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Looking into the brain through the retinal ganglion cells in psychiatric disorders: A review of evidences

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ABSTRACT

Psychiatry and neuroscience research need novel approaches to indirectly investigate brain function. As the retina is an anatomical and developmental extension of the central nervous system (CNS), changes in retinal function may reflect neurological dysfunctions in psychiatric disorders. The last and most integrated retinal relay before visual information transfer to the brain is the ganglion cell layer. Here, based on collected arguments, we argue that these cells offer a crucial site for indirectly investigating brain function. We describe the anatomical and physiological properties of these cells together with measurements of their functional properties named pattern electroretinogram (PERG). Based on ganglion cell dysfunctions measured with PERG in neurological disorders, we argue for the relevance of studying ganglion cell function in psychiatric research. We review studies that have evaluated ganglion cell function in psychiatric and addictive disorders and discuss how changes in PERG measurements could be functional markers of pathophysiological mechanisms of psychiatric disorders.

1. Introduction

Studying the living brain to advance knowledge on the biological mechanisms underpinning brain dysfunctions in psychiatric disorders is still a major challenge for psychiatric research. As direct access to the functioning brain remains difficult, novel approaches are needed to indirectly study neurological functions in the hope that they will allow better understanding of the pathophysiology of psychiatric diseases, improve diagnoses, and guide therapy in these disorders. One candidate is the retina, which is emerging as a crucial site for indirect investigation of brain function in central nervous system (CNS) disorders (London et al., 2013), especially psychiatric (Lavoie et al., 2014b, 2014a; Schwitzer et al., 2015a, 2016d) and addictive disorders (Laprevote et al., 2015b; Schwitzer et al., 2015b, 2016c, 2016a). Retinal function opens opportunities to study an accessible complex neural network that is part of the CNS and whose critical functional stages are readily accessible to standardized measurements (Bach et al., 2013; Holder et al., 2010; Hoon et al., 2012; Marmor et al., 2011; McCulloch et al., 2015). The study of retinal function in psychiatric diseases is still a nascent field yet has already yielded significant and relevant results (Lavoie et al., 2014b; Schwitzer et al., 2015a). For example, in seasonal affective disorder (SAD), cone, mixed rod-cone and rod responses are altered in wintertime, but rod function normalizes in summertime (Hébert et al., 2004, 2002; Lam et al., 1992; Lavoie et al., 2009). In schizophrenia, cone response is impaired in medicated and untreated patients and rod response show abnormalities in medicated patients (Balogh et al., 2008; Warner et al., 1999). In drug addiction, cone function is dysfunctional in cocaine-dependent subjects (Roy et al., 1997a, 1997b).

The fact that the retina is a neurosensory extension of the CNS formed from the neural tube and derived from neuroblast cells makes the retinal function a particularly relevant focus of study for exploring brain abnormalities in mental disorders (Hoon et al., 2014). The retina is organized in layers of specialized neurons interconnected by synapses (Fig. 1). The main readily measurable stages involved in retinal processing are rod and cone photoreceptors and bipolar and ganglion

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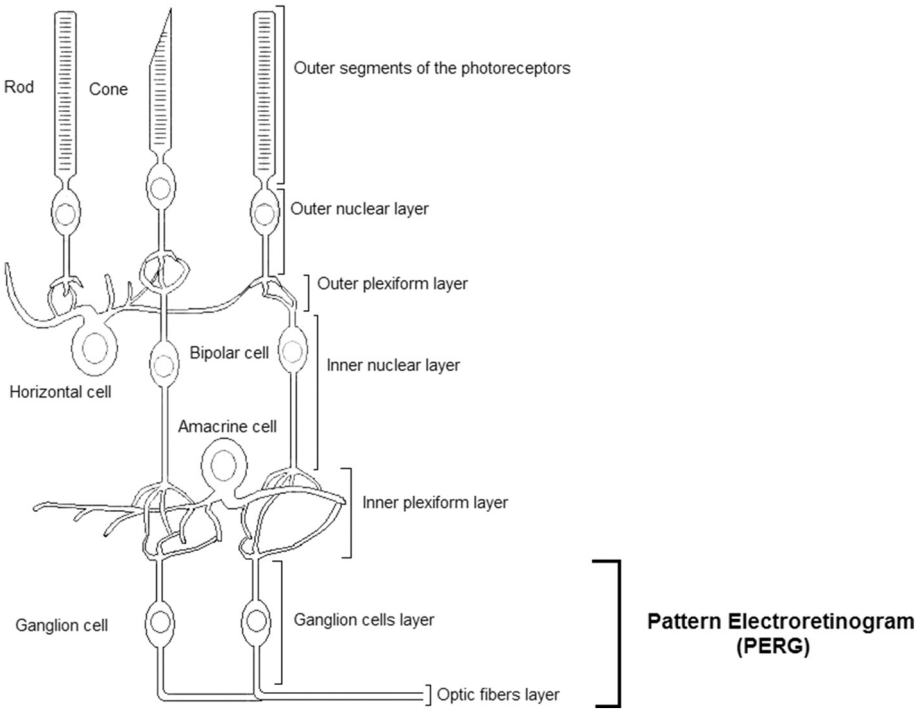

Fig. 1. Schematic representation of the retina. Ganglion cell layer function is evaluated with the pattern electroretinogram (PERG).

cells. The retina also comprises interneuron cells (amacrine cells and horizontal cells) and glial Müller cells that maintain homeostatic and metabolic properties (Hoon et al., 2014). The retina is involved in the first steps of visual processing, beginning by the conversion of light to potential variations in photoreceptors, which modifies neurotransmitter release (Hoon et al., 2014). The ganglion cells, which send off axons that form the optic nerve, then transfer the signal to the visual cortex by emitting action potentials (Famiglietti and Kolb, 1976).

Among all the retinal structures, ganglion cells offer a particularly interesting stage to study the functioning brain indirectly, due to their anatomical and functional properties and the characteristics of their electrophysiological measurements. It is well known that the pathophysiology of neurological and psychiatric disorders combines several factors, including genetics, environmental stressors, and dysfunctional molecular signaling pathways. The study of retinal ganglion cell function cannot capture all of these factors, but it can provide deeper insight into brain dysfunctions, especially synaptic transmission abnormalities in these disorders. The study of retinal ganglion cell function in psychiatric disorders is still a nascent field, but the literature has already emerged promising findings. Here we discuss why the study of the retinal ganglion cells holds such promise as an approach for study into the functioning brain and how it could enhance our understanding of the pathophysiology of psychiatric disorders.

2. Materials and methods

References for bibliographic research and data collection were selected by searching the PubMed, ScienceDirect and Google Scholar databases for full-text articles or abstracts in English, with no limitations on date of publication. The review used various combinations of the following terms: “retina”, “retinal ganglion cells”, “ganglion cells”, “optic nerve”, “psychiatric diseases”, “psychiatric disorders”, “neurotransmission”, “synaptic transmission”, “neurodegeneration”, “inflammation”, “retinal function”, “pattern electroretinogram”, “optic coherence tomography”, “visual evoked potential”. Relevant articles were also selected from the reference lists of each selected article.

3. Anatomical and physiological properties of the retinal ganglion cells

Retinal ganglion cells constitute the last and most integrated retinal stage and, in the visual pathways, offer indirect and readily-measurable access to brain function between visual phototransduction processing in photoreceptors and thalamic and cortical visual processing (Boycott and Wässle, 1999). Dendrites of ganglion cells contact axons of bipolar and amacrine cells within the retinal inner plexiform layer (Fig. 1), whereas their axons that form the optic nerve are projected out to the visual network via the lateral geniculate nucleus (Hoon et al., 2014). Consequently, the sensory information recorded at the ganglion cell layer is already coded and modulated by previous retinal stages. Unlike visual information in brain processing, it is not under the influence of high-level cognitive functions and not dependent on attentional achievement (Knight and Silverstein, 2001). Furthermore, the mapping of visual input from retina to neurons, called retinotopy, is similar between the retinal ganglion cells and thalamic neurons (Wandell and Winawer, 2011). Posterior to the eyes, the transfer of visual information from ganglion cells to later visual relays is mediated by the properties of the myelinated nerve fibers of the optic nerve formed by axons of the ganglion cells (Shum et al., 2016).

The retinal ganglion cells act as an anatomical and functional relay between the retina and the brain, and share similar anatomical and functional characteristics to thalamic and cortical neurons (Famiglietti and Kolb, 1976; Jeffries et al., 2014). Indeed, retinal ganglion cells are divided into several classes of specialized neurons and are usually composed of cell body, axons and dendrites (Sand et al., 2012; Yu et al., 2013). After stimulation, ganglion cells are the first visual stage providing response in the form of action potentials, typically along higher visual centers in the brain (Famiglietti and Kolb, 1976). This post-stimulation response differs from that of other retinal stages, especially photoreceptors where the response to stimulation is a gradual variation of membrane potential (Baylor, 1996). Ganglion cells have receptor fields with concentric ON-center and OFF-center properties, as in thalamic and cortical neurons of the visual pathways (Dacey, 2000; Famiglietti and Kolb, 1976; Masland, 2012, 2001).

Retinal ganglion cells show anatomical and functional segregation