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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

accuracy for matching happy faces, but reduced accuracy for matching fearful faces. Furthermore, region-of-interest analysis showed reduced activity while processing fearful faces in a network of brain regions including amygdala, hippocampus, orbital frontal gyrus, prefrontal cortex, parietal gyrus, and occipital cortex [41]. Fusar-Poli et al. [27] utilized a different emotion perception task in which subjects viewed faces with intensely fearful, mildly fearful or neutral expressions and were asked to distinguish male versus female faces. In this paradigm, there were no differences in task performance, but THC relative to placebo decreased activation during the processing of fearful faces in the right inferior frontal gyrus, superior temporal gyrus, and left medial frontal gyrus, while increasing activation in the left precuneus [27]. However, THC did not modulate the anterior cingulate–amygdala effective connectivity that was identified in the placebo condition when processing fearful faces [26]. Taken together, THC may have potential utility in the treatment of anxiety/social fear disorders as suggested by Phan et al. [24].

2.1.4. Attention

The effect of THC on various attention-related processes has been investigated. Utilizing a visual oddball detection task, THC compared to placebo increased response time and attenuated activation during salience processing (i.e., when presented with rare or deviant stimuli) in the right caudate/putamen, insula, and thalamus but enhanced response in the right prefrontal cortex [31]. Follow-up analysis revealed that THC reduced the fronto-striatal functional connectivity between the dorsal striatum and prefrontal cortex, but enhanced connectivity between the hippocampus and prefrontal cortex [30]. Bossong et al. [34] examined executive function using a continuous performance task in which subjects had to respond quickly when they are presented consecutive numbers that are identical. Relative to placebo, THC impaired task performance (i.e., increasing false alarms and reducing target accuracy) and induced less deactivation in regions associated with the default mode network including the posterior cingulate and angular gyrus; less deactivation was associated with poorer performance [34].

2.1.5. Reward processing

Modified versions of a monetary incentive delay task (i.e., subjects were cued as to whether or not the trial was rewarded or neutral before being given a target in which they had to press a button, followed by performance feedback) were used to investigate the effect of THC on reward processing [35,38]. THC relative to placebo did not alter the pattern of faster response times during reward trials compared to neutral trials, did not affect activation during the anticipation period, but did attenuate activation to feedback in reward trials in feedback-related brain regions including bilateral inferior parietal and temporal gyrus, posterior and anterior cingulate, and middle orbitofrontal gyrus, as well as the right superior frontal gyrus [38]. Anatomical region-of-interest analysis was later performed to investigate specific THC effects on caudate, putamen, and nucleus accumbens which are implicated in reward processing, and showed that THC elicited a significant reduction in nucleus accumbens activation during anticipation to reward in healthy individuals addicted to nicotine but not in those who were not addicted [35].

2.1.6. Summary

The overall impression of acute THC effects on human brain function is that it does not significantly impair performance on some cognitive tasks, specifically, on tasks of motor response inhibition, verbal and pictorial learning and memory, emotion processing, and reward processing as described above, but that the typical patterns of task-related activation were disrupted. The ability of THC to attenuate brain activation during the processing of threatening (i.e. angry or fearful) faces may prove beneficial in the treatment of anxiety/social fear disorders. However, performance on tasks assessing working memory (i.e. Sternberg task) and attentional processes (i.e. visual oddball and continuous performance tasks) seems to be particularly sensitive to THC-induced impairments and changes in neural recruitment.

2.2. Tetrahydrocannabivarin (THCV)

Like THC, the central effects of THCV are also mediated through CB1 receptors, but have some differing effects [20]. Namely, THCV can also act as a neutral antagonist of CB1 receptors, meaning that it does not affect the constitutive or basal activity level of CB1 receptors but can block the activity of other CB1 receptor compounds [20,42]. The neural effects of THCV in humans have been investigated using a model of reward and aversion processing during fMRI as it has been considered a possible treatment for obesity [43]. Compared to placebo, THCV increased BOLD responses to rewarding stimuli (i.e., chocolate) in the anterior cingulate cortex, caudate, putamen, and midbrain, and to aversive stimuli (image of moldy strawberries and less pleasant strawberry taste) in the caudate, putamen, amygdala, insula, and orbitofrontal cortex [43]. A follow-up resting state fMRI study showed that a single dose of THCV reduced functional connectivity between amygdala and regions in the default mode network including the posterior cingulate cortex (PCC), while also increasing connectivity between regions involved in executive control such as between the dorsal medial prefrontal cortex and the inferior frontal gyrus [44].

2.3. Cannabidiol (CBD)

Cannabidiol is a non-psychoactive component of cannabis, although it has been shown to have antipsychotic effects (see [45] for review) as well as anxiolytic properties [46,47]. The mechanism of action for CBD's central effects remains unclear, and while it is thought to be mainly independent of CB1 receptor mechanisms due to its low receptor affinity, there is some evidence that CBD can act as an inverse agonist for the CB1 receptor such that it induces effects opposite to that of an agonist like THC, which may underlie some of the observed neurophysiological and behavioral effects that are opposite to those of THC [20,48]. The same studies that had investigated acute THC effects on various brain functions in healthy males during fMRI also assessed acute effects of CBD compared to placebo [25–31,49]. The results for CBD relative to placebo in these studies will be discussed here, as findings with THC were included in the section above.

Compared to placebo, CBD elicited decreased activity during motor response inhibition in the left insula, superior temporal gyrus, and transverse temporal gyrus and did not affect task performance [25]. CBD modulated sensory processing compared to placebo by increasing activation in the temporal and insular cortex and by reducing activation in other parts of the posterior left temporal cortex, insula, and supramarginal gyrus during auditory processing, and during visual processing, CBD also increased activation in the right occipital lobe [29]. For verbal learning and memory, however, CBD did not differ from placebo in its ability to modulate activation (i.e., to decrease engagement of particular brain regions) over repeated word pair encoding and word retrieval blocks [28], consistent with previous work showing that CBD does not affect learning and memory [22,50]. CBD does appear to affect emotion processing, as it attenuated the fMRI response to fearful faces compared to placebo in the left anterior cingulate and amygdala and the right posterior cingulate and cerebellum, as well as reducing autonomic arousal [27]. Advanced analysis using dynamic causal modeling showed that during the neural response to fearful faces, the left anterior cingulate cortex and the left amygdala were functionally coupled, with the driving inputs entering through the anterior cingulate that has forward connectivity to the amygdala, and this intrinsic connection is disrupted by CBD [26]. Compared to placebo, CBD also attenuated the neural response to processing stimulus salience in the left medial prefrontal cortex, but enhanced response in the right caudate, parahippocampal gyrus, insula, precentral gyrus, and thalamus [31]. Connectivity analysis for salience processing revealed that CBD reduced functional connectivity between the prefrontal

cortex and hippocampus, but enhanced connectivity between the dorsal striatum and prefrontal cortex [30].

3. Functional MRI studies of cannabinoids in persons with epilepsy

To date, there are no publications of fMRI utilization to study brain function in patients with epilepsy taking pharmacologic cannabis products. However, these studies are currently underway. An abstract presented at the 2016 Meeting of the Organization for Human Brain Mapping evaluated the effects of CBD treatment on fMRI activity during an attentional Flanker task in which PWE were presented with congruent or incongruent visual stimuli, e.g., a row of five fish all pointing in the same direction (congruent condition) or with the center fish pointing in the direction opposite the other surrounding fish (incongruent condition). This study is part of the UAB Cannabidiol Program, an ongoing open-label study of adjunct pharmaceutical grade CBD (Epidiolex) for the treatment of treatment-resistant epilepsy (NCT02695537, NCT02700412). Initial reports on small numbers of subjects documented a trend of improvement (not statistically significant) in behavioral performance that paralleled changes in attention-related brain activity, as well as overall improvement in seizure control in patients after achieving a stable dose of CBD (20 mg/kg or 25 mg/kg) when compared to the same subjects prior to the initiation of therapy with CBD. Results of follow-up analyses in 11 PWE (6 females), that were presented at the 2016 Annual Meeting of the American Epilepsy Society (AES), showed similar trends in improving performance on an attentional Flanker task and changes in brain activity during response inhibition, particularly in the left inferior frontal gyrus (Fig. 1). Additional preliminary results for a modified Sternberg working memory task showed an overall increase in the recruitment of brain regions during load-sensitive encoding (Fig. 2A) and decreased recruitment during retrieval (Fig. 2B) after CBD treatment compared to pre-CBD; these changes in neural recruitment were coupled with a non-significant trend in improving task accuracy. The caveats to research in such a diverse patient population of treatment-resistant epilepsies include the inter-subject variability in neurophysiological and treatment response, potential interactions with other medications or comorbid conditions, and overall differences in cognitive performance of the participants, all of which could influence activation during fMRI. However, the authors concluded that the preliminary findings are promising in that they illustrate the potential for CBD treatment to improve cognition, in addition to seizure control, in PWE.

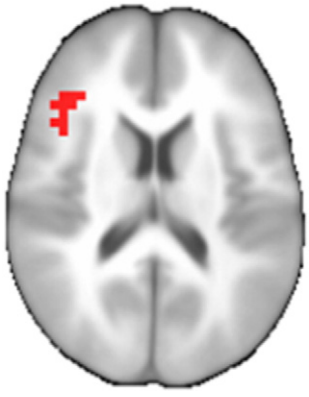

Fig. 1. Preliminary results of regression analysis in patients receiving CBD treatment for epilepsy who performed an attentional Flanker task during fMRI. Results show a greater response difference between congruent and incongruent conditions at visit 2 compared to pre-CBD fMRI in the left inferior frontal gyrus — an area involved in many cognitive processes including executive control and working memory. Left in the image is left in the brain.

4. Discussion

There is little doubt of the therapeutic potential of products derived from the *Cannabis sativa* plant. However, we still have much to learn about the safety and efficacy of such compounds for the treatment of various conditions including epilepsy and of their effects on brain and behavior. While THC is the most studied phytocannabinoid to date, the majority of pharmacological neuroimaging studies included only male subjects, calling into question the generalizability of the results. Furthermore, increased research into the effects of other phytocannabinoids is necessary as they may be of greater (or different) utility for particular medical conditions including epilepsy. For instance, if further research determines that THCV or CBD are as effective for the treatment of epilepsy, the anti-obesity effects of THCV may guide the therapy in patients with co-existing weight problems or the antipsychotic and anxiolytic effects of CBD may also be more desirable for patients with epilepsy and co-existing mood issues. Investigation into dose response and interaction effects of different cannabis compounds and their various combinations are warranted. Finally, because of the possibility of an entourage effect, while the efficacy of combinations of phytocannabinoids is being examined, the effects of such combinations on brain and behavior in patients with epilepsy need to be investigated in parallel. While the preclinical research of phytocannabinoids is necessary and informs us of the mechanisms of action, studies in humans are important for providing us with information on brain and behavior effects that cannot be mimicked in animal models. A recent example is the assessment of THCV as a possible treatment for obesity when compared to the drug Rimonabant, which was withdrawn from clinical use due to the increased rates of depression in those using it [51], an effect that was not observed in the animal screening of the drug [52].

An issue that must be considered with fMRI studies in general is the replicability of results. Many factors contribute to this including the task utilized during fMRI, the cohort of individuals being studied, sample size, data processing stream, and statistical inference applied in the interpretation of results, just to name a few. The use of standard sets of tasks (akin to the NIH Common Data Elements) and neuroimaging parameters (e.g. those developed by the Human Connectome Project) and clear dissemination of methods used in data acquisition and analysis help to alleviate this issue. However, it must also be kept in mind that human cognition is complex, and with the rapid pace of technological advancement we are continually developing potentially better ways of testing various cognitive processes and data analysis techniques. Therefore, we should not impede these advancements for the sake of standardization, but rather stress the importance of complete and transparent reporting of methods used to acquire and analyze data to allow for independent laboratories to replicate results. Since there have been relatively few pharmacological fMRI studies investigating the brain and behavior effects of cannabis-derived compounds, results of these initial studies have yet to be replicated. However, findings from pharmacological fMRI studies performed by three independent laboratories investigating acute THC effects on emotion processing of threatening (i.e. angry and/or fearful) faces have been consistent and suggest potential utility of THC in treating anxiety/social fear disorders [24,27,41]. Future studies should consider utilizing the cognitive tasks and data acquisition parameters used in these earlier reports.

There are, of course, a number of important considerations when conducting human studies of cannabis compounds. Factors that may be of significance include a person's cannabis use history (e.g., drug-naïve versus occasional versus heavy use), which has previously been shown to affect THC-induced impairments [53]. Individual differences in a person's behavioral, neural, and cognitive responses to phytocannabinoids need to be considered [32], as well as specific genetic variations that may influence a person's sensitivity to drug effects [33]. Finally, we know very little of the long-term effects of phytocannabinoids. A 2012 Cochrane Review that included four studies that used CBD as treatment in a total of 48 PWE found that a 200–300 mg/day dose of

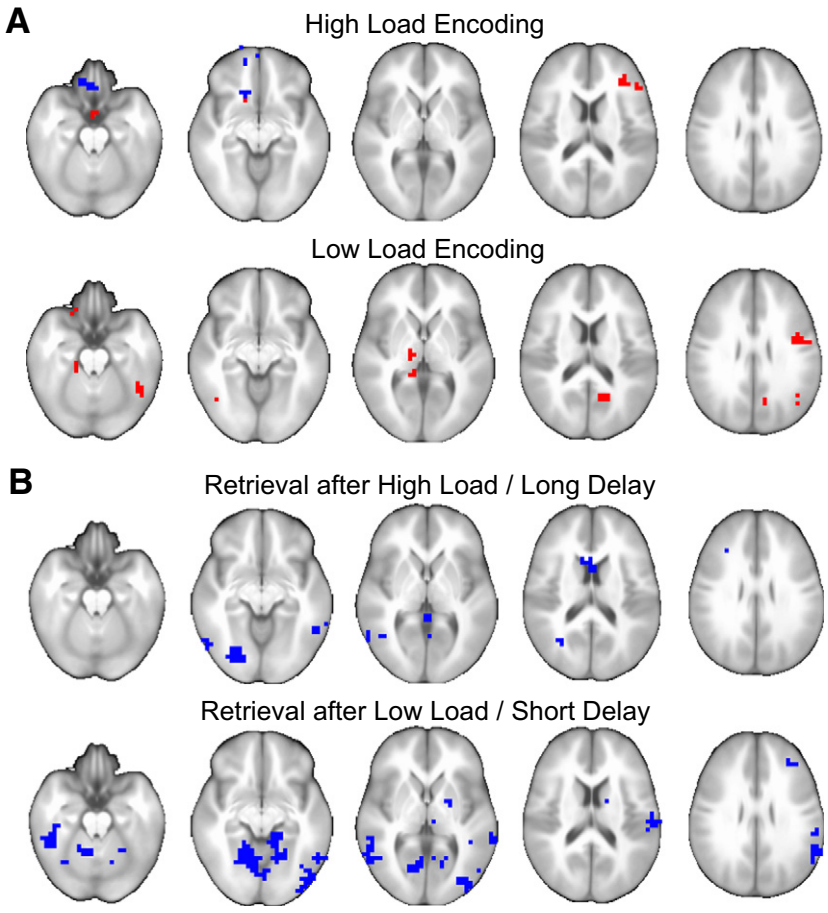

Fig. 2. Preliminary results in patients receiving CBD treatment for epilepsy who performed a modified Sternberg task during fMRI. (A) Regression analysis revealed changes in neural recruitment of brain regions from pre-CBD to visit 2 fMRI during working memory encoding of 6 letters (high load condition; top row) and 2 letters (low load condition; bottom row), with regions in orange representing increased activation and regions in blue representing decreased activation at visit 2 compared to pre-CBD fMRI. (B) Compared to pre-CBD fMRI, neural recruitment of brain regions was decreased at visit 2 fMRI during working memory retrieval following high load/long delay (6 letters/12 s; top row) and low load/short delay (2 letters/4 s; bottom row) conditions, as represented by regions in blue. Left in the image is left in the brain.

CBD was safely tolerated in the small sample of patients for a short period of time, but the authors could not form any conclusions regarding the efficacy of phytocannabinoids as a treatment for epilepsy or effects of prolonged treatment [54]. In addition to the three randomized, placebo-controlled trials of CBD (Epidiolex) showing drug efficacy and patient tolerability [3–5], a 12-week open label trial of CBD recently showed that it might reduce seizure frequency and may have an acceptable safety profile in children and young adults with treatment-resistant epilepsy [55]. Thus, the ongoing open-label CBD neuroimaging study described in Section 3 and other ongoing studies are very important for the assessment of the central effects of cannabinoids and show promising preliminary results of not only reducing seizure frequency, but also potentially improving cognitive processes and performance. However, further randomized, double-blind, placebo-controlled trials and longitudinal studies are necessary to better characterize and assess the central effects of CBD and other cannabis compounds.

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