Review

Biological Psychiatry

It's All in the Rhythm: The Role of Cannabinoids in Neural Oscillations and Psychosis

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ABSTRACT

Evidence has accumulated over the past several decades suggesting that both exocannabinoids and endocannabinoids play a role in the pathophysiology of schizophrenia. The current article presents evidence suggesting that one of the mechanisms whereby cannabinoids induce psychosis is through the alteration in synchronized neural oscillations. Neural oscillations, particularly in the gamma (30–80 Hz) and theta (4–7 Hz) ranges, are disrupted in schizophrenia and are involved in various areas of perceptual and cognitive function. Regarding cannabinoids, preclinical evidence from slice and local field potential recordings has shown that central cannabinoid receptor (cannabinoid receptor type 1) agonists decrease the power of neural oscillations, particularly in the gamma and theta bands. Further, the administration of cannabinoids during critical stages of neural development has been shown to disrupt the brain's ability to generate synchronized neural oscillations in adulthood. In humans, studies examining the effects of chronic cannabis use (utilizing electroencephalography) have shown abnormalities in neural oscillations in a pattern similar to those observed in schizophrenia. Finally, recent studies in humans have also shown disruptions in neural oscillations after the acute administration of delta-9-tetrahydrocannabinol, the primary psychoactive constituent in cannabis. Taken together, these data suggest that both acute and chronic cannabinoids can disrupt the ability of the brain to generate synchronized oscillations at functionally relevant frequencies. Hence, this may represent one of the primary mechanisms whereby cannabinoids induce disruptions in attention, working memory, sensory-motor integration, and many other psychosis-related behavioral effects.

Keywords: Cannabinoids, Cannabis, Gamma, Neural oscillations, Psychosis, Theta

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For more than a century [cf. Stransky (1) and Bleuler (2)], a host of researchers have postulated that psychosis, at its core, is a disorder characterized by a functional disharmony (intrapsychic ataxia), schism, or disorganization of brain functions such as perception, emotion, language, cognition, and behavior (3–8). In other words, classic symptoms of schizophrenia, such as disorganized behavior and language, and disorders of perception (hallucinations), beliefs (delusions), and agency (passivity phenomena) could, in part, be caused by a disruption in the integration of different information processing networks in the brain (3. It has been suggested that one of the mechanisms underlying this disintegration is a disruption of the brain's ability to generate and maintain synchronized neural oscillations across distributed brain circuits (9–13).

Complex brain functions (e.g., perception and cognition) are based on distributed processes among multiple cortical and subcortical regions. It has been shown that the neural assemblies involved in these functions engage into transient periods of synchronous oscillatory activity while processing information (14–20). In other words, the activity of separate brain areas involved in a particular functional network will oscillate in a synchronized manner at specific frequencies (16). Different frequencies have been shown to be involved in particular types of neural function. For example, gamma-range oscillations (30–80 Hz) have been linked to sensory registration, higher perception, and conscious awareness (21–25), whereas theta oscillations (4–7 Hz) are typically involved in various types of memory function (26–29).

While space limits a full review of the literature relating altered neural oscillations to psychosis, several decades of research examining transient and steady-state evoked, perceptually/cognitive-induced, and resting-state neural oscillations (see below and Figure 1) have provided converging evidence that disruptions in both theta-range and gamma-range neural synchrony is a fundamental feature of psychosis [for review, see Pittman-Polletta *et al.* (13)] (9–13,30–47). Interestingly, synchronized neural oscillations are primarily mediated by gamma-aminobutyric acid (GABA)ergic interneurons, and central cannabinoid receptors (cannabinoid receptors type 1 [CB_1Rs]) are known to modulate GABA release. Hence, cannabinoids may represent a point of convergence wherein alterations in CB_1R function could lead to perturbations in neural oscillations, thus contributing to the pathophysiology of psychosis. In the following sections, descriptions of the types of neural oscillations that can be studied will be provided (Supplement 1), along with a description of the role of neural oscillations in sensation, perception, and cognition. Further, a review of the preclinical literature examining the relationship

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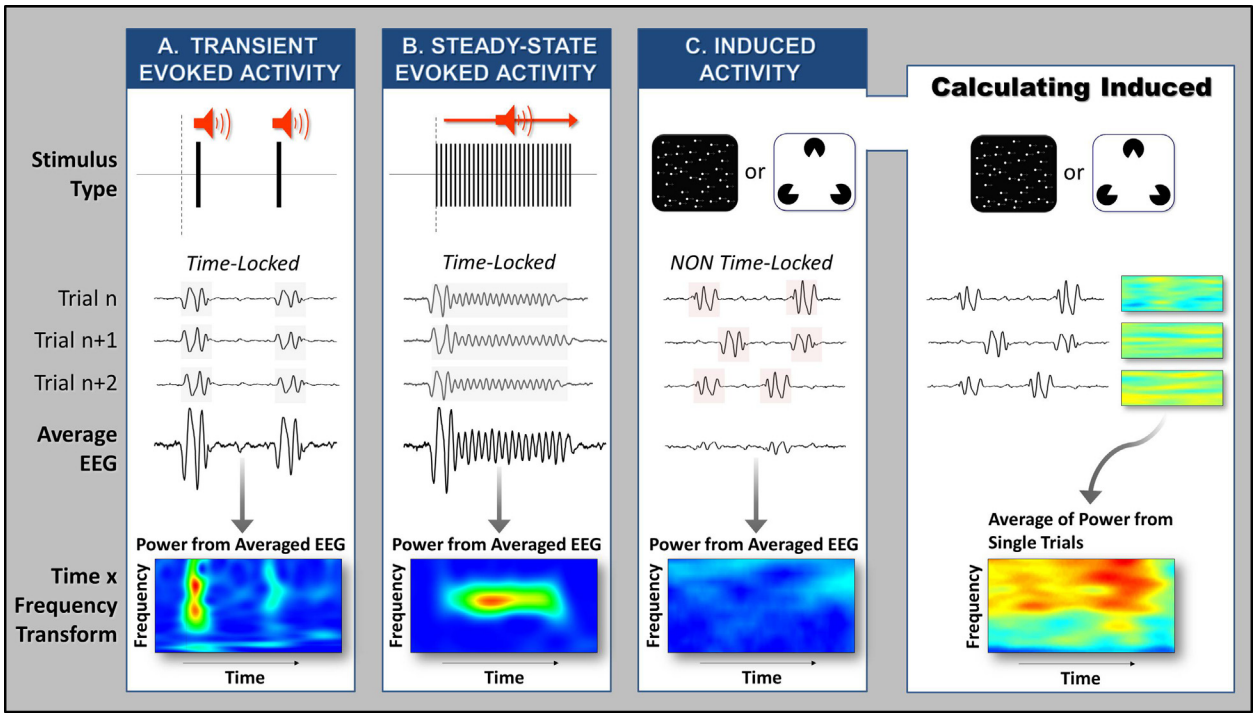

Figure 1. Transient evoked activity and steady-stated evoked activity are phase-locked and time-locked oscillations **(A, B)** elicited by discrete or steady-state sensory stimuli. For both of these types of activity, averaging across trials has the effect of cancelling out nonphase-locked oscillations (due to destructive interference), leaving the evoked response intact. Hence, time × frequency analysis can be performed on the averaged electroencephalogram (EEG) (i.e., after averaging all the individual trials). By contrast, induced activity is typically elicited by complex perceptual stimuli during coherent motion or the perception of illusory shapes **(C)**. These responses are often nontime-locked (jittered across time from trial to trial). Hence, averaging the trials cancels out the response of interest due to destructive interference and is not visible in the time × frequency transform **(C)** (bottom of panel, left). However, these responses can be detected if time × frequency analysis is performed on the single trials and the time × frequency transforms of individual trials are then averaged **(C)** (right). (Figure adapted with permission from Skosnik PD, Cortes-Briones JA (in press): Electroencephalography (EEG) and cannabis: From event-related potentials (ERPs) to oscillations. In: Preedy VR, editor. The Neuropathology of Drug Addictions and Substance Misuse: Foundations of Understanding, Tobacco, Alcohol, Cannabinoids and Opioids. Amsterdam, Netherlands: Elsevier Science.)

between cannabinoids and neural oscillations will be presented. Studies examining the effect of chronic and acute cannabinoid exposure in humans will also be reviewed, including a hypothetical model attempting to explain the potential mechanisms of CB_1R modulation on neural oscillations. Finally, the relationship between cannabinoids, oscillations, and their potential role in psychotic symptoms will be discussed.

NEURAL OSCILLATIONS AND THEIR ROLE IN SENSATION, PERCEPTION, AND COGNITION

Neural Oscillations in Sensation and Perception

There is a significant body of work suggesting a role for neural synchrony in early sensory processes. For instance, evoked neural oscillations in the gamma range emerge after exposure to a discrete stimulus (e.g., a singular tone or click) (Figure 1A) and are thought to be an index of early sensory registration (21–25). For example, Edwards *et al.* (25) demonstrated robust theta-band and gamma-band neural oscillations to brief auditory clicks during an auditory dual-click paradigm in humans. Further, studies that probe the auditory system using broadband evoked steady-state stimulation (Figure 1B) consistently show a preferred neural network resonance in the gamma range (40 Hz) (23,48,49).

In terms of higher perceptual processes, numerous studies have shown that neural oscillations, particularly in the gamma range, are involved in the Gestalt perception of coherent motion, object recognition, and face perception (50). Such gamma activity during the perception of coherent motion has also been shown in several animal studies and intracranial electroencephalography (EEG) studies and is thought to represent synchronized neural oscillations in higher visual areas (e.g., visual middle temporal area) (51–54). Object recognition, particularly the perception of illusory figures, has been shown to be related to gamma activity (10,33,55). For example, Tallon-Baudry *et al.* (55) utilized an illusory shape task (Kanizsa triangles) (Figure 1C, top right) to demonstrate the occurrence of induced gamma activity during the presentation of images that elicit real and illusory perception compared with a noise condition. Evoked gamma has also been shown to be elicited by Kanizsa illusory figures (10,33). Likewise, face recognition (as assessed with the Mooney face paradigm) has been shown to be associated with increased gamma activity (56–58). Taken together, synchronized oscillations in the gamma range may represent a key mechanism in the processing of perceptual information across

modality-specific areas of cerebral cortex, particularly in the binding of these features into a unified percept. Furthermore, long-range synchronization of neural activity in the gamma range seems to play a central role in the emergence of conscious perception (59). Alterations in these mechanisms, either as abnormal reductions or increases in gamma synchrony, may underlie some of the perceptual abnormalities observed in psychosis [for a review on neural oscillations and psychosis, see (11,13,59,60)].

Neural Oscillations in Cognition

High-frequency gamma oscillatory activity has been closely linked to attentive stimulus processing (61,62). Selective attention has been shown to enhance the amplitude and synchronization of neural activity in both animals and humans (63–66). For example, in an EEG study assessing the effect of selective attention on the auditory steady-state response (ASSR), Skosnik *et al*. (66) showed that attention to 40-Hz click trains resulted in increased evoked power and phase-locked activity in the gamma range. Considering attention as a mechanism that brings selected stimuli to the center of the perceptual field, the attention-related increases in gamma power and synchronization would be consistent with the aforementioned role played by gamma oscillations in conscious perception.

In terms of memory processes, theta oscillations were first linked to memory in animals nearly four decades ago (29). Since that time, it has become clear that theta rhythms interact with gamma oscillations, particularly in the hippocampus, and play a crucial role in the formation of episodic and spatial memory (29,67). Theta and gamma oscillations generated in the neocortex have been implicated in working memory processes, both in animals and humans (26–28,68–70). It has been argued that these oscillations are not just neural correlates of memory-related processes but instead are necessary components of the neural machinery mediating these processes (67). Theta oscillations would provide a series of sequential time slots in which gamma-mediated information processing occurs. A disruption of this mechanism could lead to an abnormal superposition and coactivation of neural ensembles processing different chunks of information, thus causing some of the cognitive abnormalities and symptoms observed in psychosis (67). Interestingly, CB_1R activation has been shown to alter the temporal structure (synchrony) of the activity of hippocampal neural ensembles, reducing theta and gamma oscillations as well as disrupting memory (71,72).

CANNABINOIDS AND NEURAL OSCILLATIONS

Endogenous Cannabinoids and Neural Oscillations in Animals

The role of endocannabinoids in neurotransmission has been intensively studied, revealing detailed mechanisms about their synthesis, release, and metabolism. Acting on CB_1Rs as retrograde transmitters, the prototypical endocannabinoids anandamide and 2-arachidonoylglycerol act via distinct cellular signaling pathways and can influence synaptic processes differently. CB_1Rs are located at axon terminals on both GABAergic and glutamatergic neurons, potentially modifying network activity in a complex manner (73).

Therefore, it is somewhat surprising that very little is known about the potential role of endocannabinoids in regulating neuronal network activities, including oscillations (in contrast to the emerging literature on the effects of exogenous CB_1R agonists; see below). Nonetheless, it has been reported that endocannabinoids can influence up/down states of cultured cortical pyramidal neurons (74), and CB_1R knockout mice have altered sleep-wake activities (75). Furthermore, genetic variability in the human CB_1R (genetic polymorphisms of rs1049353) has been shown to be associated with resting-state EEG theta power in humans (76), although its functional or behavioral relevance is unknown.

Exogenous Cannabinoids and Neural Oscillations in Animals

Pharmacologic studies have demonstrated that CB_1R activation alters neuronal network activity both in animals and humans, including changes in neuronal network oscillations. As discussed later, chronic use of cannabis or acute administration of delta-9-tetrahydrocannabinol (THC) appears to predominantly influence theta and gamma oscillations in humans (25,77–84). Given the presumed connection between abnormal neural oscillations and psychotic symptoms, a number of experimental studies have addressed the neurophysiological effects of THC or other CB_1R agonists in rodents. It is believed that neuronal network synchrony and oscillations share many common processes in humans and animals (85,86). This provides an opportunity to compare pharmacologic mechanisms of CB_1Rs on analogous neurophysiological signals recorded in both experimental animals and humans.

In vivo electrophysiological studies have demonstrated that CB_1R agonists disrupt neuronal network oscillations during a sensory gating task (87,88). Importantly, these effects were CB_1R specific, as the disruptions were fully reversed by the CB_1R antagonists AM-251 and SR141716A. Acute administration of THC or other CB_1R agonists also diminishes synchrony in hippocampal pyramidal neurons (71,72) and reduces hippocampal and cortical oscillations in the theta and gamma ranges (72,87,89,90). In fact, cognitive deficits following CB_1R agonists have been associated with reduction in synchrony of pyramidal cell firing or correlation between firing activity of neurons in the hippocampus and prefrontal cortex (71,72,89). It should be noted that changes in neuronal network oscillations following CB_1R agonists could result from various mechanisms. Since CB_1Rs are located on GABAergic and glutamatergic axon terminals, their activation attenuates release of both GABA and glutamate. Using in vitro recordings from the cornu ammonis 3 region of hippocampal slices, it has been shown that activation of CB_1Rs decreases GABA release and subsequently reduces the power of synchronous gamma oscillations (91). Considering modulation of cortical network activity by CB_1R agonists, a recent study utilizing in vivo electrophysiological recordings in conditional mutant mice lacking CB_1R expression showed that cannabinoids induce hypersynchronous thalamocortical oscillations while decreasing the amplitude of faster cortical oscillations. Furthermore, it has been reported that these opposing effects of CB_1R activation are due to the different localizations of the

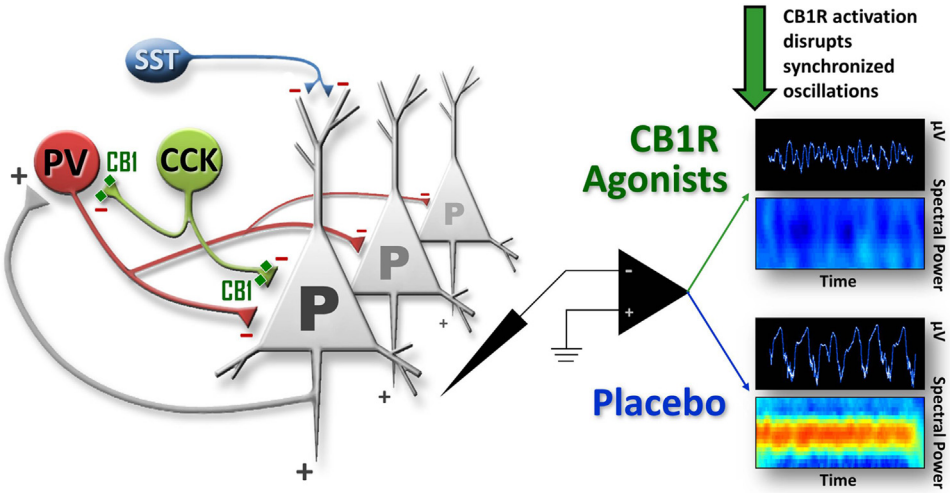

Figure 2. Hypothetical model illustrating the effect of exogenous central cannabinoid receptor type 1 (CB_1R) agonists on local field potential/electroencephalography neural network oscillations. Activated parvalbumin gamma-aminobutyric acidergic interneurons (PV) can propagate synchronized inhibitory inputs to multiple glutamatergic pyramidal cells (P) and other electrically coupled interneurons (not shown) in rhythmic bursts. However, activation of CB_1Rs by delta-9-tetrahydrocannabinol or synthetic cannabinoids reduces gamma-aminobutyric acid release, thus disinhibiting the PV and P cells. Such disinhibition would alter the network's excitatory-inhibitory balance, thus desynchronizing the rhythmic burst activity of PV cells. This could disrupt functionally relevant oscillations in the theta range and gamma range. CB1, cannabinoid receptor type 1; CCK, cholecystokinin gamma-aminobutyric acidergic interneurons; SST, somatostatin gamma-aminobutyric acidergic interneurons.

receptors, since CB_1Rs on GABAergic striatonigral neurons are responsible for thalamocortical hypersynchronization, while cortical glutamatergic neurons decrease cortical synchrony (92). However, in the primate cortex, CB_1Rs appear to be predominantly localized to GABAergic interneurons (see below and Figure 2) (93). Therefore, it appears that neuronal network responses to CB_1R agonists are mediated via complex interactions between GABAergic and glutamatergic transmitter release.

CANNABINOID EXPOSURE DURING DEVELOPMENT ALTERS NEURAL OSCILLATIONS (ANIMAL STUDIES)

Studies in rodents have shown that exposure to cannabinoids in preadolescence and/or adolescence induces long-lasting deficits in neural oscillations during adulthood. For example, repeated exposure to cannabinoids (WIN55-212,2 [WIN] or THC) during adolescence, but not during adulthood, has been shown to reduce pharmacologically induced oscillations in adult mice both in vitro and in vivo (94,95). In vitro recordings (local field potentials) showed reductions in theta (4–7 Hz), alpha (8–12 Hz), beta (13–29 Hz), and gamma (30–80 Hz) oscillations, while in vivo data (electrocorticogram) showed reductions in alpha and gamma oscillations. Importantly, these deficits appeared to be more pronounced in rostral areas of the cortex that were less mature at the time of the exposure to cannabinoids.

Interestingly, a recent study in rats may provide clues regarding the mechanism underlying these deficits. The exposure to the synthetic cannabinoid WIN during early adolescence, but not adulthood, was shown to disrupt the maturation of GABAergic function in the prefrontal cortex of mice (96). The early exposure to WIN caused a reduction in the normal inhibition of prefrontal activity (local field potentials) that results from driving the ventral hippocampus with gamma-band stimulation (40-Hz train electrical pulses). Remarkably, the pattern of prefrontal disinhibition was normalized in adult animals after increasing prefrontal GABAergic function through the local infusion of the $GABA_{A\alpha1}$ positive allosteric modulator Indiplon. In view of the role played by the GABAergic system in the generation of neural oscillations (97), these findings may provide a potential mechanism (i.e., a GABAergic deficit) for the deficits observed in neural oscillations after the exposure to cannabinoids during adolescence (94).

CHRONIC CANNABINOIDS AND NEURAL OSCILLATIONS IN HUMANS

While preclinical studies have provided compelling evidence for the role of cannabinoids in neural oscillations, a host of human studies have corroborated these findings, which provide support for the notion that CB_1Rs contribute to psychosis via disruptions in neural oscillations. For example, numerous EEG studies have shown that chronic cannabinoids are associated with disrupted theta-band and gamma-band neural oscillations (25,77–79). Regarding evoked oscillations, Skosnik *et al.* (78) demonstrated decreased evoked 40-Hz harmonic power in chronic cannabis users during 20-Hz stimulation in an ASSR task, and power values at the stimulation frequency were negatively correlated with scores of schizotypy (78). Edwards *et al.* (25) found decreased theta and gamma power during auditory click stimuli in a sensory gating paradigm. Interestingly, these disruptions were negatively correlated with self-reported levels of cannabis use (i.e., those with the lowest spectral power had the highest amounts of cannabis exposure).

In a follow-up study using the ASSR paradigm, Skosnik *et al.* (77) examined the full frequency response of neural oscillations in a larger sample of heavy cannabis users across 10 frequencies of stimulation. The results showed a selective disruption in evoked 40-Hz power in the cannabis group compared with cannabis-naïve control subjects. Further, these disruptions were associated with an earlier age of onset of cannabis use, which is in line with animal work suggesting that cannabinoid exposure during critical stages of neural

development alters the ability to generate gamma oscillations in adulthood (see above). Disruptions in induced gamma activity have also been observed in chronic cannabis users during the perception of coherent motion (79). Lastly, in a study that examined resting-state oscillations in abstinent chronic cannabis users, Herning *et al*. (98) reported a reduction in theta (4–7 Hz) and alpha1 (8–10 Hz) power in users compared with healthy control subjects. In sum, chronic cannabinoid exposure is associated with decreased evoked, induced, and resting-state neural oscillations. While the mechanism whereby chronic cannabinoids alter neural oscillations is unclear, the two most likely possibilities are residual cannabinoids (given the long half-life and lipophilic nature of THC) and/or CB_1R downregulation (99).

ACUTE CANNABINOIDS AND NEURAL OSCILLATIONS IN HUMANS

The strongest evidence suggesting that cannabinoids disrupt neural oscillations has come from controlled acute THC administration studies in humans. While only a handful of experiments have attempted to examine the effects of acute THC on neural oscillations, the results have been compelling. For example, Morrison *et al*. (81) demonstrated that a single dose of intravenous (IV) THC decreased theta power and interelectrode coherence during performance on an n-back working memory task. Relevant to the postulate that cannabinoids are related to psychosis via disruptions in neural oscillations, coherence deficits were positively correlated with psychotic-like symptoms (100). Several previous studies have shown similar results with inhaled THC, including decreased resting-state theta power and disruptions in working memory performance (82–84). More recently, a small study that tested the effect of IV THC on synchronized neural oscillations preceding self-generated speech demonstrated that THC decreased theta-range phase locking (101). These data provide evidence that THC disrupts working memory (a core abnormality in schizophrenia) via disruptions in oscillatory theta activity.

Regarding steady-state evoked gamma oscillations, Cortes-Briones *et al.* (80) showed for the first time in humans that acute IV THC disrupts evoked gamma-band oscillations using the ASSR task. Specifically, this study demonstrated a dose-dependent reduction of spectral power and intertrial coherence during gamma-range auditory stimulation (40 Hz). Most importantly, inverse relationships between 40-Hz coherence and the psychotomimetic effects of THC were observed, which provides the strongest evidence to date that THC's effect on synchronized gamma activity may underlie some of the psychosis-related effects of cannabinoids.

HYPOTHETICAL MECHANISM OF CANNABINOID MODULATION OF NEURAL OSCILLATIONS: CB_1R-MEDIATED PRESYNAPTIC INHIBITION OF NEUROTRANSMITTER RELEASE

It is well documented that endocannabinoids activate CB_1Rs via retrograde transmission and influence neurotransmitter release from neurochemically diverse neurons, including the release of the inhibitory neurotransmitter GABA (102). As alluded to above, a large body of research has shown that GABAergic interneurons are critical components of the generators of neural oscillations in the theta range and gamma range (103–109). For example, gamma oscillations are completely blocked by the $GABA_A$ receptor antagonist bicuculline (110). Further, the sizeable branching of outputs from GABAergic interneurons is ideally suited to synchronize large numbers of pyramidal cells (111). However, there are diverse types of GABAergic interneurons based upon their electrophysiological characteristics, their expression of calcium-binding proteins, and/or whether or not they are fast or nonfast spiking neurons. Of these many subtypes, the fast-spiking parvalbumin (PV)-expressing interneurons appear to be the primary generator of neural oscillations in the brain (103,112,113). PV cells typically target the pyramidal cell's axon initial segment and cell body, thus positioning their terminals in an optimal location to synchronize numerous pyramidal cells (Figure 2).

Another GABAergic interneuron subtype, namely the nonfast spiking cholecystokinin (CCK)-positive cell, is also in a prime location to fine tune the network oscillations generated by PV cells (114). Germane to the role of cannabinoids in synchronized oscillations, CCK-positive cells appear to be the only cortical and hippocampal interneuron type to express CB_1Rs (93,115–121). CCK cells also target pyramidal cell bodies, putting them in an ideal location to modulate PV to pyramidal cell oscillations (122). For example, CCK interneurons discharge action potentials early in the phase of theta (123) and gamma oscillations (124,125), and it has been argued that they set an activity threshold for the firing of pyramidal cells (CCK cell-mediated inhibition is removed from highly but not from weakly active pyramidal cells) that has the effect of a noise filter increasing the signal-to-noise ratio of neural circuits (125–127). Further, CCK cells themselves have collaterals that provide input onto PV cells (128). Thus, it appears that endocannabinoids play a role in modulating GABA release in CCK neurons, thus fine tuning network oscillations (Figure 2).

As discussed above, it should be reiterated that CB_1R modulation of glutamate release may also play a role in mediating changes in synchronized oscillations (92). Activation of CB_1Rs on glutamatergic axon terminals inhibits glutamate release, although it has been recently revealed that endocannabinoids can also facilitate glutamate release via neuron-glia interaction (129). Therefore, it can be proposed that alterations in neuronal network oscillations induced by endocannabinoids and exocannabinoids could be mediated by CB_1Rs expressed by both GABAergic and glutamatergic neurons, leading to decreased excitation and increased disinhibition. However, cannabinoids also regulate the synaptic release of other neurotransmitters, including acetylcholine, norepinephrine, and serotonin (102,130,131), which are known to effectively modulate cortical and hippocampal oscillatory activities (132–134). Hence, cannabinoids could also inhibit theta and gamma oscillations indirectly via cholinergic and monoaminergic mechanisms. Consequently, disruption of physiological endocannabinoid signaling (e.g., by the administration of an exogenous cannabinoid like THC) would lead to downstream alterations in diverse neuronal circuits and various neurotransmitter systems resulting in desynchronized neural oscillations, thus leading to disturbed sensory,

perceptual, and cognitive functions and potentially to psychosis (see below).

CANNABINOIDS AND NEURAL OSCILLATIONS: IMPLICATIONS FOR PSYCHOSIS

From the micro to the macro level, brain activity displays a rhythmic, oscillatory behavior. Similar to the complex dialog between instruments in a jazz ensemble, waves of oscillatory activity travel between the brain's network nodes as they exchange information in a rich and fluid dialog. Interacting nodes engage in transient periods of synchronized oscillatory activity while processing information, giving rise to complex brain functions.

The cannabinoid system participates in maintaining the fine tuning of oscillatory activity within the brain by regulating the release of GABA and glutamate in an activity-dependent manner. Thus, as postulated by Skosnik *et al.* (78), a disruption of normal endocannabinoid signaling (e.g., by the administration of an exogenous cannabinoid like THC) could thereby interfere with complex brain functions and "eventually lead to psychotic or altered perceptual experiences." Recent evidence suggests that some of the alterations in neural oscillations induced by exogenous cannabinoids result from increased levels of neural noise (i.e., random, nonoscillatory activity) (72,135). Considering that neural noise would interfere with and distort the information circulating within brain networks, it can be hypothesized that exogenous cannabinoids would induce a dysconnection (136) state between brain areas and that this may be one of the mechanisms underlying the acute psychotomimetic effects of these compounds. In this sense, the acute intoxication induced by exogenous cannabinoids would correspond to a mild version of the functional disharmony (intrapsychic ataxia), schism, or disorganization of brain functions that, since the times of Stransky (1) and Bleuler (2), have been described as core deficits of schizophrenia (3–8).

CONCLUSIONS AND FUTURE DIRECTIONS

This review critically examined and synthesized disparate literatures regarding the relationship between neural oscillations, cannabinoids, and psychosis. The converging evidence implicating cannabinoids, neural oscillations, and psychosis provides a backdrop for a series of intriguing future directions. As discussed above, CB_1R-mediated disruptions in neural oscillations appear to be elicited by both acute and chronic exposure to exogenous cannabinoids. Thus, the CB_1R-mediated functional disharmony hypothesized above could also be elicited by chronic cannabinoids [e.g., by CB_1R downregulation (99) or by altered neural development via adolescent cannabis exposure]. Indeed, the ability of humans to generate robust neural oscillations appears to exhibit a distinct developmental trajectory (137), indicating that the maturing brain may be particularly vulnerable to exogenous cannabinoids during certain critical periods. Future work is needed to examine the role of CB_1R downregulation and adolescent cannabis exposure in the context of neural oscillations and psychosis.

One issue that is worth drawing attention to is the potential contrasting effects of chronic versus acute/residual exocannabinoids. Chronic cannabinoids (CB_1R downregulation) versus acute/residual cannabinoids (CB_1R activation) could have differential effects on transmitter release and hence neural oscillations. For example, CB_1R downregulation would be expected to result in cannabinoid hypofunction (when individuals are not acutely intoxicated), which would increase transmitter release on cells with presynaptic CB_1Rs. Conversely, acute or residual cannabinoids could potentially augment the action of endocannabinoids, thus eliciting cannabinoid hyperfunction and hence decreased transmitter release. However, neural networks are tightly regulated and exist in a fragile equilibrium, and disruptions in either direction (including structural neurodevelopmental alterations) could perturb the excitatory/inhibitory balance of such networks. Regardless, disentangling the differential and net effects of chronic and acute cannabinoids [potentially with the use of computer models, as have been used in the context of other psychotomimetic drugs (138)] is an important area of future study.

Considering the effects of chronic cannabis administration or consumption on behavior, a better understanding of the physiological role of endocannabinoids in neuronal network oscillations is essential. Surprisingly, very little is known about their potential involvement in the activity of complex neuronal circuits; thus far, neither studies utilizing CB_1R knockout mice nor studies on CB_1R antagonists have provided comprehensive insight. Further, it is unknown whether different patterns of endocannabinoid release (phasic vs. tonic) could influence neuronal oscillations differently, as it does with synaptic plasticity (139). Recent findings demonstrate that cannabinoids can influence network oscillations by acting via GABAergic or glutamatergic neurons (92). However, given the diversity of neurons expressing CB_1Rs, cannabinoids could alter neuronal oscillations via reducing release of various neurotransmitters and neuromodulators. Selective activation or inhibition of subsets of neurons by optogenetic manipulation within a given neuronal network could reveal precise mechanisms involved in modulation of oscillatory activity by either endocannabinoids or exocannabinoids.

Another area of future study involves the potential role of functional interactions between different oscillation frequencies. It is well known that theta and gamma network oscillations can work in concert, particularly during cognition (e.g., working memory) (67). Hence, the role of cannabinoids in theta-gamma cross-frequency coupling necessitates further study (140). Lastly, it is well known that CB_1Rs interact with other receptor systems implicated in psychosis (e.g., *N*-methyl-D-aspartate receptors) (141,142). Hence, the interrelationship between CB_1Rs and *N*-methyl-D-aspartate receptors could be a fruitful area of future study. While these proposed areas of study represent only a handful of potential novel directions, it is clear that the time has come for more systematic research in the realm of cannabinoids, neural oscillations, and disorders within the spectrum of psychosis.

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ARTICLE INFORMATION

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