Migraine aura: new ideas about cause, classification, and clinical significance

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Purpose of review
The migraine aura is a dramatic spontaneous change in brain activity resulting in a variety of transient neurological symptoms. The purpose of this review is to address recent advances in the understanding of aura and its role in migraine.

Recent findings
The formal classification of migraine aura is becoming both broader and more detailed. Traditionally viewed as a primary event that triggers a migraine attack, studies regarding the timing of aura relative to other symptoms of migraine indicate that it may not in fact play a primary role in initiating an attack. Careful recording and analysis of visual aura symptoms provides new insight into the initiation and propagation of the underlying brain phenomenon, and the different regions of visual cortex that produce different visual perceptions. Migraine with aura may have different responses to acute and preventive therapies.

Summary
There has been significant evolution of concepts regarding the causes of migraine aura, how it is best defined, and how it fits into the picture of the migraine disorder as a whole. Regardless of its exact role in the genesis of migraine, an increased understanding of aura has the potential to provide important new insight into not only migraine but also fundamental mechanisms of brain physiology.

Keywords
brainstem, cortex, headache, spreading depression, therapy

INTRODUCTION

Migraine aura is defined as transient neurological symptoms that occur and spread gradually, and either precede or accompany the onset of headache. About a third of patients with migraine have attacks with aura [1]. In migraine with typical aura, the most prevalent aura symptoms are visual disturbances [2]. Other symptoms are quite common [3▪▪] and may include sensory, speech/language, and motor symptoms or even disturbances of higher cortical function such as difficulty thinking or concentrating [4▪].

MIGRAINE AURA CLASSIFICATION

The clinical features of migraine aura that are included in the formal migraine classification [International Classification of Headache Disorders (ICHD)] have changed over time. In the first version, ICHD-1 [5], migraine aura was defined as cortical or brainstem symptoms. In ICHD-2 [6], specific symptoms were identified, including disturbances of vision, sensation, and language. In the current version (ICHD-3 β), brainstem symptoms are included in the definition of migraine aura (with removal of the classification of basilar migraine), as are motor symptoms that occur in the case of familial hemiplegic migraine [3▪▪]. The current ICHD also includes monocular visual symptoms, classified as retinal migraine.

The visual, sensory, language, and motor symptoms are consistent with a wave of altered brain activity that spreads slowly across the cortex. Since shortly after its original description by Leão [7],

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KEY POINTS

- The formal classification of migraine aura now includes visual, sensory, language, motor, brainstem, and retinal symptoms.
- The timing of aura relative to headache and premonitory symptoms raises further questions about its role in the initiation of headache.
- Detailed characterization of migraine visual aura symptoms in a single individual reveals multiple sites of onset in the visual cortex and nonconcentric spread of wave of cortical activity.
- The presence and features of clinical symptoms of the migraine aura vary depending on the region of the cortex through which the wave is traveling.
- Migraine with aura may have a different response to acute and preventive therapy as compared with migraine without aura.

cortical spreading depression (CSD) has been hypothesized to be the physiological mechanism underlying the migraine visual aura [8], although the occurrence of CSD as a cause of migraine aura has yet to be definitively demonstrated. It has also been speculated that the monocular symptoms could be caused by a spreading depression event in the retina with associated vasoconstriction [9]. The mechanisms underlying brainstem aura symptoms are less clear. Spreading depression can be elicited in the brainstem in animal models, but the conditions required to trigger it are more extreme than those that trigger spreading depression in the cortex [10]. Brainstem aura symptoms are particularly common in familial hemiplegic migraine [11], suggesting that a specific genetic susceptibility may be required in order for aura mechanisms to involve the brainstem.

Another change in the ICHD-3 β is the removal of the classification 'migraine with prolonged aura' to describe aura symptoms lasting more than 1 h. Such attacks are now classified as 'probable migraine with aura'. It is not uncommon, however, for aura symptoms to last longer than 60 min; this is particularly the case for sensory or language aura symptoms [12].

Consistent throughout the classifications is the definition that a diagnosis of migraine with aura requires at least two attacks meeting the remainder of the diagnostic criteria. A significant majority of patients who have a diagnosis of migraine with aura also have attacks (and therefore a diagnosis) of migraine without aura. This underscores a fundamentally important and unanswered question: what are the mechanisms by which aura occurs in some attacks but not others in the same individual?

The common co-occurrence of migraine with aura and without aura in the same patient also creates issues for the design and interpretation of clinical studies. In many epidemiological studies and clinical trials, patients are assigned a diagnosis of migraine either with or without aura, when in fact many of the patients assigned to the migraine with aura category have both. This may confound distinctions between the two groups. It is preferable for clinical studies to categorize patients as having migraine with aura only when a majority of their attacks include aura, in order to more accurately determine the clinical significance of a diagnosis of migraine with aura [13].

DOES MIGRAINE AURA TRIGGER HEADACHE?

The fact that aura is a variable feature of a migraine attack for many patients raises questions about whether it plays an essential role in triggering headache. Although it is possible that the brain phenomenon underlying aura could occur without generating clinical symptoms ('silent aura' – see next section), it seems more likely that this phenomenon is in fact not occurring at all in the majority of migraine attacks. It is also common for aura to occur without subsequent headache, particularly in older men [2]. Thus, aura is neither necessary nor sufficient for headache.

Recent studies also suggest that the timing of aura relative to headache may not be as consistent as previously believed [14]. Examination of the results of a clinical trial that prospectively recorded aura symptoms in conjunction with other migraine attack symptoms found that a majority of patients reported headache, as well as other defining migraine symptoms at the same time that they reported onset of aura. These results contradict the widely held idea that migraine aura consistently precedes headache.

The occurrence of premonitory symptoms prior to any other migraine symptoms also suggests that aura is not a primary trigger for a migraine attack. During premonitory symptoms, changes in brain activity can be seen on PET scans even hours before headache – thus occurring at a time clearly preceding classical aura [15▪▪]. A recent study investigated interictal resting-state functional brain connectivity in migraine with aura patients and found no abnormalities of intrinsic brain connectivity [16]. Taken together, these observations indicate that the aura is not a fundamental initiating event of a migraine attack. Rather, it seems more likely that the aura is a variable component of an aberrant 'brain state' that occurs during a migraine attack [17].

INITIATION AND PROPAGATION OF AURA SYMPTOMS: INSIGHTS FROM CLINICAL OBSERVATIONS

Detailed recordings of the visual percept of migraine aura have led to new insight into its initiation and propagation. There is a long history of drawing of aura phenomena by individuals, including the drawings done by Lashley that led to the initial understanding that one form of visual aura, the 'fortification spectrum', is caused by a slowly propagated wave in the correlated retinotopic representation in the visual cortex [18,19]. Recently, a unique set of aura drawings done by a single individual has added substantially to this understanding [20▪▪] (Fig. 1). This individual traced the visual aura wavefront at 1-min time intervals for more than 1000 attacks. A number of interesting conclusions can be drawn from this dataset. First, there are multiple sites of initiation of auras in both the visual fields, indicating that auras do not necessarily originate from a single consistent cortical focus in a given individual. Second, while a typical aura spread throughout one entire visual field, others were 'aborted' after only several minutes of spread. This implies that the aura phenomenon may not necessarily be an all or none process. It suggests that either the initiating stimulus may vary in intensity or there may be variability in the permissiveness of the cortex to the spread of the underlying phenomenon. Third, the paths and rates of propagation of the visual percept were consistent throughout the entire course of spread, and regardless of the direction of spread. This indicates preferred and consistent paths of propagation, regardless of whether the phenomenon started centrally or peripherally in the visual cortex. Fourth, when the visual phenomenon

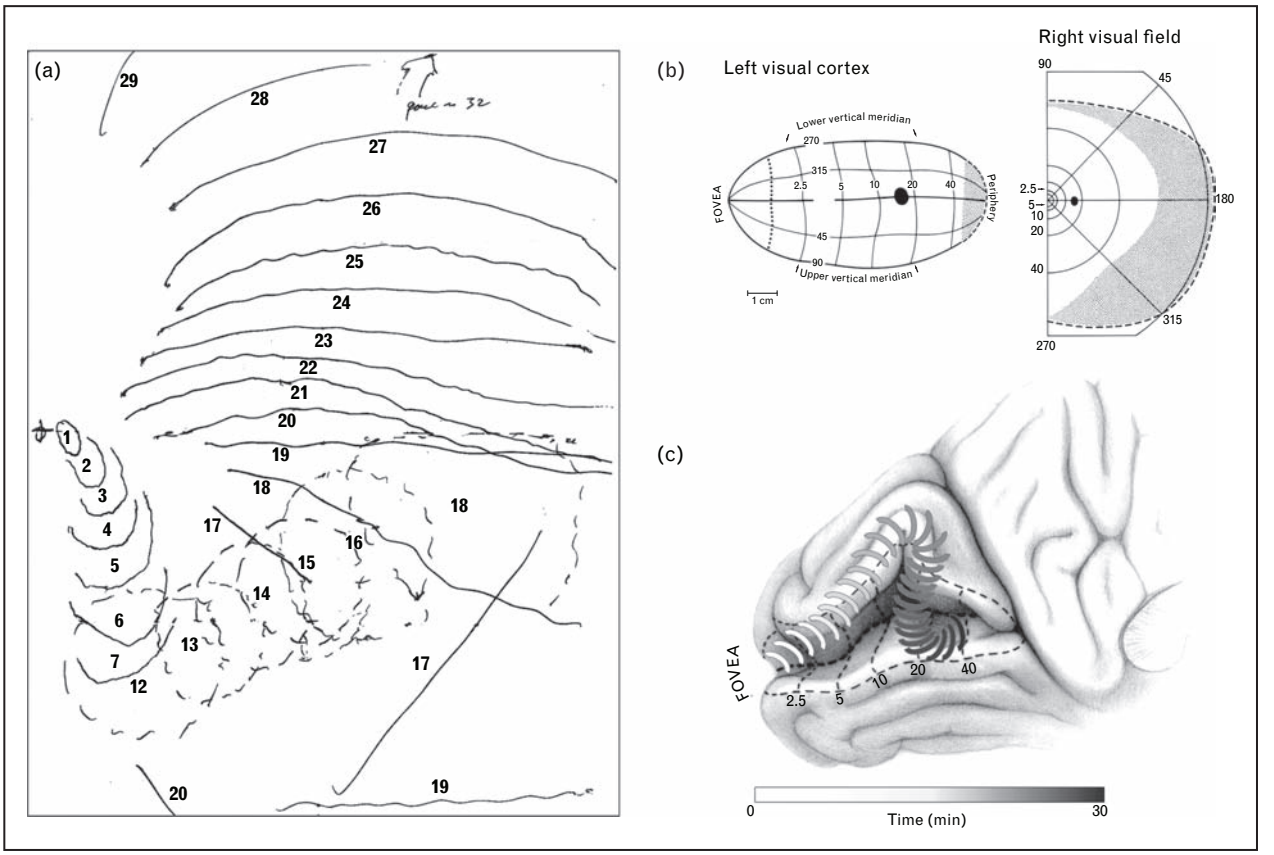

FIGURE 1. Mapping of visual aura symptoms onto visual cortex. (a) Drawing of migraine aura propagation. Solid lines represent the wavefront of a typical scintillating scotoma. Dotted lines represent a scotoma without scintillation. The positive visual phenomenon tracks toward the vertical meridian, disappears for several seconds, reappears as a scotoma, and then reappears as a positive phenomenon that propagates to the periphery. (b) Representation of the retinal visual fields on the visual cortex (unfolded occipital lobe). (c) Hypothesized propagation of the aura visual phenomenon drawn in (a) onto an idealized visual cortex. The visual phenomenon of the migraine aura is consistent with a relatively narrow wavefont that propagates along a gyrus or sulcus. When the visual phenomenon crosses from the V1 to the V2 region of the occipital cortex, it disappears transiently for several minutes, and then becomes a scotoma while the wave is propagating in V2. When the phenomenon re-enters V1, it reappears as a scintillating wavefront. Reproduced with permission from [20▪▪].

approached the vertical meridian consistent with the cortical wave crossing from the V1 to the V2 region of the visual cortex, the visual percept changed from a scintillating wavefront to a scotoma. This observation indicates that the positive and negative symptoms of migraine aura may be caused by not only the physiological features of the underlying cortical wave but also the functional anatomy of the brain region through which this wave is traveling. Fifth, in some cases, the visual phenomenon disappeared for a few minutes, and then reappeared in a location consistent with 'silent' propagation of the cortical wave. This observation provides evidence for the possibility of 'silent aura'. Finally, the pattern of propagation of the visual phenomenon is consistent with that of a relatively narrow wavefront propagating along a sulcus or gyrus, rather than a concentric 'pebble in a pond' cortical spread as is commonly represented. It is interesting to note that this gyral or sulcal pattern of propagation is not necessarily what is observed with functional imaging studies of blood flow during migraine, which may show broad waves of altered blood flow spanning multiple gyri. This discrepancy indicates that blood flow changes may occur on a much broader spatial scale than the changes in visual cortical activity that are correlated with aura symptoms [21,22].

In light of the findings described earlier, it is interesting to consider how the aura might spread from the visual cortex to other brain regions. When more than one aura symptom is reported, they often occur in succession [2] suggesting that the brain phenomenon underlying aura may spread in contiguous fashion from one region of cortex to another. Assuming a continuous gyral or sulcal pattern of spread, it is not straightforward to map a path from visual cortex to somatosensory cortex to language cortex [23]. Extensive cortical propagation in association with clinical symptoms has not been unequivocally demonstrated in migraine with aura patients. MRI studies of patients with visual aura found that regional cerebral blood flow [24] and blood oxygen level dependent signal [25] changes during aura were confined to the visual cortex. Multifocal origination of migraine aura is possible; this was reported for hemiplegic migraine in which regional cerebral blood flow studies during spontaneous migraine aura found oligemia in the frontal lobe, independently of posterior oligemia [26].

In individuals with brainstem symptoms, it is also unclear whether there is spread of changes in brain activity from cortex to brainstem, or if changes are occurring in parallel in each brain region. Functional imaging studies now have the capacity to visualize in detail the propagation of changes in brain activity associated with migraine aura symptoms, but as yet none have captured spread from one region of cortex directly correlated with migraine aura symptoms. Such a study is critical in order to more definitively understand the propagation of brain changes underlying the variety of neurological symptoms that migraine aura may cause.

In addition to the different neurological symptoms experienced in attacks of migraine with aura, these attacks may be have other clinical features including different responses to therapeutic interventions. Recent analysis of data from a large clinical trial database examined the relative efficacy of sumatriptan in migraine with aura vs. without aura [27]. This study found that sumatriptan was less effective as an acute therapy for migraine with aura vs. without aura, based on the 2-h pain-free endpoint. In addition, the study found that patients who were entered in clinical trials with a diagnosis of migraine with aura showed reduced efficacy of sumatriptan as compared with those whose diagnosis was migraine without aura. Interestingly, analysis of a single large trial of inhaled dihydroergotamine as an acute therapy for migraine found that it was equally effective for attacks of migraine with vs. without aura. These results indicate that different responses of migraine with aura vs. migraine without aura to acute therapies have the potential to influence the outcome of clinical trials for specific medications.

In most individuals, aura symptoms are not sustained or severe, and therefore do not require specific therapy. For some, however, the duration and severity of aura symptoms leads to substantial disability. For these patients, specific treatments for aura have been investigated. A randomized, controlled study of intranasal ketamine found that it reduced the severity but not the duration of prolonged aura [28]. A smaller, uncontrolled study found that in some patients with hemiplegic migraine, ketamine reduced both the severity and the duration of aura [29].

There have also been some studies of preventive therapies that have indicated different efficacy for migraine with aura vs. migraine without aura. The medication tonabersat was found to be ineffective as an acute or preventive therapy for migraine without aura [30,31], but a small study indicated that it was effective in reducing migraine with aura attacks [32]. Similarly, a recent study of patent foramen ovale (PFO) closure as a preventive therapy for migraine (NCT00505570) indicated that although the procedure did not reduce the number of migraine days (primary endpoint), PFO closure did significantly reduce migraine days with aura [33]. The pathophysiological basis for this difference is unclear. A

number of studies have suggested an association between migraine, and particularly migraine with aura, with PFO [34–37]. CSD, the wave of cortical activity believed to be the physiological substrate of the migraine aura, can be triggered by particulate or air emboli in rodent models, leading to the speculation that emboli passing from the right to the left heart through a PFO could trigger CSD and therefore aura [38]. If this were the case, however, it would mean that an embolic mechanism would be a trigger for only some, but not all, attacks.

CONCLUSION

The migraine aura is a unique event: a spontaneous, episodic, often reproducible alteration in brain activity. It therefore provides an important window not only in to brain function, particularly in the visual cortex, but also in the sensory and motor cortex and brainstem. It can also lead to critical new understanding of anatomical and physiological changes that occur during a migraine attack, and is a clinical feature that may predict response to specific therapies. Careful and systematic observation, by both individuals and clinical investigators, as well as electrophysiological and functional imaging studies continue to provide opportunities for significant new insight into the mechanisms of aura and its significance as a common brain phenomenon.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Russell MB, Rasmussen BK, Thorvaldsen P, *et al.* Prevalence and sex-ratio of the subtypes of migraine. Int J Epidemiol 1995; 24:612–618.
2. Eriksen MK, Thomsen LL, Andersen I, *et al.* Clinical characteristics of 362 patients with familial migraine with aura. Cephalalgia 2004; 24:564–575.
3. ■■ IHS. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013; 33:629–808.

This article is not only an essential document for headache classification but also a useful review of clinical characteristics of headache.

4. ■ Petrusic I, Zidverc-Trajkovic J, Podgorac A, *et al.* Underestimated phenomena: higher cortical dysfunctions during migraine aura. Cephalalgia 2013; 33:861–867.

An interesting study describing the cortical dyfunctions that are not included in the definition of migraine aura, but are nonetheless commonly observed in patients.

5. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Headache Classification Committee of the International Headache Society. Cephalalgia 1988; 8 (Suppl 7):1–96.
6. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004; 24 (Suppl 1):9–160.
7. Leão AAP. Spreading depression of activity in the cerebral cortex. J Neurophysiol 1944; 7:359–390.
8. Leao AA. Further observations on the spreading depression of activity in the cerebral cortex. J Neurophysiol 1947; 10:409–414.
9. Ota I, Kuroshima K, Nagaoka T. Fundus video of retinal migraine. JAMA Ophthalmol 2013; 131:1481–1482.
10. Richter F, Bauer R, Lehmenkuhler A, *et al.* Spreading depression in the brainstem of the adult rat: electrophysiological parameters and influences on regional brainstem blood flow. J Cereb Blood Flow Metab 2008; 28:984–994.
11. Thomsen LL, Eriksen MK, Roemer SF, *et al.* A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria. Brain 2002; 125:1379–1391.
12. Viana M, Sprenger T, Andelova M, *et al.* The typical duration of migraine aura: a systematic review. Cephalalgia 2013; 33:483–490.
13. Tfelt-Hansen P, Pascual J, Ramadan N, *et al.* Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. Cephalalgia 2012; 32:6–38.
14. Hansen JM, Lipton RB, Dodick DW, *et al.* Migraine headache is present in the aura phase: a prospective study. Neurology 2012; 79:2044–2049.
15. ■■ Maniyar FH, Sprenger T, Monteith T, *et al.* Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain 2014; 137:232–241.

A critically important study demonstrating changes in brain activity corresponding with premonitory features that may occur up to hours before migraine headache.

16. Hougaard A, Amin FM, Magon S, *et al.* No abnormalities of intrinsic brain connectivity in the interictal phase of migraine with aura. Eur J Neurol 2015; 22:702-e46.
17. Charles A. Migraine: a brain state. Curr Opin Neurol 2013; 26:235–239.
18. Schott GD. Exploring the visual hallucinations of migraine aura: the tacit contribution of illustration. Brain 2007; 130:1690–1703.
19. Lashley KS. Patterns of cerebral integration indicated by the socotomas of migraine. Arch Neurol Psychiatry 1941; 46:331–339.
20. ■■ Hansen JM, Baca SM, Vanvalkenburgh P, *et al.* Distinctive anatomical and physiological features of migraine aura revealed by 18 years of recording. Brain 2013; 136:3589–3595.

Analysis of a remarkable set of aura drawings created by a single individual that provides significant insight into features of migraine aura initiation and propagation.

21. Olesen J, Friberg L, Olsen TS, *et al.* Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. Ann Neurol 1990; 28:791–798.
22. Woods RP, Iacoboni M, Mazziotta JC. Bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. N Engl J Med 1994; 331:1689–1692.
23. Petrusic I, Zidverc-Trajkovic J. Cortical spreading depression: origins and paths as inferred from the sequence of events during migraine aura. Funct Neurol 2014; 29:207–212.
24. Sanchez del Rio M, Bakker D, Wu O, *et al.* Perfusion weighted imaging during migraine: spontaneous visual aura and headache. Cephalalgia 1999; 19:701–707.
25. Hadjikhani N, Sanchez Del Rio M, Wu O, *et al.* Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci USA 2001; 98:4687–4692.
26. Lauritzen M, Skyhoj Olsen T, Lassen NA, *et al.* Changes in regional cerebral blood flow during the course of classic migraine attacks. Ann Neurol 1983; 13:633–641.
27. Hansen JM, Goadsby PJ, Charles AC. Reduced efficacy of sumatriptan in migraine with aura vs. without aura. Neurology 2015. (in press).
28. Afridi SK, Giffin NJ, Kaube H, *et al.* A randomized controlled trial of intranasal ketamine in migraine with prolonged aura. Neurology 2013; 80:642–647.
29. Kaube H, Herzog J, Kaufer T, *et al.* Aura in some patients with familial hemiplegic migraine can be stopped by intranasal ketamine. Neurology 2000; 55:139–141.
30. Goadsby PJ, Ferrari MD, Csanyi A, *et al.* Randomized, double-blind, placebo-controlled, proof-of-concept study of the cortical spreading depression inhibiting agent tonabersat in migraine prophylaxis. Cephalalgia 2009; 29:742–750.
31. Silberstein SD, Schoenen J, Gobel H, *et al.* Tonabersat, a gap-junction modulator: efficacy and safety in two randomized, placebo-controlled, dose-ranging studies of acute migraine. Cephalalgia 2009; 29 (Suppl 2):17–27.

32. Hauge AW, Asghar MS, Schytz HW, *et al.* Effects of tonabersat on migraine with aura: a randomised, double-blind, placebo-controlled crossover study. Lancet Neurol 2009; 8:718–723.

33. Hiddick-Smith D. PRIMA: a prospective randomized trial of PFO closure in patients with refractory migraine with aura. In: Transcatheter cardiovascular therapeutics. Washington, DC: TCTMD; 2014.

34. Choi DY, Shin DH, Cho KH, *et al.* Migraine with aura: a predictor of patent foramen ovale in children and adolescents. Cephalalgia 2013; 33:463–468.

35. Domitrz I, Styczynski G, Wilczko J, *et al.* An association between migraines and heart anomalies – true or false? A heart ultrasound study using cTTE in migraine patients and control participants. Pain Med 2014; 15:2156–2160.

36. Lantz M, Kostulas K, Waldenlind E, Sjöstrand C. Prevalence of migraine headache in an in-patient stroke population. Acta Neurol Scand 2015; 131:290–297.

37. Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. Cephalalgia 2008; 28:531–540.

38. Nozari A, Dilekoz E, Sukhotinsky I, *et al.* Microemboli may link spreading depression, migraine aura, and patent foramen ovale. Ann Neurol 2010; 67:221–229.