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Review

Neuroimaging studies towards understanding the central effects of pharmacological cannabis products on patients with epilepsy

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ABSTRACT

Recent interest for the use of cannabis-derived products as therapeutic agents in the treatment of epilepsies has necessitated a reevaluation of their effects on brain and behavior. Overall, prolonged cannabis use is thought to result in functional and structural brain alterations. These effects may be dependent on a number of factors: e.g., which phytocannabinoid is used (e.g., cannabidiol (CBD) vs. tetrahyrocannabinol (THC)), the frequency of use (occasional vs. heavy), and at what age (prenatal, childhood, adulthood) the use began. However, due to the fact that there are over seven hundred constituents that make up the *Cannabis sativa* plant, it is difficult to determine which compound or combination of compounds is responsible for specific effects when studying recreational users. Therefore, this review focuses only on the functional MRI studies investigating the effects of specific pharmacological preparations of cannabis compounds, specifically THC, tetrahydrocannabivarin (THCV), and CBD, on brain function in healthy individuals and persons with epilepsy with references to non-epilepsy studies only to underline the gaps in research that need to be filled before cannabis-derived products are considered for a wide use in the treatment of epilepsy.

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1. Introduction

The use of products derived from *Cannabis sativa* for the treatment of various medical conditions has long been of popular, research, and medical interest; its use has been widely debated (e.g., the CNN "*Weed*" series by Dr. Sanjay Gupta). This public resurgence in interest for the indication of cannabis products as therapeutic agents in the treatment of epilepsies has necessitated a reevaluation of the known effects on brain and behavior [1,2]. These popular trends and assertions were recently fueled by positive results from three cannabidiol (CBD) studies for the treatment of the Dravet and Lennox–Gastaut syndromes [3–5] and by human data supporting the importance of the endocannabinoid system to the onset and generation of seizures [6–8]. In particular, one study documented lower levels of anandamide in the cerebrospinal fluid of patients with new-onset temporal lobe epilepsy when compared to healthy controls [6], another study indicated a downregulation of cannabinoid 1 (CB1) receptor mRNA when compared to non-epilepsy controls that resulted in lower production of diacylglycerol lipase-alpha, an enzyme responsible for "on demand" production of 2-arachidonoylglycerol (2-AG) [7] and, finally, a PET study showed increased availability of CB1 receptors in the temporal lobes of patients with epilepsy when compared to healthy controls [8]. These and other studies support further development of cannabinoids for the treatment of epilepsy [9,10]. But, the potential benefits of phytocannabinoids need to be viewed through the prism of their known and unknown effects on brain development and function. The overall consensus is that prolonged cannabis use may result in functional and structural brain alterations that persist beyond the intoxication period, and that onset of use during the neurodevelopmental period may be associated with greater cognitive deficits [11–13]. For example, evidence from early development studies indicates that recreational cannabis use in expectant mothers has short- and long-term effects on the developing and mature brain and that these effects are different from the effects of tobacco use [11]. Another recent cannabis and neuroimaging study of structural changes in the developing brain documented negative effects on brain diffusion parameters that were dependent on the age of cannabis use initiation [14]. Thus, early exposure to cannabis products may result in the alteration of the endocannabinoid system function which may be important for cognitive development [15] and relevant to the use of such products in children and adolescents.

Functional neuroimaging, in particular, functional magnetic resonance imaging (fMRI), allows for the non-invasive examination of how cannabis acts on the human brain to affect, behavior. A recent

Abbreviations: fMRI, functional magnetic resonance imaging; THC, tetrahydrocannabinol; CBD, cannabidiol; THCV, tetrahydrocannabivarin; PWE, persons with epilepsy.

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review in chronic cannabis users described varying patterns of resting brain activity in adolescents and adults, as well as altered brain activation while performing cognitive tasks (e.g., tasks assessing attention, memory, motor function, inhibition, affect, and decision-making) when compared to healthy control subjects; the authors suggest that these differences are compensatory as a result of chronic cannabis use [11]. Functional magnetic resonance imaging (fMRI) has also been helpful in investigating the acute effects of cannabis and specific cannabis compounds on brain functions, with a review of drug challenge studies that utilized either cannabis or tetrahydrocannabinol (THC) showing that task difficulty affects the impact of drug administration and that participants can achieve normal performance after drug administration on less demanding tasks but with alterations in neural recruitment or increased neural effort [16].

An important consideration in cannabis studies is that there are over seven hundred constituents that make up the *Cannabis sativa* plant, more than 100 of which are classified as cannabinoids [17]. Due to the numerous available preparations of cannabis and the variability in concentrations of different compounds in such preparations [18], not to mention the potential for and high likelihood of contaminants, it is difficult to ascertain which compound or combination(s) of compounds are responsible for specific effects, cognitive or otherwise, when studying recreational users. Pharmacological studies using purified cannabis compounds provide insight into specific effects on human brain and behavior, and are more informative when considering the use of such compounds for therapeutic indications. Tetrahydrocannabinol (THC) is the most studied cannabis compound, although there have not been as many human studies investigating its neural effects as there have been on its subjective, cognitive, and behavioral effects. In addition to studies of the effects of THC, few recent neuroimaging studies have focused on the central effects of other phytocannabinoids — tetrahydrocannabivarin (THCV) and cannabidiol (CBD). In this review, we will summarize fMRI studies focusing on the effects of pharmacological preparations of THC, THCV, and CBD on brain function in healthy individuals and persons with epilepsy (PWE).

2. Functional MRI studies of cannabis compounds in healthy individuals

2.1. Tetrahydrocannabinol (THC)

Tetrahydrocannabinol, the main psychoactive component of cannabis, acts centrally as a partial agonist to CB1 receptors in the brain to mediate release of various neurotransmitters including acetylcholine, glutamate, and dopamine to name a few [19,20]. In humans, CB1 receptors have a high density in the medial temporal, prefrontal, and anterior cingulate cortex [21], brain regions that are critical to a number of cognitive and emotion processes which are frequently affected by epilepsy. In healthy individuals, THC has been shown to impair learning and memory performance [22], as well as performance on motor control, executive function, motor impulsivity, and risk-taking tasks [23]. The earliest reported human fMRI study of pharmacological THC administration was a double-blind, placebo-controlled investigation of amygdala reactivity to explore the anxiolytic properties of THC and the potential to target the endocannabinoid system in the treatment of anxiety/social fear disorders [24]. This was followed by a series of fMRI studies investigating the acute effects of THC on sensory, motor, emotion, and cognitive processing in healthy male volunteers using a double-blind, placebo-controlled cross-over design [25–33]. The Pharmacological Imaging of the Cannabinoid System study also utilized a randomized, placebo-controlled cross-over design to assess acute effects of THC on memory, reward, attention, emotion, motor, and resting state processes in males [34–41]. Further, THC has been shown to alter resting state brain activity with increased amplitude of fluctuations compared to placebo in a number of brain regions including the insula, substantia nigra, and cerebellum [36]. The studies described in greater detail below further illustrate how THC acutely alters patterns of activation during a number of cognitive processes.

2.1.1. Sensory and motor processes

The first fMRI study investigating the effects of THC on neural circuitry showed no effect on primary visual and motor activation during a passive visual/motor task in which subjects viewed a flashing checkerboard while pressing their right index finger [24]. However, another study utilizing a passive sensory stimulation task showed that THC elicited both decreased and increased activation in regions of the visual cortex and cerebellum bilaterally during visual processing of a radial checkerboard with different flicker rates [29]. These two studies suggest that THC may not alter brain activity in response to simple visual and motor stimuli but does so with respect to more complex visual stimuli. Winton-Brown et al. also showed that during auditory processing, THC decreased activation compared to placebo bilaterally in temporal regions, insulae, and supramarginal gyri, and in the right inferior frontal gyrus and cerebellum [29]. Compared to placebo, THC also elicited reduced activation during motor response inhibition in the right inferior frontal gyrus, and in the bilateral anterior cingulate and precuneus, but increased activation in right temporal and subcortical brain regions as well as the left posterior cingulate and precuneus [25]. There was no difference between task performance following administration of placebo or THC in the study by Borgwardt et al. [25] but a later study showed that those who experienced THC-induced psychotic effects had decreased task performance and decreased activation in the left parahippocampal/fusiform gyrus, left middle temporal gyrus, and right cerebellum extending into the fusiform gyrus, as well as increased activation in the right middle temporal gyrus in those who did not experience psychotic effects [32].

2.1.2. Learning and memory

For verbal learning and memory, THC disturbed the normal pattern observed with placebo of decreasing activation with repeated presentation of encoding blocks (e.g., in parahippocampal gyrus and cerebellum) and recall blocks (e.g., in dorsoanterior cingulate/medial prefrontal cortex) during a paired associates learning task; this decrement in neural recruitment with learning was associated with an improvement in recall score in the placebo condition; this effect was abolished with THC administration [28]. A follow-up study revealed that a particular genetic profile for the dopamine transporter (DAT1) and the protein kinase B (AKT1), both involved in dopamine neurotransmission, increased sensitivity to the effects of THC and altered activity in the striatum during encoding as well as in the midbrain during recall [33]. For pictorial learning and memory, THC decreased activation in the right inferior frontal gyrus, right insula, and left middle occipital gyrus during encoding, and increased precuneus activation bilaterally during recall [39]. While there was no difference in task performance between placebo and THC conditions, the negative correlation between task accuracy and brain activity during recall (in the left fusiform/parahippocampal gyrus and bilateral middle occipital gyrus) that was observed for the placebo condition did not exist under the THC condition [39], similar to the pattern of disruption observed by Bhattacharyya et al. [28] with the paired associates task. Finally, THC was shown to impair working memory performance on the Sternberg item-recognition task compared to placebo, and instead of the linear increase in brain activity with increasing working memory load that was observed with placebo, THC enhanced brain activity even in the low working memory load conditions [40].

2.1.3. Emotion processing

Using an emotion perception task in which subjects had to match up faces displaying the same emotion (i.e., angry, fearful or happy), THC was shown to attenuate activation in the right amygdala compared to placebo when processing threatening (i.e., angry and fearful) faces but did not affect task accuracy or response times [24]. Utilizing a similar emotion perception task, Bossong et al. [41] showed that THC relative to the placebo condition did not affect overall response times or