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Review

The emerging field of retinal electrophysiological measurements in psychiatric research: A review of the findings and the perspectives in major depressive disorder

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ABSTRACT

Major depressive disorder (MDD) is a severe mental illness leading to long-term disabilities. One of the current challenges in psychiatric research is to develop new approaches to investigate the pathophysiology of MDD and monitor drug response in order to provide better therapeutic strategies to the patients. Since the retina is considered as part of the central nervous system, it was suggested that it constitutes an appropriate site to investigate mental illnesses. In the past years, several teams assessed the retinal function of patients with mood disorders and many relevant abnormalities have been reported. Investigation of the retinal electrophysiological abnormalities in MDD remains a young emerging field, but we believe that the current findings are very promising and we argue that objective retinal electrophysiological measurements may eventually become relevant tools to investigate the pathophysiology of MDD. Here, we review the retinal abnormalities detected with objective electrophysiological measurements such as the flash electroretinogram (fERG), the pattern electroretinogram (PERG) and the electrooculogram (EOG) in patients with MDD. We discuss how these changes might reflect the pathophysiology of MDD in both clinical and scientific points of view, according especially to the monoamine neurotransmission deficiency hypothesis. We also discuss the technical details that must be taken into consideration for a potential use of the objective retinal electrophysiological measurements as tools to investigate the pathophysiology of MDD.

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1. Introduction

Major depressive disorder (MDD) is one of the most severe mental diseases affecting hundreds of millions of people worldwide (Smith, 2014). Although it is currently ranked as the fourth leading cause of disability by the World Health Organization, it is projected that it will become the second leading cause in 2020 (Kessler and Bromet, 2013). To date, it is known that the pathophysiology of MDD combines genetic factors, past or current psychosocial stresses, as well as disruptions in several molecular signaling pathways (Charney and Manji, 2004). With its extreme gravity, the current treatment used for MDD is antidepressant therapy alone or in combination with psychotherapy (Friedman, 2014). Pharmacotherapy in MDD predominantly targets monoamine neurotransmitter signaling pathways, such as dopamine, serotonin and norepinephrine, which suggests a potential implication of these molecules in the pathophysiology of this disorder (Hamon and Blier, 2013). The pharmacological approaches are generally safe, but the clinical benefits are often observed after weeks or even months of administration (Berton and Nestler, 2006). Moreover, it was demonstrated that up to 50%–60% of the patients do not achieve adequate response to antidepressant therapy (Fava, 2003), with 12% of them achieving a partial response and 19%–34% being non-responders (Fava and Davidson, 1996). Consequently, there is a need to develop new approaches to better access and investigate the molecular mechanisms implicated in MDD pathophysiology, as well as to monitor drug response in patients. Considering the high risk of morbidity and mortality of untreated MDD patients (Kessler and Bromet, 2013), this currently constitutes a crucial step in psychiatric research and practice in order to provide better therapeutic strategies to the patients.

The retina represents an easy-to-access part of the central nervous system and it was therefore suggested that it constitutes an appropriate site to investigate major neuropsychiatric illnesses (Lavoie et al., 2014b) and addictive disorders (Schwitzer et al., 2015; Laprevote et al., 2015). This structure is composed of several cell layers implicated in the first stages of visual processing. Briefly, light is absorbed by the photopigments of the photoreceptors, named rods and cones, thus initiating the conversion of light into electric signal. Following this phenomenon called phototransduction, the signal is transferred to the bipolar and ganglion cells and the visual information is relayed to the brain, especially to the visual cortex, via the optic nerve and the lateral geniculate nucleus. Moreover, the retina contains amacrine and horizontal cells acting as interneurons, as well as Müller cells that have a glial function. The retinal pigment epithelium is also part of the retina and plays a role in several trophic functions, including light absorption, photoreceptor disk renewal mechanisms and immune modulation, to name a few (Wimmers et al., 2007; Hoon et al., 2014). The retinal function can be measured using non-invasive techniques, such as the flash electroretinogram (fERG), the pattern electroretinogram (PERG), the multifocal electroretinogram (mfERG) and the electrooculogram (EOG). These techniques yield measures and allow the function assessment of the different cell types found in the retina.

The fERG measures the electric biopotential evoked mainly by the photoreceptor cells, namely rods and cones, and the ON-bipolar and Müller cells complex, in response to a light stimulation. fERG recordings performed under photopic and scotopic conditions are called light- and dark-adapted fERG respectively, according to the flash luminance intensity used, which is measured in candelas.s.m^{-2} (cds.s.m^{-2}) (McCulloch et al., 2015). Two main components are usually observed on a typical fERG trace: an electronegative component called a-wave, followed by an electropositive component named b-wave. The a-wave is generated by the hyperpolarization of the photoreceptors and the b-wave reflects the depolarization of the ON-bipolar and Müller cells complex. Two main parameters are derived from these components, named by convention the amplitude measured in microvolts (μV) and the implicit time measured in milliseconds (ms) (McCulloch et al., 2015). The a-wave amplitude is measured from the baseline to the trough, and the b-wave amplitude is measured from the trough of the a-wave to the peak of the b-wave. The implicit time represents the time necessary to reach the maximal amplitude of the waves. Typical fERG traces and their main components are represented in Fig. 1. These measures represent the initial responses at the retinal level.

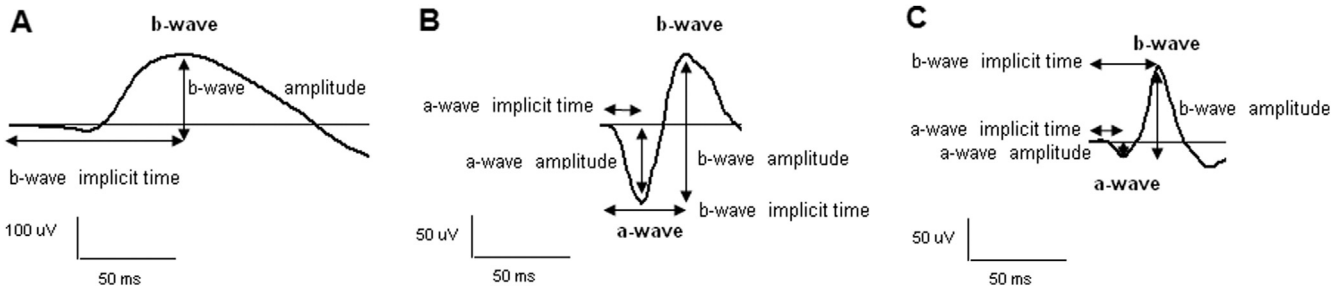

Fig. 1. Typical fERG traces obtained when assessing the rod response (A), the mixed rod and cone response (B) and the cone response (C). The arrows represent the way the parameters are measured, namely the a- and b-wave amplitude and implicit time.