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Drawings of the strange visual phenomena seen by people who experience auras are helping scientists to understand the condition.

A richer view of aura

Migraines are often associated with colourful visual disturbances called auras, but many mysteries remain about how they fit into the wider biology of the syndrome. **By Liam Drew**

In 2012, neurologist Andrew Charles received a phone call from a septuagenarian engineer who had begun having migraines with aura at the age of 14. The man, who asked to be identified as P.V., told Charles that for the previous 18 years he had been drawing every single aura he had experienced – an average of 80 per year.

Whenever he sensed an aura beginning, P.V. grabbed a sheet of paper and sketched what he saw. With an engineer's meticulousness, he ran a stopwatch and redrew the shifting mirage every minute until it ended, typically 25–30 minutes later. He asked Charles whether his drawings might be useful to scientists interested in migraine. Soon after, P.V. arrived in Charles's office at the David Geffen School of Medicine at the University of California, Los Angeles, and deposited a thousand-strong stack of papers on the desk.

P.V.'s auras began as a small focal disturbance, which then expanded into a slowly spreading, crescent-like shape. The leading edge of this crescent was a flickering, morphing band of zigzagging, multicoloured lines known as a fortification spectrum. In the spectrum's wake was an area of diminished vision called a scotoma.

Transient neurological disturbances such as these are typical of auras. More than 90% affect

vision, but symptoms can take various other forms, including tingling or numbness around the body and an impaired ability to speak.

Auras are widely viewed as a hallmark of migraine, but they remain an enigmatic phenomenon. Research has focused on suppressing the debilitating pain of migraine headaches. How the short-term neurological features of auras relate to headaches and other aspects of migraine remains uncertain. Some researchers think that auras cause headaches; others posit that they are just another aspect of a multifaceted syndrome.

A major challenge of pinning down auras is their inconsistency. They regularly affect only around 20–40% of people with migraine, and for many of them, not every headache has an accompanying aura. Also, many people experience auras without getting headaches. This pattern, in addition to the fact that auras are subjective experiences that occur sporadically and unpredictably, have made them frustratingly difficult to study — investigating auras often requires invention.

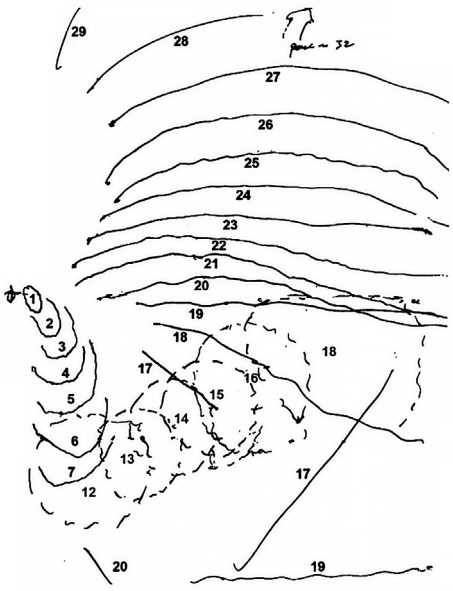
Charles saw in P.V.'s record-keeping an opportunity to delve into the precise nature of one person's experience, and to gain clues to the wider nature of auras. Charles and his colleagues systematically analysed P.V.'s illustrations[1] and learnt, among other things, how his auras varied from episode to episode; how intervals of normal vision could occur in the middle of an aura; and how auras sometimes began, only to quickly abort. All of this now needs to be fitted into a theory of what exactly happens in the brain during an aura.

The first wave

To show where each of P.V.'s auras began, Charles and his colleagues placed dots on a circular plot of the visual field — most dots clustered near the centre, but a substantial fraction began elsewhere. Another plot showed that the auras also travelled in different directions.

"This variability from attack to attack is very characteristic of migraine aura," says Anders Hougaard, a neurologist at the University of Copenhagen. In epilepsy, symptoms are highly stereotypical, in part because seizures always begin in the same part of the brain. P.V.'s drawings, however, show that his auras did not begin in a single spot, and for some other people, auras vary even more from episode to episode. Whatever physiological trigger lies behind these neurological disturbances, it must be able to arise in various areas of the brain and spread across the tissue in different directions.

In 1941, psychologist Karl Lashley at Harvard University in Cambridge, Massachusetts, provided a clue to the identity of that trigger[2].



A drawing by P.V. showing the progression of an aura at one-minute intervals.

Like P.V., he tracked and timed a fortification spectrum as it spread across his visual field. (Lashley experienced these often, but never suffered headaches.) Knowing the size of the human visual cortex, he inferred that whatever caused his auras moved across the brain at a speed of roughly 3 millimetres per minute.

Just two years later, biologist Aristides Leão at Harvard Medical School in Boston, Massachusetts, electrically shocked the cerebral cortex of an anaesthetized rabbit and saw a concentric wave of profoundly reduced neuronal activity spread across the brain's surface[3]. Unaware of Lashley's insight, Leão nevertheless suggested that this wave of inactivity might underlie migraine aura. Other scientists later calculated the speed at which this wave, now called cortical spreading depression or depolarization (CSD), crosses the brain: it is roughly 3 millimetres per minute.

Today, CSD is well characterized in animal brains. It can be induced by multiple types of brain insult, and cortical neurons at the wave's leading edge are briefly hyperactive before falling silent — an activity that fits with the appearance of fortification spectra. Numerous neurochemical changes have been linked to CSD, with potassium, various neurotransmitters and other signalling molecules temporarily accumulating in the fluid that bathes neurons as the wave passes.

Testing times

Most researchers accept CSD as the best working model of migraine aura. However, some embrace the theory less fully than do others. "The main issue," says Charles, "is that it's never been clearly documented in a migraine patient. It has to remain a hypothesis until that time." Frustratingly, CSD cannot be observed using electrodes on a person's scalp. The only direct recordings of CSD in people come from intensive-care units, where electrodes directly on or inside people's brains have caught CSD happening in response to traumatic brain injury or stroke.

In rabbits and rodents, CSD alters cerebral blood flow. Such changes are detectable in non-invasive brain scans, and are therefore more straightforward to look for in people. However, even this has proved problematic. Because migraine attacks are typically unpredictable, researchers seeking to image the brain during an attack use drugs to induce a headache. But these drugs have the curious property of inducing only pain, not auras — even in people who routinely have them. As a result, only a handful of people have ever been imaged while experiencing aura.

REF. 1

One of the most famous of these studies[4] was conducted by Nouchine Hadjikhani, a clinical neuroscientist at Harvard Medical School. In the early 2000s, Hadjikhani met a man who was able to induce an aura by playing basketball. She took him to courts near Massachusetts General Hospital in Boston, where he played for 80 minutes before saying that he could feel an aura coming on.

Hadjikhani ushered him into one of the hospital's scanners, where his aura began — a sort of white noise in his vision. As this happened, she witnessed a brief dilation of the man's cerebral blood vessels, resulting in increased blood flow across an area of his visual cortex. This was followed by a more prolonged vasoconstriction. The location of the observations corresponded precisely to where he described seeing visual noise. "There was a one-to-one relationship," Hadjikhani says.

Without direct electrical recordings of what is happening in the human brain during an aura, there will always be uncertainty as to how closely the mechanism in people matches the CSD seen in small mammals. Turgay Dalkara, a neurologist at Hacettepe University in Ankara who studies CSD and headache in animals, points out that CSD is an all-or-nothing event in mice; once started, it spreads across the whole cortical hemisphere. In people, the symptoms indicate that a much smaller region is affected — most commonly, as in P.V.'s case, part of the visual cortex. P.V. would also occasionally begin to experience the initial symptoms of aura, only for it to peter out — something that would not be expected of an all-or-nothing event.

Nevertheless, CSD remains the likeliest

candidate for what underpins migraine aura. Some researchers suggest that structural differences between human brains and those of rodents and rabbits might account for apparent inconsistencies in the presentation of aura. The brains of these small mammals lack the characteristic folds of the human cortex, for instance, which could limit and direct the spread of CSD in people. Neuroscientists have also not found any other potential mechanism that explains the travelling nature of auras so well. Some work suggests that, rather than neurons, astrocytes — the brain's most abundant non-neuronal glial cells — could carry a wave across the brain, but this idea has not gained traction.

A painful connection

Although some people experience auras without headaches, for many others an aura signals the imminent onset of pain. How exactly auras and the pain of a migraine are linked, however, is the subject of considerable debate.

Some think that auras directly cause headaches. The strongest evidence for this comes again from animal work. Most migraine researchers think that the pain of an attack is generated by increased firing of the trigeminal nerves, which carry sensory information from the face and the meninges that sheathe the brain (see page S2). CSD has been shown to activate these nerves in rodents.

For many years, the favoured explanation for how CSD does this was that the potassium and neurotransmitters released as the wave passes through the brain directly stimulate the trigeminal nerves. But this theory had a timing problem: these events last for only the few minutes that CSD does, whereas the pain lasts for hours or more.

In 2013, Dalkara proposed an alternative mechanism to account for this discrepancy[5]. He and his colleagues showed that CSD opens channels in the membranes of neurons that had previously been implicated in immune-cell function. This initiates a cascade of inflammatory signalling, first by neurons and then by glial cells, that activates the trigeminal nerves. Signalling in this network becomes self-sustaining and keeps the trigeminal nerves firing long after the CSD has passed.

Dalkara suggests that this apparent causal link between aura and the pain of a migraine casts the headache as a warning signal of disturbances in the brain. What migraine headaches do, he says, is alert a person that something is wrong with their brain — in this case, an event that causes a wave of reduced neuronal activity to pass through it. "Look at the pain systems in the body — this is their function," he says.

So far, Dalkara has studied these mechanisms only in rodents. However, he points out, human neuroimaging data published over the past couple of years by Hadjikhani and her colleagues[6,7] suggest that people who have migraines with auras show signs of inflammation in areas of the brain involved in pain processing, as well as in the meninges adjacent to the visual cortex. Hadjikhani says she is now investigating whether the inflammation subsides when migraine is successfully treated.

From a certain point of view

Not everyone is as enthusiastic as Dalkara about the assertion that aura causes the pain of migraine headaches. For some researchers, the variability of auras, and their occurrence with and without headache, counts against the theory. "There is very limited evidence in humans that aura is actually what's causing the pain," Charles says. "It's neither necessary nor sufficient for headache."

Dalkara theorizes that the inconsistent relationship between aura and headache might be in part due to variation in the intensity and propagation of CSD events. Stronger CSDs could first generate an aura, then initiate an inflammatory cascade leading to headache, whereas weaker CSDs might cause neurological symptoms, but be too insubstantial to activate inflammatory signalling — which would explain auras without a headache.

As for headaches that arise without aura, Dalkara points to a 2018 study in mice in which he showed that both sleep deprivation and depletion of the brain's energy stores can also initiate the inflammatory cascades seen in migraine[8]. This suggests that there are multiple routes to migraine headache — CSD might cause pain, but perhaps not exclusively.

Hadjikhani is exploring another possible explanation for why people experience migraine headaches without aura. Most researchers attribute the high prevalence of visual auras to the visual cortex being especially susceptible to CSD. But Hadjikhani wonders whether visual disturbances are simply very noticeable, and that many people have CSD-like events without realizing.

When Hadjikhani sent detailed questionnaires to people with migraine asking them to list any transient neurological symptoms, many reported issues with recognizing faces or objects, changes in colour perception, and problems with memory and language. They also described more abstract phenomena, such as a feeling of not being in control of their own hand. "If you start asking, you find a lot of interesting evidence," Hadjikhani says.

She also thinks that CSD events might sometimes pass without any perceptible symptoms — a silent aura. P.V.'s observations lend weight to this idea. Sometimes his auras begin to spread across his vision, then apparently stop, only to pick up again later. Crucially, they recommence at a place consistent with them having continued across his visual cortex. The most straightforward interpretation is that the underlying cause never went away, but for a time he was unaware of any symptoms. If silent auras are common, Hadjikhani says, it would make migraine a more uniform condition than it first seems, and lend weight to the idea that CSD events might induce headaches even in people who do not perceive auras.

"There is very limited evidence in humans that aura is actually what's causing the pain."

Not everyone is convinced. Peter Goadsby, a neurologist at King's College London, thinks that it is problematic to attribute any transient neurological disturbance to CSD without direct evidence linking the two — especially if the symptoms don't proceed in a way that suggests the underlying cause is travelling across brain tissue. And Charles notes that detailed self-reporting by people with migraine has shown that aura and headache can be present at the same time, rather than occurring in sequence.

Fully grasping aura and its relationship with headache requires more-incisive observations of migraine. Without a way to robustly detect CSD — or any other physical indicator of an aura — in a person's brain, Hougaard thinks it is impossible to rigorously test the various hypotheses. He is currently seeking a drug that induces auras in people, which could allow neuroimaging studies to more precisely reveal what happens in the brain during these events. Granted an opportunity to routinely peer directly into the brain during aura, in many different people, researchers might at last be able to marry the careful descriptions of auras, made by people who experience them, with their biological basis.

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