

## Review Article

# Hazardous Effects of Light Stimulation in the Central Nervous System

**Masaaki Tanaka<sup>1\*</sup>, Akira Ishii<sup>1</sup> and Yasuyoshi Watanabe<sup>1,2</sup>**<sup>1</sup>Department of Physiology, Osaka City University, Japan<sup>2</sup>Department of Physiology, RIKEN Center for Life Science Technologies, Japan

**\*Corresponding author:** Masaaki Tanaka, Department of Physiology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka City, Osaka 545-8585, Japan, Tel: 81666453711; Fax: 81666453712; Email: masa-t@msic.med.osaka-cu.ac.jp

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We are continually exposed to various visual stimuli in our contemporary society. Temporal frequency characteristics of the neural response to visual stimuli have been reported: Some temporal stimulation frequencies enhance neural responses and these frequencies are harmonically related, with a greatest common divisor frequency of approximately 6.5 Hz. Such stimuli, especially when high in temporal frequency, sometimes cause unexpected events such as photosensitive seizures. High-temporal-frequency visual stimuli can yield hazardous responses in the central nervous system. The mechanisms by which it does so have begun to be clarified using neuro imaging techniques such as magnetoencephalography. In addition, our knowledge about the relationship between the neural response to the high-temporal-frequency visual stimuli and fatigue in the central nervous system is increasing. Furthermore, the neural mechanisms to cause fatigue in the central nervous system by the visual stimuli has begun to be clarified. In this review, we describe the temporal frequency characteristics of the neural response to visual stimuli and the potential hazardous effects of high-temporal-frequency visual stimuli, particularly focused on the fatigue in the central nervous system.

**Keywords:** Stimulation; Central nervous system; Hazardous; Magnetoencephalography; visual evoked magnetic fields

## Introduction and Background

Recently, information technologies have come into common use. As a result, we are continually exposed to various visual stimuli. Such visual stimuli, especially when high in temporal frequency (> 3 Hz), sometimes result in unexpected events [1-4]: One of the most serious events is photosensitive seizures (PSS's) caused by watching television broadcast materials or playing video games. In 1997, approximately 700 young people were rushed to hospitals and treated for seizure symptoms in Japan. They were watching animated cartoon series, "Pocket Monsters", on television [5-7]. The cartoon contained 12 Hz red/blue flicker images lasting for 4 seconds, and it was considered that watching these images induced the "Pocket Monster" incident. There have been similar incidents in which many young people in various countries caused neuropsychological abnormalities, including PSS's, while watching television programs [8,9]. It is considered that the temporal frequency and brightness of visual stimuli are the two primary factors producing such events [8,10]. Such stimuli, especially when high in temporal frequency, sometimes cause unexpected events such as photosensitive seizures. High-temporal-frequency visual stimuli may yield hazardous responses in the central nervous system. The mechanisms by which it does so have begun to be clarified using neuro imaging techniques such as magnetoencephalography (MEG). In addition, the relationship between the neural response to the high-temporal-frequency visual stimuli and fatigue in the central nervous system as well as the neural mechanisms to cause fatigue in the central nervous system by the visual stimuli has been identified. In this review, we describe the temporal frequency characteristics of the neural response to visual stimuli and the potential hazardous effects

of high-temporal-frequency visual stimuli, particularly focused on the fatigue in the central nervous system.

## Analysis and Interpretation

### Hazardous nature of light stimulation

It has been believed that stimulation frequencies between 15 and 25 Hz can provoke seizure activity in the brain [9]. Broadcasting of high-temporal-frequency (> 3 Hz) strobe light is prohibited in some countries [11,12], although the scientific basis for this prohibition is still insufficient. Most of the patients with PSS's are children or adolescents, and that few healthy adults are affected by the high-temporal-frequency strobe light [8]. However, even in the healthy adult population, high-temporal-frequency visual stimulation can potentially cause abnormalities in the central nervous system functioning such as photo paroxysmal responses and occipital spikes [1-4].

### Previous neuro imaging and electrophysiological studies

Studies using electroencephalography (EEG) showed that steady-state visual evoked responses were maximal when temporal stimulation frequency of visual stimuli was 3 - 8 Hz or 16 - 20 Hz [10,13]. Studies using magnetoencephalography (MEG), which has higher spatial resolution than EEG, were also performed [14-16]. Transient-type luminance contrast visual stimulation, which evoked neural responses in the area V5/MT, has been shown to be broadly tuned from 1 - 30 Hz [14], with steady-state luminance contrast stimulation eliciting peak magnetic responses in the area V1 at a temporal frequency of 8 Hz [15]; and steady-state chromatic contrast

visual stimuli elicited peak MEG responses at a temporal frequency of 4 Hz [16]. In functional magnetic resonance imaging (fMRI) studies, flicker visual stimulation elicited peak blood oxygenation level-dependent responses at a temporal frequency of 8 Hz [17,18]. In a positron emission tomography (PET) study, strobe light stimulation elicited peak regional cerebral blood flow in the visual cortex at a temporal frequency of 8 Hz [13,19]. These findings indicate that high-temporal-frequency visual stimuli had effects on the central nervous system; however, the feature of the neural responses to visual stimuli across temporal frequencies has been inconsistent.

### MEG study

It was attempted to clarify the temporal frequency characteristics of visual evoked magnetic fields (VEF's) and the neural bases of the potential hazardous features of high-temporal-frequency strobe light stimuli in the central nervous system [20]. To specify these features and to clarify the mechanisms of photo-induced neural perturbations, it was essential to determine brain responses using MEG, in which neural responses can be examined with high temporal resolution in order not to miss characteristic neural responses across temporal visual stimulation frequencies and to use a transient-type visual stimulation method rather than steady-state method in order neither to mask nor miss transitional neural activities. High-temporal-frequency visual stimuli faster than 3 Hz were considered to be hazardous to the central nervous system [11,12,21] and red color is more likely to provoke PSS's than blue or white color [22-24]. Therefore, transient-type red flashing strobe light stimuli between 4 and 20 Hz with intervals of 2 Hz were used to obtain sufficient high-temporal-frequency resolution, and during visual stimuli, the neural response in the visual cortex with MEG was measured. As a result, the visual stimuli at the multiples of fundamental frequency (approximately 6.5 Hz) enhanced the magnetic responses. The mean values of the MEG responses for all the participants across the temporal stimulation frequencies did not exhibit significant frequency dependence. However, coefficient of variance curves of the MEG responses against the temporal stimulation frequencies demonstrated that there are some temporal frequency characteristics of VEF's. These frequencies were harmonically related, and the fundamental frequency could be determined [20].

The existence of a fundamental frequency suggests the presence of a periodic system in the central nervous system. Every periodic system exhibits some degree of sympathetic vibration. The wind-induced structural collapse of Tacoma Narrows Bridge in WA in 1940 is a famous example of the hazardous nature of this type of vibration. Strobe light stimuli might thus affect a periodic system in the brain, and neuropsychological abnormalities might be manifestations of perturbations of such systems.

### fMRI and PET studies

Peak blood oxygenation level in fMRI studies [17,18,25] and peak regional cerebral blood flow in PET studies [13,19] during strobe light visual stimuli were observed at a temporal frequency of 8 Hz. fMRI and PET are neuro imaging techniques that can measure activation of regional cerebral blood flow. It was reported that electrophysiological response and vascular response may be discrepant [26]. In this study, EEG and near-infrared spectroscopy, the former one depends on

electrophysiological response and latter one depends on vascular response, were used and response magnitudes for flicker stimuli were compared. The electrophysiological response showed the discontinuous peak around the alpha frequency, however the vascular response showed broad peak around 8-9 Hz. It was considered that the neuronal networks encode information by synchronization of spontaneous oscillations. Therefore, the discrepancy in peak responses assessed using fMRI and PET on the one hand and MEG on the other might be caused through different aspects of neural and vascular responses; and we might just see two sides of the same coin.

### Fatigue

Fatigue can be defined as difficulty in initiating or sustaining voluntary activities [27]. It is a common symptom; large community surveys have reported that up to half of the general adult population complains of fatigue [28,29]. Acute fatigue is a normal phenomenon that disappears after a period of rest; in contrast, chronic or long-term fatigue is sometimes irreversible and the compensation mechanisms that are useful in reducing acute fatigue are not effective [30]. Since fatigue induces a variety of diseases, it is of great importance to clarify the neural mechanisms underlying fatigue.

### Fatigue and photosensitivity

Photosensitivity is thought to cause various signs of hypersensitivity to visual stimuli in the central nervous system, and hypersensitivity is believed to be related to fatigue [31]. Fatigue can exacerbate photosensitivity in child patients with photosensitive epilepsy [32,33] and in children with video game-induced seizures [34]. These indicate that fatigue is associated with photosensitivity. In addition, a relationship between fatigue and photosensitivity was demonstrated in patients with photosensitive epilepsy [32,33] and even in subjects with video game-induced seizures [34]. A relationship between fatigue and photosensitivity was also identified even among the healthy participants using a questionnaire [35]. The mechanism by which fatigue is associated with photosensitivity remains to be clarified; however, since sleep deprivation induces fatigue and hypersensitivity in the central nervous system causes excessive photosensitivity [31], one possible explanation for this association is that fatigue enhances photosensitivity by decreasing excitation in the central nervous system. Another possible explanation is that, since overwork induces fatigue, increased neuronal activity caused by the photosensitive state induces fatigue.

The relationship between fatigue and photosensitivity was also identified by using a neuro imaging technique [36]. Since various aspects of acute mental fatigue can be influenced by mental load, 2-back test and 0-back test trials for a long period were used as acute mental fatigue-inducing tasks: the 0-back test represented a lower mental-load task, which could be performed without the use of working memory, while the 2-back test represented a higher mental-load task, which requires the use of working memory [37]. During the visual stimuli, VEF's could be observed and the VEF's consisted of two phases, i.e., earlier Phase 1 and later Phase 2. Acute fatigue did not alter the VEF intensities in either of the two Phases. In addition, although the VEF intensities before the acute fatigue-inducing mental task sessions were not correlated with the chronic level of fatigue as evaluated using a questionnaire in either of the two Phases, the VEF intensities after the 0-back test trials for 30 min in Phase 1 and those

after the 2-back test trials in Phase 2 were significantly correlated with the chronic fatigue scale scores [36]. Visual-evoked electrical response is a function of the total number of cortical neurons responding to each stimulus presentation, with the greatest number of neurons responding to repetition rates matching the activity-recovery cycle duration of the pathway from retina to cortex [37]. Although acute or chronic fatigue alone did not alter VEF intensities, the chronic level of fatigue was positively correlated with VEF intensities after the acute mental fatigue load [36]. Chronic fatigue might be a fragile condition by acute fatigue load and the potential compensation mechanisms against acute fatigue insult might be impaired according to the level of chronic fatigue [38], and thus this impaired neural condition might be manifested as the activated response to visual stimuli. In contrast, the VEF intensities before the acute fatigue-inducing mental task sessions were not correlated with the chronic level of fatigue in either of the two Phases, because the VEF intensities was related to the fatigability rather than the fatigued condition. Both bottom-up and top down mechanisms such as altered sensory processing, malfunctioning of inhibitory mechanisms, increased activity of facilitation pathway and temporal summation of sensory stimuli or wind-up are considered to be associated with the hypersensitivity [39], and these might have a relationship with the mechanisms of the hypersensitivity for visual stimuli related to the chronic level of fatigue.

### Types of fatigue and photosensitivity

Two different types of acute fatigue-inducing tasks affected VEF intensities in different magnetic temporal phases. It was reported that neural responses to visual stimuli were influenced by the alteration of the attention and arousal levels [40,41]. It was thought that visual information was firstly screened and inefficient information was suppressed, and secondly that efficient information passed through the screening process. The chronic level of fatigue was positively correlated with the VEF intensity in Phase 1 after the 0-back test session, which caused sleepiness [36]. Sleepiness is a type of request for rest in order to recover from fatigue [42] and sleepiness, i.e., low arousal level, might cause impaired screening function. On the other hand, the chronic level of fatigue was positively correlated with the VEF intensity in Phase 2 after the 2-back test session, which required working memory load [36]. The 2-back test trials might thus cause impaired function of information processing in the central nervous system. Chronic fatigue might make both sub cortical (arousal) and cortical (cognitive) systems fragile, and the 0-back test may mainly affect the sub cortical system and modify the VEF intensities in Phase 1; while the 2-back test may mainly affect the cortical system and modify the VEF intensities in Phase 2. The different results indicate the complex relationships between photosensitivity and fatigue, and further studies would clarify the complicated neural mechanisms of photosensitivity and fatigue.

### Limitations and future research direction

There are potential limitations to the previous studies. Participants were limited to healthy subjects. Thus, it is not certain that our results can apply to the patients with central nervous system disorders. Studies involving the patients with central nervous system disorders such as PSS would contribute to understanding of the neural bases of potentially hazardous high-temporal-frequency strobe light stimulation in the central nervous system.

## Conclusion

In this review, we describe the temporal frequency characteristics of the neural response to the visual stimuli and the potential hazardous effects of high-temporal-frequency visual stimuli, particularly focused on the fatigue in the central nervous system. These findings would contribute to the better understanding of the basic periodic systems of human brain as well as the neural bases of response to visual stimuli in the central nervous system. In addition, these cast new lights on the high risk for fatigue in the central nervous system in our modern society, in which we are continually exposed to various visual stimuli day and night. Early interventions, such as use of a low-luminance environment and avoiding viewing of television monitors, for groups at a high risk of fatigue may contribute to a lower incidence of and/or higher rates of recovery from fatigue in the central nervous system.

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## References

1. Tarumi K, Nagami M, Kadowaki I. An inquiry into the factors affecting the complaints of subjective symptoms in VDT operators. *Sangyo Igaku*. 1990; 32: 77-88.
2. Williams J, Ramaswamy D, Oulhaj A. 10 Hz flicker improves recognition memory in older people. *BMC Neurosci*. 2006; 7: 21.
3. Sen A, Richardson S. A study of computer-related upper limb discomfort and computer vision syndrome. *J Hum Ergol (Tokyo)*. 2007; 36: 45-50.
4. Takano K, Komatsu T, Hata N, Nakajima Y, Kansaku K. Visual stimuli for the P300 brain-computer interface: A comparison of white/gray and green/blue flicker matrices. *Clin Neurophysiol*. 2009; 120: 1562-1566.
5. Sheryl WuDunn. *The New York Times TV Cartoon's Flashes Send 700 Japanese Into Seizures*. 1997.
6. CNN interactive. *Japanese cartoon triggers seizures in hundreds of children*. 1997.
7. Ishida S, Yamashita Y, Matsuishi T, Ohshima M, Ohshima H, Kato H, et al. Photosensitive seizures provoked while viewing "Pocket Monsters" a made-for-television animation program in Japan. *Epilepsia*. 1998; 39: 1340-1344.
8. Fisher RS, Harding G, Erba G, Barkley GL, Wilkins A. Photoc- and pattern-induced seizures: A review for the Epilepsy Foundation of America Working Group. *Epilepsia*. 2005; 46: 1426-1441.
9. Harding GF, Harding PF. Televised material and photosensitive epilepsy. 1999; 40: 65-69.
10. Porciatti V, Burr DC, Morrone MC, Fiorentini A. The effects of aging on the pattern electroretinogram and visual evoked potential in humans. *Vision Res*. 1992; 32: 1199-1209.
11. The Independent Television Commission (ITC). *Guideline on the safety of TV screen images*, London: ITC. 1994.
12. The National Association of Commercial Broadcasters in Japan (NAB) and the Japan Broadcasting Corporation (NHK). *Guidelines for picture techniques used in broadcast programs*. 1998.
13. Pastor MA, Artieda J, Arbizu J, Valencia M, Masdeu JC. Human cerebral activation during steady-state visual-evoked responses. *J Neurosci*. 2003; 23: 11621-11627.
14. Anderson SJ, Holliday IE, Singh KD, Harding GFA. Localization and functional

- analysis of human cortical area V5 using magneto-encephalography. *Proc Biol Sci.* 1996; 263: 423-431.
15. Fawcett IP, Barnes GR, Hillebrand A, Singh KD. The temporal frequency tuning of human visual cortex investigated using synthetic aperture magnetometry. *Neuroimage.* 2004; 21: 1542-1553.
  16. Fylan F, Holliday IE, Singh KD, Anderson SJ, Harding GF. Magnetoencephalographic investigation of human cortical area V1 using color stimuli. *Neuroimage.* 1997; 6: 47-57.
  17. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci U S A.* 1992; 89: 5675-5679.
  18. Kaufmann C, Elbel GK, Gossl C, Putz B, Auer DP. Frequency dependence and gender effects in visual cortical regions involved in temporal frequency dependent pattern processing. *Hum Brain Mapp.* 2001; 14: 28-38.
  19. Fox PT, Raichle ME. Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission tomography. *J Neurophysiol.* 1984; 51: 1109-1120.
  20. Shigihara Y, Tanaka M, Tsuyuguchi N, Tanaka H, Watanabe Y. Hazardous nature of high-temporal-frequency strobe light stimulation: neural mechanisms revealed by magnetoencephalography. *Neuroscience.* 2010; 166: 482-490.
  21. Harding G, Wilkins AJ, Erba G, Barkley GL, Fisher RS. Photic- and pattern-induced seizures: expert consensus of the Epilepsy Foundation of America Working Group. *Epilepsia.* 2005; 46: 1423-1425.
  22. Takahashi T, Tsukahara Y. Influence of color on the photoconvulsive response. *Electroencephalogr Clin Neurophysiol.* 1976; 41:124-136.
  23. Tobimatsu S, Zhang YM, Tomoda Y, Mitsudome A, Kato M. Chromatic sensitive epilepsy: a variant of photosensitive epilepsy. *Ann Neurol.* 1999; 45: 790-793.
  24. Rubboli G, Parra J, Seri S, Takahashi T, Thomas P. EEG diagnostic procedures and special investigations in the assessment of photosensitivity. *Epilepsia.* 2004; 45: 35-39.
  25. Hagenbeek RE, Rombouts SA, van Dijk BW, Barkhof F. Determination of individual stimulus-response curves in the visual cortex. *Hum Brain Mapp.* 2002; 17: 244-250.
  26. Koch SP, Steinbrink J, Villringer A, Obrig H. Synchronization between background activity and visually evoked potential is not mirrored by focal hyperoxygenation: implications for the interpretation of vascular brain imaging. *J Neurosci.* 2006; 26: 4940-4948.
  27. Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet.* 2004; 363: 978-988.
  28. Pawlikowska T, Chalder T, Hirsch SR, Wallace P, Wright DJ, Wessely SC. Population based study of fatigue and psychological distress. *BMJ.* 1994; 308: 763-766.
  29. Chen MK. The epidemiology of self-perceived fatigue among adults. *Prev Med.* 1986; 15: 74-81.
  30. Beurskens AJ, Bültmann U, Kant I, Vercoulen JH, Bleijenberg G, Swaen GM. Fatigue among working people: validity of a questionnaire measure. *Occup Environ Med.* 2000; 57: 353-357.
  31. Bac P, Pages N, Maurois P, German-Fattal M, Durlach J. A new actimetry-based test of photic sensitization in a murine photosensitive magnesium depletion model. *Methods Find Exp Clin Pharmacol.* 2005; 27: 681-684.
  32. Covanis A, Stodieck SR, Wilkins AJ. Treatment of photosensitivity. *Epilepsia.* 2004; 45: 40-45.
  33. Verrotti A, Tocco AM, Salladini C, Latini G, Chiarelli F. Human photosensitivity: from pathophysiology to treatment. *Eur J Neurol.* 2005; 12: 828-841.
  34. Ferrie CD, De Marco P, Grünewald RA, Giannakodimos S, Panayiotopoulos CP. Video game induced seizures. *J Neurol Neurosurg Psychiatry.* 1994; 57: 925-931.
  35. Shigihara Y, Tanaka M, Watanabe Y. Relationship between fatigue and photosensitivity. *Behav Med.* 2010; 36: 109-112.
  36. Shigihara Y, Tanaka M, Mizuno K, Ishii A, Yamano E, Funakura M, et al. Effects of daily levels of fatigue and acutely induced fatigue on the visual evoked magnetic response. *Brain Res.* 2012; 1457: 44-50.
  37. Bartley SH. Temporal features of input as crucial factors in vision. Neff WD, editors. In: *Contribution to Sensory Physiology.* New York: Academic. 1968; 3:81-124.
  38. Tanaka M, Watanabe Y. A new hypothesis of chronic fatigue syndrome: Co-conditioning theory. *Med Hypotheses.* 2010; 75: 244-249.
  39. Nijs J, Meeus M, Van Oosterwijck J, Ickmans K, Moorkens G, Hans G. In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. *Eur J Clin Invest.* 2012; 42: 203-212.
  40. Mangun GR, Hillyard SA. Spatial gradients of visual attention: behavioral and electrophysiological evidence. *Electroencephalogr Clin Neurophysiol.* 1988; 70: 417-428.
  41. Morris AM, So Y, Lee KA, Lash AA, Becker CE. The P300 event-related potential. The effects of sleep deprivation. *J Occup Med.* 1992; 34: 1143-1152.
  42. Kumar VM. Sleep and sleep disorders. *Indian J Chest Dis Allied Sci.* 2008; 50: 129-135.