-up OCT (yr)</td>
<td>7.4</td>
<td>8.0 (5.3, 10.2)</td>
<td>3.3</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Table 6-4: The summary statistics of the demographic information for the 17 individuals exposed to vigabatrin at the follow-up examination.

The difference between the baseline and follow-up peripapillary retinal nerve fibre layer thickness against the interval between the two examinations is shown in Figures 6-1 to 6-4 for the global value and for the inferior, superior nasal and temporal quadrants, respectively.
Figure 6-1: The difference in the global peripapillary retinal nerve fibre layer thickness between the follow-up and the baseline examinations against the interval between the two examinations for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination.
Figure 6-2: The difference in the inferior quadrant peripapillary retinal nerve fibre layer thickness between the follow-up and the baseline examinations against the interval between the two examinations for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination.
Figure 6-3: The difference in the superior quadrant peripapillary retinal nerve fibre layer thickness between the follow-up and the baseline examinations against the interval between the two examinations for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination.
Figure 6-4: The difference in the nasal quadrant peripapillary retinal nerve fibre layer thickness between the follow-up and the baseline examinations against the interval between the two examinations for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination.
Figure 6-5: The difference in the temporal quadrant peripapillary retinal nerve fibre layer thickness between the follow-up and the baseline examinations against the interval between the two examinations for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination.
The difference between the follow-up and baseline peripapillary retinal nerve fibre layer thickness against the difference between the baseline and follow-up MD and the difference between the baseline and follow-up CPSD are shown in Figure 6-6 and Figure 6-7, respectively.

Figure 6-6: The difference in the Mean Deviation between the follow-up and the baseline examinations against the corresponding change in the global peripapillary retinal nerve fibre layer thickness for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination.
Figure 6-7: The difference in the Corrected Pattern Standard Deviation between the follow-up and the baseline examinations against the corresponding change in the global peripapillary retinal nerve fibre layer thickness for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination.
The lack of relationship between the change in the retinal nerve fibre layer between the follow-up and the baseline examinations and the interval between the optical coherence tomography for those with vigabatrin-associated visual field loss was present regardless of whether the individuals had been withdrawn from, or were receiving vigabatrin, at baseline ($R^2 = 0.04$, $R^2 = 0.02$, $R^2 = 0.11$, $R^2 = 0.11$, and $R^2 = 0.02$ for the global, inferior, superior, nasal and temporal quadrants, respectively) (Table 6-5).

The mean (SD) of the difference in the peripapillary retinal nerve fibre layer thickness, globally and by quadrant, between the baseline and follow-up examinations for the 13 individuals with vigabatrin-associated visual field loss and for the 4 individuals with a normal visual field are given in Table 6-6 (Top and Bottom).
<table>
<thead>
<tr>
<th>Characteristics of individuals with vigabatrin-associated visual field loss</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global (µm)</td>
<td>-4.8 (8.8)</td>
<td>-3.3 (-10.5, 0.9)</td>
<td>-22.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Inferior quadrant (µm)</td>
<td>-10.1 (18.0)</td>
<td>-8.0 (-21.5, 7.0)</td>
<td>-48.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Superior quadrant (µm)</td>
<td>-8.8 (9.2)</td>
<td>-8.0 (-15.5, 0.0)</td>
<td>-24.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Nasal quadrant (µm)</td>
<td>1.6 (19.1)</td>
<td>6.0 (-5.0, 12.0)</td>
<td>-42.0</td>
<td>36.0</td>
</tr>
<tr>
<td>Temporal quadrant (µm)</td>
<td>-1.4 (8.1)</td>
<td>-3.0 (-7.0, 3.5)</td>
<td>-15.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Mean Deviation MD (dB)</td>
<td>-0.8 (2.5)</td>
<td>-0.8 (-2.3, 0.7)</td>
<td>-6.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Corrected Pattern Standard Deviation (dB)</td>
<td>0.3 (2.0)</td>
<td>0.7 (-1.2, 1.3)</td>
<td>-3.2</td>
<td>4.7</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Characteristics of individuals with a normal field</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global (µm)</td>
<td>4.9 (20.4)</td>
<td>-2.8 (-8.3, 25.8)</td>
<td>-9.9</td>
<td>35.0</td>
</tr>
<tr>
<td>Inferior quadrant (µm)</td>
<td>5.5 (29.2)</td>
<td>-7.0 (-12.0, 35.0)</td>
<td>-13.0</td>
<td>49.0</td>
</tr>
<tr>
<td>Superior quadrant (µm)</td>
<td>-1.7 (19.8)</td>
<td>-6.0 (-17.7, 18.5)</td>
<td>-21.0</td>
<td>26.0</td>
</tr>
<tr>
<td>Nasal quadrant (µm)</td>
<td>20.3 (20.0)</td>
<td>13.0 (6.3, 41.5)</td>
<td>6.0</td>
<td>49.0</td>
</tr>
<tr>
<td>Temporal quadrant (µm)</td>
<td>0.5 (15.7)</td>
<td>-1.0 (-15.3, 14.7)</td>
<td>-17.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Mean Deviation MD (dB)</td>
<td>-0.04 (1.4)</td>
<td>0.1 (-1.5, 1.2)</td>
<td>-1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Corrected Pattern Standard Deviation (dB)</td>
<td>0.9 (1.2)</td>
<td>1.2 (-0.4, 1.8)</td>
<td>-0.9</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Table 6-6: The summary statistics of the differences in the peripapillary retinal nerve fibre layer thickness between the follow-up and baseline examination, globally, and by quadrant; and of the differences in the Mean Deviation and Corrected Pattern Standard Deviation visual field indices for the 13 individuals with vigabatrin-associated visual field loss (top) and for the 4 individuals with a normal field and a normal retinal nerve fibre layer (bottom).
The retinal nerve fibre layer thickness at the follow-up examination against that at the baseline examination for the 13 individuals with vigabatrin associated visual field loss is illustrated in Figure 6-8 to Figure 6-12 for global, inferior, superior, nasal and, temporal quadrants, respectively.

Figure 6-8: The global retinal nerve fibre layer thickness at the follow-up examination against that at the baseline examination for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination.
Figure 6-9: The inferior quadrant retinal nerve fibre layer thickness at the follow-up examination against that at the baseline examination for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination.
Figure 6-10: The nasal quadrant retinal nerve fibre layer thickness at the follow-up examination against that at the baseline examination for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination.
Figure 6-11: The superior quadrant retinal nerve fibre layer thickness at the follow-up examination against that at the baseline examination for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination.
Figure 6-12: The temporal quadrant retinal nerve fibre layer thickness at the follow-up examination against that at the baseline examination for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination.
The Mean ±2SD of the difference in the global, the inferior, superior, nasal and temporal retinal nerve fibre layer thickness, between the follow-up and the baseline examinations, for the 13 individuals with vigabatrin-associated visual field loss, are given in Figure 6-13 to Figure 6-17 global, respectively.

Figure 6-13: The difference in the global peripapillary retinal nerve fibre layer thickness between the follow-up examination and the baseline examination against the mean of the two examinations for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean.
Figure 6-14: The difference in the inferior quadrant peripapillary retinal nerve fibre layer thickness between the follow-up examination and the baseline examination against the mean of these examinations for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean.
Figure 6-15: The difference in the superior quadrant peripapillary retinal nerve fibre layer thickness between the follow-up examination and the baseline examination against the mean of these examinations for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean.
Figure 6-16: The difference in the nasal quadrant peripapillary retinal nerve fibre layer thickness between the follow-up examination and the baseline examination against the mean of these examinations for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean.
Figure 6-17: The difference in the temporal quadrant peripapillary retinal nerve fibre layer thickness between the follow-up examination and the baseline examination against the mean of these examinations for the 13 individuals with vigabatrin-associated visual field loss and an attenuated retinal nerve fibre layer. The filled symbols indicate each of the 11 individuals who had withdrawn from vigabatrin prior to the baseline examination and the open symbols each of the 2 individuals who were receiving vigabatrin at the time of the baseline examination. The solid black line represents the mean of the differences and the dotted black lines +/- 2SD of the mean.
The difference between the follow-up and baseline peripapillary retinal nerve fibre layer thickness for 4 individuals with a normal field against the interval between the two examinations are shown in Figure 6-18 to Figure 6-22 for the global value and for the inferior, superior nasal, temporal quadrants respectively.

**Figure 6-18:** The difference in the global retinal nerve fibre thickness between the follow-up and the baseline examinations against the interval between the two examinations for the 4 individuals with normal fields. All individuals were withdrawn from vigabatrin prior to the baseline examination.
Figure 6-19: The difference in the retinal nerve fibre thickness of the inferior quadrant between the follow-up and the baseline examinations against the interval between the two examinations for the 4 individuals with normal fields. All individuals were withdrawn from vigabatrin prior to the baseline examination.
Figure 6-20: The difference in the retinal nerve fibre thickness of the superior quadrant between the follow-up and the baseline examinations against the interval between the two examinations for the 4 individuals with normal fields. All individuals were withdrawn from vigabatrin prior to the baseline examination.
Figure 6-21: The difference in the retinal nerve fibre thickness of the nasal quadrant between the follow-up and the baseline examinations against the interval between the two examinations for the 4 individuals with normal fields. All individuals were withdrawn from vigabatrin prior to the baseline examination.
Figure 6-22: The difference in the retinal nerve fibre thickness of the temporal quadrant between the follow-up and the baseline examinations against the interval between the two examinations for the 4 individuals with normal fields. All individuals were withdrawn from vigabatrin prior to the baseline examination.
The Mean of the retinal nerve fibre layer at the follow-up examination, for an individual, against that at the baseline examination for the 4 individuals with vigabatrin-associated visual field loss is illustrated in Figure 6-23 to Figure 6-29 for the global, inferior, superior, nasal and, temporal quadrants, respectively.

Figure 6-23: The mean of the global retinal nerve fibre thickness at the follow-up examination against that at the baseline examination for the 4 individuals with normal fields. All individuals were withdrawn from vigabatrin prior to the baseline examination.
Figure 6-24: The mean of the retinal nerve fibre thickness of the inferior quadrant at the follow-up examination against that at the baseline examination for the 4 individuals with normal fields. All individuals were withdrawn from vigabatrin prior to the baseline examination.
Figure 6-25: The mean of the retinal nerve fibre thickness of nasal quadrant at the follow-up examination against that at the baseline examination for the 4 individuals with normal fields. All individuals were withdrawn from vigabatrin prior to the baseline examination.
Figure 6-26: The mean of the retinal nerve fibre thickness of superior quadrant at the follow-up examination against that at the baseline examination for the 4 individuals with normal fields. All individuals were withdrawn from vigabatrin prior to the baseline examination.
Figure 6-27: The mean of the retinal nerve fibre thickness of temporal quadrant at the follow-up examination against that at the baseline examination for the 4 individuals with normal fields. All individuals were withdrawn from vigabatrin prior to the baseline examination.
6.5 Discussion

The outcome of any study of retinal nerve fibre layer is influenced by the number of optical coherence tomography examinations within the given time period and by the length of the time period, itself. Clearly, the conclusions that can be obtained from a time period which involves only two optical coherence tomography examinations are limited.

If no alteration occurred in the retinal nerve fibre layer thickness between the two examinations, and given that it would be unlikely that the given pairs of measurements would exhibit identical values, one half of the individuals would exhibit an apparent deterioration at the follow-up examination and one half would exhibit an apparent improvement at the follow-up examination. Clearly, either a ‘true’ deterioration or a ‘true’ improvement would be indicated by a greater proportion of individuals exhibiting the particular trend/ direction.

In the current study, the median of the difference in the global retinal nerve fibre layer thickness between the two examinations for the 13 individuals with vigabatrin-associated visual field loss was -3.3μm, i.e., an apparent thinning at the follow-up examination. The corresponding value for each of the four quadrants ranged between 6μm (i.e., an apparent increase in thickness) and -8μm. These values lie within the corresponding test-retest variability, using the same protocol as the current study for 5 sessions over a two month period, for the retinal nerve fibre layer thickness of individuals with stable open angle glaucoma (Budenz et al., 2008) and within the axial resolution of approximately 8-10μm of Time-domain optical coherence tomography.
Similar, or slightly smaller, values were also obtained for the individuals exposed to vigabatrin but with normal fields.

Interestingly, only three of the thirteen individuals exhibited an apparent deterioration in both the Mean Deviation of the visual field and the retinal nerve fibre layer. Of the three individuals, two exhibited a worsening in the MD of approximately 2.8dB, which is inside the value of 3.0dB often used as an empirical cut-off value for visual field progression, and a reduction in the retinal nerve fibre layer thicknesses of approximately 20μm and of approximately 5μm, respectively. The remaining individual exhibited only a modest worsening of the Mean Deviation, of 0.9dB, and a reduction in the retinal nerve fibre layer thickness of approximately 23μm.

Clearly, there is no recovery of the attenuated retinal nerve fibre layer arising from vigabatrin and no recovery of the visual field following long-term withdrawal from vigabatrin for up to 8 years, i.e., the damage is irreversible.

It is highly unlikely that an improvement would occur in the retinal nerve fibre layer without an improvement in the visual field and vice versa.

It has been suggested that measurement of the retinal nerve fibre layer thickness using optical coherence tomography provides a highly sensitive and specific technique for the detection of vigabatrin ocular toxicity (Lawthom et al., 2009; Clayton et al., 2011; Clayton et al., 2012). The medians of the respective differences in the retinal nerve fibre layer between examinations conducted approximately six years apart were remarkably small. This suggests that prospective optical coherence tomography of the retinal nerve fibre layer would provide a sensitive marker for the emergence of vigabatrin ocular
toxicity, particularly with spectral-domain optical coherence tomography which exhibits better test-retest reliability than Time-domain optical coherence tomography used in the current study (Budenz et al., 2008; Tzamalis et al., 2009; Garcia-Martin et al., 2012; Polo et al., 2014). Such an approach would be undertaken in conjunction with standard automated perimetry and could be facilitated by a joint probability analysis.

### 6.6 Conclusion

Overall, and within the limits both of the number of examinations and of the limited number of individuals within the cohort, no convincing evidence was found for either a deterioration or for an improvement in either the visual field or the retinal nerve fibre layer thickness following long-term (median 8 years) withdrawal from vigabatrin, i.e., the damage associated with vigabatrin is irreversible.
Chapter 7. The Macular Complex thickness of individuals exposed to vigabatrin

7.1 Introduction

The integrity of the macula in vigabatrin ocular toxicity has received little attention particularly in regard to high resolution imaging. The presence of an epiretinal membrane at the macula in those with vigabatrin-associated visual field loss has been noted in several reports but does not appear to be a common manifestation (Krauss and Miller, 1999; Suarez-Baraza and Suarez-Parra, 2007).

Conventional high contrast visual acuity in those with vigabatrin-associated visual field loss is considered to be within the normal range (Nousiainen, Kalviainen and Mantyjarvi, 2000b; Hilton et al., 2002). However, in one study, spatial contrast sensitivity, measured with the Pelli-Robson chart, was positively correlated with the extent of the remaining temporal field in individuals treated with vigabatrin monotherapy (Nousiainen et al 2000). In another study, eight of 12 individuals exposed to vigabatrin exhibited non-specific but predominantly higher spatial frequency attenuation in contrast sensitivity when measured with the CSV-1000 test which consists of four rows of eight paired circular test patches (one of the pair does not contain a grating) that decrease in contrast from left to right and increase in spatial frequency from top to bottom; however only 2 of the 12 individuals had received vigabatrin monotherapy (Hilton et al 2002).
Several studies have reported the presence of colour vision abnormalities in some individuals exposed to vigabatrin; such abnormalities are either non-specific (Hilton et al., 2002) or along the tritanopic axis (Nousiainen, Kalviainen and Mantyjarvi, 2000a). The latter, although interesting, is confounded by the fact that a tritanopic defect can also be found after a single 2000mg exposure to vigabatrin in normal individuals (Nousiainen et al., 2000b) and also in individuals with epilepsy treated with carbamazepine (Nousiainen et al., 2000b).

Given, the presence, and the equivocal nature, of the above studies, it seemed reasonable to undertake an assessment of the macular complex thickness in individuals exposed to vigabatrin.

In addition, during the evolution of the study, several studies implicated damage to the macular ganglion cells in primary open angle glaucoma, manifested as a reduction in the thickness of the macular ganglion cell/ inner plexiform layer complex (Tan et al., 2009; Hood et al., 2012; Hood et al 2013). The association between vigabatrin toxicity and retinal ganglion cell dysfunction, described in Chapter 4, together with these recent findings in glaucoma, provided further rationale for the investigation of macular complex thickness.

7.2 Aim

The primary aim of the study, therefore, was to compare the macular thickness of individuals with vigabatrin-associated visual field loss to the macular thickness of those exposed to vigabatrin but exhibiting a normal visual field.
The secondary aim of the study was to determine any association between the macular thickness and the peripapillary retinal nerve fibre layer thickness in those exhibiting vigabatrin-associated visual field loss and in those exposed to vigabatrin but exhibiting a normal visual field.

7.3 Methods

The study was a prospective cross-sectional cohort study.

7.3.1 Cohort

The cohort comprised 52 consecutively presenting individuals with refractory complex partial (focal) seizures who had been exposed to vigabatrin and who were attending the Alan Richens Unit, Welsh Epilepsy Centre, University Hospital of Wales, Cardiff.

7.3.2 Optical Coherence Tomography

All individuals underwent measurement of the peripapillary retinal nerve fibre layer in each eye using the standard 3.4 Scan protocol and the Fast Macular Thickness Map protocol of the StratusOCT (Software Version 3.0) (Carl Zeiss, Meditec, Dublin, CA).

The scan pattern for the Fast Macular Thickness Map protocol consists of six equally separated radial line scans, centred on the fovea, which each covering a diameter of 6mm. TD-OCT defines retinal thickness as the distance from the surface of the inner limiting membrane to the boundary between the inner and outer segments of the photoreceptors. The Fast Macular Thickness Map protocol was used since, although the resolution is lower compared to the Macular Thickness Map (128 A/B-scan compared to 512 A/B-scan), the scan time is faster (1.92 seconds for the entire scan compared to 1.28
seconds for each radial line). The analysis software provides a thickness for each of three annuli (within 1.0mm diameter, between 1.0 and 3.0mm diameter and between 3.0 and 6.0mm diameter, respectively) which are further divided into inferior, superior, nasal and temporal quadrants, respectively thereby enabling nine separate measurements. This division has become a standard following its use in the Early Treatment of Diabetic Retinopathy Study (ETDRS) (Huang et al., 2011) (Figure 7-1).

7.3.3 Visual Field Examination

Each individual underwent visual field examination with Program 30-2 and the FASTPAC strategy of the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA) in an identical manner to that described in Chapters 4, 5, and 6.

![Figure 7-1: The sectors of the Fast Macular Thickness scan of the StratusOCT. SQ indicates the superior quadrant, IQ indicates the inferior quadrant, NQ indicates the nasal quadrant, and TQ indicates the temporal quadrant.](image)

The pupil was dilated, if necessary, with one drop of 0.5% tropicamide and one drop of 2.5% phenylephrine hydrochloride. Individuals were instructed to fixate the external
fixation target which was suitably positioned by the operator to ensure optimum centration of the scan on the optic nerve head. The polarization and Z-axis offset were optimised to gain maximum reflection of the signal. Between three and six images were retained for each individual. The retained images were free from blink or movement artefacts and had a signal to noise ratio of $\geq 33$dB. All images were acquired by a senior medical photographer highly experienced in optical coherence tomography.

The image exhibiting the best placement of the scan centre, compatible with the maximum signal to noise ratio, was then selected for each individual by the Author and by Professor Wild independently of each other. In cases of discordance between, the images for the given individual a consensus was reached following a discussion.

7.3.4 Statistical Analysis

Global and quadrant retinal nerve fibre layer thicknesses and the 9 separate macular thicknesses, automatically calculated for each given scan using the commercially available StatusOCT analysis software (Version 3.0), were extracted from the print-out for each individual and inputted into an Excel spreadsheet.

The difference in the outcome of the macular thickness at each of the 9 sectors between those with vigabatrin-associated visual field loss and those exposed to vigabatrin but with normal fields was undertaken using a two-tailed Student’s t test for independent samples. Given that the study was observational in nature, no correction was made for the possibility of a Type I error arising amongst the 9 comparisons for each eye. Similarly, no correction was made for the inclusion of the two eyes from each individual within the study.
The linearity of any association between the sectorial macular thickness and the peripapillary retinal nerve fibre layer thickness was expressed by the Pearson correlation coefficient, r. Similarly, the linearity of any association between the macular thickness, averaged across the 9 sectors, and the Mean Deviation visual field index was expressed by the Pearson correlation coefficient, r.

7.4 Results

Thirty two of the 52 individuals exhibited vigabatrin-associated visual field loss (17 females [53.1%), 15 males [46.9%] p<0.24). Six individuals exhibited additional homonymous quadrant loss and were excluded from the analysis. Fourteen individuals exhibited a normal field.

The demographic characteristics of the remaining 46 individuals are given in Table 7-1. The 46 individuals comprised 27 females (58.7%) and 19 males (41.3) aged 19 to 72 years with a mean (SD) age of 47 years (11.3) and a median (IQR) of 47.6 years (41.4, 57.4).

The macular thickness in each eye for those with and without vigabatrin-associated visual field loss is given in Table 7-2. None of the paired comparisons, in either eye, between those with and those without vigabatrin-associated visual field loss reached statistical significance.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Visual field outcome</th>
<th>Normal</th>
<th>VAVFL</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of individuals</td>
<td></td>
<td>14</td>
<td>32</td>
<td>46</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Male</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td></td>
<td>Mean (SD)</td>
<td>45.2 (9.5)</td>
<td>48.7 (11.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (IQR)</td>
<td>43.9 (39.5, 49.9)</td>
<td>50.0 (41.8, 57.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>32.3-65.5</td>
<td>22.8-72.5</td>
</tr>
<tr>
<td>Cumulative dose of vigabatrin (kg)</td>
<td></td>
<td>Mean (SD)</td>
<td>4.7 (4.7)</td>
<td>7.2 (5.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (IQR)</td>
<td>2.7 (1.2, 8.1)</td>
<td>7.3 (2.3, 11.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>0.06-14.2</td>
<td>0.3-19.0</td>
</tr>
<tr>
<td>Duration of vigabatrin (yrs)</td>
<td></td>
<td>Mean (SD)</td>
<td>5.9 (4.6)</td>
<td>8.1 (4.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (IQR)</td>
<td>5.7 (1.3, 9.8)</td>
<td>8.7 (4.9, 11.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>0.08-13.6</td>
<td>0.3-16.0</td>
</tr>
<tr>
<td>Interval from withdrawal of vigabatrin (yrs)</td>
<td></td>
<td>Mean (SD)</td>
<td>10.0 (4.9)</td>
<td>7.7 (2.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (IQR)</td>
<td>9.0 (5.7, 14.5)</td>
<td>7.2 (6.3, 8.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>4.5-18.8</td>
<td>3.0-17.6</td>
</tr>
<tr>
<td>MD average of both eyes (dB)</td>
<td></td>
<td>Mean (SD)</td>
<td>-0.8 (1.3)</td>
<td>-10.5 (5.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (IQR)</td>
<td>-0.4 (-1.5, 0.04)</td>
<td>-11.4 (-14.3, -4.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>-4.9-0.4</td>
<td>-21.7—21</td>
</tr>
<tr>
<td>PSD averaged of both eyes (dB)</td>
<td></td>
<td>Mean (SD)</td>
<td>2.0 (0.6)</td>
<td>9.1 (3.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (IQR)</td>
<td>2.1 (1.8, 2.4)</td>
<td>10.0 (5.2, 12.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>1.1-2.8</td>
<td>2.5-14.7</td>
</tr>
</tbody>
</table>

Table 7-1: The summary statistics, mean, standard deviation (SD) median, interquartile range (IQR) and range, for the demographic characteristics of the 46 individuals exposed to vigabatrin by visual field outcome (VAVFL indicates vigabatrin-associated visual field loss. MD indicates Mean Deviation, PSD indicates Pattern Standard Deviation).

The Coefficient of Determination for the association between each sectoral macular thickness and the corresponding peripapillary retinal nerve fibre layer thickness for the 32 individuals with vigabatrin-associated visual field loss and for the 14 individuals exposed to vigabatrin but exhibiting normal fields in is given in Table 7-3.
The strongest associations were present, as might be expected, between the temporal quadrant of the optic nerve head and the 3 and 6mm annuli nasal sectors of the macular thickness in the right eye (R² =0.291 and R² =0.20, respectively, for those with vigabatrin-associated visual field loss; and R² =0.27 and R² =0.18 for those with normal fields). However, surprisingly, no association was present for the left eye.

The Coefficient of Determination for the association between the macular thickness averaged across the 9 sectors and the global peripapillary retinal nerve fibre layer thickness was 0.03 and 0.00 for the right and left eyes, respectively, for the 32 individuals with vigabatrin-associated visual field loss and 0.04 and 0.03, respectively, for the 14 individuals exposed to vigabatrin but exhibiting normal fields, i.e., no correlation, whatsoever.
<table>
<thead>
<tr>
<th>Region</th>
<th>Right Eye</th>
<th>Left Eye</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VAVFL</td>
<td>Normal</td>
<td>p</td>
<td>VAVFL</td>
<td>Normal</td>
<td>p</td>
</tr>
<tr>
<td>Central annulus (within 1.0 mm)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 (29)</td>
<td>188 (20)</td>
<td>0.14</td>
<td>204 (30)</td>
<td>187 (19)</td>
<td>0.09</td>
</tr>
<tr>
<td>Inner annulus (between 1.0mm and 3.0 mm)</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Inferior (µm)</td>
<td>253 (17)</td>
<td>245 (27)</td>
<td>0.98</td>
<td>249 (26)</td>
<td>253 (14)</td>
<td>0.76</td>
</tr>
<tr>
<td>Nasal (µm)</td>
<td>252 (18)</td>
<td>256 (16)</td>
<td>0.21</td>
<td>260 (21)</td>
<td>254 (15)</td>
<td>0.58</td>
</tr>
<tr>
<td>Superior (µm)</td>
<td>255 (20)</td>
<td>256 (18)</td>
<td>0.97</td>
<td>257 (17)</td>
<td>256 (17)</td>
<td>0.77</td>
</tr>
<tr>
<td>Temporal (µm)</td>
<td>240 (21)</td>
<td>241 (17)</td>
<td>0.92</td>
<td>243 (22)</td>
<td>241 (13)</td>
<td>0.67</td>
</tr>
<tr>
<td>Outer annulus (between 3.0mm and 6.0 mm)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior (µm)</td>
<td>212 (15)</td>
<td>213 (20)</td>
<td>0.49</td>
<td>211 (17)</td>
<td>215 (20)</td>
<td>0.61</td>
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<tr>
<td>Nasal (µm)</td>
<td>234 (21)</td>
<td>239 (20)</td>
<td>0.79</td>
<td>236 (18)</td>
<td>243 (21)</td>
<td>0.70</td>
</tr>
<tr>
<td>Superior (µm)</td>
<td>223 (17)</td>
<td>226 (18)</td>
<td>0.68</td>
<td>222 (16)</td>
<td>226 (18)</td>
<td>0.50</td>
</tr>
<tr>
<td>Temporal (µm)</td>
<td>205 (15)</td>
<td>208 (16)</td>
<td>0.68</td>
<td>211 (19)</td>
<td>204 (15)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Table 7-2: Macular thickness (Stratus OCT Fast Macular Thickness scan) in each eye for each of the 9 sectors for the 32 individuals with vigabatrin-associated visual field loss and for the 14 individuals exposed to vigabatrin but with a normal field and the accompanying probability value derived by a two-tailed Student’s t test for independent samples.
<table>
<thead>
<tr>
<th>#</th>
<th>Quadrant</th>
<th>VAVFL Right Eye</th>
<th>VAVFL Left Eye</th>
<th>Normal field Right Eye</th>
<th>Normal field Left Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Inferior quadrant RNFL</td>
<td>0.011</td>
<td>0.00</td>
<td>0.28</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Inferior quadrant 3mm ring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Inferior quadrant RNFL</td>
<td>0.012</td>
<td>0.001</td>
<td>0.2</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Inferior quadrant 6mm ring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Temporal quadrant RNFL</td>
<td>0.29</td>
<td>0.10</td>
<td>0.27</td>
<td>0.086</td>
</tr>
<tr>
<td></td>
<td>Nasal quadrant 3mm ring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Temporal quadrant RNFL</td>
<td>0.20</td>
<td>0.03</td>
<td>0.18</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Nasal quadrant 6mm ring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Superior quadrant RNFL</td>
<td>0.006</td>
<td>0.00</td>
<td>0.33</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>Superior quadrant 3mm ring</td>
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<tr>
<td>6</td>
<td>Superior quadrant RNFL</td>
<td>0.00</td>
<td>0.01</td>
<td>0.27</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>Superior quadrant 6mm ring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7-3: The Coefficient of Determination, $R^2$, for the association between the peripapillary retinal nerve fibre layer thickness and the macular thickness for the 32 individuals with vigabatrin-associated visual field loss and for the 14 individuals exposed to vigabatrin but with a normal field.
7.5 Discussion

Optical coherence tomography (OCT) has become an important technique for detecting and monitoring macular changes (Bijlsma and Stilma, 2005) and provides repeatable measurements (Massin et al., 2001; Muscat et al., 2002; Virgili et al., 2007).

The results indicate that there was no difference in the macular thickness between those with vigabatrin-associated visual field loss and those exposed to vigabatrin but with a normal field for any one of the nine sectors.

Unfortunately, the manufacturer of the StratusOCT has not produced a database of age-corrected normative values of the macular thickness. Given the advent of the higher resolution Spectral domain optical coherence tomography during the course of this Thesis and given the similarity of the thickness values in each sector between those with and without vigabatrin-associated visual field loss, it was decided not to undertake the time consuming task of establishing an age-corrected normative database for the nine sectors in each eye for StratusOCT. The more recent Spectral domain optical coherence tomographers, which have superseded the Time-domain optical coherence tomographers, all possess normative databases for the macular thickness and for the number of macular ganglion cells.

Three studies describe normative values for macular thickness with the Fast Macular Thickness scan of the StratusOCT although one of these (Duan et al., 2010) is from Chinese eyes; the values from the other two studies are listed in Table 7-4. The group median (Grover et al., 2010) or group mean (SD) (Kelty et al., 2008) macular thickness derived from each of the two studies on Caucasian individuals are compared with the
group mean from the current study in those with and without vigabatrin-associated visual field loss. It can be seen from Table that the normal values for macular thickness derived by Kelty et al (2008) are lower than those derived by Grover et al (2010). These differences are unlikely to be explained by the differences in age between the two cohorts or by the difference between the median and mean. In addition, it can be seen from the same Table that the macular thickness of those with vigabatrin-associated visual field loss and of those exposed to vigabatrin but with normal fields are substantially lower than the normal values of either Kelty et al (2008) or Gover et al (2010).
Table 7-4: The group median (Grover. et al., 2010) and group mean (SD) (Kelty et al., 2008) normal values of macular and foveal thickness, by sector, compared to the group mean macular and foveal thicknesses for those with vigabatrin-associated visual field loss and for those exposed to vigabatrin but with normal fields.

Given the involvement of the retinal ganglion cells in the pathophysiology of vigabatrin ocular toxicity, it can be speculated that the reduction in the macular thickness present in both groups can be attributed to a reduction in the number of ganglion cells at the macular.
The retinal ganglion cells and their axons constitute 30-35% of the macular thickness. Approximately 50% of the retinal ganglion cells are located within 4 to 5 mm from the centre of the fovea (Curcio and Allen, 1990) and the peak density occurs at an eccentricity of between 750 and 1100µm where the cell density may be 4 to 6 soma thick (Wässle et al., 1989).

A reduction in the macular thickness, due to atrophy of the ganglion cells and axons, has long been noted in glaucoma (Curcio and Allen, 1990; Zeimer et al., 1998; Guedes et al., 2003). Macular thickness measurements in glaucoma, determined by Time-domain optical coherence tomography, correlate well with the outcome of the visual field (Greenfield, Bagga and Knighton, 2003; Seiji et al., 2011) and with those determined by scanning laser ophthalmoscopy and correlate well with other structural parameters (Seiji et al., 2011). The advent of Spectral domain optical coherence tomography, which enables segmentation of the retinal ganglion cells at the macula, has shown that, in early glaucoma, both deep local, and shallow widespread, retinal nerve fibre damage of the macular region is present (Hood et al., 2014). The localised retinal ganglion cell loss is associated with localised visual field loss, having accounted for the displacement of the retinal ganglion cells from the foveal centre (Hood et al., 2013). The damage to the retinal ganglion cell layer is typically arcuate and is often associated with localised peripapillary nerve fibre layer thinning at a narrow region of the inferior quadrant of the disc labelled the macular vulnerability zone (MVZ). A small (cecocentral) region of the inferior macula, and all of the superior macula (inferior visual field), project to the temporal quadrant, a region that is less susceptible to damage (Hood et al., 2013). The damage to the retinal ganglion cell complex can be easily overlooked by standard automated perimetry using the 6° square stimulus grid of Program 24-2 or 30-2. Reduced ganglion cell attenuation occurs in the presence of a
normal MD by Program 24-2 (Hood et al., 2012). The use of Program 10-2 is now advocated for the investigation of early glaucoma (Hood et al., 2012; Traynis et al., 2014) along with combined probability maps of the visual field and ganglion cell layer outcomes (Hood et al., 2012) when the stimulus locations are adjusted to account for the displacement of the ganglion cell soma around the fovea (Hood and Raza, 2011). From a perimetric perspective, more than 50% of the eyes with predominantly mild to moderate glaucomatous field loss exhibit abnormality in the immediate superior paracentral region within an eccentricity of 3° (Schiefer et al., 2010). In addition, 9% of either glaucoma suspects or individuals with early glaucoma will be classified as normal when evaluated with Program 30-2 compared to Program (10-2) and the severity of glaucomatous damage will be underestimated in 13% of the hemifields (Traynis et al., 2014).

Clearly, with the advent of spatially- and time-encoded frequency domain OCT, the clinical utility of the dataset recorded by Time domain optical coherence tomography in the present study, is limited. However, the similarity of the macular thickness values between those with and without vigabatrin-associated visual field loss, the suggestion that both sets of values are lower than those found in the normal eye and the findings from Chapter Six which indicate that vigabatrin ocular toxicity is associated with a bilateral optic neuropathy, indicate the direction of future work. A study should be undertaken using Program 10-2, or even a more appropriate customised test for macular function, and either Spectral domain optical coherence tomography or swept source optical coherence tomography which would evaluate the structural and functional outcomes in individuals commencing vigabatrin therapy, in those previously and/ or currently exposed to vigabatrin but with apparently normal fields, and in those with vigabatrin-associated visual field loss. If it can be shown that the time course of the
vigabatrin toxicity is such as to affect the ganglion cell layer at the macula prior to the more immediate periphery, then a macular investigation protocol incorporating both perimetry and Spectral domain optical coherence tomography, segmented for ganglion cell soma and/or axonal count, could be used at regular intervals for those newly treated with vigabatrin. Any indication of a macular abnormality, either by perimetry or by optical coherence tomography, or both, would result in withdrawal from vigabatrin without loss of the more peripheral visual field. Such an approach would be of considerable benefit to both individuals and clinicians, alike.
Chapter 8. Summary of the studies and conclusions

8.1 Modelling the risk of visual field loss arising from long-term exposure to vigabatrin: a cross-sectional approach

The study described in Chapter Three was the first to evaluate the visual field outcome after long-term therapy with vigabatrin. The risk (frequency) of vigabatrin-associated visual field loss was assessed in terms of cumulative dose and duration of vigabatrin. The cohort comprised 147 adults with refractory complex partial (focal) seizures. The median duration of vigabatrin therapy was 7.9 years (IQR 3.6, 11.0) and the median cumulative dose 5.8kg (IQR 2.5, 8.7).

The frequency of vigabatrin-associated visual field loss increased with increase in cumulative dose and in treatment duration, reaching a frequency of 75-80% at approximately 5kg dose or 6 years of therapy; however, cumulative dose seemed to exert a greater influence than duration.

The frequency was substantially higher than the ‘consensus’ figure of 30-40% and substantially increases the risk-benefit of treatment with vigabatrin and, with the greater requirement for more clinical examinations, increases the cost-benefit of the drug (Wild et al., 2013).
8.2 Topographical variations in the ganglion cell structural and functional association in vigabatrin toxicity

The study described in Chapter Four determined the relationship, in individuals with vigabatrin-associated visual field loss and in individuals exposed to vigabatrin but with normal fields, between the functional and structural outcomes expressed in terms of the number of residual ganglion cell soma derived by standard automated perimetry and of the number of residual ganglion cell axons derived by Time-domain optical coherence tomography. The cohort comprised 40 consecutively presenting individuals who had previously been treated with vigabatrin for refractory complex partial (focal) seizures and who had volunteered to take part in the study. Two control groups, namely, 18 individuals with open angle glaucoma and 22 normal individuals were used for comparative purposes.

A strong linear association was present between the number of residual ganglion cell soma derived by standard automated perimetry and the number of residual ganglion cell axons derived by the Time-domain optical coherence tomography. The trend lay slightly above the line of unity indicating a slightly greater estimate of ganglion cell soma compared to ganglion cell axons. A similar strong linear association was present, as expected, for the individuals with open angle glaucoma and confirms that found by others (Hood et al., 2007; Hood and Kardon, 2007; Hood et al., 2008; Medeiros et al., 2012a; Medeiros et al., 2012b). Derivation of the association by sector of the optic nerve head was limited by the undersampling of the stimulus locations of the Humphrey Field Analyzer Program 24-2.
The findings indicate that vigabatrin-associated ocular toxicity causes an optic neuropathy; however; it is not known whether the mechanism is of primary or secondary in nature.

8.3 The outcome of the visual field following long-term withdrawal of vigabatrin

The study described in Chapter Five determined the outcome of the long-term visual field examination in relation to the time-course of exposure to vigabatrin with particular reference either for further deterioration or for improvement in those with vigabatrin-associated visual field loss or for a deterioration in those with previously normal fields. The final cohort comprised 27 individuals, 19 of whom had vigabatrin-associated visual field loss and 8 who had been exposed to vigabatrin but manifested normal fields. All individuals were off-drug at the time of the follow-up visual field examination. The median length of withdrawal from vigabatrin, at the time of the follow-up examination was 7.1 years (IQR 5.4, 8.4). The median interval between the baseline and follow-up examinations was 7.0 years (IQR 6.5, 7.6).

Within the limits of the size of the cohort, and of the two visual field examinations, i.e., at baseline and at follow-up, vigabatrin-associated visual field loss did not appear, overall, to show either a worsening or an improvement relative to that at baseline. Similarly, those individuals exposed to the drug but with normal fields at baseline did not manifest any subsequent deterioration.
8.4 The outcome of the retinal nerve fibre layer following long-term withdrawal of vigabatrin

The study described in Chapter Six determined the outcome of long-term Time-domain optical coherence tomography imaging in relation to the time-course of exposure to vigabatrin with particular reference either for further deterioration or for improvement in the retinal nerve fibre layer thickness. The final cohort comprised 17 individuals, 13 of whom had vigabatrin-associated visual field loss and 4 who had been exposed to vigabatrin but manifested normal fields. All individuals were off-drug at the time of the follow-up examination. The median length of withdrawal from vigabatrin, at the time of the follow-up examination, was 8.0 years (IQR 5.3, 10.2). The median interval between the baseline and follow-up examinations was 6.5 years (IQR 5.8, 6.9).

Within the limits of the size of the cohort, and of the two optical coherence tomography examinations, i.e., at baseline and at follow-up, the retinal nerve fibre layer thickness did not appear, overall, to show either a worsening or an improvement relative to that at baseline in either those with vigabatrin-associated visual field loss or in those individuals exposed to the drug but with normal fields.

8.5 Macular thickness evaluation

The study described in Chapter Seven determined the macular thickness by Time-domain optical coherence tomography of individuals with vigabatrin-associated visual field loss and of individuals exposed to vigabatrin but with a normal visual field. The cohort comprised 32 individuals with vigabatrin-associated visual field loss and 14 exposed to vigabatrin but with a normal visual field.
The group mean macular thickness was similar between those with and without vigabatrin associated visual field loss. Although, no corresponding age-corrected normal values are supplied by the StratusOCT, the group means from both groups were lower than those in the literature. Even so, there is some difference within the literature as to the normal value(s) for macular thickness. Given the advent of the higher resolution Spectral-domain optical coherence tomography during the compilation of this thesis, it was decided not to undertake the lengthy and costly task of collecting a data base of age-corrected normal values for macular thickness.

8.6 Future work

One pressing topic for the future study of vigabatrin-ocular toxicity centres upon the use of Spectral-domain optical coherence tomography to ascertain the retinal ganglion cell axonal count from the peripapillary retinal nerve fibre layer thickness. A combined structural and functional index based upon residual ganglion cell soma and ganglion cell axonal counts, derived by standard automated perimetry and (Spectral-domain) optical coherence tomography appears to be of value in the detection and follow-up of open angle glaucoma (Medeiros et al., 2012a; Medeiros et al., 2012b; Marvasti et al., 2013; Tatham et al., 2013a) and this approach should be applied to the monitoring of patients undergoing treatment with vigabatrin.

A second pressing topic, centres upon the use of Spectral-domain optical coherence tomography to determine the macular ganglion cell inner plexiform layer thickness. The thickness is compared to the age-corrected normal values within the database of the instrument. Macular ganglion cell thickness has been shown to be abnormal in open
angle glaucoma (Hwang and Kim, 2012; Hwang et al., 2014), and to be comparable in diagnostic performance to the peripapillary retinal nerve fibre layer thickness and the neuroretinal rim area in preperimetric glaucoma (Shin et al., 2013; Kim et al., 2014) and to be statistically significantly thinner in normal relatives of individuals with open angle glaucoma than in healthy individuals with a negative family history of open angle glaucoma (Mwanza et al., 2011; Mwanza et al., 2012; Rolle et al., 2014).

Given the outcome of the macular thickness study (Chapter Seven) and given the concept from Chapter Four that vigabatrin ocular toxicity is an optic neuropathy, measurement of macular thickness should also be undertaken in patients undergoing treatment with vigabatrin. However, care will need to be exercised in that a reduced macular ganglion cell inner plexiform layer thickness, arising from trans-synaptic degeneration, has been found in hemianopianopsia or quadrantanopia arising from brain lesions due to stroke or surgery (Keller, Sanchez-Dalmau and Villoslada, 2014) and in optic pathway glioma (Gu et al., 2014).

The use of the macular ganglion cell inner plexiform layer thickness, in this way, would be supplemented by the use of the Humphrey Field analyzer Program 10-2. The latter program comprises 68 stimulus locations with an inter-stimulus separation of 2°, centred upon the fovea, and with the stimuli adjacent to the vertical and horizontal midlines offset by 1°. Such an approach would facilitate the structural and functional outcome within the macular region. If the macular ganglion cell soma and or axons exhibited abnormality prior to the more peripheral ganglion cells, an individual could be withdrawn from vigabatrin prior to the occurrence of more widespread ocular damage.
Finally, a national register should be compiled of those undergoing, de novo, vigabatrin therapy. Such a register would contain the outputs from the various ophthalmological tests etc. and would provide an open access anonymised natural history of the evolution of vigabatrin ocular toxicity.
References


Appendix

Modelling the Risk of Visual Field Loss Arising from Long-Term Exposure to the Antiepileptic Drug Vigabatrin: A Cross-Sectional Approach

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Abstract

Background The antiepileptic drug vigabatrin has been used widely since 1989, but has only been approved for use in the US since 2009. The risk:benefit of vigabatrin is generally predicated upon an assumed frequency of associated visual field loss (VAVFL) of approximately 31%. This estimate is based upon relatively short-term usage (up to 4-5 years) and it is essential to determine whether the frequency of VAVFL increases with longer-term usage.

Objective The aim of this study was to model, from cross-sectional evidence, over greater ranges of treatment duration and cumulative dose than previously evaluated, the risk (frequency) of VAVFL with increasing exposure to vigabatrin.

Study Design and Setting This was a retrospective cohort study undertaken in a regional hospital epilepsy clinic.

Patients The cohort comprised 147 consecutive patients treated with vigabatrin for refractory complex partial (focal) seizures, who had all undergone ophthalmological examination and who had undertaken perimetry, reliably, according to a standard and robust protocol. The visual field plots were evaluated masked to treatment duration and dose.

Main Outcome Measure The risk (frequency) of VAVFL with increasing exposure to vigabatrin was modelled, from the cross-sectional evidence, by standard and plateau logistic regression.

Results The cohort comprised 80 females and 67 males (mean age 40.3 years, standard deviation 13.7). The median duration of vigabatrin exposure was 7.9 years (interquartile range 3.6–11.0, range 0.2–16.1 years); 46 patients (31%) had received vigabatrin for over 10 years. Eighty-seven patients (59%) exhibited VAVFL; the proportion with VAVFL was higher in males (66%) than females (54%). The plateau model for duration and for cumulative dose exhibited a better fit than the standard model (both p < 0.001). The modelled frequency of VAVFL increased with increasing exposure up to approximately 6 years’ duration and 5 kg cumulative dose, and plateaued at approximately 76% (95% CI 67–85) and 79% (95% CI 70–87), respectively. Severity of VAVFL, classified in terms of the visual field index mean deviation, was not significantly associated with either duration or cumulative dose of therapy.

Conclusion Clinicians and patients, in enabling informed choice, should be alert to the possible substantial increased risk:benefit for VAVFL with increasing long-term exposure to vigabatrin and the ensuing increased cost:benefit resulting from the necessary additional visual assessments.
1 Introduction

Vigabatrin (Sabril®) is an effective antiepileptic drug used as adjuvant therapy for refractory complex partial (focal) seizures [1, 2] and as monotherapy for infantile spasms [3, 4]. It was approved for these uses by the US FDA in 2009 but has been available in approximately 85 countries outside of the US since 1989.

The antiepileptic effect of vigabatrin is thought to occur from an increased concentration of pre-synaptic gamma-aminobutyric acid (GABA) arising from the selective and irreversible inhibition of GABA transaminase which catalyses the inactivation of GABA [5]. Vigabatrin is associated with visual field loss (VAVFL) [6–12] secondary to retinal damage [7, 9, 13–15]; however, the mechanism of the toxicity is unknown.

The frequency of VAVFL is generally considered to be approximately 31% (95% CI 26–37) and is derived from data submitted to the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Agency in 1999 by the Marketing Authorisation Holder [16]. The cumulative incidence of VAVFL, derived from the cross-sectional data, and modelled for the time to onset, rather than the time to detection, of the field loss, increased rapidly in the first 2 years of treatment and then stabilised at 3 years of exposure [16]. The corresponding model for cumulative dose increased steeply within the first 2 kg of intake and reached a plateau after 3 kg [16]. However, the models were limited by the lack of treatment durations in excess of 5–6 years and the CPMP noted that there was no reliable evidence to indicate that the risk of developing VAVFL lessened after 3 years of treatment [16].

A systematic review of 32 observational studies of patients exposed to vigabatrin, generated a median of 45% [interquartile range (IQR) 33–60] for the proportion of patients with field loss [17]. For a mean cumulative dose of 1 kg of vigabatrin, the estimated proportion with field loss was 34% compared with 53% for 5 kg. Only nine studies specifically reported VAVFL as opposed to field loss, in general. The median for VAVFL was 31% (IQR 21–52) and that for field loss attributable to other causes was 10% (IQR 5–13). The studies were based upon relatively short-term exposures to vigabatrin [mean duration 3.9 years, standard deviation (SD) 1.5; mean cumulative dose 3.5 kg, SD 1.5].

2 Objective

Clearly, the longer-term safety profile of vigabatrin in relation to VAVFL is unknown. The purpose of this study, therefore, was to assess the risk (frequency) of VAVFL, in terms of duration and cumulative dose of vigabatrin, with particular reference to long-term usage of vigabatrin in patients with refractory complex partial (focal) seizures.

3 Methods

3.1 Patients

The study was a retrospective cohort study. The cohort was derived from the case notes of patients attending the Welsh Epilepsy Unit, University Hospital of Wales, Cardiff, UK, who had been treated with vigabatrin for refractory complex partial (focal) seizures. It comprised 147 unselected consecutive patients (80 females, 67 males) who had all undergone a full ophthalmological examination and had exhibited clear media by slit lamp biomicroscopy, had all yielded a reliable outcome to an identical and robust perimeter protocol and for whom a full antiepileptic drug history was available. Of the 147 patients, 124 were under the care of the Welsh Epilepsy Unit and 23 had been referred from other hospitals for perimetry. Almost all patients had received vigabatrin in tablet formulation.

Of the 147 patients, 137 had commenced treatment with vigabatrin between 1989, the year of its licensing, and 1997 inclusive, the year of the first publication linking vigabatrin to visual field loss. A further four patients had begun treatment prior to 1989 on an off-label compassionate basis. Of the remaining six patients, four had begun treatment in 1998, and one each in 1999 and 2000. Fifty-eight of the 147 patients (39.4%) had commenced vigabatrin between 1986 and the end of 1991.

3.2 Visual Field Examinations

A systematic programme of visual field examination of patients exposed to vigabatrin had been initiated from the year 2000 onwards as a consequence of the then emerging consensus on the association of vigabatrin with visual field loss [6–12]. All patients had been/were withdrawn from vigabatrin, as a safety measure, either prior to, or immediately following, the visual field examination.

Examination of the full field had been undertaken with three-zone age-corrected suprathreshold static perimetry [Humphrey Field Analyzer 750 (HFA) Full Field 135 Screening Test with Goldmann stimulus size III]. Patients with visual field results deemed to be abnormal, or to be suspicious of abnormality, had then undergone threshold static perimetry of the central field on a separate occasion (HFA Program 30-2: Goldmann stimulus size III and the FASTPAC Algorithm).

Each patient had received extensive instruction and practice on the requirements of the given visual field examination. Rest periods of 1 min had been given after a
maximum of 3 min of perimetry, during which time the
patient had been required to continue looking into the bowl
of the perimeter. A rest period of 30 min, in the waiting
area of the clinic, had taken place between the examination
of the two eyes. Visual field examinations that had yielded
greater than 15% incorrect responses to the false-positive
and/or greater than 20% incorrect responses to the fixation
loss catch trials and/or poor quality outcomes to the gaze
tracking had been repeated on a separate occasion. Patients
who had manifest such an outcome to the repeat exam-
ination were not included in the cohort. A similar approach
was adopted for incorrect responses to the false-negative
catch trials: the repeat criterion was greater than 30% in-
correct responses but the tolerance widened with increase
in severity of the field loss [18]. Any examination deemed
to have initially yielded an equivocal diagnostic outcome,
including an apparent learning effect, had also been re-
peated on a subsequent occasion.

The fields were reviewed, masked to antiepileptic drug
history, by three of the authors (CL, GDL and JMW). The
visual fields from 15 patients with epilepsy who had never
been treated with vigabatrin were randomly interposed within
the series of visual fields for review. The definition of VAVFL
followed that previously described, namely, a bilateral cli-
nically symmetrical, 'concentric' constriction of the peripheral
field which, by static perimetry using Goldmann stimulus size
III, is generally more pronounced nasally than temporally [19]
and which, in almost all cases, encroaches upon at least the
nasal region of the central field (i.e. out to a radius of 27° from
fixation) [19]. In severe manifestations, the defect by static
perimetry manifests as a concentric constriction to within
approximately 15° from fixation [19]. The VAVFL was
required to exhibit a consistent appearance between supra-
threshold and threshold perimetry. The perimetric algorithms,
and the definition of VAVFL, were those approved by the
COPM for investigation of the association between vigabatrin
and visual field loss [19].

The severity of the VAVFL was expressed, objectively,
in terms of the mean deviation (MD) visual field index,
averaged across the two eyes. The MD is the weighted mean
of the difference, across each stimulus location within the
central field, between the measured value of sensitivity and
the age-corrected normal value [20]. It enables a continuous
(ratio) scale of measurement, is used universally in the
clinical and the research setting and, in the context of the
current study, expresses the extent of the VAVFL within the
functionally important central field. Patients with concom-
itant field loss were omitted from this sub-analysis.

3.3 Statistical Analysis

Gender, age at the time of the visual field examination, age
at onset of epilepsy, age at onset of treatment with
vigabatrin, duration and cumulative dose of vigabatrin at
the time of the visual field examination, and antiepileptic
drugs used prior to, and concurrently with, vigabatrin were
each evaluated as explanatory variables. The extent of
GABAergic activity of each of the other antiepileptic drugs
was expressed, on a 4-point scale, in descending order of
empirically assigned magnitude. Tiagabine was graded as
level 1; the benzodiazepines as level 2; valproate, pheno-
obarbital and primodone as level 3; and the remainder as
level 4 [19].

The characteristics of the cohort were described with
descriptive statistics. Independent t tests for continuously
distributed variables, and χ² tests for categorical variables,
were used to assess univariate associations between VA-
VFL and the duration and dose of vigabatrin, and between
VAVFL and each of the other explanatory variables.

A confidence limit for the relative risk of VAVFL by
gender was calculated by the score method [21].

The degree of associations between duration and
cumulative dose of vigabatrin and the severity of VAVFL
was characterised by the Spearman rank correlation, rₚ.

The increase in the risk (frequency) of patients with
VAVFL (p) with increasing exposure to vigabatrin (x) was
evaluated by logistic regression. In addition to the standard
logistic regression model, a plateau model was utilised:

\[ p = k/(1 + \exp(-\alpha - \beta x)) \]

where \( k \) denotes a plateau value lower than 1 (100%), and
where \( \alpha \) and \( \beta \) are intercept and slope parameters, re-
spectively. For the plateau model, the risk of VAVFL at the
highest exposures approaches \( k \), not 1, whereas for the
standard regression model, \( k \equiv 1 \). The standard and pla-
teau models were fitted by maximum likelihood with pro-
file likelihood CIs for the parameters. Comparisons
between the standard and plateau models were performed
by referring the difference in deviance to the \( \chi² \) distri-
bution. The two models were each applied separately for
duration and for cumulative dose. Models of these two
exposure variables, considered together, were also
examined.

3.4 Ethics

The study had approval from the Local Research and
Ethics Committee.

4 Results

4.1 Demographics of the Cohort

The age at visual field examination ranged from 13 to
76 years with a mean of 40.3 years (SD 13.7), median 39.6
Eleven patients who had undergone neurosurgery for seizure control had resultant superior homonymous quadrantanopia; of these, seven additionally exhibited VAVFL. Twelve others had homonymous hemianopia or quadrantanopia; of these, eight had VAVFL. One patient had bilateral open-angle glaucoma; however, the VAVFL could be clearly distinguished from the glaucomatous field loss. Another had unilateral central serous retinopathy but the VAVFL was clearly evident in the contralateral eye.

No cases of field loss were designated in any of the visual fields from the 15 patients with epilepsy who had never received vigabatrin.

4.2 Evaluation of the Explanatory Variables for Vigabatrin-Associated Visual Field Loss (VAVFL)

Patients exhibiting VAVFL were slightly older at the onset of epilepsy and at the time of perimetry, but younger at the onset of treatment with vigabatrin, than those without VAVFL; however, the differences in the mean ages were not statistically significant (1.4 years, 95% CI -2.9 to 5.8, p = 0.28, 95% CI -4.3 to 4.7, and -3.4 years, 95% CI -8.0 to 1.1, respectively).

The mean duration of vigabatrin therapy, 7.4 years (SD 4.1, median 7.9, range 0.2–16.1 years, IQR 3.6–11.0), was not significantly different for gender: females 7.2 years (SD 4.2) and males 7.6 years (SD 4.0); difference between means 0.5 years (95% CI -0.9 to 1.8). Similarly, the mean cumulative dose, 6.4 kg (SD 4.6, median 5.8, range 0.2–19.8, IQR 2.5–8.7), was not significantly different for gender: females 6.0 kg (SD 4.5) and males 6.8 kg (SD 4.8); difference between means 0.8 kg (95% CI -0.8 to 2.3).

The duration and cumulative dose of vigabatrin therapy were highly correlated (r = 0.86, p < 0.001).

The mean duration and mean cumulative dose of vigabatrin therapy for those with VAVFL was 8.9 years (SD 3.1) and 8.0 kg (SD 4.4), respectively, compared with 5.2 years (SD 4.3) and 4.0 kg (SD 3.9) for those without VAVFL (difference between means 3.7 years (95% CI 2.5–4.9) and 0.6 kg, (95% CI 2.6–5.5)).

VAVFL was not significantly associated with the level of GABAergic activity of other antiepileptic drugs taken either before, or concurrently with, vigabatrin.

The summary statistics of the MD for those with VAVFL (excluding those with other concomitant field loss) were mean -8.12 dB (SD 4.89); median -6.51 dB (IQR -4.26 to -10.49). The corresponding summary statistics for the MD for those without VAVFL (excluding those with other concomitant field loss) were mean -1.43 dB (SD 1.36); median -1.41 dB (IQR -0.30 to -2.60).

No evidence was found for an association between the severity of the VAVFL, as expressed by the MD, and either duration (r = 0.22, 95% CI -0.03 to 0.45) or cumulative dose of vigabatrin (r = 0.02, 95% CI -0.24 to 0.28). Severe VAVFL was noted even at very low exposures. Three outlier patients exhibited severe VAVFL of more than two SDs from an assumed linear fitted line of best fit, which was associated with durations of 3, 6, and 13 years, and cumulative doses of 3, 7, and 19 kg, respectively.

4.3 The Risk (Frequency) of VAVFL with Increasing Exposure to Vigabatrin

The outcome of the visual field examination by decile group of exposure, by current or previous vigabatrin therapy at the time of the visual examination, and by severity of the VAVFL, expressed in terms of the MD, is given in Table 1 for duration of vigabatrin therapy, and in supplementary Table 3 for cumulative dose of vigabatrin (see electronic supplementary material).

The risk (frequency), derived by the plateau model, of developing VAVFL according to duration (Fig. 1 top) and to cumulative dose (Fig. 1 bottom) of vigabatrin was expressed as the proportion of patients with VAVFL, by decile group of exposure to vigabatrin, plotted against the median exposure for the corresponding decile group. The relevant parameter estimates are given in Table 2. The plateau, towards which the frequency of VAVFL increased with increasing exposure, was 76% (95% CI 67–85) beyond approximately 6 years’ duration, and 79% (95% CI 70–87) after approximately 5 kg cumulative dose.

In comparison to the plateau model, the standard model with k = 100% was a highly significantly poorer fit to the data (χ² = 12.75 for duration, χ² = 18.93 for cumulative dose, both p < 0.001). The standard model failed to express the very steep rise in the proportion of patients with VAVFL between exposures of approximately 2 and 6 kg. It fitted a proportion of 20–25% at zero exposure, which rose to over 90% for the highest exposures in the cohort; both these modelled proportions were much higher than the observed proportions. The observed proportion at minimal exposure in the plateau model was very low, but not zero: one patient had developed VAVFL after taking 0.189 kg of vigabatrin over 9 weeks. A model which incorporated a plateau and constrained the proportion to be zero at zero exposure was a slightly poorer fit than the unconstrained plateau model.
Table 1 Summary statistics for duration of vigabatrin therapy for each decile group by vigabatrin therapeutic status, visual field outcome and severity of the (VAVFL)

<table>
<thead>
<tr>
<th>Decile</th>
<th>Number of individuals</th>
<th>Duration of vigabatrin therapy (years)</th>
<th>Vigabatrin therapeutic status at the perimetric examination and corresponding visual field outcome</th>
<th>Severity of vigabatrin attributed visual field loss (MD (dB))</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
<td>Mean</td>
</tr>
<tr>
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<td>14</td>
<td>0.2</td>
<td>1.3</td>
<td>0.9</td>
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<td>2</td>
<td>15</td>
<td>1.3</td>
<td>2.8</td>
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<td>15</td>
<td>2.9</td>
<td>4.7</td>
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<td>14</td>
<td>12.4</td>
<td>16.1</td>
<td>13.4</td>
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</table>

* MD mean deviation, VAVFL vigabatrin attributed visual field loss

The severity of the VAVFL is expressed in terms of the visual field index, MD, averaged between the two eyes. An increasingly negative MD represents a worsening of the visual field. Note individuals with concomitant visual field loss are excluded from the distributions of the MD

Table 2 Parameter estimates for the plateau logistic regression models for the risk (frequency) of developing VAVFL by duration and cumulative dose of vigabatrin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model by duration (years)</th>
<th>Model by cumulative dose (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-3.28</td>
<td>-3.36</td>
</tr>
<tr>
<td>Slope β</td>
<td>0.98 (0.48–2.38)</td>
<td>1.29 (0.71–2.28)</td>
</tr>
<tr>
<td>Odds ratio per unit exposure, eβ</td>
<td>2.67 (1.61–10.79)</td>
<td>3.63 (2.03–9.74)</td>
</tr>
<tr>
<td>Plateau k</td>
<td>0.762 (0.665–0.853)</td>
<td>0.792 (0.699–0.872)</td>
</tr>
</tbody>
</table>

* VAVFL vigabatrin attributed visual field loss

The plateau parameter, k, may be regarded as the proportion of the caseload of patients treated with vigabatrin who would develop VAVFL following a high degree of exposure to the drug. 95% confidence limits are shown for the plateau k, for the slope parameter β and the corresponding odds ratio, eβ, representing the increase in the odds of developing VAVFL for an additional unit of exposure among those susceptible to developing it.

352 The modelled frequency of patients with VAVFL assumes that the field loss in those who had discontinued vigabatrin prior to the visual field examination was not reversible [22–24]. Seventy-one (48 %) patients were receiving vigabatrin at the time of the visual field examination. Visual field loss was marginally significantly more common in these latter patients (48/71, 68 %) than in those who had discontinued treatment (39/76, 51%; p = 0.045). However, the patients who were currently receiving vigabatrin had significantly longer durations of use (mean 8.6 years compared with 6.2 years; p < 0.001) and significantly greater cumulative doses (7.3 kg compared with 5.5 kg; p = 0.017) compared with those who were not. The incorporation of an additional term in the plateau model for current vigabatrin therapy did not give an appreciably better fit (χ² = 0.46, p = 0.50 for duration; χ² = 0.04, p = 0.84 for cumulative dose).

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5 Discussion

The current study describes the risk (frequency) of VAVFL at higher exposures to vigabatrin than previously evaluated: over half the patients (85/147, 58%) had received vigabatrin for more than 7 years and almost one-third (31%) for more than 10 years. The two novel plateau models indicate that the frequency of VAVFL, compiled from the cross-sectional evidence, rises steeply up to approximately 6 years or 5 kg cumulative dose, then levels out at a plateau of between 75 and 80%. The plateau is substantially higher than frequencies at lower exposures to vigabatrin [16, 17, 19] yet it is firmly well below 100%.

Duration and cumulative dose of vigabatrin were highly correlated, and exhibited similar patterns of increasing frequency of VAVFL with increasing exposure (Fig. 2). A plateau model incorporating duration and dose, together, described the data significantly better than the model by duration alone ($\chi^2 = 9.02, p = 0.003$) but not appreciably better than the model by cumulative dose, alone ($\chi^2 = 0.09, p = 0.77$). This suggests that the risk of developing VAVFL is determined by cumulative dose rather than duration. It can also be seen from Fig. 2 that, for any given duration (i.e., for any vertical slice), the data points representing patients with VAVFL tend to lie above (i.e., at greater cumulative doses) than those points representing patients with no VAVFL. Conversely, for any horizontal slice, there is no apparent tendency for the data points representing patients with VAVFL to lie to the right (i.e., at greater durations) of those points representing patients with no VAVFL. The greater influence of cumulative dose compared with duration is also consistent with that of the only systematic review of VAVFL [17].

The main limitation of the study is that the estimate of the increase in frequency of VAVFL with increased exposure to vigabatrin was based upon a cross-sectional evaluation of the effects of duration and of cumulative dose. Ethical considerations of the potential risk for VAVFL with continuing exposure to vigabatrin prevent a formal prospective longitudinal clinical trial over an equivalent time period. Even for such studies, the precision of the estimate of the increase in frequency would be dependent upon the number of, and interval between, the perimetric examinations. In the US, approval for vigabatrin was dependent upon implementation of a risk evaluation and mitigation strategy (REMS) which is currently administered via the US marketing authorisation holder’s programme: support, help and resources for epilepsy (SHARE) [25, 26]. As part of this programme, the outcomes from ophthalmological testing of all patients treated with vigabatrin in the US are mandatorily collated in a registry. Analysis of the registry could eventually provide some longitudinal perspective as to the increase in the frequency of VAVFL with increased exposure to vigabatrin; however, the registry will be only be analysed for the first 6 years and the outcome will not approach the level of evidence from prospective clinical trial data [26]. The most recent analysis of the registry, at 3 years, has yielded little in regard to the frequency of VAVFL. The registry comprised 4,292 patients: of these, 62% had infantile spasms, 55% of all patients had discontinued vigabatrin, and only 7% had undergone a visual field examination at baseline [27]. A current, small-scale, prospective study, over 1 year, of approximately 80 adult patients, de novo to vigabatrin and undergoing regular perimetry and optical coherence tomography (OCT), of whom it is estimated 20 will complete the study, may provide some evidence as to the short-term onset of VAVFL [28].

In the current study, the modelled frequency of patients with VAVFL at 3 years of exposure, 31.7%, is identical to that submitted to the CPMP, for an equivalent exposure [16]. The latter estimate was based upon the modelled time to onset of the field loss, whilst that of the current study was derived from the time to detection of the field loss. The modelled frequency is also in agreement with the median frequency of 31% derived by the systematic review for a similar exposure [17].

VAVFL is largely initially asymptomatic unless the field loss is concentric within the central field [9, 11–13]. The visual acuity remains normal or near-normal [11, 12] and, in less severe cases, the predominantly nasal loss in the ipsilateral eye is compensated by the relatively well-preserved temporal field in the contralateral eye [12]. As a consequence of the asymptomatic nature, it is likely that, for most patients, the time to detection will have preceded the time to self-referral on the basis of symptoms.

The marked difference in the distributions of the MD between the two cohorts (i.e., those with, and those without, VAVFL) clearly indicates the high sensitivity and high
specificity both of the perimetric protocol and of the definition of VAVFL.

The established literature on VAVFL, evidenced by the
goals of the systematic review [17], is contrary to the findings of Sergott et al. [29]. The latter were derived from a subset of the cohort described by Wild et al. [19]. Based upon a comparison of the outcome of kinetic
test in terms of the angular extent of the V4e or IVe
isotherms along the temporal meridian, and an empirical definition for normality, the approach taken by Sergott et al. [29] yielded poor sensitivity (72% of those exposed to vigabatrin exhibited field loss) and poor specificity (45% of those with no exposure to vigabatrin exhibited field loss) when compared with the outcome in the same cohort based upon the CPMP-accepted protocol and
classification system of static perimetry (Wild et al. [19]).

The temporal field exhibits the largest between- and within-individual variability in response to kinetic
test and is the least affected by VAVFL. The efficient detection of visual field loss by good-quality kinetic
perimetry can only be undertaken in terms of a comparison of the shape and extent of a number of isopters across all meridians. The guidelines provided by the marketing
authorisation holders of vigabatrin outside of the US stipulate that, when undertaken, kinetic perimetry of patients exposed to vigabatrin should examine the III4e,
14e and 12e or 11e isopters. However, Wild et al. [19] also showed that, in the full data set, VAVFL was more frequently detected with static than with kinetic perimetry [odds ratio up to 3.3; 95% CI 0.8–13.5] at a specificity of 99.2%. Sergott et al. [29] also failed to undertake any quality control of the data subset: the output from many of the visual field examinations by kinetic perimetry had been of such poor quality that Wild et al. [19] had introduced a protocol amendment that had replaced the technique with static perimetry.

The severity of the VAVFL, as expressed by the MD, was not significantly associated with either the duration or the cumulative dose of vigabatrin. Clearly, the absence of a correlation between the MD and either the cumulative dose or the duration of vigabatrin cannot be explained by any restriction in the range of severity of the VAVFL. The absence of any correlation is in agreement with some shorter-term exposure studies [24, 30] but not with others [31–33] and is consistent with the concept of an idiosyncratic drug reaction.

The lack of an association of VAVFL with any other antiepileptic drug either prior to or concurrently with vigabatrin is consistent with most studies. The absence of any association may arise from the insufficient number of cases with VAVFL to accommodate the multiplicity of therapeutic combinations. However, sodium valproate has been implicated with more severe VAVFL [34].

VAVFL is considered by some to be principally a defect of the peripheral field [35], i.e. that beyond a radius of 27° from fixation. However, all but one of the patients manifested VAVFL within the central field. Such a finding underlines the importance of threshold perimetry of the central field out to 27° eccentricity, in conjunction with three-zone age-correlated suprathreshold static perimetry of the peripheral field, for delineating VAVFL and which, together with a robust definition of VAVFL based upon abnormality exhibiting at least nasal encroachment within the central field, would reduce false-positive outcomes such as those clearly evident in the illustrations of Gonzalez et al. [36].

The visual field examination of patients receiving vigabatrin can often be inconclusive due to the inherent cognitive demands. The frequent requirement for one or more confirmatory repeat examinations further increases the cost of management of such patients. However, even after repeated examinations, the results often remain equivocal.

In the compilation of this cohort of 147 patients, a further 20 competent adult patients (12%) had been unable to produce a reliable result. This figure compares with estimates of approximately 25% in similar patients [19, 37]. However, assessment of the retinal nerve fibre layer thickness by OCT shows promise either as an alternative or as an adjunct to perimetry [37–40] and is acceptable for REMS in patients who are unable to undertake perimetry [26].

The earliest onset of VAVFL (0.189 kg over a treatment period of 8 weeks) is compatible with onsets of between 4 [33] and 6 months [41]. The obvious rapid manifestation of VAVFL in some patients, the continued increase in the frequency of VAVFL up to 6 years of exposure, reported here, and the potential for longer-term worsening of existing VAVFL [42, 43] is compatible with the REMS stipulation for perimetry at baseline and at a minimum of three monthly intervals [26] throughout the treatment period and within 3–6 months following withdrawal. These requirements are more stringent than others; which advocate a baseline examination followed by 6-monthly examinations either for the entire treatment period [44] or for the first 5 years of exposure followed by yearly examinations for those without VAVFL [45]. Based upon the results of the current study, these latter two recommendations should be brought into line with those of REMS. The resultant increased economic cost for the provision of the ensuing additional visual investigations will need to be considered in the use of vigabatrin outside of the US.

GABA elevation dampens the increase in brain dopamine responsible for drug 'highs' [46] and a maximum cumulative dose of vigabatrin of between 0.137 kg [47] and 0.218 kg [48] over 9–12 weeks, respectively, has been
proposed as anti-addiction therapy for misuse of stimulant drugs. The early onset case of VAVFL in the current study was associated with a cumulative dose of 0.190 kg.

Vigabatrin can induce clinically profound bilateral peripheral visual field loss which encroaches into the central field, to varying degrees, as evidenced by the range of the MD index encountered in the study (Table 1). There are no staging systems for VAVFL in terms of the MD; a recent study of patients with glaucomatous visual field loss designated an MD of better than −6.00 dB as mild, of between −6.00 and −12.00 dB as moderate, and worse than −12.00 dB as severe [49]. From an ophthalmological perspective, any VAVFL is unacceptable, regardless of severity, and is a major concern when superimposed upon existing loss, e.g. that from cortical involvement. Even if such patients are excluded from treatment with vigabatrin, a proportion of those who are treated and who develop VAVFL will go on to develop field loss secondary to conditions concomitant with aging such as open-angle glaucoma and/or macular degeneration. From a neurological perspective, where the goal is a reduction in seizure frequency, the VAVFL may be of secondary concern; however, it should be noted that most patients are initially asymptomatic but can subsequently attribute difficulties in particular activities of daily living to their VAVFL. The psychological and sociological ramifications of the VAVFL should also not be underestimated. For example, one patient in the cohort was dismissed from his employment as a result of VAVFL, subsequently required a guide dog and enlisted on a course of visual rehabilitation at a college for individuals with severe sight impairment.

6 Conclusion

The increasing frequency of VAVFL with long-term exposure to vigabatrin substantially increases the risk:benefit for visual field loss and, with the requirement for an increased number of perimetric and/or OCT examinations, the cost-benefit for therapy. Clinicians, patients, and carers should be aware of these findings to enable an informed choice as to the benefit of vigabatrin.

Acknowledgements No funding was received specifically for the conduct of this study. Saleh Aljarudi was supported by an unrestricted grant from the Ministry of Higher Education, Kingdom of Saudi Arabia. The latter had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. John M. Wild provided Expert Testimony, prior to the current study, for Sanofi, UK. Charlotte Lawton has received funding for travel and/or speaker fees from Eisai, GlaxoSmithKline and UCBB Pharma, and has received research funding from Eisai for topics unrelated to the current study. Philip E.M. Smith has received funding for travel from UCBB Pharma and Eisai; unrestricted research funding from UCBB Pharma; and payment for lectures and teaching courses from UCBB Pharma, all unrelated to the current study. Robert G. Newcombe has received consultancy fees from GlaxoSmithKline for a topic unrelated to the current study. David L. Fone and Gareth D. Lewis have no conflicts of interest to declare.

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