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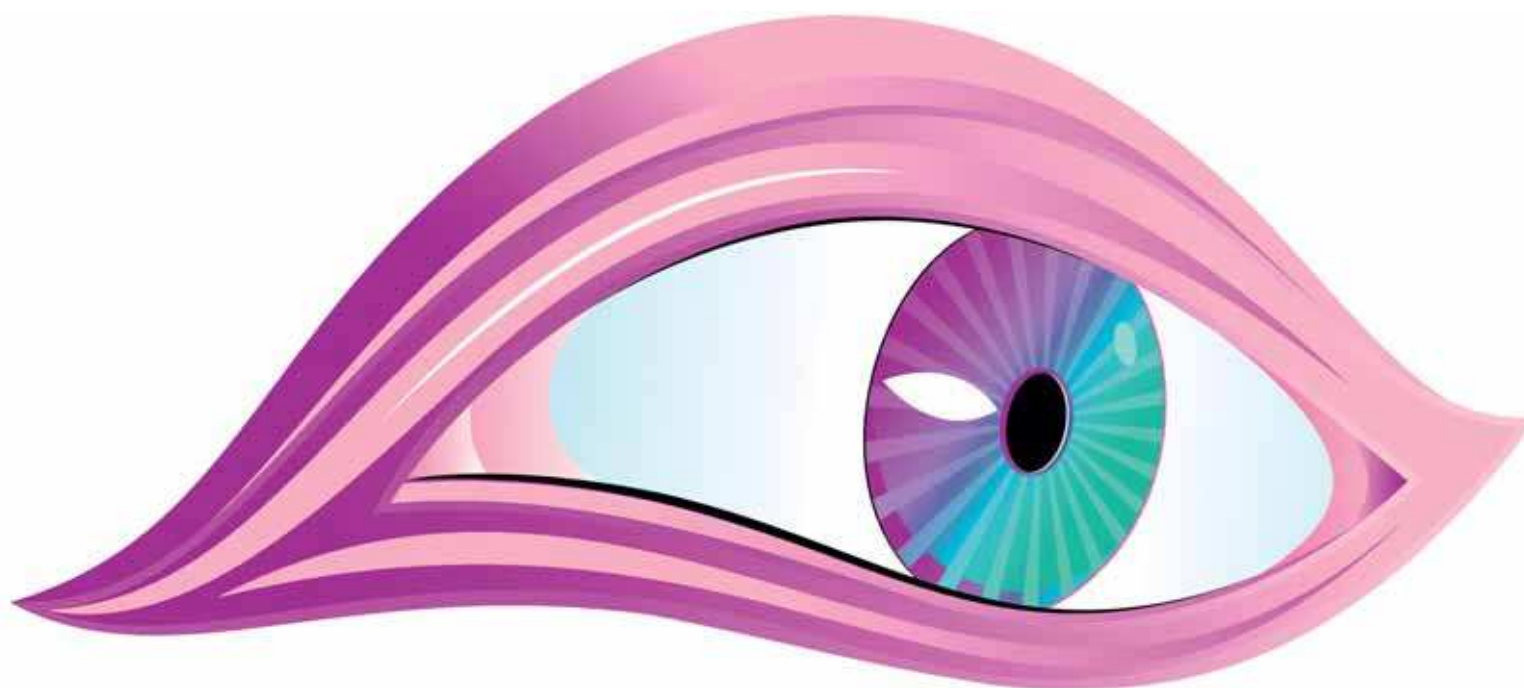
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## feature



# Seeing red

## Colour modulation and photosensitive epilepsy

By Joydeep Bhattacharya

Professor Joydeep Bhattacharya describes some groundbreaking work in the field of photosensitive epilepsy. We know that frequencies and patterns can trigger seizures – but what about colours?

A few weeks back I was at a wedding reception. The hall got suddenly dark, and a coloured strobe light started illuminating the dance floor. I watched guests getting up on their feet to dance with the newlywed couple. Bless them. But I started feeling stressed and uneasy in my head (not least because I did not join in – largely due to my lack of dancing faculty). But the reason, I eventually realised, was the flickering colourful light. I quickly left the hall.

This is not an isolated case of a visual stress caused by environmental stimuli. Consider, for example, a more serious incident in Japan that received widespread attention in recent years. At around 7pm on 16 December 1997, almost 700 children – and

some adults – were hospitalised with epileptic seizure-like symptoms. These symptoms included generalised convulsions and a loss of consciousness while watching a popular animated cartoon on TV – *Pokemon*. A few thousand more people later complained of various signs and symptoms of illness. This was a classic example of photosensitive epilepsy (PSE).

### Photosensitive epilepsy

PSE is the most common manifestation of stimulus-induced or reflexive epilepsy – where seizure activity is triggered by some external factor. PSE can be found in between 0.5 and 0.8 per cent of normal adolescent children. It also presents in 10 per cent of a paediatric epilepsy population and in five per

cent of adult patients. Further, up to 10 per cent of the wider population might carry this risk factor, without even being consciously aware of it. PSE is equally prevalent across all cultures and races, although it is more common in females than in males. PSE also appears to have a significant genetic tendency.

PSE is routinely diagnosed in the laboratory by means of intermittent photic stimulation (IPS), a symptom-provocative testing paradigm with an electronic strobe light. There is an internationally agreed method of performing IPS. Flashes at frequencies of 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 60, 50, 40 and 25 Hz – in this order – are given for five seconds. This is done first

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with the eyes open, then with the eyes closed, in a dimly lit room. EEG responses are monitored during this process. There are three main EEG responses induced by IPS, which comprise the following.

### Photic driving response

Generated in the posterior brain regions, this activity consists of stimulus-locked rhythmic activity with a frequency identical – or harmonically related to – the stimulus frequency.

### Photomyoclonic response

Generated in the anterior regions, this activity appears as brief repetitive muscle spikes and ceases once the stimulus is withdrawn.

### Photoparoxysmal response (PPR)

Generated either in the posterior region or across multiple regions, this activity is characterised by spikes or spike-and-wave complexes that often persist beyond the duration of the original stimulus.

For diagnosing PSE, PPR is of primary concern, although the other two responses contain important information that might be useful for predicting the occurrence of PPR.

The range of visual stimuli that will trigger PPR varies from natural sunlight flickering between trees to the artificial illumination in a nightclub. Among characteristics of visual stimuli, those studied in considerable detail are spatial and temporal frequency, contrast and patterns. However, the relationship between PSE and another important visual parameter – the colour-combination of a

stimulus – has been poorly understood until recently. This seems quite surprising, considering the widespread use of multicoloured displays, including TV and games consoles.

### Colour modulation and PSE

Previous studies have explored colour in PSE, but only explored the effect of a single hue. The evidence was inconclusive. UK researchers found no significant differences between red, blue, green and white light of matched luminance, while Japanese researchers found red light to be the most provocative. This contradiction was possibly caused by the wavelength differences in coloured stimuli used by different research groups.

Despite such inconclusive research, the *Pokemon* incident highlighted the importance of colour modulation (meaning colour combination) in inducing PSE. More than a quarter of the affected children had no history of earlier seizures and showed no sign of PPR when tested by the standard IPS procedure. This was due to a simple fact: IPS procedure used monochromatic flickering stimuli. The reported seizures were most likely provoked by a segment of the *Pokemon* cartoon containing rapid changes of red and blue colour frames.

This was later reconfirmed by Tobimatsu and colleagues (1999) when they systematically tested some of the affected children. They found that chromatic sensitivity – especially red-blue combination – plays a crucial role in the generation of seizures in these patients with PSE. A new term is coined:

chromatosensitive epilepsy, referring to a subtype of PSE. This term is used to designate the condition of people with epilepsy in whom colour modulation is the most symptom-provocative factor.

This issue has been further investigated by Parra and colleagues in 2007. This study aimed to determine the potential of different colours – and their combinations – and white light in triggering PPR. The study found that coloured stimuli elicited more PPRs than white light, and further that red was the most provocative of the primary colours. Among colour combinations, red-blue elicited the highest number of PPRs, and blue-green elicited the lowest.

For red-blue combination, long wavelength red colour stimulates red cones in the retina, while short wavelength blue colour stimulates blue cones. These cones receive the information, then relay it back to the primary sensory cortex in the brain – where a region of neurons interpret the data. Since the red and the blue cone impulses in the visual cortical neurons are not antagonist, no matching compensatory or inhibitory signals are elicited. Basically, the brain creates no response to balance the incoming stimuli. This results in hyperexcitation of the visual cortex – culminating in epileptic seizures in PSE individuals.

The Parra study also found that any colour combination with red was found to be more provocative than other colour combinations. Interestingly, the triggering effect of the colour modulation almost

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disappeared above 20 Hz – unlike both red and white stimulations in isolation. These results are in line with the view that coloured lenses that filter out red light are usually the most effective in reducing visual stress. Nevertheless, a combination of colours without any antagonistic relation appears more provocative than constituent individual colours.

## Dynamical neuronal responses

Interestingly, this topic was not addressed until a few years ago even in individuals without any history of epilepsy. Therefore, we conducted a study in a group of controls where they viewed three types of chromatic flickering stimuli – red-blue, red-green, and blue-green. We measured magnetoencephalogram (MEG) signals from their brains. A similar experiment was later conducted in groups of PSE patients – some unmedicated and some medicated with sodium valproate.

On analysing the MEG signals by a series of advanced analytical techniques, a range of interesting findings emerged. For example, we showed that two distinct MEG responses corresponding to stimulus frequency and its time-delayed harmonic responses were found in controls. Interestingly, the latter response was completely absent in the unmedicated patients. However, the medicated patients showed both responses, much like the controls.

This finding has a direct implication on brain modelling. The delayed harmonic response is a

characteristic of a nonlinear system. So – the controls' responses are nonlinear, while the patients' are more linear by comparison. This was later robustly corroborated by a battery of analysis. The controls' responses showed large nonlinearity, high irregularity and high entropy (entropy is a probabilistic measure of order/disorder).

Unmedicated patients' responses, on the other hand, showed linearity, more regularity and lower entropy.

The limitation of a linear system is in its inability to generate diverse patterns, while at the same time being easily excited by the external forcing stimulus. On the other hand, a nonlinear system is very flexible. It is capable of producing various patterns, each of which might be associated with a distinct operational model of information processing within constituent subsystems. Further, switching between these output patterns (in order to carry out a range of different processing tasks) is more likely in a nonlinear system. This adds enormous flexibility in how the system will behave against the external stimulation (a red-blue combination flickering stimulus, for instance). This flexibility effectively increases the internal control mechanism against any potential breakdown (namely, an epileptic discharge) due to hyperexcitation.

Interestingly, the medicated patients' responses exhibited a behaviour that was quite close to controls' – except for the occipital region. This might suggest that the medicated patient remained more vulnerable

than controls to some extent in the face of flickering stimulus. Nevertheless, the anti-epileptic drug taken by the medicated patients balanced this vulnerability. It managed to artificially maintain the general nonlinearity and disorderliness of a brain without the tendency towards epileptic activity.

Altogether, this suggests that when subjected to potentially seizure-triggering stimuli, a healthy brain manages to maintain a nonlinear state with a high degree of disorder. By comparison, an epileptic brain represents a highly ordered state – which makes it vulnerable to the forcing stimulus. Evidently disorder, as specified earlier, can be a healthy sign!

## Defensive mechanism against PSE

Here I propose a hypothesis. I believe that individuals without epilepsy possibly possess some kind of defensive mechanism that inhibits cortical hyperexcitation. The absence or impairment of such a mechanism might lead to an abnormally high cortical excitation – as experienced during a seizure in people with epilepsy.

Let me offer some evidence in support of this hypothesis. Porciatti and colleagues (2000) measured visual-evoked-potential (VEP) responses to visual patterns of high contrast with varying frequencies from patients with idiopathic photosensitive epilepsy and controls. The VEP responses of epilepsy patients subjected to lower frequencies (between four and 10 Hz) were markedly different from the controls. Typically, the VEPs saturated



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“A healthy brain manages to maintain a nonlinear state ... an epileptic brain represents a highly ordered state – which makes it vulnerable”

with increasing contrast in controls – there reached a point where responses would go no higher. In patients with epilepsy, however, the VEPs did not saturate. They continued to rise with increasing contrast – increasing the likelihood of cortical hyperexcitation. This demonstrated that the healthy controls showed a contrast gain-control cortical mechanism at low temporal frequencies, which is rather lacking or even impaired in people with epilepsy.

Drew and colleagues (2001) showed that in controls red-blue chromatic flicker had a much larger effect on the pupillary contraction than other colour combinations. The pupil serves as a gain-control device for the visual system by modulating its responses to luminance changes in the environment. Put simply, the pupil will expand or contract to allow more or less information from a particular stimulus into the eye and through into the brain. Earlier, I discussed how the specific red-blue colour combination is the most provocative colour combination. Therefore, a stronger pupillary contraction in controls reflects a defensive response to prevent hyperexcitation of the visual cortex by reducing the overall exposure to the risky stimulus. Unfortunately, no data are available on pupillary dynamics in patients with epilepsy – but I expect a lack of such contraction against red-blue flickering stimulus.

Finally, Parra and colleagues (2007) showed that if early brain responses all occurred in a similar high-

gamma frequency range they were more likely to evolve into PPRs. Such enhancement in clustering (specifically, more orderly phase responses) indicates a loss of control over brain mechanisms connecting multiple and distant brain regions. Currently, little information is available about the neural generator(s) of this postulated defensive mechanism. Some brain regions (for instance, parietal) are more likely candidates than others. The possibility of an underlying network, however, cannot be ruled out.

### Further research

It is important to investigate in more detail the role of colour modulation as a symptom-provocative stimulus. Further, there is a serious need to develop preventive and protective measures – not only for the vulnerable patients with known PSE, but also for those individuals carrying the trait who are unaware of it. Furthermore, IPS procedure is not beyond criticism. There is a certain risk of inducing discomfort and possibly even seizures. More efforts are needed to devise a non-provocative procedure, specifically one that can diagnose PSE without provoking PPR.

It is also quite surprising that flickering stimuli as encountered in our daily lives are not adequately studied. For example, invasive recordings taken from crucial elements of the human visual network has shown oscillatory activity related to the flicker in some computer screens. It is known that this type of oscillatory activity may lead to discomfort and headache. It

would be important to study the effects of long-term exposure to this flicker, or the long-term effects of sustained exposure to such flickering noise.

On a footnote, I did go back to the wedding party once the flickering lights had gone off again. The dessert was still to come!

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### Further reading

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