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Review article

Cannabis use and human retina: The path for the study of brain synaptic transmission dysfunctions in cannabis users

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ABSTRACT

Owing to the difficulty of obtaining direct access to the functioning brain, new approaches are needed for the indirect exploration of brain disorders in neuroscience research. Due to its embryonic origin, the retina is part of the central nervous system and is well suited to the investigation of neurological functions in psychiatric and addictive disorders. In this review, we focus on cannabis use, which is a crucial public health challenge, since cannabis is one of the most widely used addictive drugs in industrialized countries. We first explain why studying retinal function is relevant when exploring the effects of cannabis use on brain function. Next, we describe both the retinal electrophysiological measurements and retinal dysfunctions observed after acute and regular cannabis use. We then discuss how these retinal dysfunctions may inform brain synaptic transmission abnormalities. Finally, we present various directions for future research on the neurotoxic effects of cannabis use.

1. Introduction

As cannabis is one of the most widely used drugs worldwide, its use is a major public health concern (Degenhardt et al., 2008). Cannabis use is known to be associated with several harmful effects on human health (Volkow et al., 2014). Among these, acute and regular cannabis use are linked to alterations in central nervous system (CNS) functioning (Broyd et al., 2016). For example, a decline in the main cognitive functions such as memory, attention, executive functions, speed of information processing and intelligence quotient (IQ) is observed after acute or regular cannabis use (Broyd et al., 2016; Meier et al., 2012). The neurotoxic impact of cannabis use on CNS functioning is mediated by the effect of exocannabinoids – mainly delta-9 tetrahydrocannabinol (THC)— on cannabinoid receptors—mainly CB1- (Mechoulam and Hanus, 2000; Mechoulam and Parker, 2013). However, the precise mechanisms underlying these dysfunctions remain to be understood and are thus current research interests in neuroscience. Due to the difficulty of obtaining direct access to the functioning brain, new approaches are needed to study the neurological functions in an indirect manner.

In humans, the retina is endowed with a functional cannabinoid system, which implies that exocannabinoids should affect retinal functioning (Schwitzer et al., 2016b 2015b; Yazulla, 2008a). Cannabinoid receptors CB1 and CB2 are detected in the human retina (Porcella et al., 2000; Straiker et al., 1999a, b; Wei et al., 2009). CB1 receptors are expressed in the outer segments of photoreceptors, the inner plexiform layer, outer plexiform layer, inner nuclear layer, ganglion cell layer, and the retinal pigment epithelium. CB2 receptors are expressed in human retinal pigment epithelium cells. The two main endocannabinoid ligands -2-Arachidonoylglycerol (2-AG) and Anandamide are also detected in the human retina (Chen et al., 2005; Matias et al., 2006; Stamer et al., 2001). High levels of 2-AG are found in the retina whereas anandamide is expressed at a lower level. Several enzymes are involved in the regulation of the cellular level of retinal endocannabinoids and enable the degradation of cannabinoid ligands: fatty acid amide hydrolase (FAAH), monoacylglycerol lipase (MGL),

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and cyclooxygenase-2 (COX-2) (Wang et al., 2011; Wei et al., 2009). FAAH is an integral membrane protein that is expressed in the human retina, especially in the retinal pigment epithelium (Wei et al., 2009). Recent findings also report a detection of COX-2 in the human retina (Wang et al., 2011).

Since endocannabinoids and cannabinoid receptors are detected in animal and human work, a potential role of exocannabinoids in retinal neurotransmission may be evoked (Laprevote et al., 2015; Schwitzer et al., 2015b; Yazulla, 2008b). For example, cannabinoid agonists are involved in dose-dependent reversible modulations of calcium, potassium, and chloride currents in bipolar, rod, cone, and ganglion cells (Fan and Yazulla, 2003, 2004, 2005, 2007; Lalonde et al., 2006; Opere et al., 2006; Straiker et al., 1999a, b; Straiker and Sullivan, 2003; Yazulla et al., 2000; Zhang et al., 2013). A direct effect of cannabinoids on enzymatic activity and transmitter release has also been described in the retina of animal species (Gawienowski et al., 1982; Middleton and Protti, 2011; Opere et al., 2006; Schlicker et al., 1996; Warrier and Wilson, 2007; Weber and Schlicker, 2001). In the bovine retina, THC leads to a dose-dependent modulation of monoamine oxydase activity (Gawienowski et al., 1982). In the isolated bovine retina, CB1 receptor agonists inhibit aspartate release, which is blocked by cannabinoid antagonists (Opere et al., 2006). In perfused guinea-pig retinal discs, dopamine and noradrenaline transmission release is inhibited by the activation of CB1 receptors, which is blocked by cannabinoid antagonists (Schlicker et al., 1996; Weber and Schlicker, 2001). Interestingly, the release of dopamine, GABA and glutamate can be modulated by cannabinoids (Middleton and Protti, 2011; Opere et al., 2006; Schlicker et al., 1996; Straiker and Sullivan, 2003; Warrier and Wilson, 2007; Weber and Schlicker, 2001). The retinal endocannabinoid system is also involved in other physiological neural mechanisms such as neural plasticity and neuroprotection (Schwitzer et al., 2016b).

The retina is a highly conducive site for the investigation of brain functioning in CNS and neuroscience research (Bernardin et al., 2017; Garcia-Martin et al., 2014; Laprevote et al., 2015; Lavoie et al., 2014c; London et al., 2013; Schwitzer et al., 2017b 2015a).The retina is an anatomical and developmental extension of the CNS due to its embryonic origin (Hoon et al., 2014). The retina and the brain are interconnected by the optic nerve, which is composed of the axons of ganglion cells, i.e. the final and more integrated retinal stage (Hoon et al., 2014). Retinal architecture, including retinal neurons and retinal microvasculature, shares similar features with these structures in the brain (Cheung et al., 2017). Retinal arterioles and venules and cerebral small vessels display similar size and regulatory mechanisms (Cheung et al., 2015, 2014; Patton et al., 2006, 2005). Retinopathy and retinal arteriovenous nicking are associated with an increasing risk of developing cerebral infraction and stroke. The retina is composed of layers of specialized neurons which are interconnected by synapses and under the influence of a complex neurotransmission system (Hoon et al., 2014). Retinal neurons are made up of a cell body, axons and dendrites, like the neurons in the brain. The axons of the retinal ganglion cells are myelinated when they leave the eye to form the optic nerve. This structure is particularly sensitive to inflammatory and immunological processes. For example, in multiple sclerosis, retinal architecture and functioning are altered, as observed with retinal imaging (optical coherence tomography: OCT) and functional (pattern electroretinogram) techniques, and vary with the course of the disease (Celesia et al., 1986; Holder et al., 2009; Sergott et al., 2007). The optic nerve converges at the optic tracts and the visual information is then relayed to the visual cortex. There is a significant connection between the retina and the brain which explains that pathological processes of the brain such as vascular, inflammatory, immunological, neurodegenerative processes and neurotransmission can also propagate in the retina (Ho et al., 2012; London et al., 2013). This can also explain why visual and retinal impairments are often observed in CNS diseases. As examples, in Alzheimer's disease (AD) or Parkinson's disease (PD), visual impairments often occur during disease evolution, suggesting alterations of the visual system (Ascaso et al., 2014; Bodis-Wollner et al., 1987; Bodis-Wollner and Yahr, 1978; Cronin-Golomb et al., 1991; Crow et al., 2003; Garcia-Martin et al., 2014; Gottlob et al., 1987; Krasodomska et al., 2010; Langheinrich, 2000; Lu et al., 2010; Moschos et al., 2012; Palmowski-Wolfe et al., 2006; Parisi et al., 2001; Peppe et al., 1995). In particular, recent results suggest that the architectural and functional properties of the retina are affected early in CNS diseases, implying that they may be early markers of CNS alterations (Lu et al., 2010; Moschos et al., 2012). Additionally, clinical studies support a link between visual and retinal impairments and clinical manifestations of CNS disorders. For example, in AD cognitive deficits such as loss of memory and attention are frequently associated with visual dysfunctions such as anomalies in contrast sensitivity, color discrimination, to name a few (Cronin-Golomb et al., 1991; Crow et al., 2003; Moschos et al., 2012; Yamasaki et al., 2016). Abnormalities at the retinal level may participate to these deficits. Another finding in AD animal models and patients showed that beta amyloid (Aβ) accumulation is detected in the retina and accompanied by degeneration of retinal ganglion cells (Koronyo-Hamaoui et al., 2011; La Morgia et al., 2016; Parthasarathy et al., 2015). Interestingly, the accumulation of Aβ plaques occurs first in the retina and then in the brain. In immunological diseases, the retina can be affected before the brain and other CNS structures and retinal manifestations help us to reach a diagnosis, such as in several kinds of lymphoma (Buggage et al., 2001). Interestingly, such etiologies—inflammation, neurodegeneration, vascular, immunological and neurotransmission processes—are also suggested in the physiopathology of psychiatric disorders (Borroto-Escuela et al., 2016; Brites and Fernandes, 2015; Glausier and Lewis, 2017; Huang and Lin, 2015; Khandaker et al., 2015; Khandaker and Dantzer, 2016; Kim et al., 2016; Leboyer et al., 2016; Lopresti et al., 2014; Pasternak et al., 2015; Sanacora et al., 2003, 1999; Stuart et al., 2015).

Retinal function can be assessed by electrophysiological techniques known respectively as full-field electroretinogram (ffERG), pattern electroretinogram (PERG), multifocal ERG (mfERG) and electrooculogram (EOG) (Holder et al., 2010). ffERG, PERG and mfERG are objective and non-invasive techniques which record the electrical biopotential evoked by retinal cells in response to a light stimulation. Each exam allows for the assessment of specific functional properties of retinal neurons (Holder et al., 2010). EOG measures the variation of electrical potentials between skin electrodes located in external and internal canthus and reflects retinal pigment epithelium and photoreceptor activity (Marmor et al., 2011). ffERG, PERG, mfERG and EOG have been evaluated in many neuropsychiatric disorders (Lavoie et al., 2014c; London et al., 2013; Schwitzer et al., 2015a). Although the study of the neurobiological effects of cannabis use only recently included the exploration of retinal function, several retinal dysfunctions have been observed with retinal electrophysiological techniques in cannabis users, after acute or regular use (Faure et al., 2016; Schwitzer et al., 2018 2017a 2016a; Zobor et al., 2015). It is thought that these retinal abnormalities reflect modulations in neurotransmission-signaling pathways and could thus reveal brain neurotransmission dysfunctions following acute or regular cannabis use.

This review first summarizes the arguments suggesting the retina is a relevant site to investigate brain neurotransmission anomalies in cannabis users. We then describe retinal electrophysiological measurements methods, as used in research with cannabis users. We also report on studies which have evaluated the impact of cannabis use on retinal functioning. Based on the distribution of dopaminergic, glutamatergic and GABAergic retinal synaptic transmission and their role in retinal processing, we finally discuss the extent to which retinal dysfunctions detected in cannabis users could be markers of brain neurotransmission abnormalities.

2. The benefits provided by retinal processing measurements in neuroscience research

As already emphasized, the retina is an integral part of the CNS. The retina represents the first stage of visual processing when the light enters the eyes and thus represents an easy-to-access part of the CNS. The retinal function is not under the influence of high level cognitive functions—attention for example—such as when cortical visual processing is recorded. Retinal processing is a well-studied function (Hoon et al., 2014). Measurements of retinal processing are well standardized, allowing for good reproducibility (Holder et al., 2010). Electrophysiological tests may be used alone or coupled with another measure to accurately evaluate retinal functioning. Using these exams, the study of the retinal function is fast, inexpensive, and easy to conduct. It can be mobile and small. Retinal function anomalies evaluated by retinal electrophysiological measurements are associated with a series of neuropsychiatric disorders (Lavoie et al., 2014d; Schwitzer et al., 2017b 2015a; Silverstein and Rosen, 2015). Despite the fact that the majority of these studies are performed on small sample sizes and that the specificity of these markers should be confirmed, parameters extracted from retinal electrophysiological measurements may be candidates for use as functional indicators of neuropsychiatric disorders such as schizophrenia, bipolar and depressive disorder, neurodegenerative disorders, to name but a few. More specifically, ffERG may be used to examine neurotransmission abnormalities in neuropsychiatric disorders. Lavoie et al. (Lavoie et al., 2014a) showed that alterations in central dopamine and serotonin neurotransmission—two neurotransmitters involved in the pathophysiology of neuropsychiatric and addictive disorders—affected the ffERG responses in mice. ffERG may also provide early and specific functional markers of risk in developing neuropsychiatric disorders. In young non-affected and non-medicated offspring at high genetic risk of neuropsychiatric disorders, a specific electroretinographic anomaly was observed in the rod retinal response (Hébert et al., 2010). In this study, ffERG was performed in 29 high risk offspring having one parent affected by schizophrenia or bipolar disorder and 29 healthy control subjects. b-wave amplitude of the rod response in high risk offspring was significantly lower than in control subjects whereas the cone response showed no difference. This anomaly in retinal response was observed independently of parents' diagnosis (schizophrenia or bipolar disorder) and was present in both the younger and older high risk offspring. Additionally, modifications of ffERG parameters, as shown by the alteration of the scotopic b-wave implicit time, were observed in mice after long term treatment by lithium, a mood stabilizer frequently used in bipolar disorder (Lavoie et al., 2015). This study shows that administration of lithium influences ffERG responses in mice and underlines the need to examine whether ffERG might provide relevant functional markers for pharmacotherapeutic evaluation.

Retinal electrophysiological measurements currently represent one of several tools available to neuroscience research to directly or indirectly study brain activity and accurately objectify brain dysfunctions in neuropsychiatric disorders in order to enhance understanding of brain function. Using the current standard toolbox in neuroscientific research, brain measurements are mainly represented by functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). Indirect physiological signals of CNS activity include electrodermal activity, heart rate variability, pupillary response, and blink-startle, amongst others. As with retinal electrophysiological measurements, many of these are inexpensive and easy to implement. In this section, the relevance of retinal electrophysiological measurements is discussed relative to fMRI and EEG, two measures of brain activity. EEG provides a measure of the brain's electrical activity and visual evoked potentials (VEP) allow the assessment of the visual system (Odom et al., 2010). VEP can be coupled with retinal electrophysiological measurements—ffERG, PERG and mfERG—to give a clearer picture of the visual system functioning. Interestingly, measurements of retinal activity using ffERG, PERG and mfERG and the measurements of cortical function with VEP share the same methodological characteristics (Bach et al., 2013; Holder et al., 2010; Odom et al., 2010). Both techniques can be performed with stimuli such as flashes or checkerboards, whose parameters such as intensity, contrast level, rate of stimulation, and size can be adapted to specific protocols (Bach et al., 2013; Holder et al., 2010; Odom et al., 2010). Moreover, the same stimulations can be used during simultaneous recording of retinal and visual cortical activity. Similarly, VEP and retinal electrophysiological measurements can be performed during visual tasks such as contrast sensitivity, or synchrony-asynchrony to observe how and where the visual system is affected. Since visual deficits are often associated with neuropsychiatric disorders, the combined measures of retinal electrophysiological measurements and VEP may provide information on the early and later localization of functional deficits within the visual system. Based on the hypothesis that early anomalies may be located in the retina, retinal electrophysiological measurements and VEP can be used in the follow up of visual system dysfunctions occurring in neuropsychiatric disorders. Besides electrophysiological techniques, MRI is a direct architectural brain measure whereas optic coherence tomography (OCT) is a direct anatomical retinal measure (Baghaie et al., 2015a; Hong et al., 2005). MRI and OCT do not provide information on function but can detect underlying morphological anomalies. Interestingly, MRI and OCT provide a continuous viewing of neuronal structure from retinal photoreceptors to visual cortical neurons. Above all, the optic nerve, which connects the retina and central structures in the brain, can be studied using both techniques. Adding functional or architectural retinal measurements to brain measures can offer the unique opportunity to study the CNS at two critical levels involved in visual processing, each of which can provide relevant information on the pathophysiological mechanisms involved in neuropsychiatric disorders. Additionally, eye and brain measures are based on the extraction of similar parameters. Amplitude and implicit time are derived from waveforms of VEP and retinal electrophysiological measurements (Holder et al., 2010; Odom et al., 2010). Morphological aspect, size and thickness are derived from structures observed with MRI and OCT (Baghaie et al., 2015b; Ives-Deliperi et al., 2013). Importantly, cortical and retinal electrophysiological measurements, as well as cortical and retinal imaging techniques, are currently seen as complementary measurements for detecting and monitoring eye and central visual deficits in neuro-ophthalmological disorders (Holder, 2001). Although this is an emerging field in neuroscience, using the coupled measures of retinal and cortical activity and/or retinal and cortical morphology enhances the powerfulness of exploration techniques in CNS disorders and may provide additional insights into diagnosis, prognosis, or therapeutic use to clinicians or researchers.

3. Measurements of retinal function

Several measurements of retinal functioning are currently available to neuroscience research. Each one of these techniques can provide information about the specific anomalies of the various retinal cell types. Since they allow for the precise evaluation of retinal cell functioning, they can be expected to provide specific markers of synaptic transmission abnormalities, thereby helping us understand brain dysfunctions in cannabis users.

3.1. Experimental protocol

Retinal electrophysiological measurements are recorded in precise conditions in a specific room in which parameters such as obscurity and ambient light must be adjusted. In each of these conditions, the patients are placed facing a stimulator that emits visual stimuli, such as flashes, alternating black and white checkerboards, or an array of a rapidly changing sequence of black and white hexagons. Depending on the exams, the patient is placed at various distances from the screen.

Electrical signals can be recorded on non-dilated and dilated pupils, generally with DTL (Dawson, Trick & Litzkow) or sclerocorneal electrodes, to name a few examples. The pupil's size is noted, when appropriate, before and after recordings and should remain systematically constant during the whole testing period. Ground and reference electrodes are usually attached to the forehead and external canthi. Before placing the electrodes, the skin is prepared and cleaned with pumice paste and alcohol to extract all deposits. There is usually an adaptation period before the exams are completed. Electrical signals are usually recorded simultaneously from both eyes, apart from mfERG. The electrical signals are then amplified with an amplifier and transmitted to a computer connected to the stimulator. Average retinal responses are first obtained from each eye and then the values of the parameters—implicit time and amplitude—are averaged over both eyes for analysis. The Guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV) for EOG, PERG, ffERG nd mfERG help to standardize the methods (Bach et al., 2013; Hood et al., 2012; Marmor et al., 2011; McCulloch et al., 2015).

3.2. Full-field electroretinogram (ffERG)

The ffERG records the electric bio-potential evoked by the photoreceptors, known as rods and cones, and the ON-bipolar and Müller cells complex, in response to a light stimulation delivered as a flash (Holder et al., 2010). ffERG recordings are performed under scotopic and photopic conditions and are labelled dark- and light-adapted ffERG respectively, according to the flash luminance intensity used in candelas·s·m^2 (cd·s·m^{-2}) (McCulloch et al., 2015). They are dark-adapted for a period of 20 min before dark-adapted ffERG is recorded. They are light-adapted for 10 min to a light background set at 30 cd·m^2 (cd·m^2) managed by the stimulator before light-adapted ffERG is conducted. Recordings can be performed first in light condition and then in dark condition and reciprocally. At least 8 and 16 responses, for dark- and light-adapted ffERG respectively, are usually recorded. Each retinal response is labeled according to the strength of the flash in cd·s·m^{-2}. To assess the functioning of the rod and cone system separately, dark-adapted 0.01 ffERG and light-adapted 3.0 ffERG are performed respectively. Other dark-adapted and light adapted ffERG can also be used such as the mixed rod-cone response, also known as dark-adapted 3.0 ffERG. The two main components usually described on a typical ffERG are an electronegative component, a-wave, followed by an electropositive component, b-wave. The a-wave is not detected in the dark-adapted 0.01 ffERG response because it is masked by the b-wave. An a-wave is attributed to the retinal photoreceptors and a b-wave is attributed to the retinal bipolar cells, postsynaptic to photoreceptors. Two main parameters are derived from a- and b-waves, known by convention as the amplitude measured in microvolts (μV) and the implicit time measured in milliseconds (ms). The a-wave amplitude is measured from the baseline to the trough of the a-wave. The b-wave amplitude is measured from the trough of the a-wave to the peak of the b-wave. Implicit time denotes the time taken to reach the maximum a- and b-wave amplitudes (Holder et al., 2010; McCulloch et al., 2015). ffERG traces are represented in Fig. 1. ISCEV standard are available for ffERG (McCulloch et al., 2015).

3.3. Pattern electroretinogram (PERG)

The PERG records the central macular function of the retina, as well as the retinal ganglion cell response, using reversing black and white checkerboards (Holder et al., 2010). For example, to investigate the transient PERG according to international guidelines, a black and white contrast reversible checkerboard, with 0.8° check size, 93.3% contrast level, 100 cd·m^2 constant luminance white area, and 2–6 reversals per second (1–3 Hz) may be used. In the case of participants with refractive disorders, an appropriate optic correction is provided. At least 220 retinal responses are recorded for each participant, using constant ambient room-lighting to achieve the best signal-to-noise ratio. Two main components are usually described on a typical PERG trace: an electropositive component, P50, followed by an electronegative component, N95. N95 is believed to reflect the response of the retinal ganglion cells. P50 reflects the response of the retinal ganglion cells and macular photoreceptors and is used to evaluate the macular function. Two main parameters are derived from P50 and N95, known by convention as the amplitude measured in microvolts (μV) and the implicit time measured in milliseconds (ms). N95 amplitude is measured from the trough of the N95 to the peak of the P50. P50 amplitude is measured from the trough of the inconstant N35—or from the baseline—to the peak of the P50. Peak time denotes the time taken to reach the maximum N95 and P50 amplitudes (Bach et al., 2013; Holder et al., 2010). A PERG trace is represented in Fig. 1. ISCEV standard are available for PERG (Bach et al., 2013).

3.4. Multifocal electroretinogram (mfERG)

The mfERG records the spatial properties of the retinal cone function (Hood et al., 2012). The mfERG measurements are performed in photopic conditions, generally with dilated pupils, but can also be performed with no eye dilatation. Each eye is usually tested monocularly, the other being occulted during the stimulation but mfERG can also be recorded in both eyes at the same time. The stimulus is composed of multiple hexagons gradually increasing in size from the center to the periphery of the screen (Holder et al., 2010). Each hexagon is illuminated pseudo-randomly by a flash stimulation and elicits a local response of the retinal cone system. The mfERG recordings allow for the evaluation of multiple local responses derived from each hexagon. Subjects are fully corrected optically for the viewing distance and asked to fixate on the central target. Any segments associated with blinks or eye movements are immediately rejected. At least 5000 responses are recorded for each eye of each participant with a level of noise maintained under 5 Kiloohm (KΩ) to achieve the best signal-to-noise ratio. mfERG responses are averaged over five retinal regions: $< 2^\circ$ (deg), 2–5 deg, 5–10 deg, 10–15 deg, and > 15 deg. Three main components are usually described on a typical mfERG trace: a first negative wave called N1, followed by an electropositive component P1, and then a second negative wave N2. Two main parameters are derived from N1, P1 and N2, known by convention as the amplitude measured in microvolts (uV) and the implicit time measured in milliseconds (ms). The amplitude of N1 was measured from the baseline to the trough of N1. The amplitude of P1 and N2 are the trough-to-peak amplitude, measured respectively from the trough of N1 to the peak of P1 and from the peak of P1 to the trough of N2. Implicit time denotes the time taken to reach the maximum N1, P1 and N2 amplitudes. N1 results from the hyperpolarization of the OFF-bipolar cells and P1 results of the depolarization of ON-bipolar cells (Holder et al., 2010; Hood et al., 2012). mfERG traces are represented in Fig. 1. ISCEV standard are available for mfERG (Hood et al., 2012).

3.5. Electrooculogram (EOG)

The EOG allows to study the retinal pigment epithelium (RPE), and the interaction between the RPE and the photoreceptors via the variations of electrical potentials through the RPE (Holder et al., 2010; Marmor et al., 2011). Variations are measured by skin electrodes placed at the level of the internal and external canthus of the eyes (Arden and Constable, 2006). They correspond to an electrical potential between the front and the back of the eye and are known as standing potentials (Marmor et al., 2011). This potential mainly originates from the RPE and varies with the retinal illumination. It is recorded during a period of 15–20 min dark adaptation, and then during a 12–15 min period of light adaptation. The subject is asked to make 30-degree lateral eye movements alternately to the right and to the left, without moving the head. The eye movements are realized every 1–2 s for approximately

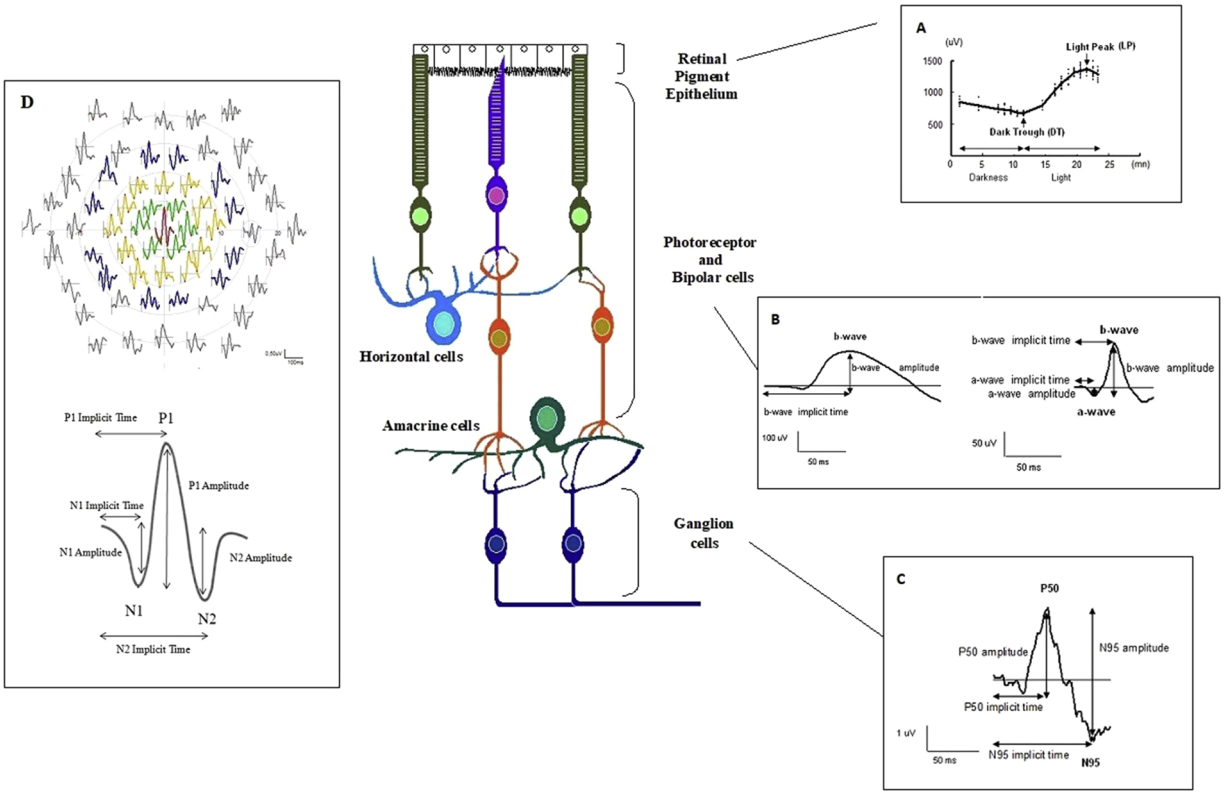

Fig. 1. Schematic representation of the retina with retinal electrophysiological measurements: A. Electrooculogram (EOG), B. Full-field Electroretinogram (ffERG), C. Pattern Electroretinogram (PERG), D. Multifocal Electroretinogram (mfERG).

10 s every minute. Two parameters are derived from the EOG trace, namely the dark trough, which represents the trough of the curve in dark condition whose origin remains unclear, and the light peak, which represents the maximal peak in light condition and corresponds to the maximal depolarization of the basal membrane of the RPE. The ratio of the two gives the Arden ratio, normally greater than 180% and corresponding to the kinetics of apparition of the LP, reflecting the functioning of the basal membrane of the RPE. A decrease in the Arden ratio then supports anomalies in the depolarization of the basal membrane and photoreceptor activity, either by the failure of the signal to be transmitted by the rods to the internal layers of the retina and to the RPE, or by dysfunctions of the chloride channels at the level of the basal membrane (Holder et al., 2010; Marmor et al., 2011). Results obtained with EOG depend on the capacity of the subject to perform the eye saccades at a specific rate. If not performed correctly, the EOG will be abnormal. An EOG trace is represented in Fig. 1. ISCEV standards are available for EOG (Constable et al., 2017).

4. Retinal dysfunctions in cannabis users

The study of the retinal function in cannabis users is a recent field of investigation, but some results have nevertheless been observed after both acute and regular cannabis use. Our group investigated retinal function in a group of 53 cannabis users compared with 29 controls. In cannabis users vs. controls, we observed a delay in retinal response at two retinal levels: at the level of ON-bipolar cells of the cone system and at ganglion cell level (Schwitzer et al., 2017a 2018). The regular use of cannabis may alter the retinal function at two critical stages of retinal processing and involved in the vertical transmission of visual information in the retina, i.e. bipolar and ganglion cells, suggesting potential alterations in vision. No dysfunction was observed at the level of photoreceptor cells, suggesting that the phototransduction process is conserved. The main result concerns the delay observed in the ganglion cell response i.e. in the N95 implicit time measured with the PERG and calculated at approximatively 6 ms. This implies that visual information is delayed before leaving the retina through the optic nerve. Retinal ganglion cells form a complex neuronal network in the retina that features anatomical and functional properties similar to those of brain neurons, suggesting that they are a relevant site for the investigation of brain functioning in neuroscience research (Cheung et al., 2017; London et al., 2013; Schwitzer et al., 2017b). Retinal ganglion cells constitute the final and most integrated retinal stage which is located between visual phototransduction processing occurring in photoreceptors, and thalamic and cortical visual processing (Boycott and Wässle, 1999). The axons of ganglion cells, which transfer visual information to the brain, are myelinated nerve fibers (Shum et al., 2016). Ganglion cells provide response in the form of action potentials, as observed in brain neurons (Famiglietti and Kolb, 1976). Several kinds of ganglion cells—beta, alpha and gamma—already initiate the parvocellular, magnocellular and koniocellular pathways, respectively, and most importantly display specific properties adapted to each pathway (Yoonessi and Yoonessi, 2011). The excitation and inhibition of ganglion cell response is mediated through feedback and feedforward mechanisms by several neurotransmitters, such as dopamine, serotonin, glutamate and γ-aminobutyric acid (GABA) (Hoon et al., 2014). Based on these similarities with brain transmission, retinal ganglion cell dysfunctions may help to provide an insight into brain abnormalities in CNS disorders (Fig. 2). However, electrophysiological tests should be coupled with other measurements such as molecular and genetic measures in order to validate and confirm pathophysiological hypotheses that may be evoked using retinal electrophysiological measurements.

We also found a delay of approximatively 1 ms in the ON-bipolar cell response—a retinal stage that precedes the ganglion cell stage—as shown by an increase in the b-wave implicit time of the ffERG photopic 3.0 (Schwitzer et al., 2018). Thus, visual information is already delayed before retinal ganglion cell processing but with smaller delays. The responses of retinal stages situated before ganglion cells—photoreceptors and bipolar cells—differ from ganglion cell response,

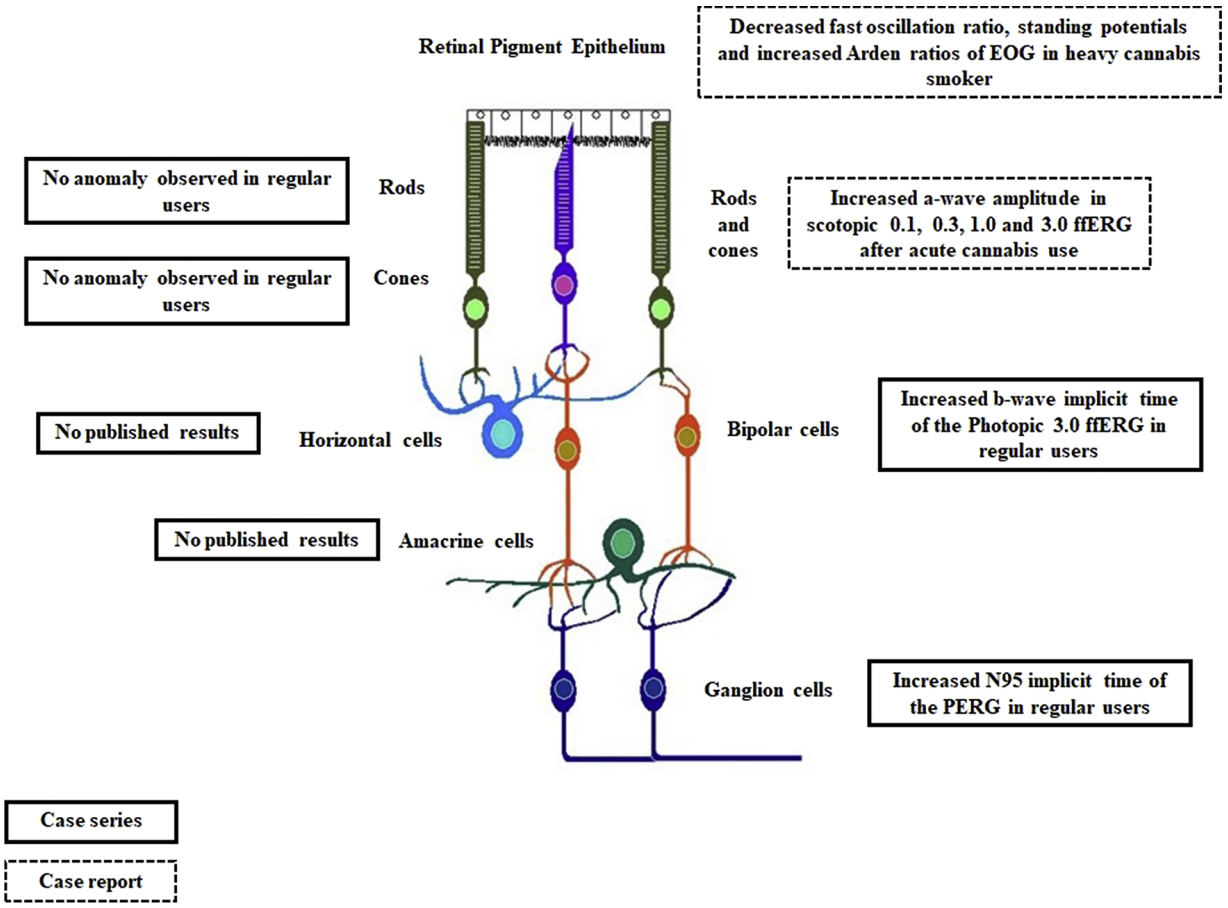

Fig. 2. Summary of retinal dysfunctions measured with electrophysiological techniques after acute and regular cannabis use and observed in case reports and case series.

since their responses to stimulation are a gradual variation of membrane potential (Baylor, 1996). Importantly, the depolarization and hyperpolarization of these cells occur mainly under the influence of glutamatergic signaling pathways, since glutamate is the key neurotransmitter involved in the transmission of vertical information within the retina (de Souza et al., 2013; Wu and Maple, 1998). In the case of cannabis use, anomalies in glutamatergic transmission might lie at the origin of these retinal dysfunctions since the pre-synaptic glutamate release is inhibited by the regular use of cannabis in central neurons (Bossong and Niesink, 2010). This inhibition is mediated through the blockade of CB1 receptors by exogenous cannabinoids such as THC, leading to an excess of post-synaptic influx of calcium. In the retina, cannabinoid agonists are involved in dose-dependent reversible modulation of several ionic currents—calcium, potassium, chloride—and in the direct regulation of glutamatergic transmission in bipolar and ganglion cells (Schwitzer et al., 2016b 2015b; Yazulla, 2008b). When we studied the sensitivity and specificity of these findings with a receiver operating characteristic (ROC) analysis, we observed that the N95 implicit time of the PERG (sensitivity = 79,2%, specificity = 79,3%) is a better marker than the b-wave implicit time of the ffERG photopic 3.0 (sensitivity = 71,7%, specificity = 69%), to correctly differentiate cannabis users from controls (Schwitzer et al., 2018).

In a single case, our group has also observed retinal dysfunctions after acute cannabis smoking (Schwitzer et al., 2016a). This observation was made possible by the need to conduct an annual ophthalmic evaluation in the context of a chloroquine intake for a systemic lupus erythematosus in a 47-year-old regular cannabis user. A complete ophthalmic evaluation—including retinal electrophysiological measurements—was performed twice, 30 min and 5 h after cannabis use. A large decrease of up to 48% in the ffERG a-wave amplitude was observed 30 min after cannabis intake for all scotopic responses compared with the responses 5 h after smoking. Acute use of cannabis may affect photoreceptor function. In another study using retinal electrophysiological measurements, no ffERG anomaly was found, either in a man suffering from a persistent perception disorder after cannabis use, or in four heavy cannabis users with no visual disturbance (Zobor et al., 2015). However, dysfunctions of the RPE were observed with EOG in the patient with perceptual hallucinations. These results should be viewed with caution (see also section 3.5) since an intrasubject reliability coefficient of 0.70 was reported by Seggie et al. (Seggie et al., 1991). This coefficient is lower compared to those reported with the ffERG (Hébert et al., 1999, 1995). In another single case observed in a 25-year-old man suffering from blurred vision of the right eye and who described a cannabis use of approximatively 5 joints per day, multiple subretinal blebs were observed with OCT. These alterations were associated with a reduced light peak of the right eye measured with EOG, without ffERG anomaly (Faure et al., 2016). In this situation, intoxication due to cannabis was suspected. Interestingly, morphological anomalies observed with OCT gradually decreased with the reduction in cannabis use. Although there was no ffERG abnormality detected in this patient, retinal morphological changes were observed, suggesting that OCT measurements could be another avenue available for research in cannabis users.

We suppose that these retinal dysfunctions, observed after acute or regular cannabis use, might be viewed as retinal synaptic transmission anomalies and might provide insights into brain neurotransmission abnormalities in cannabis users.

5. Cannabis and retinal synaptic transmission

In the CNS, the neural modulation of synaptic transmission induced by exocannabinoids is mediated through the endocannabinoid system including cannabinoid receptors, ligands and enzymes (Mechoulam and Parker, 2013). This system is located in neurons involved in both excitatory and inhibitory regulation of central synaptic transmission (Mechoulam et al., 2007; Mechoulam and Hanus, 2000; Mechoulam and Parker, 2013; Pertwee et al., 2010). More precisely, it is located in neurons involved in GABAergic (Caballero-Florán et al., 2016; Szabo et al., 2002, 1998), glutamatergic (Auclair et al., 2000; Kim and Thayer, 2000; Robbe et al., 2001) and dopaminergic (Wu and French, 2000) synaptic transmission and mediates the effects of exocannabinoids on CNS functioning. As part of the CNS, the retina is endowed with complex neurotransmission-signaling pathways, including dopaminergic, glutamatergic and GABAergic pathways (Hoon et al., 2014). Interestingly, due to the anatomical distribution of these pathways throughout the retina and their role in retinal processing, we can assume that exocannabinoids modulate retinal processing and induce retinal dysfunctions, as observed with retinal electrophysiological measurements.

Dopamine is the main catecholamine in the retina of mammal species (Witkovsky, 2004) and dopaminergic retinal synaptic transmission may thus be modulated by exocannabinoids. Dopamine is synthesized from the L-amino acid tyrosine by the tyrosine hydroxylase (Reis et al., 2007) and acts on five G-coupled protein receptors divided into two subcategories: D1-class (D1-R) and D2-class (D2-R) receptors (Beaulieu and Gainetdinov, 2011; Frederick et al., 1982). Interestingly, D1-R are found in bipolar, ganglion and horizontal cells whereas D2-R are detected in horizontal, bipolar and photoreceptor cells (Nguyen-Legros et al., 1997). Dopamine is used by amacrine and interplexiform cells in most mammalian species (Dowling and Ehinger, 1978; Witkovsky, 2004) and plays a major role in light adaptation (Marshak, 2001). The role of dopamine in modulating electrophysiological signals in the human retina remains unclear (for a review on the role of dopamine in modulating retinal electrical activity recorded with ffERG, see Popova, 2014a). Many studies have investigated the role of dopamine neural transmission and the involvement of dopaminergic receptors in retinal functioning using electrophysiological measurements in a high number of non-mammalian and mammalian species. Many contradictory results exist concerning the dopamine effects on the retinal electrical activity evaluated with electrophysiological measurements as well as concerning the receptors involved in these effects (Popova, 2014a). Our results suggest ON-bipolar cell dysfunctions—observed in the form of a delay, as shown by an increase in photopic b-wave implicit time—under the influence of the regular use of cannabis (Schwitzer et al., 2018). The role of dopamine in modulating the ON and OFF pathways is well described but the precise mechanisms for the differential effects of dopamine agonists and antagonists remain unclear (Popova, 2014a). Modulation of the retinal dopaminergic pathway through agonists or antagonists leads to modifications in both amplitude and implicit time of the photopic b-wave, which depends on the receptors involved in the effects. At present, it is difficult to draw conclusions about the precise mechanisms of dopaminergic modulations underlying retinal dysfunctions found in cannabis users. The fact that we showed an implicit time anomaly rather than an amplitude variation suggests that the total amount of functional ON-bipolar cells involved in the retinal response is conserved but also that their functional properties are altered. This can be explained by the fact that the cannabis users recruited in our study were young consumers (18–35 years old). Similar measures will be performed in older consumers in order to show whether the total number of cells participating in the response will be decreased, as showed by decreased amplitude.

Glutamate—an excitatory amino-acid—is another key neurotransmitter involved in retinal processing and glutamatergic transmission could thus be altered by exocannabinoids. It is synthesized from glutamine by the aspartate aminotransferase (Brandon and Lam, 1983) and acts on five post-synaptic glutamatergic receptors detected in retinal synapses: kainate, AMPA and NMDA are ionotropic receptors whereas L-AP4 and ACPD are metabotropic receptors (Koulen, 1999). Glutamate is detected in photoreceptors, ganglion and bipolar cells, the three critical vertical stages of retinal processing (de Souza et al., 2013). NMDA receptors are mainly detected in bipolar and ganglion cells and L-AP4 receptors are found in photoreceptors and bipolar cells (Wu and Maple, 1998). The impact of exocannabinoids such as THC on glutamatergic transmission in CNS neurons has previously been described (Bossong and Niesink, 2010). This effect is mediated through CB1 presynaptic receptors and leads to apoptosis of the cell, suggesting a neurotoxic effect of the modulation of glutamatergic transmission by exocannabinoids on CNS neurons (Schwitzer et al., 2015b). In the bovine retina, the administration of 250 µm glutamate—a glutamate stress model—induced both a- and b-wave amplitude reductions (Januschowski et al., 2015). Using whole-cell voltage-clamp recordings in adult and young mice (P14–P21), exogenous cannabinoid agonists reduced the frequency of spontaneous postsynaptic currents in retinal ganglion cells (Middleton and Protti, 2011). Of interest, these results argue for a presynaptic action of cannabinoid agonists, as is observed in brain neurons, and are associated with a decrease in glutamate release (and GABA), suggesting the possible effect of exocannabinoids on retinal glutamatergic transmission (and GABAergic transmission).

Since GABAergic transmission is targeted by exocannabinoids and it plays a role in retinal processing, GABA could be another transmitter involved in retinal dysfunctions observed in cannabis users. GABA, an inhibitory neurotransmitter, is synthesized from glutamate by the glutamate decarboxylase (Brandon and Lam, 1983) and acts on ionotropic GABAa and GABAc receptors and on metabotropic GABAb receptors (Lukasiewicz and Shields, 1998). GABA is expressed in horizontal, amacrine, bipolar and ganglion cells in the retina of vertebrate species (Davanger et al., 1991; de Souza et al., 2013; Marc et al., 1995; Wu and Maple, 1998). GABAa and GABAb receptors are located in bipolar and ganglion cells and GABAc receptors in horizontal and bipolar cells (Lukasiewicz and Shields, 1998; Wu and Maple, 1998). The role of GABA acting through GABA receptors in regulating the ON and OFF responses in the retina, which are mediated by ON and OFF bipolar cells, is a matter of debate (Popova, 2014b). The summarized results suggest that GABA plays an inhibitory effect on both the ON and OFF retinal activity recorded with ffERG. This role of GABA signaling pathways depends on the type of the GABA receptors involved in the retinal response and is associated with various kinds of ffERG anomalies, namely alterations of the b- (generated by the ON pathways) and D-wave (generated by the OFF pathways) amplitude and implicit time (Popova, 2014b). The ionotropic GABA receptors regulate chloride currents in bipolar cells but the precise effects on retinal activity of the ON and OFF bipolar cells remain to be determined. The GABAergic signaling pathways are involved in the ON-OFF asymmetry and sensitivity of the ffERG responses performed under various conditions of light adaptation in amphibian retina (Popova, 2014b). Further studies should establish whether GABA agonists and antagonists acting through ionotropic GABA receptors have the same role in human retina. Interestingly, horizontal cells could be a relevant focus for investigation of GABAergic transmission dysfunctions. According to Rangaswamy et al., the i-wave has an origin distal to the retinal ganglion cells, probably in the OFF-pathways, and could arise from horizontal cells (Rangaswamy et al., 2004). Although the origin of the i-wave is still under discussion, other authors also suggest that this wave reflects the ganglion cell function (Rosolen et al., 2004). The i-wave is a positive wave, posterior to the b-wave and observed in ffERG measurements in photopic conditions. In typical ffERG performed according to the ISCEV guidelines, the i-wave can be extracted from the photopic 3.0 ffERG. Amplitude and implicit time are derived from this wave.

In summary, the modulations of dopaminergic, glutamatergic and GABAergic transmission in animals are associated with several alterations of retinal electrophysiological parameters, as revealed by

contradictory findings. Importantly, findings in animals cannot be translated to humans in the present form since animal physiology differs from the human variety. Also, it is crucial to consider that retinal responses recorded with electrophysiological measurements are under the influence of several neurotransmission signaling pathways and particularly depend on their reciprocal excitatory and inhibitory interactions. As a critical consequence, conclusions on modifications of an isolated retinal neurotransmission signaling pathways cannot be drawn. Future studies should focus on molecular analysis in order to directly link retinal dysfunctions with specific retinal neurotransmission abnormalities. To conclude, since exocannabinoids act on dopaminergic, glutamatergic and GABAergic retinal transmissions, retinal dysfunctions observed in cannabis users can be viewed as consequences of the modulation of these signaling pathways. However, the precise mechanisms underlying these dysfunctions needs to be accurately determined.

6. Future directions

Cannabis use is often associated with the use of other psychoactive substances, such as tobacco and alcohol (Agrawal et al., 2012; Meier et al., 2012). When assessing the impact of cannabis use on neurological functioning, it is difficult to draw conclusions on the direct and isolated impact of cannabis use without considering the interaction with tobacco and/or alcohol use. This is crucial since these drugs act on neural synaptic signaling pathways involved in the effects of cannabis. For example, another retinal measurement extracted from ffERG and called the retinal background noise may help to study the effect of cannabis and alcohol use on retinal synaptic transmission since an increase in the magnitude of the retinal background noise was observed in users with co-occurrent consumption of cannabis and alcohol (Lucas et al., 2018). Alcohol is known to be a modulator substance acting on dopaminergic, glutamatergic, and GABAergic signaling pathways (Miguel-Hidalgo, 2018) whereas tobacco is known to modulate dopaminergic, glutamatergic, GABAergic and nicotinic acetylcholinergic pathways (D'Souza and Markou, 2013; Koukouli and Maskos, 2015; Pistillo et al., 2015). Thus, control groups of tobacco and alcohol users are needed to isolate the effects of each drug on central synaptic transmission. To date, acute administration of chewing gum containing 2 and 4 mg of nicotine 30 min before testing ffERG in adults who were nonsmokers induced a decrease in dark-adapted b-wave amplitude response as well as a decrease or an increase in light-adapted b-wave amplitude after chewing gum containing 4 mg of nicotine (depending on the protocol used: recording of dark- and light-adapted ffERG or only light-adapted ffERG, respectively) (Varghese et al., 2011). A recent study has evaluated the effect of cigarette smoking on structural and functional characteristics of the retina in 100 active smokers and 100 age- and sex-matched healthy passive smokers using mfERG and OCT (El-Shazly et al., 2018). P1 amplitudes of the mfERG in ring 1 were decreased and P1 implicit times in ring 1 were increased in active smokers vs passive smokers. Although this is an interesting result, it does not allow us to reach a conclusion on the effect of tobacco use vs no tobacco use on the retinal function. To our knowledge, the regular use of tobacco in humans on ffERG and PERG has not yet been investigated and could be of interest in future research. Similarly, the impact of acute or regular use of alcohol has not yet been evaluated and should be the goal of future studies in the field. Since the retina is endowed with molecular signaling pathways involved in the effects of these drugs on the CNS, we can expect retinal electrophysiological measurements to provide numerous markers of specific alterations of brain synaptic transmission.

Although the pathophysiology of psychiatric and addictive disorders is more complex than neurotransmission abnormalities, pharmacotherapy used in these disorders is currently based on these anomalies. There is substantial evidence that measurements of retinal function show markers of alterations in neurotransmission signaling pathways in neuropsychiatric and addictive disorders (Garcia-Martin et al., 2014; Lavoie et al., 2014c 2014a; Schwitzer et al., 2015a). For example, the retinal contrast processing obtained with steady-state PERG and consisting in the manipulation of the contrast levels of reversing checkerboards, is decreased in major depressive disorder (MDD) (Bubl et al., 2015, 2012, 2010). Other parameters derived from the transient PERG namely P50 and N95 amplitude as well as P50 implicit time were decreased in Parkinson's disease (Garcia-Martin et al., 2014). These two neuropsychiatric disorders are associated in an opposite way with alterations in dopaminergic transmission. Interestingly, different electrophysiological components extracted from different protocols of the same exam, the PERG, may vary in the same direction. These results suggest a potential way to study CNS dopaminergic dysfunctions (Schwitzer et al., 2016c). Further dopaminergic markers may be isolated from retinal function. Cocaine is a dopaminergic modulator substance which acts on the reward system. In a study in cocaine-dependent patients after cocaine withdrawal, approximately 50% of them showed a decrease in blue cone b-wave amplitude (Roy et al., 1997a, b). The ffERG of these patients was subsequently examined every 2 weeks for an 8-week period. Since no difference was observed over this period, this suggests that the reduced blue cone amplitude was stable in cocaine-dependent patients even during abstinence (Roy et al., 1997a, b). Interestingly, the reduced blue cone b-wave amplitude was significantly correlated with the cerebrospinal concentration of the dopamine metabolite homovanillic acid (HVA). Most importantly, HVA concentration was all the lowest that the blue cone amplitude was the lower (Roy et al., 2003). This reinforces the idea that the retinal signal is related to brain levels of dopamine, such as it was demonstrated in animals (Lavoie et al., 2014b). The retinal function may also provide markers of glutamatergic transmission. The transient PERG was altered in regular cannabis users, as shown by an increase in N95 implicit time (Schwitzer et al., 2017a 2018). Alterations in glutamatergic transmission may be at the origin of these abnormalities since exocannabinoids such as THC act on glutamatergic synaptic transmission (Bossong and Niesink, 2010) and glutamate is a key transmitter involved in the vertical transmission of visual information in the retina (de Souza et al., 2013; Wu and Maple, 1998). Markers of other signaling pathways such as serotoninergic or noradrenergic pathways may be extracted from retinal functional measurements. In the study of Hébert et al. (Hébert et al., 2017), ffERG cone and rod luminance response functions were recorded in non-dilated eyes in 100 MDD patients, of whom 17 were drug free, along with 100 controls. In medicated MDD patients, a prolonged b-wave was observed at the cone level, the mixed rods/cones a-wave was reduced and a trend was observed for a reduced rod b-wave. Interestingly, medicated and nonmedicated patients share several similar retinal deficits suggesting that these retinal anomalies may be linked to the disease and not due to medication. Fountoulakis et al., (Fountoulakis et al., 2005) found correlations between ffERG parameters and psychometric assessments and symptoms occurring in MDD, such as General Assessment of Functioning Scale (GAF), or a number of atypical features or life events, although there were no a- or b-wave amplitude or implicit time differences between 50 MDD patients and 15 controls. Fornaro et al., (Fornaro et al., 2014) assessed, in 23 healthy volunteers aged between 22 and 35 years old, the impact of a single dose of 25 mg of agomelatine, a melatoninergic antidepressant, on ffERG. The retinal modification was a slight increase in the cone's b-wave amplitude and implicit time. Fornaro et al., (Fornaro et al., 2011) recorded ffERG in 20 patients with MDD and 20 healthy matched controls before and after 12 weeks of 60 mg duloxetine treatment, a Serotonin Norepinephrine Reuptake Inhibitor antidepressant. In patients suffering from MDD, a significant decrease in ffERG scotopic b-wave amplitude was observed from baseline to week 12 in depressed subjects achieving final response to an antidepressant therapy using duloxetine—a serotonin-norepinephrine reuptake inhibitor. This result suggests a potential retinal marker of modifications in serotoninergic and noradrenergic pathways. Another study found that visual contrast sensitivity was significantly lower in MDD patients compared to

controls based on the Landolt C visual contrast test, but no difference was found between groups using PERG and ffERG (Fam et al., 2013). In schizophrenia—a mental disorder involving in part dopaminergic dysfunctions—various ffERG abnormalities were observed in drug-naïve and treated patients, with a probable interaction between the effects of disease and pharmacotherapy—mainly antipsychotics and anxiolytics—on neurotransmission (Balogh et al., 2008; Hébert et al., 2015). As these treatments act on dopaminergic and serotoninergic signaling pathways for antipsychotics, and GABAergic pathways for anxiolytics, retinal dysfunctions may be viewed as modifications of synaptic transmission. In these studies, the main limitations concern the precise interpretation of these findings since both disease and medication intake are associated with modulation of several synaptic transmission pathways. In future research, it will be crucial to accurately evaluate the precise modifications of retinal function in response to the modulations of each neurotransmission signaling pathway. In other words, specific markers of the anomalies of each synaptic transmission pathway will be extracted from the retinal function.

Beside the parameters extracted from retinal electrophysiological measurements and evaluated in patients with neuropsychiatric and addictive disorders, numerous other retinal parameters will be evaluated to inform neurotransmission dysfunctions. Part of these parameters include well known indicators of retinal function, while others can be derived from electrophysiological measures of brain functioning. As an example, retinal oscillatory potentials, measured with ffERG under scotopic or photopic conditions, are markers of retinal amacrine cell functioning (Marmor et al., 1988a; Wachtmeister, 1998). The functioning of these cells is influenced by retinal dopaminergic transmission (Marmor et al., 1988b; Wachtmeister, 1998). Retinal oscillatory potentials may thus offer markers of dopaminergic transmission dysfunctions. The mfERG can also give interesting information in cannabis consumers. Since it examines the spatial properties of the cone system, it can be used to explore whether dysfunctions previously observed at the level of the ON-bipolar cells are localized in specific retinal areas or whether they are distributed over the whole retinal area. Other measurements can be derived from electrophysiological measurements of cortical functioning. As an example, neuronal background noise is a measure of a neuronal activity without stimulation, which is also known as non-stimulus-driven neural activity. One study evaluated the retinal background noise in attention deficit hyperactivity disorder (ADHD) (Bubl et al., 2013). In this study, the noise amplitude was significantly higher in patients with ADHD compared with controls and was significantly correlated with psychometric measures for ADHD, especially inattention. In this study, retinal background noise was viewed as a marker of dopaminergic dysfunctions.

In conclusion, there a large number of steps need to be taken before concluding on the relevance of these measurements to help us understand the precise effects of cannabinoids on brain functioning. Since the retina is an easy-to-access site for the investigation of brain disorders in neuropsychiatric and addictive disorders, measurements of retinal function may provide crucial information on the effects of cannabis use on brain synaptic transmission.

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Conflict of interest

None.

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