Visual Distortion Provoked by a Stimulus in Migraine Associated With Hyperneuronal Activity

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Background.—Migraineurs with visual aura are highly susceptible to illusions and visual distortion and are particularly sensitive to a pattern of regularly spaced parallel lines or stripes.

Purpose.—To determine whether the high degree of susceptibility to illusions and visual distortion in migraineurs with aura is associated with hyperneurological activity of the occipital cortex.

Methods.—In order to investigate any relationships among neuronal activity, spatial frequency of square-wave gratings, and self-described visual distortion, we investigated the neuronal and psychophysical responses to square-wave gratings in migraineurs with visual aura and in nonheadache controls.

Results.—Square-wave gratings provoked various types of visual distortion and illusions and induced a hyperneuronal response in the visual cortex of migraineurs with visual aura, a response that strongly depended upon the stimulus spatial frequency.

Conclusion.—The hyperneuronal activity of the occipital cortex is consistent with general cortical hyperexcitability in migraine.

Key words: migraine, visual distortion, visual activation, functional MRI

Abbreviations: SF spatial frequency, NHCs nonheadache controls, MWA migraine with aura, cpd cycles per degree, BOLD blood oxygenation level dependent

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In addition to debilitating pain, migraine is frequently accompanied by various visual disturbances or aura. These auras can occur prior to the onset of migraine headache and include scintillation, fortification spectra, and scotomata. Photophobia is also associated with most migraine attacks, with or without visual aura, and therefore is included in the criteria of migraine classification by the International Headache Society (IHS).[1] Bright light and certain visual patterns provoke severe visual discomfort and distortion in individuals with migraine, and even can induce a migraine attack.[2-6] Square-wave gratings provoked severe visual discomfort and illusion in individuals with frequent headache and migraine with and without aura.[2,3] The photosensitivity in migraineurs with visual aura motivated us to trigger migraine symptoms by repetitive visual stimulation in order to study cortical function changes during early onset of the symptoms, in which symptoms were successfully induced in more than 55% of 27 patients with migraine within 15 to 20 minutes.[5,6]

Wilkins and colleagues investigated the patterns and parameters of visual stimuli that provoked severe visual distortion and stress in frequent headache sufferers and elicited epileptiform electroencephalographic (EEG) abnormalities in patients who had photosensitive epilepsy.[2,7] An increase in brightness, contrast, or visual field of a pattern intensifies visual stress or promotes epileptic EEG waveforms. An overwhelming finding of their studies was that a stim-

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ulus comprised of regularly spaced parallel stripes, regardless of their absolute spatial orientation, provoked more visual distortion and illusions than a checkerboard or a concentric-ring pattern. Also, the degree and severity of visual distortion and illusions depended upon the spatial frequency (SF) and the frequency of contrast reversed.[2,7] Wilkins and colleagues hypothesized that high susceptibility of visual distortion and illusions in the frequent headache sufferers was caused by hyperneurological activity of the occipital cortex, with epileptogenic stimuli producing abnormal spread of excitation as in epilepsy (though less marked) and causing neurons to fire inappropriately, giving rise to illusions; this has yet to be demonstrated. Despite frequent complaints of visual stress and illusion by migraineurs, few studies have attempted to replicate the findings of Wilkins' studies in the migraine population.[3] Also, the relation remains unknown between visual aura and interictal illusion and visual distortion induced by a stimulus in the migraineurs with aura; the first features a biphase process—a transient hyperneuronal activity followed by a prolonged neuronal suppression.[8-10] An understanding of interictal visual disturbance in the migraineurs with aura and its relation to visual aura might provide a new insight into preventive therapy of migraine.

In this pilot study, we investigated neurological and psychophysical responses to square-wave gratings in migraineurs with visual aura and in nonheadache subjects, and determined the relationship among the neuronal activity, SF of the stimuli, and self-described visual distortion. We expected that SFs of 1 to 3 cycles per degree (cpd) in black-white square-wave gratings, which provoked a maximum amount of epileptiform EEG activity, would produce hypervisual neuronal activity in migraineurs with aura, compared with nonheadache controls (NHCs).

METHODS

Subjects.—Six migraineurs with visual aura (4 women, 2 men; aged 31 to 52 years) participated in the study (Table 1). Diagnosis was established using the criteria of the IHS.[1] Six nonheadache, age-matched controls (5 women, 1 man; aged 29 to 51 years) were enrolled in the study. The inclusion crite-

Table 1.—Subject Characteristics*

Subjects	Sex	Age, y†	Visual Aura, Affected Visual Field	Headache Location	Visual Distortion Score	Discomfort Score
Migraineurs						
1	M	52	Scintillating spots, LVHF	B, front, lateral side	2	1
2	F	35	Scintillating spots, RVHF	R, front, lateral side	2	1
3	F	31	Scotoma, severe in LVHF, mild/less in RVHF	B, back, lateral side	2	0
4	M	32	Scotoma, initiated at near center of RVHF, expanding into both LVHF and RVHF	R, front, lateral side	2	1
5	F	51	Scintillating spots and circles in LLQ, sometimes involving RVHF	R, front	2	5
6	F	37	Scintillating stars, BVF	L, front, lateral side	1	0
Controls						
1	F	34			0	0
2	F	29			0	0
3	M	51			2	0
4	F	31			1	0
5	F	40			1	0
6	F	41			1	0

* LVHF indicates left visual hemifield; B, bilateral; RVHF, right visual hemifield; R, right; LLQ, lower left quadrant; BVF, bilateral visual field; L, left.

† Mean age of migraineurs was 39.7 years; controls, 37.7 years.

ria for patients were: diagnosed as having migraine with visual aura according to the criteria of the IHS,[1] older than 18 years, recurrence of migraine attacks no more than 3 times per month and less than 3 times per year, and no migraine headache at least 5 days prior to the study. The inclusion criteria for NHCs were: no history of headache, tension-type recurring headaches no more than 3 per year and controlled by using over-the-counter medication, and no headache at least 14 days prior to the study. The exclusion criteria for both groups included: frequent tension headaches (1 per month or more), ill-defined head pain, history of seizures or a strong familial history of generalized seizures, prior head injury or brain surgery, other diagnosed neurological or psychiatric (or both) disorders, other diagnosed cardiovascular disorders, and other illness (eg, cancer, diabetes, and anemia). We also excluded individuals from the control group if they had first-order biological family members who had been diagnosed with migraine. The University Committee on Research Involving Human Subjects at Michigan State University approved the study. Prior to the study, written informed consent was obtained from all subjects.

In migraineurs with aura, self-reported migraine attack frequency varied from 3 episodes per month to 3 per year in the preceding 12 months. In the migraine with aura (MWA) group, the aura was described as scintillation and scotoma (see Table 1). Locations of migraine head pain are also detailed in Table 1. All migraineurs with aura reported photophobia during migraine attacks, and were sensitive to bright light or stripelike patterns. Nausea and pulsatility were associated with migraine in all patients except patient 6. In all migraineurs with aura, the headaches had occurred previously without aura. No patient was on preventive migraine drugs at the time of the study.

Stimulus.—The stimuli chosen in the present study were based on a large quantity of psychophysical observations in frequent headache sufferers by Wilkins and colleagues, and the literature regarding interictal visual disturbances in migraine. The Wilkins' studies suggest the following features of a stimulus that might particularly affect migraineurs: regularly spaced stripes or lines, SF around 3 cpd, and temporal frequency of 15 Hz or above.[2,7] That is greater than the frequency of 8 to 10 Hz inducing the peak neuronal response in healthy subjects.[11] The exact effect of a color stimulus on the migraine or headache population is little known,[2,3,7] although a red-green annular checkerboard has successfully triggered symptoms in 55% of migraineurs.[5] Thus, in this pilot study, we chose square-wave gratings in black and white as the stimulus. We did not investigate the temporal-frequency effect because we could not achieve a fast enough reversed rate on the liquid crystal display (LCD) used during functional magnetic resonance imaging (fMRI) due to its slow response time.

The stimulus consisted of square-wave gratings with contrast of 75% and with a fixation mark (0.3° square) at the center of the visual field. The stimulus subtended a 13° visual angle. Spatial frequency of the square-wave gratings varied from 0.25 to 19.2 cpd.

Tests of Visual Distortion and Discomfort.—All subjects were tested for visual discomfort and distortion when viewing the square-wave gratings with the SFs from 0.25 to 19.2 cpd. During testing, the subject was seated 2 feet from the monitor of a personal computer in a darkened room, and was instructed to focus their eyes on a fixation mark at the center of the monitor. Each stimulus was displayed for 5 seconds, and then the subject was instructed to freely make comments on what they perceived and felt before continuing to the next stimulus. An investigator recorded the subject's comments at each SF. After all stimuli were viewed, the subject was asked to report, as measures of discomfort, whether they felt any of the following sensations: eye ache, queasiness, headache, nausea, or dizziness.

Score of Visual Distortion.—Any self-reported illusion involving blurring lines, zigzag lines, wavering or moving lines and patterns, flickering spots and lines, 3-dimensional effects, or colors was classified as visual distortion. As demonstrated in Wilkins' studies, stimuli with SFs ranging from 1 to 4 cpd induced the maximum numbers of illusions of color, shape, or motion in the frequent headache sufferers and the maximum probability of epileptiform EEG activity in the patients who had photosensitive epilepsy.[7] The number of illusions and the probability of epileptiform EEG activity decreased at SFs lower than 1 or higher than

4 cpd. Thus, we used a 0 to 2 scale to score subjects' self-reported degree of visual distortion. Zero represented no visual distortion reported at any SF, 1 denoted distortion reported at the most sensitive SFs ranging from 1.2 to 3.0 cpd, and 2 represented distortion at the most sensitive SFs and at the lower or higher SFs (<1.2 cpd or >3.0 cpd).

Score of Discomfort.—A 0 to 5 scale was used to score discomfort evoked by the stimulus of square-wave gratings according to the number of items of discomfort reported. For example, zero represented none of the 5 items in the discomfort test that were reported, while 5 represented all 5 items reported.

Functional MRI Protocols.—Five selected stimuli with SFs 0.3, 1.2, 3.0, 6.0, and 9.0 cpd were presented to subjects while T_2^*-weighted MR images were acquired. The stimuli were presented on an LCD display that was controlled via Integrated Functional Imaging Systems (IFIS, Psychology Software Tools, Inc, Milwaukee, WI, U.S.A.). For the subjects who need vision correction, MRI-compatible lens were used. During fMRI, ten 15-second fixation blocks were interleaved with ten 15-second stimulation blocks with each of 5 SFs repeated in 2 blocks. The SFs of the stimulus in the 10 stimulation blocks were set in a pseudo-random order. Ten 6-mm axial-oblique sections parallel to the calcarine fissure (CF) were acquired using gradient echo-planar-imaging (EPI) on a 1.5 tesla NV/i clinical scanner (General Electric Medical Systems, Pittsburg, PA, U.S.A.) with TR = 1000 ms, TE = 50 ms, and an in-plane resolution of 3.75×3.75 mm^2. T1-weighted MR images were collected at the same anatomic sections using a spin-echo pulse sequence with TR = 500 ms, TE = 14 ms, slice thickness = 6 mm, and an in-plane resolution of 0.94×1.25 mm^2.

Image Processing.—Functional images were corrected for possible in-plane translation and rotation.[12] The signal intensity time course was corrected for slow baseline drifts, and was normalized to allow signal averaging over voxels and across subjects. To avoid subjective influence on data analysis, all information indicating the subject's migraine status was removed from the data. An investigator unaware of the subject's migraine status performed the following analyses. The pixel signal intensity time course was cross-correlated with sine and cosine reference functions and a cutoff threshold was established with a cross-correlated coefficient of 0.15 and an estimated P value of <.01.[13,14]

We expected the square-wave gratings would provoke hyperactivity in the migraineurs with aura compared with the NHCs, and anticipated the hyperactivity to be reflected primarily in the blood oxygenation level dependent (BOLD) signal intensity changes. Considering that the low spatial specificity of the BOLD contrast results in a spread and damping of the BOLD signals from the center of activation,[15] we analyzed T_2^*-weighted signal intensity changes in the center area of the activation clusters that were in the cortex adjacent to the left or right CF (Figure 1). The BOLD signal intensity time courses were averaged over an area of 84.4 mm^2 (6 pixels) having the largest cross-correlated coefficients in the activation cluster. Then, for each subject the mean percentage signal intensity changes in response to each SF were averaged over the 2 repeated blocks.

RESULTS

Visual Distortion.—All migraineurs with visual aura reported more than one type of visual distortion or illusion, eg, colors, wavering lines and spots, and 3-dimensional effects. These visual distortions/illusions occurred not just at the most sensitive SFs from 1.2 to 3.0 cpd but also at the lower and/or higher SFs (Table 1). The spatial location of the illusion and distortion varied with SF, and was not limited to the hemifield or quadrant in which their aura occurred. All migraineurs had visual distortion scores of 2 except patient 6 whose score was 1. In the nonheadache subjects, 2 reported no visual distortion at any SFs (score = 0), 3 described minor distortion (ie, vision blurring) in the most sensitive frequency range (score = 1), and 1 had visual distortion that occurred in the most sensitive frequencies and lower frequencies (score = 2) (Table 1). The migraineurs with aura were significantly more susceptible to visual distortion while viewing the square-wave gratings than the NHCs (Mann-Whitney rank *U* test, $P < .018$, 1-tailed).

Discomfort Evoked by Square-Wave Gratings.—No NHCs reported any discomfort when viewing the stimuli, whereas 4 subjects with migraine experienced

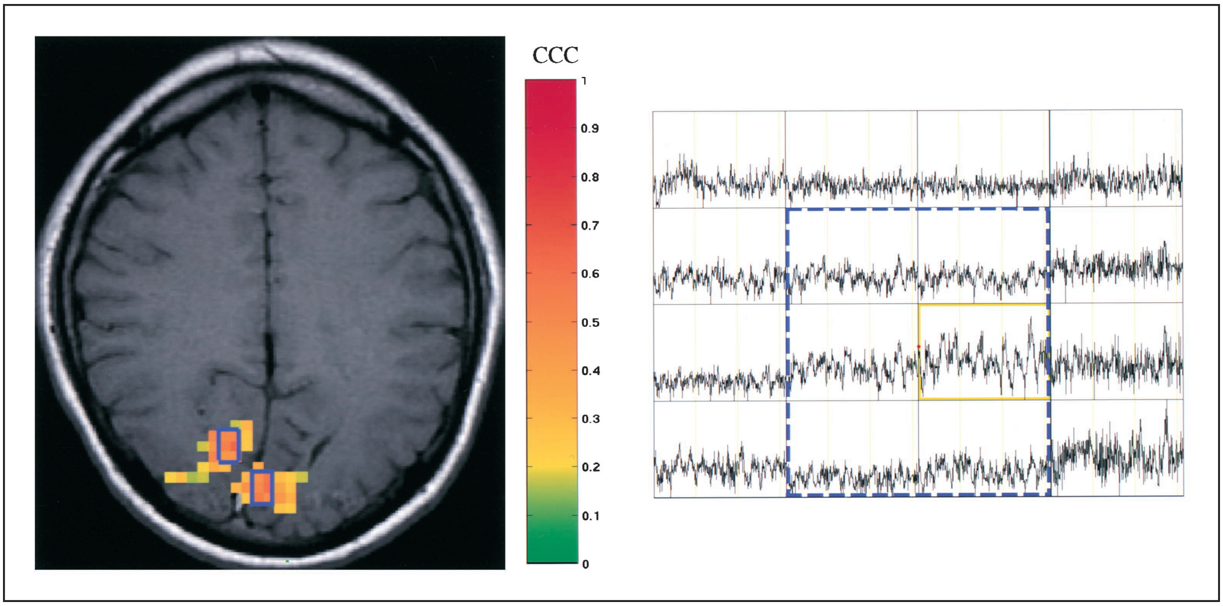

Fig. 1.—Time courses of the activated voxels in the cluster adjacent to the right calcarine fissure (right panel) show that activation diminishes from the central voxel (enclosed by the yellow line) having the largest cross-correlated coefficient (CCC). Six voxels enclosed by the blue dashed line in the left or right putative V1 (left panel) and with the largest cross-correlated coefficients in the cluster were selected as regions-of-interest for averaging the time courses of signal intensity changes over the cortical area with large activation.

discomfort involving one or more items, eg, dizziness and nausea (Table 1). Difference between the 2 groups was significant (Mann-Whitney rank *U* test, $P < .03$, 1-tailed).

Activation in the Visual Cortex.—In the NHC group, BOLD signal intensity changes in the left and right visual cortex adjacent to the CF did not show any significant difference (Student *t* test, $P > .2$). The signals from both the left and right visual cortex were therefore combined (Figure 2). In the NHCs, the BOLD signal intensity changes in response to the square-wave gratings exhibited an SF dependency with a peak response of 1.9% ± 0.27% at 1.2 cpd and decreased to approximately 1.3% at both low and high SFs (Figure 2); the trend of SF dependency is consistent with an observation from another group.[16]

In the MWA group, a similar SF dependency of visual activity was observed with a maximum activity at 1.2 cpd and a decrease at both lower and higher SFs (Figure 2). The laterality of visual aura in our MWA group varied from clear unilateral in patients 1 and 2 to bilateral in patient 6, and with patients 3, 4, and 5 between the 2 extremes. Comparing the BOLD signal changes between the 2 sides of the visual cortex, only patient 1 showed a large difference with higher BOLD signal changes on the side of the visual cortex contralateral to the hemivisual field where aura occurred; while there was little difference in the other patients (Table 2). Therefore, the migraine group data were pooled from both sides of the visual cortex and compared with the NHCs. The means of the BOLD signal intensity changes in the MWA group were 2.1% ± 0.23% and 3.1% ± 0.27% for SFs of 0.3 and 1.2 cpd, respectively, which were significantly greater than the NHC group's with respective *P* values of .02 and .005 (Student *t* test, 2-tailed) (see Figure 2). If the side of the visual cortex of which the contralateral visual hemifield never was affected by aura was excluded from the pooled MWA data, ie, the left side of patient 1 and the right side of patient 2, the mean BOLD signal intensity change at 1.2 cpd was 3.2%, which was little different from 3.1% obtained when all left and right sides were included in the computation.

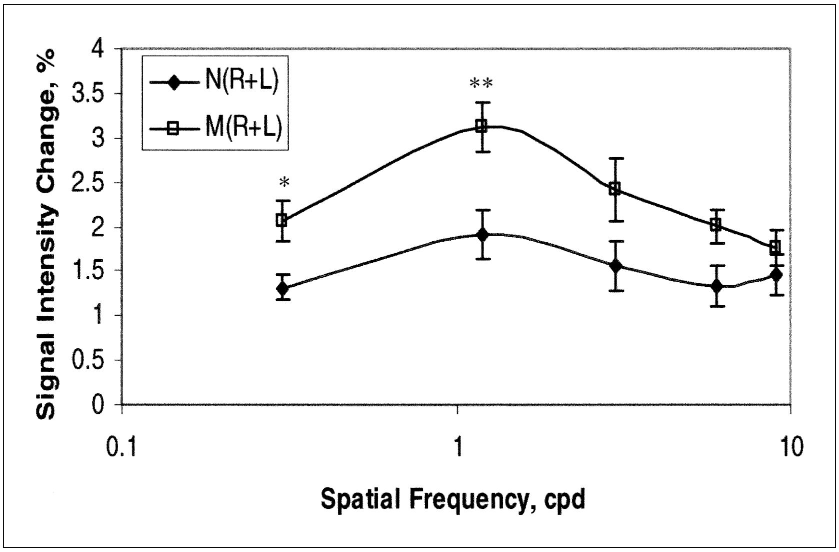

Fig. 2.—Spatial frequency dependence of the averaged blood oxygenation level dependent (BOLD) signal intensity changes in the nonheadache controls (closed diamond) and migraineurs with visual aura (open square). The peak BOLD responses occurred at spatial frequency of 1.2 cycles per degree (cpd) for both groups. The averaged BOLD signal intensity changes of the migraine group were significantly increased at the spatial frequencies of 1.2 and 0.3 cpd compared with the control group. The error bars denote the standard error of the mean. *$P < .02$. **$P < .005$.

Table 2.—Blood Oxygenation Level Dependent (BOLD) Signal Intensity Changes in Migraineurs With Aura and Nonheadache Controls*

	BOLD Signal Intensity Changes, % at 1.2 Cycles per Degree Spatial Frequency	
Subjects	Left Hemivisual Field	Right Hemivisual Field
Migraineurs		
1	1.1	3.9 (CA)
2	4.2 (CA)	4.3
3	2.1 (CA)	2.6 (CA)
4	3.8 (CA)	3.6 (CA)
5	2.5 (CA)	2.9 (CA)
6	3.1 (CA)	3.3 (CA)
Controls		
1	3.8	2.6
2	0.9	1.8
3	1.6	2.7
4	0.6	1.2
5	2.2	1.0
6	2.9	1.7

* CA indicates contralateral to the visual hemifield where aura occurred.

COMMENTS

In the present study, we found a similar trend of an SF dependency of the BOLD responses to square-wave gratings in both the NHC and MWA groups—a peak activity at 1.2 cpd and a decrease at both lower and higher SFs; while the peak response in the MWA group was significantly greater than the NHC group's. The SF at the peak visual response was coincident to frequencies with which the stimulus irritated the MWA group most. Therefore, the hyperneuronal activity in the MWA group was associated with their high susceptibility to visual distortions and illusions provoked by the stimulus. The neuronal visual activity in the MWA group appears to be elevated in both left and right sides of the visual cortex, except patient 1 who was 1 of 2 having aura confined to one lateral side of the visual hemifields. Due to lack of absolute laterality of aura in most of our migraineurs, we cannot determine whether the hyperneuronal activity is induced only in the visual cortex contralateral to the hemifield where aura occurred or in both contralateral and ipsilateral sides.

Our observations regarding the hyperinterictal visual activity in response to square-wave gratings in the

MWA group supports a general hyperexcitability theory of the pathophysiology of migraine.[17] By this theory, migraineurs with aura experience a state of central neuronal hyperexcitability that predisposes them to develop spontaneous neuron depolarization, followed by a spreading suppression of neuronal function. This chain of neuronal events is possibly mediated by the release of the excitatory amino acid glutamate or the increase in extracellular K^+.[17] Also, glutamatergic neurons are most likely responsible for neuronal hyperexcitability, particularly in the occipital cortex.[18] Glial cells carry out most of glutamate re-uptake and synthesis of inhibitory neurotransmitter δ-aminobutyric acid (GABA). Clearance of K^+ is also heavily dependent upon the capacity of glial cells.[19] This hyperexcitability theory has been thought responsible for the migraineurs with aura having an increase in the amplitude of visual evoked potentials, interictal habituation deficits, and phosphenes induced by occipital transcortical magnetic stimulation at a lower threshold.[20-22]

The stimuli that produced hyperneuronal visual activity in migraineurs with aura observed in the present study provoke epileptic EEG activity in patients who have photosensitive epilepsy.[7] The epileptogenic stimuli give rise to massive physiological excitation which compromises intracortical inhibition (level available GABA) as in epilepsy (though less marked), causing neurons to fire inappropriately and thereby generating illusions and visual distortion.[7] The amount of visual distortions and illusions are associated with the "strength" of stimuli and the cortical hyperexcitation and inhibitory status. The present study demonstrated the link between strong stimulation, illusion, and hyperneuronal activity. Impaired visual intracortical inhibitory functions in migraineurs with aura have been reported and attributed to damage of GABAergic neurons due to hypoperfusion/hypoxia occurring during the late phase of migraine aura.[23] In addition, orientation-selective neurons in the primary visual cortex and their horizontal connections might be particularly responsible for hyperneuronal activity to square-wave gratings, but other visual areas could also be involved due to various types of illusions and visual distortions.

The relation between visual distortion/illusions provoked by stimuli and visual aura remains undetermined. In this preliminary investigation, we observed several distinctions between interictal illusion/distortion and visual aura: every migraineur with aura reported more than one type of illusion and visual distortion; and a slight change in the SF of the stimulus can induce different types of visual distortions and illusions (potentially indicating more than one visual area involved)[10]; after the stimulus was off, illusion disappeared either immediately or within 1 to 2 minutes, while visual aura usually persists 15 to 40 minutes and is independent upon any external stimulus; and the interictal visual cortical activity in response to the stimulus that provoked illusion and visual distortion was hyperexcitable, whereas during visual aura cortical activity in response to external stimulation was suppressed or diminished.[5,10] During migraine aura, neurons of the occipital cortex contralateral to the aura undergo an abnormal process of transit and hyperexcitation and prolonged inhibition.[17] Analysis of types and sources of illusions and visual distortions, which presents a great challenge due to large degrees of variations in illusion types and their transient nature, and determination of the relation between visual aura and interictal visual disturbance will be the focus of future work.

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