Visual Noise Selectively Degrades Vision in Migraine

Doreen Wagner, Velitchko Manahilov, Gunter Loffler, Gael E. Gordon, and Gordon N. Dutton

Purpose. Migraine is a disabling condition with underlying neuronal mechanisms that remain elusive. Migraineurs experience hyperresponsivity to visual stimuli and frequently experience visual disturbances. In the present study, the equivalent input noise approach was used to reveal abnormalities of visual processing and to isolate factors responsible for any such deficits. This approach partitions visual sensitivity into components that represent the efficiency of using the available stimulus information, the background internal noise due to irregular neuronal fluctuations, and the neuronal noise induced by the external stimulation.

Methods. Ten migraine with aura, ten migraine without aura, and ten age-matched headache-free subjects participated. Performance in detecting luminance targets embedded in visual noise, resembling grainy photographs, was measured at various noise levels.

Results. Contrast thresholds of the three subject groups were similar in the absence of noise, but both migraine groups performed worse in the presence of high noise levels, with performance of migraineurs with aura significantly poorer ($P < 0.05$) than that of control subjects. Data were fitted with a perceptual template model that showed that the model parameter determining the internal (neuronal) noise triggered by the external (stimulus) noise was significantly higher ($P < 0.001$) in both migraine groups than in the non-migraineur group. Migraineurs without aura also showed a significant ($P < 0.05$) though weak reduction of sampling efficiency (0.12 ± 0.02) compared with control subjects (0.17 ± 0.02).

Conclusions. The results revealed substantial external noise-exclusion deficits in migraine with aura and a minor impairment of noise exclusion in migraine without aura. Migraineurs appeared prone to abnormally high variability of neuronal activity. This result provides a promising explanation of observed visual deficits in migraine. (*Invest Ophthalmol Vis Sci.* 2010;51:2294–2299) DOI:10.1167/iovs.09-4318

Migraine is a chronic disorder characterized by intermittent headache[1] that affects about 11% of the population. Approximately one third of migraineurs experience visual disturbances (aura) including flashing lights, twinkling spots, or zig-zag patterns.[2,3] A general characteristic of migraine with aura is hyperresponsivity to external stimuli during, but also between, episodes. This response may be a manifestation of increased neuronal excitability.[4] Increased excitability of the occipital cortex has also been found in migraine without aura.[5]

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Central neuronal hyperexcitability should result in higher sensitivity to near-threshold stimuli, but this prediction has not been verified experimentally.[6–8]

Determining the lowest contrast necessary to perceive a visual target on a uniform background provides some information about the ability to process visual signals. However, normal performance under these circumstances does not necessarily imply normal processing. Deficits in the efficiency with which observers use the available stimulus information, on account of increased internal noise due to irregular neuronal fluctuations,[9,10] may not result in increased detection thresholds in standard tasks but may require external noise before their effect becomes manifest.

The purpose of this study was to establish whether migraineurs with or without aura behave differently from normal subjects in detecting visual stimuli embedded in luminance noise and to isolate the factors responsible for such deficits.

Methods

Participants

Ten headache-free volunteers (mean age ± SD: 30 ± 4.7 years), ten migraine-with-aura subjects (33 ± 6.0 years), and ten migraine-without-aura (29 ± 8.4 years) subjects took part in the experiment. The gender distribution in each group was 8:2 (female:male). Informed consent was obtained from all participants. All subjects underwent optometric screening. Headache status was verified, first by a structured questionnaire in accordance with the second edition of the International Headache Classification, ICHD-II,[11] and second by a MIDAS (Migraine Disability Assessment) questionnaire,[12,13] which scores migraineurs according to headache intensity. All subjects met the following visual and ocular health criteria: visual acuity of 20/30 or better, intraocular eye pressures of less than 21 mm Hg (Goldmann), and normal visual fields (Humphrey 30-2; Carl Zeiss Meditec, Inc. Dublin, CA). In addition, a fundus screening was performed on control and migraine-with-aura subjects by using scanning laser polarimetry (GDx VCC; Carl Zeiss Meditec). These 20 subjects showed normal retinal nerve fiber layer thickness (retinal nerve fiber index <30) and healthy-appearing retina in fundus photographs. Fundus screening in the migraineurs without aura could not be performed because of technical reasons. Moreover, we excluded subjects who were in any one of the following categories: pregnant, >40 years of age, and having epilepsy, dyslexia, amblyopia, or diabetes. The migraine groups took no preventative medication and had no migraine episodes during the 3 days before or after the experiment. The control group had never had an episode of migraine and had no more than one headache a month.

The study was approved by the ethics committee of Glasgow Caledonian University. The research adhered to the tenets of the Declaration of Helsinki.

Apparatus

Stimuli were generated on a computer and presented on a high-resolution RGB monitor (VisionMaster Pro 450; Iiyama, Tokyo, Japan) with a temporal resolution of 120 Hz, a spatial resolution of 1024 × 768 pixels, and a mean luminance of 28 cd/m^2. We used a custom

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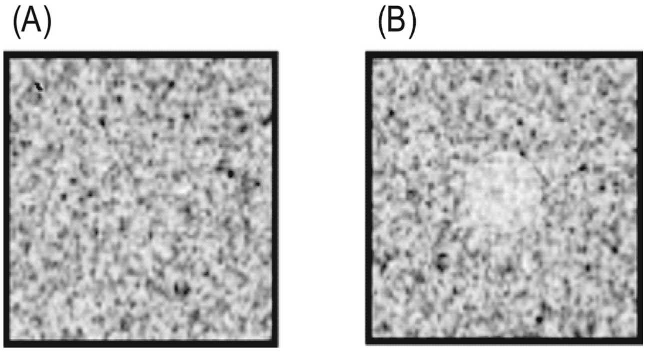

FIGURE 1. Stimuli: a target disk of 0.25° diameter was randomly positioned in one of two square fields: one field (**A**) contained only a static 2-D noise sample, the other (**B**) contained the target disk superimposed on the same noise.

video summation device[14] that provided 256 gray levels with 12-bit precision. The monitor's gamma nonlinearity was calibrated and regularly verified by a photometer (OptiCal; CRS Ltd., Cambridge, UK). The viewing distance was 150 cm.

Stimuli

The stimulus consisted of two square fields (1 × 1 degree of arc) presented side-by-side with a center-to-center distance of 1.8° (Fig. 1). A gray border, subtending 2 minutes of arc surrounded each field. Both fields contained 2-D static Gaussian noise samples of varying standard deviation whose noise pixel size was 1.4 × 1.4 minutes of arc. The test signal was a disk of 0.25° diameter presented in the center of one randomly selected field. Stimuli were presented for 1 second.

Procedure

Observers were instructed to fixate on each square field during the stimulus presentation before making a decision.[15] They indicated which field contained the target by pressing one of two buttons (spatial two-alternative, forced-choice). A feedback tone indicated an incorrect response. Four different noise levels (0, 1.2, 4.9, and 19.5 μdeg^2), produced by varying the standard deviation of the Gaussian noise, were run in separate blocks. Each condition started with a preliminary measurement of the contrast thresholds. For this preliminary measurement, an adaptive staircase procedure was used, converging to 79% correct responses.[16] This threshold estimate was used subsequently within a constant-stimulus procedure in which a minimum of 40 trials, of four near-threshold contrast levels of the test stimulus (0.075 and 0.15 log units above and below the estimated threshold contrast) were presented. The constant-stimulus procedures were repeated in reverse order at the same test contrast levels. This method allowed the responses to a minimum of 80 trials for each test contrast level to be collected. To maintain attention, 10% of the trials showed the test signal at 0.3 log units above the corresponding contrast threshold. These trials were not used for the data analysis. Experiments were performed with software (Wavenet, Miami, FL) custom-written in Borland Pascal for MSDOS.

Perceptual Template Model

Models based on statistical decision theory[9,10,15,17] have assumed that visual performance is limited by various sources of noise. One source is an additive internal noise, due to the variability of neural firing rate, which does not depend on the level of external stimulation. Other sources are multiplicative internal noises,[18] which are proportional to the energy of the signal or the density of the external noise. In addition, human performance depends on the sampling efficiency, which refers to the observer's ability to match an internal template to the signal profile or to integrate signals over the entire signal area.

Lu and Dosher[19] proposed a perceptual template model for the detection of luminance patterns (Fig. 2) which consists of a filter (the perceptual template) a nonlinear transducer, multiplicative internal noises with magnitudes that are monotonic functions of the energy of the signal and the external noise, an additive internal noise, and a decision process.

According to this model, the detectability index (d', determined by the signal-to-noise ratio at the decision stage) for a signal embedded in external noise can be expressed as

$$d'^2 = \frac{(kE)^\gamma}{N^\gamma + mN^\gamma + s(kE)^\gamma + N_{\text{add}}} \qquad (1)$$

where E is the contrast energy of the signal (the integral of the squared luminance function), k is the efficiency with which humans use the perceptual template to match the signal, N is the density of the external noise, γ is the exponent of the power transducer function, N_{add} is the additive internal noise with amplitude that does not depend on the input, and m and s are coefficients that determine the equivalent multiplicative noises induced by the external noise (mN^γ) and the signal ($s(kE)^\gamma$), respectively. In this version of the perceptual template model, we used different multiplicative coefficients (m and s) to

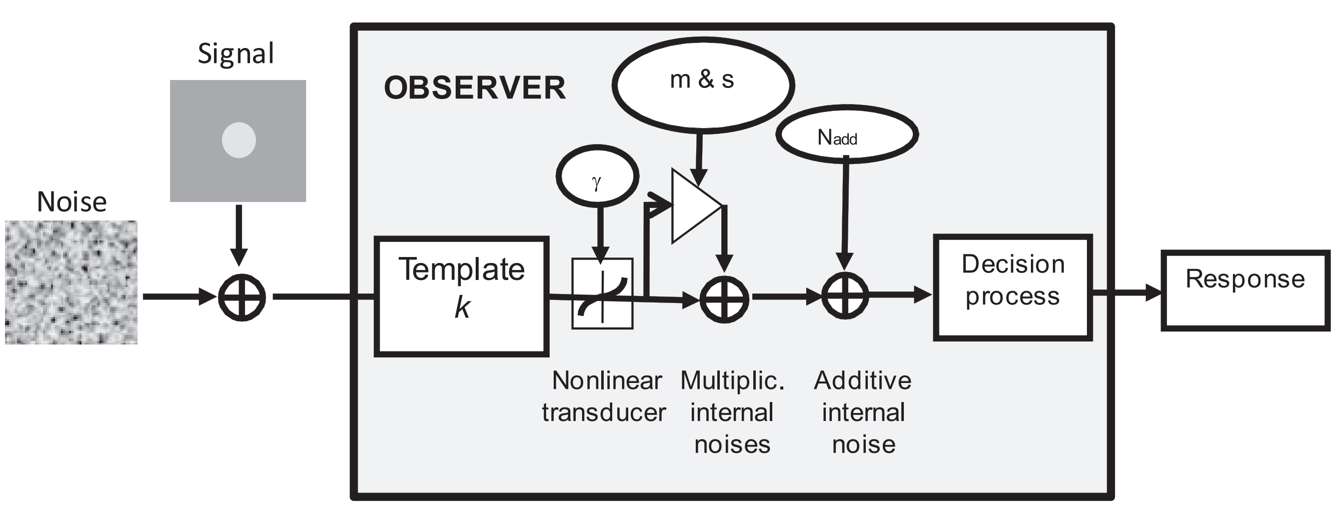

FIGURE 2. Illustration of the perceptual template model for detecting a signal embedded in external noise. The model consists of a perceptual template (k, filter), a nonlinear transducer function in the form of an expansive power function (γ), multiplicative internal noises with amplitudes proportional to the strength of the signal and the external noise (m, s), additive internal noise (N_{add}), and a decision process.

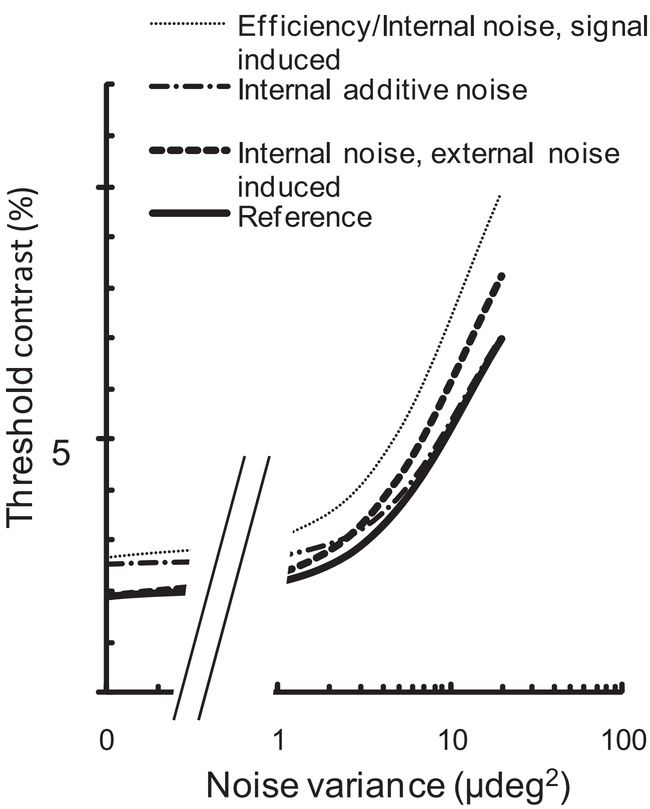

FIGURE 3. Model predictions calculated by equation 2. *Solid line*: a reference function of contrast thresholds versus external noise variance; *dotted line*: a general upward shift in the presence of reduced efficiency; *dotted-dashed line*: effect of increased additive internal noise (an increase in contrast thresholds at low but not at high levels of external noise); *dashed line*: effect of an increased internal noise level induced by the external noise, in which case deficits are only seen for high external noise.

separate the effects of external noise and signal on the induced multiplicative internal noise. The sensitivities of these two noise components was considered independently, since the component due to the external noise reflects the variability of pooled activity of channels tuned to a wide range of spatial frequencies and orientations, whereas the component due to the signal represents the variability of activity of a spatial filter matched to the test disk.

The threshold contrast [$C = (E/E_0)^{1/2}$] can be represented by rearrangement of equation 1

$$C = \frac{(N^{\gamma} + mN^{\gamma} + N_{add})^{1/2\gamma}}{(E_0 k)^{1/2}[(1/d'^2) - s]^{1/2\gamma}} \qquad (2)$$

where E_0 represents the energy of the signal with unit contrast (E_0 = 45,600 μdeg^2).

Equation 2 predicts that the threshold contrast necessary to detect the target depends on the variance of the external noise added to the stimulus. The solid line in Figure 3 shows the typical behavior of a threshold contrast/external noise variance function: Thresholds remain constant when small amounts of external noise are added up to a certain level and rise when contrasts are increased beyond that level.

If migraineurs had suboptimal sampling efficiency (reduced k) for the detection of luminance patterns, they would require more contrast, shifting the entire threshold/noise variance function upward (Fig. 3, dotted line). The same upward shift would be predicted if the target (signal) induced abnormally high levels of internal noise (increased s). However, if migraineurs experienced increased additive internal noise with an amplitude that is independent of the external stimulation (N_{add}), greater contrast would be needed for detection only at low but not at high levels of external noise (Fig. 3, dotted-dashed line). Finally, if the limitation were linked to the amount of internal noise induced by the external noise (increased m), migraineurs would detect the target equally as well as normal subjects in the absence of external noise but would show deficits when external noise is high (Fig. 3, dashed line).

RESULTS

The proportions of correct responses for each participant and each experimental condition in the two-alternative, forced-choice experiments were fitted with a Weibull function,[20,21] with the use of a maximum-likelihood procedure[22] (Fig. 4, dashed lines). The quality of fit was assessed by the χ^2 statistic (df = 2). None of the 120 psychometric function fits was rejected at the 0.05 level. The average χ^2 and standard deviation of the fits for the migraineurs with aura was 1.3 ± 0.56; for

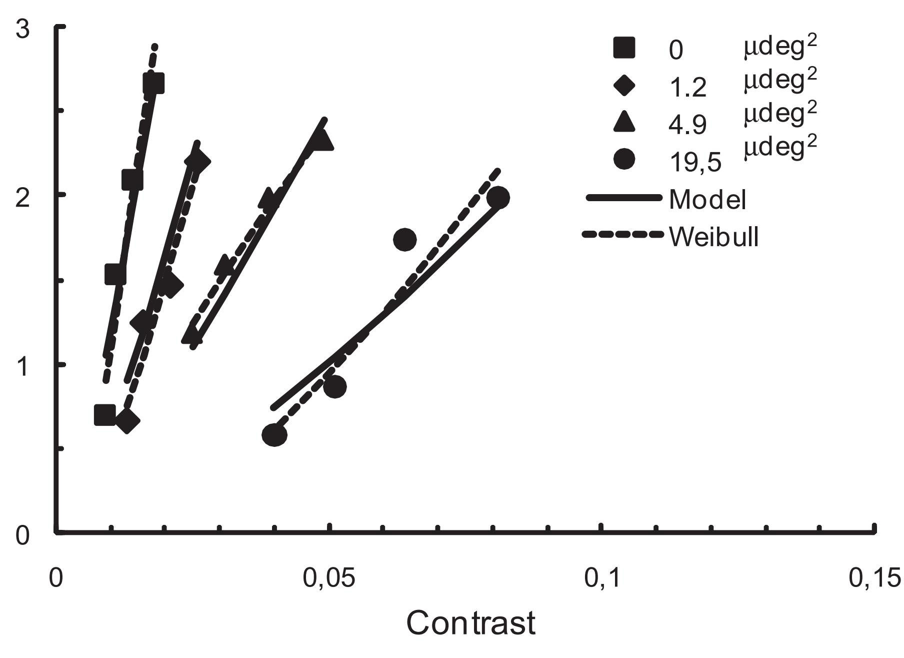

FIGURE 4. Performance (detectability index, d') as a function of target contrast at four levels of external noise variance for one observer (MT) is shown. Performance was measured at four contrast levels, straddling the threshold for each of the four levels of external noise. *Dotted lines*: psychometric functions in d' units fitted with a Weibull function using a maximum-likelihood method. *Solid lines*: the fit with the perceptual template model (equation 1).

the migraineurs without aura, 0.7 ± 0.56; and for the non-migraineurs, 0.9 ± 0.54.

Contrast thresholds were estimated from the psychometric functions at the point where observers were correct on 76% of the trials. Contrast thresholds for the three groups (migraineurs with and without aura and control subjects) were normally distributed (Shapiro-Wilk test, $P > 0.15$; SPSS 16.0; SPSS, Chicago, IL). A two-way ANOVA (three subject groups × four noise levels) was performed to assess statistical significance and showed main effects for noise level ($F_{(3108)} = 422$, $P < 0.001$, $\eta_p{}^2 = 0.921$) and subject group ($F_{(2108)} = 14$, $P < 0.001$, $\eta_p{}^2 = 0.203$).

Averaged contrast thresholds for each subject group increased as a function of external noise variance (Fig. 5A). More important, the interaction between the two-factors subject group and noise level was also significant ($F_{(6108)} = 2$, $P < 0.05$, $\eta_p{}^2 = 0.116$). Adding stimulus noise had a more detrimental effect on the migraineurs with and without aura than on the normal subjects. To understand at which noise levels significant differences occurred, we performed post hoc multiple comparisons. Because the variances of the threshold data were not equal (Levene test, $P < 0.01$), a Games-Howell post hoc test was conducted. Although migraineurs detected the target equally as well as the control subjects at low noise levels, migraineurs with aura performed significantly ($P < 0.05$) poorer at high noise levels (Fig. 5A).

To determine the factors limiting performance of migraineurs, we fitted the five free parameters of the perceptual template model (equation 1) to the proportions of correct responses expressed in d' units for each subject (16 measurements), by using the method of least squares (Fig. 4, solid lines). The quality of the model fit was assessed by using the R^2 statistic. This test evaluates the proportion of the variance accounted for by the fit, adjusted by the number of free parameters.[23] The average R^2 value and 95% confidence interval for the non-migraineurs were 0.769 ± 0.043; for the migraineurs with aura, 0.774 ± 0.066; and for the migraineurs without aura, 0.813 ± 0.049. Comparing these R^2 values with those from fitting the data with Weibull functions (eight free parameters; 0.817 ± 0.096 for control subjects, 0.817 ± 0.078 for the migraineurs with aura, and 0.872 ± 0.074 for the migraineurs without aura) shows no significant difference (two-tailed paired *t*-test). Thus, the two models provide equally good fits to the data. It should be noted that while fitting data with Weibull function makes no assumptions about observer performance, the perceptual template model fits the data and provides a quantitative description of the factors that limit performance accuracy.

Not all the five parameters of the perceptual template model (Figs. 5B, 5C) followed normal distributions (N_{add} and s; Shapiro-Wilk test $P < 0.05$). Therefore, a nonparametric Mann-Whitney U test with Bonferroni correction was performed. Two parameters showed significant differences. The multiplicative coefficient (m), which determines the internal noise induced by the external noise, was significantly ($P < 0.001$) higher in the migraineurs with aura ($m = 0.32 \pm 0.05$) that that in the non-migraineurs ($m = 0.05 \pm 0.02$). This multiplicative coefficient for the migraineurs without aura ($m = 0.11 \pm 0.03$) was significantly ($P < 0.001$) higher than for the control subjects and significantly ($P < 0.001$) lower than for the migraineurs with aura. Sampling efficiency (k) for the migraineurs with aura was not significantly different from that of the normal subjects but the migraineurs without aura ($k = 0.12 \pm 0.02$) showed a significantly ($P < 0.05$) lower efficiency than did the headache-free control subjects ($k = 0.17 \pm 0.02$).

Discussion

Previous work[24] investigating visual perception in migraineurs has found most of them to have increased thresholds for detecting coherently moving dots embedded in motion noise. This finding has led to the suggestion that they may have increased additive internal noise levels. Others[25] have shown that although migraineurs have impaired motion perception when coherently moving dots are embedded in motion noise, when moving dots are presented without distracters, migraineurs have similar or slightly better performance than do non-migraineurs. The performance impairment in the presence of motion noise has been explained by a general excitability reduction, which would weaken efficiency of visual perception.

The results of the present study do not support either of these proposals. When the equivalent input noise approach was used, the impaired contrast thresholds for detecting a luminance target embedded in high noise levels revealed that the migraineurs with aura had strong deficits in excluding external noise. The migraineurs without aura showed a minor impairment of external-noise exclusion (as determined by the model parameter that is related to the internal neuronal noise triggered by the external visual noise). On the other hand, the migraineurs without aura showed a significant, though weak, reduction of sampling efficiency compared with that shown by the headache-free persons. The effects of these two factors on detection performance of the migraineurs without aura, however, were small, since their contrast thresholds at low and higher visual noise levels were not significantly higher than those of the control subjects. The ability to exclude external noise could be due to reduced cortical suppression in migraineurs, possibly through GABAergic inputs.[26] The higher variability of neuronal responses[27] is associated with hyperexcitability[4,28] and appears to be a promising neuronal explanation of the visual deficits in migraine with aura. The crucial role of induced internal noise, which requires testing with and without added external noise may explain why some studies[24,25] (using noisy stimuli) have found migraineurs' visual performance to differ from that of control subjects, whereas others[6–8] (using noiseless stimuli) have not found such contrast threshold differences. The result of the present study showing that the migraineurs with aura exhibited greater noise-exclusion deficits than did the migraineurs without aura suggests that differences between studies of visual performance of migraineurs could also be due to the types of migraine groups tested—namely, those with aura, those without aura, or mixed groups of migraineurs.

It is interesting that similar noise-exclusion deficits have been reported in developmental dyslexia, which manifests as a difficulty with reading in the context of normal individual intelligence. Experiments on detecting flickering patterns[29] and discriminating direction of coherent motion[30] showed that dyslexics have lower detection thresholds than do nondyslexics in the presence but not in the absence of noise. Converging evidence shows that children with language learning disabilities[31] and dyslexia[32] also have substantial deficits in speech perception and detection of tonal targets, only under conditions with added auditory noise. Although migraine and dyslexia have different etiologies, an abnormal balance between excitatory and inhibitory cortical processes in migraineurs with aura and dyslexics could explain their impaired ability to extract important sensory information from irrelevant distracters in both conditions.

In everyday life, we are exposed to a stream of visual information that contains important messages usually camouflaged by various unwanted signals. In a world of abundant

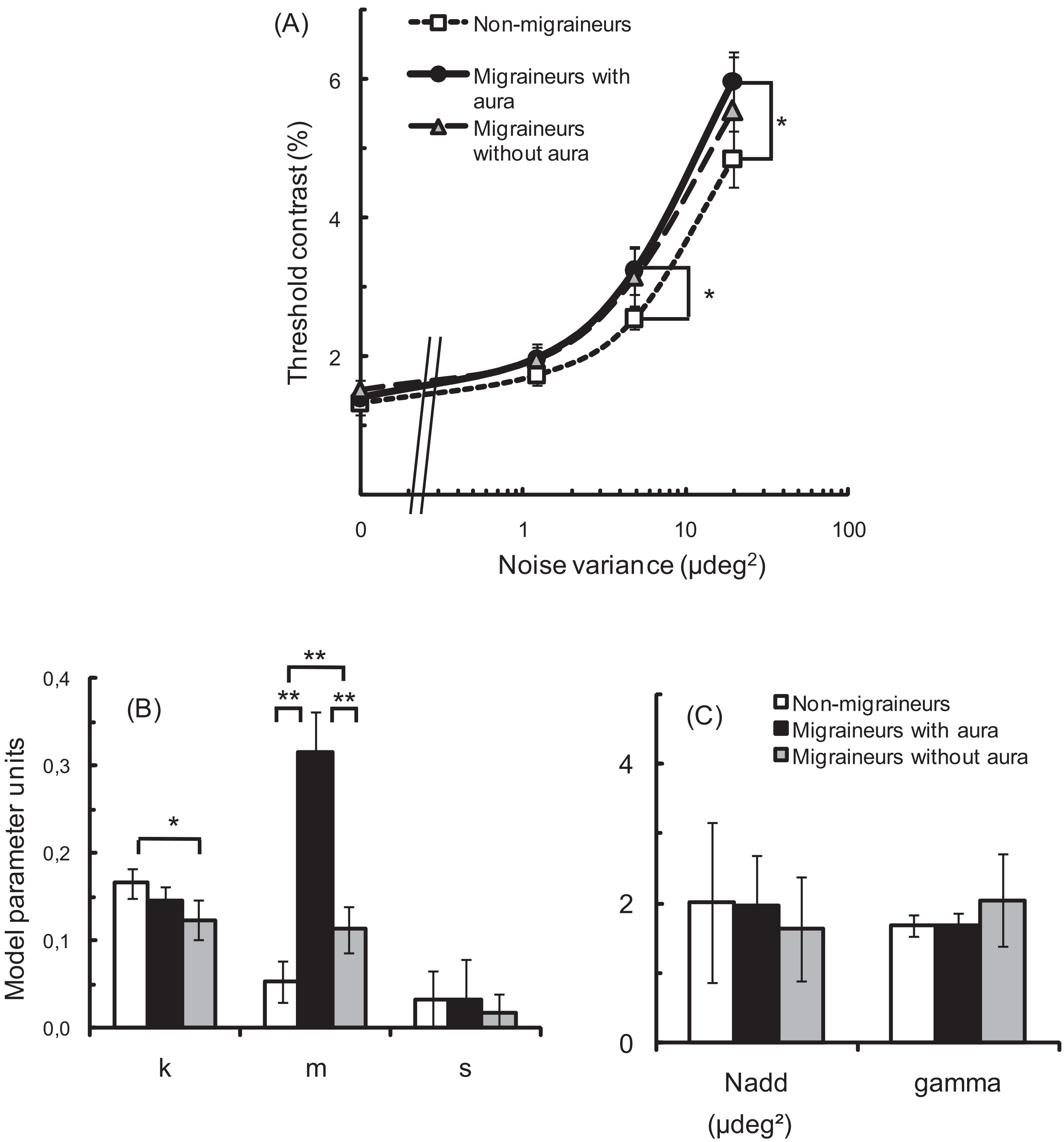

Figure 5. (**A**) Average contrast threshold as a function of external noise variance for the migraineurs with aura, the migraineurs without aura, and the non-migraineurs. Data show similar thresholds for the three groups in the absence of external noise; the migraineurs with aura showed increased thresholds for large amounts of external noise. **P* < 0.05, Games-Howell post hoc test. The migraineurs without aura show the tendency to have higher thresholds for external noise, but the difference did not reach statistical significance. Error bars, 95% confidence interval. (**B**, **C**) Best fitted values of model parameters for the migraineurs with aura, the migraineurs without aura, and the non-migraineurs. The parameter that relates to the internal noise induced by external noise differs significantly (***P* < 0.001, exact two-tailed Mann-Whitney U test, Bonferroni correction) between each of the three groups. In addition, the efficiency parameter differs significantly (**P* < 0.05, exact two-tailed Mann-Whitney U test, Bonferroni correction) between the migraineurs without aura and the control subjects. None of the other parameters shows a significant difference.

visual stimulation, our ability to extract salient signals from irrelevant distractors is vital to almost any visual task. The current results indicate that compared with the headache-free control subjects, the migraineurs experienced detection deficits when presented with noisy environments and these deficits were more pronounced in migraine with aura than in migraine without aura. This finding not only has significant implications for routine visual tasks faced by migraineurs, but it also provides novel insight into the cortical features of migraine.

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