Global Shape Processing Deficits Are Amplified by Temporal Masking in Migraine

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Purpose. Individuals with migraine show subtle defects in a range of visual tasks compared to nonmigraineurs. Increased neuronal noise can account for some of these deficits. To examine the generality of increased noise in migraine, masking effects were compared in migraineurs and headache-free controls using a shape discrimination task, thought to involve processing in extrastriate cortical areas.

Methods. Nine migraineurs with aura, nine migraineurs without aura, and nine headache-free controls participated. Observers had to detect deviations in circular shapes with or without a larger contour mask. The nonoverlapping mask was presented at five temporal intervals (stimulus onset asynchronies, SOA): 0 (simultaneous), 66, 100, 133, and 250 ms.

Results. Migraineurs with aura performed worse in all tests than migraineurs without aura and controls. Both migraine groups performed poorer than controls at discriminating shapes without masks. Typical masking functions were obtained from all groups, but they were steeper for migraineurs than controls with thresholds raised most dramatically (2.1 and 4.4 times for migraineurs without and with aura relative to controls, respectively) at SOAs where masks had their most detrimental effect (66–100 ms). Modeling the effect of masking showed that raised internal noise alone is insufficient to explain these deficits. Rather, an abnormal nonlinear transducer function (e.g., as part of gain-control) together with increased multiplicative noise is required to capture the data.

Conclusions. The findings are consistent with an extrastriate deficit in migraine that cannot be explained completely by defective inhibition. (*Invest Ophthalmol Vis Sci.* 2013; 54:1160–1168) DOI:10.1167/iovs.12-11242

Migraineurs, especially those with aura, are poorer than controls at discriminating shapes. This deficit is amplified drastically when shapes are presented in the context of a temporal mask.[1] Migraine auras are thought to result from cortical spreading depression (CSD), a wave of suppressed neuronal activity in the visual cortex.[2] It has been hypothesized that interictal cortical hyperexcitability might leave migraine patients vulnerable to the spontaneous neuronal depolarization that characterizes CSD.[3]

One possible mechanism for cortical hyperexcitability is a lack of inhibitory control,[4] resulting perhaps from impaired gamma-aminobutyric acid (GABA)-ergic inhibitory mechanisms[5] or a deficiency of inhibitory neurons.[1] This reduced-inhibition hypothesis has been tested in a number of studies. Palmer et al. measured the detrimental effect of a nonoverlapping mask presented shortly after a target[6] (metacontrast masking[7]). It has been suggested that the masking behavior results from a fast transient signal, triggered by the mask, inhibiting a slower sustained target-related activation.[8] Reduced cortical inhibition, therefore, would be expected to result in reduced masking. Consistent with this, Palmer et al. found that migraine with aura subjects performed better during metacontrast masking than either headache-free controls or migraine without aura subjects.[6]

Recently, Shepherd et al. confirmed that migraineurs experienced less masking than controls.[9] However, migraineurs also discriminated between targets better when they were unmasked, implying that a heightened neuronal response in migraine may underlie their enhanced performance, rather than a specific deficit with inhibitory processes. Other measures of inhibitory control have found migraineurs to perform at a near-normal[10,11] or reduced level,[12,13] also inconsistent with the faulty inhibition model.

An alternative explanation for perceptual differences between migraineurs and controls can be based on increased internal noise, a possible consequence of cortical hyperexcitability.[14] Migraineurs perform worse than controls in many tasks, consistent with increased levels of internal noise. Differences are reported for low-level tasks, including discrimination of spatial frequency,[15] orientation,[11] flicker,[14] color,[16,17] luminance,[18,19] and long-range inhibition,[20] as well as tasks requiring extrastriate processing, such as global shape[21,22] and global motion coherence thresholds.[14,21–23] Comparison of internal noise levels has shown differences between migraine and controls.[18,19,24]

The aim of our study was to investigate the nature and extent of visual deficits in migraineurs, and to distinguish between two possible factors: abnormal inhibition and abnormal internal noise. The task required the discrimination of circular shapes in the absence and presence of a mask. Human sensitivity for detecting subtle deformations of circular shapes is in the hyperacuity range.[25] Psychophysical,[26–28] monkey physiology,[29] and human fMRI[30] studies support the view that the high sensitivity may be a result of processing at intermediate, extrastriate stages.[31] According to the reduced inhibition hypothesis, if masking was a consequence of inhibition, migraineur performance should be similar to controls without a mask, but better than controls when masked. If, however, migraineurs have raised internal noise levels, they should perform equally poorly in both conditions. Our results supported neither prediction. Migraineurs (especially those who experience visual auras) performed slightly worse than controls in the absence of a mask, but this difference was amplified significantly by the presence of a mask.

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METHODS

Participants

Headache-free controls were recruited at Glasgow Caledonian University, Glasgow, UK. The control group had never experienced a migraine and reported no more than one headache a month. This was verified by a structured questionnaire in accordance with the second edition of the International Headache Classification (ICHD-II).[32] Migraineurs were recruited at the Middle-German Headache Centre, Neurology Department, University Clinic Jena, Jena, Germany. For subjects to be included as migraineurs, they were required to fulfill the classification criteria of the International Headache Society. Diagnosis was undertaken by a neurologist. Migraineurs were divided into two groups: migraine with aura (MA) or migraine without aura (MO). Subjects in the migraine groups also completed the Migraine Disability Assessment (MIDAS) questionnaire.[33]

A total of 27 subjects participated in this study: 9 headache-free control subjects (mean age ± SD, 28 ± 5.4 years), 9 MA (31 ± 7.1), and 9 MO (26 ± 8.0). The sex distribution in each group was 7:2 (female-to-male ratio). The migraine groups took no preventative medication in the three months before the study, and had no migraine episodes during the 3 days before or after the experiment. Median headache frequency in the month before the study was 5.0 and 2.0 for MO and MA, respectively, and did not differ between the two groups (2 tailed *t*-test, $P = 0.330$). Median MIDAS scores were 16.0 and 11.0 for MO and MA, and were not significantly different (2 tailed *t*-test, $P = 0.235$). Migraine participants were ranked for the duration of their migraine (1–2, 2–5, and >5 years); the two groups did not differ from each other (Wilcoxon signed rank test, $P > 0.05$).

All subjects had normal or corrected-to-normal vision, and wore their habitual correction. Each participant met the following ocular criteria: visual acuity of 20/30 or better, intraocular pressures of less than 21 mm Hg (Goldmann applanation tonometry), and normal visual fields (Humphrey 30-2 or Oculus fast threshold). Exclusion criteria were pregnancy, age above 40 years, epilepsy, dyslexia, and diabetes. All subjects gave written informed consent in accordance with a protocol approved by the ethics committees of Glasgow Caledonian University and the University Clinic Jena, in agreement with the tenets of the Declaration of Helsinki.

Apparatus

Stimuli were presented on a high-resolution computer screen (Iiyama Vision Master Pro 450; Iiyama International, Oude Meer, The Netherlands) with spatial resolution of 1024 × 768 pixels and 120 Hz refresh rate, from a distance of 85 cm. Viewing was binocular. The room was semidarkened (5.1 ± 3.5 cd/m^2) and the mean luminance of the screen was 27.9 ± 0.07 cd/m^2. A custom-made video summation device[34] was used to give 12-bit precision. The monitor gamma nonlinearity was calibrated and verified regularly with an OptiCAL photometer (Cambridge Research Systems, Ltd., Rochester, Kent, UK).

Stimuli

The study used a set of radial frequency (RF) patterns,[25] which are defined as a sinusoidal modulation to the radius of a circle in polar coordinates (Fig. 1). Different shapes can be generated by varying the frequency (number of lobes) or amplitude (sharpness of each lobe) of the sinusoid. The shape used throughout this study was an RF5 (i.e., five-sided, pentagon-like shape). The amplitude of the RF5 was manipulated to obtain shape discrimination thresholds, that is the minimum amplitude required to discriminate reliably between an RF5 and a circle.

Procedure

Participants received detailed instructions before an experimental session. A temporal two-alternative forced choice paradigm was used: observers were required to report which of two target shapes, presented sequentially, appeared less circular. The screen was set initially to a uniform grey field of mean luminance. A fixation point appeared at the center of the screen, followed by target shapes presented briefly (25 ms, 3 frames) either in isolation (without masking), with a simultaneous mask, or followed by a mask of equally short duration (backward masking). Shape discrimination was measured for five different stimulus-onset asynchronies (SOAs; 0 = simultaneous masking, 66.7, 100, 133.3, and 250 ms). Different SOAs were run in separate blocks. The order in which observers ran blocks was randomized. During the SOA period, the screen returned to the uniform grey field. Before the testing commenced, subjects were given the opportunity to familiarize themselves with the setup. No feedback was provided during practice period or data collection. Each observer ran all conditions.

Statistical Analysis

Before group analyses, individual data were compared to group means to identify outliers that are three or more standard deviations from the mean. None of the data fell outside this range. Data for the no-mask condition were compared using an ANOVA with subject group (migraine, MA, MO) as factor. Data for the masked condition were compared using a repeated-measures ANOVA with mask timing (SOAs of 0, 66, 100, 133, and 250 ms) and group (migraine, MA, MO) as factors. All subsequent pairwise comparisons were done using *t*-tests with Bonferroni adjustments for multiple comparisons.

RESULTS

Shape Discrimination

Thresholds for shape discrimination were measured as the minimum amplitude of the RF pattern required to discriminate it from a circle and they are expressed in percent of the radius of the circle. Without masking, the average sensitivity (±SD) for discriminating between a circle and an RF5 (pentagon-like shape) for the control subjects was 0.6 ± 0.26% (Fig. 2). Hence, normal observers can just discriminate between the two left-most shapes in Figure 1A. Migraineurs performed poorer than controls: average thresholds were 0.82 ± 0.36% and 1.35 ± 0.96 for MO and MA, respectively. There was a significant main effect of subject condition ($F_{(2,24)} = 3.58$, $P < 0.05$). MA performed significantly ($P < 0.05$) poorer than controls. MA thresholds were 2.2 times higher than the control group. A typical MA can just discriminate between the contour on the left hand side of Figure 1A and the third shape from the left. Average thresholds for MO were raised 1.37 times compared to controls, but this difference did not reach significance. The difference between MO and MA also was not significant.

Shape Discrimination in the Presence of a Mask

The second experiment investigated the effect of masking on shape discrimination. Figure 3 presents the data for the three groups at the five different SOAs (0, 66.7, 100, 133.3, and 250 ms). Backward masking studies have shown that the detrimental effect of a mask on a target depends on the SOA, producing a typical inverted U-shaped function.[35] Little masking is seen when target and mask are presented simultaneously (SOA = 0) or when they are sufficiently separated in time.

The data (Fig. 3) show the typical masking pattern[36] for all three groups with significantly raised thresholds for SOAs between 66 and 100 ms. For controls, a peak masking effect between 66 and 100 ms is in broad agreement with Habak et al., who reported a peak between 80 and 110 ms for the three normals tested in their study.[36] Repeated-measures ANOVAs

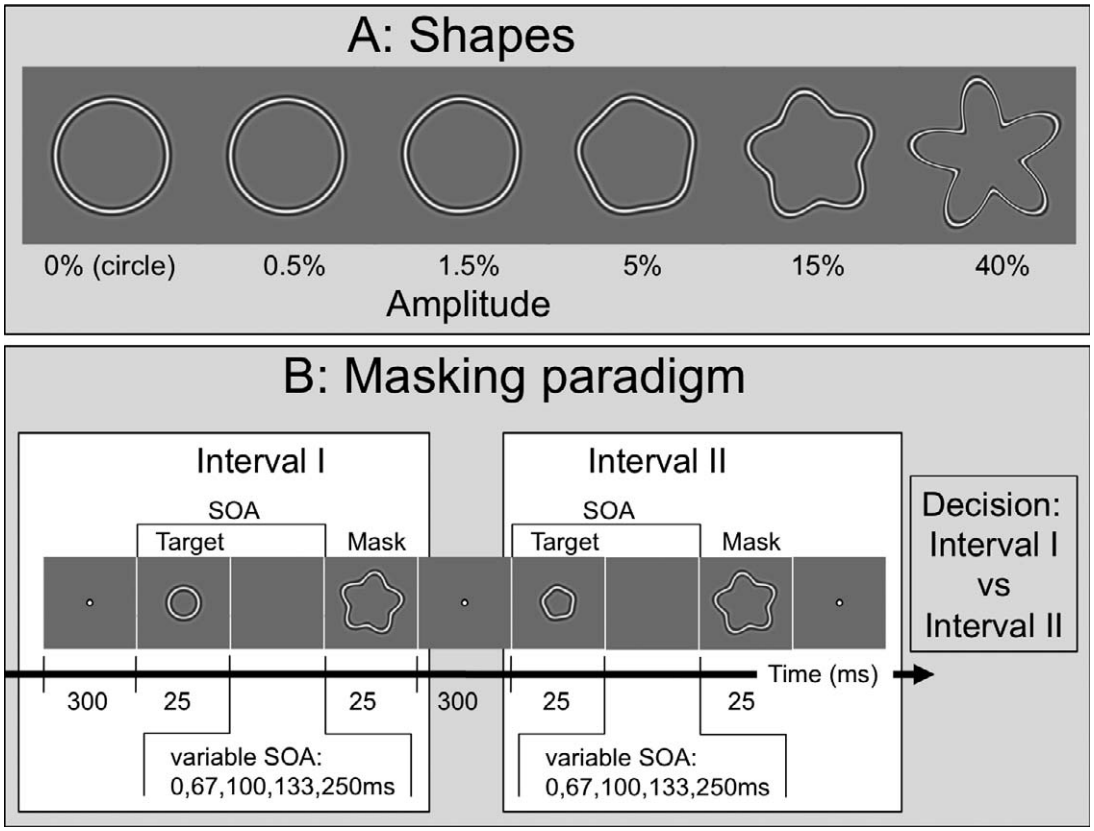

Figure 1. Shape stimuli and masking paradigm. Shape discrimination thresholds were measured for continuous RF patterns with five lobes. Observers had to discriminate between test shapes of varying amplitudes and a reference (*circle*). The cross-sectional luminance profile of the shapes was defined by a fourth spatial derivative of a Gaussian and set to a peak spatial frequency of 8 cpd. Contrast was 90%. (**A**) Shapes are shown with different amplitudes ranging from zero (*circle*) to 40% modulation relative to the mean radius. Typical observers require an amplitude of 0.5% to discriminate a circle from an RF5 contour. Migraine with aura (MA) were less sensitive for this task and showed thresholds of approximately 1.5%. When the stimuli to be discriminated are followed by masks (see [**B**]), all observers became less sensitive. For the most disruptive mask time (66 ms), thresholds for controls were at approximately 15%. For MA, they were at approximately 40%. Hence, MA can only just distinguish between the shapes at the *far right* and *far left* in (**A**) when masked. (**B**) Experimental paradigm. Observers were presented with two targets and had to indicate which of the two contained the noncircular shape (*Interval II* in this example). The amplitude of the noncircular target was under the control of the computer in a staircase procedure to determine thresholds. Shapes were presented briefly (25 ms) either in isolation or in the presence of a mask. The mean radius of the shapes to be discriminated (targets) was 1°. When present, the mask always was bigger in size than the target (1.5°) to avoid spatial overlap between target and mask. The amplitude of the mask was set at 16 times the detection threshold of an RF5 against a circle and, therefore, was visible clearly as a noncircular shape. Pattern orientation was assigned randomly from trial to trial, but the orientations of the mask and test always were locked in-phase. This and the mask amplitude yield maximum masking effects for RF shapes. Thresholds were measured for different onset times of the mask relative to the target (SOA). Masks were shown for the same short duration as the targets.

found significant main effects of SOA for controls ($F_{(4,32)} = 7.07$, $P < 0.001$), MO ($F_{(4,32)} = 4.20$, $P < 0.01$), and MA ($F_{(4,32)} = 10.23$, $P < 0.001$). For all three groups, pairwise comparisons showed significantly ($P < 0.05$) elevated thresholds for SOA = 66 ms compared to SOA = 0 ms and SOA = 250 ms. For MA, differences between SOA = 66 ms and SOA = 133 ms also were significant. Thresholds for normal observers were elevated 6.3 times for an SOA of 66 ms relative to the simultaneous condition (SOA = 0 ms). The two migraine groups showed the same general pattern of masking and the same timing for the peak masking effect. However, the magnitude of the peak masking effect was substantially greater in migraine. The peak threshold elevation was 11.8 times for MO and 21.6 for MA.

To assess differences between groups, data were analyzed by a two-way (3 × 5) repeated measures ANOVA with subject group (controls, MA, MO) and masking SOA (0, 67, 100, 133, and 250 ms) as main factors. This revealed significant main effects for both factors: subject group ($F_{(2,24)} = 3.72$, $P < 0.05$) and SOA ($F_{(4,96)} = 17.92$, $P < 0.001$). There also was a significant interaction between the two factors ($F_{(8,96)} = 3.12$, $P < 0.05$). The differences between controls and MA, but not between MO and MA or MO and controls, were significant. At the peak SOA (66 ms), the MA group performed significantly poorer than the other two groups. Thresholds for the MA group were higher by factors of 2.1 and 4.4 compared to MO and controls, respectively. Those for MO were raised 2.1-fold compared to controls.

The finding that migraineurs performed poorer than controls under masking conditions is contrary to what has been reported for meta-contrast masking. As has been pointed out recently,[9] care should be taken when considering differences between groups for backward masking conditions when these groups also behave differently in the absence of a mask. Accordingly, we normalized the data for the masked conditions (Fig. 3) by the baseline sensitivity for the no-mask condition (Fig. 2) for each observer. The resulting threshold elevations are plotted in Figure 4. Differences between groups still were evident for the most disruptive SOA (66 ms). This difference remained significant for MA compared to controls ($P < 0.05$). For the other SOAs, the main effect of clinical group did not reach significance ($F_{(2,24)} = 1.33$, $P > 0.05$). This suggests that masking per se disrupts processing in MA and

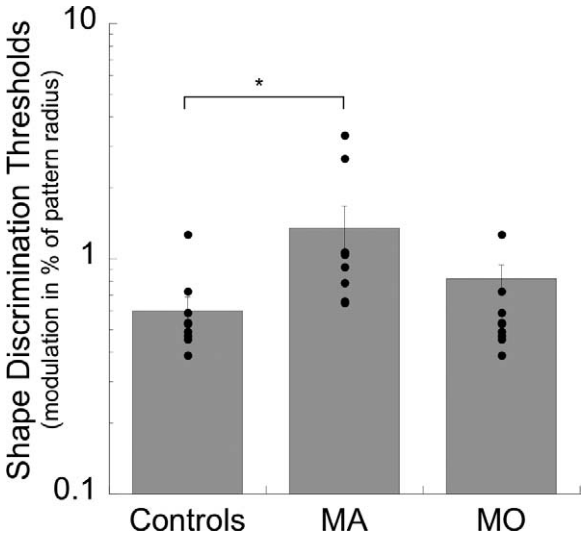

Figure 2. Shape discrimination thresholds for discriminating between a circle and an RF5. Thresholds are defined as the amplitude of the RF5 pattern at which observers could discriminate it reliably from a circle and given relative to the size of the pattern (in percent). Data for the control group (*left hand bar*) averaged 0.6 ± 0.09%, which is in the hyperacuity range. MO (*right hand bar*, average thresholds of 0.82 ± 0.12%) performed worse than the control group, but this does not reach significance. Indicated by the *asterisk*, however, thresholds for MA were significantly elevated (1.35 ± 0.32%) compared to controls ($P < 0.05$). *Black circles* show thresholds for individual participants. *Error bars* here and elsewhere are standard errors of the mean.

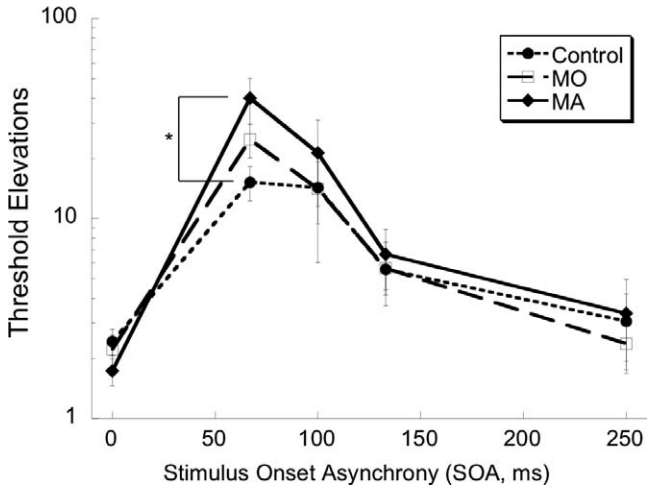

Figure 4. Normalized data for shape discrimination in the presence of a mask. Data for each observer from Figure 3 were normalized against their respective thresholds for the condition without a mask. The difference between groups decreased because the two migraine groups showed reduced general sensitivity for the baseline condition (without mask, Fig. 2), but did not disappear. For the SOA where peak masking occurred, threshold elevations are significantly higher for MA compared to controls. $^*P < 0.05$.

decreases further the already reduced overall shape discrimination sensitivity in migraine without mask.

Model Predictions

We compared various model predictions to the data in an attempt to identify the source of the deficits in migraine. The model used here is a modified version of the Perceptual Template Model (PTM)[37,38] that has been used widely to quantify the amount of various internal noise sources. The model (Fig. 5, Appendix) uses a divisive, inhibitory gain control process, which reduces the response of the target.[39] Gain control mechanisms normalize the response of a neuron with regards to, for example, contrast,[40,41] consistent with physiologic and psychophysical evidence.[42] The consequences of gain control have been linked to the effect of masking on target visibility.[39,40,43] Figure 5A illustrates the model in the case of a

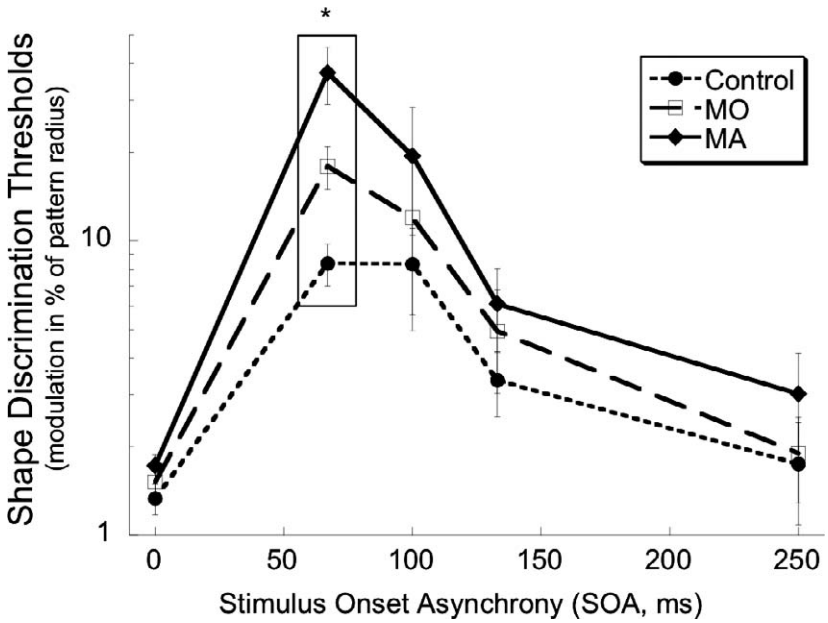

Figure 3. Shape discrimination in the presence of a mask. Thresholds present the average for each of the three groups as a function of target-mask SOA. All groups exhibited the typical masking pattern with substantial threshold elevations for backward masking, and peak masking effect for SOAs between 66 and 100 ms. Compared to controls, both migraine groups experienced a significantly stronger general masking effect with poorer overall performance. Differences between groups were most prominent where the mask for all groups exerts its strongest effect (SOA of 66 ms). The *asterisk* indicates that the thresholds for MA were elevated significantly compared to each of the other two groups.

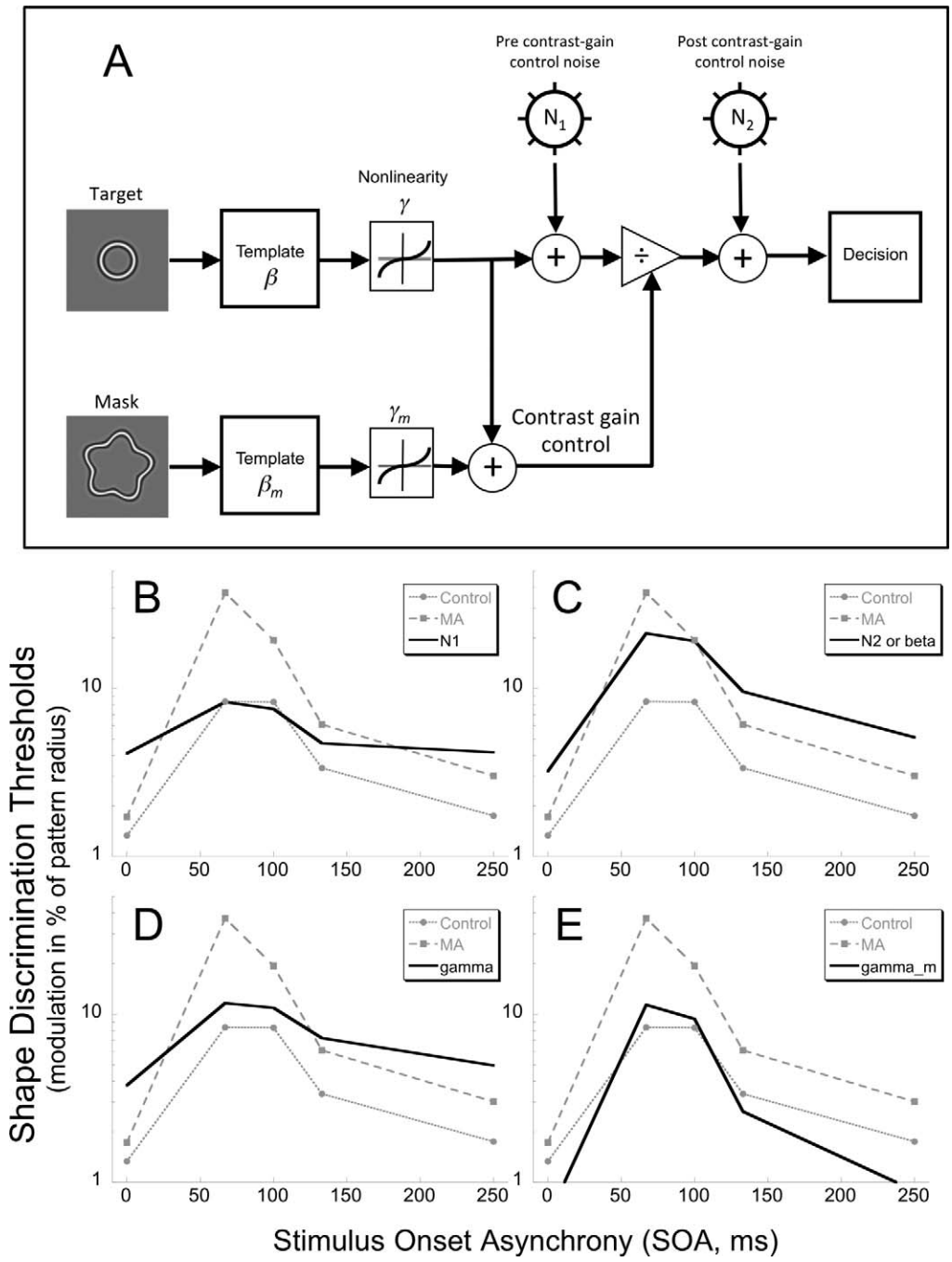

Figure 5. The structure of the gain control model (**A**) and model predictions for various parameter manipulations (**B–E**). (**A**) Target and mask stimuli are processed by perceptual templates with gains of β and β_m, and their outputs are subject to nonlinearities (γ and γ_m). Two internal noise sources occur before and after the gain control stage. The response to the target stimulus is inhibited by a divisive gain control process, which consists of the combined activity to the target and mask. Finally, stimulus discriminability is calculated by the total signal-to-noise ratio (see Appendix). (**B–E**) Model predictions. The *dotted* and *dashed curves* show the data for the control group and the MA group, respectively (for clarity the MO data are not shown). To show the effect of different model parameters on the masking profiles, parameters initially were set to capture the control group's behavior ($\beta = 5$, $\gamma = 1.8$, $\beta_m = \text{f(SOA)} = [3, 20, 18, 9, 4.8]$ for SOA = [0, 66, 100, 133, 250 ms], $\gamma_m = \gamma = 1.8$, $N_1 = 0.0015$, $N_2 = 0.1$). (**B–E**) The *solid curves* show how the control's thresholds would be affected when one individual model parameter is varied ([**B**]: for internal noise $N_1 = 0.06$; [**C**]: $N_2 = 0.5$; [**D**]: exponent of the nonlinear transducer function for the target $\gamma = 3$; [**E**]: exponent of the nonlinear transducer function for the mask $\gamma_m = 3.3$). See text for further details.

target and a mask stimulus. The gain control in this model is related to the interactions between shape encoding processes, that is neurons selective for the target and the mask. Evidence supports this type of interaction at higher stages of the ventral pathway.[29,31,36,44]

Poorer performance in migraine can be explained in a number of ways. An increase in either of the two internal noise sources (N_1 or N_2, pre- and post-gain control, respectively) will cause thresholds to rise. Similarly, a less efficient perceptual template (β) or a different nonlinear transducer function (e.g.,

an increased exponent of the power function) also would predict lower sensitivity. The way in which the masking curves (Figs. 3, 4) for the three groups differ provides an opportunity to distinguish between these possibilities. Initially, the gain of the mask (β_m), which is a function of time (SOA), was set to fit the data for the control group (dotted-line labeled "control-model" in Fig. 6B). β_m is the model parameter that produces the inverted U-shaped masking profile. The effect of various model parameters on the shape of the masking function then can be investigated by comparing this "original" masking curve (Fig. 6B, dotted curve) to those resulting from individual parameter changes (Figs. 5B–E, solid curves).

Increasing the variance of the internal noise source that precedes the divisive inhibition (N_1) raises thresholds for short and long SOAs without affecting the peak SOA (Fig. 5B). This causes the masking function to flatten, which fails to capture the performance of the MA group (dashed line). Increasing the variance of the internal noise that follows the divisive inhibition (N_2) predicts a general upward shift of thresholds (Fig. 5C). This shift is uniform across SOA and results in constant threshold elevations, also inconsistent with the MA data. Reducing the gain (β) results in the same prediction. Increasing the exponent of the nonlinear transducer function for the target (γ) has a similar effect to increasing the N_1 noise (Fig. 5D). It predicts threshold elevations that disproportionally affect long and short SOAs where the mask has a relatively minor effect, resulting in an overall flattening of the masking curve. Finally, increasing the exponent of the nonlinear transducer function in the gain control pathway (γ_m) disproportionally affects the peak SOA, causing the masking curve to become steeper (Fig. 5E). This manipulation results in a curve that closely follows the overall shape of the MA group, but underestimates absolute thresholds.

It follows that the only model parameter that predicts that thresholds for peak SOAs are most dramatically elevated in migraine is the nonlinearity in the gain control network (γ_2). This can be combined with an increase in internal noise (N_2), which by itself causes threshold to be elevated uniformly, to capture the specific deficits in migraine. To provide quantitative model predictions, we fixed all other parameters on the data for the controls. The data for MA and MO without mask then were used to determine N_2 (Fig. 6A) and the backward masking curves to determine γ_m (Fig. 6B). The model provides a satisfactory prediction of the data.

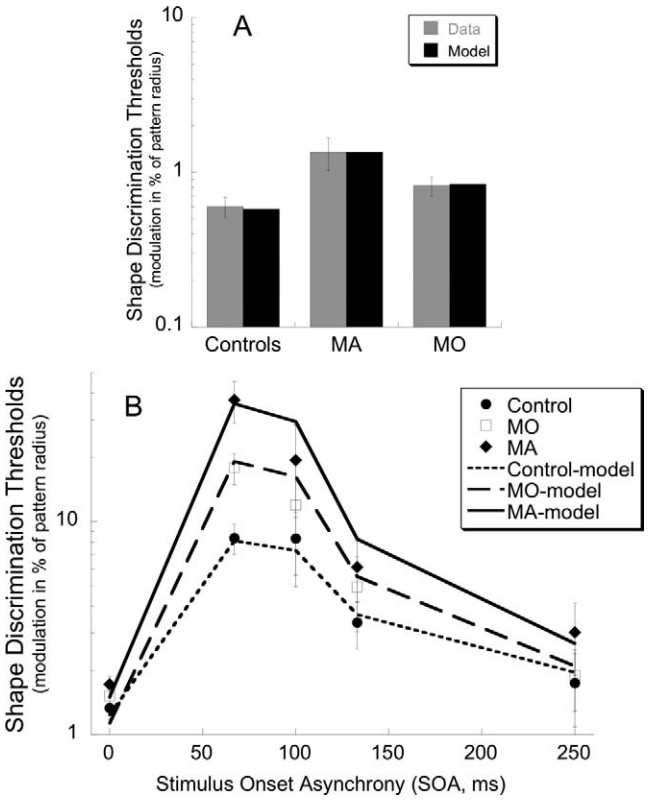

Figure 6. Model predictions. (**A**) The data for the shape discrimination task in the absence of a mask were fitted with the model (see Appendix). Model parameters were set to fit the data for the control group ($\beta = 5$, $\beta_m = f(SOA) = [3, 20, 18, 9, 4.8]$ for SOA = [0, 66, 100, 133, 250 ms], $\gamma_m = \gamma = 1.8$, $N_1 = 0.0015$, $N_2 = 0.1$). All but N_2 then were fixed, and values for N_2 determined that fit the data for MO ($N_2 = 0.3$) and MA ($N_2 = 0.63$). (**B**) Backward masking data for the three groups, including model predictions (controls: $\gamma_m = 1.8$; MO: $\gamma_m = 2.8$; MA: $\gamma_m = 3.3$). See text for details.

Discussion

Migraineurs, especially those with aura (MA), show lower sensitivity than controls for closed contour shape discrimination. This difference was not found in a recent study with sampled shapes.[19] In that study, external noise was added to the samples and internal noise levels estimated. Consistent with our analysis, increase in internal noise was present in migraine (although the additive internal noise was raised). However, this was coupled with an increased efficiency offsetting increased noise levels and resulting in the same overall performance.

Reduced sensitivity in migraine observed in our study, however, is in line with earlier reports on global form perception,[22] where migraineurs were poorer at detecting a circular texture than headache-free controls. Like our shape tests, these tasks require global pooling and are consistent with a deficit in extrastriate ventral stream in migraine.

It may be argued that early processing deficits (e.g., processing of local contour orientation in V1) could account for lower sensitivity for tasks targeting higher stage processing. This possibility has been ruled out for global form processing in migraine[45] on the basis of normal processing at the level of V1. Early deficits also are unlikely to explain migraineurs performance in this study. The masking effect for RF shapes is highly contextual. Masking strength depends on the relationship between the orientations of the mask and target,[36] and such a global-shape specific effect is inconsistent with V1 processing.

Moreover, masking of V1 processes (meta-contrast masking) results in migraineurs performing better than controls,[6,9] opposite to the effect described here. When target shapes are backward masked, migraineurs, especially MA, performed poorer than controls. Although all groups exhibit the typical inverted U-shaped pattern of backward masking, the masking curves are steeper for the migraine groups with thresholds particularly elevated when the mask is most disruptive (Figs. 3, 4).

The timing of masking effects has been used to infer the duration of cortical processing. In backward masking, if the target computation is incomplete when the mask is presented, it can interrupt target processing and impair perception. The temporal window over which a mask exerts its effect is thought to reflect the duration of the underlying computation.[35,36,46] If migraineurs had a processing delay, the masking functions should be shifted horizontally and the peak masking effect would be seen for longer SOAs. Such a shift clearly is not supported by the data, and the peak SOA is the same for controls and migraineurs. This argues against a general processing delay in migraine.

One of the most consistent findings in migraine is a lack of habituation for sensory evoked potentials.[47] Prolonged expo-

sure to a high-contrast reversing checkerboard results in a reducing amplitude for pattern-reversal visual evoked potential (VEP) in normal observers. The VEP amplitude for migraineurs by contrast does not reduce and in some cases it may even increase (potentiation). Similarly, altered visual adaptation effects have been reported recently in migraine. The typical adaptation effect of decreased sensitivity following adaptation to a high contrast flicker was seen for normals and migraineurs when tested with low contrasts.[48] However, following adaption migraineurs showed the opposite effect for high contrast: increased contrast sensitivity. This facilitation effect was not observed in controls. Psychophysical studies of visual aftereffects also have described longer aftereffect durations in migraineurs.[12] These findings likewise point toward altered cortical adaptation processes. It may be that the same processes underlie the deficiencies measured psychophysically and with VEPs.[48]

Repeated exposure to the shapes in our experiment is inevitable and the possibility of this resulting in adaptation effects must be considered. Individuals ran different conditions (with and without mask as well as different SOAs) in different blocks. The order in which SOAs were run was randomized across participants. Regular breaks were taken between blocks, reducing the possibility of significant adaptation effects across conditions. It nevertheless remains a possibility that an adaptation effect may have occurred during blocks. Given the balanced design of the order in which different SOA conditions were completed, we think it unlikely that the pattern of results—with increased thresholds mainly for intermediate SOAs in migraine—is the result of uniform adaptation. In the absence of a specific effect of adaptation for some but not other SOAs, we would expect all SOAs to be affected similarly, resulting in masking functions that are elevated equally throughout the range of SOAs. This is not what we observed.

That said, the PTM, on which our simulations were based, was developed originally to describe contrast adaptation effects.[39] Hence, our results, as well as those described above may point to a common deficit in migraine related to the process of adaptation/habituation. Based on the potentiation observed with high contrasts when measuring contrast sensitivity following adaptation, one might have predicted an enhanced performance for the migraine groups with high contrast stimuli in our experiments. The masking effect in our case, however, is more likely to arise as the result of interactions between shape-specific mechanisms at higher stages of visual processing, rather than interactions at the relatively early levels underpinning contrast adaptation effects. Future investigations are required to address this issue.

Masking has been attributed to cortical inhibition between neurons tuned to target and masks.[49] If masking is a consequence of inhibitory interactions, decreased inhibition in migraineurs should result in less masking compared to controls. It has been shown recently that the better performance of migraineurs on a metacontrast masking task can be explained by a generally higher sensitivity compared to controls rather than a difference in masking.[9] Our results are consonant with the notion that inhibition generally is not reduced in migraine, at least for those neuronal pathways that are responsible for masking.[9,50]

An alternative account for the differences between migraineurs and controls is neuronal noise. An increase in internal noise can explain why migraineurs perform poorer than controls in a range of tasks.[11,18,19,22,51,52] Indeed, those studies explicitly determining the amount of internal noise[18,19,24] have found it to be abnormal in migraine.

To provide an analysis of the effect of increased internal noise levels in our study, we applied a model that has been used widely in estimating internal noise,[37] which recently has been modified to include a divisive gain-control process that can be applied to masking[39] (Appendix). The model has a number of parameters, including two internal noise sources occurring before (N_1) and after (N_2) the contrast gain control, similar to additive and multiplicative noises in the original model.[39] Increasing the early noise (N_1) makes incorrect predictions (Fig. 5). Increasing the late noise (N_2) predicts a general upward shift of the masking function that captures the higher thresholds in migraine, but would overestimate the difference between controls and migraine for short and long SOAs. Hence, neither increased additive nor multiplicative noise is sufficient to explain the pattern of reduced sensitivity in migraine. Another explanation is required. The only factor that produces a steeper masking function is the nonlinearity within the neuronal network responsible for masking. This is reasonable, since the transducer function is regarded as a key component for models explaining pattern masking.[53,54] An abnormally high nonlinearity in the gain-control process coupled with an increased multiplicative internal noise in migraine can capture the data successfully with and without masking (Fig. 6). Both factors require a higher increase for migraineurs who experience visual auras (MA) compared to those who do not (MO).

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Appendix

Gain-Control Model for Masking

The model is a modified version of the PTM[37,38] that has been used widely to quantify the amount of various internal noise sources. In the original model, the signal initially is filtered (perceptual template) and the filter response is passed through a nonlinear transducer function, consistent with psychophysical observations (e.g., Weber's law in perceptual tasks[53]). This is subject to two internal noise sources: multiplicative noise, with variance that is proportional to the response magnitude elicited by the stimulus as well as additive noise with fixed, stimulus/response-independent variance. The final part consists of a decision stage. This model can be applied directly to experimental conditions where external noise is added to the stimulus.

Recently, a modified version of this model, replacing the multiplicative noise stage with a divisive contrast gain-control process, has been applied successfully to predict the detrimental effect of visual adaptation on the visibility of sine-wave gratings.[39] Figure 5A illustrates the model in the case of a target and a mask. An inhibitory gain control reduces the response of the target, consistent with physiological, psychophysical, and modeling evidence, which has shown that such an operation modifies the stimulus gain and allows neurons to remain in an optimal regime despite large variation in stimulus intensities.[40–42] Contrast-gain control has been linked to the effect of masking on target visibility[39,40,43] and we have applied this model to our data. Note that the gain control in this model is related to the interactions between shape encoding processes unlike the interactions underlying contrast-gain control at the earlier stages of visual processing.

The target and the mask are processed by perceptual templates with gains of β and β_m, respectively. Consistent with psychophysical and imaging studies, the output of RF templates should depend on a number of factors, including

RF contour contrast,[28] amplitude,[26,30,36,55] radial frequency,[26,28,55] size,[56] and orientation.[36] We only consider contrast (c and c_m) and amplitude (A and A_m) here as the other parameters did not vary in the experiments:

$$S = \beta cA$$

$$S_m = \beta_m c_m A_m \quad (1)$$

These outputs for target and mask are subject to a nonlinearity (γ and γ_m) modeled by a power function[53,54]:

$$S' = \beta^{\gamma} c^{\gamma} A^{\gamma}$$

$$S'_m = \beta_m^{\gamma_m} c_m^{\gamma_m} A_m^{\gamma_m} \quad (2)$$

An internal noise is added after the transducer, but before the gain control with a mean of 0 and a standard deviation of N_1. The combined activity (E) in the gain control pathway at this stage is:

$$E = S'^2 + S'^2_m + N_1^2 \quad (3)$$

Divisive, inhibitory gain control reduces the response of the target (S''):

$$S'' = \frac{S'}{\sqrt{b + E}} \quad (4)$$

where b is a threshold to avoid the divisive gain term taking on zero values if target and mask contrasts are close to zero. The noise variance similarly is normalized by the same divisive term:

$$\sigma'^2 = \frac{N_1^2}{b + E} \quad (5)$$

A second internal noise source follows after the gain control, with a mean of 0 and standard deviation of N_2. The overall noise variance is given by the sum of all noise variances:

$$\sigma^2_{total} = \frac{N_1^2}{b + E} + N_2^2 \quad (6)$$

Note that the two noise sources in this model, N_1 and N_2, are related to the activity of putative shape-encoding mechanisms and are not luminance-related noise as in the original model.[38]

Finally, the stimulus discriminability is given by the total signal-to-noise ratio:

$$d' = \frac{S''}{\sigma_{total}} \frac{\beta^{\gamma} c^{\gamma} A^{\gamma}}{\sqrt{N_2^2(\beta^{2\gamma} c^{2\gamma} A^{2\gamma} + \beta_{m2}^{2\gamma_m} c_m^{2\gamma_m} A_m^{2\gamma_m}) + N_1^2 + N_2^2(b + N_1^2)}} \quad (7)$$

The nominator describes the response to the stimulus and the denominator describes the gain control, consisting of the sum of the responses to the stimulus and the mask plus noise. Note that the two noise sources occurring before or after the gain control (N_1 and N_2) can be linked to additive and multiplicative internal noises.[39]

The target and mask contrasts were set to 1 for our experiments in all masking conditions and c_m was set to zero in the baseline condition without mask. γ and γ_m describe the behavior of the nonlinear transducers, and are assigned different parameters to allow the gain control nonlinearity (γ_m) to behave different from that responding to the target.

Threshold amplitudes (A) for the shape discrimination task for a given sensitivity d' can be calculated by solving Equation 7 for A:

$$A_{\tau} = \left[\frac{N_2^2 \beta_m^{2\gamma_m} c_m^{2\gamma_m} A_m^{2\gamma_m} + N_1^2 + N_2^2(b + N_1^2)}{\frac{\beta^{2\gamma}}{d'} - N_2^2 \beta^{2\gamma}} \right]^{\frac{1}{2\gamma}} \quad (8)$$

To produce the typical U-shaped backward masking profile, we assume that the gain of the mask (β_m) is a function of time (SOA). The model does not include the temporal dynamics that underlie backward masking. A unified model for backward masking that could be applied to the data is not available. Several models have been proposed (see the study of Francis[57] for a summary) that can capture some, but not all aspects of masking.[57] While all models produce the typical U-shaped masking function and are similar in spirit,[57] they differ substantially in detail. Therefore, we assumed a masking effect with magnitudes depending on SOA and restricted our analysis to the effects of a number of parameters, which have been considered in earlier studies on migraine,[18,19] including internal noise, processing efficiency, and response nonlinearity.

In addition to the dependence on SOA, masking for contour discrimination also has been shown to depend on a number of static parameters, including the mask amplitude, phase relative to the target as well as mask size.[36] Some of these effects are highly nonlinear. Such individual effects could be included into the model by introducing separate variables, but given that they were not varied in our experiments and because our aim was to compare performance between groups, they were collapsed into a single variable, A_m.

The baseline threshold amplitude ($A_{\tau,base}$) for shape discrimination without a mask is given by setting $c_m = 0$ in Equation 8:

$$A_{\tau,base} = \left[\frac{N_1^2 + N_2^2(b + N_1^2)}{\frac{\beta^{2\gamma}}{d'} - N_2^2 \beta^{2\gamma}} \right]^{\frac{1}{2\gamma}} \quad (9)$$

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