



Cannabis users exhibit increased cortical activation during resting state compared to non-users



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ABSTRACT

Studies have shown altered task-based brain functioning as a result of cannabis use. To date, however, whether similar alterations in baseline resting state and functional organization of neural activity are observable in cannabis users remains unknown. We characterized global resting state cortical activations and functional connectivity via electroencephalography (EEG) in cannabis users and related these activations to measures of cannabis use. Resting state EEG in the eyes closed condition was collected from age- and sex-matched cannabis users ($N = 17$; 6 females; mean age = 30.9 ± 7.4 years) and non-using controls ($N = 21$; 9 females; mean age = 33.1 ± 11.6 years). Power spectral density and spectral coherence were computed to determine differences in cortical activations and connectivity between the two groups in the delta (1–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (31–50 Hz) frequency bands. Cannabis users exhibited decreased delta and increased theta, beta, and gamma power compared to controls, suggesting increased cortical activation in resting state and a disinhibition of inhibitory functions that may interrupt cognitive processes. Cannabis users also exhibited increased interhemispheric and intrahemispheric coherence relative to controls, reduced mean network degree, and increased clustering coefficient in specific regions and frequencies. This increased cortical activity may indicate a loss of neural refinement and efficiency that may indicate a “noisy” brain. Lastly, measures related to cannabis use were correlated with spectral power and functional connectivity measures, indicating that specific electrophysiological signals are associated with cannabis use. These results suggest that there are differences in cortical activity and connectivity between cannabis users and non-using controls in the resting state that may be related to putative cognitive impairments and can inform effectiveness of intervention programs.

Introduction

The brain's resting state is defined as intrinsic activity generated by the brain when one is awake, but not engaged in a task (Biswal et al., 1997; Mantini et al., 2007). Although the resting state is independent of task-related neural activity, it is attenuated when engaged in a task and thus, could be viewed as a measure of baseline functional organization of brain activity (Raichle et al., 2001; Raichle, 2011). Resting state networks have been well-established by various neuroimaging techniques that reveal consistent and stable networks organized in spatial and temporal synchrony (Raichle et al., 2001; Greicius et al., 2003; Damoiseaux et al., 2006; Mantini et al., 2007; Bonnard et al., 2016a). Importantly, resting state does not imply inactivity, but rather a state that can quickly respond to changing external stimuli (Deco et al., 2009) and thus, is important to be characterized in neuropathologies.

EEG measures the synchrony of electrical signals that are emitted from large populations of pyramidal postsynaptic potentials. Resting state, when measured by EEG, reflects underlying cortical activations and is related to cognitive functioning (Laufs et al., 2003; Mantini et al., 2007; Chen et al., 2008). Spectral power in EEG is typically measured by separating the EEG signal into different frequency bands: delta (~1–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (30 Hz and above) by using signal processing techniques, such as Fourier transform. Oscillations in these frequency bands are present in varying relative capacity during the resting state and change dynamically when engaged in a task. The underlying neural communication (Schnitzler and Gross, 2005) may reflect electrophysiological neural correlates of the cortical networks (Jann et al., 2010). For example, alpha frequencies are synchronized (i.e., greater power) in the resting state, but are attenuated when performing a cognitive task, while beta and gamma frequencies are

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synchronized when engaged in a task. Indeed, simultaneous functional MRI (fMRI) and EEG studies have found that there is a strong correlation between activation in the frontal and parietal cortices and the default mode network specifically with alpha power during resting state (Goldman et al., 2002; Laufs et al., 2003; Miller et al., 2009; Bonnard et al., 2016a). Due to the high temporal resolution of EEG, it can provide insight into transient connectivity between cortical regions (Scheeringa et al., 2012).

Differences in resting state may reflect changes in cognition that are related to neuropathology (Gu et al., 2010; Ma et al., 2010; Sutherland et al., 2012; Zhu et al., 2017). Thus, resting state may be an important indicator of the robustness of networks underlying cognition and may provide potential neural associations for assessing cognitive health (Broyd et al., 2009). Previous EEG studies indicate that neural synchronies during resting state are altered with substance use as reflected in changes in spectral power. An increase in alpha, beta, and delta was reported in users of cocaine both during eyes closed resting state (Herning et al., 1994; Reid et al., 2006) and task-related activity (Herning et al., 1985; Reid et al., 2003). Alcohol users (Bauer, 2001; Rangaswamy et al., 2002) and heroin-dependent individuals (Franken et al., 2004) exhibited an increase in beta during eyes closed resting state. However, a decrease in eyes closed resting beta and increase in alpha in users of heroin have also been reported (Polunina and Davydov, 2004). These discrepancies may be related to differences in samples (e.g., various states of abstinence). A study that directly compared eyes closed and eyes open resting state EEG in alcohol-, cocaine-, and heroin-dependent users only found an increase in beta power in alcohol- and cocaine-dependent users compared to controls and no difference in other frequencies, regardless of the eyes open or eyes closed condition (Costa and Bauer, 1997). In methamphetamine-dependent individuals, increased eyes closed resting state delta and theta power were found compared to non-using controls, but no differences were present in alpha and beta (Newton et al., 2003). Additional inconsistencies appear in animal models that report changes with cocaine use as a decrease in power in the alpha, theta, and delta frequencies and a dose dependent change in beta power in rats (Chang et al., 1994). Oscillations in the delta frequencies have been associated with motivation and reward in preclinical studies, indicating that delta is generated in subcortical regions including the nucleus accumbens and ventral tegmental area as well as the medial prefrontal cortex and that delta oscillations play a role in the communication between these regions (Leung and Yim, 1993; Knyazev, 2007; Gruber et al., 2009; Fujisawa and Buzsáki, 2011). In cocaine users, studies have reported an increase in task-related delta power that may be related to the effect of cocaine on the reward system (Herning et al., 1985; Reid et al., 2006) and was correlated with cue-elicited craving of cocaine (Reid et al., 2003). Studies examining the effect of repetitive transcranial magnetic stimulation (rTMS) on craving indicate that rTMS of the dorsolateral prefrontal cortex significantly reduced cue-elicited craving to nicotine (Amiaz et al., 2009; Hayashi et al., 2013; Li et al., 2013; Pripfl et al., 2014) and decreased delta power (Pripfl et al., 2014), suggesting that spectral power, specifically in the delta frequencies, may be associated with substance use measures.

The relationship between cannabis use and resting state via EEG remains equivocal. Böcker and colleagues found that eyes closed resting state theta was correlated with performance on a working memory task after acute cannabis intoxication (Böcker et al., 2009), demonstrating that resting state EEG may be associated with cognitive performance. They also reported dose-related effects in the theta and beta bands, indicating that these specific frequencies may be more susceptible to changes in cortical activity related to cannabis use (Böcker et al., 2009). Ehlers and colleagues investigated the correlation of eyes closed resting state EEG with cannabis- and alcohol-dependent users and reported a positive correlation between delta power and cannabis dependence (Ehlers et al., 2010). Struve and colleagues have consistently found an increase in alpha and theta power and decrease in delta and beta power in eyes closed resting state in long-term cannabis users (Struve et al.,

1994, 1998, 1999); however, other studies have found a decrease in alpha and beta frequencies in the posterior regions in abstinent cannabis users (Herning et al., 2008). Preclinical studies in rodents have suggested that gamma oscillations arising from GABA receptors that connect cortical networks are important for cognitive function (Whittington et al., 1995; Wang and Buzsáki, 1996). Further, acute delta-9-tetrahydrocannabinol (THC) and activation of CB1 receptors by agonists may disrupt gamma oscillations through inhibitory interneurons (Hájos et al., 2000; Robbe et al., 2006; Hájos et al., 2008), suggesting that gamma oscillations may be disrupted in cannabis users. To our knowledge, no studies have examined spectral coherence, and thus global cortico-cortical communication, in cannabis users.

In this study, our aim was to characterize resting state EEG in cannabis users to examine: 1) cortical activations via power spectral density, 2) global cortical functional connectivity via spectral coherence, and 3) correlations between spectral power, functional connectivity, and cannabis use measures. Based on the scant literature in electrophysiology in cannabis users, we hypothesized that cannabis users will exhibit changes in spectral power, specifically decreased power in delta and beta and increased power in theta and alpha. We also hypothesized a correlation between delta, theta, and beta power and cannabis use measures. Based on previous functional connectivity fMRI studies (Filbey and Yezhuvath, 2013; Filbey et al., 2014), we hypothesized an increase in spectral coherence in cannabis users.

Material and methods

Participants

Thirty-eight participants provided informed consent to take part in this study. Seventeen participants were cannabis users with at least seven days of use in the past 30 days (mean age = 30.9 ± 7.4 years; 6 females) and 21 participants were non-using controls with fewer than five separate occasions of cannabis use in their lifetime and no use in the preceding 90 days (mean age = 32.6 ± 11.6 years; 10 females; see Table 1 for demographic information). All participants were proficient in

Table 1
Participant demographics (mean \pm SD).

	Cannabis users	Non-using controls	p-value
N	17	21	–
Age (years)	30.9 ± 7.4	33.1 ± 11.6	0.49
Gender (M/F)	11/6	12/9	0.64
Years of education	13.9 ± 3.2	16.6 ± 2.1	0.003*
Ethnicity			
Hispanic/Latino	2	5	
Non-Hispanic/Latino	15	16	0.34
Race			
Caucasian	8	11	
African American	5	2	
Asian	1	6	
Other	3	2	0.16
Number of alcohol drinking days in preceding 90 days	13.7 ± 12.3	3.9 ± 6.1	0.006*
Number of smoking days in preceding 90 days	16.4 ± 35.0	0.0 ± 0.0	0.072
Number of cannabis use days in preceding 90 days	70.8 ± 20.0	0.0 ± 0.0	<0.001*
Time since last use (hours)	36.8 ± 12.1	n/a	–
Number of participants meeting criteria for cannabis abuse (current/lifetime)	2/6	0/0	0.52/ 0.028*
Number of participants meeting criteria for cannabis dependence (current/lifetime)	1/3	0/0	0.25/ 0.024*
MPS	3.4 ± 3.6	0.0 ± 0.0	0.001*
MCQ	306.4 ± 204.3	102.2 ± 35.4	0.001*

Abbreviations: M/F, male/female; MPS, Marijuana Problem Scale; MCQ, Marijuana Craving Questionnaire.

English, right-handed, and gave their personal informed consent in accordance with the Institutional Review Board (IRB) of the University of Texas at Dallas. Participants were excluded if they had a history of brain injury, neurological or psychiatric diagnoses, Axis I disorder (other than CUD in the cannabis using group), or any EEG contraindications. Verification of cannabis use was conducted by quantification of THC metabolites in urine via gas chromatography/mass spectrometry (GC/MS) from Quest Diagnostics (<https://www.questdiagnostics.com/>). Participants were asked to refrain from cannabis use 24 h prior to their session time to ensure no acute intoxication during data collection and abstinence was verified via the Time Line Follow Back (TLFB; Sobell and Sobell, 1992) questionnaire indicating absence of cannabis use in the past 24 h, self-reported time and date of last use, and no observable signs of intoxication.

Measures of cannabis use

Cannabis use measures were obtained from the TLFB to calculate the number of cannabis use days in the preceding 90 days and hours since last cannabis use. Additionally, cannabis craving was assessed via a modified version of the Marijuana Craving Questionnaire (MCQ; Heishman et al., 2009) and negative consequences of cannabis use in daily life were assessed by the Marijuana Problem Scale (MPS; Stephens et al., 2002).

EEG acquisition

EEG data were recorded from a high density 64-electrode Neuroscan Quickcap, Neuroscan Synamps2 amplifier, and Scan 4.3.2 software. The electrodes were placed using the international 10–20 system and recorded with a sampling frequency of 1000Hz. The reference electrode was placed on the left mastoid and re-referenced offline to both left and right mastoids. The channel impedances were kept below 7k Ω . EEG was recorded in the eyes closed resting state condition.

EEG analyses

The EEG signals were band-pass filtered at 0.1–55Hz to eliminate electrical noise. Independent component analysis (ICA) was used to remove eye artifacts (e.g., eye blinks, eye movements) and muscle artifacts. Pre-processing of the recorded EEG signals was performed in EEGLAB (Delorme and Makeig, 2004) and further analyses (spectral power and coherence) were conducted using custom scripts written in MATLAB (MathWorks, Natick, MA).

Spectral power

Spectral power was calculated for all EEG channels using fast Fourier transforms (FFT) and applied in the delta (1–4Hz), theta (4–7Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (31–50 Hz) bands. Relative power was calculated as a percentage of the total power (1–50 Hz) for each frequency band. The EEG channels were grouped into eight regions corresponding to the major cortical areas: frontal (F), central (C), parietal (P), and occipital (O) in the left (L) and right (R) hemispheres (Fig. 1A). The midline channels were excluded from the analyses.

Spectral coherence

Spectral coherence between pairs of electrodes in specific frequency bands was calculated to assess functional connectivity (i.e., statistical dependence of signals) among cortical regions (Rubinov and Sporns, 2010; Babiloni et al., 2016) as defined by each electrode. Coherence quantifies the amount of synchrony of electrophysiological signals with respect to their frequency and amplitude (Fries, 2005). Oscillating brain activity has been suggested to be the mechanism of cortical communication (Schnitzler and Gross, 2005) with highly coherent signals indicating communication between the two regions from which the signals originate (Fries, 2005). Thus, coherence of EEG signals is a measure of communication between cortical regions underlying two electrode sites (Srinivasan et al., 1998; Nunez, 2000; Fries, 2005; Bowyer, 2016). It is important to note that coherence as defined and applied in this analysis is prone to distortion by volume conduction. Although there are techniques that are less affected by volume conduction by using phase to calculate coherence, the classic definition of coherence is applied here for direct comparison with other studies. This is an important consideration given that resting state EEG coherence has not yet been characterized in cannabis users and the ability to compare with other studies is critical.

In order to determine differences in cortical communication between the regions, intrahemispheric and interhemispheric coherence was calculated. The mean coherence values from all possible pairs of electrodes between two corresponding regions represented the interhemispheric coherence (see Fig. 1B). The mean coherence values from all possible pairs of electrodes between the four regions was used to calculate intrahemispheric coherence within the left and right hemispheres (see Fig. 1C). A similar approach to measure global coherence has been reported previously (Stoffers et al., 2007, 2008).

Functional connectivity

Specific functional connectivity measures of degree, clustering

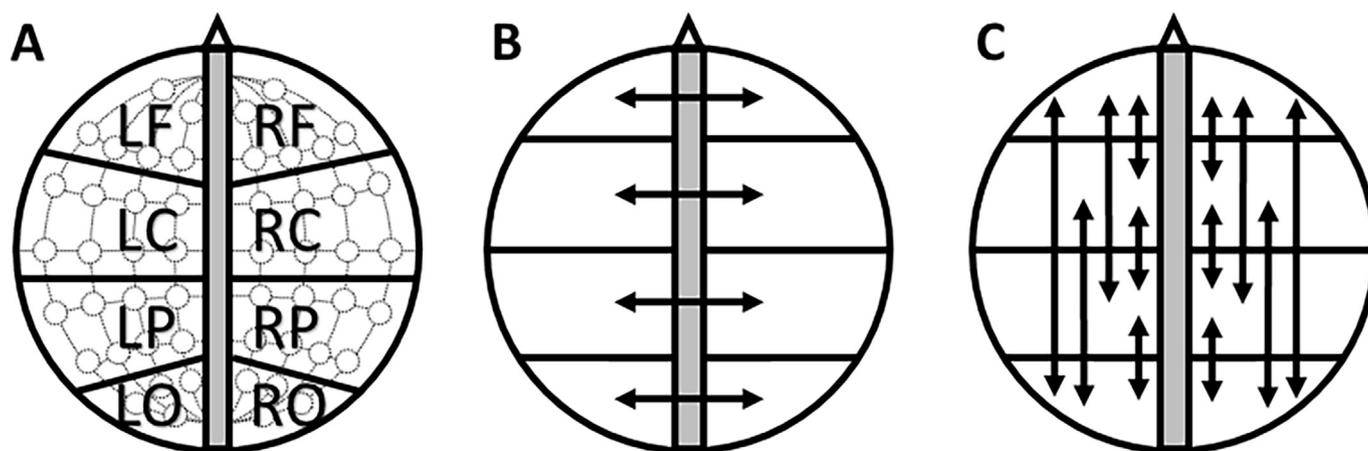


Fig. 1. Grouping of EEG channels. A) The EEG channels were grouped into eight regions. The midline electrodes were excluded from the analyses. B) Arrows indicate the regions used to calculate interhemispheric and C) intrahemispheric coherence. L = left, R = right, F = frontal, C = central, P = parietal, O = occipital.

coefficient, path length, and global efficiency were calculated on the coherence values using scripts from the Brain Connectivity Toolbox (Rubinov and Sporns, 2010) and have been defined previously by Rubinov and Sporns (2010):

Degree

The degree of a node (i.e., an electrode) is the number of other nodes to which it is connected and is a measure of the density of the network. Thus, with respect to coherence, it is the number of electrodes that have high coherency with an electrode's own signal.

Clustering coefficient

The clustering coefficient quantifies what fraction of a node's connections are also connected to each other and quantifies connectivity around specific nodes.

Path length

Characteristic path length is the average of the shortest path length between all pairs of nodes in the network.

Global efficiency

Global efficiency is a measure of functional integration and is the

inverse of the mean shortest path length between each pair of nodes.

Statistical analyses

A three-way mixed factorial ($2 \times 2 \times 4$) ANCOVA on Group (cannabis users, non-using controls) x Hemisphere (left, right) x Region (frontal, central, parietal, occipital) on the spectral power with Hemisphere and Region as within-subject variables and Group as the between-subject variable was conducted for each frequency band. Education, alcohol, and nicotine use were selected to be added as covariates *a priori* as these variables tend to differ between these groups (Gfroerer et al. 1997). As the assumption of sphericity was violated in these analyses, Greenhouse-Geisser corrected *p*-values were used with significance defined at $p < 0.05$. Significant effects were decomposed with *post-hoc* analyses using a Bonferroni correction. To assess differences in intra-hemispheric and interhemispheric coherence and the functional connectivity measures, two-tailed independent *t*-tests were conducted for each region with Bonferroni correction for multiple comparisons. Lastly, partial Pearson's correlations were calculated between variables related to cannabis use, spectral power, and coherence to control for the covariates.

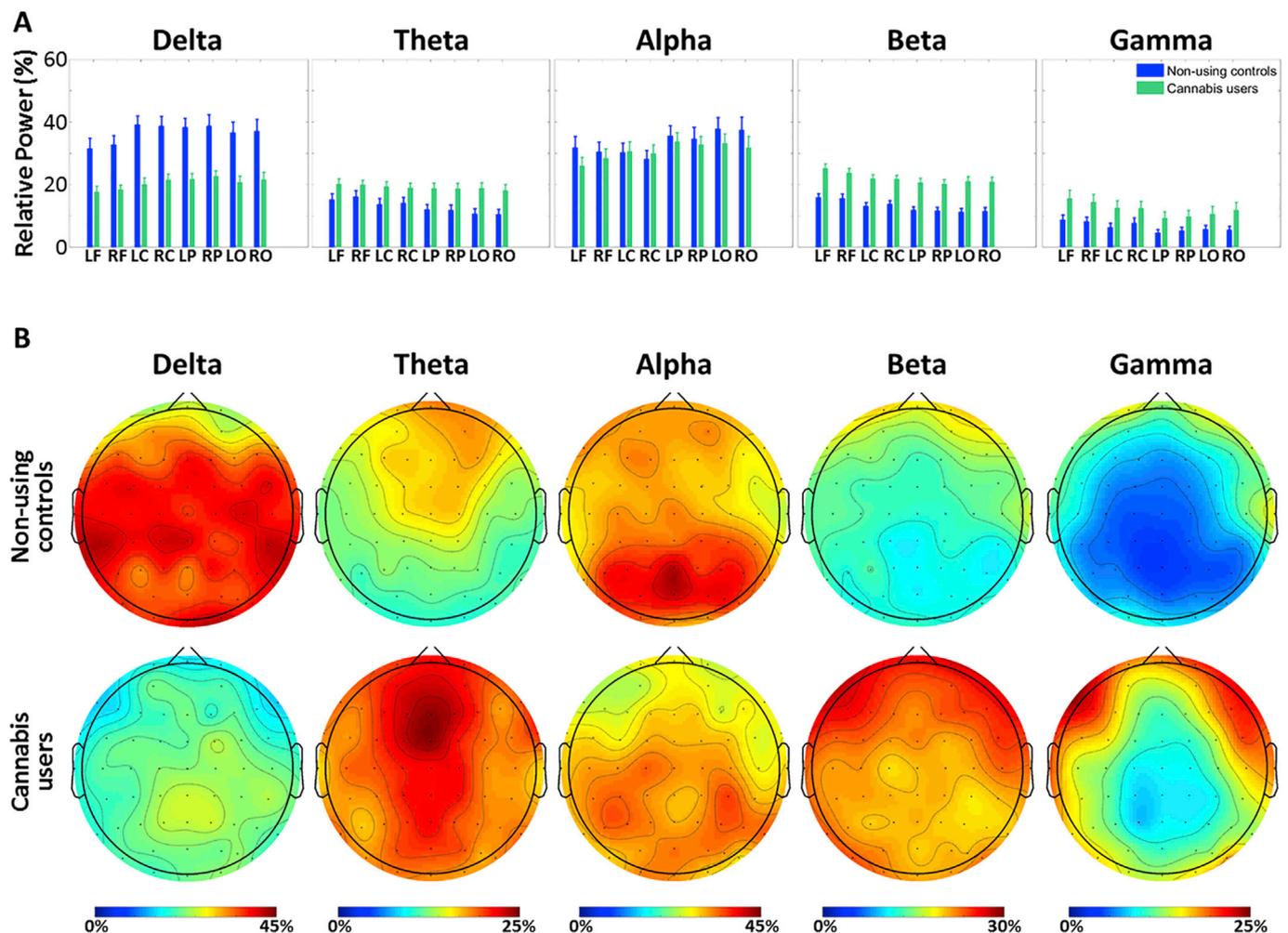


Fig. 2. Spectral power across regions and frequency bands. A) Cannabis users exhibited significantly decreased power in the delta band, significantly increased power in the theta and beta bands, increased power in the gamma band that approached significance, and no difference in the alpha band compared to controls. B) Topographic comparison between the groups. Each dot represents an electrode, colors represent high (red) or low (blue) power. Error bars indicate standard error.

Results

Participant characteristics

Table 1 summarizes the participant demographics and cannabis use measures. There were no significant differences in age, gender, or nicotine use (all $p > 0.05$); however, there were differences in education ($p = 0.003$) and alcohol use ($p = 0.006$). These differences were accounted for by including these variables as covariates in the statistical analyses.

Spectral power

Separate mixed factorial ANCOVAs on power indicated a significant main effect of Group in the delta ($F(1,33) = 10.5$, $p = 0.003$, partial $\eta^2 = 0.24$), theta ($F(1,33) = 4.65$, $p = 0.038$, partial $\eta^2 = 0.12$), and beta ($F(1,33) = 21.3$, $p < 0.001$, partial $\eta^2 = 0.39$) bands and approached significance in the gamma band ($F(1,33) = 3.31$, $p = 0.078$, partial $\eta^2 = 0.091$). No difference was found in the alpha band ($F(1,33) = 0.11$, $p = 0.74$, partial $\eta^2 = 0.003$). Cannabis users exhibited significantly reduced delta power compared to controls (Fig. 2A). Significant Group \times Hemisphere interactions were revealed in the theta ($F(1,33) = 8.54$, $p = 0.006$, partial $\eta^2 = 0.21$) and beta ($F(1,33) = 5.26$, $p = 0.028$, partial $\eta^2 = 0.14$) bands. *Post-hoc* comparisons with Bonferroni corrections indicated significantly reduced theta power in the left hemisphere in users compared to controls ($p = 0.011$, Cohen's $d = 0.66$), but not the right hemisphere ($p = 0.12$, Cohen's $d = 0.39$) and greater beta power in users compared to controls in both hemispheres (both $p < 0.001$, left: Cohen's $d = 0.41$, right: Cohen's $d = 0.34$). Global spectral densities in each frequency are displayed in Fig. 2B.

Spectral coherence

Two-tailed independent t -tests with Bonferroni correction for multiple comparisons revealed significantly greater interhemispheric coherence in cannabis users in the delta and theta bands in the frontal (delta: $p = 0.011$, Cohen's $d = 0.65$; theta: $p = 0.023$, Cohen's $d = 0.58$) and central (delta: $p = 0.006$, Cohen's $d = 0.69$; theta: $p = 0.041$, Cohen's $d = 0.51$) regions and approaching significance the frontal regions in the alpha band ($p = 0.055$, Cohen's $d = 0.49$). There were no differences in the beta or gamma bands (Fig. 3).

Cannabis users also exhibited greater intrahemispheric coherence in the left hemisphere between the frontal-central regions in the delta ($p = 0.017$, Cohen's $d = 0.61$) and theta ($p = 0.003$, Cohen's $d = 0.77$) bands compared to controls. Group differences in intrahemispheric coherence approached significance in the frontal-occipital ($p = 0.066$, Cohen's $d = 0.47$) and central-occipital ($p = 0.051$, Cohen's $d = 0.50$) regions in the beta band. In the right hemisphere, cannabis users exhibited greater coherence in the frontal-central regions in the delta ($p = 0.023$, Cohen's $d = 0.58$), theta ($p = 0.018$, Cohen's $d = 0.61$), alpha ($p = 0.021$, Cohen's $d = 0.58$), and beta ($p = 0.020$, Cohen's $d = 0.59$) bands. Cannabis users also exhibited reduced coherence in the parietal-occipital regions in the theta band compared to controls ($p = 0.031$, Cohen's $d = 0.55$; Fig. 4). Overall group differences found in both interhemispheric and intrahemispheric coherence are displayed in Fig. 5.

Functional connectivity

Two-tailed independent t -tests with Bonferroni correction for multiple comparisons on degree revealed a significantly increased mean degree in the left frontal region ($p = 0.048$, Cohen's $d = 0.50$) in the delta

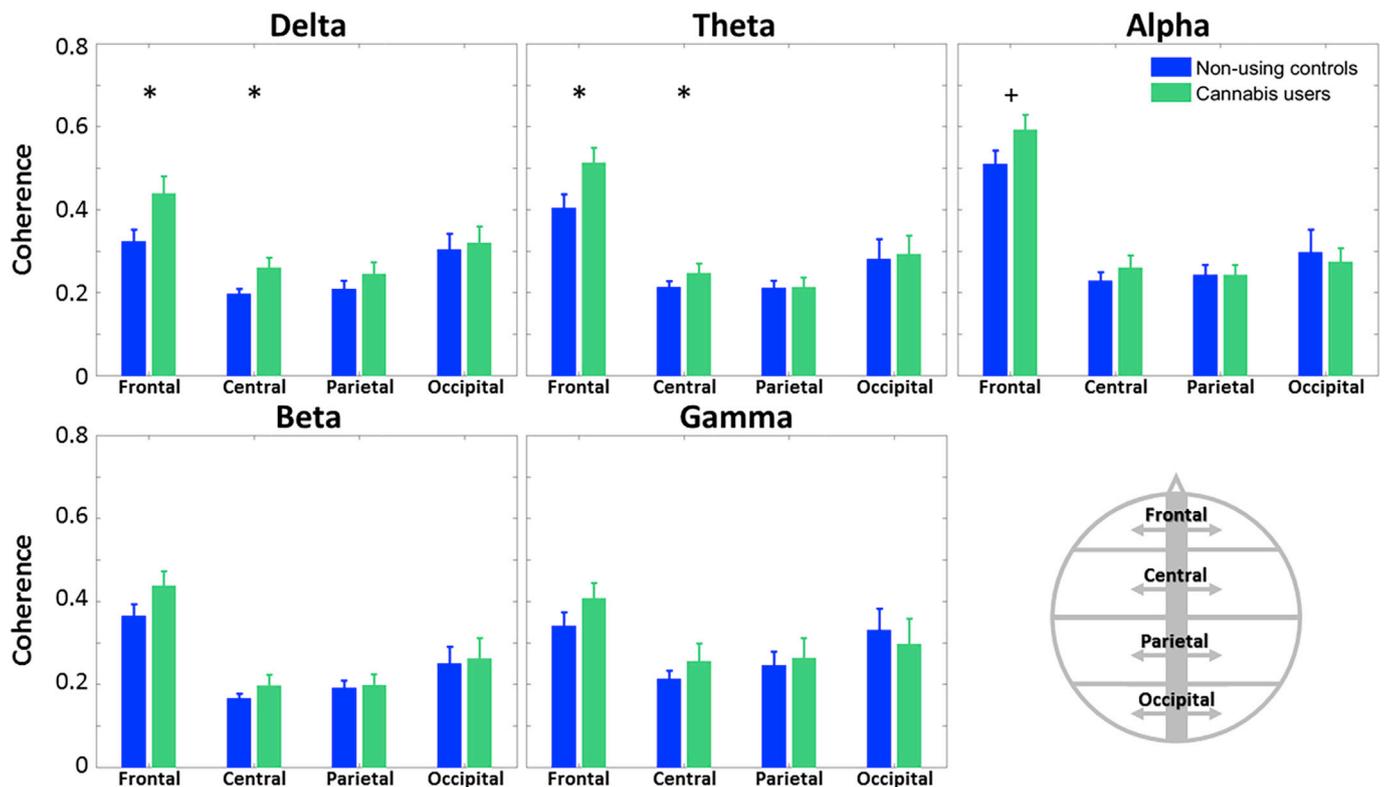


Fig. 3. Interhemispheric coherence. Cannabis users exhibited increased coherence between hemispheres in the delta and theta bands in both frontal and central regions compared to controls. The schematic in the bottom right represents the regions that were used to calculate the coherence. * indicates $p < 0.05$, + indicates $p < 0.08$, error bars indicate standard error.

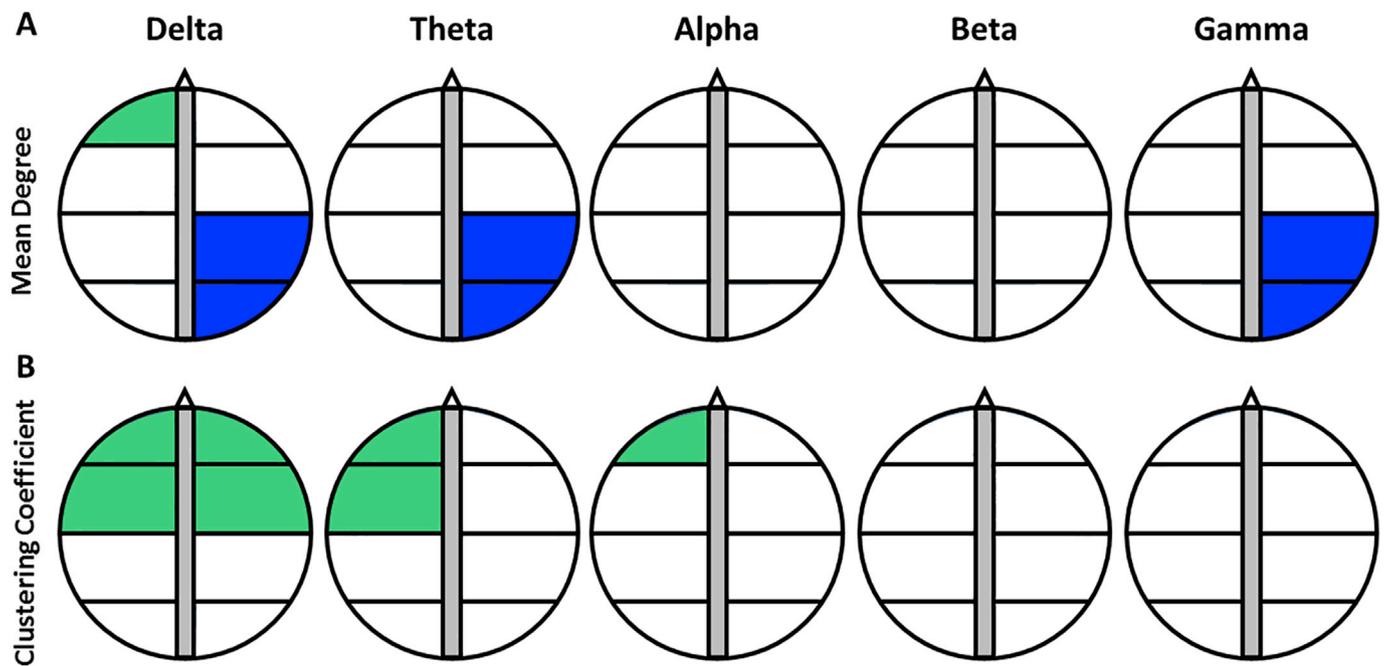


Fig. 6. Schematic of differences in functional connectivity measures. A) Cannabis users exhibited greater mean degree in the left frontal region in delta, but reduced degree in the right parietal and posterior regions in delta, theta, and gamma compared to controls. B) Cannabis users exhibited greater clustering coefficient in the frontal and central regions in delta, theta, and alpha bands compared to controls. Green represents cannabis users > control, blue represents control > cannabis users.

Correlations between cannabis use measures, spectral power, and functional connectivity

Spectral power

Cannabis use days was positively correlated with delta and theta in the LF region (delta: $r = 0.62$, $p = 0.032$; theta: $r = 0.62$, $p = 0.030$). The MPS score was negatively correlated with delta in the LC ($r = -0.64$, $p = 0.026$), LP ($r = -0.65$, $p = 0.021$), and LO ($r = -0.76$, $p = 0.004$) regions. There were no significant correlations with hours since last use or craving.

Functional connectivity measures

Cannabis use days was positively correlated with the clustering coefficient in theta in the LF ($r = 0.58$, $p = 0.049$) and LO ($r = 0.58$, $p = 0.046$) regions and in alpha in the LO region ($r = 0.58$, $p = 0.047$). The MPS score was positively correlated with degree in theta in the LF region ($r = 0.59$, $p = 0.042$) and clustering coefficient in alpha in the RP region ($r = 0.59$, $p = 0.042$). Craving was correlated with clustering coefficient in the gamma band in the LP ($r = 0.60$, $p = 0.038$), LO, ($r = 0.68$, $p = 0.015$), RF ($r = 0.64$, $p = 0.024$), and RC ($r = 0.59$, $p = 0.045$) regions. There were no significant correlations with hours since last use.

Discussion

Characterizing global resting state cortical activations and functional connectivity in cannabis users can provide insight into cortical network alterations associated with habitual cannabis use. This study examined resting state cortical dynamics in cannabis users by measuring EEG signals during resting state and calculated spectral power, spectral coherence, and functional connectivity measures. The findings suggest that: 1) cannabis users exhibited increased cortical activation during rest compared to controls (increased theta, beta, and gamma synchrony and reduced delta synchrony), 2) cannabis users exhibited greater coherence in the frontal regions compared to controls, 3) cannabis users exhibited significantly decreased mean degree in the posterior regions in the delta, theta, and gamma bands and increased clustering coefficient in the frontal regions in the delta, theta, and alpha bands compared to controls,

and 4) cannabis use variables were correlated with spectral power (specifically delta, theta, and alpha) and functional connectivity measures, indicating that EEG signals in specific frequencies may be electrophysiological signatures of cannabis use.

Cannabis users exhibited increased cortical activation compared to controls

Resting state activity in cannabis users was characterized as the inverse of typical frequency dynamics in that they exhibited decreased delta and increased theta, beta, and gamma. This trend in neural oscillations is typically associated with task-related EEG signals, suggesting that cannabis users exhibited increased cortical activation even when in rest. Similar patterns in resting state have been reported in heroin-dependent users (Franken et al., 2004), alcohol-dependent users (Bauer, 2001; Rangaswamy et al., 2002), and cocaine-dependent users (Costa and Bauer, 1997).

The overall spectral power results in this study are consistent with some previous studies that reported an increase in theta power (Struve et al., 1998) and decrease in delta (Struve et al., 1994, 1998, 1999), but are inconsistent with those that found a decrease in theta and beta power (Ilan et al., 2004; Böcker et al., 2009) and an increase in alpha power (Struve et al., 1994, 1998, 1999). These inconsistencies may arise due to differences in characteristics of cannabis users as there was a wide range of cannabis use reported within the samples in these studies. Additionally, the data in these studies were collected during differing states of intoxication, with some participants tested during acute intoxication, while others were abstinent users (long-term and short-term).

The increased cortical activation in cannabis users may reflect a loss of cortical refinement compared to non-using controls. This increased activity is in contrast to the decrease in activation observed in individuals with expertise (e.g., elite athletes) compared to novices (Haufler et al., 2000; Hatfield et al., 2004; Del Percio et al., 2009; Babiloni et al., 2010), individuals with increased working memory capacity (Rypma et al., 2002; Grabner et al., 2004), and individuals performing easier compared to difficult levels in a cognitive-motor task (Rietschel et al., 2012). Improved motor performance related to reduced cortico-cortical communication in frontal regions has also been reported (Gentili et al.,

2015). Together, these studies suggest that reduced cortical activation reflects increased neural efficiency and reduced effort. Specifically in cannabis users, Cortes-Briones and colleagues have reported increased cortical noise associated with acute THC during the baseline period preceding stimulus onset in an oddball task (Cortes-Briones et al., 2015). In this framework, the increased cortical activity combined with greater cortico-cortical communication of frontal regions exhibited by cannabis users in the present study may be associated with an increased engagement of executive functions. These factors may contribute to the loss of neural refinement (Gentili et al., 2015) and reflect the reduced cortical efficiency of a noisy brain.

The absence of a difference in alpha power between the groups was surprising given the differences in the other frequency bands. Desynchrony (i.e., attenuation) of alpha frequencies is associated with ongoing cognitive process related to a task (Pfurtscheller, 2001; Buzsaki, 2004), while synchronous alpha power has been related to reduced information processing and inhibition (Klimesch et al., 2007; Jerbi, 2010). Increased alpha power is typically prevalent during resting state, an observation that is further corroborated by simultaneous fMRI and EEG recordings that reveal a correlation between the default mode network and alpha power (Bonnard et al., 2016b). The absence of differences in alpha suggests alpha synchrony during eyes closed resting state in cannabis users that may reflect a compensatory mechanism to alleviate ongoing increased neural activity and prevent inhibition of cognitive processing (Klimesch, 1999). However, since alpha power was comparable to that of controls, it remains to be examined whether it is sufficient to alleviate effects of increased cortical activity.

Cannabis users exhibited greater cortico-cortical communication in the frontal regions

This is the first study to characterize global connectivity by comparing cortical interhemispheric and intrahemispheric coherence in cannabis users. Compared to controls, cannabis users exhibited greater cortico-cortical connectivity bilaterally in the frontal and central regions in the delta, theta, and alpha bands. Users also exhibited greater connectivity in the frontal-occipital regions and parietal-occipital regions in the beta band. These increases in cortico-cortical connectivity are consistent with the increased cortical activation revealed by spectral power and may thus be related to an inability to inhibit ongoing neural activity as described above. Neuroimaging studies suggest that cannabis users exert greater effort in the stop signal task to inhibit ongoing movement that is reflected in increased functional connectivity in the cortico-striatal network (Filbey and Yezhuvath, 2013) and the anterior cingulate cortex (Gruber and Yurgelun-Todd, 2005; Hester et al., 2009), suggesting an impairment in inhibitory control. Further, a reduction in cortico-cortical connectivity in frontal regions may suggest improved motor performance (Gentili et al., 2015), thus the increase found in cannabis users may indicate deficits in cognitive motor processing (Prashad and Filbey, 2017).

Increased coherence during resting state has been reported by Winterer and colleagues who examined EEG coherence in long-term abstinent and non-abstinent alcohol-dependent users and controls (Winterer et al., 2003). They found greater coherence in the alpha and beta frequencies in both groups of alcohol-dependent users in the temporal, parietal, and occipital regions. The authors suggest that these differences may be representative of a neural association of alcohol-dependence and are consistent with other studies in alcohol users (Michael et al., 1993). Similar increases in coherence during resting state have been found in abstinent heroin-dependent users who exhibited increased coherence in the frontal-occipital region in gamma frequencies compared to controls, but no interhemispheric differences (Franken et al., 2004). Our results are consistent with these studies as cannabis users exhibited increased coherence in the frontal-occipital and parietal-occipital regions in the beta frequencies compared to controls; however, we additionally found increased coherence in the frontal

regions in the delta, theta, and alpha frequencies. These differences suggest that there may be atypical electrophysiological signatures that are consistent across substances of abuse and those that are specific to substances. These specific differences between substances of abuse have been reported in long-term amphetamine-dependent users who exhibited decreased resting state coherence in posterior regions (Dafters et al., 1999). Kelly and colleagues reported a decrease in interhemispheric connectivity in resting state fMRI in cocaine-dependent users in prefrontal, frontal, medial premotor, and posterior parietal regions (Kelly et al., 2011). Studies have also found an increase in coherence in long-term abstinent alcohol- and heroin-dependent users (Winterer et al., 2003; Franken et al., 2004) suggesting that changes in coherence persist beyond cessation of use and should be further investigated in cannabis users, where long-term structural changes have been previously reported (Filbey et al., 2014).

These increases in cortico-cortical connectivity in the frontal regions were consistent with significantly decreased mean degree in the posterior regions in the delta, theta, and gamma bands in cannabis users compared to controls, suggesting reduced network density in the posterior region, and increased clustering coefficient in the frontal and central regions in the delta and theta frequencies. Ahmadlou and colleagues conducted a similar functional connectivity analysis on EEG coherence in methamphetamine-dependent users and reported an increased clustering coefficient and reduced mean path length in the gamma band, suggesting an overall increased hyper-synchronization between nearby electrode sites in gamma (Ahmadlou et al., 2013). Interestingly, Klumpers and colleagues have reported in a resting state fMRI study that acute THC administration had a differential effect on network connectivity, with both increased and decreased functional connectivity in regions with high densities of CB1 receptors (Klumpers et al., 2012). In an fMRI study examining the effects of acute administration of THC and cannabidiol (CBD) during an oddball task found that while administration of both THC and CBD decreased performance in the task, there was a differential effect on connectivity where THC administration reduced fronto-striatal connectivity, while CBD administration increased connectivity (Bhattacharyya et al., 2015).

A reduction in mean degree and increase in the clustering coefficient indicates a decline in long-range connections and thus communication within global networks (Latora and Marchiori, 2001). These long-range connections are important for typical development as they support integration of regions and allow for the segregation of networks (Fair et al., 2007). The disruption of long-range connections may be related to disorders and have been reported in ADHD via MRI and diffusion tensor imaging (Hill et al., 2003; Ashtari et al., 2005), schizophrenia via EEG (Uhlhaas et al., 2006), and autism via fMRI (Courchesne and Pierce, 2005; Just et al., 2007), but are yet to be examined in cannabis users. Studies have found that heavy cannabis users have reduced volume in the orbitofrontal cortex (OFC), but higher structural connectivity in tracts that innervate the OFC (Filbey et al., 2014). Others have corroborated changes in volume in cannabis users with reduced volume in the hippocampus (Matochik et al., 2005; Ashtari et al., 2011) and amygdala (Yücel et al., 2008), but increased volume in the cerebellum (Cousijn et al., 2012), as well as changes in white matter integrity (Arnone et al., 2008; Gruber et al., 2011).

Cannabis use variables were correlated with spectral power and functional connectivity

We found correlations between cannabis use measures and spectral power. Delta and theta were positively correlated with cannabis use days, while problems with cannabis use were negatively correlated with delta. These associations indicate that specific frequencies may be sensitive to cannabis use and may be relevant electrophysiological neural correlates for intoxication as well as cannabis use disorder severity. The inverse correlations between these frequencies and cannabis use measures suggest a differential effect of cannabis on cortical dynamics of

electrophysiological signals.

There were few correlations with the functional connectivity measures. Degree in the alpha band was correlated with the MPS score and the clustering coefficient in the theta and alpha bands was significantly correlated with cannabis use days and with craving in the gamma band. This association between spectral power and craving has also been reported in nicotine users in the delta band (Pripfl et al., 2014), suggesting that different electrophysiological signals may need to be identified for specific substances. Importantly, these frequency bands may be significant electrophysiological signatures of craving that can be examined in the context of cue-elicited craving paradigms. These paradigms have been studied with respect to neural response in cannabis users using fMRI (Filbey et al., 2014) as well as EEG studies that investigate repetitive transcranial magnetic stimulation (rTMS) as a mechanism to reduce craving in nicotine users (Li et al., 2013; Pripfl et al., 2014), but electrophysiological signals have not yet been associated with cannabis craving.

Limitations

The results from this study must be taken in the context of its limitations. Participants were required to be abstinent from cannabis use 24 h prior to the scheduled session to avoid effects of acute intoxication, making it unclear whether the present results reflect changes as a result of this short-term abstinence or an ongoing change due to cannabis use. However, of note, no significant correlation was found between spectral power and hours since last use, suggesting that EEG signals may not be sensitive to recent cannabis use. Nonetheless, the results suggest a significant influence of cannabis on electrophysiological signals. Future studies should examine differences between states of abstinence (long-term vs. short-term abstinence) and acute intoxication. This is particularly important given the persistence of changes even after long-term abstinence in alcohol- and heroin-dependent users (Winterer et al., 2003; Franken et al., 2004). Examining resting state electrophysiology in users with cannabis use disorder would also provide insight into changing cortical activity and will likely show greater differences compared to controls. While the current sample consisted of almost daily users (cannabis use of 70.8 ± 20.0 days in the preceding 90 days), few met criteria for cannabis abuse or dependence (current or lifetime; see Table 1).

The measure of functional connectivity used here was coherence, which is a linear measure of cortico-cortical communication and thus does not reflect any non-linear associations between signals. Accordingly, future studies would benefit from using additional measures, such as mutual information or synchronization likelihood, to further examine changes in resting state cortical networks and to overcome distortions from volume conduction. It is important to note that since the focus of these analyses was global cortico-cortical connectivity between regions, there may have been more localized differences in connectivity between specific electrodes that may have been undetected. Given the consistent findings in increased coherence in beta frequencies across substances, future studies should directly compare EEG resting state in different substances of abuse to further characterize general electrophysiological signatures of substance abuse and those specific to substances. These signatures may be indicative of neural markers that can be explored in future studies.

Conclusions

This study is the first to characterize global cortical activation and interhemispheric and intrahemispheric functional connectivity during resting state in cannabis users. Cannabis users exhibited an increase in cortical activation during resting state, suggesting alterations in synchrony of neural oscillations. This loss of neural refinement indicates a noisy brain and an impairment in inhibiting ongoing neural activity that may interrupt cognitive processing. A decrease in posterior network

degree and an increase in the clustering coefficient in frontal regions suggests changes in long-range communications that allow for cortico-cortical interactions between networks and may be related to cognitive impairments associated with cannabis use. Significant correlations were found between cannabis use measures and spectral power and functional connectivity, highlighting electrophysiological signals as relevant neural associations that may be essential in examining effects related to cannabis use. Importantly, the presence of these differences in cortical dynamics and associations with behavior necessitate further investigations into changes in cortical neural synchronies during task-related activity. This paper provides a first step towards the characterization of the changing patterns of resting state cortical networks in cannabis users that may lead to the understanding of the basis of cognitive impairments and the development of electrophysiological neural correlates that may prove valuable for tracking progression and efficacy of intervention strategies.

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Conflicts of interest

None.

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References

- Ahmadlou, M., Ahmadi, K., Rezaade, M., Azad-Marzabadi, E., 2013. Global organization of functional brain connectivity in methamphetamine abusers. *Clin. Neurophysiol.* 124, 1122–1131.
- Amiaz, R., Levy, D., Vainiger, D., Grunhaus, L., Zangen, A., 2009. Repeated high-frequency transcranial magnetic stimulation over the dorsolateral prefrontal cortex reduces cigarette craving and consumption. *Addiction* 104, 653–660.
- Arnone, D., Barrick, T.R., Chengappa, S., Mackay, C.E., Clark, C.A., Abou-Saleh, M.T., 2008. Corpus callosum damage in heavy marijuana use: preliminary evidence from diffusion tensor tractography and tract-based spatial statistics. *NeuroImage* 41, 1067–1074.
- Ashtari, M., Avants, B., Cyckowski, L., Cervellione, K.L., Roofeh, D., Cook, P., Gee, J., Sevy, S., Kumra, S., 2011. Medial temporal structures and memory functions in adolescents with heavy cannabis use. *J. Psychiatr. Res.* 45, 1055–1066.
- Ashtari, M., Kumra, S., Bhaskar, S.L., Clarke, T., Thaden, E., Cervellione, K.L., Rhinewine, J., Kane, J.M., Adesman, A., Milanaik, R., Maytal, J., Diamond, A., Szesko, P., Ardekani, B.A., 2005. Attention-deficit/hyperactivity disorder: a preliminary diffusion tensor imaging study. *Biol. Psychiatr.* 57, 448–455.
- Babiloni, C., Lizio, R., Marzano, N., Capotosto, P., Soricelli, A., Triggiani, A.I., Cordone, S., Gesualdo, L., Del Percio, C., 2016. Brain neural synchronization and functional coupling in Alzheimer's disease as revealed by resting state EEG rhythms. *Int. J. Psychophysiol.* 103, 88–102.
- Babiloni, C., Marzano, N., Infarinato, F., Iacoboni, M., Rizza, G., Aschieri, P., Cibelli, G., Soricelli, A., Eusebi, F., Del Percio, C., 2010. "Neural efficiency" of experts' brain during judgment of actions: a high-resolution EEG study in elite and amateur karate athletes. *Behav. Brain Res.* 207, 466–475.
- Bauer, L.O., 2001. Predicting relapse to alcohol and drug abuse via quantitative electroencephalography. *Neuropsychopharmacology* 25, 332.
- Bhattacharyya, S., Falkenberg, I., Martin-Santos, R., Atakan, Z., Crippa, J.A., Giampietro, V., Brammer, M., McGuire, P., 2015. Cannabinoid modulation of functional connectivity within regions processing attentional salience. *Neuropsychopharmacology* 40, 1343.
- Biswal, B.B., Klyen, J.V., Hyde, J.S., 1997. Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. *NMR Biomed.* 10, 165–170.
- Böcker, K.B., Hunault, C.C., Gerritsen, J., Kruidenier, M., Mensinga, T.T., Kenemans, J.L., 2009. Cannabinoid modulations of resting state EEG theta power and working memory are correlated in humans. *J. Cognit. Neurosci.* 22, 1906–1916.
- Bonnard, M., Chen, S., Gaychet, J., Carrere, M., Woodman, M., Giusiano, B., Jirsa, V., 2016a. Resting state brain dynamics and its transients: a combined TMS-EEG study. *Sci. Rep.* 6.
- Bonnard, M., Chen, S., Gaychet, J., Carrere, M., Woodman, M., Giusiano, B., Jirsa, V., 2016b. Resting state brain dynamics and its transients: a combined TMS-EEG study. *Sci. Rep.* 6.

- Bowyer, S.M., 2016. Coherence a measure of the brain networks: past and present. *Neuropsychiatr Electrophysiol.* 2.
- Broyd, S.J., Demanuele, C., Debener, S., Helps, S.K., James, C.J., Sonuga-Barke, E.J.S., 2009. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci. Biobehav. Rev.* 33, 279–296.
- Buzsáki, G., 2004. Neuronal oscillations in cortical networks. *Science* 304, 1926–1929.
- Chang, A.Y.W., Kuo, T.B.J., Chan, S.H.H., 1994. Power spectral analysis of electroencephalographic desynchronization induced by cocaine in the rat. *Neurosci. Lett.* 170, 175–178.
- Chen, A.C.N., Feng, W., Zhao, H., Yin, Y., Wang, P., 2008. EEG default mode network in the human brain: spectral regional field powers. *Neuroimage* 41, 561–574.
- Cortes-Briones, J.A., Cahill, J.D., Skosnik, P.D., Mathalon, D.H., Williams, A., Sewell, R.A., Roach, B.J., Ford, J.M., Ranganathan, M., D'Souza, D.C., 2015. The psychosis-like effects of $\Delta 9$ -tetrahydrocannabinol are associated with increased cortical noise in healthy humans. *Biol. Psychiatr.* 78, 805–813.
- Costa, L., Bauer, L., 1997. Quantitative electroencephalographic differences associated with alcohol, cocaine, heroin and dual-substance dependence. *Drug Alcohol Depend.* 46, 87–93.
- Courchesne, E., Pierce, K., 2005. Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. *Curr. Opin. Neurobiol.* 15, 225–230.
- Cousijn, J., Wiers, R.W., Ridderinkhof, K.R., van den Brink, W., Veltman, D.J., Goudriaan, A.E., 2012. Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls. *Neuroimage* 59, 3845–3851.
- Dafters, R.I., Duffy, F., O'Donnell, P.J., Bouquet, C., 1999. Level of use of 3, 4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence. *Psychopharmacology (Berlin)* 145, 82–90.
- Damoiseaux, J.S., Rombouts, S., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F., 2006. Consistent resting-state networks across healthy subjects. *Proc. Natl. Acad. Sci. Unit. States Am.* 103, 13848–13853.
- Deco, G., Jirsa, V., McIntosh, A.R., Sporns, O., Kötter, R., 2009. Key role of coupling, delay, and noise in resting brain fluctuations. *Proc. Natl. Acad. Sci. Unit. States Am.* 106, 10302–10307.
- Del Percio, C., Babiloni, C., Marzano, N., Iacoboni, M., Infarinato, F., Vecchio, F., Lizio, R., Aschieri, P., Fiore, A., Toràn, G., Gallamini, M., Baratto, M., Eusebi, F., 2009. "Neural efficiency" of athletes' brain for upright standing: a high-resolution EEG study. *Brain Res. Bull.* 79, 193–200.
- Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Meth.* 134, 9–21.
- Ehlers, C.L., Phillips, E., Gizer, I.R., Gilder, D.A., Wilhelmsen, K.C., 2010. EEG spectral phenotypes: heritability and association with marijuana and alcohol dependence in an American Indian community study. *Drug Alcohol Depend.* 106, 101–110.
- Fair, D.A., Dosenbach, N.U., Church, J.A., Cohen, A.L., Brahmbhatt, S., Miezin, F.M., Barch, D.M., Raichle, M.E., Petersen, S.E., Schlaggar, B.L., 2007. Development of distinct control networks through segregation and integration. *Proc. Natl. Acad. Sci. Unit. States Am.* 104, 13507–13512.
- Filbey, F.M., Aslan, S., Calhoun, V.D., Spence, J.S., Damaraju, E., Caprihan, A., Segall, J., 2014. Long-term effects of marijuana use on the brain. *Proc. Natl. Acad. Sci. Unit. States Am.* 111, 16913–16918.
- Filbey, F.M., Yezhuvath, U., 2013. Functional connectivity in inhibitory control networks and severity of cannabis use disorder. *Am. J. Drug Alcohol Abuse* 39, 382–391.
- Franken, I.H.A., Stam, C.J., Hendriks, V.M., van den Brink, W., 2004. Electroencephalographic power and coherence analyses suggest altered brain function in abstinent male heroin-dependent patients. *Neuropsychobiology* 49, 105–110.
- Fries, P., 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cognit. Sci.* 9, 474–480.
- Fujisawa, S., Buzsáki, G., 2011. A 4 Hz oscillation adaptively synchronizes prefrontal, VTA, and hippocampal activities. *Neuron* 72, 153–165.
- Gentili, R.J., Bradberry, T.J., Oh, H., Costanzo, M.E., Kerick, S.E., Contreras-Vidal, J.L., Hatfield, B.D., 2015. Evolution of cerebral cortico-cortical communication during visuomotor adaptation to a cognitive-motor executive challenge. *Biol. Psychol.* 105, 51–65.
- Gfroerer, J.C., Greenblatt, J.C., Wright, D.A., 1997. Substance use in the US college-age population: differences according to educational status and living arrangement. *Am. J. Publ. Health* 87, 62–65.
- Goldman, R.I., Stern, J.M., Engel Jr., J., Cohen, M.S., 2002. Simultaneous EEG and fMRI of the alpha rhythm. *Neuroreport* 13, 2487–2492.
- Grabner, R., Fink, A., Stipacek, A., Neuper, C., Neubauer, A., 2004. Intelligence and working memory systems: evidence of neural efficiency in alpha band ERD. *Cognit. Brain Res.* 20, 212–225.
- Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc. Natl. Acad. Sci. Unit. States Am.* 100, 253–258.
- Gruber, A.J., Hussain, R.J., O'Donnell, P., 2009. The nucleus accumbens: a switchboard for goal-directed behaviors. *PLoS One* 4, e5062.
- Gruber, S.A., Silveri, M.M., Dahlgren, M.K., Yurgelun-Todd, D., 2011. Why so impulsive? White matter alterations are associated with impulsivity in chronic marijuana smokers. *Exp. Clin. Psychopharmacol* 19, 231–242.
- Gruber, S.A., Yurgelun-Todd, D.A., 2005. Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation. *Cognit. Brain Res.* 23, 107–118.
- Gu, H., Salmeron, B.J., Ross, T.J., Geng, X., Zhan, W., Stein, E.A., Yang, Y., 2010. Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity. *Neuroimage* 53, 593–601.
- Hajós, M., Hoffmann, W.E., Kocsis, B., 2008. Activation of Cannabinoid-1 receptors disrupts sensory gating and neuronal oscillation: relevance to schizophrenia. *Biol. Psychiatr.* 63, 1075–1083.
- Hajós, N., Katona, I., Naiem, S.S., Mackie, K., Ledent, C., Mody, I., Freund, T.F., 2000. Cannabinoids inhibit hippocampal GABAergic transmission and network oscillations. *Eur. J. Neurosci.* 12, 3239–3249.
- Hatfield, B.D., Haufler, A.J., Hung, T.-M., Spalding, T.W., 2004. Electroencephalographic studies of skilled psychomotor performance. *J. Clin. Neurophysiol.* 21, 144–156.
- Haufler, A.J., Spalding, T.W., Santa Maria, D.L., Hatfield, B.D., 2000. Neuro-cognitive activity during a self-paced visuospatial task: comparative EEG profiles in marksmen and novice shooters. *Biol. Psychol.* 53, 131–160.
- Hayashi, T., Ko, J.H., Strafella, A.P., Dagher, A., 2013. Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving. *Proc. Natl. Acad. Sci. Unit. States Am.* 110, 4422–4427.
- Heishman, S.J., Evans, R.J., Singleton, E.G., Levin, K.H., Copersino, M.L., Gorelick, D.A., 2009. Reliability and validity of a short form of the marijuana craving questionnaire. *Drug Alcohol Depend.* 102, 35–40.
- Herning, R.I., Better, W., Cadet, J.L., 2008. EEG of chronic marijuana users during abstinence: relationship to years of marijuana use, cerebral blood flow and thyroid function. *Clin. Neurophysiol.* 119, 321–331.
- Herning, R.I., Glover, B.J., Koeppl, B., Phillips, R.L., London, E.D., 1994. Cocaine-Induced increases in EEG alpha and beta activity: evidence for reduced cortical processing. *Neuropsychopharmacology* 11, 1–9.
- Herning, R.I., Jones, R.T., Hooker, W.D., Mendelson, J., Blackwell, L., 1985. Cocaine increases EEG beta: a replication and extension of Hans Berger's historic experiments. *Electroencephalogr. Clin. Neurophysiol.* 1985, 470–477.
- Hester, R., Nestor, L., Garavan, H., 2009. Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. *Neuropsychopharmacology* 34, 2450–2458.
- Hill, D.E., Yeo, R.A., Campbell, R.A., Hart, B., Vigil, J., Brooks, W., 2003. Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. *Neuropsychology* 17, 496–506.
- Ilan, A.B., Smith, M.E., Gevins, A., 2004. Effects of marijuana on neurophysiological signals of working and episodic memory. *Psychopharmacology (Berlin)* 176, 214–222.
- Jann, K., Kottlow, M., Dierks, T., Boesch, C., Koenig, T., 2010. Topographic electrophysiological signatures of fMRI resting state networks. *PLoS One* 5, e12945.
- Jerbi, 2010. Exploring the electrophysiological correlates of the default-mode network with intracerebral EEG. *Front. Syst. Neurosci.*
- Just, M.A., Cherkassky, V.L., Keller, T.A., Kana, R.K., Minshew, N.J., 2007. Functional and anatomical cortical underconnectivity in autism: evidence from an executive function task and corpus callosum morphometry. *Cerebr. Cortex* 17, 951–961.
- Kelly, C., Zuo, X.-N., Gotimer, K., Cox, C.L., Lynch, L., Brock, D., Imperati, D., Garavan, H., Rotrosen, J., Castellanos, F.X., Milham, M.P., 2011. Reduced interhemispheric resting state functional connectivity in cocaine addiction. *Biol. Psychiatr.* 69, 684–692.
- Klimesch, W., 1999. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Res. Rev.* 29, 169–195.
- Klimesch, W., Sauseng, P., Hanslmayr, S., 2007. EEG alpha oscillations: the inhibition–timing hypothesis. *Brain Res. Rev.* 53, 63–88.
- Klumpers, L.E., Cole, D.M., Khalili-Mahani, N., Soeter, R.P., de Beek, E.T., Rombouts, S.A.R.B., van Gerven, J.M.A., 2012. Manipulating brain connectivity with $\delta 9$ -tetrahydrocannabinol: a pharmacological resting state fMRI study. *Neuroimage* 63, 1701–1711.
- Knyazev, G.G., 2007. Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neurosci. Biobehav. Rev.* 31, 377–395.
- Latora, V., Marchiori, M., 2001. Efficient behavior of small-world networks. *Phys. Rev. Lett.* 87.
- Laufs, H., Krakow, K., Sterzer, P., Eger, E., Beyerle, A., Salek-Haddadi, A., Kleinschmidt, A., 2003. Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. *Proc. Natl. Acad. Sci. Unit. States Am.* 100, 11053–11058.
- Leung, L.S., Yim, C.C., 1993. Rhythmic delta-frequency activities in the nucleus accumbens of anesthetized and freely moving rats. *Can. J. Physiol. Pharmacol.* 71, 311–320.
- Li, X., Hartwell, K.J., Owens, M., LeMatty, T., Borckardt, J.J., Hanlon, C.A., Brady, K.T., George, M.S., 2013. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex reduces nicotine cue craving. *Biol. Psychiatr.* 73, 714–720.
- Ma, N., Liu, Y., Li, N., Wang, C.-X., Zhang, H., Jiang, X.-F., Xu, H.-S., Fu, X.-M., Hu, X., Zhang, D.-R., 2010. Addiction related alteration in resting-state brain connectivity. *Neuroimage* 49, 738–744.
- Mantini, D., Perrucci, M.G., Del Gratta, C., Romani, G.L., Corbetta, M., 2007. Electrophysiological signatures of resting state networks in the human brain. *Proc. Natl. Acad. Sci. Unit. States Am.* 104, 13170–13175.
- Matochik, J.A., Eldreth, D.A., Cadet, J.-L., Bolla, K.I., 2005. Altered brain tissue composition in heavy marijuana users. *Drug Alcohol Depend.* 77, 23–30.
- Michael, A., Mirza, K.A.H., Mukundan, C.R., Channabasavanna, S.M., 1993. Interhemispheric electroencephalographic coherence as a biological marker in alcoholism. *Acta Psychiatr. Scand.* 87, 213–217.
- Miller, K.J., Weaver, K.E., Ojemann, J.G., 2009. Direct electrophysiological measurement of human default network areas. *Proc. Natl. Acad. Sci. Unit. States Am.* 106, 12174–12177.
- Newton, T.F., Cook, I.A., Kalechstein, A.D., Duran, S., Monroy, F., Ling, W., Leuchter, A.F., 2003. Quantitative EEG abnormalities in recently abstinent methamphetamine dependent individuals. *Clin. Neurophysiol.* 114, 410–415.

- Nunez, P.L., 2000. Toward a quantitative description of large-scale neocortical dynamic function and EEG. *Behav. Brain Sci.* 23, 371–398.
- Pfurtscheller, G., 2001. Functional brain imaging based on ERD/ERS. *Vis. Res.* 41, 1257–1260.
- Polunina, A.G., Davydov, D.M., 2004. EEG spectral power and mean frequencies in early heroin abstinence. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 28, 73–82.
- Prashad, S., Filbey, F.M., 2017. Cognitive motor deficits in cannabis users. *Curr Opin Behav Sci.* 13, 1–7.
- Pripfl, J., Tomova, L., Riečanský, I., Lamm, C., 2014. Transcranial magnetic stimulation of the left dorsolateral prefrontal cortex decreases cue-induced nicotine craving and EEG delta power. *Brain Stimulat* 7, 226–233.
- Raichle, M.E., 2011. The restless brain. *Brain Connect.* 1, 3–12.
- Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. *Proc. Natl. Acad. Sci. Unit. States Am.* 98, 676–682.
- Rangaswamy, M., Porjesz, B., Chorlian, D.B., Wang, K., Jones, K.A., Bauer, L.O., Rohrbaugh, J., O'connor, S.J., Kuperman, S., Reich, T., others, 2002. Beta power in the EEG of alcoholics. *Biol. Psychiatr.* 52, 831–842.
- Reid, M.S., Flammino, F., Bryant, H., Nilsen, D., Pritchep, L.S., 2006. Topographic imaging of quantitative EEG in response to smoked cocaine self-administration in humans. *Neuropsychopharmacology* 31, 872.
- Reid, M.S., Pritchep, L.S., Ciple, D., O'Leary, S., Tom, M., Howard, B., Rotrosen, J., John, E.R., 2003. Quantitative electroencephalographic studies of cue-induced cocaine craving. *Clin. Electroencephalogr.* 34, 110–123.
- Rietschel, J.C., Miller, M.W., Gentili, R.J., Goodman, R.N., McDonald, C.G., Hatfield, B.D., 2012. Cerebral-cortical networking and activation increase as a function of cognitive-motor task difficulty. *Biol. Psychol.* 90, 127–133.
- Robbe, D., Montgomery, S.M., Thome, A., Rueda-Orozco, P.E., McNaughton, B.L., Buzsáki, G., 2006. Cannabinoids reveal importance of spike timing coordination in hippocampal function. *Nat. Neurosci.* 9, 1526–1533.
- Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage* 52, 1059–1069.
- Rypma, B., Berger, J.S., D'Esposito, M., 2002. The influence of working-memory demand and subject performance on prefrontal cortical activity. *J. Cognit. Neurosci.* 14, 721–731.
- Scheeringa, R., Petersson, K.M., Kleinschmidt, A., Jensen, O., Bastiaansen, M.C.M., 2012. EEG alpha power modulation of fMRI resting-state connectivity. *Brain Connect.* 2, 254–264.
- Schnitzler, A., Gross, J., 2005. Normal and pathological oscillatory communication in the brain. *Nat. Rev. Neurosci.* 6, 285–296.
- Sobell, L.C., Sobell, M.B., 1992. Timeline follow-back. In: Litten, R.Z., Allen, J.P. (Eds.), *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods*. Humana Press, Totowa, NJ, pp. 41–72.
- Srinivasan, R., Nunez, P.L., Silberstein, R.B., 1998. Spatial filtering and neocortical dynamics: estimates of EEG coherence. *IEEE Trans. Biomed. Eng.* 45, 814–826.
- Stephens, R.S., Babor, T.F., Kadden, R., Miller, M., 2002. The Marijuana Treatment Project: rationale, design and participant characteristics. *Addiction* 97, 109–124.
- Stoffers, D., Bosboom, J.L.W., Deijen, J.B., Wolters, E.C., Berendse, H.W., Stam, C.J., 2007. Slowing of oscillatory brain activity is a stable characteristic of Parkinson's disease without dementia. *Brain* 130, 1847–1860.
- Stoffers, D., Bosboom, J.L.W., Deijen, J.B., Wolters, E.C., Stam, C.J., Berendse, H.W., 2008. Increased cortico-cortical functional connectivity in early-stage Parkinson's disease: an MEG study. *Neuroimage* 41, 212–222.
- Struve, F.A., Patrick, G., Straumanis, J.J., Fitz-Gerald, M.J., Manno, J.E., 1998. Possible EEG sequelae of very long duration marijuana use: pilot findings from topographic quantitative EEG analyses of subjects with 15 to 24 years of cumulative daily exposure to THC. *Clin. Electroencephalogr.* 29, 31–36.
- Struve, F.A., Straumanis, J.J., Patrick, G., 1994. Persistent topographic quantitative EEG sequelae of chronic marijuana use: a replication study and initial discriminant function analysis. *Clin. Electroencephalogr.* 25, 63–75.
- Struve, F.A., Straumanis, J.J., Patrick, G., Leavitt, J., Manno, J.E., Manno, B.R., 1999. Topographic quantitative EEG sequelae of chronic marijuana use: a replication using medically and psychiatrically screened normal subjects. *Drug Alcohol Depend.* 56, 167–179.
- Sutherland, M.T., McHugh, M.J., Pariyadath, V., Stein, E.A., 2012. Resting state functional connectivity in addiction: lessons learned and a road ahead. *Neuroimage* 62, 2281–2295.
- Uhlhaas, P.J., Linden, D.E.J., Singer, W., Haenschel, C., Lindner, M., Maurer, K., Rodriguez, E., 2006. Dysfunctional long-range coordination of neural activity during gestalt perception in schizophrenia. *J. Neurosci.* 26, 8168–8175.
- Wang, X.-J., Buzsáki, G., 1996. Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *J. Neurosci.* 16, 6402–6413.
- Whittington, M.A., Traub, R.D., Jefferys, J.G.R., 1995. Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation. *Nature* 373, 612–615.
- Winterer, G., Enoch, M.-A., White, K.V., Saylan, M., Coppola, R., Goldman, D., 2003. EEG phenotype in alcoholism: increased coherence in the depressive subtype. *Acta Psychiatr. Scand.* 108, 51–60.
- Yücel, M., Solowij, N., Respondek, C., Whittle, S., Fornito, A., Pantelis, C., Lubman, D.I., 2008. Regional brain abnormalities associated with long-term heavy cannabis use. *Arch. Gen. Psychiatr.* 65, 694–701.
- Zhu, X., Cortes, C.R., Mathur, K., Tomasi, D., Momenan, R., 2017. Model-free functional connectivity and impulsivity correlates of alcohol dependence: a resting-state study: functional connectivity and impulsivity correlates of alcohol dependence. *Addiction Biol.* 22, 206–217.