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CNS Drugs

Objective derivation of the morphology and staging of visual field loss associated with long-term vigabatrin therapy --Manuscript Draft--

Manuscript Number:	CNSA-D-19-00041R1
Full Title:	Objective derivation of the morphology and staging of visual field loss associated with long-term vigabatrin therapy
Article Type:	Original Research Article
Funding Information:	
Abstract:	<p>Background The morphology and between-eye symmetry of the visual field loss associated with the anti-epileptic drug vigabatrin (VAVFL) has received little attention. Objective To model the appearance, and ensuing staging, of VAVFL, derived with the European Medicines Agency approved perimetric protocol.</p> <p>Methods A retrospective, cross-sectional, observational design identified 123 adults who had received vigabatrin for refractory seizures and who had no evidence of co-existing retino-geniculo-cortical visual pathway abnormality. Thirty-eight adults with refractory seizures and identical inclusion criteria, but no exposure to vigabatrin, acted as controls. For each group, the median outcome at each stimulus location in each eye (of absolute loss, relative loss or Pattern Deviation probability level, as appropriate) was derived for each successive ten pairs of fields, ranked for severity. Between-eye symmetry was quantified by an index which accounted for severity of loss and which was referenced to the likelihood of the occurrence of symmetry due to chance.</p> <p>Results The modelled VAVFL was bilateral and highly symmetrical and was described by six stages which were all independent of the extent of vigabatrin exposure. The loss originated in the extreme temporal periphery and encroached centripetally along all meridians towards fixation. The initial appearance within the central field (Stage Two) occurred inferior-nasally. Subsequent stages exhibited increasing loss which was greater nasally than temporally. Stage Six described concentric loss extending to approximately 15° eccentricity from fixation.</p> <p>Conclusion The model exhibited a consistent pattern of VAVFL. The staging of the loss could assist the risk:benefit analysis of vigabatrin for the treatment of epilepsy.</p>
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Order of Authors:	John Wild, PhD, DSc Phillip E M Smith, MD, FRCP Carlo Knupp, PhD
Order of Authors Secondary Information:	
Author Comments:	<p>Given the issue with one of the referees of our last manuscript, we would respectfully insist that the manuscript is NOT refereed by anyone who has previously declared a conflict of interest with Lundbeck LLC and/ or with Ovation Pharmaceuticals, Inc.</p> <p>The referees who reviewed the 'appealed' version of our last manuscript were both interested in, and knowledgeable about, vigabatrin toxicity. Perhaps they could be</p>

	<p>approached again?</p>
<p>Response to Reviewers:</p>	<p>CNSA-D-19-00041</p> <p>Objective derivation of the morphology and staging of visual field loss associated with long-term vigabatrin therapy</p> <p>We acknowledge the contribution from each of the reviewers. The review process has resulted in a much better manuscript.</p> <p>All changes included in the revised manuscript are highlighted in green and are described below.</p> <p>Response to Reviewer #1</p> <p>1.The subjects are adults. The authors have avoided discussing children but do they have any sense of whether this data would be of alarm to younger age groups. We did not 'avoid(ed) discussing children'. The case series was compiled from adults on the basis of their ability to perform perimetry.</p> <p>We have inserted a paragraph in the Discussion at the bottom of page 14/ top of page 15 of the revised manuscript.</p> <p>The model was developed from the visual fields of adults. The reduction in amplitude of the 30Hz flicker cone electroretinogram (ERG) in infants treated with vigabatrin for infantile spasms [31] is compatible with that for adults manifesting VAVFL [32]. Similarly, the topographical characteristics of the reduced peripapillary retinal nerve fibre layer thickness in children [33] is also compatible with that found in adults [34-38]. Those with vigabatrin-associated 30Hz flicker cone ERG abnormality in infancy subsequently manifest VAVFL, and corresponding retinal nerve fibre layer thinning, in later childhood/ early adolescence [39]. There is no reason to suggest, therefore, that the vigabatrin toxicity manifested in infancy will result in a different appearance to the VAVFL when the latter measure is obtained in later life.</p> <p>2.The reader would like to know, just generally, how impaired these subjects were? Were some in wheelchairs? Head control or eye movement control problem? Any with frequent seizures e.g., more than a few per day.</p> <p>The Reviewer seems to have overlooked our commentary at the top of page 17 of the initial version of the manuscript, namely:</p> <p>All 14 individuals exhibited impaired mobility and reported symptoms explainable by their field loss, the most common of which was bumping into individuals in crowded locations.</p> <p>Nevertheless, we have modified the paragraph (now top of page 19 of the revised manuscript). The new text is given in non-italicised text.</p> <p>All 14 individuals exhibited profoundly impaired mobility and reported symptoms explainable by their VAVFL, the most common of which was bumping into individuals in crowded locations. However, some individuals with Stage 5 VAVFL also reported a negative impact on their activities of daily living.</p> <p>We have also inserted a sentence in the Methodology at the end of the paragraph on Page 7</p> <p>All individuals had been seizure free for a minimum of 24 hours prior to the visual field examination.</p> <p>3.I don't see any data on false-positive and negatives to the field tests – were there any? This makes it easier to judge the validity of the tests.</p>

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Please see the response to Query #1 from Reviewer #2. The following text has been inserted into the manuscript.

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(least severe) to Stage 6 (most severe), they have not confirmed that such progression occurs. Most importantly, how can staging data be interpreted without knowledge of the probability of progression at each stage, and an estimate of the rate of progression? These concerns are reinforced by the finding that the occurrence of visual field defects was related to cumulative dose and duration of treatment, but there was no correlation between stages and exposure. The authors' comment that toxicity is 'idiosyncratic' does not explain the lack of correlation between severity of the defect and dose/duration of exposure. These issues need to be discussed.

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The Registry was an FDA mandated requirement for the marketing authorisation of Sabril within the USA. The data analysis for the Krauss et al (2016) paper was undertaken by a third party institution and the editorial support for the paper was funded by the Marketing Authorisation Holder for Sabril in the USA. The paper is carefully worded, is ambiguous in crucial places, and largely concentrates on the number of individuals enrolled within the Registry and the likelihood of retention of these individuals over time. The referee is correct in his/ her assertion that the paper by Krauss et al (2016) 'does not provide (sic) baseline data on visual fields'; however, the paper states that:

'Clinicians reported that eight patients discontinued treatment because of visual field defects (VFD). The patients ranged from ages 18 to 55 years at entry into the SHARE program and were divided equally by gender. One 19 year old patient was reported to have an indication of IS, the other patients had CPS. Three patients entered the program with previous vigabatrin exposure. The five patients who were newly treated had vigabatrin discontinued by their clinicians because of VFD after exposures of 13 months to 3.3 years (Mean: 23 months).'

T

The clear implication from the above is that the visual field loss in at least five patients occurred after the baseline examination.

There is no discussion in the paper on the (low) prevalence of visual field loss and no

	<p>mention of the fact that ‘the data are not interpreted as indicating lack of visual toxicity.’ Although not stated, the clear implication to the reader is that the prevalence of the toxicity, derived from a [this] prospective study, is much lower than that derived from the (European) retrospective studies.</p> <p>ii)The Sergott et al (2016) paper is described as a ‘small study sponsored by Lundbeck.’ It should be noted that this study was a one year prospective study was mandated by the FDA.</p> <p>Given the above and given the acceptance by Reviewer #1, we have not altered the paragraph.</p> <p>Response to Comments from Editor</p> <ol style="list-style-type: none"> 1. We have moved the definition of VAVFL to the end of the figure legend 2. We have renumbered the figures as advised 3. We have revised the format of the supplementary content as advised <p>Our preference would be to embed a link to the videos within the article.</p>
<p>Suggested Reviewers:</p>	<p>Mark Lawden, PhD, FRCP Consultant Neurologist, University Hospitals Of Leicester NHS Trust mark.lawden@uhl-tr.nhs.co.uk International authority on vigabatrin toxicity</p> <hr/> <p>Emilio Perruca, MD, PhD Professor. Director, University of Pavia. IRCCS. Mondino National Neurological Institute in Pavia perucca@unipv.it International reputation for the neurology and clinical pharmacology of epilepsy</p> <hr/> <p>James Acheson, FRCOPhth, FRCP National Hospital for Neurology and Neurosurgery and Moorfields Eye Hospital, London james.acheson@nhs.net Internationally renown clinical neuro-ophthalmologist with an interest in vigabatrin toxicity</p> <hr/> <p>Lars Frisen, MD Institute of Neuroscience and Physiology, University of Gothenburg lars.frisen@neuro.gu.se Internationally acclaimed neuro-ophthalmologist with a knowledge of vigabatrin toxicity</p> <hr/> <p>Ivan Goldberg, MD Professor, University of Sydney ivan.goldberg@sydney.edu.au Internationally acclaimed ophthalmologist with a special interest in perimetry</p>



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Sue Pochon
Editor
CNS drugs

22nd February 2019

Dear Sue

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As promised in an earlier email relating to our last manuscript on vigabatrin (which is now published in *CNS Drugs*), please find uploaded a new manuscript entitled:

Objective derivation of the morphology and staging of visual field loss associated with long-term vigabatrin therapy

which we hope will be found suitable for publication in *CNS Drugs*.

The manuscript is particularly aimed at neurologists, neuro-ophthalmologists, general ophthalmologists and other healthcare workers associated with the care of patients with epilepsy.

Due to the cross-discipline nature of the topic, and given our past publications in the journal, we feel that *CNS Drugs* is the most appropriate setting for the above readership.

As you know vigabatrin is a highly effective drug for the treatment of refractory focal seizures but, for almost two decades, has been associated with visual field loss and with various other retinal/optic nerve structural and functional abnormalities.

Inexplicably, the appearance of vigabatrin-associated visual field loss (VAVFL) has never been illustrated/ described in detail.

The manuscript is topical in that:

- The use of vigabatrin is likely to increase, given



- the apparent lack of evidence for the toxicity arising from the two recent prospective studies (but these only involved *short-term* exposures)
- the drug has recently become available as a generic
- the drug is also freely obtainable on-line without prescription

The manuscript is novel in that it:

- Presents the first ever staging of VAVFL
 - the staging is based upon an objective model derived from signal-to-noise processing, the technique of which, in itself, is novel
 - the modelling could also be applied to other types of visual field loss arising from drug toxicity
 - the field loss is recorded with a widely available, and regulatory authority approved, perimetric protocol
- Presents the first quantitative description of the inter-ocular mirror symmetry of VAVFL
 - the technique for quantifying symmetry has not been described before and could also be applied to other types of visual field loss
- Is based upon long-term usage of vigabatrin (median 8.8 years; IQR 5.7 to 11.3; range 0.33 to 16.1); many of these long-term exposures are unprecedented in the literature
- Contains the first illustration of a case of progressive VAVFL obtained (over a seven year period) by standard automated perimetry.
- The modelled fields from those exposed to vigabatrin are illustrated as videos in Online Resource Videos 1 2, and 3 respectively, and from the control individuals in Online Resource Video 4.

- these videos are the product of sophisticated computational methodologies
- the use of such a presentation to illustrate the appearance of the visual field is, to our knowledge, a 'first' for any journal
- the use of video material is also a first for *CNS Drugs*

The Online Resource Video files form the basis of the manuscript and it is essential that each referee is able to view the content of these files.

Given the issue with one of the referees of our last manuscript, we would respectfully insist that the manuscript is NOT refereed by anyone who has previously declared a conflict of interest with Lundbeck LLC and/ or with Ovation Pharmaceuticals, Inc.

Best wishes.

Yours Sincerely,



John Wild

CNSA-D-19-00041**Objective derivation of the morphology and staging of visual field loss associated with long-term vigabatrin therapy**

We acknowledge the contribution from each of the reviewers. The review process has resulted in a much better manuscript.

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'Regular ophthalmologic assessments are required throughout vigabatrin therapy: at baseline (≤ 4 weeks after therapy initiation), at least every 3 months during therapy and 3 to 6 months after discontinuation. Fulfilment of this mandate is documented by registry receipt of an ophthalmologic assessment form.....In many instances, the first actual vision test may be conducted well after entry into the registry.'

The Registry was an FDA mandated requirement for the marketing authorisation of Sabril within the USA. The data analysis for the Krauss et al (2016) paper was undertaken by a third party institution and the editorial support for the paper was funded by the Marketing Authorisation Holder for Sabril in the USA. The paper is carefully worded, is ambiguous in crucial places, and largely concentrates on the number of individuals enrolled within the Registry and the likelihood of retention of these individuals over time. The referee is correct in his/ her assertion that the paper by Krauss et al (2016) 'does not provide (sic) baseline data on visual fields'; however, the paper states that:

'Clinicians reported that eight patients discontinued treatment because of visual field defects (VFD). The patients ranged from ages 18 to 55 years at entry into the SHARE program and were divided equally by gender. One 19 year old patient was reported to have an indication of IS, the other patients had CPS. Three patients entered the program with previous vigabatrin exposure. The five patients who were newly treated had vigabatrin discontinued by their clinicians because of VFD after exposures of 13 months to 3.3 years (Mean: 23 months).'

The clear implication from the above is that the visual field loss in at least five patients occurred after the baseline examination.

There is no discussion in the paper on the (low) prevalence of visual field loss and no mention of the fact that 'the data are not interpreted as indicating lack of visual toxicity.'

Although not stated, the clear implication to the reader is that the prevalence of the toxicity, derived from a [this] prospective study, is much lower than that derived from the (European) retrospective studies.

- ii) *The Sergott et al (2016) paper is described as a 'small study sponsored by Lundbeck.' It should be noted that this study was a one year prospective study was mandated by the FDA.*

Given the above and given the acceptance by Reviewer #1, we have not altered the paragraph.

Response to Comments from Editor

- 1. We have moved the definition of VAVFL to the end of the figure legend*
- 2. We have renumbered the figures as advised*
- 3. We have revised the format of the supplementary content as advised*

Our preference would be to embed a link to the videos within the article.

Staging of vigabatrin-associated visual field loss

Objective derivation of the morphology and staging of visual field loss associated with long-term vigabatrin therapy

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Running head: Staging of vigabatrin-associated visual field loss

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Abstract

Background The morphology and between-eye symmetry of the visual field loss associated with the anti-epileptic drug vigabatrin (VAVFL) has received little attention.

Objective To model the appearance, and ensuing staging, of VAVFL, derived with the European Medicines Agency approved perimetric protocol.

Methods A retrospective, cross-sectional, observational design identified 123 adults who had received vigabatrin for refractory seizures and who had no evidence of co-existing retinogeniculo-cortical visual pathway abnormality. Thirty-eight adults with refractory seizures and identical inclusion criteria, but no exposure to vigabatrin, acted as controls. For each group, the median outcome at each stimulus location in each eye (of absolute loss, relative loss or Pattern Deviation probability level, as appropriate) was derived for each successive ten pairs of fields, ranked for severity. Between-eye symmetry was quantified by an index which accounted for severity of loss and which was referenced to the likelihood of the occurrence of symmetry due to chance.

Results The modelled VAVFL was bilateral and highly symmetrical and was described by six stages which were all independent of the extent of vigabatrin exposure. The loss originated in the extreme temporal periphery and encroached centripetally along all meridians towards fixation. The initial appearance within the central field (Stage Two) occurred inferior-nasally. Subsequent stages exhibited increasing loss which was greater nasally than temporally. Stage Six described concentric loss extending to approximately 15° eccentricity from fixation.

Conclusion The model exhibited a consistent pattern of VAVFL. The staging of the loss could assist the risk:benefit analysis of vigabatrin for the treatment of epilepsy.

Key Points

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4 In this study of 123 individuals treated with vigabatrin as adjunct therapy for refractory focal
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6 seizures and without evidence of other retino-geniculo-cortical visual pathway abnormality,
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8 objective modelling, based upon convolution theory used in signal-to-noise processing,
9
10 identified a consistent pattern of bilateral symmetrical visual field loss obtained using a
11
12 regulatory approved perimetric protocol. No modelled field loss was present for the 38
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14 individuals with identical inclusion criteria but no exposure to vigabatrin.
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20 Six stages of modelled vigabatrin-associated field loss (VAVFL) were evident. Originating in
21
22 the extreme temporal periphery, the field loss encroached, with increasing severity,
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24 centripetally along all meridians towards fixation with greater nasal than temporal loss. Stage
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26 Six manifested as concentric loss to within approximately 15° from fixation.
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31 The between-eye mirror symmetry of the VAVFL at all stages, quantified by a novel index,
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33 which accounted for the severity of loss, was not attributable to chance ($p \leq 0.01$).
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38 The use of either the Central 30-2 or the Central 24-2 Threshold Tests, alone, will not identify
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40 VAVFL until late Stage Two and late Stage Three, respectively.
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2 **1.0 Introduction**
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5 The anti-epileptic drug vigabatrin has long been associated with visual field loss (VAVFL) [1-2]
6 which manifests as a bilateral concentric peripheral defect over a continuum of severity and
7 which, generally, also involves the central field to varying extents [3-4]. The field loss is
8 considered to be slowly progressive [5-7] irreversible but non-progressive on withdrawal from
9 vigabatrin [8-9] and asymptomatic until severe loss is present [3, 10-12]. The modelled
10 prevalence of VAVFL in adults increases rapidly after the first two years (2kg cumulative dose)
11 of exposure [13-14] and can reach 75-80% after approximately six years (5kg cumulative dose)
12 [14]. Vigabatrin is now available generically.
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28 The association between vigabatrin and ocular toxicity is currently being re-evaluated [15-17] on
29 the basis that the attribution of the toxicity emanates from retrospective studies which do not
30 include a pre-treatment baseline evaluation. The lack of evidence for the toxicity in the two
31 prospective studies alongside the finding that approximately 25% of individuals suitable for
32 vigabatrin exhibited clinically significant pre-existing reduced visual acuity and/ or visual field
33 loss and/ or peripapillary retinal nerve fibre layer thinning, has led to the suggestion that
34 abnormalities of the afferent system are a co-morbidity of severe refractory epilepsy and are
35 unrelated to vigabatrin [15-16]. However, the limited exposures to vigabatrin and the poor
36 retention of individuals, within these two studies [15-16], together with inappropriate visual field
37 methodologies and analyses, have not facilitated detection of the toxicity.
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56 Surprisingly, there has been little emphasis on the areal and depth characteristics, the between
57 eye-symmetry, and the staging, of VAVFL. Such information is essential not only to identify the
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1 onset and the progression of the VAVFL but also to differentiate it from other types of
2 (concomitant) field loss.
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9 The areal extent and the depth of any type of visual field loss is highly dependent upon the
10 perimetric technique used for the examination. VAVFL has been investigated by a variety of
11 methods [7, 10-11, 16, 18-23] but the characteristics of the field loss by each technique have
12 received little attention. Unfortunately, due to the peripheral nature of the field loss, there is no
13 one ideal technique, across the current range of commercially available perimeters, for the
14 assessment of VAVFL. The most pragmatic approach is that approved by the European
15 Medicines Agency (EMA) [23] namely, Three Zone (two luminance level) suprathreshold
16 perimetry, referenced to the age-corrected threshold, of the peripheral field out to a maximum
17 temporal extent of 90° eccentricity and standard automated perimetry of the central field (SAP).
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34 Given the on-going re-evaluation of the association between vigabatrin and visual field loss and
35 the wider availability of the drug, a description of the morphology and staging of the VAVFL
36 resulting from the EMA approved protocol, and derived from individuals with long-term
37 exposures to vigabatrin, would be of benefit to clinicians and to patients, alike. If such a
38 description was based upon a technique which reduced the signal-to-noise ratio and was derived
39 from individuals with no evidence of retino-geniculo-cortical visual pathway abnormality, except
40 that of potential vigabatrin toxicity, the characteristics of the field loss attributable to vigabatrin
41 would become manifest from backgrounds of any unexpected field loss and of any increased
42 variability associated with the response by the patient. Such an approach would also enable the
43 use of the visual fields from individuals with long-term exposures to vigabatrin but with no pre-
44 treatment baseline.
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1 The aim of the study, therefore, was threefold: to model the morphology of VAVFL obtained
2 with the EMA approved perimetric protocol and resulting from long-term vigabatrin therapy; to
3 quantify any between-eye symmetry; and to describe the ensuing staging of the field loss.
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10 **2.0 Methods**

11 **2.1 Case series**

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15 A retrospective case series comprising 161 adults with refractory complex partial (focal) seizures
16 was compiled from those presenting to the Alan Richens Unit of the Welsh Epilepsy Centre,
17 University Hospital of Wales, Cardiff, UK, and to associated clinics. All individuals had
18 undergone part or all of the EMA approved protocol with the Humphrey Field Analyzer 750
19 (Carl Zeiss, Meditec, Dublin, CA) namely, the Full Field 135 Point Test with the three zone age-
20 corrected strategy (FF135) and the Central 30-2 Threshold Test (C30-2T) with the FASTPAC
21 strategy. None exhibited ocular or intra-cranial conditions resulting in, or likely to cause, visual
22 field loss, as determined by ophthalmological and neurological examination including whole-
23 brain magnetic resonance imaging. Further exclusion criteria comprised the presence of
24 structural and/or functional ocular abnormalities likely to impede or confound the outcome of
25 perimetry and which are described elsewhere [24]. There was no conscious selection bias.
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27 Individuals were included on the basis of sequential retrieval of cases which met the inclusion/
28 exclusion criteria.
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2.2 Vigabatrin exposure

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3 Of the 161 individuals (Fig 1, top row), 123 had been exposed to vigabatrin as add-on therapy.
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5 The remaining 38 individuals had received a variety of other antiepileptic drugs and were
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7 included as age-matched controls.
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2.3 Perimetry

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17 Sixty-three of the 123 individuals exposed to vigabatrin and all 38 of those exposed to other
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19 antiepileptic drugs had undergone the complete EMA approved protocol (Fig 1, second row). Of
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21 the remaining 60 individuals exposed to vigabatrin, 24 had undergone the FF135, only, and 36
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23 had undergone the C30-2T, only (Fig 1, second row) as ordered by the treating neurologist on
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25 clinical grounds. Thus, 87 of the 123 individuals exposed to vigabatrin had undertaken the
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27 FF135 and 99 individuals had undertaken the C30-2T.
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36 The visual fields from the first occasion, after the first visit, at which reliable perimetric
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38 outcomes had been achieved were used for the individuals in each of the two groups. The
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40 reliability criteria comprised $\leq 20\%$ incorrect responses to the fixation loss catch trials and $\leq 15\%$
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42 incorrect responses to the false-positive catch trials. A criterion of $\leq 30\%$ incorrect responses was
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44 used for the false-negative catch trials although this was widened with increasing severity of the
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46 field loss [25]. All individuals had been seizure free for a minimum of 24 hours prior to the
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48 visual field examination.
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2.4 Morphology of visual field loss

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3 The Single Field Printouts of the FF135 and of the C30-2T were exported to a personal computer
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5 via a Humphrey Field Analyzer 820 and saved in Tagged Image File Format. The outputs from
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7 each eye for both types of perimetry were then read by custom Naïve Bayesian character
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9 recognition software [26].
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17 The fields were separately sorted for each group, and for each type of perimetry, as right and left
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19 eye pairs, and ranked from the least to the most affected field. The severity of the given pair of
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21 fields was defined as the sum, across the two eyes, of the number of defects, weighted to account
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23 for relative or absolute loss, respectively, derived by the FF135 and/ or for the probability level
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25 of the Pattern Deviation probability map derived by the C30-2T. In the case of those undergoing
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27 both tests, the outcome from the C30-2T was more heavily weighted.
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35 The median outcome for each group at each stimulus location in each eye for each type of
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37 perimetry was then separately calculated for each successive ten pairs of fields, ranked for
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39 severity. Such an approach was based upon convolution theory used in signal processing [27].
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42 The procedure resulted in 54 pairs of modelled fields from the 63 individuals exposed to
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44 vigabatrin who had undergone the combined EMA protocol; 78 pairs for the FF135 and 90 for
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46 the C30-2T. Twenty-nine pairs of modelled fields resulted from the 38 individuals with no
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48 vigabatrin exposure. The outcomes for the right and left eyes, separately, were then displayed in
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50 terms of Audio Video Interleaved (AVI) movies.
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2.5 Between-eye mirror symmetry of visual field loss

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3 The between-eye mirror symmetry of the field was expressed in terms of a single index which
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5 comprised two components, each of which was a fraction. The index accounted for the severity
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7 of loss and was compared to the likelihood of obtaining symmetrical field loss due to chance.
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10 The numerator and denominator of the first component constituted of, respectively, the number
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12 of mirror image stimulus locations between the two eyes which exhibited either relative or
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14 absolute loss for the FF135, or abnormality at $p \leq 0.02$ by Pattern Deviation probability analysis
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16 for the C30-2T, and the total number of locations exhibiting abnormality across the two eyes.
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19 The numerator and denominator of the second component comprised, respectively, the total
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21 number of locations exhibiting abnormality across the two eyes and the total number of stimulus
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23 locations across the two eyes. The index was compared to that obtained from the simulation of
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25 one million randomly generated pairs of abnormal fields which manifested varying locations,
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27 areas and depths of field loss both within- and between-eyes. The concept was such that
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29 symmetry would become apparent when compared to a series of pairs of fields with varying
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31 characteristics of asymmetric field loss.
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41 The symmetry index was separately calculated for each pair of peripheral, and each pair of
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43 central fields, for the modelled fields and for the measured fields.
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2.6 Staging of the measured fields for those exposed to vigabatrin

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51 The staging of the VAVFL was derived from the modelled fields. The stages were empirically
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53 selected on the basis of clinically meaningful intervals of peripheral field loss and, subsequently,
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55 of central field loss. These intervals, in turn, were based upon the magnitude of the between-
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57 examination physiological variability in the differential light sensitivity as a function of severity
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1 of loss [28-29]. The derivation ensured continuity across stages. The staging of the modelled
2 peripheral fields was undertaken masked to that of the modelled central fields. The outcome of
3 the staging of the central and peripheral fields, with respect to one another, was then validated
4 based upon the outcome of the model from the individuals who had undergone the combined
5 protocol. The staging was then applied to each of the 87 pairs of measured fields from the FF135
6 and to each of the 99 measured fields from the C30-2T.
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18 **3.0 Results**

19 **3.1 Demographic characteristics of the case series**

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27 Of the 123 individuals exposed to vigabatrin, 50 were male and 73 female. Thirty-five were
28 receiving vigabatrin at the time of perimetry. Of the 38 age-matched controls, 17 were male
29 and 21 female. The mean ages of the two groups, at the time of perimetry, were 40.8 years
30 (SD 13.6) and 38.5 years (SD 10.0), respectively.
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40 **3.2 Morphology of VAVFL**

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43 The rolling medians of the 78 pairs of modelled fields for the FF135 from those exposed to
44 vigabatrin; of the 90 pairs for the C30-2T; and of the 54 pairs for the combined EMA
45 protocol are given in video format in Online Resource Figs 1, 2 and 3, respectively (available
46 from URL: <https://doi.org/10.6084/m9.figshare.7981592>).
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57 The rolling medians of the 29 pairs of modelled fields for the combined EMA protocol from
58 those with no exposure to vigabatrin are given in video format in Online Resource Fig 4
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(available from URL: <https://doi.org/10.6084/m9.figshare.7981592>). The modelled fields showed was no evidence of visual field loss.

3.3 Staging of VAVFL

The staging of the FF135 and of the C30-2T modelled fields for those exposed to vigabatrin is shown in Figs 2 to 4.

Sixteen of the 36 individuals exposed to vigabatrin, who had undergone the C30-2T, only, manifested a normal measured central field (Fig 1 third row). These 16 fields were included in the model, but, in the absence of a peripheral field assessment, the individuals could not be categorised as to the potential outcome of the toxicity and were considered as equivocal.

Of the remaining 107 individuals exposed to vigabatrin (Fig 1, fourth row), 12 exhibited normal measured fields and 95 field loss which conformed to the modelled fields and which was therefore designated as VAVFL.

The frequency, by stage, of VAVFL is shown in Fig 1 (bottom row). Fourteen of the 95 individuals with VAVFL exhibited Stage One VAVFL, 21 Stage Two, 14 Stage Three, 22 Stage Four, 10 Stage Five and 14 Stage Six.

The relationship between the stage of loss and the summary measures of the visual field, Mean Deviation (MD) and Pattern Standard Deviation, for the C30-2T measured fields is shown in Fig 5.

3.4 Between-Eye Mirror Symmetry of VAVFL

The two components of the symmetry index for the FF135 and for the C30-2T are shown in Online Resource Videos 1, 2 and 3; at each stage of the modelled VAVFL in Figs 2 to 4; and for each measured field of those exposed to vigabatrin in Fig 6.

3.5 Demographics of VAVFL

The difference in the proportion with VAVFL by gender, 39 out of 44 males and 56 out of 63 females, was not statistically significant.

The mean age, at the time of perimetry, of those with VAVFL, 41.6 years (SD 14.4), was also similar to that of those exposed to vigabatrin but with normal fields, mean 37.9 years (SD 7.9).

Those with VAVFL manifested a greater cumulative dose (mean 7.94kg; SD 4.45; range 1.1 to 20.7) and a longer duration of therapy (8.86 years; SD 3.51; range 0.66 to 16.05) at the time of perimetry than those without field loss (mean 3.36kg; SD 4.77; range 0.11 to 16.14; and mean 3.62 years; SD 3.94; range 0.33 to 11.83; respectively). The difference between means (Student's t-test for two independent samples) were 4.58 kg (95% CI 1.71-7.45; $p < 0.001$) and 5.25 years (95% CI 2.98-7.53; $p < 0.001$), respectively.

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There was no evidence of a relationship between the stage of the VAVFL and the extent of the exposure to vigabatrin at the time of perimetry. The median exposures at the time of perimetry which resulted in Stage One loss were 7.7kg cumulative dose (IQR 4.8, 12.1; range 1.5-13.3) and 9.4 years (IQR 6.2, 12.1; range 2.4-16.1) and which resulted in Stage 6 loss were 6.7kg cumulative dose (IQR 4.4, 10.6; range 2.8-19.0) and 7.7 years (IQR 5.3, 10.6; range 3.1-13.0).

There was also no association between the stage of VAVFL and either age, age at onset of epilepsy or age at onset of vigabatrin.

4.0 Discussion

The objective rolling median and symmetry index outcomes from the FF135 and the C30-2T confirm that vigabatrin is associated with symmetrical bilateral visual field loss. The VAVFL manifests over a range of severities that can be described in six stages. The field loss originates in the extreme temporal periphery and, as the severity increases, encroaches centripetally along all meridians towards fixation resulting in bi-nasal loss and relative temporal sparing until the end stage (Stage Six) which manifests as a concentric loss to within approximately 15° from fixation. The initial appearance in the central field (Stages Two and Three) is primarily inferior-nasally. VAVFL exhibits a high degree of between-eye mirror symmetry at each stage of loss. In contrast, the modelled field for the age-matched control individuals with no exposure to vigabatrin was entirely normal.

1 The apparent absence of initial loss superior-nasally within the central field is most likely
2 attributable to the greater defect depth in this region required to achieve statistical
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4 significance. The latter, in turn, arises from the wider distribution of normal values arising
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6 from the between-individual variation in the position of the upper eyelid and from the
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8 increased variability in response associated with the steeper gradient of the superior visual
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10 field, compared to those inferior-nasally.
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18 The fundamental strengths of this retrospective study were the robust exclusion of individuals
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20 with retino-geniculo-cortical visual pathway abnormality; the inclusion of long-term
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22 exposures to vigabatrin (median 8.8 years; IQR 5.7 to 11.3; range 0.1 to 16.1) many of which
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24 are unparalleled in the literature; and the utilisation of the two novel objective techniques
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26 which have not previously been applied to perimetry. These latter techniques enabled
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28 objective descriptions of the characteristics and between-eye mirror symmetry of VAVFL.
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37 The modelled field at all six stages is in agreement with that derived from cross-sectional
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39 retrospective evidence with kinetic perimetry [4]. The initial manifestation of the VAVFL in
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41 this latter model was defined as a ‘non-seen’ response to the Goldmann V4e isopter at 80°
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43 temporally and/ or at 40° nasally. This definition is entirely consistent with the location and
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45 depth of the loss described as Stage One in the current study: the absolute loss designated by
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47 the FF135 is equivalent to the Goldmann V4e stimulus. The increasing encroachment into the
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49 nasal field with relative sparing of the temporal field, during Stages Two to Five, is
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51 compatible with the model out to approximately 80° temporally, derived from cross-sectional
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53 evidence, using suprathreshold perimetry equivalent to the I4e isopter [30].
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1 The model was developed from the visual fields of adults. The reduction in amplitude of the
2 30Hz flicker cone electroretinogram (ERG) in infants treated with vigabatrin for infantile
3 spasms [31] is compatible with that for adults manifesting VAVFL [32]. Similarly, the
4 topographical characteristics of the reduced peripapillary retinal nerve fibre layer thickness in
5 children [33] is also compatible with that found in adults [34-38]. Those with vigabatrin-
6 associated 30Hz flicker cone ERG abnormality in infancy subsequently manifest VAVFL,
7 and corresponding retinal nerve fibre layer thinning, in later childhood/ early adolescence
8 [39]. There is no reason to suggest, therefore, that the vigabatrin toxicity manifested in
9 infancy will result in a different appearance to the VAVFL when the latter measure is
10 obtained in later life.
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28 The ophthalmological examinations were undertaken by any one of four ophthalmologists,
29 depending upon the particular clinic, who were all unaware of the findings from their
30 colleagues. All four were aware of the anti-epileptic drug history and, usually, of the visual
31 field outcome. However, the modelling of the visual fields from those exposed to vigabatrin
32 and from the control individuals was objective and independent of the outcome from the
33 ophthalmological and neurological examinations.
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46 The most common bilateral finding by fundoscopy, through a dilated pupil, was either
47 generalised or localised arteriolar narrowing which was noted at all stages of VAVFL.
48 However, this finding was occasionally found in the presence of a normal field and,
49 therefore, may well be associated with vigabatrin usage. Subtle bilateral retinal nerve fibre
50 layer changes and optic nerve head pallor were noted from Stage 4 onwards. A variety of
51 bilateral peripheral degenerative changes were also noted including hypo-pigmented/ white
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1 spots and surface wrinkling. However, there was considerable variation in the fundal
2 appearance between-individuals within a given stage. The various features are in agreement
3 with those reported previously [3, 22, 40-41], were often subtle, and suggest that there is a
4 wide spectrum of potential retinopathy associated with vigabatrin toxicity. There was no
5 evidence of such findings in the individuals with no exposure to vigabatrin. Twenty-nine
6 individuals exposed to vigabatrin had undergone optical coherence tomography of the
7 peripapillary retinal nerve fibre layer at the time of the examination. All three individuals
8 who manifested a normal visual field exhibited a normal nerve fibre layer thickness. Of the
9 three individuals who had Stage 1 loss, two exhibited a normal thickness. An abnormally thin
10 nerve fibre layer, characteristic of vigabatrin toxicity [34-38], was present from Stage 2
11 onwards in 22 individuals. The one remaining individual manifested early Stage 2 VAVFL
12 and a normal a normal nerve fibre layer thickness.

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33 The outcome of the current study and of the earlier models [4, 28] indicates that perimetry
34 out to 60° eccentricity [42] is inadequate to detect Stage One and also possibly early Stage
35 Two loss. Similarly, a worsening of 3dB from the baseline Mean Deviation (MD) index for
36 the C30-2T, which was used as a primary outcome measure for the presence of VAVFL in
37 the prospective Phase IV study [16], will not detect VAVFL until late in Stage Two or early
38 in Stage Three. The MD is a summary measure of the central field and does not describe the
39 spatial appearance of visual field loss: in the current study, the median MDs for the
40 individuals exposed to vigabatrin and for the controls was -1.75dB and -1.23dB, respectively.

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56 It is clear from the staging of the VAVFL that perimetry should initially be undertaken with,
57 in the case of the Humphrey Field Analyzer, the FF135. If the field is normal to the FF135 or
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1 exhibits Stage One abnormality, the C30-2T is unnecessary. If the peripheral field exhibits
2 Stage Two abnormality to the FF135, the C30-2T should also be undertaken to reveal the full
3 depth of the loss since the magnitude of the Pattern Deviation value required for statistical
4 significance at the extreme nasal locations within the central field can be less than the 8dB
5 suprathreshold increment of the stimulus luminance of the FF135. If the FF135 indicates
6 both peripheral and central loss, i.e., Stage Three and worse, subsequent examinations need
7 only be undertaken with the C30-2T. The Central 24-2 Threshold Test, alone, should only be
8 used for Stage Six. The characteristics of VAVFL are more prominent with the FASTPAC
9 algorithm than with the SITA Standard or Fast algorithms which were designed to detect
10 glaucomatous field loss. The peripheral manifestation of VAVFL is fortuitous since, in our
11 experience, patients exposed to vigabatrin find suprathreshold perimetry considerably easier
12 to perform than SAP. In cases where patients are unable to undertake SAP, assessment with
13 the FF135, although collecting less information about relative loss, is acceptable.
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32 The staging of VAVFL was derived from cross-sectional evidence and does not imply
33 progressive loss. Due to the potency of the potential toxicity, most individuals had been
34 withdrawn from vigabatrin either immediately prior to the introduction into the care regime
35 of the visual field examination or following confirmation of the VAVFL. As such, neither the
36 probability of progression at each stage nor an estimate of the rate of progression can be
37 determined. However, the presumption is that, given continued vigabatrin therapy, VAVFL
38 will progress through the various stages. The lack of an association between the stage of loss,
39 at detection, and either the duration or the cumulative dose of vigabatrin implies that the
40 relationship between the extent of exposure and both the onset and the severity of VAVFL
41 varies depending upon the individual susceptibility to vigabatrin. However, the time of
42 detection is not the time to onset of the VAVFL. The rate of any subsequent progression,
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1 therefore, remains unknown. A case of progressive loss during approximately 7.75 years of
2 vigabatrin therapy and illustrated in terms of the Pattern Deviation probability map of the
3 Central 24-2 Threshold Test and, subsequently, the C30-2T is shown in Fig 6. The outcome
4 of the corresponding FF135 at the final visit is shown in Online Resource Fig 4. Progressive
5 loss whilst on therapy has been shown over a mean follow-up of 10.7 years; the rate of
6 reduction in the I4e isopter of kinetic perimetry increased with increase in cumulative dose
7 [6]. An unpublished audit of the long-term follow-up, over a maximum of eight years, of
8 individuals in the current study indicates that the VAVFL neither improves nor deteriorates
9 following withdrawal of vigabatrin.
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25 The appearance of Stage One VAVFL should act as an alert signal for a re-evaluation of the
26 management of the epilepsy. This may encompass either a change in anti-epileptic drug
27 therapy or an increase in the frequency of neuro-ophthalmological monitoring. However, the
28 extreme peripheral stimulus locations of the FF135 are also influenced by the facial anatomy,
29 particularly superiorly and inferior-nasally. The outcome of the examination at such
30 locations, and those in the extreme temporal periphery, is also dependent upon the vigilance
31 of the patient. Indeed, normal individuals do not necessarily produce statistically normal
32 visual fields. The FF135 commences with the examination of the central field. Once
33 completed, the examination pauses for removal of the trial lenses prior to the examination of
34 the peripheral field. Instructions to the patient, during this pause, to the effect that the stimuli
35 are about to appear in the (extreme) periphery, together with an exhortation to keep the eye
36 ‘wide open’, generally leads to a ‘seen’ response, in the normal eye, at these extreme
37 locations. However, individuals with epilepsy frequently exhibit greater within-examination
38 variability than normal individuals, which can lead to the impression of visual field loss, and
39 approximately 30% of individuals with epilepsy are unable to undertake perimetry of any
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1 type [15, 32]. The clinical skill lies in the identification of actual visual field loss,
2 characteristic of the given lesion, from apparent visual field loss due to increased variability
3 and/ or an inability to understand the requirements of the test. In addition, VAVFL frequently
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5 co-exists with that arising from an intra-cranial lesion.
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13 Fourteen individuals exhibited Stage Six VAVFL. Great care was taken to exclude
14 individuals manifesting visual field loss of suspected psychogenic origin from the case series
15 [44]. Three of these 14 individuals had undergone optical coherence tomography and
16 exhibited severe thinning of the retinal nerve fibre layer. All 14 individuals exhibited
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18 profoundly impaired mobility and reported symptoms explainable by their VAVFL, the most
19 common of which was bumping into individuals in crowded locations. However, some
20 individuals with Stage 5 VAVFL also reported a negative impact on their activities of daily
21 living.
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36 The study utilised a retrospective cross-sectional design. However, the objective derivation of
37 field loss based upon signal-to-noise theory, further supported by the stringent
38 ophthalmological and neurological inclusion criteria, uniquely facilitated a retrospective
39 design and largely obviated the need for a prospective study referenced to a pre-treatment
40 baseline.
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53 The variable and lengthy time to onset of VAVFL together with the opportunity to study a
54 wide range of long-term exposures, further highlights the pragmatism of this retrospective
55 study compared to a prospective study. Nevertheless, prospective longitudinal studies over
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1 the long-term would unequivocally rule out the presence of abnormality at baseline and
2 would also determine the evolution of the field loss.
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8 **5.0 Conclusions**

10 The appearance of VAVFL has received little attention. This absence of knowledge hinders not
11 only the recognition of the onset, and of any progression, of the field loss but also the
12 differentiation from other (concomitant) types of loss. The staging of the VAVFL derived from a
13 regulatory approved perimetric protocol, and reported here, should assist clinicians and patients,
14 alike, in the risk:benefit analysis of vigabatrin for the treatment of epilepsy.
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27 **6.0 Compliance with Ethical Standards**

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34 **Funding** None
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40 **Conflicts of interest** John M Wild, Phillip EM Smith and Carlo Knupp declare that they have no
41 conflicts of interest.
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49 **Ethical approval** All procedures performed in studies involving human participants were in
50 accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical
51 standards. The Local Research and Ethics Committee ruled that approval was not required for
52 this study. The visual field assessments were considered to be part of normal good clinical
53 practice. The visual fields were de-identified and so written informed consent was not required.
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3 **Data availability** The datasets generated and/or analysed during the current study are available
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5 from the corresponding author on reasonable request.
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8 **7.0 References**
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2 **Figure Captions**
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6 **Fig 1** The number of individuals by anti-epileptic drug exposure, type of perimetry and visual
7 field outcome. Equivocal indicates a normal outcome to the Central 30-2 Threshold Test;
8 however, in the absence of the Full Field 135 Point Screening Test with the three zone age-
9 corrected strategy, an evaluation for VAVFL was not possible. VAVFL indicates vigabatrin-
10 associated visual field loss
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17 **Fig 2** Stages One and Two of vigabatrin-associated visual field loss for the Full Field 135
18 Point Screening Test with the three zone age-corrected strategy and for the Central 30-2
19 Threshold Test
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21 For the Full Field 135 Point Screening Test, ◻ represents a ‘seen’ response to the initial
22 (dimkest) stimulus luminance; ✕ represents a ‘non-seen’ response to the initial (dimkest)
23 stimulus luminance but a ‘seen’ response to the maximum (brightest) stimulus luminance; ■
24 represents a ‘non-seen’ response to the maximum (brightest) stimulus luminance
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27 For the Central 30-2 Threshold Test, MD indicates Mean Deviation, PSD indicates Pattern
28 Standard Deviation and SI indicates Symmetry Index. The symbols ∴, ✕, ■ and ■ indicate the
29 probability of the difference between the measured value of sensitivity and the corresponding
30 age-corrected normal value, after the general height adjustment, lying within the statistically
31 normal range at $p < 5\%$, $p < 2\%$, $p < 1\%$ and $p < 0.5\%$, respectively
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39 **Fig 3** Stages Three and Four of vigabatrin-associated visual field loss for the Full Field 135
40 Point Screening Test with the three zone age-corrected strategy and for the Central 30-2
41 Threshold Test.
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43 For the Full Field 135 Point Screening Test, ◻ represents a ‘seen’ response to the initial
44 (dimkest) stimulus luminance; ✕ represents a ‘non-seen’ response to the initial (dimkest)
45 stimulus luminance but a ‘seen’ response to the maximum (brightest) stimulus luminance; ■
46 represents a ‘non-seen’ response to the maximum (brightest) stimulus luminance
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49 For the Central 30-2 Threshold Test, MD indicates Mean Deviation, PSD indicates Pattern
50 Standard Deviation and SI indicates Symmetry Index. The symbols ∴, ✕, ■ and ■ indicate the
51 probability of the difference between the measured value of sensitivity and the corresponding
52 age-corrected normal value, after the general height adjustment, lying within the statistically
53 normal range at $p < 5\%$, $p < 2\%$, $p < 1\%$ and $p < 0.5\%$, respectively
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Fig 4 Stages Five and Six of vigabatrin-associated visual field loss for the Full Field 135 Point Screening Test with the three zone age-corrected strategy and for the Central 30-2 Threshold Test.

For the Full Field 135 Point Screening Test, ◻ represents a 'seen' response to the initial (dimmiest) stimulus luminance; ✕ represents a 'non-seen' response to the initial (dimmiest) stimulus luminance but a 'seen' response to the maximum (brightest) stimulus luminance; ■ represents a 'non-seen' response to the maximum (brightest) stimulus luminance

For the Central 30-2 Threshold Test, MD indicates Mean Deviation, PSD indicates Pattern Standard Deviation and SI indicates Symmetry Index. The symbols ∴, ✕, ✕ and ■ indicate the probability of the difference between the measured value of sensitivity and the corresponding age-corrected normal value, after the general height adjustment, lying within the statistically normal range at $p < 5\%$, $p < 2\%$, $p < 1\%$ and $p < 0.5\%$, respectively

Fig 5 The Mean Deviation and Pattern Standard Deviation as a function of the ranked outcome of the Central 30-2 Threshold Test for each eye of the 99 individuals. The circles represent the Mean Deviation and the squares the Pattern Standard Deviation. The black symbols represent the outcome from the right eye and the open symbols that from the left eye

Fig 6. The two components of the symmetry index. The coloured area comprises the data points from one million randomly generated pairs of fields, each of which possesses differing within- and between-eye levels of field loss and represents the likelihood of the symmetry outcome occurring due to chance at $p > 0.01$. The black circles represent individuals exposed to vigabatrin, the vast majority of which lie above the shaded area indicating a high level of symmetry. Note the circles in the bottom left hand corner indicate an absence of symmetry since the fields are normal and those in the top right corner indicate a high degree of symmetry since the fields exhibit advanced loss. The scale on the right hand ordinate indicates the level of probability attributable to a random occurrence of symmetry: any circle lying within the white region exhibits a $p \leq 0.01$ of symmetry occurring due to chance

Fig 7 A case of progressive VAVFL within the central field of each eye, illustrated in terms of the Pattern Deviation probability map. The visual fields up to 82 months from onset of therapy were obtained using the Central 24-2 Threshold Test and subsequently with the Central 30-2 Threshold Test. Vigabatrin was withdrawn after 93 months of therapy. The patient remained asymptomatic. MD indicates Mean Deviation and PSD indicates Pattern Standard Deviation. The outcome of the Full Field 135 Point Screening Test at 101 months is given in Online Resource Fig 5

Staging of vigabatrin-associated visual field loss

Objective derivation of the morphology and staging of visual field loss associated with long-term vigabatrin therapy

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Abstract

Background The morphology and between-eye symmetry of the visual field loss associated with the anti-epileptic drug vigabatrin (VAVFL) has received little attention.

Objective To model the appearance, and ensuing staging, of VAVFL, derived with the European Medicines Agency approved perimetric protocol.

Methods A retrospective, cross-sectional, observational design identified 123 adults who had received vigabatrin for refractory seizures and who had no evidence of co-existing retinogeniculo-cortical visual pathway abnormality. Thirty-eight adults with refractory seizures and identical inclusion criteria, but **no exposure** to vigabatrin, acted as controls. For each group, the median outcome at each stimulus location in each eye (of absolute loss, relative loss or Pattern Deviation probability level, as appropriate) was derived for each successive ten pairs of fields, ranked for severity. Between-eye symmetry was quantified by an index which accounted for severity of loss and which was referenced to the likelihood of the occurrence of symmetry due to chance.

Results The modelled VAVFL was bilateral and highly symmetrical and was described by six stages which were all independent of the extent of vigabatrin exposure. The loss originated in the extreme temporal periphery and encroached centripetally along all meridians towards fixation. The initial appearance within the central field (Stage Two) occurred inferior-nasally. Subsequent stages exhibited increasing loss which was greater nasally than temporally. Stage Six described concentric loss extending to approximately 15° eccentricity from fixation.

Conclusion The model exhibited a consistent pattern of VAVFL. The staging of the loss could assist the risk:benefit analysis of vigabatrin for the treatment of epilepsy.

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3 **Key Points**
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7 In this study of 123 individuals treated with vigabatrin as adjunct therapy for refractory focal
8 seizures and without evidence of other retino-geniculo-cortical visual pathway abnormality,
9 objective modelling, based upon convolution theory used in signal-to-noise processing,
10 identified a consistent pattern of bilateral symmetrical visual field loss obtained using a
11 regulatory approved perimetric protocol. No modelled field loss was present for the 38
12 individuals with identical inclusion criteria but no exposure to vigabatrin.
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22 Six stages of modelled vigabatrin-associated field loss (VAVFL) were evident. Originating in
23 the extreme temporal periphery, the field loss encroached, with increasing severity,
24 centripetally along all meridians towards fixation with greater nasal than temporal loss. Stage
25 Six manifested as concentric loss to within approximately 15° from fixation.
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33 The between-eye mirror symmetry of the VAVFL at all stages, quantified by a novel index,
34 which accounted for the severity of loss, was not attributable to chance ($p \leq 0.01$).
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40 The use of either the Central 30-2 or the Central 24-2 Threshold Tests, alone, will not identify
41 VAVFL until late Stage Two and late stage Three, respectively.
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2 **1.0 Introduction**
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5 The anti-epileptic drug vigabatrin has long been associated with visual field loss (VAVFL) [1-2]
6 which manifests as a bilateral concentric peripheral defect over a continuum of severity and
7 which, generally, also involves the central field to varying extents [3-4]. The field loss is
8 considered to be slowly progressive [5-7] irreversible but non-progressive on withdrawal from
9 vigabatrin [8-9] and asymptomatic until severe loss is present [3, 10-12]. The modelled
10 prevalence of VAVFL in adults increases rapidly after the first two years (2kg cumulative dose)
11 of exposure [13-14] and can reach 75-80% after approximately six years (5kg cumulative dose)
12 [14]. Vigabatrin is now available generically.
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28 The association between vigabatrin and ocular toxicity is currently being re-evaluated [15-17] on
29 the basis that the attribution of the toxicity emanates from retrospective studies which do not
30 include a pre-treatment baseline evaluation. The lack of evidence for the toxicity in the two
31 prospective studies alongside the finding that approximately 25% of individuals suitable for
32 vigabatrin exhibited clinically significant pre-existing reduced visual acuity and/ or visual field
33 loss and/ or peripapillary retinal nerve fibre layer thinning, has led to the suggestion that
34 abnormalities of the afferent system are a co-morbidity of severe refractory epilepsy and are
35 unrelated to vigabatrin [15-16]. However, the limited exposures to vigabatrin and the poor
36 retention of individuals, within these two studies [15-16], together with inappropriate visual field
37 methodologies and analyses, have not facilitated detection of the toxicity.
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56 Surprisingly, there has been little emphasis on the areal and depth characteristics, the between
57 eye-symmetry, and the staging, of VAVFL. Such information is essential not only to identify the
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3 onset and the progression of the VAVFL but also to differentiate it from other types of
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9 (concomitant) field loss.

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The areal extent and the depth of any type of visual field loss is highly dependent upon the perimetric technique used for the examination. VAVFL has been investigated by a variety of methods [7, 10-11, 16, 18-23] but the characteristics of the field loss by each technique have received little attention. Unfortunately, due to the peripheral nature of the field loss, there is no one ideal technique, across the current range of commercially available perimeters, for the assessment of VAVFL. The most pragmatic approach is that approved by the European Medicines Agency (EMA) [23] namely, Three Zone (two luminance level) suprathreshold perimetry, referenced to the age-corrected threshold, of the peripheral field out to a maximum temporal extent of 90° eccentricity and standard automated perimetry of the central field (SAP).

Given the on-going re-evaluation of the association between vigabatrin and visual field loss and the wider availability of the drug, a description of the morphology and staging of the VAVFL resulting from the EMA approved protocol, and derived from individuals with long-term exposures to vigabatrin, would be of benefit to clinicians and to patients, alike. If such a description was based upon a technique which reduced the signal-to-noise ratio and was derived from individuals with no evidence of retino-geniculo-cortical visual pathway abnormality, except that of potential vigabatrin toxicity, the characteristics of the field loss attributable to vigabatrin would become manifest from backgrounds of any unexpected field loss and of any increased variability associated with the response by the patient. Such an approach would also enable the use of the visual fields from individuals with long-term exposures to vigabatrin but with no pre-treatment baseline.

1 The aim of the study, therefore, was threefold: to model the morphology of VAVFL obtained
2 with the EMA approved perimetric protocol and resulting from long-term vigabatrin therapy; to
3 quantify any between-eye symmetry; and to describe the ensuing staging of the field loss.
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10 **2.0 Methods**

11 **2.1 Case series**

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15 A retrospective case series comprising 161 adults with refractory complex partial (focal) seizures
16 was compiled from those presenting to the Alan Richens Unit of the Welsh Epilepsy Centre,
17 University Hospital of Wales, Cardiff, UK, and to associated clinics. All individuals had
18 undergone part or all of the EMA approved protocol with the Humphrey Field Analyzer 750
19 (Carl Zeiss, Meditec, Dublin, CA) namely, the Full Field 135 Point Test with the three zone age-
20 corrected strategy (FF135) and the Central 30-2 Threshold Test (C30-2T) with the FASTPAC
21 strategy. None exhibited ocular or intra-cranial conditions resulting in, or likely to cause, visual
22 field loss, as determined by ophthalmological and neurological examination including whole-
23 brain magnetic resonance imaging. Further exclusion criteria comprised the presence of
24 structural and/or functional ocular abnormalities likely to impede or confound the outcome of
25 perimetry and which are described elsewhere [24]. **There was no conscious selection bias.**
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27 **Individuals were included on the basis of sequential retrieval of cases which met the inclusion/
28 exclusion criteria.**
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2.2 Vigabatrin exposure

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3 Of the 161 individuals (Fig 1, top row), 123 had been exposed to vigabatrin as add-on therapy.
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5 The remaining 38 individuals had received a variety of other antiepileptic drugs and were included
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7 as age-matched controls.
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2.3 Perimetry

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17 Sixty-three of the 123 individuals exposed to vigabatrin and all 38 of those exposed to other
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19 antiepileptic drugs had undergone the complete EMA approved protocol (Fig 1, second row). Of
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21 the remaining 60 individuals exposed to vigabatrin, 24 had undergone the FF135, only, and 36
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23 had undergone the C30-2T, only (Fig 1, second row) as ordered by the treating neurologist on
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25 clinical grounds. Thus, 87 of the 123 individuals exposed to vigabatrin had undertaken the
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27 FF135 and 99 individuals had undertaken the C30-2T.
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36 The visual fields from the first occasion, after the first visit, at which reliable perimetric
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38 outcomes had been achieved were used for the individuals in each of the two groups. The
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40 reliability criteria comprised $\leq 20\%$ incorrect responses to the fixation loss catch trials and $\leq 15\%$
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42 incorrect responses to the false-positive catch trials. A criterion of $\leq 30\%$ incorrect responses was
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44 used for the false-negative catch trials although this was widened with increasing severity of the
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46 field loss [25]. All individuals had been seizure free for a minimum of 24 hours prior to the
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48 visual field examination.
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2.4 Morphology of visual field loss

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3 The Single Field Printouts of the FF135 and of the C30-2T were exported to a personal computer
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5 via a Humphrey Field Analyzer 820 and saved in Tagged Image File Format. The outputs from
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7 each eye for both types of perimetry were then read by custom Naïve Bayesian character
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9 recognition software [26].
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16 The fields were separately sorted for each group, and for each type of perimetry, as right and left
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18 eye pairs, and ranked from the least to the most affected field. The severity of the given pair of
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20 fields was defined as the sum, across the two eyes, of the number of defects, weighted to account
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22 for relative or absolute loss, respectively, derived by the FF135 and/ or for the probability level
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24 of the Pattern Deviation probability map derived by the C30-2T. In the case of those undergoing
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26 both tests, the outcome from the C30-2T was more heavily weighted.
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35 The median outcome for each group at each stimulus location in each eye for each type of
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37 perimetry was then separately calculated for each successive ten pairs of fields, ranked for
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39 severity. Such an approach was based upon convolution theory used in signal processing [27].
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42 The procedure resulted in 54 pairs of modelled fields from the 63 individuals exposed to
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44 vigabatrin who had undergone the combined EMA protocol; 78 pairs for the FF135 and 90 for
45
46 the C30-2T. Twenty-nine pairs of modelled fields resulted from the 38 individuals with no
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48 vigabatrin exposure. The outcomes for the right and left eyes, separately, were then displayed in
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50 terms of Audio Video Interleaved (AVI) movies.
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2.5 Between-eye mirror symmetry of visual field loss

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3 The between-eye mirror symmetry of the field was expressed in terms of a single index which
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5 comprised two components, each of which was a fraction. The index accounted for the severity
6
7 of loss and was compared to the likelihood of obtaining symmetrical field loss due to chance.
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10 The numerator and denominator of the first component constituted of, respectively, the number
11
12 of mirror image stimulus locations between the two eyes which exhibited either relative or
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14 absolute loss for the FF135, or abnormality at $p \leq 0.02$ by Pattern Deviation probability analysis
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16 for the C30-2T, and the total number of locations exhibiting abnormality across the two eyes.
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20 The numerator and denominator of the second component comprised, respectively, the total
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22 number of locations exhibiting abnormality across the two eyes and the total number of stimulus
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24 locations across the two eyes. The index was compared to that obtained from the simulation of
25
26 one million randomly generated pairs of abnormal fields which manifested varying locations,
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28 areas and depths of field loss both within- and between-eyes. The concept was such that
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30 symmetry would become apparent when compared to a series of pairs of fields with varying
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32 characteristics of asymmetric field loss.
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41 The symmetry index was separately calculated for each pair of peripheral, and each pair of
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43 central fields, for the modelled fields and for the measured fields.
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2.6 Staging of the measured fields for those exposed to vigabatrin

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52 The staging of the VAVFL was derived from the modelled fields. The stages were empirically
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54 selected on the basis of clinically meaningful intervals of peripheral field loss and, subsequently,
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56 of central field loss. **These intervals, in turn, were based upon the magnitude of the between-**
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58 **examination physiological variability in the differential light sensitivity as a function of severity**
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of loss [28-29]. The derivation ensured continuity across stages. The staging of the modelled peripheral fields was undertaken masked to that of the modelled central fields. The outcome of the staging of the central and peripheral fields, with respect to one another, was then validated based upon the outcome of the model from the individuals who had undergone the combined protocol. The staging was then applied to each of the 87 pairs of measured fields from the FF135 and to each of the 99 measured fields from the C30-2T.

3.0 Results

3.1 Demographic characteristics of the case series

Of the 123 individuals exposed to vigabatrin, 50 were male and 73 female. Thirty-five were receiving vigabatrin at the time of perimetry. Of the 38 age-matched controls, 17 were male and 21 female. The mean ages of the two groups, at the time of perimetry, were 40.8 years (SD 13.6) and 38.5 years (SD 10.0), respectively.

3.2 Morphology of VAVFL

The rolling medians of the 78 pairs of modelled fields for the FF135 from those exposed to vigabatrin; of the 90 pairs for the C30-2T; and of the 54 pairs for the combined EMA protocol are given in video format in Online Resource Figs 1, 2 and 3, respectively.

The rolling medians of the 29 pairs of modelled fields for the combined EMA protocol from those with no exposure to vigabatrin are given in video format in Online Resource Fig 4. The modelled fields showed was no evidence of visual field loss.

3.3 Staging of VAVFL

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3 The staging of the FF135 and of the C30-2T modelled fields for those exposed to vigabatrin
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5 is shown in Figs 2 to 4.

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11 Sixteen of the 36 individuals exposed to vigabatrin, who had undergone the C30-2T, only,
12 manifested a normal measured central field (Fig 1 third row). These 16 fields were included
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14 in the model, but, in the absence of a peripheral field assessment, the individuals could not be
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19 categorised as to the potential outcome of the toxicity and were considered as equivocal.
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25 Of the remaining 107 individuals exposed to vigabatrin (Fig 1, fourth row), 12 exhibited
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27 normal measured fields and 95 field loss which conformed to the modelled fields and which
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30 was therefore designated as VAVFL.
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36 The frequency, by stage, of VAVFL is shown in Fig 1 (bottom row). Fourteen of the 95
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38 individuals with VAVFL exhibited Stage One VAVFL, 21 Stage Two, 14 Stage Three, 22
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41 Stage Four, 10 Stage Five and 14 Stage Six.
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47 The relationship between the stage of loss and the summary measures of the visual field,
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49 Mean Deviation (MD) and Pattern Standard Deviation, for the C30-2T measured fields is
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52 shown in Fig 5.
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3.4 Between-Eye Mirror Symmetry of VAVFL

The two components of the symmetry index for the FF135 and for the C30-2T are shown in Online Resource Videos 1, 2 and 3; at each stage of the modelled VAVFL in Figs 2 to 4; and for each measured field of those exposed to vigabatrin in Fig 6.

3.5 Demographics of VAVFL

The difference in the proportion with VAVFL by gender, 39 out of 44 males and 56 out of 63 females, was not statistically significant.

The mean age, at the time of perimetry, of those with VAVFL, 41.6 years (SD 14.4), was also similar to that of those exposed to vigabatrin but with normal fields, mean 37.9 years (SD 7.9).

Those with VAVFL manifested a greater cumulative dose (mean 7.94kg; SD 4.45; range 1.1 to 20.7) and a longer duration of therapy (8.86 years; SD 3.51; range 0.66 to 16.05) at the time of perimetry than those without field loss (mean 3.36kg; SD 4.77; range 0.11 to 16.14; and mean 3.62 years; SD 3.94; range 0.33 to 11.83; respectively). The difference between means (Student's t-test for two independent samples) were 4.58 kg (95% CI 1.71-7.45; $p < 0.001$) and 5.25 years (95% CI 2.98-7.53; $p < 0.001$), respectively.

There was no evidence of a relationship between the stage of the VAVFL and the extent of the exposure to vigabatrin at the time of perimetry. The median exposures at the time of

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perimetry which resulted in Stage One loss were 7.7kg cumulative dose (IQR 4.8, 12.1; range 1.5-13.3) and 9.4 years (IQR 6.2, 12.1; range 2.4-16.1) and which resulted in Stage 6 loss were 6.7kg cumulative dose (IQR 4.4, 10.6; range 2.8-19.0) and 7.7 years (IQR 5.3, 10.6; range 3.1-13.0).

There was also no association between the stage of VAVFL and either age, age at onset of epilepsy or age at onset of vigabatrin.

4.0 Discussion

The objective rolling median and symmetry index outcomes from the FF135 and the C30-2T confirm that vigabatrin is associated with symmetrical bilateral visual field loss. The VAVFL manifests over a range of severities that can be described in six stages. The field loss originates in the extreme temporal periphery and, as the severity increases, encroaches centripetally along all meridians towards fixation resulting in bi-nasal loss and relative temporal sparing until the end stage (Stage Six) which manifests as a concentric loss to within approximately 15° from fixation. The initial appearance in the central field (Stages Two and Three) is primarily inferior-nasally. VAVFL exhibits a high degree of between-eye mirror symmetry at each stage of loss. In contrast, the modelled field for the age-matched control individuals with no exposure to vigabatrin was entirely normal.

The apparent absence of initial loss superior-nasally within the central field is most likely attributable to the greater defect depth in this region required to achieve statistical significance. The latter, in turn, arises from the wider distribution of normal values arising

1 from the between-individual variation in the position of the upper eyelid and from the
2 increased variability in response associated with the steeper gradient of the superior visual
3 field, compared to those inferior-nasally.
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10 The fundamental strengths of this retrospective study were the robust exclusion of individuals
11 with retino-geniculo-cortical visual pathway abnormality; the inclusion of long-term
12 exposures to vigabatrin (median 8.8 years; IQR 5.7 to 11.3; range 0.1 to 16.1) many of which
13 are unparalleled in the literature; and the utilisation of the two novel objective techniques
14 which have not previously been applied to perimetry. These latter techniques enabled
15 objective descriptions of the characteristics and between-eye mirror symmetry of VAVFL.
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29 The modelled field at all six stages is in agreement with that derived from cross-sectional
30 retrospective evidence with kinetic perimetry [4]. The initial manifestation of the VAVFL in
31 this latter model was defined as a 'non-seen' response to the Goldmann V4e isopter at 80°
32 temporally and/ or at 40° nasally. This definition is entirely consistent with the location and
33 depth of the loss described as Stage One in the current study: the absolute loss designated by
34 the FF135 is equivalent to the Goldmann V4e stimulus. The increasing encroachment into the
35 nasal field with relative sparing of the temporal field, during Stages Two to Five, is
36 compatible with the model out to approximately 80° temporally, derived from cross-sectional
37 evidence, using suprathreshold perimetry equivalent to the I4e isopter [30].
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55 The model was developed from the visual fields of adults. The reduction in amplitude of the
56 30Hz flicker cone electroretinogram (ERG) in infants treated with vigabatrin for infantile
57 spasms [31] is compatible with that for adults manifesting VAVFL [32]. Similarly, the
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1 topographical characteristics of the reduced peripapillary retinal nerve fibre layer thickness in
2 children [33] is also compatible with that found in adults [34-38]. Those with vigabatrin-
3 associated 30Hz flicker cone ERG abnormality in infancy subsequently manifest VAVFL,
4 and corresponding retinal nerve fibre layer thinning, in later childhood/ early adolescence
5 [39]. There is no reason to suggest, therefore, that the vigabatrin toxicity manifested in
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The ophthalmological examinations were undertaken by any one of four ophthalmologists,
depending upon the particular clinic, who were all unaware of the findings from their
colleagues. All four were aware of the anti-epileptic drug history and, usually, of the visual
field outcome. However, the modelling of the visual fields from those exposed to vigabatrin
and from the control individuals was objective and independent of the outcome from the
ophthalmological and neurological examinations.

The most common bilateral finding by fundoscopy, through a dilated pupil, was either
generalised or localised arteriolar narrowing which was noted at all stages of VAVFL.
However, this finding was occasionally found in the presence of a normal field and,
therefore, may well be associated with vigabatrin usage. Subtle bilateral retinal nerve fibre
layer changes and optic nerve head pallor were noted from Stage 4 onwards. A variety of
bilateral peripheral degenerative changes were also noted including hypopigmented/ white
spots and surface wrinkling. However, there was considerable variation in the fundal
appearance between-individuals within a given stage. The various features are in agreement
with those reported previously [3, 22, 40-41], were often subtle, and suggest that there is a

1 wide spectrum of potential retinopathy associated with vigabatrin toxicity. There was no
2 evidence of such findings in the individuals with no exposure to vigabatrin. Twenty-nine
3 individuals exposed to vigabatrin had undergone optical coherence tomography of the
4 peripapillary retinal nerve fibre layer at the time of the examination. All three individuals
5 who manifested a normal visual field exhibited a normal nerve fibre layer thickness. Of the
6 three individuals who had Stage 1 loss, two exhibited a normal thickness. An abnormally thin
7 nerve fibre layer, characteristic of vigabatrin toxicity [34-38], was present from Stage 2
8 onwards in 22 individuals. The one remaining individual manifested early Stage 2 VAVFL
9 and a normal a normal nerve fibre layer thickness.
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25 The outcome of the current study and of the earlier models [4, 28] indicates that perimetry
26 out to 60° eccentricity [42] is inadequate to detect Stage One and also possibly early Stage
27 Two loss. Similarly, a worsening of 3dB from the baseline Mean Deviation (MD) index for
28 the C30-2T, which was used as a primary outcome measure for the presence of VAVFL in
29 the prospective Phase IV study [16], will not detect VAVFL until late in Stage Two or early
30 in Stage Three. The MD is a summary measure of the central field and does not describe the
31 spatial appearance of visual field loss: in the current study, the median MDs for the
32 individuals exposed to vigabatrin and for the controls was -1.75dB and -1.23dB, respectively.
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49 It is clear from the staging of the VAVFL that perimetry should initially be undertaken with,
50 in the case of the Humphrey Field Analyzer, the FF135. If the field is normal to the FF135 or
51 exhibits Stage One abnormality, the C30-2T is unnecessary. If the peripheral field exhibits
52 Stage Two abnormality to the FF135, the C30-2T should also be undertaken to reveal the full
53 depth of the loss since the magnitude of the Pattern Deviation value required for statistical
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1 significance at the extreme nasal locations within the central field can be less than the 8dB
2 suprathreshold increment of the stimulus luminance of the FF135. If the FF135 indicates
3 both peripheral and central loss, i.e., Stage Three and worse, subsequent examinations need
4 only be undertaken with the C30-2T. The Central 24-2 Threshold Test, alone, should only be
5 used for Stage Six. The characteristics of VAVFL are more prominent with the FASTPAC
6 algorithm than with the SITA Standard or Fast algorithms which were designed to detect
7 glaucomatous field loss. The peripheral manifestation of VAVFL is fortuitous since, in our
8 experience, patients exposed to vigabatrin find suprathreshold perimetry considerably easier
9 to perform than SAP. In cases where patients are unable to undertake SAP, assessment with
10 the FF135, although collecting less information about relative loss, is acceptable.
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28 The staging of VAVFL was derived from cross-sectional evidence and does not imply
29 progressive loss. Due to the potency of the potential toxicity, most individuals had been
30 withdrawn from vigabatrin either immediately prior to the introduction into the care regime
31 of the visual field examination or following confirmation of the VAVFL. As such, neither the
32 probability of progression at each stage nor an estimate of the rate of progression can be
33 determined. However, the presumption is that, given continued vigabatrin therapy, VAVFL
34 will progress through the various stages. The lack of an association between the stage of loss,
35 at detection, and either the duration or the cumulative dose of vigabatrin implies that the
36 relationship between the extent of exposure and both the onset and the severity of VAVFL
37 varies depending upon the individual susceptibility to vigabatrin. However, the time of
38 detection is not the time to onset of the VAVFL. The rate of any subsequent progression,
39 therefore, remains unknown. A case of progressive loss during approximately 7.75 years of
40 vigabatrin therapy and illustrated in terms of the Pattern Deviation probability map of the
41 Central 24-2 Threshold Test and, subsequently, the C30-2T is shown in Fig 6. The outcome
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1 of the corresponding FF135 at the final visit is shown in Online Resource Fig 4. Progressive
2 loss whilst on therapy has been shown over a mean follow-up of 10.7 years; the rate of
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4 reduction in the I4e isopter of kinetic perimetry increased with increase in cumulative dose
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6 [6]. An unpublished audit of the long-term follow-up, over a maximum of eight years, of
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8 individuals in the current study indicates that the VAVFL neither improves nor deteriorates
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10 following withdrawal of vigabatrin.
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18 The appearance of Stage One VAVFL should act as an alert signal for a re-evaluation of the
19 management of the epilepsy. This may encompass either a change in anti-epileptic drug
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21 therapy or an increase in the frequency of neuro-ophthalmological monitoring. However, the
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23 extreme peripheral stimulus locations of the FF135 are also influenced by the facial anatomy,
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25 particularly superiorly and inferior-nasally. The outcome of the examination at such
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27 locations, and those in the extreme temporal periphery, is also dependent upon the vigilance
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29 of the patient. Indeed, normal individuals do not necessarily produce statistically normal
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31 visual fields. The FF135 commences with the examination of the central field. Once
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33 completed, the examination pauses for removal of the trial lenses prior to the examination of
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35 the peripheral field. Instructions to the patient, during this pause, to the effect that the stimuli
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37 are about to appear in the (extreme) periphery, together with an exhortation to keep the eye
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39 ‘wide open’, generally leads to a ‘seen’ response, in the normal eye, at these extreme
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41 locations. However, individuals with epilepsy frequently exhibit greater within-examination
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43 variability than normal individuals, which can lead to the impression of visual field loss, and
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45 approximately 30% of individuals with epilepsy are unable to undertake perimetry of any
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47 type [15,32]. The clinical skill lies in the identification of actual visual field loss,
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49 characteristic of the given lesion, from apparent visual field loss due to increased variability
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1 and/ or an inability to understand the requirements of the test. In addition, VAVFL frequently
2 co-exists with that arising from an intra-cranial lesion.
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8 Fourteen individuals exhibited Stage Six VAVFL. Great care was taken to exclude individuals
9 manifesting visual field loss of suspected psychogenic origin from the case series [43]. Three
10 of these 14 individuals had undergone optical coherence tomography and exhibited severe
11 thinning of the retinal nerve fibre layer. All 14 individuals exhibited profoundly impaired
12 mobility and reported symptoms explainable by their VAVFL, the most common of which was
13 bumping into individuals in crowded locations. However, some individuals with Stage 5
14 VAVFL also reported a negative impact on their activities of daily living.
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29 The study utilised a retrospective cross-sectional design. However, the objective derivation of
30 field loss based upon signal-to-noise theory, further supported by the stringent
31 ophthalmological and neurological inclusion criteria, uniquely facilitated a retrospective
32 design and largely obviated the need for a prospective study referenced to a pre-treatment
33 baseline.
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45 The variable and lengthy time to onset of VAVFL together with the opportunity to study a
46 wide range of long-term exposures, further highlights the pragmatism of this retrospective
47 study compared to a prospective study. Nevertheless, prospective longitudinal studies over
48 the long-term would unequivocally rule out the presence of abnormality at baseline and
49 would also determine the evolution of the field loss.
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5.0 Conclusions

The appearance of VAVFL has received little attention. This absence of knowledge hinders not only the recognition of the onset, and of any progression, of the field loss but also the differentiation from other (concomitant) types of loss. The staging of the VAVFL derived from a regulatory approved perimetric protocol, and reported here, should assist clinicians and patients, alike, in the risk:benefit analysis of vigabatrin for the treatment of epilepsy.

6.0 Compliance with Ethical Standards

Funding None

Conflicts of interest John M Wild, Phillip EM Smith and Carlo Knupp declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Local Research and Ethics Committee ruled that approval was not required for this study. The visual field assessments were considered to be part of normal good clinical practice. The visual fields were de-identified and so written informed consent was not required.

Data availability The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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2 **Figure Captions**
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6 **Fig 1** The number of individuals by anti-epileptic drug exposure, type of perimetry and visual
7 field outcome. Equivocal indicates a normal outcome to the Central 30-2 Threshold Test;
8 however, in the absence of the Full Field 135 Point Screening Test with the three zone age-
9 corrected strategy, an evaluation for VAVFL was not possible. VAVFL indicates vigabatrin-
10 associated visual field loss
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17 **Fig 2** Stages One and Two of vigabatrin-associated visual field loss for the Full Field 135
18 Point Screening Test with the three zone age-corrected strategy and for the Central 30-2
19 Threshold Test
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21 For the Full Field 135 Point Screening Test, ◻ represents a 'seen' response to the initial
22 (dimmest) stimulus luminance; ✕ represents a 'non-seen' response to the initial (dimmest)
23 stimulus luminance but a 'seen' response to the maximum (brightest) stimulus luminance; ■
24 represents a 'non-seen' response to the maximum (brightest) stimulus luminance
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27 For the Central 30-2 Threshold Test, MD indicates Mean Deviation, PSD indicates Pattern
28 Standard Deviation and SI indicates Symmetry Index. The symbols ◻, ✕, ■ and ■ indicate the
29 probability of the difference between the measured value of sensitivity and the corresponding
30 age-corrected normal value, after the general height adjustment, lying within the statistically
31 normal range at $p < 5\%$, $p < 2\%$, $p < 1\%$ and $p < 0.5\%$, respectively
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41 **Fig 3** Stages Three and Four of vigabatrin-associated visual field loss for the Full Field 135
42 Point Screening Test with the three zone age-corrected strategy and for the Central 30-2
43 Threshold Test.
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45 For the Full Field 135 Point Screening Test, ◻ represents a 'seen' response to the initial
46 (dimmest) stimulus luminance; ✕ represents a 'non-seen' response to the initial (dimmest)
47 stimulus luminance but a 'seen' response to the maximum (brightest) stimulus luminance; ■
48 represents a 'non-seen' response to the maximum (brightest) stimulus luminance
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51 For the Central 30-2 Threshold Test, MD indicates Mean Deviation, PSD indicates Pattern
52 Standard Deviation and SI indicates Symmetry Index. The symbols ◻, ✕, ■ and ■ indicate the
53 probability of the difference between the measured value of sensitivity and the corresponding
54 age-corrected normal value, after the general height adjustment, lying within the statistically
55 normal range at $p < 5\%$, $p < 2\%$, $p < 1\%$ and $p < 0.5\%$, respectively
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6 **Fig 4** Stages Five and Six of vigabatrin-associated visual field loss for the Full Field 135
7 Point Screening Test with the three zone age-corrected strategy and for the Central 30-2
8 Threshold Test.
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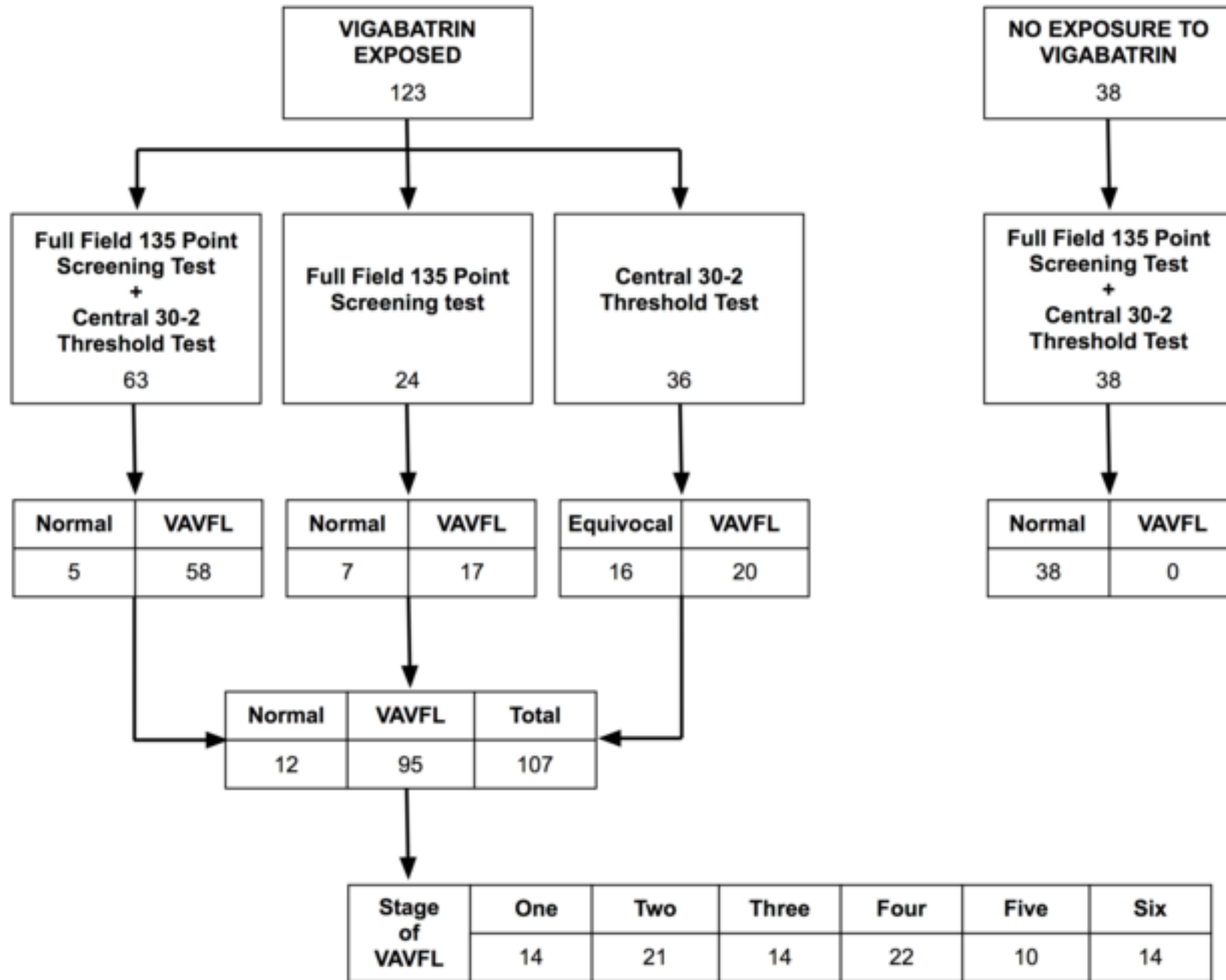
10 For the Full Field 135 Point Screening Test, ◻ represents a 'seen' response to the initial
11 (dimkest) stimulus luminance; ✕ represents a 'non-seen' response to the initial (dimkest)
12 stimulus luminance but a 'seen' response to the maximum (brightest) stimulus luminance; ■
13 represents a 'non-seen' response to the maximum (brightest) stimulus luminance
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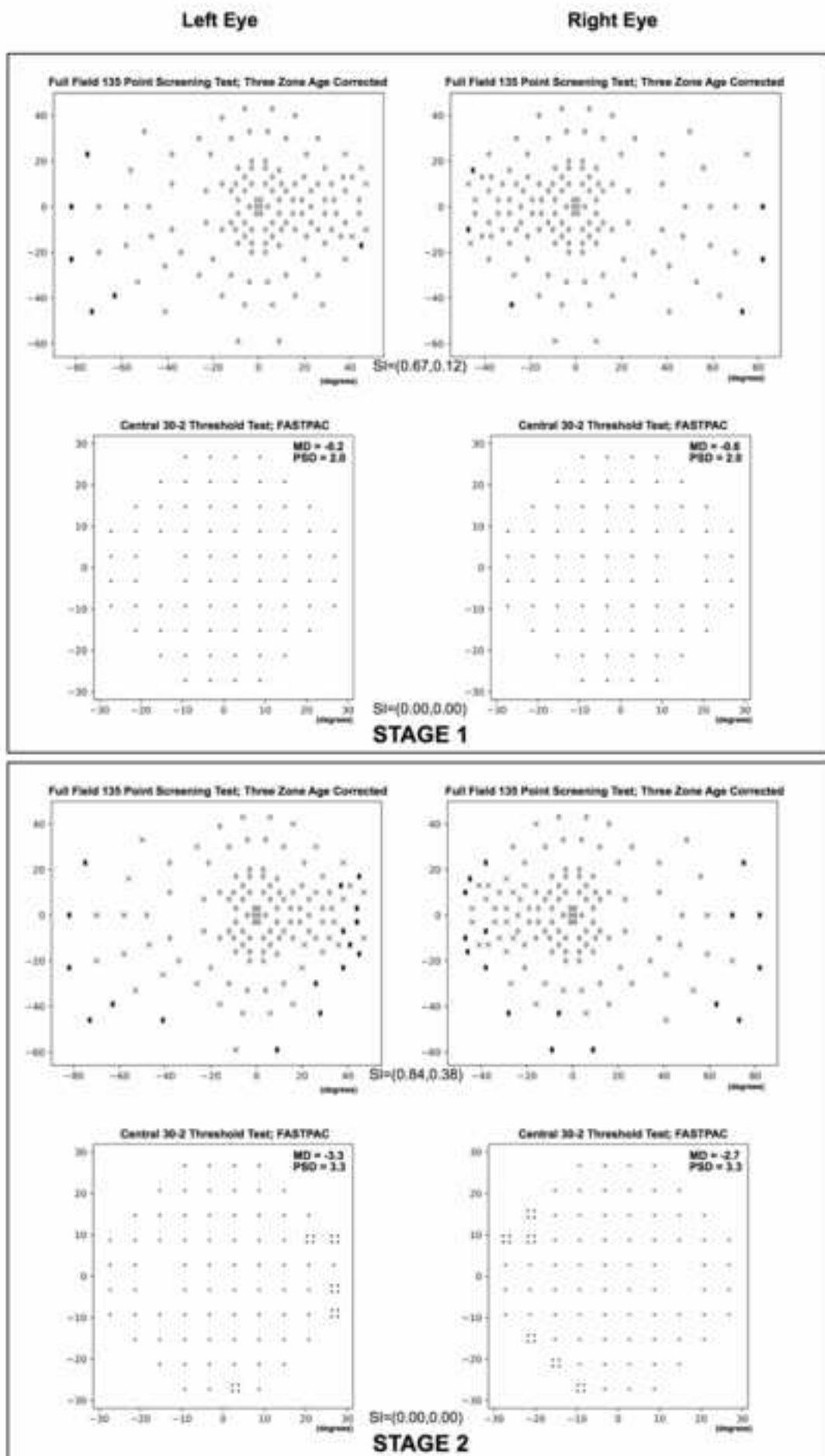
16 For the Central 30-2 Threshold Test, MD indicates Mean Deviation, PSD indicates Pattern
17 Standard Deviation and SI indicates Symmetry Index. The symbols ∴, ✕, ✕ and ■ indicate the
18 probability of the difference between the measured value of sensitivity and the corresponding
19 age-corrected normal value, after the general height adjustment, lying within the statistically
20 normal range at $p < 5\%$, $p < 2\%$, $p < 1\%$ and $p < 0.5\%$, respectively
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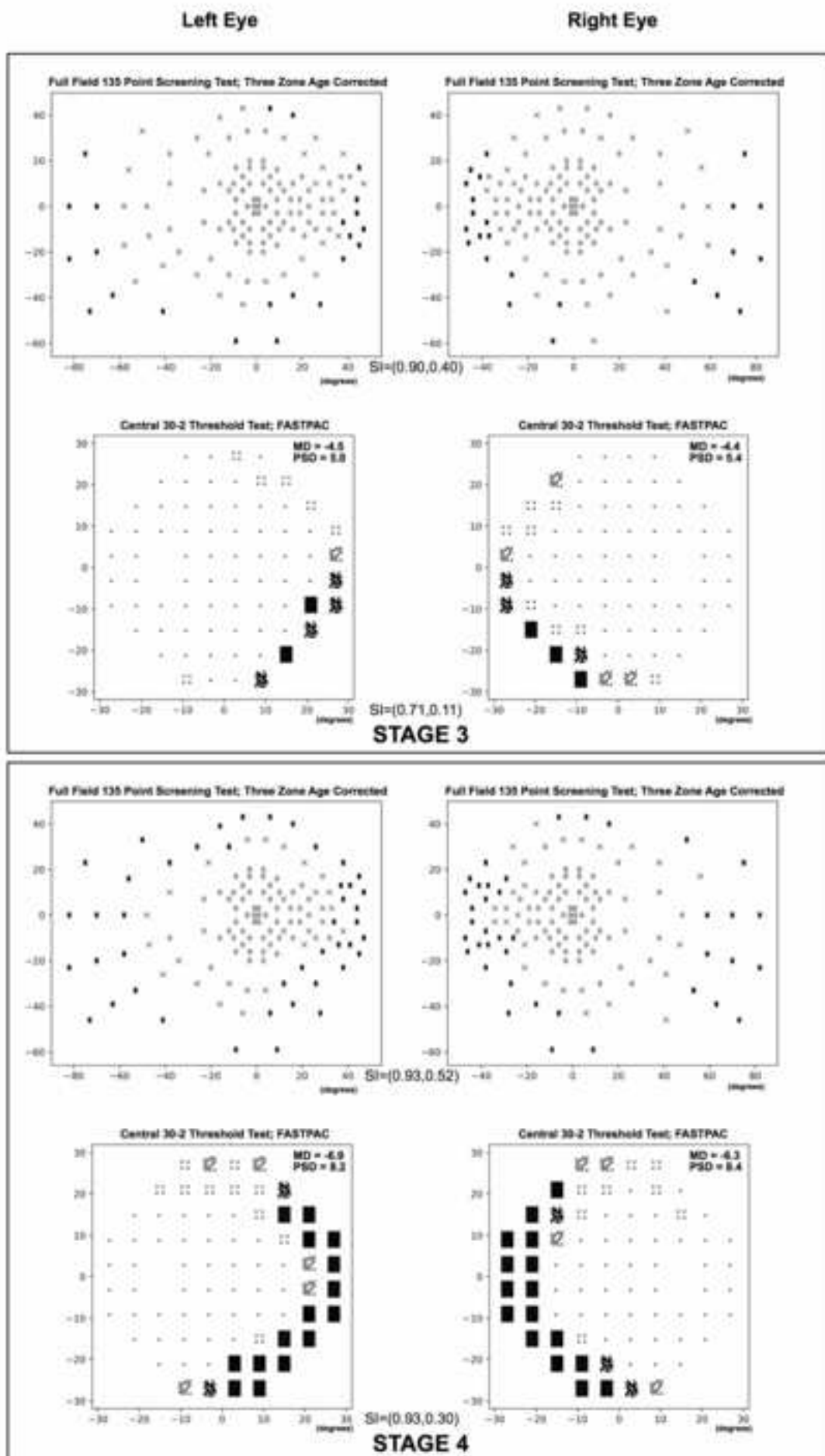
25 **Fig 5** The Mean Deviation and Pattern Standard Deviation as a function of the ranked
26 outcome of the Central 30-2 Threshold Test for each eye of the 99 individuals. The circles
27 represent the Mean Deviation and the squares the Pattern Standard Deviation. The black
28 symbols represent the outcome from the right eye and the open symbols that from the left eye
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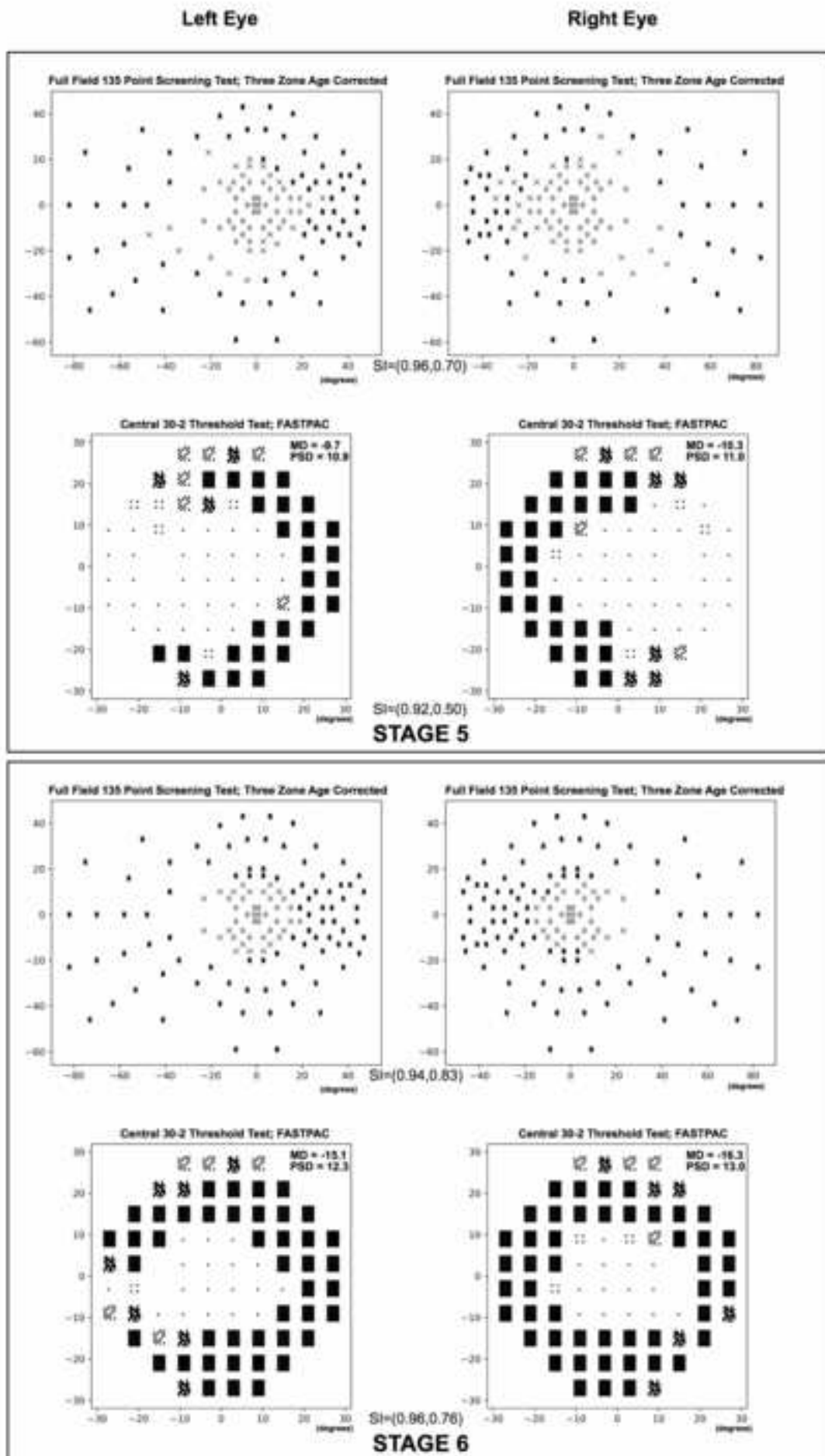
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35 **Fig 6.** The two components of the symmetry index. The coloured area comprises the data
36 points from one million randomly generated pairs of fields, each of which possesses differing
37 within- and between-eye levels of field loss and represents the likelihood of the symmetry
38 outcome occurring due to chance at $p > 0.01$. The black circles represent individuals exposed
39 to vigabatrin, the vast majority of which lie above the shaded area indicating a high level of
40 symmetry. Note the circles in the bottom left hand corner indicate an absence of symmetry
41 since the fields are normal and those in the top right corner indicate a high degree of
42 symmetry since the fields exhibit advanced loss. The scale on the right hand ordinate
43 indicates the level of probability attributable to a random occurrence of symmetry: any circle
44 lying within the white region exhibits a $p \leq 0.01$ of symmetry occurring due to chance
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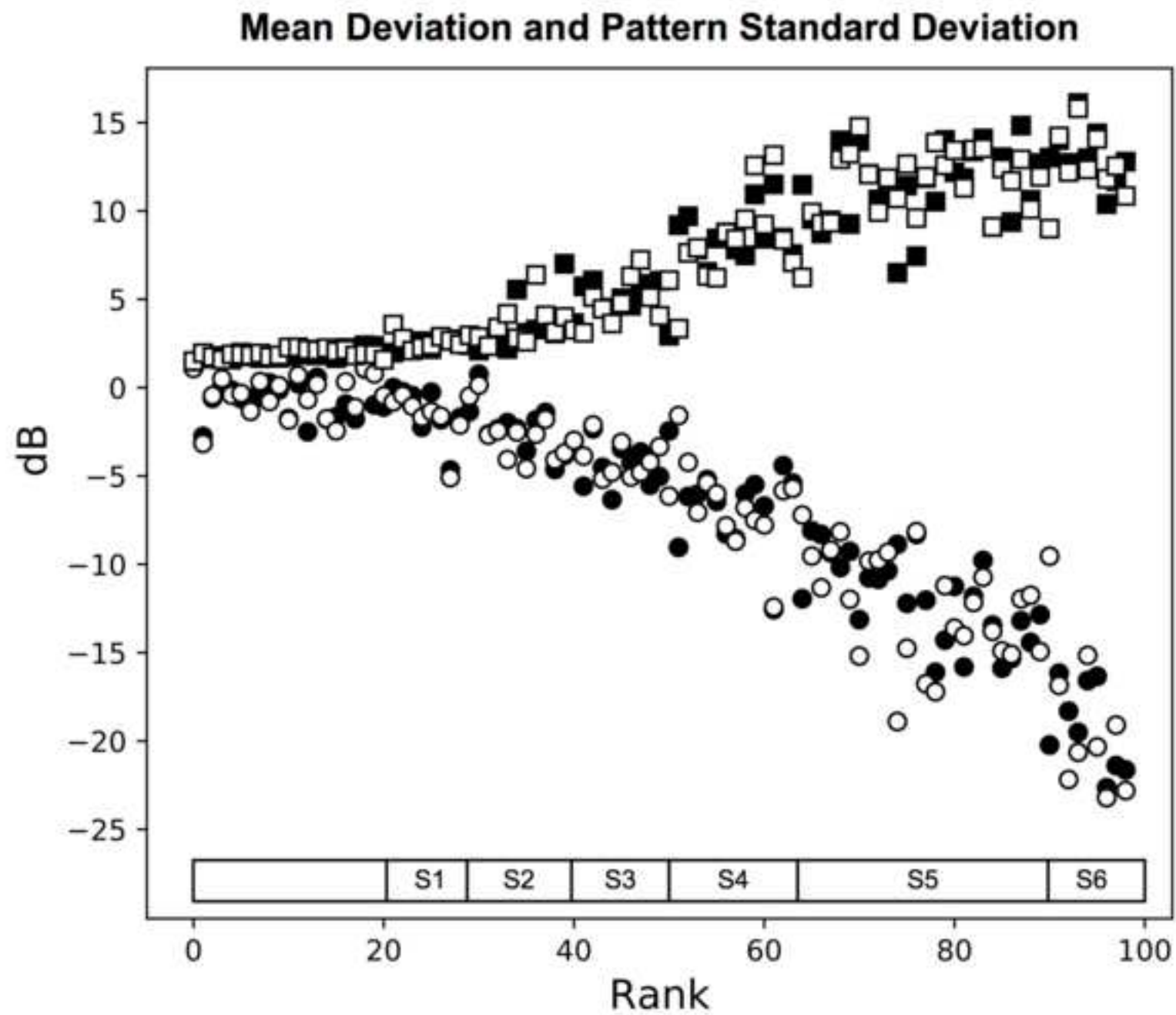
51 **Fig 7** A case of progressive VAVFL within the central field of each eye, illustrated in terms
52 of the Pattern Deviation probability map. The visual fields up to 82 months from onset of
53 therapy were obtained using the Central 24-2 Threshold Test and subsequently with the
54 Central 30-2 Threshold Test. Vigabatrin was withdrawn after 93 months of therapy. The
55 patient remained asymptomatic. MD indicates Mean Deviation and PSD indicates Pattern
56 Standard Deviation. The outcome of the Full Field 135 Point Screening Test at 101 months is
57 given in Online Resource Fig 5
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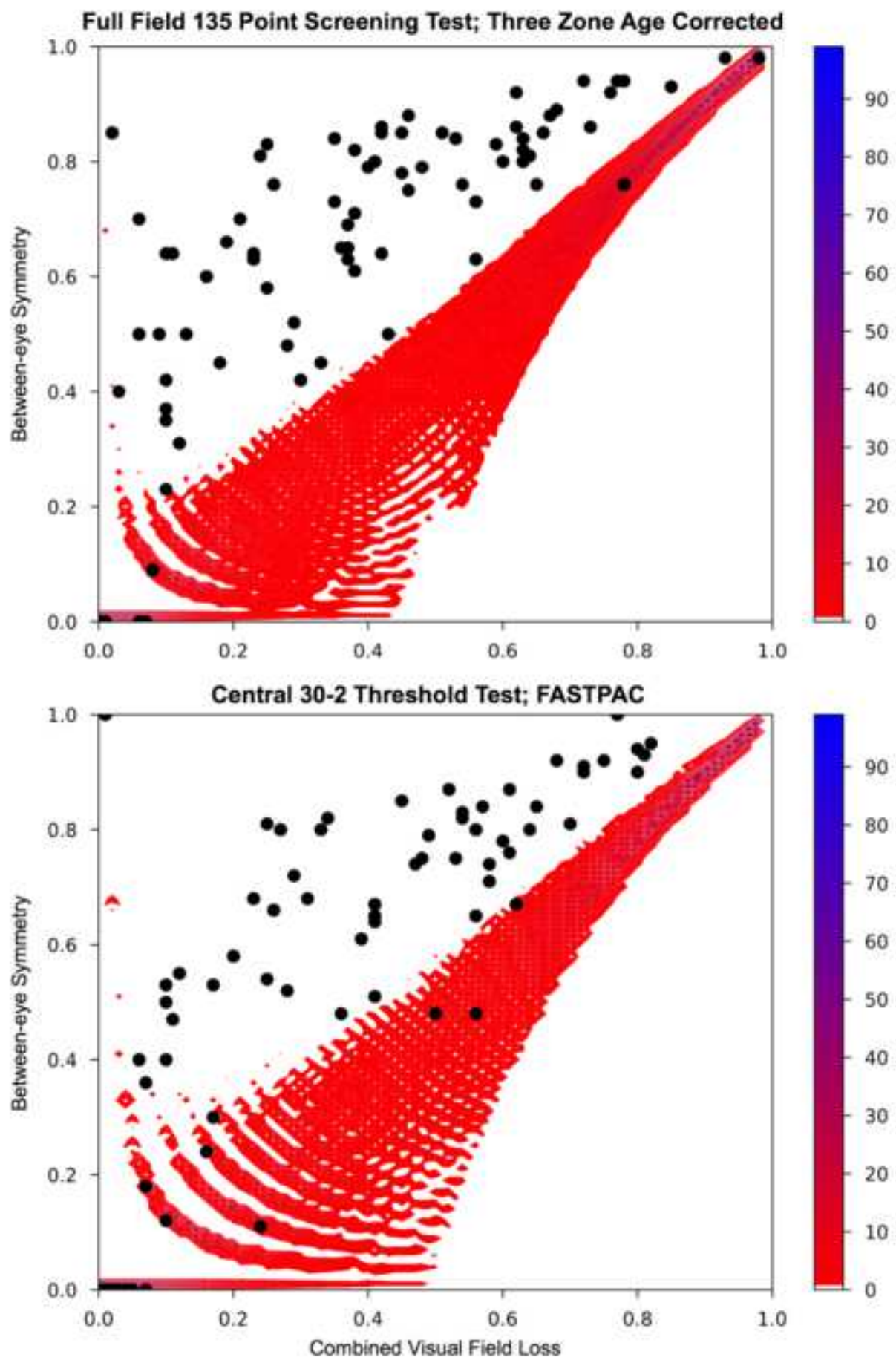


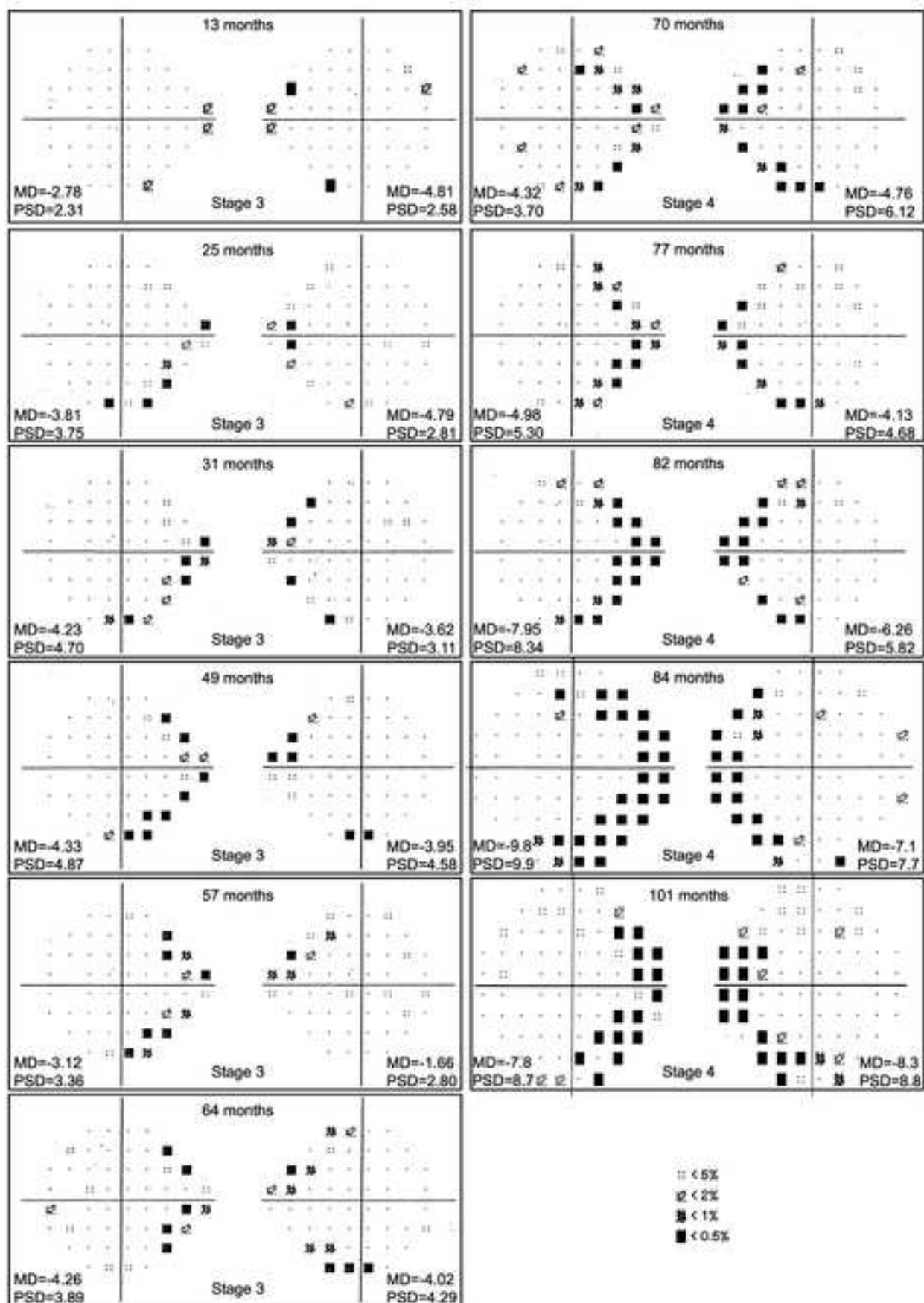












Objective derivation of the morphology and staging of visual field loss associated with long-term vigabatrin therapy

CNS Drugs

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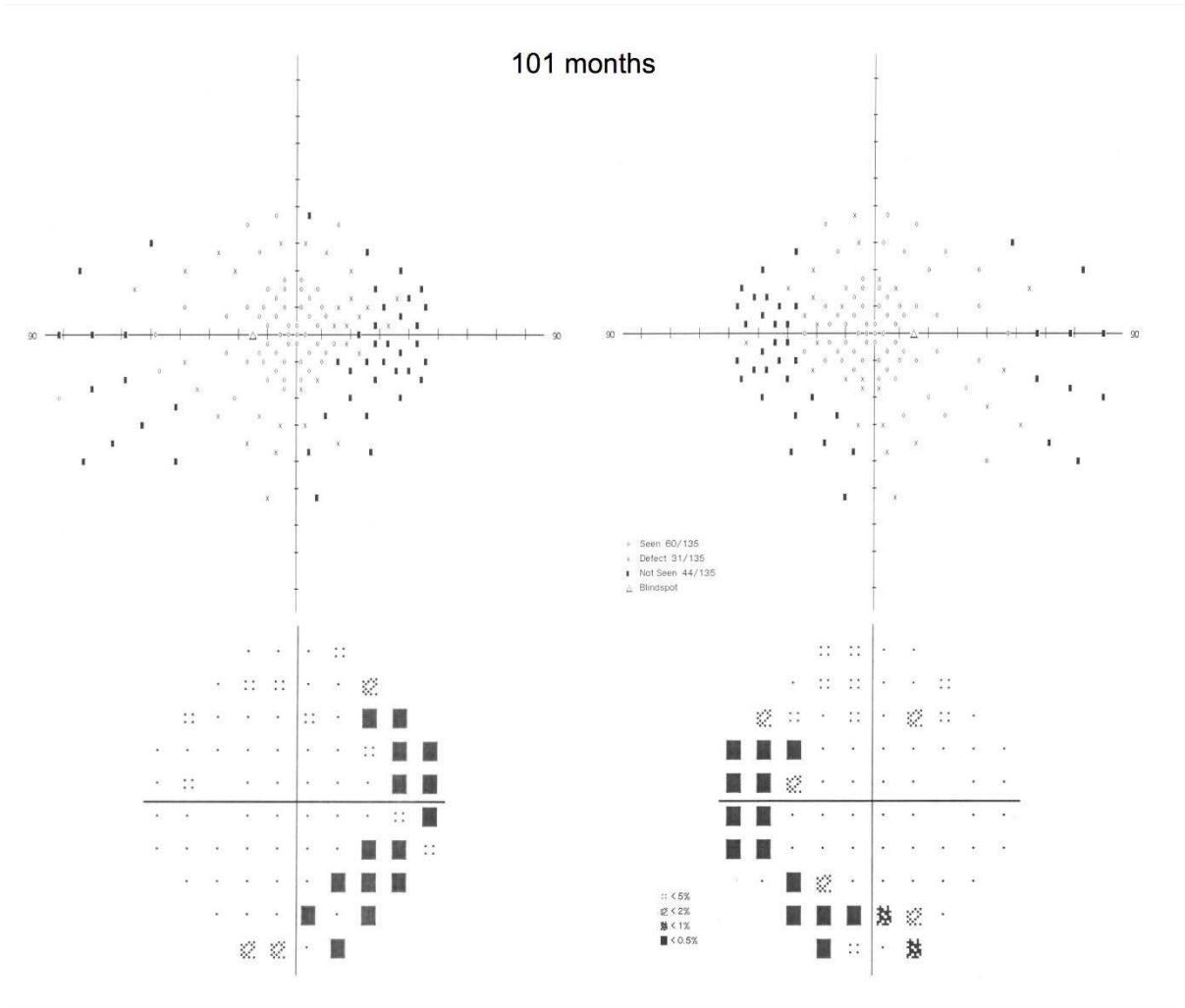
Online Resource Fig 1 Video of the rolling median of the 78 modelled fields from the 87 individuals who had been exposed to vigabatrin and who had undertaken the Full Field 135 Point Test with the three zone age-corrected strategy

Online Resource Fig 2 Video of the rolling median of the 90 modelled fields from the 99 individuals who had been exposed to vigabatrin and who had undertaken the Central 30-2 Threshold Test

Online Resource Fig 3 Video of the rolling median of the 54 modelled fields from the 63 individuals who had been exposed to vigabatrin and who had undertaken the combined Full Field 135 Point Test with the three zone age-corrected strategy and the Central 30-2 Threshold Test

Online Resource Fig 4 Video of the rolling median of the 29 modelled fields from the 38 individuals with no exposure to vigabatrin and who had undertaken the combined Full Field 135 Point Test with the three zone age-corrected strategy and the Central 30-2 Threshold Test

All video files are available here: <https://doi.org/10.6084/m9.figshare.7981592>



Online Resource Fig 5 The outcome of the Full Field 135 Point Screening Test at 101 months for the case shown in Fig 5 together with that of the Central 30-2 Threshold Test



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