

Sustained visual cortex hyperexcitability in migraine with persistent visual aura

Wei-Ta Chen,^{1,2,3,*} Yung-Yang Lin,^{1,2,4,5,6,*} Jong-Ling Fuh,^{1,2} Matti S. Hämäläinen,³ Yu-Chieh Ko^{1,7} and Shuu-Jiun Wang^{1,2}

1 School of Medicine, National Yang-Ming University, 155 Li-Nong Street, Section 2, Peitou, Taipei 112, Taiwan

2 Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, 201 Section 2, Shih-Pai Road, Taipei 112, Taiwan

3 Athinoula A. Martinos Centre for Biomedical Imaging, Massachusetts General Hospital/Harvard Medical School, Charlestown, MA 02129, USA

4 Institute of Physiology, National Yang-Ming University, 155 Li-Nong Street, Section 2, Peitou, Taipei 112, Taiwan

5 Institute of Brain Science, National Yang-Ming University, 155 Li-Nong Street, Section 2, Peitou, Taipei 112, Taiwan

6 Department of Medical Research and Education, Taipei Veterans General Hospital, 201 Section 2, Shih-Pai Road, Taipei 112, Taiwan

7 Department of Ophthalmology, Taipei Veterans General Hospital, 201 Section 2, Shih-Pai Road, Taipei 112, Taiwan

*These authors contributed equally to this work.

Correspondence to: Shuu-Jiun Wang,
The Neurological Institute,
Taipei Veterans General Hospital,
201 Section 2,
Shih-Pai Road,
Taipei 112, Taiwan
E-mail: sjwang@vghtpe.gov.tw

Persistent aura without infarction, a rare migraine disorder, is defined by aura symptoms that persist for >1 week without radiological evidence of cerebral infarction. To unveil its pathophysiological mechanisms, this study used magnetoencephalography to characterize the visual cortex excitability in persistent aura by comparison with episodic and chronic migraine. We recruited six patients with persistent visual aura, 39 patients with episodic migraine [12 in ictal phase; 27 in interictal phase (with aura, $n = 9$; without aura, $n = 18$)], 18 patients with chronic migraine and 24 healthy controls. Five sequential blocks of 50 neuromagnetic prominent 100 ms responses were obtained, and the dynamic change in visual cortex excitability was evaluated by the percentage changes of individual mean prominent 100 ms amplitudes at blocks 2–5 compared with block 1, with a significant increase indicating potentiation. We found that in patients with persistent aura, there was significant potentiation during ictal periods ($P = 0.009$ and 0.006 at blocks 2 and 5, respectively), and the excitability change was inversely correlated with the duration of aura persistence (correlation coefficient -0.812 , $P = 0.050$, block 2). The interictal recordings ($n = 3$) also showed potentiation. In terms of the other migraine spectrum disorders, persistent aura differed from episodic migraine in the presence of ictal potentiation. Persistent aura further differed from chronic migraine in the absence of interictal potentiation in chronic migraine. There was a higher percentage change of response amplitude at the end of stimulation (block 5) in persistent aura (43.3 ± 11.7) than in chronic migraine (-7.6 ± 5.5 , $P = 0.006$) and ictal recordings of episodic migraine (-4.9 ± 9.6 , $P = 0.020$). Normal control subjects had no significant response changes. This magnetoencephalographic study showed that the visual cortex in patients with persistent visual aura maintains a steady-state hyperexcitability without significant dynamic modulation. The excitability characteristic supports persistent visual aura as a nosological entity in migraine spectrum disorders and suggests a pathophysiological link to sustained excitatory effects possibly related to reverberating cortical spreading depression.

Keywords: migraine; migraine with aura; chronic migraine; persistent aura without infarction; magnetoencephalography

Introduction

Migraine auras are reversible visual, sensory, motor or language deficits that typically last <1 h preceding migraine attacks (Russell and Olesen, 1996). However, the International Classification of Headache Disorders, second edition (2004), has recognized a rare condition in which the aura symptoms persist for >1 week without concomitant radiological evidence of cerebral infarction. This is referred to as 'persistent aura without infarction' (code 1.5.3). To date, only ~40 patients with persistent visual aura have been reported (San-Juan and Zermeno, 2007; Wang *et al.*, 2008), eight of which were from our group (Chen *et al.*, 2001; Wang *et al.*, 2008). Most of these patients had very frequent headache attacks, similar to chronic migraine. Further studies are needed to expand our understanding of the pathomechanisms underlying persistent visual aura.

The clinical manifestations of migraine may be related to alterations in central excitability. Evoked potential studies have shown that both migraine with aura and migraine without aura in the interictal state are characterized by the lack of habituation and that the cortical responses to repetitive sensory stimulations may be potentiated (Schoenen *et al.*, 2003; Ambrosini and Schoenen, 2006). Habituation may be protective against sensory overload and energy depletion of the cerebral cortex, which reflects the function of large-scale cortical–subcortical networks, especially those involving serotonin as a neurotransmitter (Coppola *et al.*, 2009; Rankin *et al.*, 2009). It is intriguing that during the peri-ictal or ictal state of migraine, the habituation phenomenon and serotonin transmission correspondingly normalize (Judith *et al.*, 2000; Sakai *et al.*, 2008). Magnetoencephalography is easier to use to measure cortical excitability, due to small effects of the different tissue conductivities and the lack of the 'paradoxical lateralization' in visual evoked responses (Barret *et al.*, 1976; Hämäläinen, 1993). Recently, using magnetoencephalography, our group demonstrated central excitability in episodic migraine (Chen *et al.*, 2009) and interictal habituation rather than potentiation in patients with chronic migraine (Chen *et al.*, 2011). These findings suggested a persistent ictal-like cortical excitability pattern in chronic migraine and a loss of interictal–ictal modulation during the chronification of migraine (Chen *et al.*, 2011). On the other hand, central excitability in persistent visual aura has not been well studied.

Persistent aura can be relieved clinically with the anti-convulsants divalproex sodium (Rothrock, 1997) or lamotrigine, (Chen *et al.*, 2001), suggesting a potential pathophysiological link to abnormal cerebral excitability. Further, the linkage between migraine aura and cortical spreading depression (Lauritzen, 1994) was validated in humans a decade ago (Bowyer *et al.*, 2001; Hadjikhani *et al.*, 2001). An [18]-F labelled deoxyglucose PET study of two patients with persistent visual aura showed a sustained metabolic activation in the medial occipital cortex (Mathew *et al.*, 1998). The interesting clinical observation that some patients with persistent visual aura described their positive aura symptoms as 'moving stars' or 'rippling waves' also supports central excitation in these patients (Haas, 1982; Liu *et al.*, 1995; Chen *et al.*, 2001). Because cortical spreading depression is a neuronal depolarization wave originating from the occipital cortex with

subsequent suppression of electrical activity, we have hypothesized that the visual cortex in persistent visual aura may be dominated by the sustained, recurrent excitatory activations piloting cortical spreading depression waves, which dampen the habituation phenomenon in the cerebral cortex.

To test this hypothesis, we probed visual cortex activity in patients suffering from persistent visual aura, using magnetoencephalography recordings. We especially focused on the measurement during ictal periods (acute migraine), because the presumed activation by cortical spreading depression reverberations may hinder the ictal normalization of excitability, a salient feature of episodic migraine. The specific aims of this study were to: (i) characterize the visual cortex excitability in persistent visual aura, both qualitatively (potentiation versus habituation) and quantitatively; (ii) elucidate the ictal-interictal variation of excitability change in persistent visual aura; (iii) differentiate persistent visual aura from other migraine disorders by visual cortex excitability; and (iv) identify clinically predictive factors of the excitability change.

Materials and methods

Subjects

Six migraine patients from the Headache Clinic of Taipei Veterans General Hospital were compatible with the International Classification of Headache Disorders, second edition (2004) diagnosis of persistent visual aura (code 1.5.3) and eligible to participate in this study. To characterize visual cortex excitability in these patients with persistent visual aura, this study enrolled four more groups of subjects from the same clinic: migraine without aura, migraine with aura, chronic migraine and healthy volunteers. Diagnoses of these migraine spectrum disorders were in accordance with the International Classification of Headache Disorders, second edition (2004) and the revised criteria (Olesen *et al.*, 2006).

The visual symptoms and clinical data of the patients with persistent visual aura are detailed elsewhere (Wang *et al.*, 2008) and are summarized in Table 1. All patients with persistent visual aura but one, had ≥ 15 headache days per month. The specific inclusion criteria were 1–6 migraine attacks (1–12 headache days) per month for patients with migraine without aura or migraine with aura, and ≥ 8 monthly migraine days and ≥ 15 headache days for at least 3 months for patients with chronic migraine. All patients with migraine with aura had to have a visual aura. Healthy volunteers had no past or family history of migraine. All participants were right handed and normal in physical and neurological examinations without histories of systemic or neurological diseases. Patients with medication overuse or those taking any medications or hormone replacement on a daily basis were excluded except for the two patients with persistent visual aura who used migraine preventatives (Patient 2: topiramate 100 mg/day; Patient 3: propranolol 60 mg/day and topiramate 100 mg/day) for <2 months with unchanged visual symptoms. The hospital's Institutional Review Board approved the study protocol and each participant provided written informed consent before entering the study.

All patients completed a semi-structured questionnaire on demographics and headache profile during their first visit. They also kept a headache diary after recruitment. The Migraine Disability Assessment questionnaire assessed migraine-related disability (Hung *et al.*, 2006).

Table 1 Clinical profiles of visual symptoms and headache in migraine patients with persistent visual aura (*n* = 6)

Patient	Age/sex	Description of visual symptoms	Distribution	Illness duration ^a (years)	Headache days per month	History of migraine (years)
1	25/F	TV static	BH	10	15	10
2	36/M	TV static	BH	5	30	27
3	55/F	Colorful moving light bars or spots	BH	20	30	41
4	40/F	Light flashes	RH	1	30	15
5	50/F	Light spots	BH	1 month	12	25
6	26/M	White/silver light bars	LH	1	24	13

^a Duration of aura persistence.

BH = bilateral hemifield; LH = left hemifield; RH = right hemifield.

Visual-evoked magnetic fields were recorded in each patient. The recording was rescheduled if the participant had used analgesics, triptans or ergots for any reason within the previous 48 h. Before recording, the severity of headache, if any, was rated using an 11-point (0–10) verbal numerical scale. The magnetoencephalography recordings from patients with no migraine attack within a period of 2 days before (Days –1 and –2) and after (Days +1 and +2) the recording (Day 0) were classified as 'interictal' data. The recordings from patients with acute migraine attacks during the recording (Day 0) were classified as 'ictal' data. The patients reporting migraine attacks on Days –1, –2, +1 and +2, but no headache on Day 0, were rescheduled for the magnetoencephalography measurement. Patients with chronic migraine were recorded interictally, regardless of the presence of mild background (or interval) headache. Based on the study hypothesis, the patients with persistent visual aura were recorded during ictal periods (acute migraine attacks in the presence of visual aura). However, all patients with persistent visual aura were encouraged to undergo a follow-up recording during interictal periods (no headache in the presence of aura), although it was difficult for some patients with persistent visual aura due to the high frequency of migraine attacks. The above temporal relationship between magnetoencephalography recording and migraine attacks was determined by the headache diary, telephone follow-ups and face-to-face interviews on the day of recording.

To minimize any hormonal effect, female participants were recorded in the luteal phase estimated by their last menstrual cycle and confirmed by the next menstruation according to the headache diaries or telephone interviews.

Visual stimulation

Pattern reversal white and black checkerboard stimuli were generated using Presentation 0.52 NBS (Neurobehavioral Systems, Inc.) and were projected onto a screen ~110 cm in front of the subject by an LCD projector (PLUS Vision Corporation). The checkerboard reversed every second (1 Hz) and the full pattern extended 15° (width) × 22° (height) in the left hemifield of the subject. The individual check size was 120 min of arc. The mean luminance of the checkerboard pattern was 12 cd/m², with the contrast kept at 0.94. The time lag between trigger onset and stimulus presentation on the screen was 19.0 ± 0.6 (mean ± SEM) ms; this delay was subtracted from visual-evoked magnetic field latencies.

Visual-evoked magnetic field recording, source modelling and data analysis

The methodology of this section has been detailed elsewhere (Chen *et al.*, 2009). Briefly, the subject sat in a magnetically shielded room with the head supported against the helmet-shaped bottom of a whole-scalp 306-channel neuromagnetometer (Vectorview™, Elekta Neuromag). A total of 250 visual responses were collected, with 50 responses subaveraged in five sequential blocks to evaluate the amplitude changes of visual-evoked magnetic fields (described below). Signals were band-pass filtered at 0.1–130 Hz and digitized at 500 Hz.

In source modelling, the single equivalent current dipole in a spherically symmetric conductor that best describes the measured activities (P100m) was determined. The optimal origin of the conductor model was determined by fitting a sphere to the occipital portion of the brain using the co-registered MRIs of the subject. We also superimposed the equivalent current dipole locations on the anatomical MRI to infer the cortical site corresponding to the activity. Using the P100m equivalent current dipole, a dipole amplitude time course (source waveform) was then determined for the entire response using a linear least-squares fit.

Based on the source waveforms of the grand-averaged (250 responses) and subaveraged (50 responses) responses, peak latency and baseline-to-peak amplitude of P100m were obtained. The amplitude of block 1 (initial block) was assumed as the initial excitability of the visual cortex. To assess the habituation behaviour of the visual cortex, percentage changes of amplitude in blocks 2–5 compared with block 1 were calculated and referred to as 'sub-averaged amplitude change'. All visual-evoked magnetic fields data were presented as mean ± SEM.

Statistical analysis

Group differences in clinical profiles or the magnetoencephalography data were analysed by Student's *t*-test, one-way ANOVA or non-parametric Mann–Whitney U test when appropriate. For subaveraged visual-evoked magnetic fields data, the amplitude of block 5 was compared with that of block 1 by the paired *t*-test to identify the trend of visual-evoked magnetic fields change in each subject group. A significant amplitude increase in block 5 was regarded as a potentiation, while a decrease was considered a habituation phenomenon. A group difference of subaveraged visual-evoked magnetic fields data were also evaluated by two-way ANOVA with repeated measures, using the trial block as a within-subject factor and the subject group as a between-subject factor. *Post hoc* analyses for the above comparisons

were conducted using the least square difference test. The Pearson's or non-parametric Spearman's correlation test was used to examine the correlations between subaveraged amplitude changes and clinical profiles. For all analyses, the level of significance was set at $P < 0.05$.

Results

Eighty-seven subjects completed this study and were grouped by clinical diagnosis and headache phases: (i) persistent visual aura ($n = 6$, ictal phase, mean age \pm SD 38.7 ± 12.2 years); (ii) interictal migraine without aura ($n = 18$, 36.9 ± 7.4 years); (iii) interictal migraine with aura ($n = 9$, 39.8 ± 11.8 years); (iv) ictal migraine without aura and migraine with aura ($n = 12$, 35.3 ± 7.0 years); (v) chronic migraine ($n = 18$, interictal phase, 37.7 ± 7.7 years); and (vi) healthy controls ($n = 24$, 38.9 ± 9.6 years). All groups were sex-matched (female:male = 2:1) and their ages were not statistically different. Clinical profiles were comparable among patient groups, except the higher headache frequency and Migraine Disability Assessment score in the persistent visual aura and chronic migraine groups (both $P < 0.001$, one-way ANOVA) (Table 2). The mean ratings of headache intensity (0–10) during the recording were 6.4 ± 1.8 in ictal migraine, 0.8 ± 1.0 in chronic migraine (without migraine attacks) and 6.7 ± 1.8 in persistent visual aura. In all subjects, the P100m dipole was oriented medially with common source localization in the vicinity of the right striate cortex.

The parameters of grand averaged P100m for patients with persistent visual aura are shown in Table 3. On stimulus repetition, P100m amplitudes at blocks 2–5 were significantly increased compared with block 1 ($P = 0.009$ and 0.006 at blocks 2 and 5, respectively), suggesting a potentiation (Table 4). The subaveraged amplitude change at block 2 tended to correlate negatively with illness duration (the number of months of aura persistence) (correlation coefficient = -0.812 , $P = 0.050$, Spearman's correlation). There was no difference in any P100m parameter between subgroups of patients with persistent visual aura dichotomized by gender, headache frequency (≥ 15 versus < 15 days/month), presence of TV static or distribution of the visual symptoms (bilateral versus unilateral hemifield) (Mann–Whitney U test).

Three patients with persistent visual aura (Patients 1, 2 and 6 in Table 1) also underwent interictal recordings (no headache in the presence of aura) to provide both ictal and interictal data for further comparisons. The mean peak latency (ms) and amplitude (nAm) of P100m were 96.3 ± 1.3 , 50.0 ± 7.5 for ictal and 92.7 ± 1.5 , 47.0 ± 5.6 for interictal recordings. There was consistent response augmentation of P100m at blocks 2–5 in both periods; the subaveraged amplitude changes were 36.5 ± 16.9 , 26.5 ± 7.9 , 33.3 ± 15.2 and 36.3 ± 11.6 in interictal, and 24.2 ± 11.0 , 34.7 ± 7.5 , 25.3 ± 4.2 , and 29.7 ± 6.2 in ictal recordings.

Compared with the other five groups, the patients with persistent visual aura tended to have an early and intense P100m response, although the difference did not reach significance (Table 3). The source waveform in one selected subject from each group is shown in Fig. 1A. At the initial block, there was an overall difference across groups in the mean amplitudes of P100m ($P = 0.034$, one-way ANOVA), but persistent visual aura did not differ from other groups in the *post hoc* least square difference tests (results shown in Table 4).

On stimulus repetition, there was also potentiation in interictal migraine without aura ($P = 0.010$ and 0.007 for blocks 3 and 5, respectively) and interictal migraine with aura ($P = 0.014$ and 0.012 for blocks 2 and 5, respectively), but no change in the controls, ictal migraine and chronic migraine. Subaveraged amplitude changes at blocks 2–5 were consistently higher in the persistent visual aura group than in the other groups (Fig. 1B). There was a group difference in subaveraged amplitude changes [$F(5,81) = 4.0$, $P = 0.003$, two-way ANOVA with repeated measures]. The block effect and Group \times Block interaction were not significant. At block 5, the subaveraged amplitude change in persistent visual aura (43.3 ± 11.7) was higher than in ictal migraine (-4.9 ± 9.6 , $P = 0.020$) and chronic migraine (-7.6 ± 5.5 , $P = 0.006$).

In contrast with patients with persistent visual aura, there was no correlation between the P100m parameters and any clinical profiles in the other subject groups.

The analysis merging interictal migraine without aura and interictal migraine with aura together yielded findings similar to those above, except the difference in the subaveraged amplitude change at block 5 between the persistent visual aura and control groups (5.4 ± 4.3 , $P = 0.038$).

Table 2 Headache profiles (mean \pm SD) of patients with persistent visual aura (PA), interictal migraine without aura (MO), interictal migraine with aura (MA), acute migraine attack (ictal migraine) and chronic migraine (CM)

	PA	Interictal MO	Interictal MA	Ictal migraine	CM
Female/male (n)	4/2	12/6	6/3	8/4	12/6
Age (years)	38.7 ± 12.3	36.9 ± 7.4	39.8 ± 11.8	35.3 ± 7.1	37.7 ± 7.7
Mean length of migraine history (years)	21.5 ± 11.4	14.2 ± 7.7	16.7 ± 10.1	13.5 ± 7.1	15.1 ± 8.6
Mean severity of migraine (0–10)	7.5 ± 1.8	6.7 ± 1.4	6.2 ± 0.9	7.0 ± 1.8	6.4 ± 1.6
Mean duration of migraine attack (h)	30.0 ± 17.8	17.3 ± 10.9	20.0 ± 13.4	19.5 ± 14.7	18.3 ± 10.6
Mean headache days per month	$23.5 \pm 8.1^*$	4.6 ± 2.7	4.0 ± 2.0	4.6 ± 3.4	$19.5 \pm 5.7^*$
Mean MIDAS score (0–270)	60.8 ± 57.4	11.7 ± 9.4	10.8 ± 7.2	10.7 ± 11.9	$66.3 \pm 58.4^{**}$

* $P < 0.001$ versus interictal migraine without aura, interictal migraine with aura and ictal migraine. ** < 0.05 versus interictal migraine without aura, interictal migraine with aura and ictal migraine.

0–10 = numerical scale; MIDAS = Migraine Disability Assessment Questionnaire.

Table 3 The mean (\pm SEM) peak latency (ms), peak amplitude (nAm) and localization (x, y, z coordinate values) of the P100m response elicited by checkerboard reversals in the patients with persistent visual aura (PA), interictal migraine without aura (MO), interictal migraine with aura (MA), acute migraine attack (ictal migraine), chronic migraine (CM) and the healthy controls

Group	Latency	Amplitude	x	y	z
PA	94.5 \pm 1.5	40.0 \pm 6.1	19.0 \pm 3.6	-45.0 \pm 1.6	45.4 \pm 1.3
Interictal MO	98.9 \pm 1.2	31.1 \pm 2.5	20.7 \pm 2.4	-46.1 \pm 1.6	47.3 \pm 1.3
Interictal MA	99.6 \pm 2.0	31.7 \pm 2.8	19.1 \pm 2.7	-42.9 \pm 2.0	49.6 \pm 1.7
Ictal migraine	101.6 \pm 1.2	38.6 \pm 3.6	20.0 \pm 1.6	-43.8 \pm 2.0	49.6 \pm 1.2
CM	98.0 \pm 1.3	36.0 \pm 2.8	19.4 \pm 1.8	-46.3 \pm 1.9	48.0 \pm 1.7
Healthy control	99.1 \pm 1.5	32.7 \pm 2.3	19.6 \pm 1.3	-45.9 \pm 1.9	47.2 \pm 1.0

The positive x-, y- and z-axes go towards the right pre-auricular point, nasion and head vertex, respectively.

Table 4 Mean (\pm SEM) amplitude (nAm) of the P100m source obtained in the five sequential blocks in the patients with persistent visual aura (PA), interictal migraine without aura (MO), interictal migraine with aura (MA), acute migraine attack (ictal migraine), chronic migraine (CM) and the healthy controls

Block	PA	Interictal MO	Interictal MA	Ictal migraine	CM	Healthy control
1**	34.6 \pm 6.2	28.6 \pm 2.4	27.8 \pm 3.6	41.3 \pm 4.0	38.9 \pm 3.9	31.7 \pm 2.1
2	42.1 \pm 6.5*	32.3 \pm 2.5	35.0 \pm 4.5*	39.6 \pm 3.7	39.6 \pm 4.0	33.1 \pm 2.5
3	42.8 \pm 7.3	32.9 \pm 3.2*	31.5 \pm 2.7	41.5 \pm 3.8	37.7 \pm 2.9	34.5 \pm 2.2
4	38.7 \pm 7.2	30.6 \pm 2.1	31.0 \pm 3.1	37.4 \pm 4.0	36.3 \pm 2.8	34.2 \pm 2.6
5	47.9 \pm 7.7*	32.9 \pm 2.7*	33.2 \pm 3.4*	37.9 \pm 3.8	33.9 \pm 2.5	33.6 \pm 2.7

* $P < 0.05$ versus block 1. ** $P = 0.034$ for overall difference across groups (one-way ANOVA) (*post hoc* least square difference test: $P < 0.05$ for ictal migraine versus interictal migraine without aura or interictal migraine with aura or control and chronic migraine versus interictal migraine without aura or interictal migraine with aura).

Discussion

Visual cortex excitability of persistent aura without infarction and differentiation from other migraine disorders

The main finding of this study is the visual cortex hyperexcitability of patients with persistent visual aura whose P100m responses to repetitive visual stimulations showed significant potentiation. The excitability change persisted across ictal–interictal periods and was inversely correlated with the duration of illness.

The potentiation pattern in persistent visual aura was also found in interictal migraine with and without aura; however, it was not observed during the ictal migraine state, suggesting the excitability change in migraine with and without aura differs from that of persistent visual aura in terms of ictal–interictal modulations. As with the ictal migraine, interictal chronic migraine did not show a response potentiation, which was compatible with our previous finding of an ictal-like excitability change in chronic migraine (Chen *et al.*, 2011). Persistent visual aura can be further differentiated from chronic migraine and ictal migraine in excitability by degree of potentiation. Therefore, the findings of the present and our two earlier magnetoencephalography studies suggest that persistent visual aura is a separate nosological entity in the migraine spectrum (Table 5).

The excitability change in persistent aura without infarction may be linked to sustained cortical spreading depression reverberations

The present finding of persistent hyperexcitability across ictal–interictal phases suggests that sustained cortical spreading depression reverberations might be the culprit in persistent visual aura. We hereby provide two possible reasons why a vicious cycle of sustained cortical spreading depression is formed in persistent visual aura. First, persistent potentiation in persistent visual aura may lead to enduring and excessive neuronal stress, and the accumulation of metabolites such as lactate and protons that may induce repetitive cortical spreading depression (Scheller *et al.*, 1992). Given the protective nature of habituation, persistent potentiation leads to brain sensory overload, depletes the cortical energy reserve and finally leads to neuronal stress and a biochemical shift that triggers cortical spreading depression (Coppola *et al.*, 2009; Rankin *et al.*, 2009). On the other hand, the excitatory waves piloting each cortical spreading depression propagation and the detrimental effects of repetitive cortical spreading depression upon intracortical inhibition (Kruger *et al.*, 1996) may upregulate cerebral excitability and eventually increase vulnerability to cortical spreading depression (Holland *et al.*, 2010). The association between cortical spreading depression and

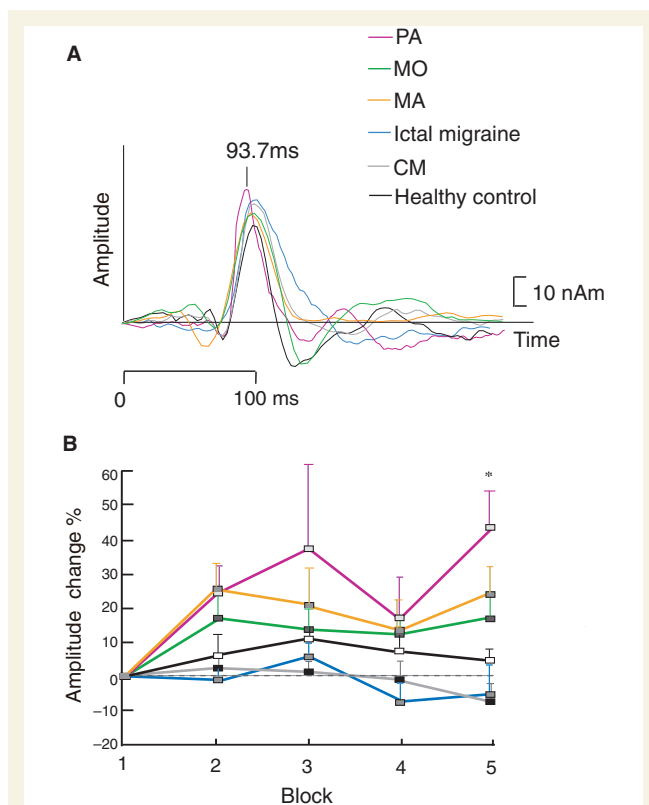


Figure 1 (A) The grand average of P100m waveforms (250 responses). Each tracing depicts one selected subject from each of the six study groups: persistent visual aura (PA), interictal migraine without aura (MO), interictal migraine with aura (MA), ictal migraine, chronic migraine (CM) and healthy controls. Note the heavy overlap of all tracings. The latency value denotes the peak latency of P100m obtained from the selected patient with persistent visual aura. (B) Percentage changes of subaveraged P100m amplitudes (mean + SEM) at blocks 2–5 compared with the initial block (block 1) in patients with persistent visual aura, migraine without aura, migraine with aura, ictal migraine, chronic migraine and healthy controls. The six groups had different trends of subaveraged amplitude changes during visual stimulation [$F(5,81) = 4.0, P = 0.003$, two-way ANOVA with repeated measures]. * $P < 0.05$ for PA versus ictal migraine and PA versus CM.

hyperexcitability here is further supported by a clinical observation that ~45% of patients with persistent visual aura had worsening headache during aura persistence (Wang *et al.*, 2008).

Despite PET evidence of sustained metabolic activation in the medial occipital cortex with persistent visual aura, there was no corresponding metabolic change during a typical migraine aura (Andersson *et al.*, 1997). Therefore, single cortical spreading depression propagation *per se* (hence migraine aura) cannot explain the persistent potentiation in persistent visual aura. The culprit should be, again, the complex interaction between cortical spreading depression reverberations and central excitability. The entanglement between central excitability and cortical spreading depression reverberations may further explain the lack of

Table 5 Visual cortex excitability characterized by magnetoencephalography in persistent visual aura, episodic migraine (migraine with or without aura) and chronic migraine

	Interictal excitability	Ictal excitability
Episodic migraine (with/without aura)	Potentiation	Habituation or no change ^a
Chronic migraine	Habituation or no change ^a	Habituation or no change ^a
Persistent visual aura	Potentiation	Potentiation

The comparison is based on the present and two earlier magnetoencephalography studies (Chen *et al.*, 2009, 2011) using checkerboard reversals to obtain percentage changes of P100m amplitudes as a measure of visual cortex excitability. Potentiation indicates significant response augmentation on stimulus repetitions while habituation denotes response attenuation.

^a The degree of habituation is dependent on stimulation methods [e.g. temporal frequency, as discussed in Chen *et al.* (2009)].

correlation between magnetoencephalography and most clinical measures.

The clinical course and consequences of persistent aura without infarction

The sensory overload and energy crisis resulting from persistent central excitation in persistent visual aura is in line with a phosphorus magnetic resonance spectroscopy (³¹P-MRS) study showing a severe interictal decrease in cortical energy reserve in these patients (Schulz *et al.*, 2007). It is intriguing that the same authors also used magnetic resonance spectroscopy to show normal cortical energy metabolism in patients with migrainous stroke, suggesting different pathomechanisms between migrainous infarction and persistent visual aura (Schulz *et al.*, 2009). In agreement with that study, the present study also implicates the non-progressive nature of the excitability change in persistent visual aura due to its negative correlation with duration of persistent visual aura. The finding partly rationalizes why persistent visual aura, albeit a chronic and intractable clinical course, is not jeopardized by an energy crisis leading to eventual neuronal death or ischaemic infarction. The possibility of a shattered, disorganized cortical spreading depression after long-term reverberations (Wang *et al.*, 2008) makes the above speculation even more explicable.

Is persistent aura without infarction a severe form of migraine with aura?

The above link of persistent hyperexcitability to cortical spreading depression reverberations suggests that persistent visual aura, in terms of cortical spreading depression frequency, is a form of migraine with aura with extreme severity. Note the interictal recordings of three patients with persistent visual aura (data shown in Results section) are more potentiated than those of patients with migraine with aura (data in Fig. 1B) at blocks 3–5. In line with this, the interictal decrease of cortical energy reserve in migraine with

aura investigated by ^{31}P -MRS showed a dose–response relationship between aura severity and cortical energy metabolism, suggesting that persistent visual aura is the most severe form of migraine with aura, with the lowest energy reserve (Schulz *et al.*, 2007). Nevertheless, there still may exist a qualitative difference in central excitabilities between persistent visual aura (ictal hyperexcitability) and migraine with aura (ictal normalization), which is not explicable simply by the quantitative differences. The ictal normalization effect upon excitability, after all, seems more salient than the interictal excitability difference between persistent visual aura and migraine with aura (Fig. 1B). Therefore, the above-mentioned physiological consequence of cortical spreading depression reverberations, such as down-regulated intracortical inhibition, should be taken into account. This inference somewhat echoes the International Classification of Headache Disorders (2004), categorizing persistent visual aura as a complication of migraine rather than a severe form of migraine with aura.

On the other hand, the observation that persistent visual aura is intractable to various migraine preventatives (San-Juan *et al.*, 2007) is probably also against a continuum between migraine with aura and persistent visual aura. Migraine preventatives can suppress cortical spreading depression in animal models (Ayata *et al.*, 2006; Bogdanov *et al.*, 2011). The intractability of persistent visual aura, again, may be explicable by long-term neuroplasticity brought on by cortical spreading depression reverberations because a shorter illness duration of persistent visual aura predicts a better clinical outcome (Wang *et al.*, 2008).

Caveats and limitations

We recognize that the number of patients with persistent visual aura studied here is small, which is due to disease rarity. Since the magnetoencephalography data obtained in such a small patient group varied considerably (Supplementary Table 1) and overlapped with those from other patient groups, the present methodology cannot be used clinically for the diagnosis of persistent visual aura. Moreover, the causative connection between cortical spreading depression and migraine aura is not completely conclusive, which may render the link of persistent visual aura to cortical spreading depression reverberations here somewhat speculative. It is possible that cortical spreading depression just represents one manifestation of cellular and intercellular functional changes such as glial calcium waves that occur diffusely in the brain (Charles *et al.*, 1991; Scemes and Giaume, 2006; Charles, 2010). However, given the experimental and clinical evidence accumulated so far, it is challenging to postulate a mechanism for migraine aura that accounts for all the observations without implicating cortical spreading depression (Ayata, 2010).

It is impractical for the present methodology to obtain a complete magnetoencephalography recording in the presence of a typical aura. The ictal effects on excitability may occur as long as 1 day in advance (Judit *et al.*, 2000). Therefore, we are unable to verify the pathophysiological link of persistent visual aura to cortical spreading depression reverberations by elucidating

the effects of a single cortical spreading depression propagation (hence a typical migraine aura) upon central excitability. We are planning to follow up magnetoencephalography recordings after resolution of persistent visual aura, which may help disentangle this puzzling issue and reconfirm the present findings.

The control subjects and the patients with ictal migraine and chronic migraine did not show significant habituation, as in our previous magnetoencephalography study (Chen *et al.*, 2011). This may be due to the lower reversal rate of the visual stimuli in the present study, which may have decreased the degree of habituation. The higher reversal rate was avoided here because various types of visual distortions, illusions and adverse effects may occur in patients with migraine with aura and persistent visual aura (Huang *et al.*, 2003), rendering the recording condition inhomogeneous across groups. On the other hand, we believe the lower reversal rate is validated for the aims of the present study, because most of the excitability features of chronic migraine obtained from the previous study (Chen *et al.*, 2011) were replicated here, including P100m parameters comparable with those of ictal migraine, and a higher block 1 amplitude than that of interictal migraine without aura and migraine with aura. The above, again, suggests that the excitability change in migraine can be addressed in quantity (degree of response augmentation) or in quality (habituation versus potentiation) (Chen *et al.*, 2009).

Another caveat is left hemifield visual stimulation, which elicits responses in the right visual cortex only. This may bias data interpretation if there is asymmetry of central excitability. Although visual-evoked potential asymmetry remains a controversial issue in migraine without aura (Tagliati *et al.*, 1995; Shibata *et al.*, 1997; Logi *et al.*, 2001), some reports do note visual-evoked potential asymmetry in migraine with aura (Tagliati *et al.*, 1995; Shibata *et al.*, 1997). To date, however, there is no evidence of visual-evoked magnetic field asymmetry in either migraine without aura or migraine with aura. It is unknown whether habituation differs in bilateral hemispheres. Moreover, the majority of our migraine patients reported their headache and aura symptoms (if present) were alternately sided or bilateral rather than side locked (data not shown). On the other hand, physiological nystagmus or small deviations of eye fixation may occur during visual stimulation, despite cueing by a fixation point and monitoring of eye movements. However, the results of the source modelling confirmed our fixation control, since cortical activation was adequately explained by a dipole located near or around the right striate cortex.

Conclusion

Persistent visual aura is characterized by persistent hyperexcitability of the visual cortex without interictal-ictal variation, compatible with the excitatory effect of sustained reverberations of cortical spreading depression. Our magnetoencephalography data on the excitability changes in the visual cortex differentiates persistent visual aura from other migraine disorders (migraine with aura, migraine without aura and chronic migraine). Therefore, while

belonging to the migraine spectrum, persistent visual aura may be considered a distinct disorder.

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Supplementary material

Supplementary material is available at *Brain* online.

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