Chapter 69

Cannabis, Endocannabinoid CB1 Receptors, and the Neuropathology of Vision

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Abbreviations

2-AG 2-Arachidonoylglycerol
5-HTTP L-5-Hydroxytryptophan
CB Cannabinoid
CB1 Cannabinoid receptor type 1
EEG Electroencephalogram
LFP Local field potential
mRNA Messenger ribonucleic acid
SR141716A *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride
SSVEP Steady-state visual evoked potential
THC Δ^9-Tetrahydrocannabinol
WIN 55,212-2 (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo[1,2,3-*de*]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone

INTRODUCTION

Pathology of vision is known to occur as the result of drug action and side effects in a number of well-known cases (Li, Tripathi, & Tripathi, 2008). While anecdotal and apocryphal descriptions of changes in visual experiences as a result of cannabis ingestion abound, hard evidence for pathologies resulting from, for example, cellular firing changes in the early visual system, which might underpin these reported effects, is much rarer. Indeed, many descriptions of cannabis-induced visual changes use emotive phrases involving "perception," "interpretation," and "appreciation" rather than scientifically measurable disturbances of physiology. The discovery of the endocannabinoid system came about from the characterization of the chemical structure of Δ^9-tetrahydrocannabinol (THC), the main active component of the *Cannabis sativa* plant (Mechoulam & Shvo, 1963). This allowed the identification and cloning of the two main membrane receptors with which THC interacts: cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) (Devane, Dysarz, Johnson, Melvin, & Howlett, 1988; Matsuda, Lolait, Brownstein, Young, & Bonner, 1990). Later the two main endogenous ligands for these receptors were discovered: anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (Devane et al., 1992; Sugiura et al., 1995). Since then, our knowledge of the endocannabinoid system has grown quickly. Today, it is widely accepted that endocannabinoid system components—both ligands and receptors—are broadly distributed throughout the central nervous system (Matias, Bisogno, & Di Marzo, 2006; Tsou, Brown, Sañudo-Peña, Mackie, & Walker, 1998), where endocannabinoids play important roles in various aspects of its physiology, development, and organization. However, even though CBs have been shown to mediate elements of cognitive processes such as attention and memory (Kanayama, Rogowska, Pope, Gruber, & Yurgelun-Todd, 2004), few studies have explored the effects of the endocannabinoid system on sensory processing, especially vision.

Several factors have contributed to this lack of research. First, cannabis is simply the name for a genus of plants (*Cannabis* spp.) from which an active substance or substances (cannabis, marijuana, hashish) have been extracted—little information was available about these substances and the mechanisms by which they affected behavior and cognition before the endocannabinoid system was discovered and characterized. The effects of marijuana on general state and attention and the difficulty of establishing appropriate controls had also made it difficult to obtain and interpret psychophysical data related to vision (Hollister, 1971; Weil, Zinberg, & Nelsen, 1968). The reputation of marijuana as a drug of abuse and its legal status had also for a long time hampered a systematic and concise study of the psychophysical and physiological mechanisms involved in its effects on brain activity. Finally, histological studies aimed at detecting the expression of CB receptors in the brain had classically shown weak or no expression in primary sensory pathways (Herkenham et al., 1991; Moldrich & Wenger, 2000).

More recently, however, studies have found contrasting results in key components of sensory systems with regard to the distribution of the components of the endocannabinoid system, suggesting a higher incidence of CB ligands and receptors (Sun, Wu, Lu, & Beierlein, 2011), along with the machinery involved in their synthesis and degradation (Felder et al., 1996). Furthermore, studies specifically aimed at studying the role of endocannabinoids in various parts of the visual system have greatly supported this conclusion (Dasilva, Grieve, Cudeiro, & Rivadulla, 2012, 2014; Ohiorhenuan et al., 2014; Sales-Carbonell et al., 2013; Sun et al.,

2011). Indeed, a careful scrutiny of the previous literature offers numerous direct and indirect insights on the close relationship between CBs and vision. Thus, the evidence now supports the existence of a significant relationship between the components of the endocannabinoid system and visual function, a relationship that can be observed from a psychophysical and electrophysiological point of view.

PSYCHOPHYSICAL EFFECTS OF CANNABINOIDS ON VISION

Early psychophysical studies on the effect of marijuana on visual perception in human subjects found no significant results when orally administering cannabis and assessing behavior (Clark & Nakashima, 1968) or during visual brightness discrimination tasks after smoking marijuana (Caldwell, Myers, Domino, & Merriam, 1969). However, these conclusions were challenged by a contemporary study in animals, which found cannabis to affect color but not form perception when administered intraperitoneally to pigeons trained in a visual discrimination task (Siegel, 1969). These results were corroborated soon after in humans by studies demonstrating an acute effect of smoked marijuana on color discrimination (Domino, Rennick, & Pearl, 1976; Kiplinger, Manno, Rodda, & Forney, 1971) and were extended further showing a decrement in the ability to detect geometric shapes in human subjects intoxicated with marijuana (Carlin, Bakker, Halpern, & Post, 1972).

An effect of marijuana on peripheral vision was also demonstrated (Moskowitz, Sharma, & McGlothlin, 1972); in this study participants were tested under control conditions and after the administration of marijuana during a peripheral light detection task. Interestingly, peripheral vision decreased up to 50% after the consumption of marijuana. The authors correctly demonstrated that these effects were not the simple consequence of the induction of a general drowsiness, as reaction times were not significantly affected.

Another effect of marijuana on vision was revealed by studying the phenomenon of apparent visual motion (Sharma & Moskowitz, 1972). In this study human subjects were instructed to report whether they observed any movement of a centrally presented flashing stationary light. After smoking marijuana subjects reported a higher index of apparent visual motion during the presentation of the stimulus and reported this to happen with complex patterns like zigzag, elliptical, or circular movements and changes in apparent intensity (closer/farther movements). However, this early study did not measure eye movements.

Around the same time, a set of studies focused on the general effects of marijuana in humans reported a decrease in Vernier visual acuity (Agurell, 1976) and eye accommodation (Thomas & Chester, 1973) after smoking marijuana, results that were replicated by another study on the ocular manifestations of CBs, which observed a decrease in Snellen visual acuity (Shapiro, 1974).

However, even though those preliminary studies had suggested an effect of marijuana on various aspects of vision, it was not until the study by Dawson, Jiménez-Antillon, Perez, and Zeskind (1977), that a systematic approach to the effects of marijuana on vision was accomplished. Here the authors studied the effects of chronic marijuana use on various eye functions in human subjects. They found that marijuana users presented consistently smaller pupil diameters compared to nonusers. They also reported, in agreement with previous studies (Agurell, 1976; Shapiro, 1974), a decrease in visual acuity during monocular vision, measured by the ability to read Snellen letters. However, they did not find significant differences in this parameter between luminance levels when comparing users with nonusers. The authors also analyzed color and brightness matching. For this purpose subjects were presented with stimuli of different tones and intensities of red and green in each visual hemifield and were asked to change either parameter until both stimuli appeared equal. Marijuana users presented values similar to those of nonusers in terms of midpoint color match and brightness, but users showed a significant decrease in the range of color and brightness at which they could successfully perform the task, confirming the previous findings in pigeons (Siegel, 1969). In addition, Dawson and colleagues also reported less complete dark adaptation and increased photosensitivity in marijuana users compared to nonusers (Dawson et al., 1977), results that were subsequently partially corroborated (Adams, Brown, Haegerstrom-Portnoy, Flom, & Jones, 1978), showing that marijuana had a significant acute effect, decreasing the time delay to recover from an intense light exposure (measured as the ability to detect low-contrast stimuli).

In line with these previous studies, more recent research has reported the presence of visual disturbances in human subjects both acutely after smoking marijuana and as flashbacks after ceasing cannabis use (Lerner, Goodman, Rudinski, & Bleich, 2011). In this study subjects claimed the presence of seven types of visual disturbances including blurred perception, distorted perception of distance, movement illusions, color intensification, color dimness, distortions in size perception, and blending of patterns. These disturbances were perceived up to 12 weeks after the cessation of cannabis use, becoming less intense and frequent over this period until completely disappearing. Thus, although not tested, the authors argued the possibility of a downregulation in serotonergic neurotransmission by marijuana, as cannabis has been previously seen to affect serotonin neurotransmission, and various medicines acting on the mechanism of action of this neurotransmitter have been shown to induce visual disturbances (Lauterbach, Abdelhamid, & Annandale, 2000).

Marijuana has a potential facilitatory action on night vision. The phenomenon was first reported by West in 1991 in a short communication (West, 1991). In this, the author reflected on his observations about the astonishing improvement in night vision of Jamaican fishermen who could navigate with their boats through difficult coral reefs during the night after smoking or ingesting marihuana. A similar study some years later by Merzouki and Molero Messa (1999) reported the same effects observed by West, but in Moroccan fishermen. These fishermen attributed the ability of seeing during the night to the consumption of "kif," a mixture of tobacco and marijuana. However, neither of these authors attempted a systematic measurement of their observations. It was not until 2004 that Russo and colleagues objectively tested this phenomenon (Russo, Merzouki, Mesa, Frey, & Bach, 2004). They studied a group of fishermen of northern Morocco and reported a significant decrease in scotopic sensitivity and dark adaptation after smoking kif (Figure 1(A)). However, and even though these effects seemed to be dose dependent, they did not find any alteration in Snellen chart visual acuity as previously reported (Dawson et al., 1977). When trying to explain their results the authors suggested an action of marijuana on the retina as the likeliest mechanism, basing this assertion on the fact that the retina expresses

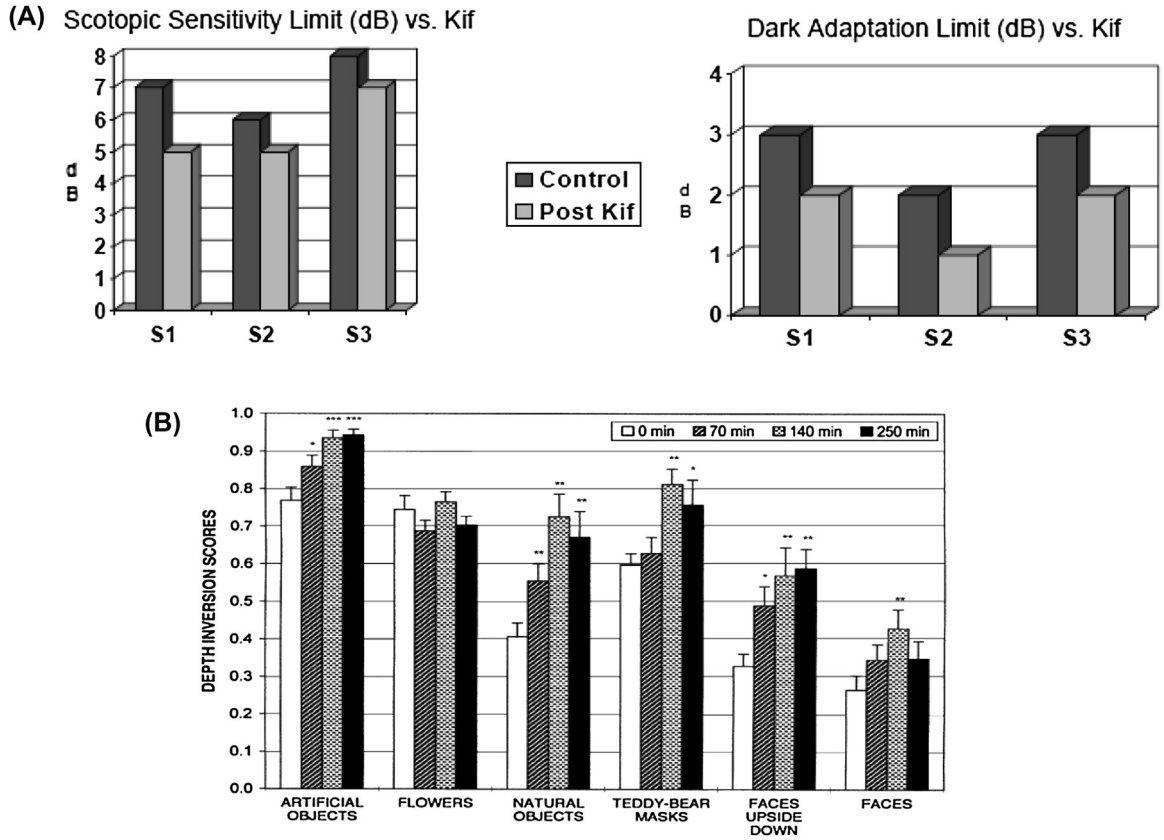

FIGURE 1 **Effects of cannabis on visual function.** (A) Scotopic sensitivity limit (left) and dark adaptation limit (right) before and after smoking cannabis in three subjects. A decrease of at least 1 dB occurred in all subjects for both conditions. *(Adapted from Russo et al. (2004).)* (B) Depth inversion scores during the presentation of various classes of objects to human subjects before and after the administration of THC. Scores were decreased for all objects but flowers. Asterisks indicate the error probability revealed by respective Wilcoxon tests (*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$). *Adapted from Leweke et al. (1999).*

CB receptors in higher concentrations than other parts of the central nervous system. They also suggested a stimulatory effect of marijuana on rods to be responsible for the improvement in night vision, but they did not go further into the issue.

Another phenomenon that has thrown some light on our current knowledge of the effects of CBs on vision is binocular depth inversion (an illusion created by the brain to make sense of visual irrational experiences generated when the visual information that should normally reach one eye is sent to the other, e.g., an "inside-out face"). In this situation, the information provided by bottom-up mechanisms must be modified or disregarded by top-down influences, as otherwise the system would not be able to properly represent the erroneous information provided by bottom-up pathways during the illusion. Using this tool, Emrich et al. (1991), found a strong impairment of depth inversion in human subjects after smoking marijuana. They attributed these results to an action of marijuana as a modulator in the interactions between visual sensation and perceptual awareness.

Leweke, Schneider, Thies, Münte, and Emrich (1999), went a step further in the study of this relationship by investigating the effect of oral administration of the synthetic THC dronabinol on the binocular depth inversion of various classes of natural and artificial objects. In this study dronabinol was chosen to provide a less contaminated source of THC than in previous studies (Figure 1(B)). In agreement with Emrich et al. (1991), the authors found that dronabinol induced a strong impairment of binocular depth inversion for both types of stimuli—natural and artificial—with the interesting exception of flowers. Accordingly, and considering that binocular depth inversion results from a domination of top-down over bottom-up signals, the authors assumed that the fact that binocular depth inversion is reduced by THC indicates an effect of this compound on the top-down processing of visual information. They support this assumption by the observation that binocular depth inversion for objects with high levels of familiarity showed less reduction than artificial ones, which is in agreement with the observation that the influence of top-down processing on the depth inversion of objects with high familiarity is higher than for objects with lower familiarity. So, if THC is affecting top-down processing, the stronger this path, the less affected by the drug it should be. The hypothesis was further supported by the observation of a time decline on the effects of THC, which suggested a dose-dependent effect.

Another study led by Leweke, Schneider, Radwan, Schmidt, and Emrich (2000) aimed to test the theory that the disruption of binocular depth inversion induced by cannabis is due to an impairment of the top-down mechanisms involved in interpreting and contextualizing visual information. To this end the authors tested the effect of psychotropic (nabilone) and nonpsychotropic

(cannabidiol) CBs on binocular depth inversion. As they predicted, they found that binocular depth inversion was significantly affected only during the administration of the psychotropic CB nabilone and concluded that psychotropic CBs weakened the correction effect of top-down pathways during the presentation of erroneous visual information (binocular depth inversion). These results were further confirmed by two other works (Koethe et al., 2006; Semple, Ramsden, & McIntosh, 2003) in healthy individuals and schizophrenic patients, respectively.

Also interesting are two case studies reporting an improvement in nystagmus in an individual with a congenital manifestation of this condition (Pradeep, Thomas, Roberts, Proudlock, & Gottlob, 2008) and in a patient suffering from multiple sclerosis (Schon et al., 1999). In both cases smoking marijuana decreased amplitude, frequency, and intensity of nystagmus, which was reflected in an improvement in visual acuity. Interestingly, a previous study by Brown, Adams, Haegerstrom-Portnoy, and Jones (1975), reported a decrease in visual acuity induced by marijuana only when targets were in motion and required coordinated eye movements, and Adams, Brown, Flom, Jones, and Jampolsky (1975), found no alterations in static visual acuity after consumption of marijuana.

Several studies on different pathological conditions have also offered support for the role of CBs on vision. In some cancer patients the analgesic effect induced by the administration of THC is often accompanied by alterations in vision (Noyes, Brunk, Baram, & Canter, 1975). It has also been reported while assessing the effects of smoked cannabis on multiple sclerosis that patients not only had improved motor symptoms or reduced pain, but also experienced a decrease in the incidence of double and blurred vision associated with the illness (Consroe, Musty, Rein, Tillery, & Pertwee, 1997). Patients have also reported previously irrelevant visual patterns to become potent distracters after the intravenous injection of THC in a study relating the CB system with psychosis (D'Souza et al., 2004). And very recently Lax, Esquiva, Altavilla, and Cuenca (2014) demonstrated a protective effect of the synthetic CB HU210 on retinal structure and function against retinitis pigmentosa.

Although less often, the effect of marijuana on vision has also been studied in animals from a psychophysical point of view. Here results are even more scarce and contradictory and would need further investigation. Apart from the aforementioned study by Siegel on pigeons (Siegel, 1969), Hockman, Perrin, and Kalant (1971), observed strange behaviors in cats after intraperitoneal injections of THC, reporting that these animals usually stared into space and followed nonexistent stimuli with their eyes. In contrast, a pair of studies in behaving monkeys (Schulze et al., 1988) found no significant effects on a task involving color discrimination or remembrance–identification of geometric shapes before and after the intravenous administration of THC or the breathing of marijuana smoke. However, Aigner found a significant drop in performance of as much as 20% during a visual recognition task in monkeys after either acute or chronic oral administration of THC (Aigner, 1988). More recently, a study in behaving rats performing a visual discrimination task found an impairment in brightness detection after the administration of the synthetic CB1 agonist WIN 55,212-2 (Arguello & Jentsch, 2004). Interestingly, these effects were abolished by the coadministration of SR141716A, a specific CB1 antagonist, which had no action when administered alone.

ELECTROPHYSIOLOGICAL EFFECTS OF CANNABINOIDS ON VISION

Electroencephalography (EEG) has been one of the main electrophysiological techniques used to assess the relationship between CBs and visual perception. Early studies found no significant changes in EEG of human subjects after smoking marijuana. However, Tinklenberg, Kopell, Melges, and Hollister (1972), reported an increase in the amplitude and latency of components within visually evoked responses. These results were confirmed later (Lewis, Dustman, Peters, Straight, & Beck, 1973) in a study in which visual evoked responses to flashing stimuli were recorded on occipital, central, and frontal scalp areas in healthy subjects, before and after the oral administration of THC. Here, a significant increase in the latency of primary and secondary components of visual evoked responses was observed at all recorded regions, although the effects were more pronounced on the occipital scalp. In addition, effects on the magnitude of visual evoked responses were much less evident, showing a general decremental trend, which achieved significance only at the occipital area. The authors suggested that this result was unusual, as most drug-induced alterations in EEG evoked responses, like those induced by barbiturates, affected only the amplitude and not the latency of the responses. They proposed that this lack of action of marijuana on the amplitude of visual evoked responses along with the consistently increased latencies reflected a lack of drug action on brainstem centers, since brainstem centers were known to be greatly affected by drugs modulating the amplitude of late components. Finally they also suggested a general increase in the firing threshold of all neuronal elements involved in the circuit underpinning visual evoked responses as a possible mechanism to explain their results.

More recently Patrick et al. (1995), found no significant differences in the magnitude of P300 in chronic marijuana smokers. However, P300 is an EEG waveform that appears symmetrically around the central–parietal cortex and reflects complex information processing and attentional vigilance rather than a purely sensory signal. Thus, it is likely that the authors did not see any effect because of the nature of the signal itself, which seems unlikely to be highly modulated by visual processing or any other modulation of primary sensory perception.

Another important EEG study investigating the effects of marijuana on vision was accomplished by Skosnik, Krishnan, Vohs, and O'Donnell (2006). In this study the authors measured occipital steady-state visual evoked potentials (SSVEPs) during passive photic stimulation with flickering lights on habitual cannabis users versus normal human controls (Figure 2(A)). SSVEPs are an EEG response to visual periodic stimulation generated by the tuning of the primary visual cortex to both the frequency and the phase of the stimulus, so it is an indicator of the functional state of the neural circuits in the visual cortex. The authors observed a decrease in the magnitude of SSVEPs in the cannabis users and this observation was positively correlated with the age of first cannabis use. Thus, these results clearly point to an alteration in sensory function in V1 of human subjects, probably due to an alteration in the oscillatory activity of the neurons in this cortical area.

Böcker et al. (2010), studied the effect of smoked marijuana with high levels of THC on visual evoked response potentials during a visual selective attention task in which subjects had to

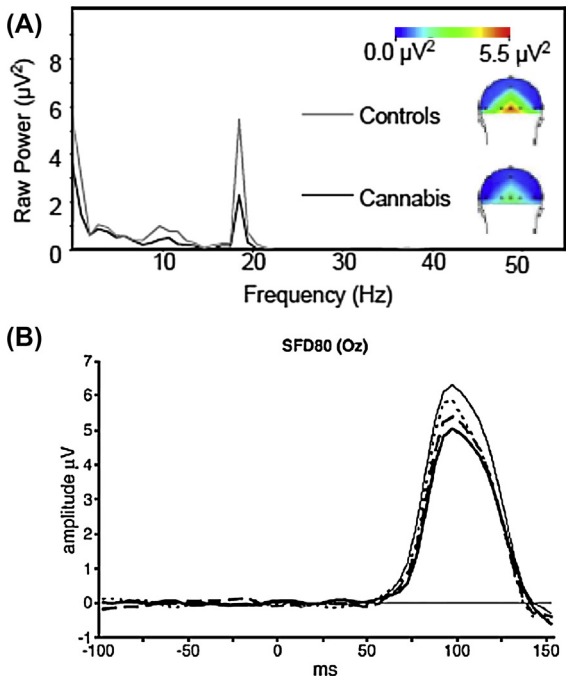

FIGURE 2 Cannabis exposure alters EEG. (A) Averaged power spectra recorded on the occipital area of the skull in human cannabis users and controls. Topographic maps from EEGs recorded on the same subjects in response to periodic photic stimuli at 18 Hz are also shown. *(Adapted from Sosnik et al. (2006).)* (B) Averaged evoked response potentials to gratings recorded on the occipital area of the skull in groups of human subjects exposed to various concentrations of CBs. Placebo (continuous thin line), low CB concentration (thin dashed line), medium CB concentration (thick dashed line), high CB concentration (continuous thick line). The amplitude of the response decreased with increasing exposure. *Adapted from Böcker et al. (2010).*

discriminate between spatial frequency and orientation of square-wave gratings (Figure 2(B)). They found that marijuana induced a dose-dependent decrease in the amplitude of occipital SDF80, an evoked response potential that represents sensory processing that is not affected by attention. As a consequence, this study corroborated earlier findings (Sknosnik et al., 2006) and reflected a dose-dependent effect of THC on brain correlates of sensory processing affecting bottom-up pathways involved in spatial frequency discrimination. Similar decrements in evoked response potentials related to visual sensory processing have also been reported for both acute (Ilan, Gevins, Coleman, ElSohly, & de Wit, 2005) and chronic cannabis use (Patrick, Straumanis, Struve, Fitzgerald, & Manno, 1997).

There is less available published work on the effects of cannabis at a cellular, neurophysiological level within the sensory systems. The presence of CB receptors at the level of the retina was first demonstrated by detecting the presence of mRNAs for these receptors in the rat retina (Buckley, Hansson, Harta, & Mezey, 1998; Porcella, Casellas, Gessa, & Pani, 1998). A detailed study of the cellular distribution of CB1 receptors came soon after in two contemporaneous studies (Straiker, Maguire, Mackie, & Lindsey, 1999; Yazulla, Studholme, McIntosh, & Deutsch, 1999). These studies found CB1 receptors in retinal inner and outer plexiform layers of rhesus monkeys, mice, rats, chicken, goldfish, and tiger salamander, especially in the synaptic terminals of photoreceptors, although amacrine, horizontal, and ganglion cells were also positive in the majority of these species.

The physiological role of CBs in the retina has been a subject of extensive research. It has been demonstrated that the activation of CB1 receptors inhibits the release of noradrenaline, dopamine, and glutamate (Opere et al., 2006; Schlicker, Timm, & Göthert, 1996) and disrupts γ-aminobutyric acid (GABA)-ergic inhibitory neurotransmission (Warrier & Wilson, 2007). In addition, CB agonists have also been seen to inhibit the presence of high-voltage calcium currents in retinal ganglion cells, effectively modulating retinal output (Lalonde, Jollimore, Stevens, Barnes, & Kelly, 2006). Suppression of calcium and potassium currents in bipolar cells has also been reported, suggesting a retrograde CB-mediated inhibition by retinal ganglion cells (Straiker et al., 1999). Interestingly, all *on* bipolar cells are affected by CBs, while only one-third of *off* cells are modulated. It is under debate, thus, whether endocannabinoids experience a bias toward the *on* pathway in the retina, which would imply ganglion cell CB-mediated retrograde inhibition of bipolar cells as present mainly during increments rather than decrements of light intensity.

With regard to the effect of CBs on photoreceptors, it has been reported that bipolar cells can exert a retrograde inhibitory action on cone excitability by synthesizing and releasing CBs in a calcium-dependent manner (Fan & Yazulla, 2007). This inhibition may follow both a voltage-dependent and a voltage-independent mechanism. Thus the former would allow bipolar cells to act as a positive feedback, amplifying the reduction of glutamate release during increments in light intensity, while the latter would act as a negative feedback enhancing the effect of light increments (Fan & Yazulla, 2007; Klooster, Studholme, & Yazulla, 2001).

The presence of CB receptors in the elements of the visual pathway beyond the retina has been seldom studied. General immunohistochemical localization of CB1 receptors in the rat and mouse brain originally reported only sparse staining in the dorsal thalamus, including the dorsal lateral geniculate nucleus and visual cortex (Herkenham et al., 1991; Moldrich & Wenger, 2000). Nonetheless, high levels of AEA have been found in the thalamus (Felder et al., 1996) along with high levels of fatty acid amide hydrolase, its degradative enzyme (Thomas & Chester, 1973). These results have been supported by studies specifically targeting the localization of CB1 receptors in the lateral geniculate nucleus and visual cortex, which have found high levels of these receptors in both areas of the mouse (Sun et al., 2011; Yoneda et al., 2013).

Perhaps the fact that CB1 receptors were traditionally considered to be absent from central brain structures involved in visual processing hampered a systematic study on the effects of CBs in these areas from a cellular/system neurophysiological point of view. There are, however, a handful of studies that have thrown some light on the issue. The first report found in the literature relating the visual effects of CBs from a cellular perspective was the study by Bieger and Hockman (1973). In this work the authors studied the response of lateral geniculate nucleus neurons in the hooded rat during the intravenous administration of THC. They found a consistent THC-induced inhibition in the firing rate of cells activated by light, while cells inhibited by light either remained unchanged or experienced an

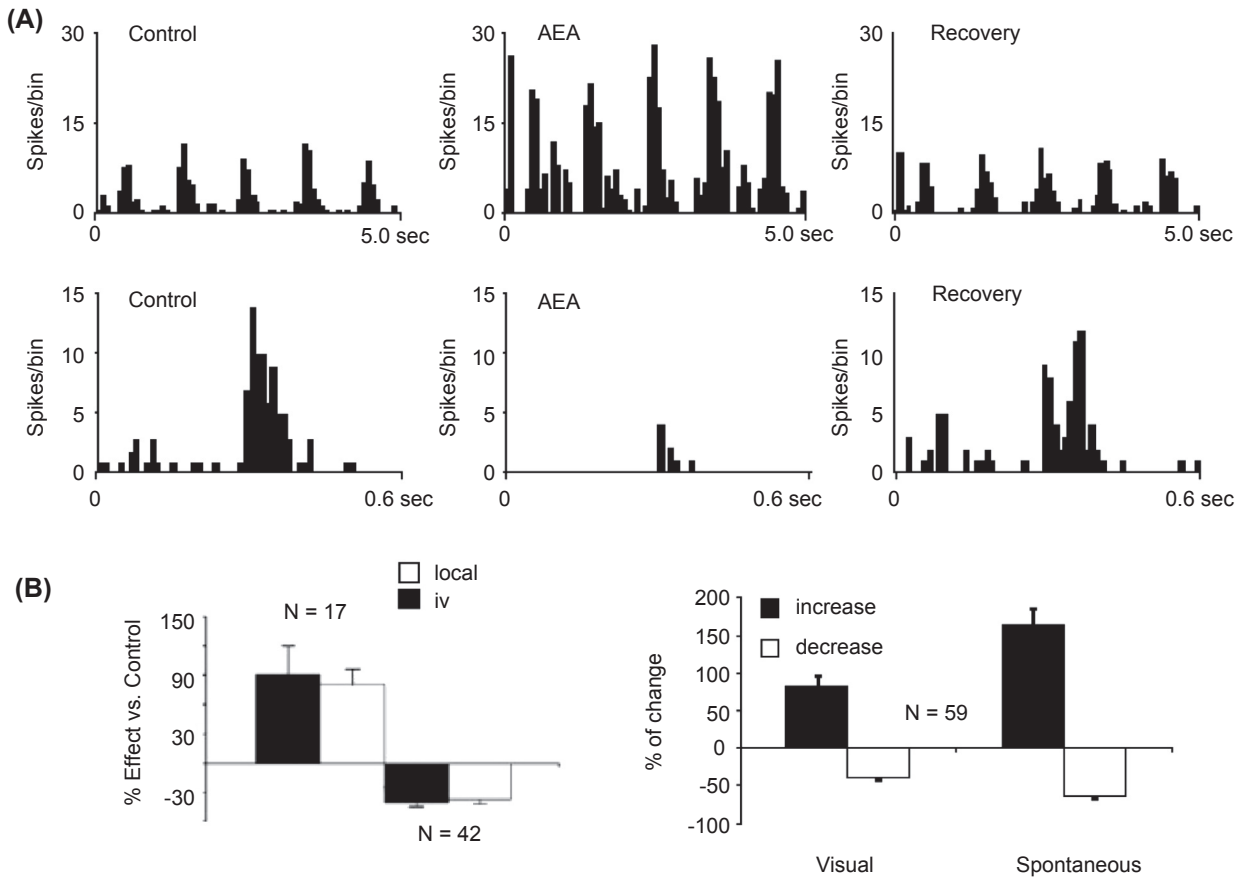

FIGURE 3 **Endocannabinoids modulate thalamic neuronal responses.** (A) Responses of two well-isolated neurons in the dorsolateral geniculate nucleus (dLGN) of the rat to a grating (upper traces) and spot (lower traces) of optimal characteristics before and after local administration of AEA by pressure ejection. The response of the first neuron to the visual stimulus increases during the administration of AEA, reverting to control conditions during recovery. The contrary happens to the other neuron. (B) Bar graphs showing averaged population responses of single cells in the dLGN of the rat during local and systemic administration of endocannabinoid agonists. Both routes of administration induced similar results in sign and magnitude (left), although effects were more prominent during spontaneous than during visual responses (right), effectively increasing signal-to-noise ratio. *Adapted from Dasilva et al. (2012).*

increase in firing. When stimulating the optic nerve and recording evoked field potentials in the lateral geniculate nucleus, the authors found that THC affected only field potential components due to intrinsic geniculate activity and not to the activation by the optic nerve. Further, when the biogenic amine precursor L-5-hydroxytryptophan was administered after THC, the original effect of cannabis on light-sensitive neurons was reversed. Accordingly, the authors proposed THC to have a direct action on lateral geniculate nucleus neurons, probably by interfering with serotonergic midbrain projections, which could result in blurred vision and distortions of perception.

While Bieger and Hockman's (1973) study was the first attempt to relate visual function and neuronal activity in terms of CB modulation, this was very preliminary work. Only multiunit activity and local field potentials were studied, without a detailed characterization of neuronal responses. Consequently neither receptive fields nor response properties were fully characterized. Visual stimulation consisted of a broad illumination of the entire eye, which raises the question of whether the recorded responses were the result of groups of rather than single neurons. Further, owing to the intravenous administration of THC, the authors expressed doubt about whether the observed effects were the result of a direct action on lateral geniculate nucleus neurons or whether they were the consequence of a more general alteration in brain function at higher levels.

A new study came about more recently attempting a systematic characterization of the effect of CBs in the visual thalamus (Dasilva et al., 2012). Here the extracellular activity of well-isolated single neurons was recorded in the lateral geniculate nucleus of the hooded rat while manipulating the activation of CB1 receptors (Figure 3(A) and (B)). In agreement with the earlier study of Bieger and Hockman (1973), the intravenous administration of various CB agonists induced an inhibition of visual responses in the majority of the cells tested, while a minority of the cells expressed an excitatory effect. However, in contrast to that previous study, Dasilva and coworkers did not find any relationship between the observed effects and the physiological characterization of cells (on vs off, sustained vs transient). Similar effects were observed when the CB agonists were administered locally into the lateral geniculate nucleus by iontophoresis, indicating a local effect of CBs in the thalamus (Figure 3(A) and (B)), thereby further validating the observations

of Bieger and Hockman. In addition, the observed effects were demonstrated to be specifically mediated by CB1 receptors and to affect also spontaneous activity. Spontaneous activity, like the visual responses, increased or decreased in magnitude during the administration of CB1 agonists, although the magnitude of the effect was higher than during visual responses. This work confirmed that CBs can act locally in the visual thalamus and that the endocannabinoid system modulates the processing of information by this nucleus, altering how this information is transmitted to the cortex. In this regard, the authors described how CBs effectively increased the signal-to-noise ratio and decreased the variability of neuronal responses in their population of cells and suggested these results to support a putative role of CBs in sending clearer and less variable information to the visual cortex. The results corroborate previous proposals on the "filtering" of information by CBs in the visual system (D'Souza et al., 2004; Solowij, Michie, & Fox, 1991).

As of this writing only one study has been published testing the effect of CBs in the visual cortex at the cellular level (Ohiorhenuan et al., 2014). In this study (Figure 4(A)) the intravenous administration of a synthetic CB receptor agonist (CP 55,940) induced an alteration in network dynamics consisting of a decrease in EEG and local field potential (LFP) power at the low gamma range (25–50 Hz), with a decrease in LFP–LFP coherence. Interestingly, the authors were unable to correlate these obvious changes in the firing pattern of individual neurons with alterations at the population level, the only exception being a decrease in firing rate in neurons that experienced an increase in latency and duration of visual responses. This CB-induced decrease in firing rate is in agreement with Dasilva et al. (2012), who, as mentioned above, observed a general decrease in the firing rate of thalamic neurons. Taken together, these results raise the intriguing possibility of a synergistic effect of CBs at different levels of the thalamocortical circuit and beyond.

In support of this hypothesis, a 2012 study (Figure 4(B)) in the somatosensory system (Sales-Carbonell et al., 2013) has found that the activation of CB1 receptors present at glutamatergic cortical neurons decreased cortical synchrony at relatively high frequencies (>12 Hz), while, in the same study, increased synchrony of thalamocortical oscillations in the spindle-like range (4–8 Hz) was also reported as a consequence of the activation of CB1 receptors present at thalamic striatonigral synapses. Similar results have been found in the visual system at the level of the thalamus (Dasilva et al., 2014), where the activation of CB1 receptors specifically induced the appearance of delta-like oscillations (1–4 Hz) as a consequence of a general hyperpolarizing effect of CBs in this nucleus. This hyperpolarizing effect of endocannabinoids in the visual thalamus could thus result from the effect of these neuromodulators in the thalamic reticular nucleus, where 2-AG inhibits intrinsic inhibitory synapses (Sun et al., 2011). These synapses limit oscillatory activity in thalamic circuits (Figure 4(C)) and as a consequence, its inhibition by endocannabinoids would enhance intrinsic thalamic synchronicity in the spindle and delta-like ranges as demonstrated by Sales-Carbonell et al., 2013, and Dasilva et al. (2014). Thus, these results, along with the findings of Ohiorhenuan et al. (2014), in the cortex, seem to confirm a dynamic role of endocannabinoid signaling in regulating synchronous activity at various levels of the thalamocortical circuit with obvious implications for visual function. While these basic cellular mechanisms may underpin some of the visual shifts seen at the psychophysical level, they will require further work at higher cognitive levels to fully understand the pathology associated with cannabis misuse.

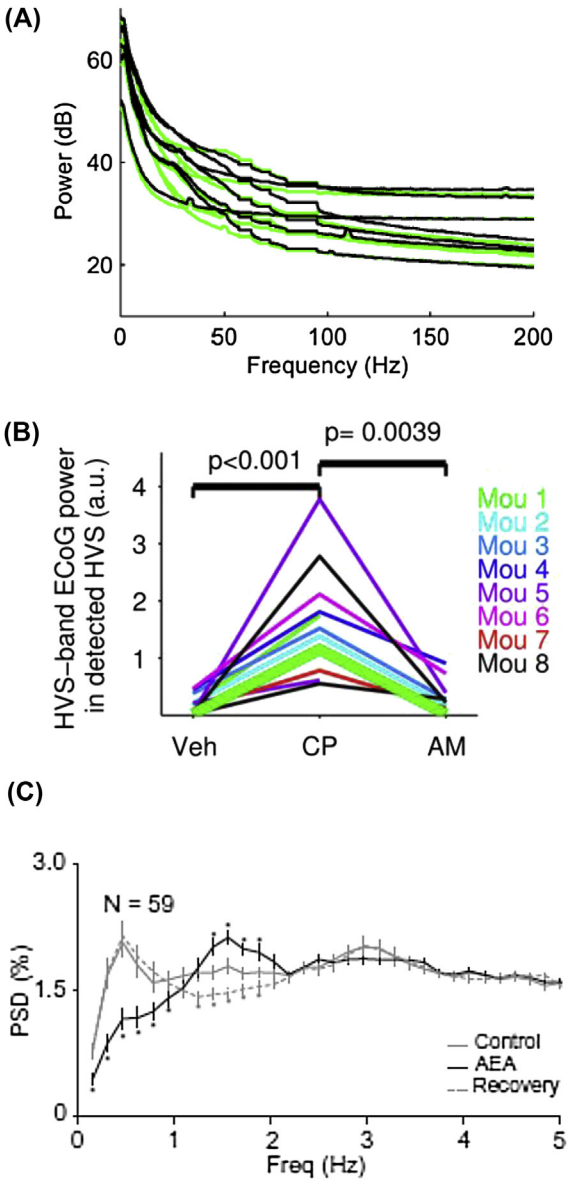

FIGURE 4 Endocannabinoids play a role in neuronal rhythmicity and synchrony. (A) LFP power of seven recording protocols in the visual cortex of two anesthetized monkeys before (black) and after (green) the intravenous administration of the CB agonist CP 55,940. The agonist decreased the power of low-gamma frequencies in both animals. (B) Systemic administration of CP 55,940 induces high-voltage spindles (HVS) in the cortex of mice. This effect is abolished by the administration of the CB antagonist AM251. Each line represents an experiment and each color an animal. *(Adapted from Sales-Carbonell et al. (2013).)* (C) Power spectral density (PSD) graph showing the effect induced by the intravenous administration of AEA on the oscillatory activity of simultaneously recorded groups of rat dLGN neurons. Note how cells start to oscillate at delta-like frequencies (~1.5 Hz) in the presence of AEA. $*p \leq 0.05$ vs control. *Adapted from Dasilva et al. (2014).*

CONCLUSIONS AND FUTURE DIRECTIONS

The role of endogenous and exogenous CBs in the visual system has been little studied. However, evidence from the literature suggests that the endocannabinoid system is an important component of visual processing. It is important to understand the basic physiology to fully understand the potentially pathological effects of exogenous substances acting on this system, which may have complex effects at various levels in visual processing.

Psychophysical studies both in humans and in animals have demonstrated several effects of CBs, administered both as pure compounds and as the drug marijuana, on color, form, and brightness perception; peripheral vision and visual acuity; night vision; perception of motion; and reconstruction of illusory and erroneous visual information. In addition, direct and indirect evidence has been brought about from EEG studies observing different alterations in visual evoked responses after acute or chronic consumption of various CB agonists during the performance of a wide range of behavioral tasks. Finally, although less intensively studied, firm evidence on the role of CBs in visual processing has been shown at various hierarchical levels from a neurophysiological perspective/cellular level. Not only the internal processing of visual information by the retina, but also further processing and computation of visual signals by the thalamus and cortex have been demonstrated to be modulated by CBs at both single-cell and population levels. However, multiple questions remain unanswered with regard to the exact mechanisms by which endocannabinoids modulate the processing of visual information in the retina and different levels of the thalamocortical circuit. New in vitro studies in the retina and beyond will be needed to clarify the exact synaptic mechanisms and neurotransmitters involved in the modulation of visual information processing by endocannabinoids and new and more detailed in vivo studies will also be necessary to integrate the mechanism of action of endocannabinoids into the physiology of the visual system. Only once these basic issues are resolved will we be fully able to explain the effects of cannabis on vision, as mediated via the endocannabinoid CB1 receptor.

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

The endocannabinoid system utilizes its own receptors through which it regulates the activity of the main neurotransmitter systems of the brain. Hence it has the capability of influencing the action of many other substances. For instance, CBs modulate the release of GABA in many brain areas; these receptors are the target receptors for ethanol or barbiturates.

Furthermore, the CBs can alter the activity of the dopamine-mediated process of reward, with a prominent role in the neurobiology of addiction.

The CB system has been implicated in the pharmacological and behavioral effects of ethanol, including tolerance development. Blocking the CB1 receptor has been shown to reduce voluntary ethanol intake in rats.

Similarly, a relationship between the endocannabinoid system and cocaine, morphine, and amphetamine abuse has been shown.

On the other hand, CBs demonstrate neuroprotective properties against methamphetamine-induced damage and interact with opioid agonists for inducing an enhanced antinociceptive response.

In the visual system, the interaction between CBs and other substances has not been studied in detail; however, it is clear that the effect of simultaneous consumption of several substances could produce interactions between them, since they act in similar processes, such as visual memory, attention, and ocular movements.

DEFINITION OF TERMS

Apparent motion This is a phenomenon that occurs when visual stimuli that are successively presented at different locations are perceived as a continuous motion.

Peripheral vision This is the ability to see objects and movement outside the fixation point, in contrast to central vision, which refers to vision at the fixation spot.

Vernier visual acuity This is a visual acuity test that measures the ability to detect a misalignment between two line segments or gratings.

Bottom-up and top-down processing This refers to different mechanisms of processing sensory inputs. In the bottom-up system each station of the process analyzes the input and sends the result to the next level of processing. In the top-down mechanism, the information from higher levels is sent to the previous ones, influencing, even controlling, the information processing.

Multiple sclerosis This is a syndrome in which the insulating myelin layer of nerve cells in the brain and spinal cord is damaged. It can cause visual deficits such as optic neuritis, diplopia, or nystagmus.

Neural oscillatory activity This is a pattern of rhythmic or repetitive activity of neurons in the central nervous system. This activity can be recorded at the cellular level or the system level. Different frequencies have been associated with different levels of consciousness.

Retinitis pigmentosa This is an inherited, degenerative eye disease that causes vision impairment and often progresses to blindness.

KEY FACTS OF THE CANNABINOID SYSTEM

- The endocannabinoid receptors were discovered at the beginning of the 1990s.
- They contain two main receptors broadly distributed through the central nervous system.
- The CB system has been implicated in processes such as regulation of appetite, memory, analgesia, or sleep.
- Research interest on the system has grown with the development of molecules targeting the CB receptors.
- It has been described in many animals.
- The endocannabinoid system is an important component of visual processing.
- The CB system shows promising therapeutic possibilities for the treatment of addiction to many substances other than cannabis.
- Medical disorders such as multiple sclerosis or anorexia are also potential targets for CB-mediated therapies.

SUMMARY POINTS

- Endocannabinoid system components—both ligands and receptors—are broadly distributed throughout the central nervous system.
- Studies reflect a critical role for CBs in visual perception from the retina to higher cortical centers.

- CBs affect color, form, and brightness perception; peripheral vision and visual acuity; night vision; perception of motion; and reconstruction of illusory and erroneous visual information.
- Marijuana facilitates night vision. Jamaican fishermen navigate with their boats through difficult coral reefs during the night after smoking or ingesting marijuana.
- Knowing the synaptic mechanisms and neurotransmitters involved in the modulation of visual information processing by endocannabinoids is an open question to be answered in the future.
- Not only vision, but also other sensory systems are influenced by CB-mediated activity.
- CBs mediate the reward system of the brain, hence they are implicated in the abuse of many other substances.

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