

# When Seeing Is Not Believing

By Frederick E. Lepore

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*Seeing things that aren't there—flashing lights, geometric shapes, or spectral faces? You must have taken a hallucinogenic drug or be in need of a referral to a good mental health practitioner.*

*Not so fast, says neuro-ophthalmologist Frederick Lepore, M.D. Hallucinations are actually quite common and can occur not only in diseases such as epilepsy and migraine, but following vision loss. They have a lot to teach us about how our brains put together a coherent picture of the world around us.*

In the Age of the Internet, a computer-savvy patient with a stubborn medical problem can reach into cyberspace to find help. So it was that on an evening in July the unsolicited medical history of a midwestern man appeared on my computer screen. Thirty years earlier, an accident hit his right eye with a bit of glass, scarring the retina and causing 90 percent blindness of that eye. In 2000, the eye's retina had detached and, following surgical repair, he began experiencing visual hallucinations of shaking jagged lines and swirling objects. Attempting to correct this, surgeons had deliberately severed the optic nerve, but, although his right eye then became entirely blind, the hallucinations continued unabated. Magnetic resonance imaging (MRI) and electroencephalography (EEG) had not revealed any brain disease, and a five-month trial of an antidepressant medication had not relieved the hallucinations. My newfound cyberpatient concluded his e-mail by soliciting my suggestions for treatment.

The patient's short medical history did not suggest that his hallucinations arose from epilepsy, migraine, drug intoxication, or psychosis. I was struck, however, by the similarity of this patient's symptoms to those of Charles Bonnet syndrome. In 1760, the Swiss naturalist and philosopher Charles Bonnet described the remarkable visual hallucinations experienced by his grandfather, who had undergone "couching"—a primitive cataract surgery practiced in the mid-18th century. This intellectually intact 90-year-old man reported that silent figures of men, women, birds, and carriages would appear and disappear in the twinkling of an eye, approach or recede, and increase or decrease in size. Buildings would rise in front of his eyes; a tapestry would suddenly become covered with clover or paintings. Bonnet's grandfather was usually able to differentiate these visions from real objects.

In 1936, Georges de Morsier described additional cases and proposed that Charles Bonnet syndrome was characterized by visual hallucinations occurring in elderly people with intact intellects. Like many doctors, I had found that patients with vision loss frequently reported both simple and complex hallucinations. These patients were sane and not necessarily elderly. My review of other medical reports of Charles Bonnet syndrome revealed that, as in the case of Bonnet's grandfather, impaired vision was frequently noted, although sometimes there was not a detailed ophthalmologic exam. Could vision loss, not advanced age, underlie these hallucinations?

I pursued this question by determining the frequency of simple or complex visual hallucinations in 104 consecutive patients whom I evaluated for visual loss from a variety of causes, ranging from retinal disorders to stroke. The patients' average age was 45 years; none showed any clinical evidence of psychosis. To my astonishment, 57 percent of these patients reported hallucinations, both simple (such as unformed lights or basic geometric shapes) and complex (people, faces, or vehicles). The complexity of their visual hallucinations did not correlate with damage in any particular region of the visual pathway. Patients with lesions of the cortical visual pathways deep within the brain were no more likely to experience complex hallucinations than patients with lesions of the retina or optic nerve. Although patients with visual acuity of 20/50 or worse in both eyes were likelier to experience visual

hallucinations, even those with normal visual acuity but mild peripheral vision loss occasionally would report hallucinations. These patients clearly knew that what they saw did not exist in the outside world, but some confided that they had avoided discussing their hallucinations for fear of being regarded as mentally ill.<sup>1</sup>

This suggests that we must stop thinking of hallucinations only in connection with the drugged or psychotic. Far more commonly than is usually recognized, “sane hallucinations” are on a continuum of normal visual experience. The scientific inroads into understanding this age-old symptom are seen in the new information being reported on hallucinations caused not only by drugs such as mescaline and LSD, but by migraine, epilepsy, and visual loss. Recognizing the association between these conditions and hallucinations allows us to investigate what they can reveal about the highest levels of brain function.

## THE DOOR IN THE WALL

Recounting his experiences with mescaline in *Heaven and Hell*, Aldous Huxley pointed to “a larger more comprehensive mystery—the nature of the relations between visionary experience and events on the cellular, chemical and electrical levels.” Huxley’s evocative depiction of hallucinations as a “door in the wall into the world of transcendental experience” is a compelling metaphor, but hardly a rigorous approach to the mystery of false sensory perceptions. William James observed that a hallucination is “as good and true a sensation as if there were a real object there. The object happens not to be there, that is all.” But the author of *Principles of Psychology* may have lost sight here of the poorly demarcated border between hallucinations and illusions. Illusions represent distorted perceptions of external reality, while hallucinations are thought to arise independently of external stimuli.

Although hard to specify precisely, hallucinations are actually common in our visual experience. Human reaction to them ranges from the passion of religious visionaries to the dread of psychotic patients. Much of our scientific knowledge of hallucinations remains descriptive, based on self-experimentation by investigators such as Heinrich Klüver, who reported the effects of mescaline in his studies at the University of Chicago beginning in 1926.<sup>2</sup> He classified the “form-constants” of mescaline-induced visions as “grating, lattice, fretwork, filigree, honeycomb, or chessboard design,” “cobweb,” “tunnel, funnel, alley, cone, or vessel,” and “spiral.” Klüver did not propose that these hallucinations were unique to mescaline; he said that they could appear “under many different conditions and in diseases of different etiology.” The “form-constants” were one handle on describing visual hallucinations, but not a way of explaining their pathophysiology. Klüver rightly concluded that his analysis was “only concerned with the ‘how’ of the optical effects” and not the “‘why,’ which must rely on future experimental work.”

A further limitation of the purely descriptive approach to hallucinations is its subjectivity. Consider this exchange reported in the April 13, 2001, issue of the *New York Times* between William Burroughs and Richard Schultes, the latter arguably the 20th century’s premier ethnobotanist studying hallucinogens of plant origin: “When Mr. Burroughs once described a psychedelic trip as an earth-shaking metaphysical experience, Dr. Schultes’s response was, ‘That’s funny, Bill, all I saw was colors.’”

The problems of subjective reports have not deterred researchers from exploring the breeding grounds for hallucinations, including the twilight states preceding or following sleep (hypnagogic and hypnopompic hallucinations), alcohol withdrawal, sensory and sleep deprivation, schizophrenia, Parkinson’s disease, and hallucinogenic drugs. In studying these grounds, science has progressed from methods akin to Freud and Jung’s dream analysis to a neurochemical assault on the problem.

On April 16, 1943, a Sandoz Company biochemist, Albert Hofman, had just created his 25th semi-synthetic ergot alkaloid (a mixture of plant-derived chemicals), when he had to interrupt his laboratory work. He was suddenly overtaken by a “remarkable restlessness combined with slight dizziness.” Arriving home, Hofman closed his eyes and “perceived an uninterrupted stream of fantastic pictures,

extraordinary shapes with intense, kaleidoscopic play of colors.”<sup>3</sup> Hofman had just discovered lysergic acid diethylamide (LSD); two decades later, it would be hailed as the archetypal hallucinogen of the “Age of Aquarius.”

The LSD molecule bore many resemblances to the structure of a neurotransmitter found only in cells in the midline or raphe regions of the upper brain stem, known as 5-hydroxytryptamine (5-HT), or more commonly as serotonin. In the early 1950s, researchers proposed that the hallucinogenic effects of LSD might result from blocking 5-HT receptors in the central nervous system. Almost 50 years later, this theory collapsed when LSD (and other hallucinogens such as mescaline) was shown to stimulate (rather than antagonize) a subset of 5-HT receptors in the part of the brainstem known as the locus coeruleus, which has extensive projections to the cortex, thalamus, hypothalamus, cerebellum, and rest of the brain stem.<sup>4</sup> LSD in combination with sensory stimulation will increase the firing rate of locus coeruleus neurons, leading Solomon Snyder of Johns Hopkins to comment “how nicely” these findings “correspond to what we know about the effects of psychedelic drugs in humans, and how readily they explain the way psychedelic drugs accentuate all our sensory perceptions.”

Others remained unconvinced, including Jack R. Cooper, Floyd E. Bloom, and Robert H. Roth, authors of the classic monograph *The Biochemical Basis of Neuropharmacology*, who warn that “it is extremely difficult to track down all of the individual cellular actions of an extremely potent drug like LSD and to fit these effects together in a jigsaw puzzle-like effort to solve the question of how LSD produces hallucinations.” So perhaps it is too early to say whether the jigsaw puzzle of LSD-induced hallucinations has been assembled correctly. But the converging disciplines of pharmacology, clinical observation, electrophysiology, and neuroanatomy offer realistic hope that the puzzle of hallucinations will yield to scientific rigor.

## PHOTOGRAPHING A MIGRAINE

On the morning of October 6, 1854, Dr. Hubert Airy experienced his first attack of a strange visual phenomenon. A century and a half later, his vivid depiction still serves as a guide to the visual symptoms of migraine:

At first it looked just like the spot which you see after having looked at the sun or some bright object; I thought it might be an eyelash in the way, or something of that sort, but I was soon undeceived when it began to increase....so I let it alone, knowing that it would go off in time, which it did, leaving a most terrible headache behind it, which is the worst part of it, the blindness itself giving no pain whatever. When it was in its height it seemed like a fortified town with bastions all round it, these bastions being coloured most gorgeously. If I put my pen into the space where there was this dimness, I could not see it at all, I could not even distinguish the colour of the ink at the end. All the interior of the fortification, so to speak, was boiling and rolling about in a most wonderful manner as if it was some thick liquid all alive. It did not belong only to one eye, but to both, the right eye having the most.<sup>5</sup>

The zigzag outline of the migraine “aura” has led many observers to describe this bold visual apparition as a “fortification” (as Airy did), or “teichopsia” (from the Greek meaning “town-wall” and “vision”), evoking the appearance of a medieval walled town. To bring this “morbid affection of the eyesight” to the attention of his medical colleagues, Airy recounted his striking visual symptoms, and those of other people with migraine, in the *Philosophical Transactions of the Royal Society of London* in 1870. Airy felt certain that the anatomical site of migraine was the brain, but the relatively rudimentary state of functional neuroanatomy made it impossible to do more than guess at a precise location. “The nature of the local mischief” was equally uncertain, and Airy proposed that “vascular congestion” temporarily suspended function “among the nerve-cells of visual sensorium.” Airy was convinced that teichopsia should be regarded as a “veritable ‘photograph’ of a morbid process going on in the brain,” and his

meticulous firsthand account helped to heighten clinicians' awareness of the visual symptoms of migraine.

Prior to Airy's publication in 1870, the definitive diagnosis of migraine might elude even an ophthalmologist of such great attainments as Sir William Bowman, F.R.S., whom Lewis Carroll consulted in 1856. In a diary entry almost 30 years later, the author of *Alice's Adventures in Wonderland* described "moving fortifications followed by a headache." The clinical terminology in Carroll's diary suggests that growing awareness of migraine had been spurred by dissemination of Airy's reports and other scientists contributing to the medical literature on the disorder.

The concept of vascular congestion as the cause of migraine did not originate with Airy; he merely echoed long-standing conventional wisdom, which carried forward into the next century. The vascular basis of migraine aura and headache was rigorously investigated by Harold Wolff at New York Hospital in the 1930s and 1940s. Wolff deduced that the visual defect of migraine, the aura, was caused by cerebral vasoconstriction and that the subsequent headache arose from distention and increased pulsations of branches of the external carotid artery, which supply blood to the dura mater, the pain-sensitive covering of the brain. This vasoconstriction-vasodilation hypothesis of migraine dominated mid-20th-century medical thought about migraine.

In 1941, flying in the face of largely uncritical acceptance of Wolff's vascular theory of migraine, Karl Lashley published a study of his own "scintillating scotomas" (areas of diminished sight accompanied by flashing lights) during a migraine.<sup>6</sup> An experimental psychologist of the first rank, Lashley had proclaimed while still a college student that he would study a set of slides of the frog brain and draw all the connections between the nerve cells so "then we would know how the frog worked." Toward the end of his career, he remarked that he had destroyed all theories of behavior, including his own.

As he was observing his scintillating scotoma, Lashley would gaze steadily at a fixation point on a sheet of paper, move his pencil toward the blind area, and mark where the pencil point disappeared. Using this technique, he mapped the size and shape of the scotoma and timed its progression from the center of his field of vision to the very edge of his peripheral field. Lashley proposed that a "wave of strong excitation" (eliciting the dazzling scintillations), followed by a phase of total inhibition (causing blindness), was progressing across the primary visual cortex. Citing 67 mm as the length of the visual cortex and about 20 minutes as the time needed for the scintillating scotoma to traverse his visual field, Lashley estimated the rate of propagation of the "disturbance" to be 3 mm per minute or less. Although he could time the disturbance and speculate that it reflected the architecture of the cortex, Lashley confessed that "nothing is known of the actual nervous activity during the migraine."

A potential glimpse of this "actual nervous activity" was forthcoming in Aristide Leão's 1944 description of spreading depression in a rabbit's cerebral cortex. The Brazilian neurophysiologist found that local trauma to the surface of the brain elicited a slowly spreading extinction of neuronal activity. This wave of electrical inhibition moved at the rate of 3 mm per minute. This was exactly the rate of propagation of Lashley's scintillating scotoma, of course, and led the Canadian psychologist P. M. Milner to propose that migraine scotomas are the conscious experience of spreading depression of the cerebral cortex. The striking parallel between the progression of the visual symptoms and the brain's altered electrical activity heralded a sea change in the understanding of migraine.

Neuronal, as opposed to vascular, events now appeared to be the primary cause of migraine. Additional evidence for this came from studying blood flow in specific regions of the brain, made possible by injecting radioactive xenon-133 dissolved in a saline solution into the carotid arteries of patients experiencing migraine. These studies showed that cerebral blood flow did decrease in the occipital lobe during the scintillating scotoma, but the spread of areas of decreased blood flow did not follow the distribution of the major cerebral arteries. Certain landmarks in the brain, such as the major fissures,

served as limits to the advance of reduced blood flow. Most tellingly, the period of diminished blood flow persisted throughout the migraine scotoma and well into the headache phase, refuting the contention that excessive blood flow to the brain and its coverings caused the pounding headache.

Scientists continue to debate the relative merits of the neuronal and vascular theories of migraine's causes. Proponents of the vascular theory point out that neither epileptic seizures nor electrode stimulation of both the brain's occipital lobes produce scintillating scotomas, so how could abnormal neuronal discharge be the cause of the migraine's visual hallucinations? Against this, adherents of the neuronal theory point out that the stately progression of a flashing visual apparition in migraine is very unlike the cadence and mixture of motor and sensory symptoms that characterize insufficient blood flow in a stroke or transient ischemic attack, which weighs against a purely vascular mechanism for migraine.

Although the cause of migraines remains in dispute, the study of what is arguably humanity's most common but elaborate visual hallucination has provided two critical insights. First and foremost, the locus of hallucinations in general, and of migraine's scintillating scotomas in particular, is in the brain, not in the eyes or elsewhere. This is reinforced by clinical reports that patients whose eyes have been surgically removed can still experience visual auras followed by migraine headache. Second, the similarity between the progression of scintillating scotoma and Leão's spreading depression across the brain's cortex compels us to look at migraine as primarily a neuronal disease, not a circulatory disturbance. Further research is necessary to determine whether studying migraine's visual symptoms can help explain the cortical architecture or the anatomy of a hallucination.

## **MAPPING EPILEPSY'S HALLUCINATIONS**

Wilder Graves Penfield, who founded the Montreal Neurological Institute in 1934, recounted a defining moment in the history of neurophysiology while a woman in late 18th-century Italy was preparing frogs' legs for dinner:

“They always seem to come alive when I hang them on copper wire.” Her husband looked. He was Professor of Surgery in the University of Bologna but his name is known to us as the discoverer of electricity, Luigi Galvani. Here was the beginning of it all two hundred years ago. The cut end of the frog's nerve was in contact with the copper wire, and electric current produced by the contact was passing along the nerve to the muscle. As a result, the muscle was twitching and contracting.

Over the course of two centuries, Galvani's discerning grasp of the relationship between electricity and nerves grew into our current understanding of how electrical potentials underlie the functions of the brain.

Penfield devoted his life to the surgical treatment of epilepsy, which is a paroxysmal disorder of the brain's electrical activity. In order to identify and surgically remove the abnormally discharging brain tissue that causes epilepsy, Penfield and his team would map the surface of the brain by electrically stimulating the cortex and recording how the patient reacted. He wrote at length of the visual hallucinations of a 12-year-old patient called R.W., whose case history deepened our understanding of the organization of the visual brain.<sup>7</sup> At age nine, R.W. began having seizures in which he would see flickering colored triangles overlapping each other. Sometimes this was followed by a much more elaborate vision of a “robber coming after him with a gun.” These hallucinations would be followed by movements of which R.W. was unaware, or by a full-blown convulsion.

The source of R.W.'s symptoms was an abnormal area of electrical activity in his right occipital lobe, which Penfield detected on an electroencephalogram (EEG). Three years after the onset of his visual seizures, R.W. lay on an operating table in the Montreal Neurological Institute as Penfield gently applied a single electrode to the exposed surface of the right side of R.W.'s brain. Penfield marked each site with a sterile numbered ticket and asked R.W. to report his symptoms after the site was stimulated.

R.W. remained fully awake and free of discomfort, because local anesthesia was used to open the skull and the cortex does not have pain-sensitive nerves. In an area within 6 cm (about 2½ inches) of the tip of the occipital lobe, electrical stimulation of the cortex elicited simple visual phenomena, such as moving colored lights and triangles. As the electrode advanced a few millimeters forward, into the temporal or parietal cortex, R.W.'s observations suddenly changed. "Gosh!" he exclaimed "Robbers coming at me with guns."

When the cortical map was completed, nitrous oxide inhalation and intravenous pentothal induced a deeper stage of anesthesia, and Penfield amputated the right occipital lobe, partially removing the parietal and temporal lobes. The excision of a "yellow and tough" scar — probably due to birth trauma — on the undersurface of the right occipital lobe effectively abolished the source of R.W.'s seizures. Following surgery, R.W. adjusted to the loss of peripheral vision on his left side and remained seizure-free.

By recording the electrode's position on R.W.'s cortex, Penfield had literally mapped a hallucination taking place in a brain. A surprising feature of this map was the abrupt transition from simple to complex visions. Colored lights and triangles resulted from stimulation of a sensory area — the occipital cortex — but only a few millimeters away, in the neighboring temporal cortex, the same electric current yielded what Penfield called psychical hallucinations — vivid dreams. Penfield contended that these psychical hallucinations were as "complex as life experience itself" and independent of the external environment. They required a level of physiological integration not found in the primary visual areas of the occipital lobe.

Intriguingly, Penfield found that repeated stimulation at the same cortical spot in the same patient could bring forth different visual sensations, appearing in different locations of the visual field. In addition, the nondominant (for language) temporal lobe was likelier to be the source for complex visual hallucinations than the dominant one. Every detail of Penfield's cortical map implied that recalling complex visual experiences, whether by spontaneous epileptic discharge or by electrical stimulation, depended on reactivation of the portion of the temporal lobe that he termed the "interpretative cortex."

Thus did poorly understood clinical phenomena of the 19th century begin to yield their secrets to Penfield's electrode. A case in point was a 53-year-old cook admitted in 1887 to the National Hospital for the Epileptic and Paralyzed in London for strange episodes in which she would see an unreal little black woman flitting about the kitchen and would smell "burning dirty stuff," followed by a sense of suffocation. Her renowned physician, Dr. Hughlings Jackson, identified these sensations as components of the "dreamy state" that he had recently discovered to be a form of epilepsy. Prior to Jackson, physicians would have overlooked the apparently absurd combination of a visual hallucination and a nasty smell, or would have attributed them to hysteria.<sup>8</sup> Jackson regarded the symptoms as evidence of disturbance of brain function and was vindicated at the cook's postmortem examination, which disclosed a tumor of the extreme anterior end of the right temporal lobe. The accuracy of his intuition would be confirmed beyond a shadow of doubt in the next century, when Penfield's stimulations of the temporal lobe reproduced both visual and olfactory hallucinations.

### **"WHERE PHYSIOLOGY AND PSYCHOLOGY COME FACE TO FACE"**

From the vantage point of the 21st century, do Penfield's cortical maps accurately reflect the cerebral topography of hallucinations?

Penfield lacked today's understanding of the circuitry of the visual cortex, which derives the three dimensions of the external world from a two-dimensional image projected onto the retina. The explanation of the building blocks of visual processing awaited the groundbreaking research for which David Hubel and Torsten Wiesel won the 1981 Nobel Prize in Physiology or Medicine. Nevertheless,

Penfield's exact observations have stood the test of time and remain a benchmark for modern investigators.

Armed with increasingly precise cortical stimulation and recording techniques, these present-day scientists continue to confirm Penfield's chart of "the location of the neuronal patterns 'which dreams are made of.'" In 2000, Korean scientists elicited hallucinations of animals, faces, body parts, landscapes, or other scenes from a research subject's memory during stimulation of the temporal and temporo-occipital cortex by a subdural grid of electrodes. In the same year, investigators at the University of Bonn, who performed intracranial EEGs on patients undergoing surgery for intractable seizures, found that the onset of seizures in the anteromedial temporal or occipitotemporal lobes produced three-dimensional hallucinations of moving heads, animals, little people, or concentric constriction of the visual field (tunnel vision).

During one of Penfield's last visits to his teacher, Sir Charles Sherrington, he was asked about the results of electrical stimulation of his patients' temporal lobes. Sherrington concluded their conversation by saying, "It must be great fun to put a question to 'the preparation' [the patient] and have it answer!" Only his patients' ability to describe the visual experience arising from an epileptic seizure or electrode stimulation enabled Penfield to correlate complex visual hallucinations with locations in the temporal lobe.

Penfield's refined technique let him succeed where his contemporaries failed, but there are limits to electrode studies. Electrical stimulation of the cortex (or electrical discharge caused by epilepsy) interferes with normal function: For example, patients cannot speak while their language area is being stimulated. Similarly, stimulating the occipital lobe may produce colored lights ("positive effects"), but the patient is blind to objects placed in the part of the visual field where the lights appear ("negative effects").

Even though the complex hallucinations induced by an electrode are inherently artificial, Penfield could use them to glimpse the labyrinthine functions of the temporal lobe. He proposed that the brain creates a detailed, permanent record of our entire stream of consciousness. Although we may seem to forget events, they can be accessed in minute detail at the touch of the surgeon's electrode to the temporal cortex. That these subconscious records can pop into our awareness underscores how little we really understand about consciousness, which some refer to as the Holy Grail of neuroscience. Complex visual hallucinations helped to transport Penfield to a place where, he said, "physiology and psychology come face to face." To the end of his life, he confessed to "a restless wondering within me about the working of the brain and its relation to mind." Although sure that science would find the answer, he concluded that there was no good evidence, "such as the employment of stimulating electrodes, [or] the study of conscious patients and the analysis of epileptic attacks, that the brain alone can carry out the work that the mind does."

## **HALLUCINATIONS FOLLOWING VISION LOSS**

The hallucinations of epilepsy and migraine have only begun to reveal their secrets to researchers; other kinds of hallucinations in people we deem "sane" are even less understood—or even acknowledged.

We began this exploration with my cyberpatient, who was troubled by hallucinations following loss of his vision from an accident, a profile that fit the characteristics of Charles Bonnet syndrome. Although the association of visual loss and hallucinations in this syndrome now appears incontrovertible, we can still only speculate about the underlying neural mechanism. In 1973, David Cogan at the Massachusetts Eye and Ear Infirmary reported 12 patients with visual loss and continuously variable hallucinations, which differ from the episodic and repetitive hallucinations attributable to epileptic discharges. Epileptic hallucinations are consistent with Hughlings Jackson's theory that seizures arise from discharge of specific portions of the cortex, but Cogan invoked a different theory of Jackson's to account for

hallucinations in the blind and partially blind. In his model of dissolution of the nervous system—a pathologic process of “taking to pieces” the highest levels of nervous function—Jackson had postulated the emergence of “over-action of lower centres by the mere removal of the influence of the higher centres.” Based on this, Cogan argued that the loss of customary visual sensory input permitted his blind and partially blind patients to become aware of intrinsic brain activity that otherwise remains below the threshold of consciousness.

Unlike “irritative” hallucinations in epilepsy, the hallucinations supposedly released by vision loss need not imply the existence of a temporal lobe lesion. To depict release hallucinations, Louis West, at the 1958 American Psychiatric Association Symposium, employed the brilliant metaphor of ...a man in his study, standing at a closed glass window opposite the fireplace, looking out at his garden in the sunset. He is absorbed by the view of the outside world. He does not visualize the interior of the room in which he stands. As it becomes darker outside, however, images of the objects in the room behind him can be seen reflected dimly in the window glass. For a time he may see either the garden (if he gazes into the distance) or the reflection of the room’s interior (if he focuses on the glass a few inches from his face). Night falls, but the fire still burns brightly in the fireplace and illuminates the room. The watcher now sees in the glass a vivid reflection of the interior of the room behind him, which appears to be outside the window.

This metaphor does not, however, explain what happened in the brain so that “the daylight (sensory input) is reduced while the interior illumination (general level of arousal) remains bright and images originating within the rooms of our brains may be perceived as though they came from outside the windows of our senses.”

What eluded West in 1958 has begun to yield to present-day functional neuroimaging. We now know much more specifically what areas of the brain are involved, and how. Using functional MRI, we see that, both preceding and during hallucinations, patients with Charles Bonnet syndrome demonstrate increased activity in the ventral occipital lobe within or around the fusiform gyrus.<sup>9</sup> In patients who hallucinated in color, there was increased activity in the color center of the fusiform gyrus, while the brains of patients with black and white hallucinations showed activity outside the color center.

Of almost equal importance was the absence of consistent activity in the frontal lobes or anterolateral temporal lobes of hallucinating patients. This argues against the hypothesis that frontal lobe activity is a prerequisite for conscious vision or that complex hallucinations imply activity in the temporal lobe. Observing increased activity of the ventral occipital lobes during hallucinations gives us another piece of the puzzle, but for now we do not understand how visual loss leads to this increase of visual cortex activity.

We need to find the cause of release hallucinations so we can help patients who are troubled by them. My e-mail correspondent could be diagnosed with Charles Bonnet syndrome. Consistently successful treatment, for him and others, however, must await deeper understanding of why there is increased activity of the ventral occipital cortex in patients with vision loss. Although pharmaceutical treatment of hallucinations is in its infancy, some investigators have reported successful treatment of Charles Bonnet syndrome with the anticonvulsant medication gabapentin. It is possible that this class of medication influences the abnormal neuronal excitations of the occipital lobe. Following Sir William Osler’s aphorism that “the man who translates the hieroglyphics of science into the plain language of healing is certainly the more useful,” I advised my cyberpatient to discuss with his physician a possible trial of anticonvulsant medication for his hallucinations. As for whether this specific class of drugs will abolish hallucinations in this particular patient, I check my e-mail daily.



## “‘TIS IN THEIR BRAIN”

The lesson of the study of hallucinations is that they arise from the central nervous system, even if they appear to exist in the world outside us. In 1621, Robert Burton wrote in *The Anatomy of Melancholy* that when sick men see or hear “phantasms, chimeras, noises, [and] visions... ‘tis in their brain, which seems to be before them.” Benjamin Rush astutely attributed hallucinations to “a morbid affection of the brain” in *Medical Inquiries and Observations Upon the Diseases of the Mind* in 1812, and by the late 19th century, Hughlings Jackson would localize his “dreamy state” to the anterior temporal lobe. This ushered in a most fertile era of studying hallucinations, an era that would give us the increasingly precise cortical maps of Penfield’s and Milner’s inspired surmise of what happens in the cortex during migraine’s scintillating scotoma.

These were remarkable discoveries, but visual hallucinations have much more to teach us. Does “normal” vision portray the external world with absolute fidelity? The neuropsychologist Richard L. Gregory suggests that visual perceptions “are guesses — predictive hypotheses — of what may be out there.” As anyone viewing an optical illusion will attest, ambiguities arise in interpreting the input of our senses. One obvious source of these ambiguities is the brain’s tendency to avoid or discard nonessential information. David Hubel has commented that “many people, including myself, still have trouble accepting the idea that the interior of a form ... does not itself excite cells in our brain ... that our awareness of the interior as black or white ... depends only on the cells’ sensitivity to the borders,” that is, to the edges of the form. The interior of forms that we see, and the “filling in” of our physiologic blind spots, both suggest that in a sense hallucinations are an intrinsic component of visual perception and that, as our knowledge of hallucination increases, we will also understand more about normal vision.

In *The User Illusion*, Tor Norretranders observes that “our sensory perception admits millions of bits [the smallest units of information] a second; consciousness two score. The flow of information, measured in bits per second, is described as the bandwidth or capacity of consciousness. The bandwidth of consciousness is far lower than the bandwidth of our sensory receptors.” Clearly, elaborate cerebral algorithms are necessary to distill the glut of raw visual stimuli into conscious visual perception.

A comprehensive theory of human vision must rest on gaining more knowledge of the preliminary stages of visual processing, which are not accessible to consciousness—or are they? Is it possible that release hallucinations are examples of a kind of “protovision,” or unprocessed primal visual perception? Can study of the common properties of simple geometric hallucinatory images help us, as the mathematician Paul Bressloff suggests, understand the architecture of the visual cortex? As we strive to answer these questions, the prospect of a window on the unconscious, or a glimpse of the wiring diagram of the first stages of vision, will irresistibly attract scientists, philosophers, and possibly poets to the exploration of hallucination. Those who experience, and often suffer from, them will be the beneficiaries.

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