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Review article

The brain through the retina: The flash electroretinogram as a tool to investigate psychiatric disorders

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ABSTRACT

Investigating the living brain remains one of the major obstacles in psychiatry research in order to better understand the biological underpinning of brain disorders. Novel approaches are needed to study brain functions indirectly. Since it is part of the central nervous system, retinal functions as measured with the flash electroretinogram (ERG) may reflect the central dysfunctions reported in psychiatric disorders. This review describes the flash ERG anomalies reported in patients with psychiatric disorders such as seasonal affective disorder, schizophrenia, autism spectrum disorder and drug addiction and discusses how changes in retinal functions might be used as biomarkers for psychiatric disorder as well as a potential aid to diagnosis in psychiatry.

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1. Introduction

One of the major obstacles in neuroscience and psychiatry research is the difficult access to the functioning brain. There is a need to develop new approaches to study the neurological functions in an indirect manner. In the past decade, there have been numerous reports on the incorporation of biomarkers into psychiatry with the hope that they will significantly ameliorate diagnoses and give a better understanding of the molecular underpinning of brain disorders (Perlis, 2011).

Since the retina is part of the central nervous system due to its embryonic origin, it became a crucial site of investigation for brain disorders. The retinal functions can be assessed with the flash electroretinogram (ERG), which is an objective and non-invasive technique first used to investigate the origins of a visual loss due to a retinal disease or injury. Several ERG anomalies have been observed in patients with psychiatric disorders and it is thought that retinal activity may reflect the central neurochemistry underlying brain disorders and could represent a means to differentiate brain pathologies.

This review reports the flash ERG anomalies already observed in patients with brain disorders such as seasonal affective disorder,

Abbreviations: ASD, autism spectrum disorder; BD, bipolar disorder; ERG, electroretinogram; HR, high risk; HVA, homovanillic acid; LRF, luminance response function; SAD, seasonal affective disorder; SZ, schizophrenia.

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schizophrenia, autism spectrum disorder and drug addiction as well as how these ERG changes might serve as a tool to investigate and understand those disorders.

2. The flash electroretinogram

The retina is the neural portion of the eye and is composed of many neuronal layers. When light penetrates the eye, it passes through the anterior eye structure before reaching the outer segment of the retina containing the photoreceptors, namely the rods and cones. The light is absorbed by the photopigment of the photoreceptors, which initiates the phototransduction process. In the dark, photoreceptors are in a depolarized state and photon absorption will lead to their hyperpolarization followed by the depolarization of the ON bipolar cells. The electric signal is then transferred to ganglion cells, the axons of which form the optic nerve carrying the visual information from the retina through the brain, mostly the visual cortex. The retina also comprises horizontal cells and amacrine cells which are interneurons that are joining together photoreceptors and bipolar cells respectively, as well as Müller cells acting as glia (Purves et al., 2004).

The ERG is used to record the light-evoked electric potential originating from the retina in response to a light stimulus. It arises from currents resulting of neuronal signaling through the retina. The ERG can be recorded in scotopic condition (dark adapted) to assess the rod or mixed rod–cone functions and in photopic condition (light adapted) to investigate the cone system (Purves et al., 2004).

On a typical flash ERG trace, two major components can be observed such as an initial negative wave, called the a-wave and representing the hyperpolarization of the photoreceptors for the most part, followed by a positive wave, namely the b-wave generated mainly by bipolar cells. To analyze the ERG response, the amplitude and implicit time of the a- and b-waves are measured. On the ascending part of the b-wave, a series of high-frequency wavelets called oscillatory potentials can be observed. Although their exact origin is still unclear, they could result from the interaction between amacrine cells and bipolar cells (Wachtmeister, 1998). Examples of typical human ERG traces obtained in photopic and scotopic conditions are presented in Fig. 1. To better analyze the dynamic of the retinal response, the b-wave amplitude obtained at various intensities can be plotted against flash luminance to generate a luminance–response function (LRF) curve. Using the LRF, other ERG parameters can be derived such as the Vmax, which refers to the amplitude where the system saturates as well as the logK, which represents the flash intensity necessary to reach half of the Vmax and refers to retinal sensitivity (Hebert et al., 1995).

To record an ERG, an electrode is placed on the surface of the eye and reference and ground electrodes are placed on the skin of the subject, usually the outer canthus and forehead respectively. The eye is sometimes anesthetized (depending on the electrode used) and the pupil dilated. The light stimulation is made using a Ganzfeld bowl in order to achieve a full field stimulation of both eyes. The retinal response to light is recorded using standardized luminance background and flashes intensities according to the guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV) (Marmor et al., 2009). The flicker ERG at 30 Hz can also be recorded to assess the cone-driven response since rods do not respond fast enough to provide individual responses to each flash at this rate of stimulation.

Noteworthy, the flash ERG is used to assess only the function of the photoreceptors and the bipolar cells of the retina. This procedure is very easily applied and accepted by adult psychiatric patients and children (Hebert et al., 2010). Some ERG techniques exist to investigate the other retinal cell types such as pattern ERG to assess ganglion cell functions and there it is also possible with the multifocal ERG to record local cone responses of the central retina. However, this review focuses only on the flash ERG anomalies reported in psychiatric disorders since it is the most used technique.

3. The seasonal affective disorder

The seasonal affective disorder (SAD) is characterized by recurrent depressive episodes with atypical symptoms during fall and winter, a complete remission during spring and summer (Rosenthal et al., 1984) as well as a good response to bright light therapy (Westrin and Lam, 2007). The depressive symptoms appear to be triggered by the shortening of the photoperiod length, observed in higher latitudes but the origin of the trouble remains unknown.

A first study on the dark adapted ERG with a bright white light stimulus which elicits a mixed rod and cone response reported that patients with SAD (men and woman together) had lower b-wave amplitude (Lam et al., 1992) when measured during fall and winter. However, the analysis of the sex differences led to controversial results. It was shown that SAD women had lower b-wave amplitude compared to the women of the control group and the complete opposite was observed in the men group, where men with SAD had higher b-wave amplitude than the control group. b-Wave implicit time was also found to be shorter in SAD patients, but this result was observed only in men and not in women. According to the authors of the study, those differences might be explained by the small sample size as well as the high variability of the results, especially in the men group.

The first seasonal assessment of the retina was performed in subsyndromal SAD (S-SAD) patients, which are people who are experiencing less severe symptoms that, although bothersome, do not reach clinical significance. Using a LRF to assess rod sensitivity (only), our group observed a seasonal variation of the ERG in S-SAD subjects but not in healthy controls (Hebert et al., 2002). A right shift of the LRF was observed in wintertime in S-SAD subjects demonstrating a winterly decrease in retinal sensitivity (Hebert et al., 2002) which was further supported by our subsequent study in SAD patients (Lavoie et al., 2009). Noteworthy, in the latter

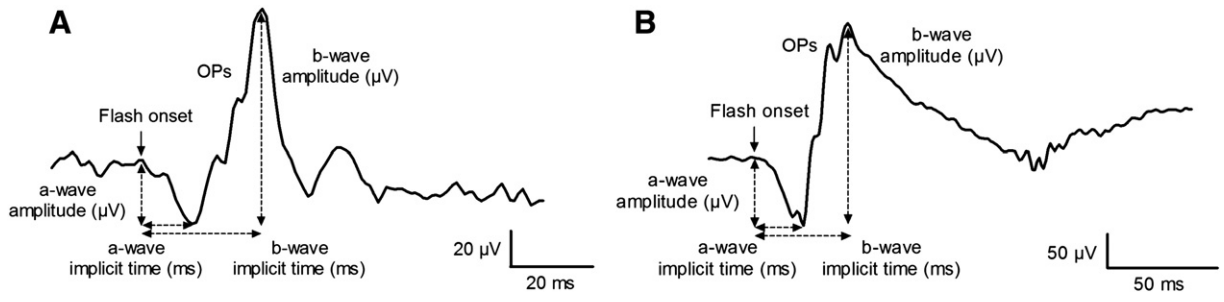

Fig. 1. Example of photopic (A) and scotopic (B) ERG traces in human. The a-wave amplitude is measured from the baseline to the trough of the a-wave, and the b-wave is measured from the trough of the a-wave to the peak of the b-wave. The arrows indicate flash onset. The oscillatory potentials (OPs) can be observed on the ascending part of the b-wave.