NeuroRegulation

Automated Detection of Cognitive Performance and Resilience Changes in Former Professional American Football Players Following the Administration of a Hemp Extract

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Abstract

Introduction. In high-contact sport athletes, repetitive head trauma might be linked to permanent brain damage. In particular, findings in professional American football players indicate that brain injury is often associated with long-term cognitive slowing. In this context, hemp extracts might have beneficial effects.

Methods. Forty-two former professional American football players were recruited (age = 49.6 ± 9.8 years). Before or immediately after the oral administration of a THC-free hemp extract, the following measures were acquired: 1) the median theta/beta ratio and posterior peak alpha frequency (PAF) during resting state; 2) P200 and P300b latencies as well as reaction times (RT) during performance of a Go/NoGo task.

Results. After treatment, a smaller median theta/beta ratio ($p < .01$) was detected. An onset latency reduction was also found for the P200 ($p < .01$) and P300b ($p < .05$) measures, which was accompanied by smaller RT variances ($p < .05$). Finally, a positive correlation between RT measures and P300b latencies was found only after treatment.

Conclusion. The administration of THC-free hemp extracts in former professional high-impact athletes might have beneficial effects on both cognitive performance and emotion regulation. Also, recent technological advances in EEG detection and analysis could play an important role in the management of patients with sport-related brain injuries.

Keywords: sports concussion; American football; EEG; ERP; CBD; CBG

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Introduction

Neurobiological Abnormalities in Former Professional American Football Players

In recent years, studies with contact sport athletes (including American football, ice hockey, soccer, baseball, rugby, boxing, and wrestling) have provided support for early findings indicating a link between repetitive head trauma and the risk for permanent brain damage (Changa et al., 2018; Ling et al., 2015; McKee et al., 2018). Emerging evidence suggests that retired professional players of American football often exhibit mild cognitive impairment (Guskiewicz et al., 2005; Randolph et al., 2013), neuroimaging abnormalities (Hart et al., 2013; Strain et al., 2013) and reduced neuronal

energy metabolism (Alosco, Tripodis, Rowland, et al., 2020), disproportionately to their age. Key insights are also offered by studies with this population suggesting Alzheimer's-like changes in the brain, such as increased microglial activation associated with higher t-tau concentrations in the cerebral spinal fluid (Alosco, Tripodis, Fritts, et al., 2018). Postmortem studies have also shown perivascular deposition of abnormal phosphorylated tau (p-tau) in neurons and astroglia at the base of cortical sulci (Manley et al., 2017).

Neuroprotective Properties of Endocannabinoids

In recent years, astrocytes have gained considerable interest as a potential target for pharmacological interventions and, while more research is needed to understand how their activity can be differentially manipulated (Ridet et al., 1997), a number of candidate molecules and systems have been proposed as targets for astrocyte-mediated neuroregulation or neuroprotection. Accumulating evidence indicates that cannabinoids, including phytocannabinoids (naturally found in plants of the genus *Cannabaceae*), endocannabinoids, and also synthetic ligands can modulate gliosis reactivity and exert neuromodulatory, anti-inflammatory, and neuroprotective effects in the brain (Navarrete et al., 2014; Stella, 2010; Vázquez et al., 2015; Walter & Stella, 2004).

The endogenous cannabinoid system consists of two Gi/o-coupled cannabinoid receptors anchored in the plasma membrane (CB1 and CB2), their endogenous ligands [N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG)] and specific synthesis or degradation enzymatic complexes (Lu & Mackie, 2016). Remarkably, the CB2 receptor density detected in microglia and astrocytes has been found to be increased in neuroinflammatory conditions (Benito et al., 2005; Cassano et al., 2017), in parallel with greater levels of endocannabinoids (Panikashvili et al., 2001; Shohami et al., 2011), which might provide support for the involvement of the cannabinoid system in brain pathology or recovery.

Preparations derived from *Cannabis sativa* are a source of a wide variety of cannabinoid chemicals with differential affinities for CB1 and CB2 receptors. In particular, the psychoactive compound Δ9-tetrahydrocannabinol (THC) as well as the nonpsychoactive cannabidiol (CBD) and cannabigerol (CBG) have been receiving growing attention from the scientific community in recent years. While these preparations have shown to have neuroprotective and antineuroinflammatory effects, only THC has affinity for CB1 and CB2 receptors, although its neuroprotective effects are likely to be driven by CB1 mediated mechanisms (Gómez del Pulgar et al., 2002; Molina-Holgado et al., 2002). However, concerns have been raised about the clinical use of THC because of the deleterious effects on cognitive functions linked to the activation of CB1 receptors (Borgan et al., 2019).

While it is less clear how CBD induces its neuroprotective effects, there is common agreement that its mechanism of action does not involve the recruitment of either CB1 or CB2 receptors, and there is evidence indicating that it indirectly influences the endocannabinoid system through its affinity for transient receptor potential vanilloid-1 (TRPV1) receptors (Muller et al., 2018), which are thought to play a role in the transmission of nociceptive impulses along pain pathways (Immke & Gavva, 2006). Further, increasing preclinical evidence demonstrates that CBD provides neuroprotection against acute and chronic brain injury (Campos et al., 2016; Fernández-Ruiz et al., 2013; Hayakawa et al., 2010), most likely exerting its modulatory effects on astrocyte activity (Kozela et al., 2017).

In many ways, CBG exhibits pharmacological characteristics that fall between Δ9-THC and CBD. Like Δ9-THC, CBG activates CB1 and CB2 receptors but with much lower affinity (Cascio et al., 2010; Navarro, Varani, Lillo, et al., 2020; Navarro, Varani, Reyes-Resina, et al., 2018; Pertwee, 2008; Pollastro et al., 2011; Rosenthaler et al., 2014). On the other hand, CBD and CBG exert comparable activity at six transient receptor potential cation channels (TRPA1, TRPV1, TRPV2, TRPV3, TRPV4, and TRPM8; De Petrocellis, Ligresti, et al., 2011; De Petrocellis, Orlando, et al., 2012; Muller et al., 2018; Pollastro et al., 2011). Importantly, CBG also has high affinity for the α_2-adrenoceptor (Cascio et al., 2010), which supports its beneficial effects on cognitive functions (Arnsten, 2010) and suggests that it might as well have antihypertensive, sedative, and analgesic properties (Ernsberger et al., 1990; Gertler et al., 2001; Hunter et al., 1997).

While there is evidence that both CBG and CBD modulate 5-HT1A receptor activity, antagonistic effects have been reported for CBG, while CBD has been found to exert indirect stimulation (Cascio et al., 2010; Rock, Bolognini, et al., 2012; Rock, Goodwin, et al., 2011; Russo et al., 2005). The modulatory effects of CBD on 5-HT1A receptor activity have been suggested to stimulate neuroprotective mechanisms that prevent cellular

apoptosis, suggesting a role for this cannabinoid in the treatment of neurodegenerative diseases (Echeverry et al., 2021).

Finally, it has been proposed that *Cannabis* extracts should also include naturally occurring terpenoids to obtain optimal standardized synergistic compositions and improve clinical outcomes. Recognized as safe by the U.S. Food and Drug Administration (FDA) and other regulatory agencies, terpenoids are fragrant essential oils that bind neurotransmitter receptors, muscle and neuronal ion channels, G-protein receptors, enzymes, cell membranes, and second messenger systems (Bowles, 2003; Husnu Can Baser & Buchbauer, 2015; Russo, 2011). They display unique therapeutic effects that could meaningfully contribute to the "entourage effects" of *Cannabis*-based medicinal extracts that may enhance the effects of cannabinoids on migraine, headache, pain, inflammation, anxiety, and depression (Baron, 2018; Lorenzetti et al., 1991).

EEG Anomalies in Traumatic Brain Injury

Several studies indicate that following traumatic brain injury (TBI) patients may exhibit cognitive deficits and also a variety of psychiatric symptoms, including affective disorders, substance abuse, psychosis, and personality changes (Jorge et al., 2005; E. Kim et al., 2007; Pelegrín-Valero et al., 2001; Sachdev et al., 2001; van Reekum et al., 2000; Zeilig et al., 1996).

Over the last two decades, studies using electrophysiological methods have significantly gained further insight into the mechanisms that underpin cognitive slowing in individuals with TBI. While rapidly evolving neuroanatomical imaging techniques have improved anatomical resolution in the quantification of the tissue loss associated with TBI, recent technological advances in electroencephalogram (EEG) data acquisition and analysis have allowed researchers to investigate neural activity with gradually greater sensitivity and higher temporal resolution. This has contributed to unveil functional abnormalities and brain-behavior relationships that could not be reliably identified in this clinical population using neuroimaging methods (Levine et al., 2006). In this context, a range of resting-state EEG measures and event-related potentials (ERPs) recorded during performance of behavioral tasks offer valuable insights into cognitive processes, and numerous studies have demonstrated that they can also be used to detect neuropathology.

There is general agreement that the alpha frequency in the EEG is an indicator of cognitive and memory performance (Klimesch, 1999). However, interindividual and age-related fluctuations of spectral boundaries in this frequency band can make the interpretation of spectral analysis problematic (Klimesch, 1999). A suggested approach to more accurately define individualized alpha frequency boundaries is to compute the average frequency of the highest power between 6 and 13 Hz across all the electrodes of the EEG montage (Angelakis, Lubar, & Stathopoulou, 2004). The result is called peak alpha frequency (PAF), which has been found to be a highly heritable physiological feature (Grandy et al., 2013; Posthuma et al., 2001; Smit et al., 2006) that typically increases throughout the first 20 years of life, starts slowing from age 40 (Aurlien et al., 2004; Bazanova & Vernon, 2014; Chiang et al., 2011) and is reduced in patients with TBI (Angelakis, Lubar, Stathopoulou, & Kounios, 2004) when compared with healthy controls.

Moreover, the ratio between the average EEG magnitude in the frequency bands theta (4–8 Hz) and beta (13–25 Hz), namely the theta/beta ratio, has been proposed as a resting-state measure of attention, logical thinking, concentration, memory, and emotional regulation (Clarke et al., 2001; Markiewcz, 2017). Increased frontal midline theta power and reduction of frontal beta power have been demonstrated to correlate with executive attention impairment in TBI subjects (Shah et al., 2017), a pattern that could reflect reduced excitatory synaptic activity in the medial frontal neuronal population (McWilliams & Schmitter-Edgecombe, 2008). Importantly, a decrease of the theta/beta ratio can be associated with improvements in both cognitive performance (Marlats et al., 2019) and emotion regulation (Sari et al., 2016).

One of the most observed impairments associated with brain injury is the reduction of cognitive processing speed (Ferraro, 1996; Mathias et al., 2004; Mathias & Wheaton, 2007), which has been associated with diffuse axonal damage and altered interhemispheric functional connectivity (Felmingham et al., 2004). Patients with brain injury are over 1.5 times slower than healthy controls, as measured by reaction time (RT) in a range of cognitive tasks (Ferraro, 1996). However, since RTs are70ffectted by both perceptual and motor execution processes, more specific measures are needed to identify the origins of processing speed deficits during task performance. In this regard, ERP research has revealed important differences between TBI patients and healthy persons. Specifically, the P300 measure (a positive going

deflection appearing in the EEG 250–500 ms after the attendance of rare target stimuli; Polich, 2007) has been shown to be a highly sensitive measure of cortical synaptic transmission deficits. The P300 deflection consists of two components: 1) a P3a component appearing in the EEG 250–280 ms after stimulus presentation, thought to originate from stimulus-driven frontal attention mechanisms during task processing and 2) a P3b component, with peak latency falling in the 250–500 ms time window after stimulus presentation, originating in the temporal-parietal region and thought to be associated with attention and subsequent memory processing (Polich, 2007). Importantly, these components can show significant changes even in mild cases of TBI or even in asymptomatic patients with history of sports concussion (Baillargeon et al., 2012; Moore et al., 2017; Thériault et al., 2009). The P200 (a positive deflection in the EEG waveform that peaks between 150 and 275 ms after stimulus onset) has also been shown to offer highly valuable insights on cognitive processes. It is thought to reflect the modulation of attention by nontarget stimuli and stimulus classification (Key et al., 2005). Reduction of P200 Go/NoGo amplitude has been linked to slower RTs and reduced accuracy in stimulus classification (Hampton & Weber-Fox, 2008).

Finally, emotional responses are also altered in TBI patients (Tateno et al., 2003, 2004), which has been proposed to be linked to the reduced ability of the anterior prefrontal cortex to regulate orbitofrontal activity (Ghajar & Ivry, 2008; Rule et al., 2002). Interestingly, in Go/NoGo tasks, patients with TBI make more errors than healthy controls, and patients with faster RTs exhibit greater level of alpha power synchronization over the fronto-central midline region, suggesting prefrontal down-regulation (Garavan et al., 2002).

State-of-the-Art Technological Innovations Allow to Automatically Detect EEG Markers of Cognitive Functions and Drug Response

Since its first discovery (Collura, 1993), EEG technology has dramatically evolved, allowing for gradually more accurate and reliable measurements of electrophysiological activity in the brain, which has significantly contributed to numerous scientific breakthroughs and to the development of highly sophisticated clinical applications (Borck, 2005).

State-of-the-art EEG machines today allow not only for resting-state, region-specific spectral analysis of the EEG but also for the automatic detection of a wide range of ERPs elicited during performance in well-established behavioral tasks (Miranda et al., 2019).

Made gradually more accessible to researchers and clinicians, modern EEG detection and analysis technology offers the opportunity to carry out accurate diagnoses and also evaluate or monitor the effects of pharmacological interventions. This has opened new avenues in psychopharmacology, contributing to the development of biomarkers that can help clinicians make more informed decisions and more reliable predictions of treatment outcomes.

In this context, while preliminary research suggests that nonpsychoactive cannabinoids might induce modulatory effects on EEG power (Alvarez et al., 2008), more research is needed to establish their effects on specific EEG markers of cognitive performance.

With this in mind, the aim of the present study was twofold: 1) to investigate the effects of orally given cannabidiol (CBD) and cannabigenol (CBG) on both resting-state EEG and ERP markers of cognitive performance in former professional American football players with a history of head injury, and 2) to demonstrate the ability of the computerized electroencephalograph BrainView NeuralScan Pro to automatically detect and measure posttreatment changes in target metrics.

Materials and Methods

Participant Recruitment and Demographics

Male former professional American football players were approached for enrollment, and those who consented to participate in the study were interviewed up to a week before the experimental session would take place (also depending on the participant's availability). During the interviews, the experimenter offered information on the study, providing a short introduction on EEG, the metrics that would be computed and analyzed before and after the administration of the experimental protocol, and the nature of the supplements to be administered.

Participants were selected if they had normal or corrected-to-normal vision and no current or history of neurological or psychiatric conditions, alcohol dependence, or drug misuse. Next, all the interviewed subjects who met the inclusion criteria were asked to sign consent to participation.

The interview process culminated with the recruitment of 42 participants (age = 49.6 ± 9.8

years). Other than age, no other demographic information could be acquired, to comply with the personal conduct policy of their former professional association. All data acquisition was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, in two different locations and times, namely the Marriott Conference Center in Allen, TX (777 Waters Creek Blvd) between January 17–19, 2020, and the Hyatt Regency Hotel in Miami, FL (400 SE 2nd Ave) between January 27–30, 2020.

EEG Data Acquisition

Continuous EEG (0.5–40 Hz bandpass; notch filter: 60 Hz) was acquired from 19 AgAgCL scalp-electrodes during resting state or task performance using the FDA-cleared BrainView NeuralScan Pro workstation (Medeia Inc., Santa Barbara, CA; https://www.brainview.com), consisting of a 21-channel EEG cap (using distance ratios consistent with the 10–20 System) and a 21-channel EEG amplifier (input impedance > 200 MΩ; common mode rejection ratio > 110 dB at 10 Hz, kept consistent across all participants) controlled by EEG data acquisition software recording at a sampling rate of 500 Hz.

At the time of recording, the ground electrode was located at Cz and the reference electrode at Pz. All recordings took place in a quiet room while the participants were seated in comfortable chairs that provided adequate support for the neck and shoulder muscles.

Spontaneous EEG (acquired at rest for 5 min while the participants' eyes were open or closed) and ERPs elicited during performance of a visual Go/NoGo task were acquired before and immediately after the oral administration of 1 ml of the hemp extract FOCUS (Sacred Ally, Missoula, MT), containing 11.3 mg cannabidiol (CBD) and 0.6 mg cannabigerol (CBG), sonicated into 20–30 nm liposomes (batch ID: PMB-FOCUS-FIN1.024; certificate number: 011020SR001; certificate of analysis prepared by PrimeMyBody, LLC, Carrolton, TX; Table 1).

Go/NoGo Task

Participants were presented with a series of blue circles (standard stimuli) appearing on the center of a white computer monitor and were asked to press a button (Go) only when a bigger circle of the same color (deviant stimulus) was randomly shown (duration of each stimulus: 400 ms; interval between each stimulus: 3000 ms; total task duration: approximately 6 minutes). The task included 110 trials, with approximately 72 deviant stimuli (65.45% of total trials).

Table 1
The Tested Sample of FOCUS, Analyzed by Liquid Chromatography-Mass Spectrometry, LC-MS for Plant-Based Cannabinoids.

ID	Conc. (mg/ml)
D-9 THC	0.0
CBD	11.307
CBG	0.611
β-Caryophyllene	4.401
Geraniol	2.722
Limonene	4.164
Linalool	1.342
Myrcene	0.602
Humulene	0.571
Terpinolene	0.333

All collected data were compared to laboratory certified reference standards at known concentrations. Compounds present in traces (< 0.15 mg/ml) or not detected (≤ 0.001 ng/ml) are not shown on the table. Modified after the original report by PrimeMyBody (ID: PMB-FOCUS-FIN1.024; Certificate number: 011020SR001). Abbreviations: D-9 THC = tetrahydrocannabinol; CBD = cannabidiol; CBG = cannabigerol.

EEG Signal Processing

Offline, the data were filtered between 1–50 Hz with a notch filter set at 60 Hz, while no change was applied to the sampling rate (500 Hz). Next, individual EEG files were automatically edited to remove non-EEG artifacts (blinks, pulse artifact, MR gradient artifact, ballisto-cardiogram, and bad blocks) using the built-in custom scripts and functions available in Brainview NeuralScan Pro (Fast Fourier Transform, Wavelet, and Independent Component Analysis; Al-Fahoum & Al-Fraihat, 2014; Iriarte et al., 2003; Jiang et al., 2019). The cleaned-up data were then used to compute absolute power in 4 different frequency bands: delta (1–4 Hz), theta (5–7 Hz), alpha (8–14 Hz), and beta (15–30 Hz).

To extract ERPs, continuous EEG was automatically segmented by BrainView into 1200 ms epochs including activity recorded 200 ms before stimulus to 1000 ms after stimulus, and baseline corrected by subtracting the mean amplitude of the prestimulus signal. Epochs with EEG or EOG amplitudes exceeding 100 μV were removed and the average

peak latencies of target components were computed for each subject.

Resting-State EEG, ERP, and Behavioral Measures

The median of the ratio between theta and beta absolute power detected from all electrodes at rest during an eyes-open condition was automatically computed by BrainView NeuralScan Pro. The PAF during an eyes-closed condition was also obtained by automatically computing the median frequency of the highest power in the 8–14 Hz frequency range at the O1 electrode site.

During performance of the Go/NoGo task, ERP onset latencies were acquired for the measures P200 (100–175 ms) recorded at O1 (Kothari et al., 2016) and P300b (370–390 ms) recorded at T5 (Polich, 2007). Also, RTs were acquired and RT variances computed.

Statistical Analysis

Statistical analysis was performed to test for before/after treatment changes, as measured by the selected resting state EEG (theta/beta ratio and PAF) and ERP (P200 and P300b latencies) measures. To do so, we first applied a Shapiro-Wilk test (Shapiro & Wilk, 1965) to all measures in order to verify whether values were normally distributed. Since only the data relative to the P300b and theta/beta ratio measures were found not to be normally distributed, we explored within-group differences for all measures using a nonparametric Wilcoxon signed-rank test (Whitley & Ball, 2002).

Moreover, a Pearson correlation was used to investigate the relationship between EEG/ERP measures and RTs or RT variances. For each statistical analysis, the significance threshold was set at 0.05 and, for each measure, the mean ± standard deviation (*SD*) was reported. All statistical analyses were performed using custom code based on python libraries (ADD).

Results

Theta/Beta Ratio

The median theta/beta ratio was reduced after treatment (before treatment = 0.71 ± 0.18; after treatment = 0.65 ± 0.20; $p < .01$; Figure 1, Table 2).

PAF

After treatment, there was no change in average posterior PAF (before treatment = 9.4 ± 1.3, after treatment = 9.5 ± 1.2, Figure 1, Table 2).

P200 and P300b

The average P200 latency was found to be shorter after treatment (before treatment = 212 ± 50.8; after treatment = 179 ± 55.7, $p < .01$). Similarly, the median P300b latency was shorter after treatment (before treatment = 370.95 ± 59.50; after treatment = 341.31 ± 58.31, $p < .05$, Figure 1, Table 2).

RT

There was no difference between the average RTs recorded during performance in the Go/NoGo task before and after treatment (before treatment = 526.26 ± 108.45; after treatment = 516.00 ± 103.64). However, a before/after treatment difference was found for the average RT variances (before treatment = 17.7 ± 11.7; after treatment = 14.5 ± 12.7; $Z = -2.07$, $p < .05$,). These results are shown in Figure 2 and summarized in Table 2.

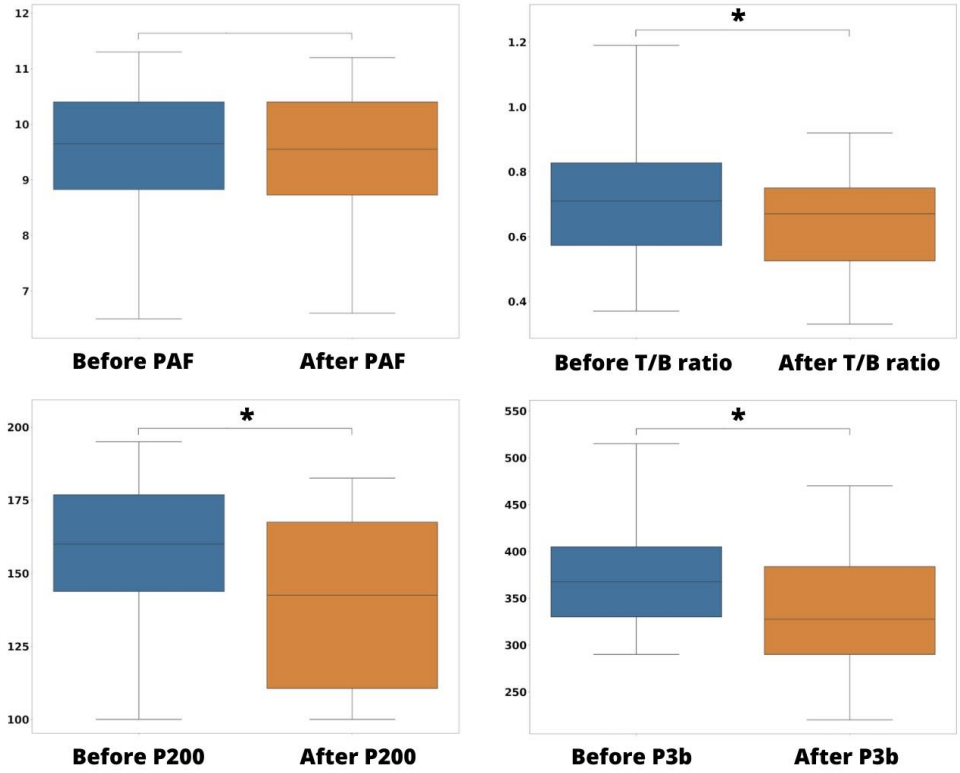
Table 2

Changes (Mean ± Standard Deviation) of Resting State (Eyes Open) Electroencephalogram, Event-related Potentials and Reaction Times Recorded During Performance of a Go/NoGo Task Before and After the Administration of FOCUS.

EEG/ERP	Before	After	*p*
Theta/beta ratio (RS – eyes open)	0.71 ± 0.18	0.65 ± 0.20	< .01
PAF (RS – eyes closed)	9.4 ± 1.3	9.5 ± 1.2	n.s.
P200	212 ± 50.8	179 ± 55.7	< .01
P300b	370.95 ± 59.50	341.31 ± 58.31	< .05
Reaction Time			
Speed	526.26 ± 108.45	516.00 ± 103.64	n.s
Variance	17.7 ± 11.7	14.5 ± 12.7	< .05

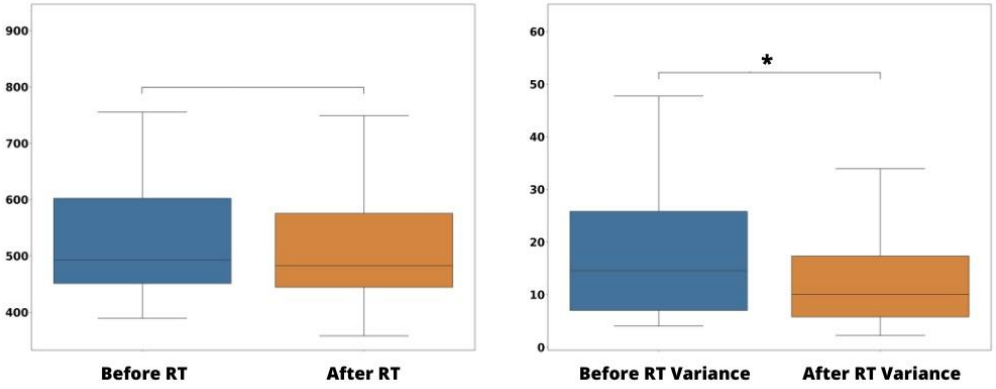
Abbreviations: EEG = electroencephalogram; ERP = event-related potentials; RS = resting state; PAF = peak alpha frequency.

Figure 1. *Resting State (Eyes Open) EEG and ERP Differences Before and After the Administration of FOCUS*.



Note. Asterisks indicate statistical significance. Abbreviations: PAF = posterior alpha frequency; T/B = theta/beta.

Figure 2. *Reaction Times and Reaction Time Variance (Go/NoGo Task) Differences Before and After the Administration of FOCUS.*

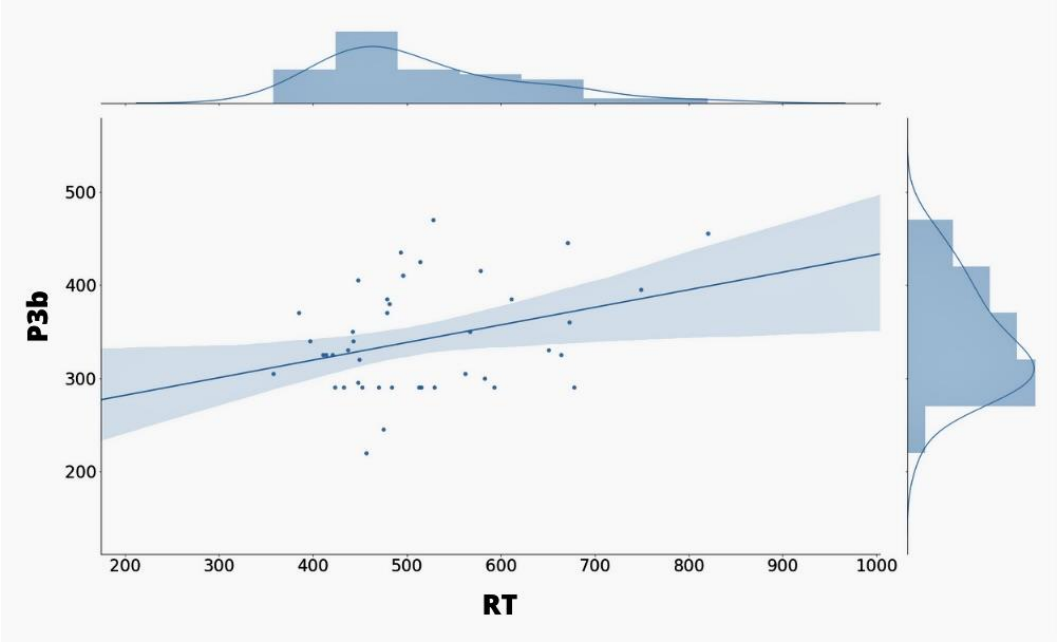


Note. Asterisk indicates statistical significance. Abbreviations: RT = reaction time.

Correlations Between RT and EEG/ERP Measures

A positive correlation (Figure 3) was found between P300b latencies and RTs after treatment (r = 0.34, p < .05). No other correlation was found before or after treatment.

Figure 3. *Correlation Between P3b Latencies and Reaction Times After the Administration of FOCUS.*



Note. Abbreviations: RT = reaction time.

Discussion

The present study found that the administration of the hemp extract FOCUS induced a number of changes in the EEG of former professional American football players and might add to previous evidence indicating that manipulations of the endocannabinoid system could contribute to ameliorate TBI pathology (Schurman & Lichtman, 2017). While we could not exactly determine which of the compounds in the preparation drove the observed resting-state EEG changes, we nonetheless confirmed the ability of a *Cannabis* extract to induce beneficial effects on brain activity in the absence of THC.

The present study also provides further support for the use of well-established EEG and ERP measures of cognitive performance, as detected by the FDA-cleared BrainView NeuralScan Pro workstation, in adult individuals with a history of head injury associated with a high-impact sport (Clark & Guskiewicz, 2016), suggesting that regular automated EEG-based assessments might contribute to reveal subclinical functional anomalies in this population and also assist clinicians in regular drug response evaluations.

The decrease in the theta/beta ratio we found after treatment during resting state suggests improved cognitive performance and emotion regulation (Gomes & Damborská, 2017; Papathanasiou et al., 2018). The interplay of cognitive functions and emotion is of particular relevance in TBI, with particular respect of its role in modulating the reductions in attentional control that may be found in this clinical population (Ríos et al., 2004), which could in turn affect their resilience to stress (Yao & Hsieh, 2019). Importantly, it has been reported that the administration of noradrenaline or dopamine agonists normalizes the theta/beta ratio (Clarke et al., 2003; Schutter & Van Honk, 2005). Given the evidence suggesting that both CBD and CBG might indirectly affect noradrenergic or dopaminergic transmission in the brain through the inhibition of CB1/CB2 receptors (Szabo & Schlicker, 2005) or selectively modulating gene expression (Gugliandolo et al., 2020), our results might suggest the ability of FOCUS to affect these mechanisms and future research should investigate the neurochemical substrates and pathways involved in region-specific slow versus fast wave EEG power regulation, in normal conditions and also in populations with a history of head injury.

Our results might also add to previous pilot findings in healthy subjects suggesting some beneficial effects of THC-free hemp extracts on both autonomic nervous system regulation and brain function (Gugliandolo et al., 2020), although our participants exhibited no change in a measure of

alpha activity (PAF). While more research is still required to more confidently determine the differential effects of hemp extracts on resting-state EEG rhythms, the present study might suggest a treatment resistant frequency-specific anomaly in the participant cohort we investigated. Interestingly, while little or no research has explored the differential effects of endocannabinoid receptor modulation on resting-state alpha EEG frequency, there is evidence indicating that increases in PAF associated with improved cognitive performance can be achieved through learning-based interventions (Angelakis et al., 2007; Dobrakowski & Lebecka, 2020). This remarks the ability of targeted EEG-based assessments to provide valuable feedback on treatment efficacy, also suggesting that EEG data acquisition and analysis platforms like BrainView NeuralScan Pro may easily automate this process, offering clinicians the opportunity to devise appropriate protocols on the basis of objectively and reliably measured biomarkers.

We also detected changes in ERP latencies after treatment. In particular, the P200 latency reduction suggests an improvement in attention and stimulus classification (Key et al., 2005), which have been found to be linked to TBI (Gomes & Damborská, 2017; Papathanasiou et al., 2018. Reduced latency was also found for the P300b response, suggesting an improvement in stimulus evaluation and classification speed (Duncan-Johnson & Donchin, 1982; Kutas et al., 1977), previously found to be altered in individuals with sports concussion (Baillargeon et al., 2012). Again, given the evidence indicating that *Cannabis* users and persons administered with THC exhibit prolonged latencies of multiple ERPs, including the P300 component (Roser et al., 2008; van Tricht et al., 2013), our results remark the importance of using only low-concentration or THC-free hemp extracts, and also strengthen the importance of regular ERP investigations in high-contact athletes, even when conventional neuropsychological tests reveal little or no cognitive slowing (Gosselin et al., 2012). Importantly, while we found no posttreatment difference in response speed, the reduced RT variability suggests improved cognitive performance (Gorus et al., 2008). Also, the correlation between RTs and P3b latencies might reflect greater association between stimulus processing time and expectancy, perhaps resulting from an improved response strategy in relation to the nature of the task (Duncan-Johnson & Donchin, 1980).

Finally, “entourage effects” due to the terpenoids present in the FOCUS preparation cannot be ruled out, given the evidence indicating the ability of these natural compounds to induce EEG changes. For example, quantitative EEG research with healthy persons suggests that changes in resting-state EEG detected after the inhalation of the essential oil *Abies koreana* (Jeong et al., 2007) may contribute to the enhancement of relaxation and alertness/attention states (Seo et al., 2016). Importantly, α-pinene, one of the major components of *Abies koreana*, has shown to have acetylcholinesterase inhibitory activity with associated memory enhancement (K. Kim et al., 2006). Of note, limonene highly influences the human autonomic nervous system and mental conditions (Heuberger et al., 2001), and recent pilot research has shown that the inhalation of a *Cannabis sativa* extract containing 35 different essential oils induced a reduction of diastolic blood pressure, an increase in heart rate, and an increase in skin temperature (Gulluni et al., 2018). Also, the analysis of resting-state EEG in the same participants showed generalized and region-specific shifts in slow versus fast frequency power, which were associated with greater self-rated relaxation and calmness.

Further research in larger sample sizes is needed to evaluate the differential effects of nonpsychoactive endocannabinoids and terpenes on both resting-state EEG and ERP measures of brain activity.

Limitations

While the present study revealed a number of important EEG changes in the population examined, a number of limitations must be remarked.

Unfortunately, given the necessary restrictions imposed by personal privacy guidelines, we could not gather any further demographic information (other than age and sex) on participants, or even use standard psychiatric questionnaires to acquire data on their cognitive abilities and emotional state. Also, it was not possible to access the medical history of any of the participants recruited, including information on the number and nature of the concussion episodes reported throughout their career, past and current medication, or any other officially diagnosed neurological and/or psychiatric conditions. Importantly, in assuming that all participants had a history of brain injury, we could not control for symptom heterogeneity and severity.

Conclusions

The present study suggests that the administration of the hemp extract FOCUS in former professional American football athletes induced a number of key changes in both resting state EEG and ERP measures. We found that the theta/beta ratio, a measure that is thought to reflect the interplay between cognitive performance and emotion regulation, was decreased immediately after the administration of the preparation, suggesting improved resilience. Additionally, our ERP results suggest an improvement in attention and information processing speed. Further research is needed to investigate the long-term effects of the FOCUS preparation in a similar cohort and to also explore its suitability in other clinical populations.

Finally, we also confirmed the ability of BrainView NeuralScan Pro to detect the above-mentioned changes, suggesting its suitability for day-to-day drug response monitoring in patients with sport-related brain injuries.

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Author Disclosures

Dr. Ruan is the Science and Safety Advisor for PrimeMyBody, clinical advisor for BrainView NeuralScan Pro, and CEO of the Texas Center for Lifestyle Medicine. Dr. Amico regularly provides neuroscience consultancy to Medeia Inc. Mr. Danev is the founder and CEO of Medeia Inc.

References

Al-Fahoum, A. S., & Al-Fraihat, A. A. (2014). Methods of EEG signal features extraction using linear analysis in frequency and time-frequency domains. *International Scholarly Research Notices, 2014*, 730218. https://doi.org/10.1155/2014/730218

Alosco, M. L., Tripodis, Y., Fritts, N. G., Heslegrave, A., Baugh, C. M., Conneely, S., Mariani, M., Martin, B. M., Frank, S., Mez, J., Stein, T. D., Cantu, R. C., McKee, A. C., Shaw, L. M., Trojanowski, J. Q., Blennow, K., Zetterberg, H., & Stern, R. A. (2018). Cerebrospinal fluid tau, Aβ, and sTREM2 in former National Football League players: Modeling the relationship between repetitive head impacts, microglial activation, and neurodegeneration. *Alzheimer's & Dementia, 14*(9), 1159–1170. https://doi.org/10.1016/j.jalz.2018.05.004

Alosco, M. L., Tripodis, Y., Rowland, B., Chua, A. S., Liao, H., Martin, B., Jarnagin, J., Chaisson, C. E., Pasternak, O., Karmacharya, S., Koerte, I. K., Cantu, R. C., Kowall, N. W., McKee, A. C., Shenton, M. E., Greenwald, R., McClean, M., Stern, R. A., & Lin, A. (2020). A magnetic resonance spectroscopy investigation in symptomatic former NFL players. *Brain Imaging and Behavior, 14*(5), 1419–1429. https://doi.org/10.1007/s11682-019-00060-4

Alvarez, F. J., Lafuente, H., Rey-Santano, M. C., Mielgo, V. E., Gastiasoro, E., Rueda, M., Pertwee, R. G., Castillo, A. I., Romero, J., & Martinez-Orgado, J. (2008). Neuroprotective effects of the nonpsychoactive cannabinoid cannabidiol in hypoxic-ischemic newborn piglets. *Pediatric Research, 64*(6), 653–658. https://doi.org/10.1203/PDR.0b013e318186e5dd

Angelakis, E., Lubar, J. F., & Stathopoulou, S. (2004). Electroencephalographic peak alpha frequency correlates of cognitive traits. *Neuroscience Letters, 371*(1), 60–63. https://doi.org/10.1016/j.neulet.2004.08.041

Angelakis, E., Lubar, J. F., Stathopoulou, S., & Kounios, J. (2004). Peak alpha frequency: An electroencephalographic measure of cognitive preparedness. *Clinical Neurophysiology, 115*(4), 887–897. https://doi.org/10.1016/j.clinph.2003.11.034

Angelakis, E., Stathopoulou, S., Frymiare, J. L., Green, D. L., Lubar, J. F., & Kounios, J. (2007). EEG neurofeedback: A brief overview and an example of peak alpha frequency training for cognitive enhancement in the elderly. *The Clinical Neuropsychologist, 21*(1), 110–129. https://doi.org/10.1080/13854040600744839

Arnsten, A. F. T. (2010). The use of α-2A adrenergic agonists for the treatment of attention-deficit/hyperactivity disorder. *Expert Review of Neurotherapeutics, 10*(10), 1595–1605. https://doi.org/10.1586/ern.10.133

Aurlien, H., Gjerde, I. O., Aarseth, J. H., Eldøen, G., Karlsen, B., Skeidsvoll, H., & Gilhus, N. E. (2004). EEG background activity described by a large computerized database. *Clinical Neurophysiology, 115*(3), 665–673. https://doi.org/10.1016/j.clinph.2003.10.019

Baillargeon, A., Lassonde, M., Leclerc, S., & Ellemberg, D. (2012). Neuropsychological and neurophysiological assessment of sport concussion in children, adolescents and adults. *Brain Injury, 26*(3), 211–220. https://doi.org/10.3109/02699052.2012.654590

Baron, E. P. (2018). Medicinal properties of cannabinoids, terpenes, and flavonoids in cannabis, and benefits in migraine, headache, and pain: An update on current evidence and cannabis science. *Headache, 58*(7), 1139–1186. https://doi.org/10.1111/head.13345

Bazanova, O. M., & Vernon, D. (2014). Interpreting EEG alpha activity. *Neurosci ence & Biobehavioral Reviews, 44*, 94–110. https://doi.org/10.1016/j.neubiorev.2013.05.007

Benito, C., Kim, W.-K., Chavarría, I., Hillard, C. J., Mackie, K., Tolón, R. M., Williams, K., & Romero, J. (2005). A glial endogenous cannabinoid system is upregulated in the brains of macaques with simian immunodeficiency virus-induced encephalitis. *The Journal of Neuroscience, 25*(10), 2530–2536. https://doi.org/10.1523/JNEUROSCI.3923-04.2005

Borck, C. (2005). Writing brains: Tracing the psyche with the graphical method. *History of Psychology, 8*(1), 79–94. https://doi.org/10.1037/1093-4510.8.1.79

Borgan, F., Beck, K., Butler, E., McCutcheon, R., Veronese, M., Vernon, A., & Howes, O. D. (2019). The effects of cannabinoid 1 receptor compounds on memory: A meta-analysis and systematic review across species. *Psychopharmacology, 236*(11), 3257–3270. https://doi.org/10.1007/s00213-019-05283-3

Bowles, E. J. (2003). The Chemistry of Aromatherapeutic Oils, 3rd Edition. Crows Nest, NSW, Australia: Allen & Unwin.

Campos, A. C., Fogaça, M. V., Sonego, A. B., & Guimarães, F. S. (2016). Cannabidiol, neuroprotection and neuropsychiatric disorders. *Pharmacological Research, 112*, 119–127. https://doi.org/10.1016/j.phrs.2016.01.033

Cascio, M. G., Gauson, L. A., Stevenson, L. A., Ross, R. A., & Pertwee, R. G. (2010). Evidence that the plant cannabinoid cannabigerol is a highly potent α_2-adrenoceptor agonist and moderately potent $5HT_{1A}$ receptor antagonist. *British Journal of Pharmacology, 159*(1), 129–141. https://doi.org/10.1111/j.1476-5381.2009.00515.x

Cassano, T., Calcagnini, S., Pace, L., De Marco, F., Romano, A., & Gaetani, S. (2017). Cannabinoid receptor 2 signaling in neurodegenerative disorders: From pathogenesis to a promising therapeutic target. *Frontiers in Neuroscience, 11*, 30. https://doi.org/10.3389/fnins.2017.00030

Changa, A. R., Vietrogoski, R. A., & Carmel, P. W. (2018). Dr Harrison Martland and the history of punch drunk syndrome. *Brain, 141*(1), 318–321. https://doi.org/10.1093/brain/awx349

Chiang, A. K. I., Rennie, C. J., Robinson, P. A., van Albada, S. J., & Kerr, C. C. (2011). Age trends and sex differences of alpha rhythms including split alpha peaks. *Clinical Neurophysiology, 122*(8), 1505–1517. https://doi.org/10.1016/j.clinph.2011.01.040

Clark, M., & Guskiewicz, K. (2016). Sport-related traumatic brain injury. In D. Laskowitz & G. Grant (Eds.), *Translational research in traumatic brain injury*. Boca Raton, FL: CRC Press/Taylor and Francis Group.

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001). EEG-defined subtypes of children with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology, 112*(11), 2098–2105. https://doi.org/10.1016/s1388-2457(01)00668-x

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., Brown, C. R., & Croft, R. J. (2003). Effects of stimulant medications on the EEG of children with attention-deficit/hyperactivity disorder predominantly inattentive type. *International Journal of Psychophysiology, 47*(2), 129–137. https://doi.org/10.1016/s0167-8760(02)00119-8

Collura, T. F. (1993). History and evolution of electroencephalographic instruments and techniques. *Journal of Clinical Neurophysiology, 10*(4), 476–504. https://doi.org/10.1097/00004691-199310000-00007

De Petrocellis, L., Ligresti, A., Moriello, A. S., Allarà, M., Bisogno, T., Petrosino, S., Stott, C. G., & Di Marzo, V. (2011). Effects of cannabinoids and cannabinoid-enriched *cannabis* extracts on TRP channels and endocannabinoid metabolic enzymes. *British Journal of Pharmacology, 163*(7), 1479–1494. https://doi.org/10.1111/j.1476-5381.2010.01166.x

De Petrocellis, L., Orlando, P., Moriello, A. S., Aviello, G., Stott, C., Izzo, A. A., & Di Marzo, V. (2012). Cannabinoid actions at TRPV channels: Effects on TRPV3 and TRPV4 and their potential relevance to gastrointestinal inflammation. *Acta Physiologica, 204*(2), 255–266. https://doi.org/10.1111/j.1748-1716.2011.02338.x

Dobrakowski, P., & Lebecka, G. (2020). Individualized neurofeedback training may help achieve long-term improvement of working memory in children with ADHD. *Clinical EEG and Neuroscience, 51*(2), 94–101. https://doi.org/10.1177/1550059419879020

Duncan-Johnson, C. C., & Donchin, E. (1980). The relation of P300 latency to reaction time as a function of expectancy. *Progress in Brain Research, 54*, 717–722. https://doi.org/10.1016/S0079-6123(08)61693-3

Duncan-Johnson, C. C., & Donchin, E. (1982). The P300 component of the event-related brain potential as an index of information processing. *Biological Psychology, 14*(1–2), 1–52. https://doi.org/10.1016/0301-0511(82)90016-3

Echeverry, C., Prunell, G., Narbondo, C., de Medina, V. S., Nadal, X., Reyes-Parada, M., & Scorza, C. (2021). A comparative in vitro study of the neuroprotective effect induced by cannabidiol, cannabigerol, and their respective acid forms: Relevance of the $5\text{-}HT_{1A}$ receptors. *Neurotoxicity Research, 39*(2), 335–348. https://doi.org/10.1007/s12640-020-00277-y

Ernsberger, P., Giuliano, R., Willette, R. N., & Reis, D. J. (1990). Role of imidazole receptors in the vasodepressor response to clonidine analogs in the rostral ventrolateral medulla. *Journal of Pharmacology and Experimental Therapeutics, 253*(1), 408–418.

Felmingham, K. L., Baguley, I. J., & Green, A. M. (2004). Effects of diffuse axonal injury on speed of information processing following severe traumatic brain injury. *Neuropsychology, 18*(3), 564–571. https://doi.org/10.1037/0894-4105.18.3.564

Fernández-Ruiz, J., Sagredo, O., Pazos, M. R., García, C., Pertwee, R., Mechoulam, R., & Martínez-Orgado, J. (2013). Cannabidiol for neurodegenerative disorders: Important new clinical applications for this phytocannabinoid? *British Journal of Clinical Pharmacology, 75*(2), 323–333. https://doi.org/10.1111/j.1365-2125.2012.04341.x

Ferraro, F. R. (1996). Cognitive slowing in closed-head injury. *Brain and Cognition, 32*(3), 429–440. https://doi.org/10.1006/brcg.1996.0075

Garavan, H., Ross, T. J., Murphy, K., Roche, R. A. P., & Stein, E. A. (2002). Dissociable executive functions in the dynamic control of behavior: Inhibition, error detection, and correction. *NeuroImage, 17*(4), 1820–1829. https://doi.org/10.1006/nimg.2002.1326

Gertler, R., Brown, H. C., Mitchell, D. H., & Silvius, E. N. (2001). Dexmedetomidine: A novel sedative-analgesic agent. *Baylor University Medical Center Proceedings, 14*(1), 13–21. https://doi.org/10.1080/08998280.2001.11927725

Ghajar, J., & Ivry, R. B. (2008). The predictive brain state: Timing deficiency in traumatic brain injury? *Neurorehabilitation and Neural Repair, 22*(3), 217–227. https://doi.org/10.1177/1545968308315600

Gomes, J., & Damborská, A. (2017). Event-Related potentials as biomarkers of mild traumatic brain injury. *Activitas Nervosa Superior, 59*, 87–90. https://doi.org/10.1007/s41470-017-0011-2

Gómez del Pulgar, T., de Ceballos, M. L., Guzmán, M., & Velasco, G. (2002). Cannabinoids protect astrocytes from ceramide-induced apoptosis through the phosphatidylinositol 3-kinase/protein kinase B pathway. *Journal of Biological Chemistry, 277*(39), 36527–36533. https://doi.org/10.1074/jbc.M205797200

Gorus, E., De Raedt, R., Lambert, M., Lemper, J. C., & Mets, T. (2008). Reaction times and performance variability in normal aging, mild cognitive impairment, and Alzheimer's disease. *Journal of Geriatric Psychiatry and Neurology, 21*(3), 204–218. https://doi.org/10.1177/0891988708320973

Gosselin, N., Bottari, C., Chen, J.-K., Huntgeburth, S. C., De Beaumont, L., Petrides, M., Cheung, B., & Ptito, A. (2012). Evaluating the cognitive consequences of mild traumatic brain injury and concussion by using electrophysiology. *Neurosurgical Focus, 33*(6), E7: 1–7. https://doi.org/10.3171/2012.10.FOCUS12253

Grandy, T. H., Werkle-Bergner, M., Chicherio, C., Schmiedek, F., Lövdén, M., & Lindenberger, U. (2013). Peak individual alpha frequency qualifies as a stable neurophysiological trait marker in healthy younger and older adults. *Psychophysiology, 50*(6), 570–582. https://doi.org/10.1111/psyp.12043

Gugliandolo, A., Silvestro, S., Chiricosta, L., Pollastro, F., Bramanti, P., & Mazzon, E. (2020). The transcriptomic analysis of NSC-34 motor neuron-like cells reveals that cannabigerol influences synaptic pathways: A comparative study with cannabidiol. *Life, 10*(10), 227. https://doi.org/10.3390/life10100227

Gulluni, N., Re, T., Loiacono, I., Lanzo, G., Gori, L., Macchi, C., Epifani, F., Bragazzi, N., & Firenzuoli, F. (2018). Cannabis essential oil: A preliminary study for the evaluation of the brain effects. *Evidence-Based Complementary Alternative Medicine, 2018*, 1709182. https://doi.org/10.1155/2018/1709182

Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Cantu, R. C., Randolph, C., & Jordan, B. D. (2005). Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery, 57*(4), 719–726. https://doi.org/10.1093/neurosurgery/57.4.719

Hampton, A., & Weber-Fox, C. (2008). Non-linguistic auditory processing in stuttering: Evidence from behavior and event-related brain potentials. *Journal of Fluency Disorders, 33*(4), 253–273. https://doi.org/10.1016/j.jfludis.2008.08.001

Hart, J., Jr., Kraut, M. A., Womack, K. B., Strain, J., Didehbani, N., Bartz, E., Conover, H., Mansinghani, S., Lu, H., & Cullum, C. M. (2013). Neuroimaging of cognitive dysfunction and depression in aging retired National Football League players: A cross-sectional study. *JAMA Neurology, 70*(3), 326–335. https://doi.org/10.1001/2013.jamaneurol.340

Hayakawa, K., Mishima, K., & Fujiwara, M. (2010). Therapeutic potential of non-psychotropic cannabidiol in ischemic stroke. *Pharmaceuticals, 3*(7), 2197–2212. https://doi.org/10.3390/ph3072197

Heuberger, E., Hongratanaworakit, T., Böhm, C., Weber, R., & Buchbauer, G. (2001). Effects of chiral fragrances on human autonomic nervous system parameters and self-evaluation. *Chemical Senses, 26*(3), 281–292. https://doi.org/10.1093/chemse/26.3.281

Hunter, J. C., Fontana, D. J., Hedley, L. R., Jasper, J. R., Lewis, R., Link, R. E., Secchi, R., Sutton, J., & Eglen, R. M. (1997). Assessment of the role of α_2-adrenoceptor subtypes in the antinociceptive, sedative and hypothermic action of dexmedetomidine in transgenic mice. *British Journal of Pharmacology, 122*(7), 1339–1344. https://doi.org/10.1038/sj.bjp.0701520

Husnu Can Baser, K., & Buchbauer, G. (2015). *Biological activities of essential oils: An update (2nd ed.)*. Boca Raton, FL: CRC Press.

Immke, D. C., & Gavva, N. R. (2006). The TRPV1 receptor and nociception. *Seminars in Cell & Developmental Biology, 17*(5), 582–591. https://doi.org/10.1016/j.semcdb.2006.09.004

Iriarte, J., Urrestarazu, E., Valencia, M., Alegre, M., Malanda, A., Viteri, C., & Artieda, J. (2003). Independent component analysis as a tool to eliminate artifacts in EEG: A quantitative study. *Journal of Clinical Neurophysiology, 20*(4), 249–257. https://doi.org/10.1097/00004691-200307000-00004

Jeong, S.-I., Lim, J.-P., & Jeon, H. (2007). Chemical composition and antibacterial activities of the essential oil from Abies koreana. *Phytotherapy Research, 21*(12), 1246–1250. https://doi.org/10.1002/ptr.2229

Jiang, X., Bian, G.-B., & Tian, Z. (2019). Removal of artifacts from EEG signals: A review. *Sensors, 19*(5), 987. https://doi.org/10.3390/s19050987

Jorge, R. E., Starkstein, S. E., Arndt, S., Moser, D., Crespo-Facorro, B., & Robinson, R. G. (2005). Alcohol misuse and mood disorders following traumatic brain injury. *Archives of General Psychiatry, 62*(7), 742–749. https://doi.org/10.1001/archpsyc.62.7.742

Key, A. P. F., Dove, G. O., & Maguire, M. J. (2005). Linking brainwaves to the brain: An ERP primer. *Developmental Neuropsychology, 27*(2), 183–215. https://doi.org/10.1207/s15326942dn2702_1

Kim, E., Lauterbach, E. C., Reeve, A., Arciniegas, D. B., Coburn, K. L., Mendez, M. F., Rummans, T. A., & Coffey, E. C. (2007). Neuropsychiatric complications of traumatic brain injury: A critical review of the literature (a report by the ANPA Committee on Research). *The Journal of Neuropsychiatry and Clinical Neurosciences, 19*(2), 106–127. https://doi.org/10.1176/jnp.2007.19.2.106

Kim, K., Bu, Y., Jeong, S., Lim, J., Kwon, Y., Cha, D. S., Kim, J., Jeon, S., Eun, J., & Jeon, H. (2006). Memory-enhancing effect of a supercritical carbon dioxide fluid extract of the needles of Abies koreana on scopolamine-induced amnesia in mice. *Bioscience, Biotechnology, and Biochemistry, 70*(8), 1821–1826. https://doi.org/10.1271/bbb.50608

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Research Reviews, 29*(2–3), 169–195. https://doi.org/10.1016/s0165-0173(98)00056-3

Kothari, R., Bokariya, P., Singh, S., & Singh, R. (2016). A comprehensive review on methodologies employed for visual evoked potentials. *Scientifica, 2016*, 9852194. https://doi.org/10.1155/2016/9852194

Kozela, E., Juknat, A., & Vogel, Z. (2017). Modulation of astrocyte activity by cannabidiol, a nonpsychoactive cannabinoid. *International Journal of Molecular Sciences, 18*(8), 1669. https://doi.org/10.3390/ijms18081669

Kutas, M., McCarthy, G., & Donchin, E. (1977). Augmenting mental chronometry: The P300 as a measure of stimulus evaluation time. *Science, 197*(4305), 792–795. https://doi.org/10.1126/science.887923

Levine, B., Fujiwara, E., O'Connor, C., Richard, N., Kovacevic, N., Mandic, M., Restagno, A., Easdon, C., Robertson, I. H., Graham, S. J., Cheung, G., Gao, F., Schwartz, M. L., & Black, S. E. (2006). In *vivo* characterization of traumatic brain injury neuropathology with structural and functional neuroimaging. *Journal of Neurotrauma, 23*(10), 1396–1411. https://doi.org/10.1089/neu.2006.23.1396

Ling, H., Hardy, J., & Zetterberg, H. (2015). Neurological consequences of traumatic brain injuries in sports. *Molecular and Cell Neuroscience, 66*(Pt. B), 114–122. https://doi.org/10.1016/j.mcn.2015.03.012

Lorenzetti, B. B., Souza, G. E., Sarti, S. J., Santos Filho, D., & Ferreira, S. H. (1991). Myrcene mimics the peripheral analgesic activity of lemongrass tea. *Journal of Ethnopharmacology, 34*(1), 43–48. https://doi.org/10.1016/0378-8741(91)90187-i

Lu, H.-C., & Mackie, K. (2016). An introduction to the endogenous cannabinoid system. *Biological Psychiatry, 79*(7), 516–525. https://doi.org/10.1016/j.biopsych.2015.07.028

Manley, G., Gardner, A. J., Schneider, K. J., Guskiewicz, K. M., Bailes, J., Cantu, R. C., Castellani, R. J., Turner, M., Jordan, B. D., Randolph, C., Dvořák, J., Hayden, K. A., Tator, C. H., McCrory, P., & Iverson, G. L. (2017). A systematic review of potential long-term effects of sport-related concussion. *British Journal of Sports Medicine, 51*(12), 969–977. https://doi.org/10.1136/bjsports-2017-097791

Markiewcz, R. (2017). The use of EEG biofeedback/neurofeedback in psychiatric rehabilitation. *Psychiatria Polska, 51*(6), 1095–1106. https://doi.org/10.12740/PP/68919

Marlats, F., Djabelkhir-Jemmi, L., Azabou, E., Boubaya, M., Pouwels, S., & Rigaud, A.-S. (2019). Comparison of effects between SMR/delta-ratio and beta1/theta-ratio neurofeedback training for older adults with Mild Cognitive Impairment: A protocol for a randomized controlled trial. *Trials, 20*(1), 88. https://doi.org/10.1186/s13063-018-3170-x

Mathias, J. L., Beall, J. A., & Bigler, E. D. (2004). Neuropsychological and information processing deficits following mild traumatic brain injury. *Journal of the International Neuropsychological Society, 10*(2), 286–297. https://doi.org/10.1017/S1355617704102117

Mathias, J. L., & Wheaton, P. (2007). Changes in attention and information-processing speed following severe traumatic brain injury: A meta-analytic review. *Neuropsychology, 21*(2), 212–223. https://doi.org/10.1037/0894-4105.21.2.212

McKee, A. C., Abdolmohammadi, B., & Stein, T. D. (2018). The neuropathology of chronic traumatic encephalopathy. *Handbook of Clinical Neurology, 158*, 297–307. https://doi.org/10.1016/B978-0-444-63954-7.00028-8

McWilliams, J., & Schmitter-Edgecombe, M. (2008). Semantic memory organization during the early stage of recovery from

traumatic brain injury. *Brain Injury, 22*(3), 243–253. https://doi.org/10.1080/02699050801935252

Miranda, P., Cox, C. D., Alexander, M., Danev, S., & Lakey, J. R. T. (2019). Overview of current diagnostic, prognostic, and therapeutic use of EEG and EEG-based markers of cognition, mental, and brain health. *Integrative Molecular Medicine, 6*, 1–9. https://doi.org/10.15761/IMM.1000378

Molina-Holgado, E., Vela, J. M., Arévalo-Martin, A., Almazán, G., Molina-Holgado, F., Borrell, J., & Guaza, C. (2002). Cannabinoids promote oligodendrocyte progenitor survival: Involvement of cannabinoid receptors and phosphatidylinositol-3 kinase/Akt signaling. *The Journal of Neuroscience, 22*(22), 9742–9753. https://doi.org/10.1523/JNEUROSCI.22-22-09742.2002

Moore, R. D., Lepine, J., & Ellemberg, D. (2017). The independent influence of concussive and sub-concussive impacts on soccer players' neurophysiological and neuropsychological function. *International Journal of Psychophysiology, 112*, 22–30. https://doi.org/10.1016/j.ijpsycho.2016.11.011

Muller, C., Morales, P., & Reggio, P. H. (2018). Cannabinoid ligands targeting TRP channels. *Frontiers in Molecular Neuroscience, 11*, 487. https://doi.org/10.3389/fnmol.2018.00487

Navarrete, M., Díez, A., & Araque, A. (2014). Astrocytes in endocannabinoid signalling. *Philosophical Transactions of the Royal Society B Biological Sciences, 369*(1654), 20130599. https://doi.org/10.1098/rstb.2013.0599

Navarro, G., Varani, K., Lillo, A., Vincenzi, F., Rivas-Santisteban, R., Raïch, I., Reyes-Resina, I., Ferreiro-Vera, C., Borea, P. A., Sánchez de Medina, V., Nadal, X., & Franco, R. (2020). Pharmacological data of cannabidiol- and cannabigerol-type phytocannabinoids acting on cannabinoid CB_1, CB_2 and CB_1/CB_2 heteromer receptors. *Pharmacological Research, 159*, 104940. https://doi.org/10.1016/j.phrs.2020.104940

Navarro, G., Varani, K., Reyes-Resina, I., Sánchez de Medina, V., Rivas-Santisteban, R., Sánchez-Carnerero Callado, C., Vincenzi, F., Casano, S., Ferreiro-Vera, C., Canela, E. I., Borea, P. A., Nadal, X., & Franco, R. (2018). Cannabigerol action at cannabinoid CB1 and CB2 receptors and at CB1-CB2 heteroreceptor complexes. *Frontiers in Pharmacology, 9*, 632. https://doi.org/10.3389/fphar.2018.00632

Panikashvili, D., Simeonidou, C., Ben-Shabat, S., Hanuš, L., Breuer, A., Mechoulam, R., & Shohami, E. (2001). An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. *Nature, 413*(6855), 527–531. https://doi.org/10.1038/35097089

Papathanasiou, E. S., Cronin, T., Seemungal, B., & Sandhu, J. (2018). Electrophysiological testing in concussion: A guide to clinical applications. *Journal of Concussion, 2*. https://doi.org/10.1177%2F2059700218812634

Pelegrín-Valero, C. A., Gómez-Hernández, R., Muñoz-Céspedes, J. M., Fernández-Guinea, S. D., & Tirapu-Ustarroz, J. (2001). Consideraciones nosológicas del cambio de personalidad postraumático [Nosologic aspects of personality change due to head trauma]. *Revista de Neurología, 32*(7), 681–687. https://doi.org/10.33588/RN.3207.2000180

Pertwee, R. G. (2008). The diverse CB_1 and CB_2 receptor pharmacology of three plant cannabinoids: Δ^9-tetrahydrocannabinol, cannabidiol and Δ^9-tetrahydrocannabivarin. *British Journal of Pharmacology, 153*(2), 199–215. https://doi.org/10.1038/sj.bjp.0707442

Polich, J. (2007). Updating P300: An integrative theory of P3a and P3b. *Clinical Neurophysiology, 118*(10), 2128–2148. https://doi.org/10.1016/j.clinph.2007.04.019

Pollastro, F., Taglialatela-Scafati, O., Allarà, M., Muñoz, E., Di Marzo, V., De Petrocellis, L., & Appendino, G. (2011). Bioactive prenylogous cannabinoid from fiber hemp (*cannabis sativa*). *Journal of Natural Products, 74*(9), 2019–2022. https://doi.org/10.1021/np200500p

Posthuma, D., Neale, M. C., Boomsma, D. I., & de Geus, E. J. (2001). Are smarter brains running faster? Heritability of alpha peak frequency, IQ, and their interrelation. *Behavior Genetics, 31*(6), 567–579. https://doi.org/10.1023/a:1013345411774

Randolph, C., Karantzoulis, S., & Guskiewicz, K. (2013). Prevalence and characterization of mild cognitive impairment in retired National Football League players. *Journal of International Neuropsychological Society, 19*(8), 873–880. https://doi.org/10.1017/S1355617713000805

Ridet, J. L., Privat, A., Malhotra, S. K., & Gage, F. H. (1997). Reactive astrocytes: Cellular and molecular cues to biological function. *Trends in Neurosciences, 20*(12), 570–577. https://doi.org/10.1016/s0166-2236(97)01139-9

Ríos, M., Periañez, J. A., & Muñoz-Céspedes, J. M. (2004). Attentional control and slowness of information processing after severe traumatic brain injury. *Brain Injury, 18*(3), 257–272. https://doi.org/10.1080/02699050310001617442

Rock, E. M., Bolognini, D., Limebeer, C. L., Cascio, M. G., Anavi-Goffer, S., Fletcher, P. J., Mechoulam, R., Pertwee, R. G., & Parker, L. A. (2012). Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT_{1A} somatodendritic autoreceptors in the dorsal raphe nucleus. *British Journal of Pharmacology, 165*(8), 2620–2634. https://doi.org/10.1111/j.1476-5381.2011.01621.x

Rock, E. M., Goodwin, J. M., Limebeer, C. L., Breuer, A., Pertwee, R. G., Mechoulam, R., & Parker, L. A. (2011). Interaction between non-psychotropic cannabinoids in marihuana: Effect of cannabigerol (CBG) on the anti-nausea or anti-emetic effects of cannabidiol (CBD) in rats and shrews. *Psychopharmacology, 215*(3), 505–512. https://doi.org/10.1007/s00213-010-2157-4

Rosenthaler, S., Pöhn, B., Kolmanz, C., Huu, C. N., Krewenka, C., Huber, A., Kranner, B., Rausch, W.-D., & Moldzio, R. (2014). Differences in receptor binding affinity of several phytocannabinoids do not explain their effects on neural cell cultures. *Neurotoxicology and Teratology, 46*, 49–56. https://doi.org/10.1016/j.ntt.2014.09.003

Roser, P., Juckel, G., Rentzsch, J., Nadulski, T., Gallinat, J., & Stadelmann, A. M. (2008). Effects of acute oral Δ^9-tetrahydrocannabinol and standardized cannabis extract on the auditory P300 event-related potential in healthy volunteers. *European Neuropsychopharmacology, 18*(8), 569–577. https://doi.org/10.1016/j.euroneuro.2008.04.008

Rule, R. R., Shimamura, A. P., & Knight, R. T. (2002). Orbitofrontal cortex and dynamic filtering of emotional stimuli. *Cognitive, Affective, & Behavioral Neuroscience, 2*(3), 264–270. https://doi.org/10.3758/cabn.2.3.264

Russo, E. B. (2011). Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology, 163*(7), 1344–1364. https://doi.org/10.1111/j.1476-5381.2011.01238.x

Russo, E. B., Burnett, A., Hall, B., & Parker, K. K. (2005). Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochemical Research, 30*(8), 1037–1043. https://doi.org/10.1007/s11064-005-6978-1

Sachdev, P., Smith, J. S., & Cathcart, S. (2001). Schizophrenia-like psychosis following traumatic brain injury: A chart-based descriptive and case-control study. *Psychological Medicine, 31*(2), 231–239. https://doi.org/10.1017/s0033291701003336

Sari, B. A., Koster, E. H. W., Pourtois, G., & Derakshan, N. (2016). Training working memory to improve attentional control in anxiety: A proof-of-principle study using behavioral and electrophysiological measures. *Biological Psychology, 121*(Pt. B), 203–212. https://doi.org/10.1016/j.biopsycho.2015.09.008

Schurman, L. D., & Lichtman, A. H. (2017). Endocannabinoids: A promising impact for traumatic brain injury. *Frontiers in Pharmacology, 8*, 69. https://doi.org/10.3389/fphar.2017.00069

Schutter, D. J. L. G., & Van Honk, J. (2005). Electrophysiological ratio markers for the balance between reward and punishment. *Cognitive Brain Research, 24*(3), 685–690. https://doi.org/10.1016/j.cogbrainres.2005.04.002

Seo, M., Sowndhararajan, K., & Kim, S. (2016). Influence of binasal and uninasal inhalations of essential oil of *Abies koreana* twigs on electroencephalographic activity of human. *Behavioural Neurology, 2016*, 9250935. https://doi.org/10.1155/2016/9250935

Shah, S. A., Goldin, Y., Conte, M. M., Goldfine, A. M., Mohamadpour, M., Fidali, B. C., Cicerone, K., & Schiff, N. D. (2017). Executive attention deficits after traumatic brain injury reflect impaired recruitment of resources. *NeuroImage: Clinical, 14*, 233–241. https://doi.org/10.1016/j.nicl.2017.01.010

Shapiro, S. S., & Wilk, M. B. (1965). An analysis of variance test for normality (complete samples). *Biometrika, 52*(3–4), 591–611. https://doi.org/10.1093/biomet/52.3-4.591

Shohami, E., Cohen-Yeshurun, A., Magid, L., Algali, M., & Mechoulam, R. (2011). Endocannabinoids and traumatic brain injury. *British Journal of Pharmacology, 163*(7), 1402–1410. https://doi.org/10.1111/j.1476-5381.2011.01343.x

Smit, C. M., Wright, M. J., Hansell, N. K., Geffen, G. M., & Martin, N. G. (2006). Genetic variation of individual alpha frequency (IAF) and alpha power in a large adolescent twin sample. *International Journal of Psychophysiology, 61*(2), 235–243. https://doi.org/10.1016/j.ijpsycho.2005.10.004

Stella, N. (2010). Cannabinoid and cannabinoid-like receptors in microglia, astrocytes, and astrocytomas. *Glia, 58*(9), 1017–1030. https://doi.org/10.1002/glia.20983

Strain, J., Didehbani, N., Cullum, C. M., Mansinghani, S., Conover, H., Kraut, M. A., Hart, J., & Womack, K. B. (2013). Depressive symptoms and white matter dysfunction in retired NFL players with concussion history. *Neurology, 81*(1), 25–32. https://doi.org/10.1212/WNL.0b013e318299ccf8

Szabo, B., & Schlicker, E. (2005). Effects of cannabinoids on neurotransmission. In R. G. Pertwee (Ed.), *Cannabinoids*. *Handbook of experimental pharmacology* (vol. 168, pp. 327–365). Springer Berlin, Heidelberg. https://doi.org/10.1007/3-540-26573-2_11

Tateno, A., Jorge, R. E., & Robinson, R. G. (2003). Clinical correlates of aggressive behavior after traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences, 15*(2), 155–160. https://doi.org/10.1176/jnp.15.2.155

Tateno, A., Jorge, R. E., & Robinson, R. G. (2004). Pathological laughing and crying following traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences, 16*(4), 426–434. https://doi.org/10.1176/jnp.16.4.426

Thériault, M., De Beaumont, L., Gosselin, N., Filipinni, M., & Lassonde, M. (2009). Electrophysiological abnormalities in well functioning multiple concussed athletes. *Brain Injury, 23*(11), 899–906. https://doi.org/10.1080/02699050903283189

van Reekum, R., Cohen, T., & Wong, J. (2000). Can traumatic brain injury cause psychiatric disorders? *The Journal of Neuropsychiatry and Clinical Neurosciences, 12*(3), 316–327. https://doi.org/10.1176/jnp.12.3.316

van Tricht, M. J., Harmsen, E. C., Koelman, J. H. T. M., Bour, L. J., van Amelsvoort, T. A., Linszen, D. H., de Haan, L. & Nieman, D. H. (2013). Effects of cannabis use on event related potentials in subjects at ultra high risk for psychosis and healthy controls. *International Journal of Psychophysiology, 88*(2), 149–156. https://doi.org/10.1016/j.ijpsycho.2013.03.012

Vázquez, C., Tolón, R. M., Pazos, M. R., Moreno, M., Koester, E. C., Cravatt, B. F., Hillard, C. J., & Romero, J. (2015). Endocannabinoids regulate the activity of astrocytic hemichannels and the microglial response against an injury: *In vivo* studies. *Neurobiology of Disease, 79*, 41–50. https://doi.org/10.1016/j.nbd.2015.04.005

Walter, L., & Stella, N. (2004). Cannabinoids and neuroinflammation. *British Journal of Pharmacology, 141*(5), 775–785. https://doi.org/10.1038/sj.bjp.0705667

Whitley, E., & Ball, J. (2002). Statistics review 6: Nonparametric methods. *Critical Care, 6*(6), 509–513. https://doi.org/10.1186/cc1820

Yao, Z.-F., & Hsieh, S. (2019). Neurocognitive mechanism of human resilience: A conceptual framework and empirical review. *International Journal of Environmental Research and Public Health, 16*(24), 5123. https://doi.org/10.3390/ijerph16245123

Zeilig, G., Drubach, D. A., Katz-Zeilig, M., & Karatinos, J. (1996). Pathological laughter and crying in patients with closed traumatic brain injury. *Brain Injury, 10*(8), 591–597. https://doi.org/10.1080/026990596124160

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