Center-Surround Visual Motion Processing in Migraine

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PURPOSE. It has been proposed that reduced cortical inhibition might be a key feature of migraine. Here the authors compared migraine and control group performance for two visual motion tasks in which performance was considered to reflect center-surround inhibitory processes. These tasks use the observations that healthy young observers require longer stimulus durations to detect the direction of motion of larger higher contrast stimuli, and these stimuli also elicit weaker motion aftereffect (MAE) strength. Both observations are considered to arise from center-surround inhibition.

METHODS. The authors measured stimulus duration thresholds for detecting the direction of motion of stimuli of different sizes and contrasts, and also examined motion aftereffect strength for similar stimuli presented for longer durations in 20 control participants and 30 people with migraine (15 with aura). The migraine group was assessed between migraines while they were asymptomatic.

RESULTS. For the motion direction task, a significant interaction existed between experimental group and contrast for large stimuli ($F_{(3,96,190,01)} = 2.95; P < 0.05$); however, the interaction was in the opposite direction from that expected from reduced inhibition. Similarly, the MAE data demonstrated a significant interaction between stimulus size and group, but it was in the opposite direction from that predicted ($F_{(4, 48)} = 4.13; P < 0.05$).

CONCLUSIONS. Consistent with previous studies, the migraine group in this study demonstrated abnormal visual motion processing. However, the data from both the motion direction detection and the motion aftereffect tasks do not support a theory of reduced cortical inhibition. (Invest Ophthalmol Vis Sci. 2010;51:6070–6076) DOI:10.1167/iovs.10-5290

Migraine, the most frequent neurologic disorder worldwide, affects approximately 12% of adults. A large number of studies have demonstrated differences in visual performance in persons with migraine, reporting abnormalities such as elevated global motion thresholds, motion aftereffect (MAE) prolongation, and differences in the ability to elicit moving phosphenes with transcranial magnetic stimulation (TMS). Other studies additionally report contrast processing deficits in migraine, elevated global form thresholds, reduced susceptibility to visual masking, and larger visual adaptation aftereffects. In this study, we were interested in performance differences that are present in between migraines, when people are migraine free, specifically those involving visual motion processing. The cause of altered visual motion processing between migraines is not yet understood.

One possible explanation for motion processing deficits is that they might arise from the aberrant cortical responsiveness, typically referred to as cortical hyperexcitability or hyperresponsivity, that is generally agreed to exist in migraine (for reviews see Refs. 12, 13). The mechanisms for this presumed neural state remains unclear (for reviews see Refs. 12, 13). Key competing theories are that there is primary neuronal hyperexcitability or that cortical hyperexcitability arises because of a reduction in cortical inhibitory function. Support for altered inhibitory function arises from studies of habituation to evoked potentials (for a review see Ref. 14) and from some studies making use of transcranial direct current stimulation (tDCS) and TMS.

The purpose of the present study was to investigate visual motion processing performance in migraine using tasks that are considered to rely on cortical inhibitory function, specifically those dependent on center-surround neural circuitry, and to explore indirect evidence for reduced inhibition. Our specific task is based on that described by Tadin et al. and involves determination of the direction of motion of drifting gratings (Gabor). For low-contrast stimuli, psychophysical direction discrimination improves with increasing size, indicating spatial summation. Somewhat counterintuitively, the direction of motion of a high-contrast stimulus requires longer presentation time for discernment as patch size increases. This deterioration in performance has been explained by a reduction in response as the size of the stimulus expands beyond the center of the receptive field of center-surround motion sensitive neurons, suggesting spatial suppression. The logic behind using a duration threshold measure is described in Tadin and Lappin, and is based on decision theory. Models of decision-making (for example, whether a stimulus is drifting to the left or the right) rely on sufficient accumulation of sensory evidence over time. Surround suppression is presumed to attenuate neural responses to the motion stimulus, resulting in a slower accumulation of sensory evidence, hence a longer required stimulus exposure duration for correct direction discrimination judgment. Similar contrast-dependent switching from suppression to summation has been reported neurophysiologically in motion-selective neurons in the middle temporal visual area (MT). Similar center-surround motion tasks have been used to demonstrate weaker surround suppression in older observers, in whom such performance was interpreted as indirect evidence for weaker GABA-mediated inhibition such as that observed in the visual cortex of aged primates. Center-surround visual motion tasks have also been used to demonstrate diminished surround suppression in schizophrenia and depression.

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In our study we used two visual motion tasks involving center-surround inhibitory processes.\textsuperscript{20,25} In experiment 1, we measured stimulus duration thresholds for motion direction discrimination for a drifting Gabor patch of varying size and contrast. For this task, healthy young observers demonstrated increased difficulty in the correct detection of the direction of motion with increasing size and contrast of the moving stimulus.\textsuperscript{20} A reduction in inhibitory function in migraine predicts better detection of the direction of motion of stimuli susceptible to inhibition relative to controls. In experiment 2, we examined MAEs for similar stimuli presented for longer durations. In healthy young observers, increasing the size of a high-contrast stimulus results in a reduction in MAE strength because of increased center-surround inhibition.\textsuperscript{20} A reduction of inhibitory strength in migraine predicts the effect of increasing size on MAE strength to be lower than that for controls.

**METHODS**

**Participants**

Our migraine group consisted of 30 participants (Table 1). Fifteen fulfilled the International Headache Society's criteria for migraine with aura (MA), and 15 fulfilled the criteria for migraine without aura (MO). Twenty control subjects approximately matched for age and sex also participated. Migraine participants (20 women, 10 men) were between 18 and 41 years of age (30.17 ± 14.13 years). There was no significant difference in mean age (t\textsubscript{18} = 0.35; P = 0.42) or sex (\chi\textsuperscript{2}(1, N=50) = 0.02; P = 0.90) between these groups. All participants were required to have best-corrected visual acuity of 0.05 or better and refractive errors less than \pm 5.00 D sphere and \pm 2.00 D astigmatism. Participants could not be taking any medications known to affect visual or cortical function, and also had to be free of systemic disease known to affect visual or cortical function. Normal findings in a comprehensive eye examination (including slit lamp biomicroscopy, ophthalmoscopy, and tonometry) conducted as part of the study were also required. Written informed consent was provided before participation, in accordance with a protocol approved by our institutional human research ethics committee and in accordance with the tenets of the Declaration of Helsinki.

To be included as controls, participants were required to have fewer than four headaches per year and never to have experienced migraine. Migraine participants were not permitted to take prophylactic medications for migraine and were tested at least 4 days since the end of their last migraine to allow washout of any medications taken to relieve migraine symptoms and to allow recovery from the episode. Participants in the migraine group completed the migraine disability assessment (MIDAS) questionnaire\textsuperscript{30} to enable a basic measure of the current impact of migraine on their lives during the past 3 months. Each person’s score was then used to determine their level of disability as follows: grade 1, minimal or infrequent disability (score 0–5); grade 2, mild or infrequent disability (score 6–10); grade 3, moderate disability (score 11–20); grade 4, severe disability (score 21+). The MIDAS scores of the participants in this study were between 0 and 46 (17.6 ± 12.27).

The motion direction discrimination (experiment 1) and motion aftereffect (experiment 2) tasks were investigated in separate runs. Each participant completed practice trials to familiarize themselves with the requirements of the task. Participants completed trials within a single session of approximately 2 hours in duration, with rest breaks permitted as required.

**Experiment 1: Motion Direction Discrimination**

Stimuli were generated with a visual stimulus generator (ViSaGe; Cambridge Research Systems, Ltd., Kent, UK) using custom software (MATLAB 7; MathWorks, Natick, MA) and presented on a γ-corrected, 21-inch monitor (resolution, 800 × 600 pixels; frame rate: 120 Hz; G520 Trinitron; Sony, Tokyo, Japan). A button box (model CB6; Cambridge Research Systems) was used by the participant to indicate responses. Participants viewed the monitor binocularly from a distance of 83 cm using a chin and forehead rest, with their required refractive correction for the viewing distance.

A small black fixation point in the center of the screen was followed by a Gabor patch (sinusoidal grating of 1 cyc/deg, windowed by a Gaussian envelope) in which the grating component of the stimulus drifted randomly left or right (Fig. 1A) at a rate of 2°/s. The Gaussian envelope was always positioned centrally. Stimulus sizes, defined as two standard deviations (2σ) of the Gaussian envelope, were 0.7° or 5° of visual angle. Participants indicated the direction of stimulus motion (left or right) by pressing one of two response keys. The next trial, beginning with the presentation of the fixation point, started 500 ms after the participant’s response.

Stimulus duration thresholds were determined with a three-down, one-up staircase by which three successive correct responses led to a 25% decrease in the motion duration of the test stimuli on the after trial, whereas every incorrect response resulted in a 25% increase. Each staircase terminated after four reversals, with the staircase result calculated as the mean of the last two reversals. Two staircases were interleaved within each run, and the final duration threshold estimate was calculated as the mean result of the two staircases.

Duration thresholds were measured for stimulus contrasts of 2.8%, 5.5%, 11%, 22%, 46%, and 92% in separate tests. Each participant, therefore, completed 12 experimental tests (2 stimulus sizes × 6 contrast levels). Stimuli were blocked by size and contrast, with the order of conditions randomized for each participant.

**Experiment 2: Motion Aftereffect**

To assess surround suppression mechanisms for stimuli of longer duration, we used similar Gabor stimuli in a MAE task. Participants adapted to a centrally viewed Gabor patch (1 cyc/deg) of two different sizes (defined as 2σ of the Gaussian envelope: 2° and 5°) and two contrast levels (2.6% and 26%). The higher contrast of 26% is consistent with previous work,\textsuperscript{20} is of sufficiently high contrast to produce surround suppression,\textsuperscript{20} and avoids higher contrasts that are less desirable because they are potentially more aversive to our migraine participants.\textsuperscript{31} During adaptation, the grating drifted to the right of the screen.

### Table 1. Demographic Details of Study Participants in the Migraine Group

<table>
<thead>
<tr>
<th>With aura (9 women, 6 men)</th>
<th>Without aura (11 women, 4 men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>Duration of Migraine (y)</td>
</tr>
<tr>
<td>Minimum</td>
<td>18</td>
</tr>
<tr>
<td>Maximum</td>
<td>30.27</td>
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<tr>
<td>Average</td>
<td>30</td>
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at a rate of 4°/s. As shown schematically in Figure 1B, initial adaptation was 30 seconds, with 10 seconds of ‘top-up’ adaptation after each trial. The test stimulus was presented for 1 second and consisted of two overlapping Gabor patches with carrier gratings drifting in opposite directions. The total size of the test stimulus was fixed at 2° (2σ of the Gaussian envelope).

In the absence of adaptation, the test stimulus appeared to flicker in place when the contrasts of the two Gabor patches were identical, making it impossible to perceive a single direction of motion. After adapting to a drifting Gabor, the sensitivity to motion of a subsequent stimulus moving in the same direction decreased, resulting in the equal-contrast compound stimulus being perceived as drifting in the opposite direction. To restore flicker perception, the contrast of the test Gabor patch moving in the adapting direction was increased, and that of the Gabor patch moving in the opposite direction was decreased. MAE strength was then defined as the contrast ratio required for discrimination of the direction of motion. Observers indicated the perceived direction of the test stimulus (left or right) using a single-interval, forced-choice paradigm by pressing one of two buttons. The contrast ratio of the test stimulus composed of the two Gabor patches was determined from two interleaved one-up–one-down staircases. A ‘left’ response resulted in the leftward-moving Gabor being reduced in contrast by 4% and the rightward-moving Gabor being increased by 4%. The converse occurred for a ‘right’ response. These contrast changes were reduced to 2% and then to 1% on the first two staircase reversals. Each staircase converged after four reversals, with the average of the last two reversals taken as the result. The final contrast ratio was calculated as the average of the final result of the two interleaved staircases. Each size and contrast was tested in separate runs (2 sizes × 2 contrasts), and trials were randomized between participants.

**Statistical Analysis**

Statistical analysis was performed using SPSS 16.0 with repeated-measures, mixed-design ANOVA analyses (within-factors: size, contrast; between factor: experimental group) of the log data. Huynh-Feldt adjustments were used for nonspherical data. No significant difference between migraine groups was demonstrated for either experiment 1 ($F_{(1, 77)} = 0.49; P > 0.05$) or experiment 2 ($F_{(2, 77)} = 2.19; P > 0.05$); therefore, the results for the MA and MO groups were pooled for all subsequent analyses.

**RESULTS**

**Experiment 1: Motion Direction Discrimination**

The results of experiment 1 are presented in Figure 2, which shows the mean log duration thresholds as a function of contrast for each stimulus size. Our findings were quantitatively similar to those previously reported for healthy young observers on this task. For the small stimulus, performance improved with contrast; for the large stimulus, performance deteriorated with increasing contrast, indicating spatial suppression. In other words, the direction of motion of large patches of grating required longer presentation durations to discern as contrast increased.

We hypothesized that reduced inhibitory function in migraine would result in less surround suppression as contrast increased for the large stimulus (a finding similar to that reported for schizophrenia and depression). Figure 2B reveals a significant interaction for the experimental group and contrast for the larger stimulus condition ($F_{(3.86, 199.01)} = 2.95, P < 0.05$), in which the migraine group had more difficulty with the task than the control group for large high-contrast stimuli. This trend was in the opposite direction from the predicted outcomes and thus was not indicative of reduced suppression. An overall group difference between migraine and controls was not present ($F_{(1, 48)} = 0.44; P > 0.05$); hence, the data also do not support a general decrease in sensitivity across the range of contrasts tested. For the large stimulus, Bonferroni-adjusted t-test analyses reveal no significant differences between groups for each contrast considered separately ($P > 0.008$). A general reduction in sensitivity would additionally predict a decrease in migraine group performance for the small stimulus (Fig. 2A); this was not present ($F_{(1, 48)} = 0.14; P > 0.05$). There was also no significant interaction for the small stimulus between contrast and group ($F_{(3.50, 168.08)} = 0.52; P > 0.05$).

**Experiment 2: Motion Aftereffect**

As expected, and clearly shown in Figure 3, the signal required to null the MAE was stronger for low contrasts ($F_{(1, 49)} = 9.60; P < 0.05$) and smaller sizes ($F_{(1, 49)} = 4.82; P < 0.05$). There was no trend for the migraine group to show an overall difference in the strength of the MAE (no significant main effect of group [$F_{(1, 48)} = 0.56; P > 0.05$]). Our hypothesis predicts a significant interaction between stimulus size and group for the high-contrast stimulus. A significant interaction was present ($F_{(1, 48)} = 4.13; P < 0.05$). However, as in experiment 1, the direction of the interaction was opposite that predicted for a reduction in surround suppression in the migraine group. Tadin et al. demonstrated that the strength of the MAE reduces as stimulus size increases for high-contrast stimuli, an initially counterintuitive effect that was explained by the authors as resulting from surround suppression weakening the adapt-
young observers to indirectly examine inhibitory processes governed by center-surround inhibitory processes in healthy observers.

In this study, we used two visual motion tasks believed to be tasks that are governed by inhibitory processing. Neither visual motion perception task in this study produced evidence for reduced inhibition in the migraine group. In fact, the trend was in the opposite direction from that predicted for both experiments, with the migraine group showing a larger effect than controls for large high-contrast stimuli. The results from this study, therefore, do not support the hypothesis of a reduction of cortical inhibitory function in the areas of the cortex responsible for visual motion processing in migraine groups.

Our findings support previous reports of abnormal visual motion processing in migraine. A consistent finding is elevated thresholds for the detection of coherent global dot motion. Global motion deficits are not specific to migraine. Similar deficits occur, for example, in cohorts with schizophrenia and as a result of normal aging. However, the surround suppression interaction profile identified here is opposite that found in aged cohorts and those with schizophrenia, in whom weakened surround suppression is present, consistent with reduced neural inhibition. In migraine, elevated global motion thresholds are present, and surround suppression is enhanced.

A simplistic interpretation of our findings is that migraine causes increased center-surround inhibition. Increased inhibition has not been previously reported in migraine. A more widely proposed theory is that cortical neuronal hyperexcitability is present in migraine. Evidence for neuronal hyperexcitability is inferred from transcranial magnetic stimulation studies demonstrating lower thresholds for the generation of phosphenes in people with migraine in both primary visual cortex and cortical area V5. Both functional magnetic resonance imaging and magnetoencephalography studies support the presence of a cortical spreading depression (CSD) event in migraine (for a review see Ref. 36), with animal models of CSD providing support for CSD arising from cortical hyperexcitability. Hyperexcitability has also been used as a model to explain elevated global motion thresholds in persons with migraine because hyperexcitability increases neural noise, resulting in elevated thresholds caused by altered signal-to-noise ratios. Is it possible that the seemingly increased inhibition demonstrated in our migraine group might arise from hyperexcitability?

Given the indirect nature of psychophysics, our discussion is necessarily speculative and depends on the validity of neurophysiological models of center-surround interactions, which are still incompletely understood. Nevertheless, the neurophysiology underpinning perceptual surround suppression is considered to involve both feedback and lateral connections. Feedback neurons are generally excitatory and are often modeled to increase inhibition in surround-suppressed neurons through the excitation of local inhibitory interneurons. Enhanced inhibition could possibly be driven by elevated excitation to inhibitory neurons rather than by increased inhibitory drive. Such a model does not preclude the presence of some alteration to inhibition, as suggested by previous authors, but simply indicates that the net result of enhanced excitation is dominant.

Most models of surround suppression attempt to explain center-surround interactions in V1; however, our behavioral data presumably also reflect surround interactions in extrastriate areas, particularly MT/V5. Surround suppression in MT is thought to be partially inherited from earlier stages of processing, to be partially generated within MT, and to be influenced by feedback, with many features in common with surround suppression in V1. Tadin et al. show that the amount of excitation within the classical receptive field is
key to whether the surround will be inhibitory. Huang et al. similarly report that stimuli that elicit the largest responses in MT produce the largest surround antagonism. Consequently, an alternative explanation for our data is that neuronal hyperexcitability in migraine results in a heightened response within the classical receptive field, in turn enhancing the likelihood and strength of surround suppression for large, high-contrast stimuli.

If hyperexcitability is present, it is unclear what response difference, if any, should be predicted between groups for the small stimulus in experiment 1. One consequence of hyperexcitability may be elevated neuronal noise, and this may explain previously reported elevated global motion thresholds in migraine. If elevated neural noise is present within the classical receptive field, thresholds might be elevated for the migraine group for the small stimulus. Alternately, if hyperexcitability results in higher resting neural potential, a smaller signal might result in a neural response predicting threshold improvement. An increased likelihood of neural firing could create a tradeoff between enhanced response to the signal and increased internal noise. In experiment 1, the control and migraine groups performed similarly for the small stimulus (Fig. 2), possibly consistent with some balancing of such opposing effects.

The results of the MAE task in experiment 2 also did not support the hypothesis of a reduction in inhibitory function. The MAE has been previously studied in migraine, and these studies did not support reduced inhibition. Shepherd identified the increased persistence of MAEs and interpreted the findings as inconsistent with reduced inhibition. The paradigm used by Shepherd was different from ours in that the MAE duration was measured subjectively when participants indicated they no longer saw illusory motion. In this study, we did not measure MAE persistence, and our participant group was, on average, younger and experienced migraines less frequently than those studied by Shepherd. Although the relationship between our results and those of Shepherd is unclear, a contrast in findings is that we did not find evidence for generally elevated MAE in the migraine group using our paradigm.

A potentially important factor complicating the comparison of studies involving participants with migraine is the transient and spontaneous nature of attacks. In this study we restricted the age range of participants, did not permit testing close to the cessation of a migraine, and did not allow migraine prophylaxis. As a consequence, our migraine group has a relatively mild migraine profile (those with frequent migraines were generally excluded). A key feature in our participants that might have affected measures of hyperexcitability/inhibition was the duration until the next migraine because the neuronal environment could alter in the build up to the next migraine event. The spontaneous nature of migraine makes this factor difficult to control systematically in a research environment; hence, perceptual studies of migraine almost invariably report only time since the last migraine. In our study, we asked participants to report whether a migraine occurred in close succession to a test session and received follow-up information from none of them.

It is possible that our results do not reflect a perceptual difference between the groups but might be linked to other task-specific differences. One possibility involves differences in attention. We have previously shown that performance deficits on a visual global motion task in migraine could not be explained by alterations in attention or other neuropsychological measures. An alternative possibility is that the migraine participants found the task that involved large, high-contrast moving stimuli aversive (a nonspecific symptom that is variously related to a poorly defined concept of hyperexcitability). This might explain the longer duration thresholds for the discrimination of motion of large, high-contrast stimuli. It is more
difficult to interpret the MAE results using aversion because, for the large, high-contrast stimulus, the migraine group was able to discriminate a dominant direction of motion with less contrast asymmetry in the combined Gabor stimulus than controls. On questioning, participants did not report the stimulus as aversive; however, different planned experiments would be required to address this issue directly.

Drifting gratings have the capacity to induce pursuit eye movements; hence, it is worth considering whether potential differences in eye movements between migraine and nonmigraine groups might influence the results. We consider this possibility unlikely, primarily because there is normally a reaction time of approximately 100 to 130 ms before the initiation of smooth pursuit eye movements (for a review see Ref. 42). Furthermore, Wilkinson et al. demonstrated no significant differences in eye movements between migraine and control participants for either smooth pursuit movements, saccades, or fixation stability, concluding that visual abnormalities reported in migraine are not artifacts of fixation or eye movements.45

To our knowledge, our study is the first to examine center-surround interactions in migraine. Other behavioral measures have been used to explore the hypothesis of reduced inhibition, including orientation discrimination44 and contrast gain control.45 These studies also did not find evidence for impaired cortical inhibitory function in migraine. However, there is psychophysical data supportive of reduced inhibitory function from one previous study,40 that reported a reduced effect of meta-contrast masking in migraine with aura but not migraine without aura. These migraine subgroup differential effects are not present in our data, and it is not readily apparent how the two datasets relate. Most of the evidence for reduced inhibitory function in migraine comes from human electrophysiology.14 The outcomes of psychophysical studies may differ from electrophysiological measures because psychophysical measures the output of the system as a whole. In summary, our data do not support a reduction of inhibition in visual motion processing in migraine.

References

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