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Migraine Phosphenes and the Retino–Cortical Magnification Factor

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Quantitative observations on the shape and position of migraine phosphenes within the visual field were obtained by controlled "perimetric" drawings of the phosphenes performed every 1–2 min during the aura state. The visual field eccentricity of the "fortification" or zig-zag patterns scintillating at about 10 Hz was plotted as a function of observation time. It is well described by an exponential function of time. This exponential function is the product of a first-order linear differential equation determined by the distribution of the retino–cortical magnification factor across the visual field and a constant diffusion speed of the cortical pathophysiological process leading to the migraine phosphene patterns. The observed "particle" size of the phosphene pattern and the width of the scotoma trailing the scintillating phosphenes could also be easily predicted from these assumptions. A model in which the main components are an increase in extracellular potassium concentration, a decrease in extracellular calcium concentration and the constant speed diffusion of the ions along the extracellular space of the stripe of Gennari within the primary visual cortex explains the observations.

Migraine Phosphenes Visual cortex

INTRODUCTION

Most likely more than 5% of the population in the western world suffer from migraine attacks. In about 10–15% of the cases the migraine headache is preceded by a visual aura, in particular migraine phosphenes (*migraine opthalmique*) (Richter, 1935; Raskin & Appenzeller, 1980; Critchley, 1985). Flickering phosphenes and the accompanying scotoma, a fairly frequent symptom of migraine, were reported repeatedly in the scripts of Greek–Roman physicians like Aretaeos of Cappadocia (Didsbury, 1936) and Galen (Hirschberg, 1899). The British physician J. Fothergill (1784) was presumably the first to describe the typical *fortification patterns* of the scintillating migraine phosphenes. The first drawings of migraine phosphenes in which the course of the scintillating zig-zag patterns across the visual field during a migraine attack was well documented were published by Airy (1870), who coined the name *teichopsia* from the Greek *teichos* (town wall) and *opsis* (vision) to describe the migraine phosphenes (Plant, 1986a). Since Airy's widely read paper, several authors have published reports and drawings of their own fortification patterns observed during migraine attacks (Jolly, 1902; Bäumler, 1925; Lashley, 1941; Pöppel, 1973; Bücking & Baumgartner, 1974; Jung, 1979), but only Hare (1966) applied a quantitative analysis to the temporal spread of the scintillating phosphenes across his visual hemifield. He reported that the *diameter of the fortification pattern*, drawn on a sheet of paper, increased exponentially with the duration of the migrainous aura. Hare did not relate the migraine phosphenes to the centre of the visual field, however, nor did he transpose his measurements into values of visual angle. Assuming a *constant spreading speed* V_c of the pathophysiological process within the primary visual cortex leading to migraine phosphenes, an average aura duration of 22–28 min and a distance of 65–70 mm from the most occipital to the most anterior part of area 17 in the human occipital cortex, the speed of the pathophysiological process has been estimated at about 3.0 ± 0.3 mm/min (Lashley, 1941; Richards, 1971; Grüsser & Landis, 1991).

In the following the results of a quantitative analysis of migraine phosphenes are described and a simple theoretical model, based on spreading depression mechanisms, of their course across the visual field is discussed. Short reports on this study were presented at recent scientific meetings (Grüsser & Grüsser-Cornehls, 1991; Grüsser, 1992).

METHODS

Over the past 15 yr I have experienced 1–4 migraine attacks yearly with typical fortification scintillations. In the course of these attacks I collected 21 quantitative protocols, 14 dealing with the perimetrically measured spread of fortification patterns across the visual field (Fig. 1). In 11 of these protocols from the now 61-yr-old right-handed subject, the pathological process started at

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or near the cortical projection site of the foveal centre. The fortification scintillations were drawn every 1–2 min by the right-handed subject with the hand ipsilateral to the affected visual hemifield on a large sheet of plain paper placed at a distance d_e of 34 or 37 cm from the observing eye cornea and perpendicular to its optical axis [Fig. 2(c) inset]. The head was fixed on a chin rest. The background illumination was set at about 0.1 cd · m^{-1}, i.e. within the mesopic range. Figure 1 is the photographic negative of a typical protocol onto which a visual angle scale was later drawn. Further protocols on scintillating migraine phosphenes obtained with the same method were kindly provided by two colleagues, Professor T.H.B. and Dr B.O.

RESULTS

Quantitative perimetry and normalization of migraine phosphenes

To evaluate the protocols (Fig. 1) quantitatively, the distance d_p of the fortification scintillation from the fixation target (i.e. from the foveal centre) was measured in mm along different radii, as illustrated in Fig. 1. From d_p and d_e the visual angle P_v was determined by computing arctan(d_p/d_e), and the angular distance P_v of the migraine phosphene from the centre of the visual field was plotted as a function of the observation time t. Figure 2(a) illustrates the results of this procedure for

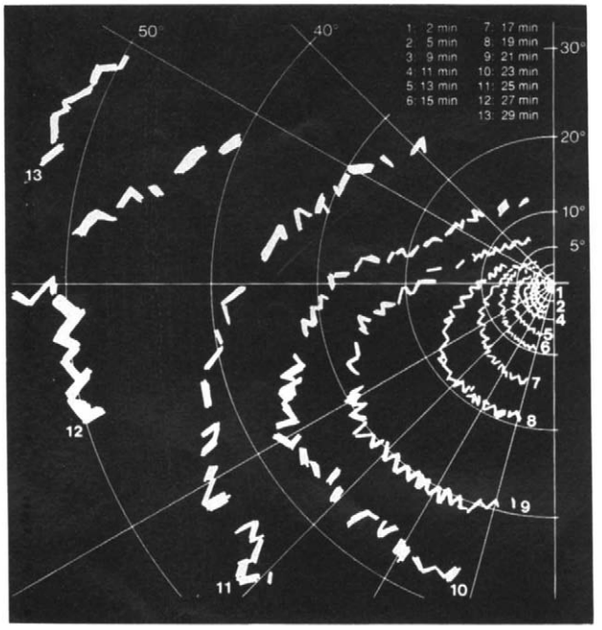

FIGURE 1. Photographic negative of a *migraine phosphene protocol.* The scintillating phosphene was progressing through the lower quadrant and part of the upper quadrant of the left visual hemifield. Thirteen drawings were made between 2 and 29 min after the phosphene appeared near the centre of the visual field. To evaluate the distance between the migraine phosphene and the centre of the visual field, several radii were drawn across the protocol. The angular distance from the fovea centre, computed in degrees of visual angle, is indicated by circles. Circles and radii were added to the protocol sheet after the observations were made. Observation distance, 34 cm.

one protocol. Since the migraine phosphenes did not always begin at the exact centre of the fovea nor spread precisely along a half-circle centred on the fovea, a *normalization of the protocols regarding the time and position within the visual field became necessary.* To this end, the moment the migraine phosphene had reached 4 deg eccentricity was defined as "12 min" and the data obtained in the protocols were replotted accordingly [Fig. 2(b–d)]. The phosphene required 12 min to reach 4 deg eccentricity in those protocols in which the migraine aura commenced directly in the centre of the visual field. For subject THB the adequate normalization was 4 deg/10 min, for subject BO 4 deg/8 min, indicating some interindividual variability in the size of the primary visual cortex (area 17) receiving projections from the *fovea centralis* or the speed of the migrainous process spreading across area V1.

In each protocol 4–6 radii were chosen for the measurement of P_v (Fig. 1). Three of the 14 protocols stemmed from the migraine phosphenes which began at 5, 6 and 12 deg eccentricity, whereby the fortification pattern extended simultaneously towards the visual field periphery and the fovea, not forming a semicircle centred approximately on the fovea. These three protocols could not be used for statistical purposes. In four protocols the extent of the scotoma trailing the scintillating pattern was determined by using a 2-mm black dot placed at the tip of a white strip of paper which was moved, as in conventional perimetry, along different radii towards or away from the centre of the visual field. The subject noted on the protocol sheet the disappearance and reappearance of the black dot. During six other migraine attacks several other experiments were performed, reported elsewhere (Grüsser & Landis, 1991).

Acceleration during the course of the migraine phosphene through the visual field

Figure 2(b) illustrates that despite the 11 evaluated protocols from one subject being collected over the long period of 12 yr, the scatter of P_v relative to the duration of the pathophysiological process leading to migraine phosphenes remained within narrow limits. To deduce an adequate mathematical function to describe the course of migraine phosphenes across the visual hemifield, some data from the literature turned out to be helpful. The local "linear" *retino–cortical magnification factor M* measured in mm/deg (Talbot & Marshall, 1941; Daniel & Whitteridge, 1961; Cowey & Rolls, 1974; Rovamo & Virsu, 1979; Drasdo, 1991) is defined by

$$M = dP_c/dP_v\,[\text{mm} \cdot \text{deg}^{-1}] \qquad (1)$$

The areal retino–cortical magnification factor (mm^2/deg^2) as defined by Myerson, Manis, Miezin and Allman (1977) was not included in the present analysis. In the case of migraine phosphenes, P_c of equation (1) is the distance in mm in the visual cortex of the pathological process from the cortical representation of the fovea centre; P_v is the corresponding value, i.e. the length of a radius within the visual field. By

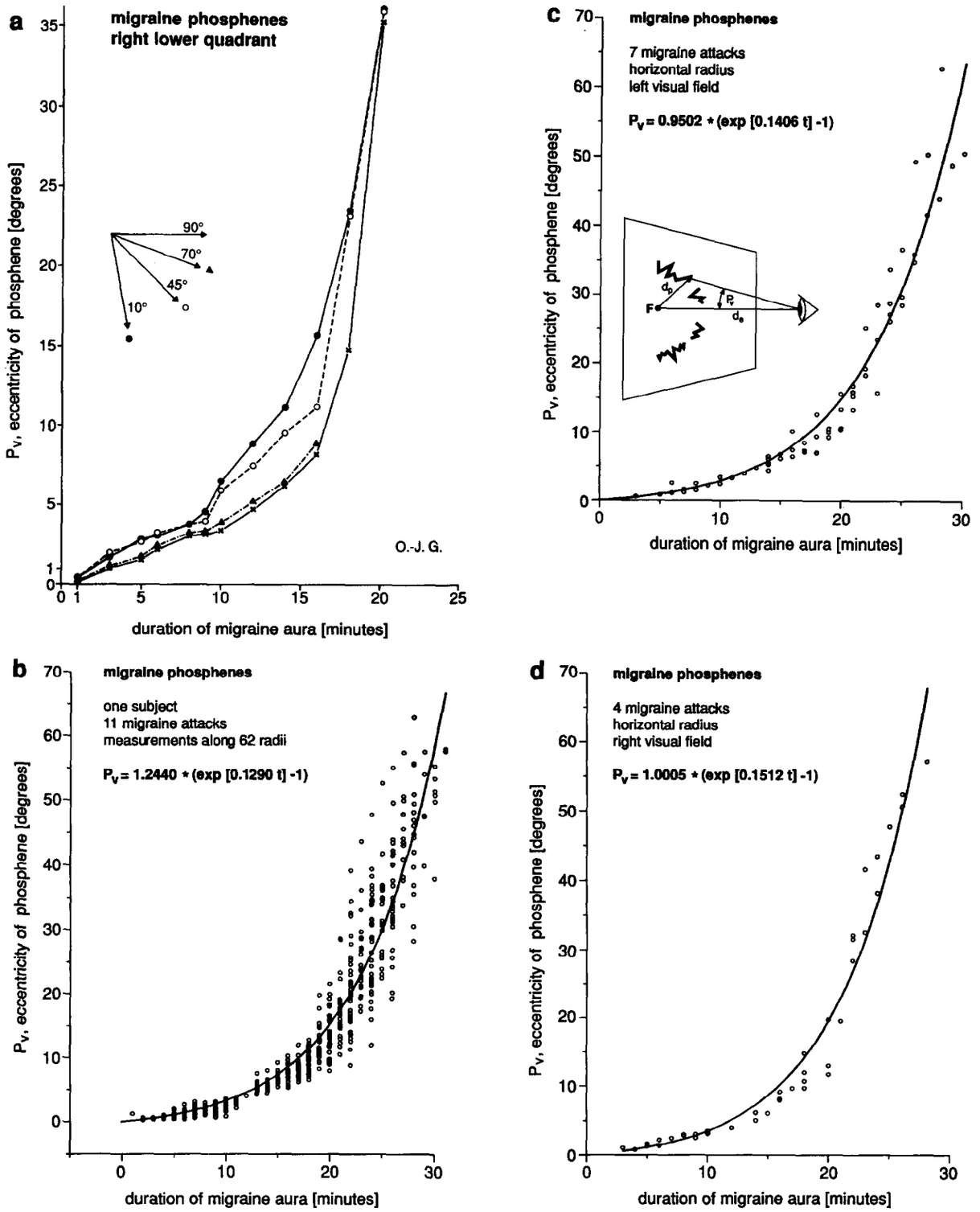

FIGURE 2. (a) The *distance* P_v (ordinate) of the migraine scintillating phosphene pattern from the centre of the visual field (Fig. 1) was measured in one protocol along four selected radii and the data plotted as a function of observation time (abscissa). (b) The *visual field eccentricity* P_v of the scintillating phosphene pattern was measured during 11 migraine attacks along 62 radii and plotted as a function of the migraine aura duration. The data were normalized to 4 deg/12 min (see text). The solid line corresponds to equation (6) and represents this function with constants resulting in a minimum sum of quadratic deviation from the experimental data. (c) Same relationship as in (b) but obtained along a horizontal radius in the left visual field in seven migraine attacks. Inset: scheme of how the migraine phosphene drawings and the computation of the angular distance P_v from the fovea centre were carried out. $P_v = \arctan(d_p/d_c)$. (d) Same as in (c) but for the right visual hemifield and four migraine attacks.

multiplying equation (1) with dt in the nominator and the denominator one finds

$$M = dP_c\,dt/dP_v\,dt = dV_c/dV_v \quad [\text{mm} \cdot \text{sec}^{-1}/\text{deg} \cdot \text{sec}^{-1}] \quad (2)$$

where V_c is the speed of the lateral spread of the cortical pathophysiological process, V_v the radial speed of the migraine phosphene travelling through the visual field.

According to Cowey and Rolls (1974), who analysed the data obtained in the study of Brindley and Lewin (1968) on the visual field location of phosphenes evoked in a blind volunteer by electrical stimulation of area V1 with a set of epidural electrodes, a simple hyperbolic function is valid between the retino–cortical magnification factor M and the distance P_v of the phosphene within the visual field, which leads to a linear relationship between the inverse retino–cortical magnification factor M^{-1} and the visual field eccentricity P_v

$$M^{-1} = a + bP_v\,[\text{deg} \cdot \text{mm}^{-1}] \quad (3)$$

where a and b are constants. The retino–cortical magnification factor M_0 for the fovea centre ($P_v = 0$) corresponds to a^{-1}. From Fig. 3(a) of Cowey and Rolls (1974) one finds $a = 0.117$, $b = 0.067$. Other estimates of the constant a are available in the literature and vary between 0.069 and 0.140 (Drasdo, 1977; Virsu & Rovamo, 1979; Dobelle, Turkel, Henderson & Evans, 1979; Tolhurst & Ling, 1988; for further discussion see Schwartz, 1980).

Provided the speed V_c is *constant* at which the cortical pathophysiological process spreads across the primary visual cortex during a migraine attack and assuming—certainly somewhat simplified—a functional and morphological sequential regularity, as expressed by the hypercolumn arrangement of the primary visual cortex (Hubel & Wiesel, 1974a, b; Tootell, Silverman, Switkes & De Valois, 1982; Horton & Hedley-Whyte, 1984; Horton & Hoyt, 1991), one easily finds from equations (1)–(3)

$$dP_v/dP_c = dP_v/V_c\,dt = a + bP_v \quad (4)$$

$$dP_v/dt = V_c a + V_c b P_v. \quad (5)$$

Providing that the initial conditions are $t = 0$, $P_v = 0$, the solution of this *first-order linear differential equation* (5) is:

$$P_v = \frac{a}{b}\,[\exp(V_c b t) - 1]\,[\text{deg}] \quad (6)$$

or

$$P_v = \alpha\,(e^{\beta t} - 1)\,[\text{deg}] \quad (7)$$

with $\alpha = a/b$ and $\beta = bV_c$. From the data plotted in Fig. 2(b) the constants α and β of equation (7) were determined leading to a function optimally fitting the overall experimental data (iterative computation, minimum sum of quadratic deviations) with $\alpha = 1.244$ and $\beta = 0.129$. Assuming V_c to be 2.2 [mm · min^{-1}], one then finds: $a = 0.073$ and $b = 0.059$. Equation (7) provided an equally optimal fit to the results obtained by the observers THB and BO.

Due to the scatter, of course, a slight variability in the constants a and b for the cortical projection lines corresponding to the respective radii in the visual field cannot be excluded. Therefore, in a further data analysis step the values observed were grouped according to the *radii* along which P_v was measured and the constants of equation (7) best fitting the data were computed for corresponding radii in the left (seven protocols) and the right (four protocols) visual hemifield. Figure 2(c, d) illustrates in two examples that the scatter of the data decreased by this procedure but the differences between the left and right visual hemifield and the different radii were marginal and equations (6) and (7) were suitable descriptions of the temporal course of the migraine phosphenes across the visual hemifield. Some difference seems to exist in the constants of equation (7) for migraine phosphenes appearing in the upper half of the

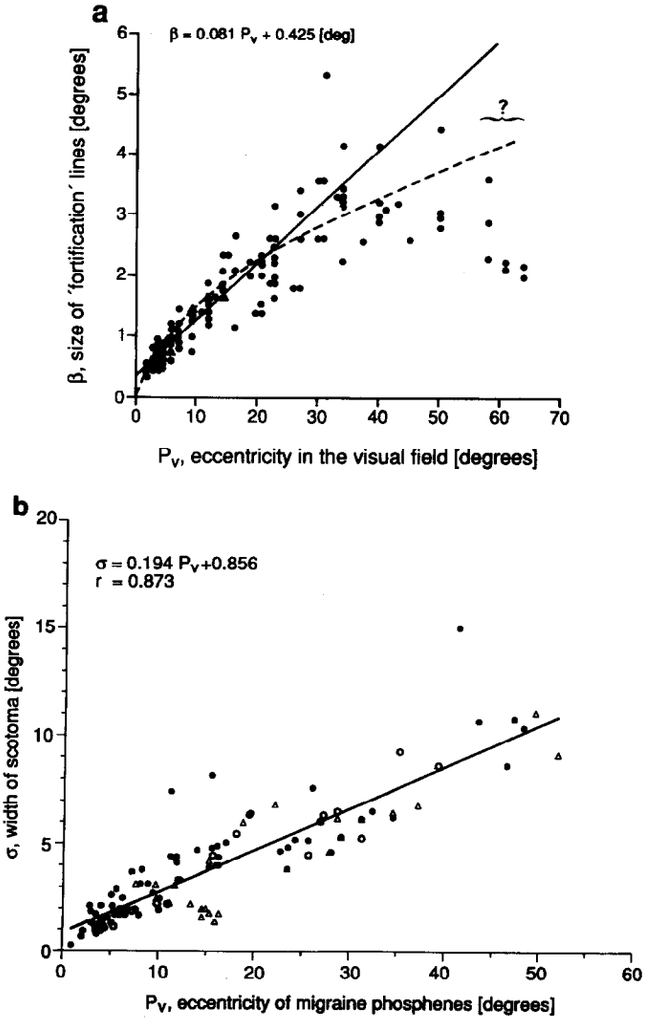

FIGURE 3. (a) Relationship of the *size β* of the fortification "particles"* (ordinate), and the *visual field eccentricity* P_v (abscissa). The solid line is the linear regression line computed from the individual data, the dashed line the power function [equation (11)] proposed by Plant (1986b). (b) Relationship between *the width σ of the migraine scotoma* (ordinate) and the *visual field eccentricity* P_v of the scintillating zig-zag phosphene (abscissa) obtained in three different migraine aurae.

visual field as compared to those appearing in the lower half. However, more data are necessary for a detailed statistical analysis as in most protocols migraine phosphenes only appeared in part of the upper visual hemifield.

The actual distance P_c of the pathophysiological migraine process from the cortical projection site of the fovea centre equals $V_c t$. To compute P_c when P_v is observed, one finds from equation (6):

$$P_c = \frac{1}{b} \ln\left(\frac{b}{a} P_v + 1\right) [\text{mm}]. \quad (8)$$

To estimate the actual position of the front of hyperactive area 17 nerve cells, the maps of the folded primary visual cortex have to be consulted (Holmes, 1918; Spalding, 1952; Teuber, Battersby & Bender, 1960). Recently a revision of Gordon Holmes' retinotopic map of the human striate cortex was published, based on the correlations of magnetic resonance scans with visual field defects of the occipital lobe in three patients (Horton & Hoyt, 1991). The foveal cortical representation was found to be considerably larger than previously assumed. The constants of the equation (3) from this work were estimated as $a = 0.043$, $b = 0.058$. These values yield an exponential function [equation (6)], slightly underestimating the experimental data [Fig. 2(b)]. Evidently some interindividual variability of the retinotopic map of area V1 has to be assumed: in non-human primates (Rhesus macaques) Van Essen, Newsome and Maunsell (1984) reported individual differences in the cortical representation of the fovea (± 2 deg) of up to 100%.

Size of phosphene particles and migraine scotoma

Figure 3(a) indicates the size β^* of the individual migraine phosphene "particles" or "bars" as a function of the eccentricity P_v in the visual field. For β^* a linear regression line was computed for $P_v < 50$ deg:

$$\beta^* = 0.081 P_v + 0.425 [\text{deg}]. \quad (9)$$

Richards (1971) had already performed the same analysis for β^* in the migraine protocols of one of his subjects and found:

$$\beta^* = 0.105 P_v + 0.107 [\text{deg}]. \quad (10)$$

Plant (1986b) reported a power function to be valid in his subject for the relationship between β^* and P_v:

$$\beta^* = 0.34 P_v^{0.6} [\text{deg}]. \quad (11)$$

Plant's equation is also plotted in Fig. 3(a). From equations (9) and (10) one can estimate the size B of a cortical hyperexcitation region corresponding to a particle β^* of the scintillating fortification pattern:

$$\beta^* = B \cdot M^{-1} [\text{deg}]. \quad (12)$$

Combining equations (3) and (12):

$$\beta^* = Ba + BbP_v [\text{deg}]. \quad (13)$$

Using equations (10) and (12) one finds $1.41 < B < 1.78$ [mm] for $a = 0.073$ and $b = 0.059$.

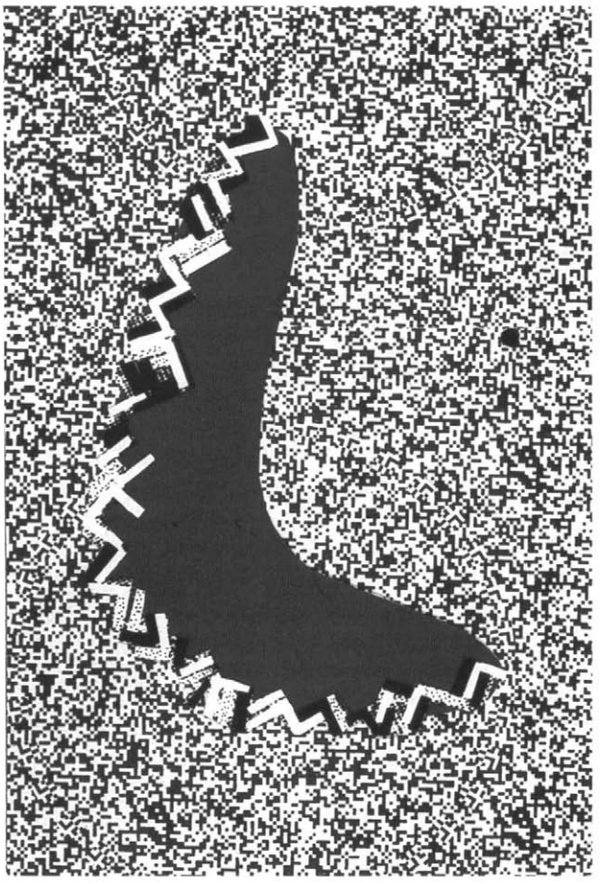

FIGURE 4. Illustration of a scintillating migraine phosphene and its trailing scotoma observed on a *dynamic random-dot noise pattern* (TV screen without program). The scotoma is perceived as a homogeneous neutral grey. Some of the phosphene particles (dotted) appeared in a pure red or green colour, some in deep black (Grüsser & Landis, 1991).

In three experiments the width σ of the *migraine scotoma* was measured as described above and plotted as a function of visual field eccentricity P_v [Fig. 3(b)]:

$$\sigma = k_0 + k_1 P_v [\text{deg}] \quad (14)$$

with the constants $k_0 = 0.856$ and $k_1 = 0.194$. The scatter of σ, however, was considerable.

On the visibility of the migraine scotoma on a dynamic visual noise background

Under normal viewing conditions the migraine scotoma is not directly visible. Its size becomes apparent when perimetric methods are applied. When the scintillating phosphenes are observed on a dynamic random-dot noise background, however, as used in the "*noise field campimetry*" of Aulhorn and Köst (1988, 1989), the scotoma is seen as a homogeneously grey quartermoon-shaped part which slowly shifts with the fortification pattern across the visual field and enlarges correspondingly. The white noise of a TV screen is a suitable and readily available background for seeing the migraine scotoma as a "positive" sensation (Fig. 4). Interestingly on a dynamic random-dot background, more particles of the scintillating pattern are seen in colours than when the pattern is observed on a homogeneous grey background.

The colours are seen as very pure; red and green are reported more frequently than the other colours of the spectrum. Some of the flickering particles are of a deep, "brillant" black, darker than any black seen in a visual pattern and difficult to describe in terms of normal achromatic vision (Grüsser & Landis, 1991).

A "positive" sensation of the scotoma is also evoked when one observes the migraine phosphene on a saturated blue background and simultaneously interrupts vision at 5–8 Hz, e.g. by looking through a rotating sector disk. The scotoma appears as an unsaturated yellowish field trailing the scintillating pattern. It has the same shape as the scotoma seen on the noise field background.

DISCUSSION

Variability of cortical visual field representation

Comparing the protocols of the three subjects, it became evident that the cortical representation of the fovea seems to vary considerably between subjects, providing the basic assumption about a constant spread velocity V_c is correct. The observation of area V1 variability is in good agreement with neuroanatomical and neurophysiological findings in man and monkeys:

(a) When one inspects the mesial occipital surface of different human brains, the diversity in the lengths of the calcarine fissure and the secondary and tertiary gyri above and below is evident.
(b) Stensaas, Eddington and Dobelle (1974) reported up to a 2.4-fold variability in the overall striate cortex area of 52 human hemispheres.
(c) The foveal projection area (± 2 deg around fovea centre) differed in Rhesus macaques by 100% (Van Essen *et al.*, 1984).

From the diversity of area V1 in the human brain one can expect a considerable variation in the constants a and b of equation (7) when phosphene protocols from many migraine patients are available. When carefully measured these protocols are handy tools for studying the individual differences in functional mapping of the human retina onto area V1. This goal can only be achieved, however, when many scientists suffering from migraine provide protocols of the migraine phosphenes (see Addendum).

From the data described in the present report, little can be said about possible local anisotropies or meridian asymmetries of the cortical visual field representation, topics extensively discussed in the literature and partially attributed to the incorrect assumption that area V1 can be adequately represented by a plane surface (for discussion see LeVay, Hubel & Wiesel, 1975; Sakitt, 1982; Rovamo & Virsu, 1984; Drasdo, 1991). Comparing the sizes of fortification particles visible at identical eccentricities ($P_v < 10$ deg) in the upper and lower visual fields indicates differences (slightly larger particles in the upper visual field) suggesting that some local anisotropies also exist in the human primary visual cortex. In general, these differences are small, however, and equations (1)–(8) provide adequate descriptions of the observations in the visual field during the spread of migraine phosphenes.

Why do migraine phosphenes begin preferentially at or near the visual field centre?

In 11 of the 14 perimetrically measured scintillating fortification patterns the phosphenes appeared first at or near (± 2 deg) the visual field centre. This preference, which is also reported by many other subjects suffering from migraine, may have different causes:

(a) The occipital end of area V1 is located at the outer margins of the arteria cerebri posterior vascular field and is therefore especially susceptible to transient and local decrease in blood supply.
(b) The preference is due to the fact that local abnormalities in blood supply appear with equal probability in all parts of area V1. Since the axons of lateral geniculate nucleus nerve cells related to the fovea and the proximate parafovea project to a large part of the striate cortex, the probability that the onset of a migraine phosphene is observed at or near the centre of the visual field is higher than at the periphery of the visual field.
(c) The foveal projection field of area V1 receives only afferent axons from lateral geniculate cells that selectively process cone signals and no rod signals. Since cone vision and foveation developed later than rod vision in the phylogenesis of primates, afferent and cortical nerve cells involved in cone vision may only use a different set of synaptic transmitter/molecular receptor interactions than nerve cells processing a mixed rod/cone input. These synaptic mechanisms (e.g. glutamate–NMDA–receptor interactions) may be more susceptible to local ischemia.

All these answers to the heading, which was a friendly question raised by an unknown referee, are speculative of course, but they may lead to new thoughts and experiments on the triggering mechanisms responsible for the initiation of visual migraine aura.

Why zig-zag patterns?

The peculiar shape of the migraine phosphenes may be explained by the well-established functional microstructure of the area V1 hypercolumns: the local increase in extracellular potassium concentration and excitatory transmitters leads to an activation of a patch of layer IV nerve cells with simple receptive fields. Their activation is transmitted within the corresponding cortical column to nerve cells of layers V, II and III. Hereby, nerve cells that have similarly oriented receptive fields are preferentially excited. Simultaneously other interneurons are activated within a cortical column, which transmit *lateral inhibition* to neighbouring cortical columns. Hereby the lateral inhibition decreases with the distance from the excited column. At the same time *lateral excitation* is transmitted by axon collaterals and interneurons. In doing so, neurons of the same receptive field orientation

are coactivated and the same would be true for neurons with receptive field orientations perpendicular to those of the excitation focus. The latter condition is due to the fact that the distance between columns and therefore the decrease in lateral inhibition within a given hypercolumn is largest in columns with a 90-deg-preferred orientation difference (Engel, König, Gray & Singer, 1990). In other words, the general rise in neuronal excitation due to increased potassium concentration along the stripe of Gennari (see below) leads to an increased activation of layer IV neurons, which is modified by lateral inhibitory and excitatory mechanisms acting mainly in cell tiers above and below layer IV. Moreover, due to feedback mechanisms the activation of nerve cells within a column induces oscillatory responses at a frequency corresponding to that of the perceived flicker of the migraine phosphenes, i.e. about 10 Hz.

In favour of this explanation of the migraine phosphene zig-zag patterns is another experimental observation: monocular deformation of the eyeball leads to a maintained selective *activation of retinal on-centre ganglion cells* and a corresponding *maintained inhibition of off-centre ganglion cells*. At the perceptual level this response causes the *deformation phosphenes* (Grüsser, Grüsser-Cornehls, Kusel & Przybyszewski, 1989). When *both eyes* are deformed simultaneously, the visual cortex receives a sustained activation from on-centre nerve cells of the lateral geniculate nucleus, while the afferent off-channels are inhibited. Under these conditions one observes a patterned binocular deformation phosphene consisting of flickering rhomboids, triangles and squares, which are very small in the centre of the visual field and increase in size towards the visual field periphery (cf. Fig. 10.1e in Grüsser & Landis, 1991). The difference in appearance between migraine phosphenes and binocular deformation phosphenes is attributed to the fact that in the latter only the on-input of area V1 is activated, while in migraine phosphenes simple field nerve cells dominated by both on- or off-mechanisms are activated.

Possible pathophysiological mechanisms underlying migraine phosphenes

The initiation of migraine phosphenes is presumably caused by an *increased release of neurotransmitters*, especially glutamate, or by *focal ischemia*, both leading to *local neuronal hyperexcitation* and partial disintegration of normal neuronal signal processing. The latter is characterized by spatially and temporally ordered neuronal excitation and inhibition related to the columnar organization of area 17 neuronal networks (Hubel & Wiesel, 1974a; Livingstone & Hubel, 1984; Eckhorn, Bauer, Jordan, Brosch, Kruse, Munk & Reitboeck, 1988; Engel *et al.*, 1990).

The initial neuronal hyperexcitation leads to a strong outflow of *potassium ions* from and an inflow of *sodium* and *calcium ions* into the intracellular space of cortical nerve cells. An increase in local extracellular potassium concentration and a decrease in extracellular calcium and sodium concentration is the result. According to the Goldman equation this fact causes a further increase in

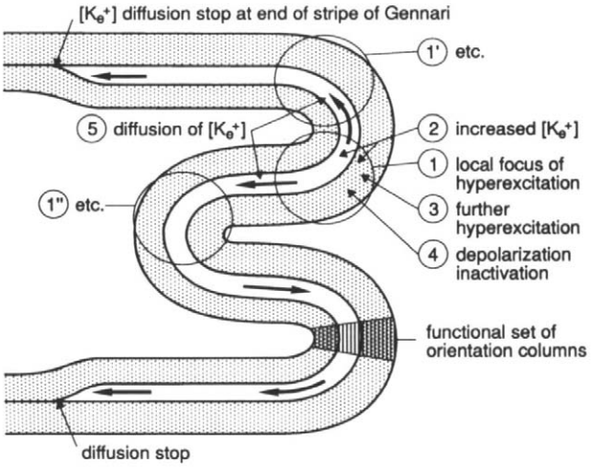

FIGURE 5. Scheme of the pathophysiological mechanisms in area V1 leading to scintillating migraine phosphenes. Further explanation in text.

neuronal membrane depolarization and in the frequency of discharging nerve cell action potentials. Increased nerve cell activity also leads to a local increase in release of synaptic transmitters as well as to an increase in the local glucose metabolism and the proton concentration. The potassium ions released into the extracellular space diffuse into *neighbouring areas* as do small transmitter molecules. Hereby the mechanism just described is repeated and a self-sustaining spread of a neuronal hyperactivity front is generated (Fig. 5). The width of this front remains about the same during a migraine aura [B of equation (13)]. Interestingly B corresponds roughly to the average distance of *neighbouring ocular dominance columns*, as expressed in the report of Horton and Headly-Whyte (1984). We evaluated their figures of stained ocular dominance columns projected onto the surface of the primary visual cortex of man by a computerized two-dimensional spatial frequency analysis. A peak in the spatial frequency distribution of ocular dominance columns corresponding to a spatial period of 1.6 ± 0.3 mm was found.

The non-flickering migraine scotoma

Whenever the increased extracellular potassium concentration leads to a nerve cell membrane depolarization of more than 35–40 mV, *depolarization inactivation* of action potential discharges occurs due to the inactivation of the "fast" sodium channels within the nerve cell soma and axon membranes. Hence the cortical nerve cell discharge activity ceases (Glötzner & Grüsser, 1968). The "trailing" migraine scotoma corresponds to such a *temporary inactivation of the previously hyperactive nerve cells* of area V1. In the present study the width σ of the trailing scotoma corresponded approximately to the dimension of 2–3 cortical hypercolumns. The *neutral grey* of the scotoma perceived in the dynamic random-noise experiment indicates that extrastriate visual cortical areas contribute to this percept, as predicted by Baumgartner (1990).

Possible participation of glial cells in the pathophysiological process

The increase in extracellular potassium ions also leads to a depolarization of the *glial cell* membrane potential. A portion of the extracellular potassium ions is pumped by an ATPase-driven and pH-sensitive "membrane pump" into the intracellular space of glial cells. This results in a secondary diffusion of water from the extracellular into the intracellular space. The resultant mild swelling of glial cells causes a local reduction in extracellular space volume, an increased mechanical pressure on blood capillaries and an increase in vascular resistance to local blood flow, resulting in a transient "secondary" mild oligaemia. After about 3–5 min of nerve cell inactivation the normal intracellular/extracellular ion concentrations are restored by the glial cell and nerve cell membrane pumps. Thereafter normal nerve cell activity returns and the scotoma disappears. A similar glial nerve cell membrane depolarization was found with intracellular microelectrode recordings from glial cells during focal epileptic discharges when extracellular potassium concentration increased (Frederking, Glötzner & Grüsser, 1971).

Migraine phosphenes, spreading depression and the stripe of Gennari

The assumed diffusion of potassium ions from the region of increased extracellular concentration to its surroundings is most likely akin to the potassium diffusion during *cortical spreading depression* observed in animals with lisencephalic brains (Leaõ, 1944; Ochs, 1962; Bures, Buresova & Krivanek, 1974; Lauritzen, 1987). Increased nerve cell activity along the front of spreading cortical depression was indeed found, and this neuronal hyperactivity was followed by a period of neuronal inactivation (Grafstein, 1956; Morlock, Mori & Ward, 1964).

It is suggested that in human migraine phosphenes potassium diffusion takes place chiefly within the *stripe of Gennari*: its extracellular space along the mainly parallel afferent axons, in comparison to that of the other cortical layers, facilitates radial diffusion of small ions in a narrow space parallel to the cortical surface. According to this hypothesis, neurons of the different tiers of area V1 layer 4 would be the essential targets of the increased extracellular potassium concentration. The extracellular space along the stripe of Gennari as the main pathway of pathophysiological mechanism spread also explains the *disappearance of migraine phosphenes* when the pathophysiological process has reached the area V1/V2 border, where the thick stripe of Gennari separating the upper and lower cortical cell layers ends and the surface-parallel fibre layer through cell layer 4 decreases considerably in width (Gennari, 1782). Therefore the unhindered diffusion of potassium ions comes to an end. The alternative hypothesis—the migraine process diffuses into the extrastriate areas but the V2 activation is not perceived due to a lack of "backprojection" to area V1—seems rather unlikely. The neutral grey of the migraine scotoma is well perceived on a dynamic noise field background despite area V1 neurons being inactivated. Moreover, as noted by Lashley (1941) and confirmed in the present study, a spatially periodic stripe pattern "fills in" the migraine scotoma, indicating that pattern perception by means of area V2 and higher order cortical visual areas is possible without any activity of the corresponding area V1 neurons (Baumgartner, 1990).

Interestingly, studies of local cerebral blood flow during migraine attacks have come to the conclusion that parallel to the scintillating phosphenes and the accompanying travelling scotoma, a similar spreading of local oligaemia occurs. The spread of this *ischaemic front* has been reported to be about 2–2.2 mm/min (Oleson, Larsen & Lauritzen, 1981; Olesen, Skyhoj Olsen & Friberg, 1990), a value corresponding well to the computed speed of the pathophysiological mechanisms leading to the migraine phosphenes analysed in the present study.

It seems probable that despite the spread of potassium ions along the stripe of Gennari coming to an end at the area V1/V2 border, some pathophysiological mechanisms such as spread of neurotransmitters acting on vascular smooth muscles transgress the area V1 border into neighbouring cortical regions. This would explain why migraine symptoms in some patients affect cortical regions far outside area V1 and eventually evoke severe headache, presumably due to activation of nociceptors located along the brain vessels. Nonetheless, the elementary pathophysiological process generating the typical migraine flickering phosphene does not seem to affect any other retinotopically organized extrastriate visual area as it does neuronal activity in area V1.

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ADDENDUM

Call for Migraine Phosphene Protocols

For a statistical analysis of the course of migraine phosphenes through the visual hemifield the author would very much appreciate receiving perimetrically drawn migraine phosphene protocols. All colleagues interested in a collaboration can obtain further information on the protocol method from the author: Professor O.-J. Grüsser, Department of Physiology, Freie Universität Berlin, Arnimallee 22, 14195 Berlin (Dahlem), Germany [*Fax* 49 30 838 2507; *Email* gruesser@fub46.zedat.fu-berlin.de].