Neurobehavioral Changes Associated with Exposure to Cannabis: Insights from Encephalography

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Introduction

The increasingly regular use of cannabis and its extracts in the general population [1] continues to raise concern among clinicians [2-4], and the quickly growing rate of dissemination of most often inaccurate information on the topic [5] has recently attracted the attention of the World Health Organization [6], in the effort of working closely with the scientific community to provide objective, clear and easy-to-understand information on the detrimental psychosocial and general health effects associated with the regular, indiscriminate and uncontrolled use of cannabis.

Cannabis Sativa is a psychoactive plant that contains more than 500 components, of which 104 have been identified as cannabinoids [7, 8]. The molecule that is primarily associated to the psychoactive effects that cannabis users commonly seek is called delta-9-tetrahydrocannabinol or THC [7], mainly present in a resin that accumulates in the flowers and upper leaves of the female plant. Most of the other cannabinoids are either inactive or weakly active, although they may interact with THC [9, 10]. THC exerts a wide range of effects on the central nervous system (CNS), including the alteration of biogenic amine systems, the reduced release and synthesis of hippocampal acetylcholine, the change of cellular membrane function, and the changes in CNS reactivity [11, 12].

Effects of cannabis on cognitive functions

A number of studies have investigated the relationship between cannabis use and quantitative EEG (qEEG), at rest or during task performance. For example, Böcker and colleagues found that **theta and beta band activity** may be more susceptible to cannabis use [13]. Similarly, other authors have reported a **positive correlation between delta power and cannabis dependence** [14], an increase in alpha and theta power, as well as a decrease in delta and beta power in long-term cannabis users [15, 16]. Interestingly, other studies with abstinent cannabis users have found a **decrease in alpha and beta power** in posterior cortical regions [17].

Preclinical studies suggest that **gamma oscillations** reflect gamma-aminobutyric acid (GABA) modulated regulation of cognitive processes [18, 19]. Of note, it has been proposed that CB1 receptor activation by THC or agonists may disrupt gamma oscillations influencing normal inhibitory interneuron activity [20-22], suggesting a line of evidence for the **disruption of cognitive functions in cannabis users.**

Other qEEG resting state research found that cannabis users exhibited **the inverse of normal frequency dynamics** in that they were characterized by decreased delta and increased theta, beta, and gamma. This trend in neural oscillations is typically observed during task performance, suggesting that cannabis users exhibited **increased cortical activation even when at rest.** Interestingly, similar patterns in resting state EEG activity have been reported in heroin-dependent [23], alcohol-dependent [24, 25] and cocaine-dependent users [26].

Together, these findings suggest that lower cortical activation at rest reflects greater neural efficiency and lower effort when a cognitive load is presented. Conversely, **cannabis users exhibit increased cortical noise** associated with acute THC intake during the pre-stimulus time window when performing in an oddball task [27]. In this context, the increased cortical activity combined with greater cortico-cortical connectivity in frontal regions found in cannabis users may be linked to greater engagement of executive functions. It has been proposed that **these functional changes may underpin a reduction in neural refinement** [28] and reflect the poorer cortical efficiency of a noisy brain.

It is important to underscore that inconsistencies may arise between studies due to profile heterogeneity in the cannabis users examined. Additionally, confounders may be represented by differing states of intoxication, with some participants tested during acute intoxication and others during long-term and short-term periods of abstinence [29].

Effects of cannabis on emotion regulation

The ability of phytocannabinoids to modulate mood and emotion processing has become of significant interest and concern in recent years, especially considering that at least 28 states and Washington, D.C., now allow the use of cannabis-based preparations for clinical purposes.

Interestingly, **cannabis is not approved to treat affective disorders in any of the states where it is legal.** Accumulating research carried out over the last decade has explored the therapeutic value of phytocannabinoids in the treatment of depression [e.g., 30, 31-33]. However, conflicting data exist as to their effects on both emotion regulation and treatment for mood disorders. For example, Degenhardt et al. [32] have remarked **a risk of depression in long-term heavy cannabis users** and other research [34-36] has shown a proportional relationship between depressive symptoms and cannabis use, especially in adolescents [33].

It is important to note that many of the studies do not control for the differences in phytocannabinoid preparations, potency, and route of administration. Of note, the strength of THC has increased over time, with data showing an increase of potency from 4% in 1995 to 12% in 2014 [37].

Also, the preferred routes of administration and development of more concentrated preparations have contributed to increase its potency [38] and the development of synthetic cannabinoids have been found to have toxic effects on brain and behavior [39].

Despite the **lack of consistent evidence for any antidepressant effects of cannabis**, phytocannabinoids are becoming increasingly popular among the general population in the United States in the attempt to control or "self-medicate" mood disorders, including depressive symptoms [36]. Hence, objective and reliable evidence needs to be put forward in the attempt of tackling this trend (particularly in Colorado where the rate of use in teens and young adults is 74% higher than average) [40].

Studies that employed EEG and more specifically of **event-related potentials (ERPs)** to identify potential biomarkers of emotion processing have found that changes in latency and/or amplitude of the P300 (or simply P3) component may reflect altered emotion processing in depression [41-46]. Importantly, it has been determined that **cannabis exposure may induce inversely proportional dose-dependent amplitude changes in the P3 measure.** [47-50]. Interestingly, recent work has shown that cannabis users with subclinical depression exhibited decreased P3 amplitude during negative emotion processing when compared to non-depressed users, particularly when processing emotional facial expressions implicitly and empathically. This suggests that **the regular use of cannabis is more likely to worsen the clinical profile of persons with depression**, altering their ability to not only process negative emotions but also to empathize with persons who experience negative emotional states.

Association between the regular use of cannabis and psychosis

Whether the regular use of cannabis, cannabis abuse or dependency can induce transient or more persistent psychotic disorders is a highly debated topic among researchers [5–8], and has important implications for healthcare systems, policy makers and society in general.

In this context, a recent review by Hasan et al. [51] found that 1) **psychotic illnesses are more likely to occur in cannabis users** when compared to non-users, 2) the regular use of cannabis throughout life and cannabis dependence increase the risk of developing psychotic disorders, and (3) that cannabis users tend to experience psychotic episodes earlier in life when compared to non-users.

These findings are corroborated by EEG data indicating that **individuals exposed to THC exhibit anomalies that are comparable to those found in schizophrenia**. For example, error-related negativity (ERN), theorized to be related to error monitoring, may be reduced in healthy persons exposed to THC [52]. Also, similarly to patients with psychosis [53], persons who smoked cannabis exhibit anomalies in the theta frequency band, and the degree of disruption correlates with the impairment of working memory performance [54]. In line with these finding, studies in animals and hippocampal slices have found that cannabinoid agonists can disrupt synchronized neural oscillations at theta and gamma frequencies [20, 21, 55-57]. Importantly a reduction of gamma power has been shown to be associated with a younger age of onset of cannabis use. This is noteworthy, given that the endogenous cannabinoid system has a key role in neurodevelopment [58-60], suggesting that c**annabis exposure during adolescence may alter neurogenesis** and permanently affect the ability of neural networks to generate synchronized oscillations.

Integration of qEEG and neurofeedback in the treatment of the cognitive and affective imbalances associated with Cannabis use

Research employing qEEG and ERP to detect the effects of psychostimulant drug abuse [61] suggests that **these techniques should be added to conventional assessment methodsand psychotherapeutic avenues**, to improve clinical outcomes in both the cognitive and affective domains. Also, qEEG guided interventions **like neurofeedback training** have significant potential for additionally identifying neurophysiological and clinical markers of **treatment progress** [62].These outcome markers may provide useful information for planning targeted and bio-behavioral interventions in cannabis users.

Conclusions

There is strong evidence that regular use of cannabis or TCH-based preparations is associated with detrimental effects on both the cognitive and affective domains. Cannabis users are also more likely to experience psychotic episodes and to develop psychotic disorders in the long term. A growing number of resting state EEG and ERP measures have been demonstrated to be affected by exposure to cannabis, which offers clinicians the ability to evaluate functional anomalies in the brain and most importantly devise targeted interventions and improve clinical outcomes.

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