Local and global motion after-effects are both enhanced in migraine, and the underlying mechanisms differ across cortical areas

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Visual after-effects are illusions that occur after prolonged viewing of visual displays (pattern adaptation). The motion after-effect (MAE), for example, is an illusory impression of motion that is seen after viewing moving displays. After-effects have been used extensively in basic vision research as well as in clinical settings, and have been reported to be enhanced in migraine. Pattern adaptation is a cortical phenomenon that reflects both cellular mechanisms acting within individual neurons and specific interactions between groups of neurons activated by the adapting display. A remarkable feature of the MAE is that its duration is only slightly reduced if a delay is inserted between the end of the adaptation and the test display (‘storage’). The reduction is consistent with recovery of the cellular component, and the residual with network changes that are maintained during the delay. This study aimed (i) to assess explanations for prolonged MAEs in migraine by teasing apart the proposed cellular and network components of adaptation using storage; (ii) to determine the extent of cortical abnormality in migraine using local and global MAEs, which reflect adaptation at different stages of the visual system. Fifty migraine (22 with, 28 without aura) and 50 control participants adapted to motion before viewing a stationary or dynamic (random motion) test, which consequently appeared to move in the opposite direction (local and global MAEs, respectively). Half of the trials included a delay between the adapting and test displays. The results extend those reported previously, as both local and global MAEs lasted longer in migraine compared with the control group. Global MAEs survived delays almost completely for both groups, whereas local MAEs were reduced to a greater extent in migraine. There were no significant differences between migraine subgroups classified according to the presence or absence of visual aura. These results suggest that cellular recovery is slowed in migraine for early but not later visual cortical areas. Sustained network changes following adaptation are implicated across cortical areas. Differences between people with and without migraine on various measures of visual perception have been attributed to abnormal cortical processing in migraine, variously described by hyperexcitability, heightened responsiveness and/or a lack of intra-cortical inhibition. The results are not consistent with hyperexcitability resulting from a lack of inhibition in migraine, but are consistent with extended suppression of intra-cortical excitation. The implications of these results for alternative models of hyperexcitability are discussed.

Keywords: migraine; adaptation; motion after-effect; storage; hyperexcitability; inhibition

Abbreviations: MAE = motion after-effect

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Introduction

The motion after-effect (MAE) is one of a number of classic illusions that can be seen after prolonged viewing of visual displays (pattern adaptation): subsequently, stationary displays appear to drift in the opposite direction (Wohlgemuth, 1911; Wade, 1994). Changes in the appearance of objects after adaptation have been demonstrated for many visual attributes in addition to motion, including size (Blakemore and Campbell, 1969), spatial frequency (Blakemore et al., 1970) and the perceived orientation of lines (Gibson and Radner, 1937;
Blakemore and Campbell, 1969). The specificity of the after-effects to particular characteristics of the adapting display has made adaptation a widely used technique to explore the organization of the visual system and the degree of independence of different visual attributes.

After-effects have also been used as a non-invasive way to assess cortical function in clinical conditions such as epilepsy (Steinhoff et al., 1997a, b), schizophrenia (Calvert et al., 1991; Harris, 1994), Parkinson’s disease (Calvert et al., 1991) and migraine (Shepherd, 2001). Shepherd (2001) reported pronounced after-effects in migraine after adaptation to motion and to oriented gratings (the tilt after-effect). Those studies were conducted to determine whether there were group differences following pattern adaptation. One aim of the present study was to assess explanations for these group differences.

Models of the MAE involve at least two processing stages. First, direction-selective cells in the visual cortex tuned to the characteristics of the adapting motion become suppressed (Sutherland, 1961; Maffei et al., 1973, van Wezel and Britten, 2002a). At a later integration stage an overall motion signal is extracted from the relative responses of all cells tuned to different motion directions (Sutherland, 1961; Mather and Harris, 1998), a process attributed to activity within V5/MT (Theoret et al., 2002) or later (van Wezel and Britten, 2002b). Since cells tuned to the adapting motion become suppressed, the relative responses of all cells mirror that elicited from weak motion in the opposite direction.

The reasons for the neuronal suppression have been investigated most thoroughly in the primary visual cortex of cat and monkey (reviewed in Niedeggen and Wist, 1998) and recently in monkey V5/MT (Priebe and Lisberger, 2002; Priebe et al., 2002; Kohn and Movshon, 2003, 2004). An early explanation, neural fatigue (Wohlgemuth, 1911; Kohler and Wallach, 1944), has been replaced by at least two mechanisms whose impact differs across cortical areas. Adaptation in the primary visual cortex (V1) is partly attributable to an intrinsic hyperpolarization of cells’ membranes, which makes cells less likely to fire again, whatever the visual input (Carpandini and Ferster, 1997; Carandini, 2000; Sanchez-Vives et al., 2000a, b). The response suppression is greatest for test displays that are the same as the adapting display, however, which requires an additional mechanism (Carandini, 2000). In both V1 and V5/MT there is evidence for an alteration in the synaptic efficacy between cells that respond to the adapting display, which involves a decrease in mutual excitation (McLean and Palmer, 1996; Carandini et al., 1998; Sanchez-Vives et al., 2000a, b; Eyton et al., 2003). The first aim of the present studies was to clarify the contribution of either, or both, of these mechanisms to pronounced after-effects in migraine.

Support for these two mechanisms has come from a number of species and techniques including human psychophysical performance. For example, immediately after adaptation the MAE can be seen in a variety of stationary test patterns, whereas later it is only seen in displays similar to the adapting stimulus (Thompson, 1998), which suggests that different mechanisms operate with different time scales. A second example is storage: if the test display does not follow the adapting display immediately, the MAE duration is only slightly reduced (Wohlgemuth, 1911; Spigel, 1960; Thompson and Wright, 1994). Storage is difficult to explain by intrinsic cellular changes following sustained activity. It is explicable by synaptic changes between the network of cells that respond to the adapting display if the network is maintained and engaged only when a display is seen that is similar to the adapting display that created it (Verstraten et al., 1996, 1998; Thompson, 1998; Culham et al., 1999).

Here, storage was used to try to tease apart the contributions of the cellular and synaptic components of adaptation to pronounced after-effects reported previously (Shepherd, 2001). The MAE duration for immediate test displays should reflect adaptation of both components. The MAE duration following a delay should reflect principally network changes, if the delay is long enough to allow cellular recovery.

The second aim was to determine the extent of any cortical dysfunction in migraine. There are two versions of the MAE: one seen in stationary test displays (a ‘local’ MAE, sMAE) and one in dynamic test displays, such as dynamic visual noise (a ‘global’ MAE, dMAE). Both reflect adaptation, but of at least two somewhat separate subpopulations of motion-sensitive neurons (Verstraten et al., 1996, 1998; Castet et al., 2002) at different stages of the visual system (see Table 1). The sMAE has been attributed principally to neuronal suppression early in the visual cortex (striate: V1), whereas the dMAE has been attributed to suppression in both early and later (extrastriate: V5/MT) cortical areas (Culham et al., 1998; Niedeggen and Wist, 1998). Here, both types of MAE were determined to assess the extent of cortical abnormality in migraine.

To sum up, the following questions were addressed. (i) Does the global MAE differ between migraine and control groups? (ii) Are group differences for the global MAE similar to those for the local MAE? (iii) Do local and global MAE survive a storage period equally well in each group? The pattern of group differences across these conditions will help clarify the extent of cortical anomaly in migraine and the causes of the pronounced after-effects reported previously. For example, if global MAEs are prolonged in migraine, it would indicate that extrastriate cortical areas are affected in migraine. If the 15 s delay reduces MAE duration substantially in migraine, it would indicate that slow cellular recovery contributes to their prolonged MAEs, whereas if the delay does not affect MAE duration, it would indicate instead that synaptic mechanisms are responsible.

Method

Participants

Fifty migraine and fifty sex- and age-matched control participants were recruited (Table 2). Twenty-five from each group participated
Local and global MAEs in migraine

Table 1 Local and global MAEs have been attributed to adaptation at different cortical sites principally due to key differences in their characteristics (A) and more recently to different response profiles in early (V1) and later V5/MT) visual cortical areas (B)

<table>
<thead>
<tr>
<th>A</th>
<th>Local MAE (sMAE)</th>
<th>Global MAE (dMAE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test displays</td>
<td>Stationary</td>
<td>Dynamic (random motion)</td>
</tr>
<tr>
<td>MAE appearance</td>
<td>Slow drift, test elements appear to move without changing their position</td>
<td>Fast, looks like real motion</td>
</tr>
<tr>
<td>Optimum adaptation speed</td>
<td>Slow (~3'/s)</td>
<td>Fast (~20'/s)</td>
</tr>
<tr>
<td>Bandwidth tuning of adapting motion</td>
<td>None</td>
<td>Broad (90–150°)</td>
</tr>
<tr>
<td>Interocular transfer</td>
<td>Partial</td>
<td>Complete</td>
</tr>
<tr>
<td>Reduced by binocular rivalry during adaptation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>First- or second-order motion</td>
<td>First</td>
<td>First or second</td>
</tr>
<tr>
<td>Site of adaptation</td>
<td>Local motion level</td>
<td>Global motion level</td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th></th>
<th>V1</th>
<th>V5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cells respond to</td>
<td>Component (local) motion</td>
<td>Component, pattern and global motion</td>
</tr>
<tr>
<td>Adaptation results in</td>
<td>Hyperpolarization</td>
<td>Synaptic changes: Reduced excitation</td>
</tr>
<tr>
<td></td>
<td>Synaptic changes: Reduced excitation</td>
<td></td>
</tr>
</tbody>
</table>

Studies cited in (A) used random dot adapting and test displays. The studies cited are also restricted to adapting patterns that use translational movement only (as opposed to expansion or contraction: Steiner et al., 1994). See Culham et al. (1998) for a review that includes adaptation to drifting sine wave gratings or to complex adapting motion.

Table 2 Migraine participant details

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Duration (years)</th>
<th>Frequency (per year)</th>
<th>Last attack</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage condition 1 (grey screen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>23</td>
<td>2</td>
<td>2</td>
<td>3 days</td>
</tr>
<tr>
<td>Maximum</td>
<td>60</td>
<td>49</td>
<td>100</td>
<td>6 months</td>
</tr>
<tr>
<td>Average</td>
<td>36</td>
<td>17</td>
<td>14</td>
<td>42 days</td>
</tr>
<tr>
<td>MO (N = 13, 3 M, 10 F)</td>
<td>34</td>
<td>17</td>
<td>16</td>
<td>36 days</td>
</tr>
<tr>
<td>VA (N = 12, 7 M, 5 F)</td>
<td>37</td>
<td>17</td>
<td>12</td>
<td>49 days</td>
</tr>
<tr>
<td>Storage condition 2 (eyes closed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>20</td>
<td>2</td>
<td>2</td>
<td>2 days</td>
</tr>
<tr>
<td>Maximum</td>
<td>47</td>
<td>30</td>
<td>72</td>
<td>6 months</td>
</tr>
<tr>
<td>Average</td>
<td>29</td>
<td>13</td>
<td>17</td>
<td>37 days</td>
</tr>
<tr>
<td>MO (N = 15, 2 M, 13 F)</td>
<td>27</td>
<td>10</td>
<td>20</td>
<td>27 days</td>
</tr>
<tr>
<td>VA (N = 10, 4 M, 6 F)</td>
<td>32</td>
<td>16</td>
<td>14</td>
<td>51 days</td>
</tr>
</tbody>
</table>

N = number; M = male; F = female. The migraine group was divided into two: those with visual aura (VA, International Headache Society, code 1.2) and those without (MO, International Headache Society, code 1.1). Frequency estimates should be treated as a guide only as they are based on retrospective self-reports and may include counts of headaches other than migraine.

in each storage condition (see below). All migraine participants fulfilled the International Headache Society (2004) criteria for migraine. None were on prophylactic treatment and none had taken acute medication within the preceding 48 h. None had experienced migraine within 48 h of testing and none reported developing a migraine within the following 48 h. None of the control group experienced headaches fulfilling the International Headache Society (2004) criteria, nor had a history of severe headaches. All participants had at least 6/9 vision monocularly and 6/6 vision binocularly either with or without optometric correction. Informed written consent was obtained in accordance with the World Medical Association Declaration of Helsinki (2004), and ethical approval from Birkbeck College’s School of Psychology ethical committee.
Displays
Stimuli were presented on a 16-in colour monitor connected to an Apple Macintosh G4 computer. The spatial and temporal resolutions were set at 832 × 624 and 80 Hz, respectively. Participants were seated 60 cm from the monitor in an otherwise dark room.

Adapting displays
A 14° square window displayed random light and mid-grey pixels (average luminance = 30 cd/m², Michelson contrast = 30%) moving coherently in one of four directions (up, down, left, right) for 45 s; see Figs 1A and 2A. Two speeds of motion were used, one that produces a strong sMAE (3°/s) and a faster speed (14°/s) that produces a strong dMAE (Verstraten et al., 1996, 1998). Participants were instructed to look at a central black fixation dot, but to pay attention to the whole display.

Test displays
After adaptation, a 14° test display was presented that contained either (i) stationary or (ii) randomly moving light and mid-grey pixels, which resembled a detuned television (Figs 1A and 2A). The random motion was generated by redrawing all pixels every four frames, giving a refresh rate of 20 Hz. They indicated when the illusory motion stopped by a keypress.

Storage
Some studies use variable storage periods for each participant matched to their usual immediate MAE duration (Wohlgemuth, 1911; Verstraten et al., 1996; Culham et al., 1999). To facilitate group comparisons here, a fixed period was chosen (15 s) on the basis of previous research (He et al., 1998; Huk et al., 2001; van de Grind et al., 2002); see Figs 1B and 2B. There were two storage conditions during which participants either viewed a grey screen or closed their eyes. The second condition was included following some reports that a sense of streaming was seen whilst looking at the grey screen. This effect has been reported previously and is considered distinct from the MAE and to be related to the illusions seen in geometrically repetitive patterns (Wade, 1994). Since people with migraine experience more vivid visual illusions when looking at striped patterns (Wilkins et al., 1984; Shepherd, 2000), there was a concern that the streaming may differ between the groups.

In the end, there were no significant differences in the MAE duration following the delay, whether the participants had their eyes open or closed (see Results).

Procedure
Eight practice trials were followed by thirty-two experimental trials divided into 8 blocks, one for each condition (test display: static or dynamic; adaptation speed: fast or slow; delay: none or 15 s). The order of the blocks of trials was randomized and, within each block,
the particular direction of motion was selected randomly with the constraint that each direction was presented once (up, down, left, right). Participants were asked to describe each MAE and whether the MAE survived after each storage trial.

Shepherd (2001) reported significant correlations between the sMAE duration and (i) pattern sensitivity, (ii) reports that migraine can be induced by visual patterns. Pattern sensitivity and the ability for visual patterns to induce migraine were therefore also assessed. Pattern sensitivity was ascertained using black and white striped patterns (diameter 7.8 degrees) with spatial frequencies of 0.8, 3, 7 and 17 cycles per degree. Each pattern was presented 4 times for 10 s to obtain a stable response. Participants were asked to describe what they saw and then note whether they experienced any illusions involving (i) motion, (ii) colour or (iii) shape. Pattern sensitivity was defined as the sum of the average number of times each type of illusion was reported for each pattern. Participants also completed a trigger inventory that included flickering light, other visual patterns (e.g. stripes and lattices) and alternating light and shade. They were asked whether each item commonly, occasionally or never triggered migraine.

Results

Statistical analyses
A preliminary analysis revealed no significant differences between the MAEs experienced after adapting to the different motion directions for either local or global MAEs; therefore, the results for each direction were averaged. A mixed factorial ANOVA (analysis of variance) was performed separately for the stationary and dynamic test displays. Each combined two between factors (group: migraine or control; storage: eyes open or closed) and two within factors (adaptation speed: slow or fast; storage: none or 15 s).

For some participants there were missing data if no MAE was reported (it can be affected by lapses in attention; Chaudhuri, 1990; Culham et al., 1998) or if the wrong key was used for response. Missing data (<7%) occurred mostly for conditions that were not optimized for each MAE (i.e. slow adaptation followed by dynamic test displays), but did not differ between groups. Missing values were replaced with group averages for that condition.

Static displays
The migraine and control groups’ data are presented in Fig. 3 and Table 3. The MAE lasted substantially longer in the migraine group than in the control group for all of the conditions, confirmed by a significant main effect of group \( F(1, 96) = 26.7, P < 0.001 \). Second, the MAE duration was reduced for both groups after the 15 s delay, and the reduction was greater in the migraine group [storage condition × group: \( F(1, 96) = 6.5, P < 0.05 \)]. The difference in MAE duration between the two adaptation speeds was also

Fig. 2  Adaptation and test displays for the global MAE. (A) Following 45 s of adaptation to translational random dot motion (downwards in this example), observers were then presented immediately with the dynamic random dot test display, in which dots moved randomly in all directions but appeared to move in the opposite direction (upwards in this example). (B) Following 45 s of adaptation to translational random dot motion there was a 15 s delay before the dynamic random dot display was presented.
There were overall significant effects of speed. There were no other significant effects involving group, but small (on average, 0.7 s) and did not differ between the groups.

There was also a significant main effect of speed \([F(1, 96) = 7.8, P < 0.01]\) and a trend for the MAE to store better in the eyes closed condition (no reduction in MAE) than when looking at a uniform grey screen (average reduction of 1.3 s), but this trend was not significant \([F(1, 96) = 3.6, P = 0.061]\) and did not differ between the groups. This trend is consistent with previous reports that storage of the global MAE depends on what is viewed during the delay (Verstraten et al., 1996; van de Grind et al., 2004).

### Migraine characteristics

For each condition the MAE lasted slightly longer for the migraine group with visual aura than for the group without aura (Table 3). Separate analyses on the migraine data with migraine type (with or without visual aura) replacing the group factor revealed, however, no significant differences between the migraine subgroups for either static or dynamic test displays.

### Pattern sensitivity and visual triggers

When the high-contrast striped patterns were viewed, illusions of shape were reported most frequently by both groups, followed by motion, and then colour. Pattern sensitivity was substantially higher for the migraine group (4.0 illusions on average) than for the control group [2.2 illusions, \(t(98) = 3.7, P < 0.001\)]. There were significant positive correlations between the dMAE and pattern sensitivity (immediate, slow: \(r = 0.28\); immediate, fast: \(r = 0.35\); delayed, slow: \(r = 0.25\); delayed, fast: \(r = 0.35\); all \(P < 0.05\), one-tailed tests), indicating that those who saw more illusions experienced longer dMAEs. Reports that visual patterns commonly triggered migraine correlated significantly with each sMAE (immediate, slow: \(r = 0.44\); immediate, fast: \(r = 0.41\); delayed, slow: \(r = 0.30\); delayed,
slow: $r = 0.38$; all $P < 0.05$, one-tailed tests), indicating that those whose migraines can be visually induced experienced longer sMAEs. The migraine group’s data were divided into four categories on the basis of reports of visual triggers—commonly versus other—and pattern sensitivity, following a median split of the pattern sensitivity scores. The longest sMAEs were experienced by the group that experienced both common visual triggers and pattern sensitivity, whereas the shortest were experienced by the group that experienced neither. The dMAEs experienced by the groups that experienced both common visual triggers and pattern sensitivity, or pattern sensitivity alone, were similar and lasted longer than either of the other two groups.

**Migraine history**
The time elapsed since the last attack also correlated positively with each sMAE (immediate, slow: $r = 0.31$; immediate, fast: $r = 0.25$; delayed, slow: $r = 0.43$; delayed, fast: $r = 0.29$; all $P < 0.05$, one-tailed tests), indicating that the sMAE duration was longest for those who had not had a migraine recently. The number of years migraine had been experienced or the frequency of migraine attacks (per year) did not correlate significantly with either MAE.

**Discussion**
The migraine group saw the MAE for substantially longer than the control group in each condition and for both static and dynamic test displays, a result that extends those reported previously (Shepherd, 2001). There were, however, no significant differences between the migraine groups with and without visual aura. Shepherd (2001) also reported no significant differences between migraine subgroups and suggested that (i) there may be a continuum of cortical anomaly in migraine regardless of aura symptoms, rather than qualitative differences between migraine subgroups; and that (ii) studies that do report differences may have recruited participants for whom migraine classification co-varies with other factors, such as pattern sensitivity or susceptibility to visually triggered migraine. The associations between pattern sensitivity and visual triggers reported here are consistent with these suggestions.

**The extent of cortical dysfunction in migraine**
The present data are consistent with the proposal that static and dynamic test displays reveal adaptation in different cell groups (Table 1). First, participants were asked to describe what they saw, and the appearance of each MAE differed substantially, consistent with previous reports (Wohlgemuth, 1911; Hiris and Blake, 1992; Culham et al., 1998; Castet et al., 2002). Second, adaptation at a single site should have produced similar, not contrasting, effects for the two adaptation speeds and storage conditions (compare Figs 3 and 4). Accordingly, the large group differences for both static and dynamic test displays indicate that both early (striate: V1) and later (extrastriate: V5/MT) cortical areas are affected in migraine both with and without visual aura.

There is only limited previous research that has explicitly assessed the integrity of extrastriate cortex in migraine. Recent TMS studies over human V5/MT (Battelli et al., 2002; Fierro et al., 2003) and functional magnetic resonance imaging in between migraine episodes (Vincent et al., 2003) are consistent with the conclusion that extrastriate cortex is affected in migraine. Psychophysical research using tasks that can reflect processing in particular cortical areas is more limited. Motion coherence thresholds (MCT) have been reported to be impaired in migraine (McKendrick and Badcock, 2004; Antal et al., 2005), which is a global motion task that has been used to assess extrastriate function (Culham et al., 1998; Braddick et al., 2001). Since prefrontal temporal mechanisms have been reported to have impaired temporal resolution (Coleston et al., 1994), however, elevated
MCT in migraine could reflect temporal limitations introduced earlier in the visual pathways rather than an inability to extract global motion from noise (Chapman et al., 2004). The present results clearly show that the (internally generated) global MAE percept is not impaired in migraine (Fig. 4).

What do differences in the storage of static and dynamic MAEs reveal about mechanisms of adaptation in different cortical areas?

The 15 s delay between the end of the real motion and the test displays was included to tease apart cellular and synaptic components of adaptation (see Introduction). For the static test displays only, the delay appears to have been sufficient to allow cellular recovery for both groups since the residual sMAE was shorter after the delay. The reduction in sMAE duration after the delay was larger for the migraine group (Fig. 3), which suggests that part of the explanation for prolonged MAEs with immediate test displays is due to slow cellular recovery in the early visual cortex in migraine.

For the static test displays, both adaptation speeds, and each group, the residual sMAE after the delay was greater than the duration of the immediate sMAE (e.g. Fig. 3: migraine, slow adaptation speed: immediate sMAE = 14.0 s; residual sMAE + delay = 23.7 s). Thus, the residual sMAE was not simply the tail end of the immediate sMAE; the sMAE did store. The group differences also continued after the delay, which suggests that, early in the cortex, the synaptic changes that build up during adaptation are maintained for longer in migraine. Whether the residual group differences after the 15 s delay include, in addition, lasting effects of the slow cellular recovery could be determined using longer storage times.

For the dynamic test displays and both groups, there was only a slight reduction in the duration of the dMAE following the 15 s delay. This suggests that most of the dMAE can be attributed to synaptic changes within the network of cells engaged by the adapting display, rather than cellular recovery, and that these network changes are maintained as well in both groups. Evidence that (i) neural circuits within MT are affected following adaptation to moving random dot displays, yet (ii) MT neurons do not suffer the same intrinsic cellular hyperpolarization as V1 neurons, has been provided recently by single-cell recordings in macaque (Priebe and Lisberger, 2002; Priebe et al., 2002).

What can prolonged MAEs reveal about cortical processing in migraine?

Shepherd (2001) discussed various abnormalities that could account for pronounced after-effects in migraine. At a cellular level, impaired central metabolism, reduced mitochondrial energy reserves or a channelpathy (Schoenen, 1996; Welch, 1997; Tepper et al., 2001) have been discussed in migraine. Any of these alternatives could disrupt the processes that regulate ionic balance and/or neurotransmitter cycling after sustained activity and result in the prolonged after-effects. Purely behavioural data cannot distinguish alternative cellular mechanisms, but some may be addressed by including an adaptation study in future clinical trials. The present data, however, are consistent with slow cellular recovery in migraine that is restricted to the early visual cortex and does not occur in extrastriate areas.

In addition, the data are consistent with prolonged synaptic changes in both early and later cortical areas in migraine. Synaptic changes following adaptation were initially modelled by an increase in inhibition (Barlow, 1990; Wilson and Kim, 1994), although diverse neurophysiological research indicates instead that adaptation causes a decrease in mutual excitation between cells that respond to the adapting display (Carandini et al., 1998; Culham et al., 1999, Sanchez-Vives et al., 2000a, b). For example, neurophysiological studies have shown that pharmacological manipulation of excitation can affect the strength of adaptation, whereas either blocking or activating inhibition does not (Vidyasagar, 1990; McLean and Palmer, 1996). If these neurophysiological data can be generalized, a lack of inhibition in migraine (Wilkins et al., 1994; Chronicle and Mulleners, 1996; Palmer et al., 2000; Mulleners et al., 2001) cannot explain their prolonged after-effects. Instead, the data support the earlier suggestion that, following adaptation, there is extended suppression of cortical excitatory connections in migraine (Shepherd, 2001).

The data may not support the lack of inhibition model of hyperexcitability in migraine, but are they consistent with hyperexcitability resulting from other mechanism(s)? It could result from abnormal release of excitatory neurotransmitters, such as glutamate (Welch et al., 1990; Welch, 1997; Tepper et al., 2001; Antal et al., 2005), or as a consequence of low pre-activation levels (Schoenen, 1996; Ambrosini et al., 2003). Before addressing this question, it should be remembered why an MAE is seen. Following adaptation, an MAE will only be seen if the MAE signal (a reduced response in a subgroup of cells) can be detected against the activity generated by the test displays (Mather and Harris, 1998; Huk et al., 2001; van Wezel and Britten, 2002a).

Three models of hyperexcitability are considered here. Hyperexcitability may lead to greater background neuronal noise in the visual system and a greater response to incoming signals. If both are elevated in proportion in migraine, then there would be little reason to expect differences between the migraine and control groups. Any greater suppression from larger signals elicited by the adapting displays would be lost in the greater background noise elicited by the test displays.

Hyperexcitability could, instead, result in increased general noise in the visual system, without entailing a greater response to incoming signals. This model has been suggested to explain higher detection thresholds in migraine (McKendrick and Badcock, 2004). Greater noise, against which the MAE signal must be detected, should produce weaker MAEs, as the MAE signal would be more readily
masked by the elevated background noise. Again, this model is not supported by the present data.

Third, hyperexcitability could raise the activity of direction-selective cells to a uniformly higher rate without increasing variability. In this case, the neuronal response elicited by a person with migraine may be comparable with another without migraine viewing a higher contrast pattern, analogous to the increase in firing rate with contrast that is observed in direction-selective cells in physiological studies (Maffei et al., 1973; Kohn and Movshon, 2003). This proposal appears consistent with pronounced after-effects in migraine: stronger activity during adaptation could subsequently produce greater suppression in adapted cells. The test displays would elicit a uniformly higher level of activity in unadapted cells, so the dip in the activity of adapted cells should be readily detected. Because the MAE is maximal for low-contrast test displays combined with equal or higher contrast adapting displays (Keck et al., 1976; Nishida et al., 1997; Thompson, 1998), however, Shepherd (2001) considered heightened responsiveness an unlikely explanation for prolonged after-effects in migraine. This account could be directly assessed by manipulating contrast and determining how the MAE varies with test display contrast in migraine and control groups.

This account of hyperexcitability is not generally supported by other research. For example, it predicts that detection thresholds should be lower in migraine, whereas discrimination thresholds may be impaired. There are some reports of just these sorts of effects, but only for very brief displays (Antal et al., 2005; A. J. Shepherd, 2005, submitted; cf. Khalil, 1991; Coleston and Kennard, 1995; Shepherd, 2000). Possibly, better detection may occur when a heightened neuronal response to target stimuli is limited by short presentation times. Impaired performance may occur when presentation time increases as the heightened response cannot be maintained. This short-lived model of hyperexcitability could be tested by reassessing detection thresholds for various visual attributes using brief and longer display durations.

An alternative explanation for prolonged after-effects is that they are related to the reported lack of habituation and even increased amplitudes of visual evoked potentials in migraine, which may result from low cortical pre-activation (reviewed in Ambrosini et al., 2003). Habituation and adaptation share certain similarities: habituation is a decline in response to repetitive stimuli, whereas adaptation is a decline in response to continuous stimuli. Both reduce redundancy, protect against response saturation and conserve energy (see Shepherd, 2001). The lack of habituation normalizes during the migraine attack (Ambrosini et al., 2003), and here shorter MAEs were recorded for people who had recently had a migraine attack. Despite these similarities, a lack of habituation is clearly not mirrored by a simple lack of adaptation. During the adaptation, however, a potentiation of response over time would mean that by the end of the adaptation, neurons tuned to the adapting motion would have responded more strongly, resulting in a greater suppression. What distinguishes the third hyperexcitability model and this potentiation of neural response is the time-course necessary to elicit a higher neuronal response. After 45 s of adaptation, the predictions from both models are the same. To separate the two models, it would be worthwhile to compare migraine and control groups using a range of shorter adaptation times (e.g. van Wezel and Britten, 2002).

In conclusion, the present data reveal prolonged neuronal suppression following 45 s of visual adaptation in migraine with and without visual aura, which can be attributed to sustained changes within neuronal circuits at both early (striate: V1) and later (extrastriate: V5/MT) cortical areas, and slow cellular recovery only early in the visual cortex. These data are not consistent with hyperexcitability resulting from a lack of inhibition but are consistent with extended suppression of intra-cortical excitation in migraine. Whether this extended suppression involves short-lived hyperexcitability, low pre-activation coupled with heightened responsiveness or some other mechanism(s) is a question for future research.

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Local and global MAEs in migraine

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