Epilepsy Research (2009) **87**, 213—222

journal homepage: www.elsevier.com/locate/epilepsyres

Visual impairment at large eccentricity in participants treated by vigabatrin: Visual, attentional or recognition deficit?

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Received 26 June 2009; received in revised form 9 August 2009; accepted 4 September 2009
Available online 2 October 2009

KEYWORDS
Epilepsy;
Vigabatrin;
Vision;
Spatial attention;
Object recognition;
Eccentricity

Summary A relationship between peripheral visual field loss and vigabatrin (VGB) has been reported in several studies but with inconsistent results. We investigated the level of visual processing at which the impairment occurs: attentional or cognitive (recognition) deficit. A simple reaction time task was used as a baseline condition. A spatial attention task measured the benefit and cost for the detection of a target appearing at a cued or at an uncued location. A rapid categorization task assessed object recognition. Performance was tested at eccentricities varying from 30° to 60° on a panoramic screen covering 180°. Participants were patients with epilepsy treated with VGB, patients treated with other drugs and healthy controls. In the VGB group 9 patients exhibited a mild visual field constriction. We observed a general slowing down of response times in participants treated by VGB, especially at 60° eccentricity but their performance remained above chance at large eccentricity in the most complex categorization task. The slowing down of visual processing at large eccentricity for flashed stimuli suggests that VGB treated patients might be impaired at detecting moving objects in the periphery and this may have consequences in behavioural tasks like driving.

Introduction

Vigabatrin (VGB) is a well-tolerated drug used for the treatment of partial seizures in adults and children. It is considered to be particularly effective in patients affected by drug-resistance epilepsy. The anticonvulsant properties of VGB increase in a dose-dependant manner. It was used until the late 1990s when isolated reports of concentric peripheral visual field loss and

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doi:10.1016/j.eplepsyres.2009.09.003

visual electrophysiological abnormalities started to be reported.

An association between visual field loss and VGB has been reported in several studies. Manuchehri et al. (2000) used the static perimetry of Humphreys to compare the visual field of patients treated with VGB and patients treated with other medications. A significant difference was found between patients treated with VGB in whom 11/15 patients exhibited greater than 10% visual field loss as compared to patients treated with other medications in whom only 1/11 patients were affected. Similar results have been reported in several other studies (Ruether et al., 1998; Lawden et al., 1999; Kälviäinen et al., 1999; Krakow et al., 2000).

Other investigations have suggested that loss of visual field under VGB might correlate with certain aspects of electrophysiological measurements. For instance Comaish et al. (2002) compared the electro-retinogram (ERG) and the electro-oculogram of 14 patients treated with VGB and 10 patients treated with other medications. Patients treated with VGB exhibited constricted visual field compared to patients treated with other drugs. Abnormalities were found in both electro-retinography and electro-oculography and the visual field loss was correlated with the reduction in oscillatory potentials. Similar results were reported by Johnson et al. (2000). The most consistent ERG changes associated with impaired visual field under VGB included increased latency of the ERG photopic b-wave, decreased magnitude of the b-wave, reduced or absent oscillatory potentials and abnormalities of the cone (30 Hz) flicker response (Krauss et al., 1998; Wild et al., 1999; Kälviäinen et al., 1999; Harding et al., 1998—1999; Harding et al., 2000a; Johnson et al., 2000; Besch et al., 2002; Westall et al., 2002). Abnormal multifocal ERGs have also been identified in patients under VGB together with co-existing visual impairments (Harding et al., 2000b; Ponjavic and Andreasson, 2001; Besch et al., 2002). However the site of abnormality is not always restricted to the area corresponding to visual field damage. Indeed, reports of altered cone responses (Krauss et al., 1998; Besch et al., 2002) indicate that VGB mediated toxicity is not confined to the peripheral retina, but is widespread including central retina. For instance, Parisi et al. (2004) reported abnormalities in ERG without visual field loss. A 13-year-old patient was tested using the Humphrey Visual Field Analyser and electro-retinography before and after the beginning of vigabatrin therapy. Both visual field and ERG were normal before the onset of VGB therapy. Six months after the beginning of VGB monotherapy, the patient underwent a further complete ophtalmological examination which was normal except for the ERG showing a decrease in the scotopic threshold response.

Abnormal colour perception has also been found in patients treated by VGB. Nousiainen et al. (2000) reported acquired colour vision deficits in patients treated with VGB monotherapy that predominated in the tritanoptic axis and were associated with the temporal extent of visual field loss. Mecarelli et al. (2001) investigated the effect of a single dose of VGB on healthy volunteers using colour visual evoked potentials and colour perimetry. They reported a selective tritanoptic visual impairment. Steinhoff et al. (1997) observed no change in the D15 colour vision test in normal healthy volunteers who had received a single AED dose of VGB but increased post-adaptation, increment and transient tritanopia thresholds did occur. Similar findings were reported with the same battery applied to a group of epileptic patients chronically treated with a mixture of VGB and carbamazepine (Steinhoff et al., 1997). In another study involving colour discrimination using the Farnsworth-Munsell 100-hue test in epileptic patients who had undergone a treatment with VGB, 33% of the patients exhibited below average colour discrimination (Hilton et al., 2002). This finding suggests a diffuse, or generalised, deficit in colour perception consistent with toxic damage affecting equally all chromatic pathways.

Nousiainen et al. (2000) measured contrast sensitivity in a VGB monotherapy epilepsy group and reported impaired contrast sensitivity function in patients. Surveys of children treated with VGB have shown that up to half of them exhibited abnormal visual acuity and reduced contrast sensitivity (Westall et al., 2000; Peron et al., 2001; Hilton et al., 2002), reported abnormal contrast sensitivity in 66% of the patients who had received VGB polytherapy.

The effects of VGB on early levels of visual processing (contrast sensitivity, colour perception, visual field) have been documented in several studies but little is known on its effect on higher level visual functions. The present study was aimed at assessing the effect of treatment by VGB on higher level cognitive processes involved in visual perception. We compared performance of participants with epilepsy treated with VGB, participants with epilepsy treated with other drugs (no VGB), and age-matched healthy controls in three different tasks: (1) a simple reaction time (RT) task was used as baseline to assess a general slowing down in response times. (2) A Posner's paradigm (Posner and Rothbart, 1980) investigated attention in a spatial exogenous attention task. A target was displayed either at a cued or at an uncued spatial location. Normal spatial attention is classically reflected by a benefit (shorter RTs) when the target appears at a cued location as compared to when it appears at an uncued location and by a cost (longer RTs) when the target appears at a location different from that of the cue because attention has to be disengaged from the cue to the target location. (3) A rapid categorization task was used to investigate object recognition at large visual eccentricities. All three experiments were performed at eccentricities varying from 30° to 60° left and right of fixation on a panoramic screen.

Methods

Participants: the participants were 11 patients with partial seizures treated with VGB (5 females) for at least 2 years, 11 participants (4 females) with partial seizures treated with carbamazepine (CBZ) or sodium valproate for 3/11 participants (we will refer to this group as no VGB), and 12 healthy controls (6 females). Participants with epilepsy were selected from the department of neurophysiology of the Lille's hospital. Patients with a MMSE lower than 27 and a IQ (assessed by the WAIS) lower than 80 were excluded. We also excluded patients who had a seizure in the 24 h preceding the experiment. Controls were students and members of the medical staff of the department of ophthalmology in the Lille's university hospital with no history of neurological, ophthalmological or psychiatric disorders. Clinical and demographic data are presented in Table 1. Fig. 2 shows the visual field of participants treated by VGB, by no VGB and healthy con-

Table 1 Demographic and clinical data for the three groups of participants.

Group	Patients	Age	Seizure type	Number seizure/month	Treatment and dose (mg/day)
Non-VGB	P1	31	Left temporal	5—6	Carbamazepine (1400) Clobazam (20)
Non-VGB	P2	18	Right temporal	2—3	Carbamazepine (1200) Clobazam (20)
Non-VGB	P3	25	Right temporal	1	Sodium valproate (1000)
Non-VGB	P4	18	Frontal	2—3	Sodium valproate (2000) Lamotrogine (200)
Non-VGB	P5	46	Left temporal	2—3	Carbamazepine (1200) Topiramate (200)
Non-VGB	P6	18	Frontal	1	Carbamazepine (400) Sodium valproate (1000)
Non-VGB	P7	18	Left temporal	2—3	Sodium valproate (1000)
Non-VGB	P8	19	Right frontal	2—3	Carbamazepine (800) Clobazam (10)
Non-VGB	P9	35	Temporal	<1	Carbamazepine (1200)
Non-VGB	P10	48	Right temporal	4—5	Carbamazepine (1200) Topiramate (200)
Non-VGB	P11	18	Right temporal	<1	Gabapentine (1800)
VGB	P1	37	Frontal	20	Vigabatrin (2000) Carbamazepine (600) Lamotrigine (600) Clobazam (30)
VGB	P2	59	Temporal	5	Vigabatrin (3000) Oxcarbazepine (1800) Clobazam (20)
VGB	P3	27	Temporal	10	Vigabatrin (3000) Topiramate (400) Clobazam (30)
VGB	P4	43	Left temporal	3—4	Vigabatrin (2000) Carbamazepine (400) Clobazam (30)
VGB	P5	28	Temporal	10	Vigabatrin (3000) Carbamazepine (1200)
VGB	P6	53	Temporal	7—8	Vigabatrin (3000) Carbamazepine (1200)
VGB	P7	37	Right temporal	5	Vigabatrin (2000) Carbamazepine (1200)
VGB	P8	39	Left temporal	10	Vigabatrin (3000) Carbamazepine (1200)
VGB	P9	45	Right temporal	<1	Vigabatrin (2000) Carbamazepine (1200)
VGB	P10	55	Right temporal	<1	Vigabatrin (2000 Carbamazepine (1000)
VGB	P11	54	Right temporal	<1	Vigabatrin (2000)

trol. The study was approved by the ethical committee of Lille University Hospital. All participants signed a written informed consent.

Perimetry

Procedure: computer assisted visual field examination was performed with a commercially available cupola stimulator (Metro-Vision Monitor, Pérenchies, France), the radius was 33 cm and background luminance was 10 cd/m^2. A kinetic Goldmann based perimetry was performed in these conditions. In the kinetic procedure, three isopters were tested at a speed of 2° s^{-1}: the peripheral isopter (III 4e Goldmann equivalent) and 2 midperipheral isopters (III 1a and II 1c Goldmann equivalent). The excentricities of initial stimulus presentation of each isopter were respectively 90°, 60° and 30°. Blind spot detection (III 4e Goldmann equivalent) was performed at 1° s^{-1}. No correction glass was used for the peripheral isopter, a correction in accordance with the refractional status was added for the two mid peripheral isopters. Patients with fixation loss, false positive or false negative responses of more than 15% were excluded from analysis. Three responses were averaged, each point was tested three times, if there was a difference of more than 10% between the best and the worst response, the procedure was repeated. A perimetric result was only accepted if the variability of each point was below 10%. The area of each isopter was determined.

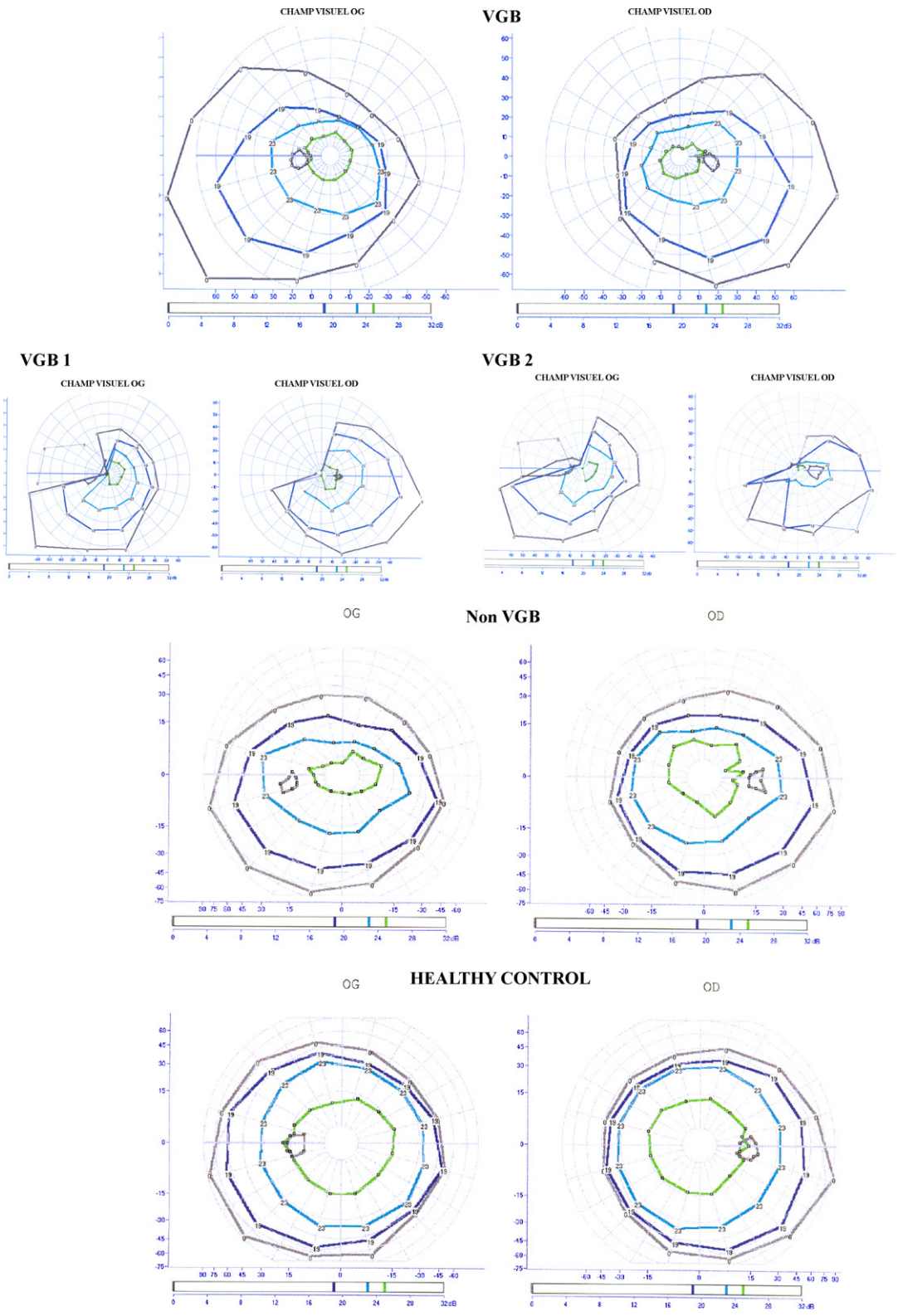

Figure 1 The visual field (left and right eye) of the participants treated by VGB, the visual fields of the two patients treated by VGB who exhibit a quadranopsy, an example of the visual field of a healthy control and of a participant treated with other drugs than VGB.

Baseline simple reaction time task

Apparatus: the stimuli were displayed by means of three projectors (SONY CS5) fixed on the ceiling. The projectors were connected to a computer (TSB). Participants were seated 2.1 m from a hemispheric rigid light grey (68 cd/m^2) screen covering 90° eccentricity on each side of a central fixation cross. Participants responded on a box containing two keys. Their head was maintained by a chin rest. Eye movements were recorded by means of an infrared camera located on the table in front of the observer. A trial started when the gaze was on the fixation cross. The equipment is shown in Fig. 1.

Stimuli: the stimulus was a black dot covering 5° of visual angle.

Procedure: a fixation cross (+) was displayed permanently on the screen in front of the observer's eyes. A black dot appeared randomly at three different eccentricities (30°, 45° and 60°) left or right of fixation. It was displayed for 50 ms. Participants were asked to press a key as soon as they saw the dot. The inter-trial interval was variable, from 1.5 to 3 s, in order to avoid regular keypresses. There were 180 trials (30 trials × 3 eccentricity × 2 locations (left/right)). 10 trials were given as practice.

Spatial attention task (Posner's paradigm)

Stimuli: the stimuli were 5 black rectangles (10° horizontally × 6° vertically) and a red star covering 5° as target.

Procedure: on each trial five empty black rectangles (2 left of fixation, 2 right of fixation and 1 at the centre) appeared on the screen. The centre of the rectangles was located 30° and 60° from fixation. 100 ms after the display, one of the rectangles became white (the cue) for 50 ms. After a delay of 50 ms a red star (the target) appeared in one of the rectangles. Participants were asked to press a key as soon as they saw the star. The star was displayed for 50 ms in the centre of a rectangle. For 70% of the trials the target appeared at the cued location (valid trials). For 15% of the trials the target appeared at an uncued location (invalid trials). These two conditions were compared to a neutral condition (15% of the trials) in which the 5 rectangles became white before the appearance of the target. The valid, invalid and neutral conditions were randomly presented. As in the simple RT task the inter-trial interval was variable. The experimental session lasted about 15 min. It was preceded by 10 practice trials.

Object categorization task

Stimuli: the stimuli were 160 coloured photographs of natural scenes taken from a commercial CD database (Corel). The mean angular size was 24°. Half of the photographs were scenes containing an animal and the other half were scenes containing various objects but neither animals nor humans. Examples are shown in Fig. 1.

Procedure: a fixation cross was located permanently at the centre of the screen. Each picture appeared for 80 ms centered either 30° or 60° left or right of fixation. The four spatial locations were randomly displayed. Participants were asked to decide whether the picture contained an animal or not. They gave their answer in pressing one response key for an animal and the other for an object. There were 160 trials (40 trials × 2 eccentricity × 2 locations (left/right)). The experimental session started with 10 practice trials.

Results

Perimetry

Among the VGB treated patients, two had left superior quadranopsy, two had moderate and 9 had mild visual field constriction. Non-VGB treated patients had normal visual fields (6 cases) or a mild constriction (5 cases). Fig. 2 shows the visual field of participants treated by VGB, by no VGB and healthy control. When comparing the quantitative results between the patients treated with VGB and the patients treated by another molecule, the area of the three different isopters were smaller in the VGB group but the difference did not reach statistical significance (see Fig. 2 and Table 2).

Figure 2 (Top) Panoramic screen (5 m diameter) covering 180° (90° on each side of central fixation). Pictures are displayed by means of three projectors fixed on the ceiling behind the participants. An infrared camera located in front of the participant records eye movements. A trial starts when the gaze is located on the fixation cross. (Bottom) An example of the stimuli (target: a scene containing an animal and distractor: a scene containing no animal) used in the object categorization task.

Baseline simple reaction time

An ANOVA using Statistica 6.1 was conducted on the response times (RTs) with eccentricity as the between subject variable and the 3 groups as the within variable. The participants were the random variable. The data are displayed in Fig. 3. As two participants with VGB had a quadranopsy (VGB1 and VGB2, see Fig. 1) their individual results are displayed bellow that of the groups.

The mean RT was 369 ms. RTs were shorter for healthy controls (341 ms) followed by no VGB participants (372 ms) and participants treated with VGB (395 ms). The effect of group was not statistically significant ($F(2, 31) = 2.43$, n.s.). RTs were significantly affected by eccentricity ($F(2, 31) = 24.7$, $p < .001$), with shorter RTs at 30° (355 ms) than at 45° (364 ms) and 60° (389 ms). The interaction between group and eccentricity just failed to reach statistical significance ($F(4, 62) = 2.42$, $p < .057$). As can be seen from Fig. 2 this resulted from a larger increase in RTs between 45° and 60° eccentricity ($F(1, 31) = 21.1$, $p < .001$) for participants treated with VGB (+41 ms, $F(1, 31) = 18.8$, $p < .001$) than for no VGB participants (+14 ms, $F = 1.9$, n.s.) and healthy controls (+21 ms, $F(1, 31) = 4.9$, $p < .0034$). The increase in RTs from 30° to 45° eccentricity was small for the three groups (controls: 1 ms, no VGB: 13 ms and VGB: 13 ms).

Table 2 The visual field results of the two groups of patients are compared. The area of each isopter was smaller in the VGB group but this difference did not reach statistical significance. RE stands for right eye, LE stands for left eye, the isopters in kinetic perimetry are given in square degrees (°2). The mean reliability parameters were comparable between the two groups.

	RE III 4E (°2)	RE III 1A(°2)	RE II 1C (°2)	Fixation loss	Attention loss
Non-VGB	8309	2312	819	5.6%	6.8%
VGB	6769	1861	759	5.3%	6.6%
Difference (*p*)	0.2169	0.4385	1	1	1
	LE III 4E (°2)	LE III 1A(°2)	LE II 1C (°2)	Fixation loss	Attention loss
Non-VGB	7558	2155	796	5.4%	6.2%
VGB	6132	2067	734	5.5%	5.9%
Difference (*p*)	0.2703	0.8977	0.9487	1	1

As can be seen from Table 1 patients treated with VGB were on average older than patients treated with no VGB. It has been shown (Panek, 1978; Gottsdanker, 1982; Godefroy et al., in press) that simple and choice reaction time tasks are affected by healthy aging. We checked whether the slowing down in RTs in patients treated with VGB resulted from older participants. We found that patients treated by VGB were slower than patients treated by no VGB by 72 ms for patients ranging in age from 18 to 29, by 67 ms for patients ranging in age from 30 to 39 and by 57 ms for patients ranging in age from 40 to 50. This indicates that the slowing down of RTs was general, occurring even for the youngest participants, in patients treated with VGB.

Spatial attention

An ANOVA using Statistica 6.1 was conducted on the data with eccentricity and condition as the between subject vari-

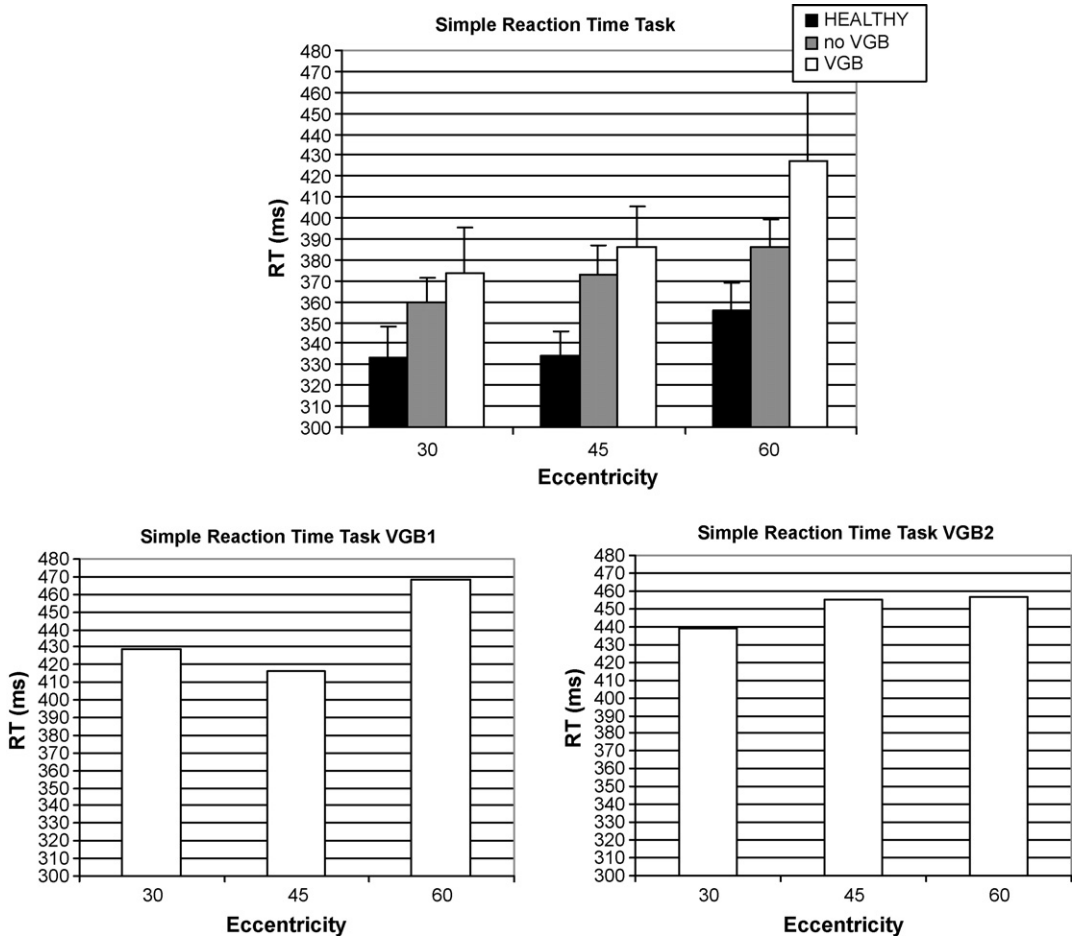

Figure 3 Mean RTs of the three groups of participants (healthy, no VGB, and VGB), and the two patients (VGB1 and VGB2) with a quadranopsy, in the simple RT task as a function of eccentricity. Vertical bars represent standard errors.

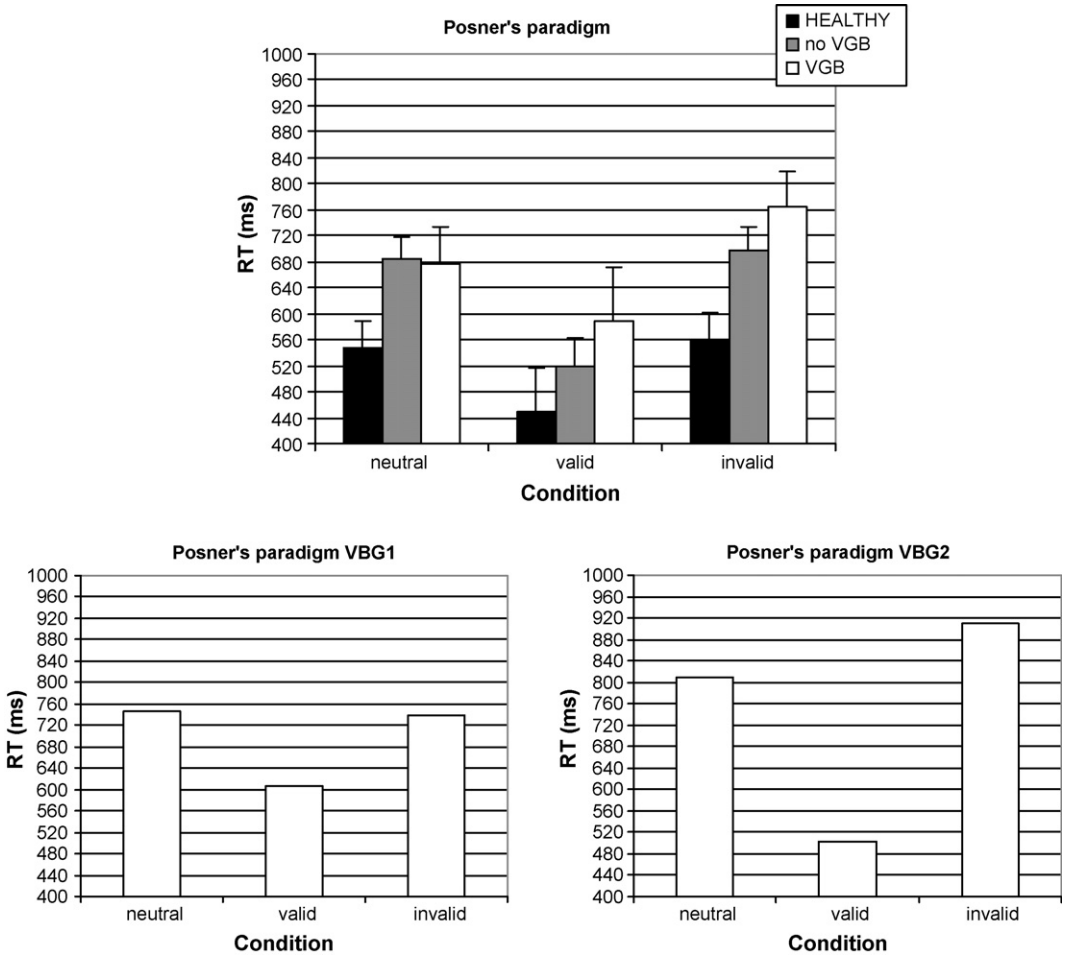

Figure 4 Mean RTs of the three groups of participants (healthy, no VGB, and VGB), and the two patients (VGB1 and VGB2) with a quadranopsy, in the spatial attention task as a function of eccentricity and condition (valid, neutral and invalid trials). Vertical bars represent standard errors.

able and the 3 groups as the within variable. The participants were the random variable.

No main effect of eccentricity or interaction involving eccentricity was observed. The data displayed in Fig. 4 are averaged over this variable. The individual results of VGB1 and VGB2 are displayed below those of the groups. There was a significant main effect of condition ($F(2, 31) = 26.2$, $p < .001$), with shorter RTs for valid trials than for neutral trials (519 ms vs. 636 ms, $F(1, 31) = 28$; $p < .001$) and than invalid trials (519 ms vs. 673 ms, $F(1, 31) = 45.3$; $p < .001$). RTs did not differ significantly between neutral and invalid trials (636 ms vs. 673 ms, $F(1, 31) = 2.9$; $p < .098$). There was no significant main effect of group ($F(2, 31) = 2.9$; $p < .068$) and no interaction between group and condition ($F(2, 62) = 1.2$; $p < .312$).

Object categorization

An ANOVA using Statistica 6.1 was conducted on the data with eccentricity and category (animal/object) as the between subject variable and the 3 groups as the within variable. The participants were the random variable. There was no main effect of category nor interaction involving this variable. The data, displayed in Fig. 5, are averaged over this variable. The results of VGB1 and VGB2 appear below those of the groups.

Performance was affected by eccentricity both for the percentage of correct responses with a higher accuracy at 30° than at 60° (92% vs. 79% ($F(2, 31) = 141$; $p < .001$)), and for RTs with shorter RTs at 30° than at 60° (773 ms vs. 882 ms ($F(2, 31) = 44.8$; $p < .001$)).

The main effect of group was significant both for accuracy ($F(2, 31) = 4$; $p < .029$) and RTs ($F(2, 31) = 4.4$; $p < .02$). Participants treated by VGB were less accurate and slower to respond than healthy controls (83% vs. 89%, $F(1, 31) = 7.1$; $p < .01$ and 913 ms vs. 780 ms, $F(1, 31) = 7.2$; $p < .01$) and than participants treated by no VGB (84% vs. 89%, $F(1, 31) = 0.4$; $p > .5$ and 913 ms vs. 789 ms, $F(1, 31) = 6.1$; $p < .019$).

Group interacted significantly with eccentricity for RTs ($F(2, 31) = 6.8$; $p < .003$). As can be seen from Fig. 5 this interaction resulted from a larger increase in RTs from 30° to 60° for participants treated with VBG (by 179 ms, $F(1, 31) = 38.9$; $p < .001$) than for healthy controls (by 119 ms, $F(1, 31) = 18.8$; $p < .001$) and than participants treated by no VGB (by 30 ms, $F(1, 31) = 1.1$; n.s.). This last result was supported by a high correlation between the accuracy and unimpaired visual field area ($r = .88$; $p < .001$).

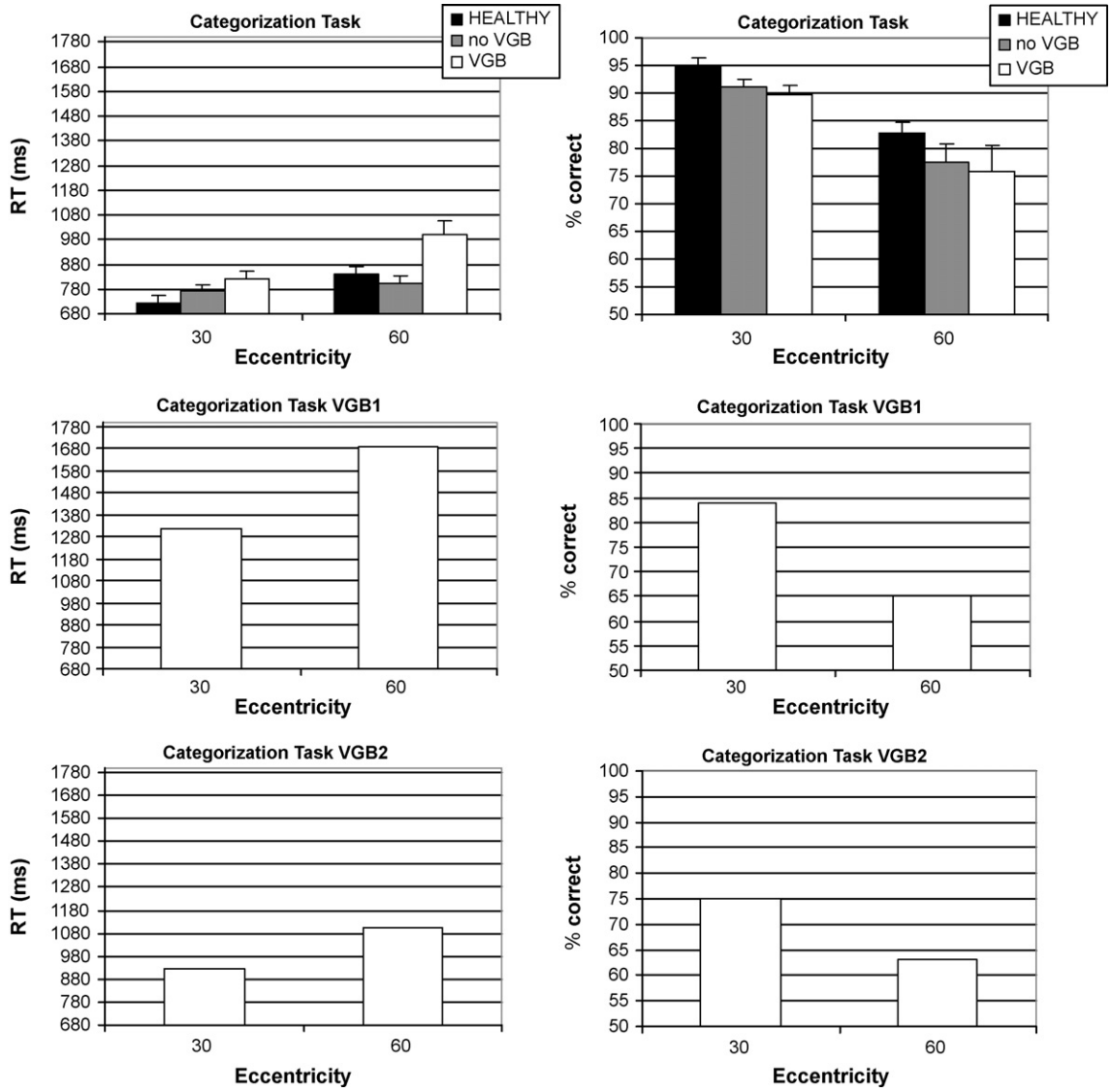

Figure 5 Mean RTs and percent correct responses in the object categorization task in the three groups of participants (healthy, no VGB, and VGB), and the two patients (VGB1 and VGB2) with a quadranopsy, as a function of eccentricity. Vertical bars represent standard errors.

Accuracy was largely above chance (>75% correct) for all groups of participants at large eccentricity except for VGB1 and VGB2 who were slower (by 100—700 ms) and less accurate (by about 10%) than the other participants treated by VGB, but their performance was still above chance (63—65%) at 60° eccentricity.

Discussion

Studies on the effect of VGB on vision have reported deficits in contrast sensitivity, colour vision and a reduction of the peripheral visual field but with inconsistent results. Indeed, there are reports of altered cone responses (Krauss et al., 1998; Besch et al., 2002) suggesting that VGBs toxicity is not confined to the peripheral retina but also affects central vision. Previous studies have mainly investigated the effect of VGB on low level visual processes. Regarding the effect of antiepileptic drugs on higher level cognitive functions, Brunbech and Sabers (2002) reported that VGB does not substantially affect verbal fluency, verbal learning, sustained attention, memory, psychomotor speed and executive functions. Kälviäinen et al. (1995) showed improved performance in the group treated by VGB as compared to a group treated by no VGB in cognitive tasks of memory, psychomotor speed and flexibility of mental processing.

We assessed whether VGB affects higher level visual processes, especially spatial attention and object recognition at different eccentricities on a panoramic screen.

The results of the visual fields show that each isopter was smaller in the VGB group but this difference did not reach statistical significance. The mean reliability parameters were comparable between the two groups of patients. Spatial attention was not affected by VGB. All participants exhibited a benefit for valid trials as reflected by facilitation (shorter RTs) for valid trials as compared to neutral

and invalid trials and a cost for invalid trials (longer RTs) as compared to valid trials. In spite of a general slowing down of RTs VGB1 and VGB2 exhibited the same pattern of results as the group of participants treated by VGB with a strong advantage for valid trials. All together, these results indicate that spatial attention is engaged (valid trials) and disengaged (invalid trials) normally in the visual field for all three groups of participants.

The baseline simple reaction time task was designed to test a general slowing down of motor response. This study showed that participants treated with VGB were slower than the control group of participants with epilepsy treated with other drugs and than the group of healthy observers. VGB1 and VGB2 were again slower that the other participants treated with VGB at all eccentricities but this slowing down was more pronounced at the largest eccentricity. This result suggests that it is not simply a slower motor response but that visual signal, even at optimal contrast (black dot on a light grey background), was processed more slowly in the peripheral field.

The most complex task was rapid detection of objects embedded in a scene. It is well known that peripheral vision is more sensitive than central vision to crowding effects (Kooi et al., 1994; Tripathy and Cavanagh, 2002; Levi, 2008; Boucart et al., in press). Crowding is defined as the deleterious effect of nearby contours on visual discrimination. It impairs the ability to recognize objects in clutters (see Levi, 2008 for a review). Though performance was above chance (varying from 63% for VGB2 to 75% for the group of VGB treated participants) the slowing down of RTs was more pronounced at 60° than at 30° in the VGB group as compared to the two control groups. As this task of detecting an object in a scene is closer to natural situations than the simple detection of a dot on a uniform background, the general slowing in response times particularly at large eccentricity, suggests that people treated with VGB may be impaired in behavioural tasks like driving or detecting a moving object in their peripheral field (another car or a person) while driving.

The general slowing can be explained by an alteration in the photoreceptors which was not detected by perimetry. This result could therefore reflect a precursor of visual field alteration. VGB irreversibly inhibits γ-aminobutyric acid (GABA) transaminase, resulting in an increase of GABA in the brain and in the retina (Schechter and Tranier, 1977; Ravindran et al., 2001). As a result, irreversible visual field defect may occur (Ruether et al., 1998; Lawden et al., 1999; Kälviäinen et al., 1999; Manuchehri et al., 2000; Krakow et al., 2000). The mechanism of visual dysfunction is poorly understood but an altered inner retinal function with ganglion cell loss may be a possible cause (Lawden et al., 1999; Daneshvar et al., 1999; Frisén and Malmgren, 2003). Postmortem pathological study supports the idea that the primary site of injury lies within the ganglions cells of the retina especially in the periphery, cells of the inner and outer retina and the optic nerve (Arndt et al., 1999; Ravindran et al., 2001). Frisén and Malmgren (2003) speculate that retinal ganglions cells axons might be damaged in the order of length of unmyelinated segments. They suggested that these axons may succumb in order of intraocular, unmyelinated length and that, this mode of evolution once established; visual field loss would proceed at slow and possibly undetectable rates. This account can explain the small difference in visual field defect between our groups of patients and that higher level visual functions are not yet markedly impaired (in term of accuracy) at large visual eccentricity. However, the general slowing in response times, particularly at large eccentricity, may have consequences in behavioural tasks like driving and detecting moving people.

Acknowledgements

The study was funded by a Programme Hospitalier de Recherche Clinique to the last author. F. Naili was supported by a Ph.D, graduate fellowship from Lille Hospital and *Nord-Pas de Calais*, France. The authors thank Sandrine Wannepain for her help to test healthy subjects.

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