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Original Paper

Cannabis-induced altered states of consciousness are associated with specific dynamic brain connectivity states

Journal of Psychopharmacology
2019, Vol. 33(7) 811–821
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DOI: 10.1177/0269881119849814
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Abstract

Background: Cannabis, and specifically one of its active compounds delta-9-tetrahydrocannabinol in recreational doses, has a variety of effects on cognitive processes. Most studies employ resting state functional magnetic resonance imaging techniques to assess the stationary effects of cannabis and to-date one report addressed the impact of delta-9-tetrahydrocannabinol on the dynamics of whole-brain functional connectivity.

Methods: Using a repeated-measures, within-subjects design, 19 healthy occasional cannabis users (smoking cannabis ⩽2 per week) underwent resting state functional magnetic resonance imaging scans. Each subject underwent two scans: in the intoxicated condition, shortly after smoking a cannabis cigarette, and in the non-intoxicated condition, with the subject being free from cannabinoids for at least one week before. All sessions were randomized and performed in a four-week interval. Data were analysed employing a standard independent component analysis approach with subsequent tracking of the functional connectivity dynamics, which allowed six connectivity clusters (states) to be individuated.

Results: Using standard independent component analysis in resting state functional connectivity, a group effect was found in the precuneus connectivity. With a dynamic independent component analysis approach, we identified one transient connectivity state, characterized by high connectivity within and between auditory and somato-motor cortices and anti-correlation with subcortical structures and the cerebellum that was only found during the intoxicated condition. Behavioural measures of the subjective experiences of changed perceptions and tetrahydrocannabinol plasma levels during intoxication were associated with this state.

Conclusions: With the help of the dynamic connectivity approach we could elucidate neural correlates of the transitory perceptual changes induced by delta-9-tetrahydrocannabinol in cannabis users, and possibly identify a biomarker of cannabis intoxication.

Keywords

Cannabis, tetrahydrocannabinol, altered states of consciousness, resting state networks, dynamic functional connectivity

Introduction

Cannabis and one of its active compounds, delta-9-tetrahydrocannabinol (Δ-9-THC), are known for a variety of general and specific effects on brain activity (Ashton, 2001). Cannabis intoxication induces experiences such as euphoria, relaxation, enhanced sensations, time perception changes, disruption in short-term memory and flow of thinking (for a review see Iversen, 2003). However, the usual and most noticeable effect is characterized by the intensification of ordinary sensory experiences and increased lucidity of perception (Tart, 1990). Such states are often referred to as altered states of consciousness, which are defined as a deviation from the normal and regular state of mind into hyper- and/or hypo-excitation states (Sayin, 2012). The psychotropic effects may vary both across and within individuals: even the same person, at the same doses, may develop several distinct experiences (Atakan et al., 2013; Musty et al., 1995).

Despite extensive neuroimaging research, it is still unclear how cannabis affects the healthy brain. The majority of studies deal with cognitive processes focusing on task-related activities in cannabis-intoxicated conditions (Bhattacharyya et al., 2012a; Crean et al., 2011). In a series of studies with recreational users, various brain structures responded differently to cognitive tasks in intoxicated as opposed to non-intoxicated condition. Specifically, it was demonstrated that cannabis use is associated with altered attentional salience attribution (Bhattacharyya et al.,

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2015) and brain reward circuitry (Fisher et al., 2014), and also with increased connectivity in the sensorimotor networks (Klumpers et al., 2012).

The effects of cannabis on the implicit (e.g. not task-related) processes of the brain can be studied by the exploration of resting state functional connectivity (FC). The technique assesses functionally-related patterns of neural activity by delineating the architecture of functional brain networks (Calhoun et al., 2002; Damoiseaux et al., 2006, Smith et al., 2009). Some studies assessed resting state FC in samples of adults and adolescents, usually measuring stationary functional connectivity in cannabis smokers versus controls, finding the activation mostly in the frontal and parietal cortices, cingulate gyrus, precentral gyrus, and reduced functional network connectivity in temporal regions (Cheng et al., 2014; Filbey et al., 2018a; Houck et al., 2013; Orr et al., 2013; Thijssen et al., 2017). However, the results were not consistent due to the different methodologies employed.

Univariate and multivariate approaches applied to the resting state data typically generate a static picture of the brain connectivity; however, it is reasonable to expect that the FC will exhibit variations over time. Indeed, it is well established that the individuals *per se* are freely engaged in several types of resting activity, such as imagery or inner language etc. It can be hypothesized that in the intoxicated condition these experiences are considerably enhanced by the above-mentioned effects of cannabis, which may increase the variability of the FC states. Only one study examined the dynamic functional connectivity in cannabis users: Vergara et al., assessing the effect on resting state FC of several substances in a large sample, showed that marijuana smokers more frequently displayed a specific connectivity state characterized by high correlation within somato-motor and visual networks, and precuneus (Vergara et al., 2018).

Although these studies assessed resting state FC in cannabis users, their design does not help us to understand to what extent resting state FC is modified during cannabis intoxication, which can only be addressed through a within-subjects design.

In the present study, we aimed at investigating whole-brain resting state FC during cannabis intoxication by utilizing both stationary and dynamic connectivity approaches in a within-subjects design, in order to detect the effects on FC states of cannabis intoxication. We also expected that subjective experiences of the intoxication would correspond to specific FC states after smoking cannabis.

Methods

Design of the study

A repeated-measures, within-subjects design was applied in two randomized sessions. Each of the participants underwent two resting state functional magnetic resonance imaging (rsfMRI) scans, in the cannabis intoxicated and in the non-intoxicated condition. The two scanning sessions were randomized and performed with a four-week interval. The study protocol was in compliance with the Declaration of Helsinki and was approved by the Ethic Committee of the Prague Psychiatric Centre, Prague/National Institute of Mental Health, Czech Republic and the Ministries of Internal Affairs, and Health, Czech Republic. All of the participants were provided with oral and written information about the study and signed an informed consent form.

Participants

Twenty-four subjects were recruited via a public advertisement and consented to participate in the study. The inclusion criteria for recreational cannabis users were: cannabis use at least once a month but twice a week maximum, right-handedness confirmed by the Edinburgh Handedness Inventory. Exclusion criteria were a history of psychiatric disease and use of psychotropic medications, current drug/alcohol abuse/dependence, a severe health condition and contraindications for functional magnetic resonance imaging (fMRI) assessment. The subjects were not allowed to use cannabis products one week before the scanning, and asked not to use alcohol, nicotine or caffeine products just before the scanning. Absence of cannabis metabolites was confirmed by blood tests immediately before both scanning sessions. Specifically, we determined the primary active cannabinoid Δ-9-THC and its active metabolite 11-hydroxy-THC (11-OH-THC), inactive metabolite THC carboxylic acid (THC-COOH) and cannabidiol (CBD) (the method is referenced below). The subjects were also instructed to get a sufficient amount of sleep before the experiment. Five cannabis recreational users were excluded due to either non-optimal fMRI data acquisition due to movement artefacts, or positive blood tests for cannabis/alcohol in the baseline blood draw. Therefore, the final sample included 19 healthy right-handed individuals, native Czech speakers (7 males/12 females; age 26.4±4.8 years).

Procedure

The subjects were randomized to the two rsfMRI scanning sessions in the intoxicated and non-intoxicated conditions. The second session took place after a four-week interval. In the intoxication session, 30 min prior to the rsfMRI scanning the subjects smoked a cannabis cigarette. Each subject smoked their 'usual joint': a dose of his/her own preference of his/her own cannabis sample; thus, a variety of species, strains and growing methods was employed. This technique was used to improve the ecological validity of the study and prevent an either too weak or too strong effect.

Biochemical and behavioural measurements

In order to obtain psychoactive phytocannabinoids plasma levels in the intoxicated condition, a blood sample was taken prior to smoking in order to check for positive cannabis metabolite values, which were an exclusion criterion, and after the rsfMRI session. The employed phytocannabinoid values were calculated by subtracting the baseline values from those obtained after intoxication. Primary active cannabinoid Δ-9-THC, its active metabolite 11-OH-THC, inactive metabolite THC-COOH and CBD concentrations were obtained from 1 mL of blood serum by an in-house developed and subsequently certified gas chromatography-mass spectrometry (GC-MS) method (certified by the Police Presidium of the Czech Republic, ref. no.: PPR-31123-7/CJ-2015-990530/record no.: 16/2015). The lower limit of quantification and limit of detection (LOD) were 1 ng/mL. For the purpose of this study, we only employed Δ-9-THC blood levels (for details see the Supplementary Material).

The revised version self-report Standardized Psychometric Assessment of Altered States of Consciousness in Humans (Dittrich) questionnaire (Bravermanova et al., 2018; Dittrich,

Table 1. Biochemical and behavioural measurements in intoxicated (Intox) and non-intoxicated (Non-intox) conditions.

	Intox	Non-intox	$t/\chi 2$	df	p
Cannabinoid serum content					
THC (ng/mL)	1.91 (1.47)	0 (0)	5.669	18	<0.001
CBD (ng/mL)	0.03 (0.09)	0 (0)	1.230	18	0.236
OH-THC (ng/mL)	0.39 (0.46)	0 (0)	3.496	18	0.003
THC-COOH (ng/mL)	5.21 (3.49)	0 (0)	6.161	18	<0.001
ASC scores					
AIA	3.6 (2.4)	1.7 (1.2)	3.071	18	0.007
OSE	2.5 (1.8)	1.3 (1.2)	2.522	18	0.021
VUS	2.3 (2.5)	0.7 (1.0)	2.378	18	0.029
VWB	2.8 (2.1)	1.1 (0.8)	3.373	18	0.003

AIA: 'Dread of ego dissolution'; ASC: altered states of consciousness; CBD: cannabidiol; OH-THC: 11-hydroxy-THC; OSE: 'Oceanic boundlessness'; THC: tetrahydrocannabinol; THC-COOH: THC carboxylic acid; VUS: 'Visionary restructuralization', VWB: Scale summarizing other experiences.

1998), a rating scale measuring altered states of consciousness (ASC), was administered after the scanning in the intoxicated and non-intoxicated conditions in order to evaluate the subjective experiences. The questionnaire included three primary dimensions such as 'Dread of ego dissolution' (AIA), which refers to experiences of derealization, fearful sensations of ego-distortions and loss of control; 'Oceanic boundlessness' (OSE), which can be experienced as a loss of boundaries, altered sense of the body and time; 'Visionary restructuralization' (VUS), which accounts for sensory illusions, synaesthesia, ideas of reference, etc. The questionnaire also included a subscale summarizing all other experiences not included in the other scales (VWB) such as spiritual experiences, fluctuations of emotions, etc. This questionnaire has been proved to have desirable psychometric properties with discriminant and convergent validities in assessing drug induced ASCs (Studerus et al., 2010).

The biochemical and behavioural measurements in the intoxicated and non-intoxicated conditions are shown in Table 1.

Data acquisition

Imaging was performed on a 3T Siemens Tim Trio scanner equipped with a standard 12-channel head coil. For the localization of the activated voxels and fMRI data preprocessing the subjects were scanned using a structural T1-weighted (T1W) 3D-MP-RAGE sequence with repetition time (TR) of 2300 ms, echo time (TE) 4.6 ms, bandwidth 130 Hz/pixel and with isotropic spatial resolution of $1\times1\times1$ mm^3.

Functional images were measured during nine minutes in the eyes-closed mode with a gradient echo echo-planar sequence (GRE-EPI, TR=2000 ms, TE=30 ms, flip angle 70°, voxel size of $3\times3\times3$ mm, field of view (FOV)=168 mm×192 mm, an acquisition matrix size 64×64, bandwidth (BW)=2232 Hz/pixel, each volume with 38 axial slices without an inter-slice gap, a total of 270 volumes).

Data pre-processing

Functional images were pre-processed using an automated pipeline in SPM 8 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm). The first four image volumes were removed to avoid T1 equilibration effects. Pre-processing included realignment, slice-timing correction using the middle slice as a reference frame. Subsequently, the data were warped to a Montreal Neurological Institute (MNI) template, resliced to 3 mm^3 isotropic voxels and smoothed with a Gaussian kernel (full width at half maximum (FWHM)=5 mm). Voxel time courses were variance normalized (at each voxel, the time series were linearly detrended and converted to z-scores) prior to the group analysis in order to improve the decomposition of the subcortical sources. The conditions were also tested for head motion by application of the mean frame-wise displacement method, showing no differences between the groups (t=−1.2467, p=0.229).

Group independent component analysis (ICA) and post-processing

Data were decomposed into functional networks using a group-level spatial ICA as implemented in the GIFT toolbox. Using a standard principal component analysis (PCA), a subject-specific data reduction step was applied to reduce the number of components from 100 components (Kiviniemi et al, 2009). The Infomax ICA algorithm (Langlois et al., 2010) was repeated 20 times in ICASSO (Himberg et al., 2003) in order to aggregate spatial maps as the models of the component clusters. Subject-specific spatial maps and time courses were acquired using back reconstruction (Calhoun et al., 2001) based on PCA compression and projection, implemented in GIFT software.

We obtained one sample t-test for each spatial map across all subjects and thresholded these maps to obtain the regions of peak activation clusters for the component, together with the mean power spectra of the corresponding time series. We characterized a subset of 100 independent component networks (ICNs) corresponding to known anatomical localization. Finally, 49 ICNs out of the 100 components free of artefacts were thus labelled as components of interest. These components had an activation peak in grey matter and minimal or no overlap with the vascular, ventricular or edge regions that correspond to head motion. We also ensured that the mean power spectra of the selected ICN time courses predominantly showed low frequency spectral power. The component time series underwent additional post-processing to remove the remaining noise sources. The post-processing steps included: detrending, regression of six motion parameters, despiking, and band pass filtering (0.01–0.15 Hz). The cluster stability quality (Iq) index of these ICNs over 20 ICASSO runs was very high (Iq⩾0.9) for all of the components.

FC analysis

The FC analysis pipeline was adopted from Allen et al. (2014). The components of interest were partitioned into sub-cortical, auditory, visual, sensorimotor, cognitive control, default-mode and cerebellar components and reordered so that the mean FC matrix was organized in a modular way. See the Supplementary Material Figures 1–6 for spatial maps and coordinates (Table 2) for more detailed information on each component.

Multivariate analysis of covariance (MANCOVA) was applied to assess the effects of the condition in the 49 preselected components of interest. We used Δ-9-THC plasma level as a covariate. Subsequent univariate tests (t-tests) were performed

using a reduced model and the results were obtained along with the false discovery rate (FDR) with a multiple correction threshold of 0.05.

To study the FC dynamics, we applied a dynamic connectivity approach by computing windowed correlation matrices from component time courses. To this end, we used the k-means clustering algorithm (Loyd, 1982) as implemented in the Group ICA of fMRI Toolbox (GIFTv3.0b). This method consists of clustering the functional connectivity matrices from all consecutive segments of the data (using a sliding window) based on similarity among the matrices (quantified by the L1-distance function also known as the Manhattan distance) and applied it to all of the data (all subjects, both in the intoxicated and non-intoxicated condition). For more information on the method and its validation see the documentation available at http://mialab.mrn.org/software/gift/documentation.html and the method introduction in Allen et al. (2012). This method provides a finite (small) set of connectivity states/clusters and a label for each of the temporal windows corresponding to the estimated state/cluster this segment belongs to. The time series of these state assignments, available for each subject both in the intoxicated and non-intoxicated state, were the subject of further analysis. The dwell time (total duration) in each state was then quantified in the intoxicated and non-intoxicated condition for each subject, and averaged across the subjects within a given condition.

To assess the significance of difference in the mean state duration in the two conditions, the observed differences were compared with a null distribution generated by a permutation procedure (switching the assignment of two conditions in subjects randomly selected with a probability of 50%). A total of 10,000 random permutations were generated for the empirical null distribution.

The association between individual state duration and Δ-9-THC levels or items of the ASC questionnaire was quantified using Spearman's correlation coefficient. Its significance was tested with a permutation test with 10,000 random permutations of the original data (random permutation of the behavioural variable).

Results

Stationary connectivity

MANCOVA on the spatial maps and time-courses of the ICNs representing sub-cortical, auditory, visual, somatomotor, cognitive control, default-mode and cerebellar components in the intoxicated and non-intoxicated conditions showed no effect of condition. Univariate analysis revealed the differences in the connectivity of the precuneus, being increased between multiple ICNs in sensory cortices (auditory, somatomotor and visual) in intoxicated condition. FC in intoxication and non-intoxication and the differences between conditions are depicted (Figure 1). The FDR-corrected threshold (0.05) on the colour bar is represented by the effect size in the range from −0.52 to 0.6.

Dynamic connectivity

To explore the possibility that certain connectivity patterns may be quasi-stable, that they reoccur over time and are represented in several subjects, we applied k-means clustering to the windowed FC matrices and identified six different clusters, representing the states that emerge during measured rsfMRI (Figure 2). Figure 2 shows the connectivity matrices of clustered ICNs, defined as 'states', identified with group ICA over all subjects and all conditions. The FC states are numbered from 1–6 in the order of emergence averaged among patients during the scans.

States 1 and 4 showed commonly strong positive correlations (correlation coefficient above 0.5) among auditory, visual and somatomotor cortices together with anticorrelations (negative correlations) with subcortical structures. In state 1, additional anticorrelations were found between the above-mentioned sensory cortices and the insula cortex and cerebellum, whereas state 4 included strong correlations between sensory cortices and part of the default mode nodes, specifically in the posterior cingulate cortex. State 6 distinguished itself from states 1 and 4 with respect to strong connections between ICNs within auditory and somatomotor cortices and anticorrelation with subcortical structures, specifically with the caudate nucleus. State 2 occurred in 40% of the total duration of the scans and is characterized by weak correlations (correlation coefficient in the rage from −0.2 to +0.2) between and within each ICN subcategory. State 5 is similar to state 2 except for connectivity within auditory and visual cortices and anticorrelations with subcortical structures, not reaching the significant threshold. State 3 showed random correlations across the brain, as well as the formed chunk within the somatomotor cortex.

Notable negative correlations were detected in the activity of the fusiform gyrus and sensory cortices in states 1, 3, 4 and 6.

As a further step, in order to evaluate the differences in transitions of the connectivity states over time in the intoxicated and non-intoxicated conditions, we plotted the six clustered states for each subject for the total duration of the magnetic resonance imaging (MRI) scans (Figure 3). Figure 3 shows the unique pattern of the interchanging states in each of the participants by means of cluster variability.

Applying the Bonferroni correction for multiple comparison among the tests yielded significant (corrected) differences in states 1, 2, 3 and 6. The corresponding *t*-statistics (note that we actually used non-parametric, permutation-based inferences) were 3.84 for state 6, 2.51 for state 1, −2.95 for state 2, −2.72 for state 3; with df=18 corresponding to results significant at $p<0.05$ also for the parametric test. Taken together, on a group level, state 6 only occurred during the intoxicated condition. State 1 was more common in the intoxicated condition ($p=0.008$), whereas state 2 and 3 were more common in the non-intoxicated condition ($p=0.042$; $p=0.006$) (Figure 4).

Biochemical and behavioural correlations

Δ-9-THC plasma levels and all ASC item scores were higher in the intoxicated vs non-intoxicated condition (Table 1). Δ-9-THC plasma levels correlated with the duration of state 6 ($r=0.45$, $p=0.025$) and inversely correlated with the duration of state 2 ($r=-0.42$, $p=0.037$). Similarly to Δ-9-THC plasma levels, the ASC item 'Oceanic Boundlessness' score positively correlated with the duration of state 6 ($r=0.46$, $p=0.022$) and inversely correlated with the duration of state 2 ($r=-0.40$, $p=0.0441$).

Discussion

In the present study, we found an association between the use of cannabis, its effects on states of consciousness and whole-brain

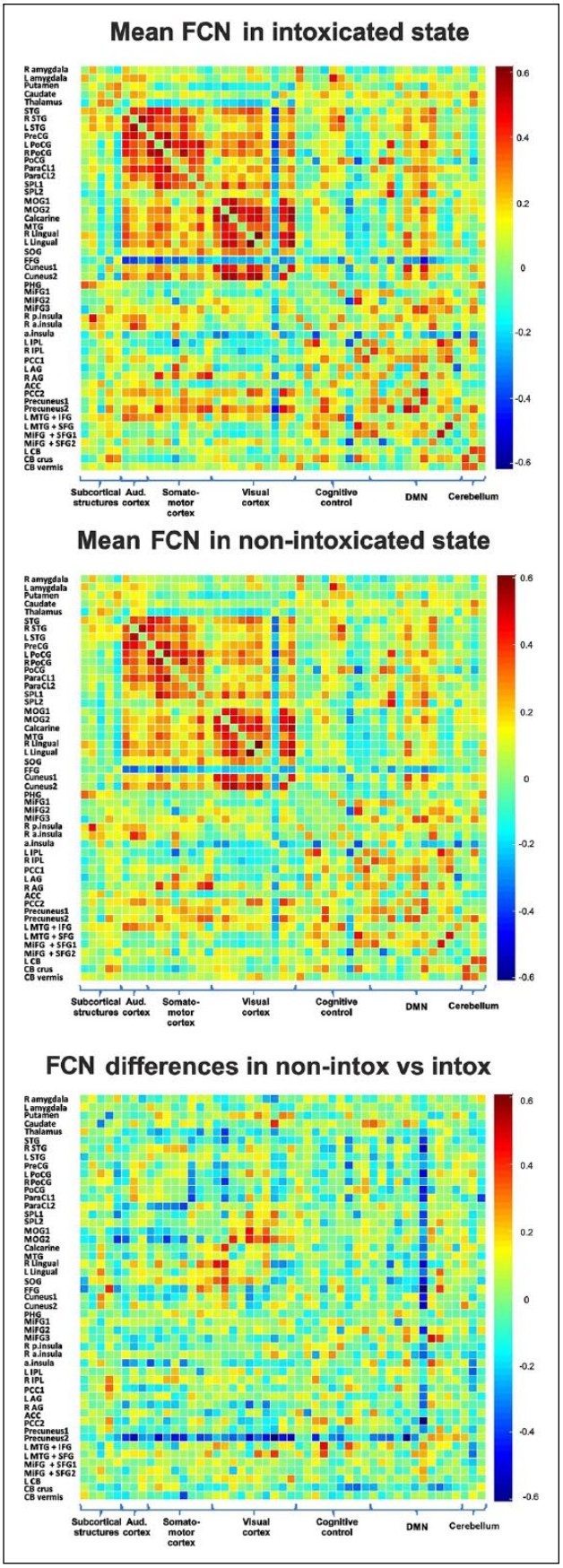

Figure 1. Stationary functional connectivity (FC) in intoxicated and non-intoxicated conditions. Independent component networks (ICNs) labels denote the brain region with peak amplitude and refer to bilateral activations unless specified as left (L) or right (R). The colour scale indicates positive (red) and negative (blue) correlations across components.

ACC: anterior cingulate cortex; AG: angular gyrus; aInsula: anterior insula; CB: cerebellum; DNM: Default Mode Network; FCN: functional connectivity networks; FFG: fusiform gyrus; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; ITG: inferior temporal gyrus; MCC: middle cingulate cortex; MiFG: middle frontal gyrus; MOG: middle occipital gyrus; MTG: middle temporal gyrus; ParaCL: paracentral lobule; PCC: posterior cingulate cortex; PHG: parahippocampal gyrus; pInsula: posterior insula; PoCG: postcentral gyrus; PreCG: precentral gyrus; SFG: superior frontal gyrus; SMA: supplementary motor area; SOG: superior occipital gyrus; SPL: superior parietal lobule; STG: superior temporal gyrus.

resting state connectivity changes. Most resting state fMRI studies on the effects of cannabinoids evaluated the extent to which cannabis modifies brain perfusion (van Hell et al., 2011) or its effects on specific brain circuits such as reward (Androvicova et al., 2017; Fischer et al., 2014), default mode network (Wetherill et al., 2015) or fronto-striatal circuit (Grimm et al., 2018; Ramaekers et al., 2016). Other studies have strived to map the connectivity changes in the entire brain, finding either reduced connectivity between networks (Thijssen et al., 2017) or reduced intra-hemispheric connectivity (Orr et al., 2013), while at the same time reporting increased functional connectivity in specific networks such as the default mode network (DMN) (Cheng et al., 2014; Thijssen et al., 2017). As Cheng et al. noted, the observed differences suggest that in cannabis the transfer of information across different brain areas may lack efficiency.

In our study, the within-subjects design allowed changes to be identified that happen right after the intoxication, not occurring as a result of chronic exposure, which may provide different results.

Through the stationary connectivity analysis, we identified increased connectivity between the precuneus and sensory cortices during intoxication. Studies on brain connectivity changes in chronic cannabis users (Pujol et al., 2014) or in healthy individuals exposed to THC and performing cognitive tasks (Bossong et al., 2013), oftentimes report a reduced deactivation of the default mode network, a circuitry that contributes to intrinsic self-focused mental activity, prospective thinking and autobiographical memory recall (Greicius et al., 2003; Northoff et al., 2006). Our study pinpoints the enhancing effect of THC on the connectivity of posterior default mode network in the absence of any instructed task. Therefore, when cannabis smokers are not focused on the external environment, they rather maximize the utility of self-generated moments. However, we could not confirm the activation of other brain areas that were observed in cannabis intoxication (Bhattacharyya et al., 2012b; Martin-Santos et al., 2010). The majority of cannabis studies are focused on the activity of predefined seeds or clusters. By utilizing this approach, decreased cerebellum and increased supramarginal gyrus connectivity were identified in adolescent cannabis users (Orr et al., 2013). Local changes in the connectivity in the cerebellum and the prefrontal cortex were also found in heavy cannabis users (Cheng et al., 2014).

Where in past studies, FC was assumed to be stable during the entire time acquisition (Meszlényi et al., 2017), recent reports showed that connectivity dynamically changes within seconds to minutes (Allen et al., 2014; Chang and Glover, 2010; Handwerker et al., 2012; Jones et al., 2012; Kiviniemi et al., 2011; Sakoğlu et al., 2010; Smith, 2012). In a recent study performed on a large

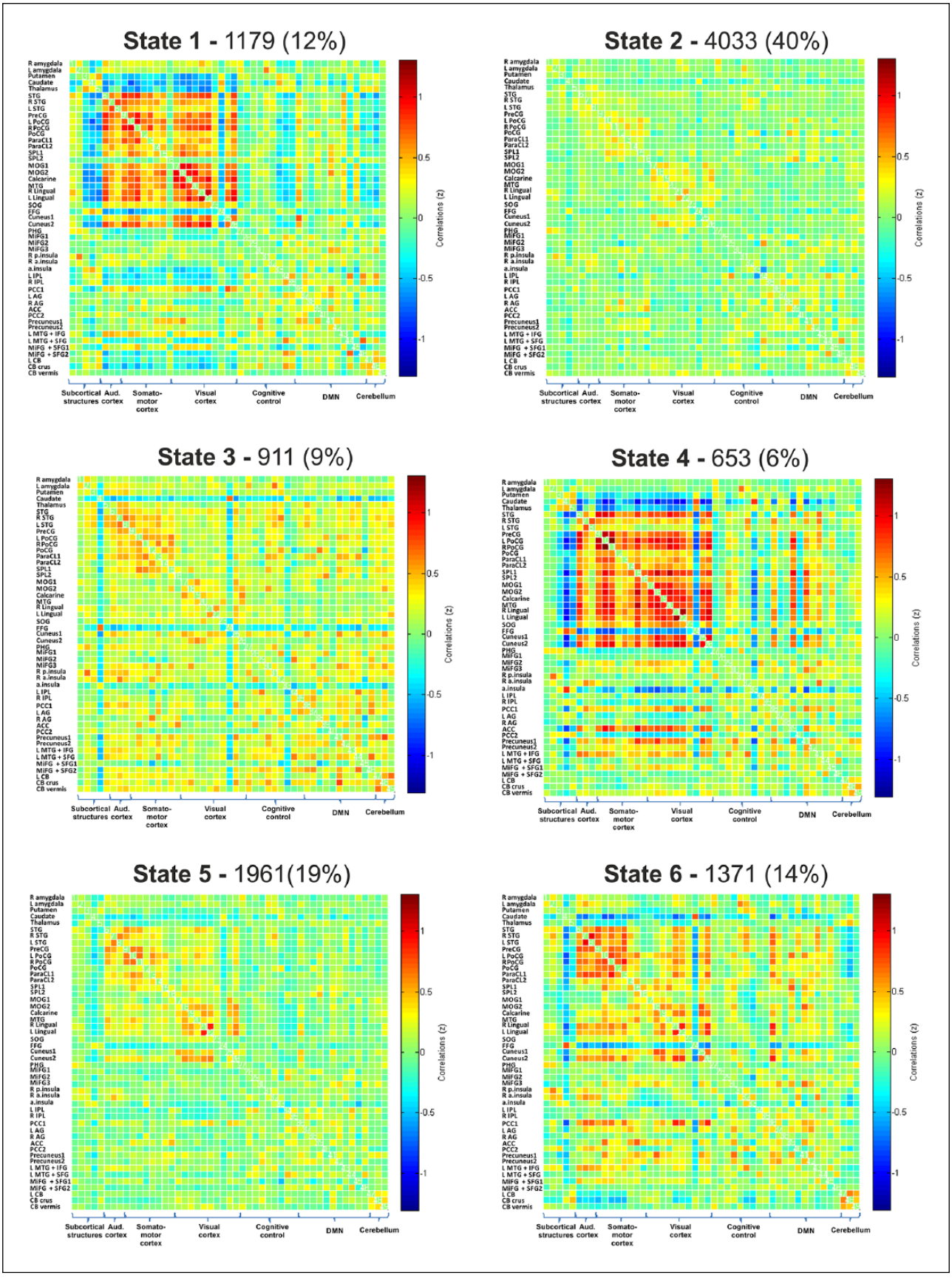

Figure 2. *(Continued)*

Figure 2. Dynamic functional connectivity (FC) states. The colour of the squares within the matrices indicates the correlation coefficient strength (red: positive correlation; blue: negative correlation). Each square represents one independent component that includes (from left to right): subcortical structures (amygdala, putamen, caudate, thalamus), auditory cortex, somatosensory cortex, visual cortex, cognitive control areas (middle frontal gyrus etc.), default mode network (precuneus etc.), cerebellum.
ACC: anterior cingulate cortex; AG: angular gyrus; aInsula: anterior insula; CB: cerebellum; DMN: Default Mode Network; FFG: fusiform gyrus; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; ITG: inferior temporal gyrus; MCC: middle cingulate cortex; MiFG: middle frontal gyrus; MOG: middle occipital gyrus; MTG: middle temporal gyrus; ParaCL: paracentral lobule; PCC: posterior cingulate cortex; PHG: parahippocampal gyrus; pInsula: posterior insula; PoCG: postcentral gyrus; PreCG: precentral gyrus; SFG: superior frontal gyrus; SMA: supplementary motor area; SOG: superior occipital gyrus; SPL: superior parietal lobule; STG: superior temporal gyrus.

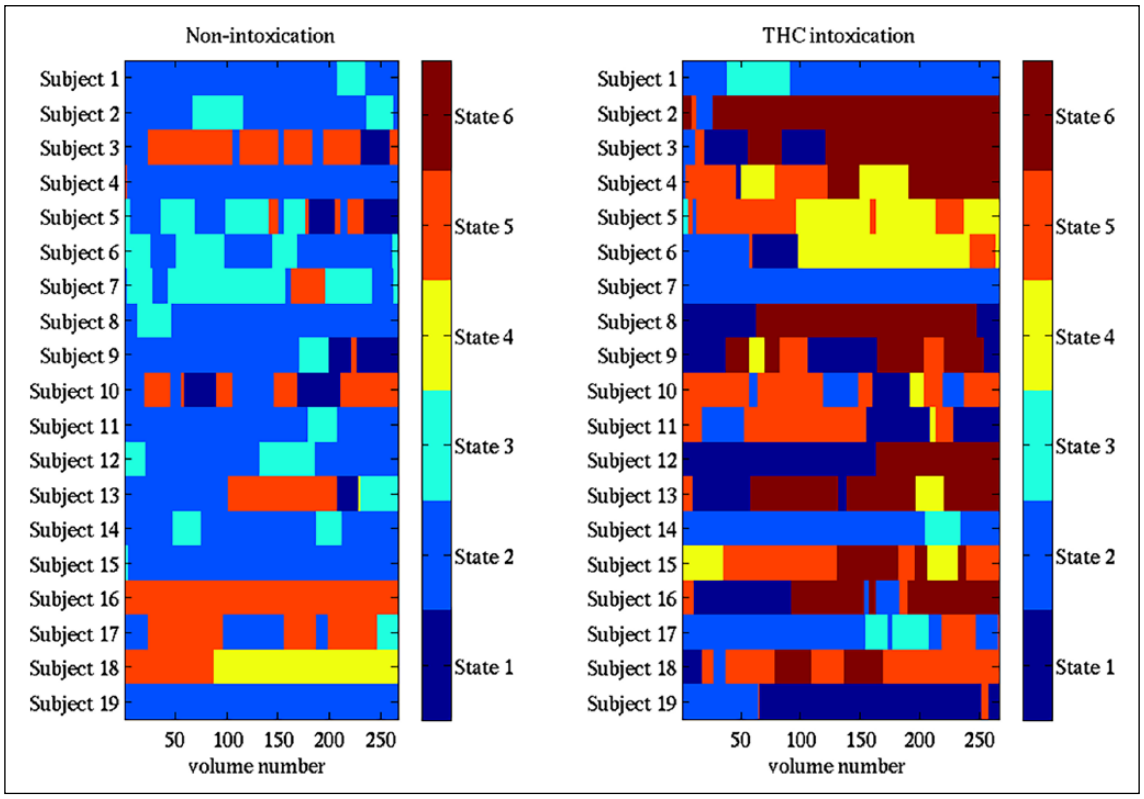

Figure 3. Transitions of dynamic functional connectivity (FC) states in the intoxicated and non-intoxicated condition. Frequency of the appointed states in the non-intoxicated (left) and tetrahydrocannabinol (THC) intoxicated condition (right) in the individual subjects. Volume numbers represent the time scale of the resting state magnetic resonance imaging (rsMRI) session.

sample of healthy subjects, the authors showed eight temporal sequences of propagated activity during a resting state, which were named 'lag threads' (Mitra et al., 2015). As further confirmation, when we employed dynamic analysis by applying sliding windowed correlation matrices from component time courses, we identified six variably occurring connectivity states. Furthermore, we demonstrated the extreme variability of states intra-individually, each of which displaying a unique pattern of resting state FC over time.

On the qualitative level, the brain connectivity patterns were not chaotic and implied a strong connectivity within sensory cortices. Specifically, our data showed high correlations between nodes in somatosensory, auditory and visual cortices that were present in state 6, which we considered as a marker of intoxication, though they were present even in higher values in other states. Our results correspond to the findings of Klumpers et al. (2012) who reported increased connectivity of somatosensory, as well as left and right visual stream networks. Presumably, the intensity of the functional coupling of sensory cortices in the intoxicated condition may have a transitory effect, becoming more or less pronounced with dynamic changes of the brain states, which may still be difficult to track in real time. In cannabis intoxication, one can experience the intensification of sensations and increased clarity of perception (Iversen, 2003). Perceived colours are brighter, senses have more depth, patterns are more evident and figure-ground relations are more distinct and more easily reversible. Another interesting finding was a decreased connectivity of the fusiform gyrus identified in the majority of the states. Indeed, a negative BOLD signal in the left fusiform gyrus was also reported by O'Hanlon et al. (2013) as a marker of the internally generated synaesthesia percepts.

Along with the increased connectivity in sensory cortices, another finding associated with cannabis intoxication was its significant effect on the connectivity in subcortical structures, notably decreased connectivity in the thalamus, putamen and caudate nucleus. The thalamus is assigned the role of a relay centre for

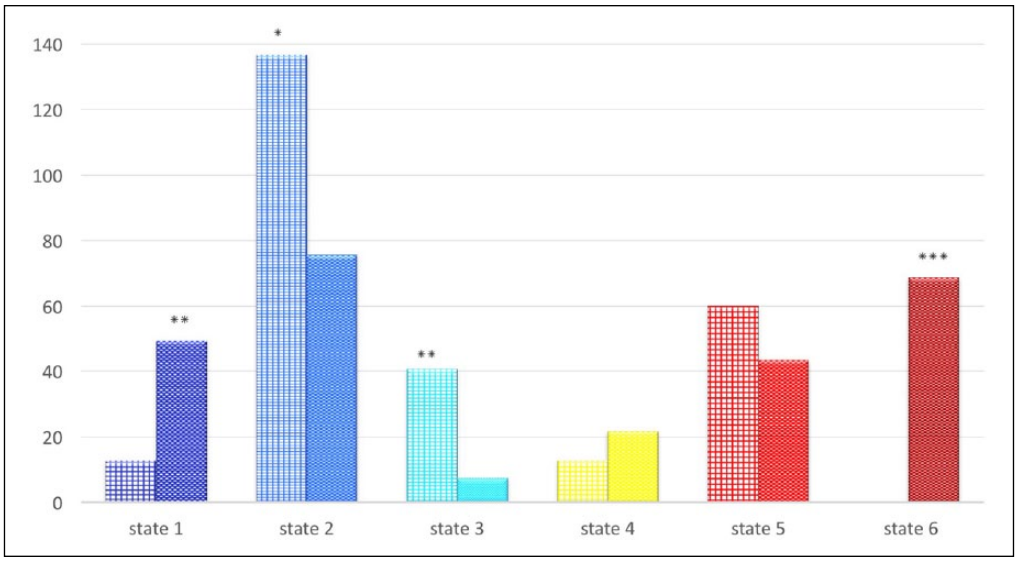

Figure 4. Dwell time of dynamic functional connectivity (FC) states in the intoxicated and non-intoxicated condition. Mean frequency of the appointed states in the non-intoxicated and intoxicated condition in the subjects. *p-level threshold at 0.05.
*$p < 0.05$; **$p < 0.01$, ***$p < 0.001$.

both sensory and motor mechanisms in the brain, providing the positive feedback to the 'correct'' input, while at the same time suppressing irrelevant information (for a review see Herrero et al., 2002). Disruption of the thalamo-cortical connections was also reported in a number of other states and disorders, for example in sleep deprivation (Shao et al., 2013) and chronic tinnitus (Zhang et al., 2015); recent findings also underline thalamic decoupling in schizophrenia and bipolar disorder (Anticevic et al., 2014; Damaraju et al., 2014; Wang et al., 2015). Besides abnormal sensory filtering, another possible explanation for thalamic deactivation is the decline of the arousal level and integration of the information that presumably may influence cognitive processing.

The role of other subcortical structures has also been studied. The caudate was found to play a role in chronic cannabis users who showed a decrease in reward anticipation activity (Androvicova et al., 2017; van Hell et al., 2010). A decrease in the activity of the putamen in frequent cannabis users was demonstrated in cue-induced reactivity tasks, which also predicted the problem severity in a three-year follow up (Vingerhoets et al., 2016). Both of the above-mentioned studies propose the decreased striatal activity to be an independent predictor of the cannabis use-related problem.

When we performed the analyses at a group level, we found that states 2 and 3 were more common in the non-intoxicated condition, while states 1 and 6 were more common during cannabis intoxication. Notably, state 6 was only expressed during cannabis intoxication. Moreover, the duration of state 6 directly correlated with Δ-9-THC plasma levels and with the subjective experiences of the intensity of the psychotropic effect of cannabis. Furthermore, the duration of state 6 directly correlated with the 'Oceanic Boundlessness' item score of the ASC questionnaire. This item is characterized by derealization and depersonalization associated with a positive basic mood ranging from heightened mood to sublime happiness and serenity or grandiosity, and alterations in the sense of time (Vollenweider, 2001). The fact that state 6 was experienced by 10 out of 19 subjects (53%) during intoxication, while it never showed up in the non-intoxicated condition, suggests that this specific FC state may stand out as a neurobiological marker of cannabis intoxication. Clearly, the validity of this novel finding should be replicated on larger samples of cannabis users.

Several strengths and weaknesses of the study have to be mentioned. The way of experimental cannabis intoxication chosen for this study was driven by the fact that the response to the drug in the person who is unfamiliar with its effects can be unpredictable, since the subjects obviously have to learn to perceive experience in a certain, different way, becoming aware of the changes in perception (Tart, 1990). In order to remediate both the factor of experience and the methodological inconsistencies of previous studies (for example, intravenous (i.v.) THC application, differences in THC dosing, etc.), we chose to expose the subjects to their 'usual joint', e.g. the marijuana dosage adjusted to individual habits, where participants intoxicated themselves by their own marijuana cigarette of familiar content and convenient intoxicating effect. This approach is characterized by a high ecological validity. On the other hand, the absence of accurate information about the type of cannabis and the dose of THC makes it difficult to replicate the study, and this looks the most relevant drawback with this ecological approach. In order to replicate our study, researchers may refer to the methodology employed by de Bruijn and colleagues: in their study healthy occasional smokers were randomized to inhaled 4 mg of THC or placebo, and THC serum levels assessed after 30 min. Subjects administered THC showed a mean 1.6 ng/ml THC levels versus 0.22 in those receiving placebo (de Bruijn et al., 2017). Being those THC levels very similar to ours, we might possibly assume that 4 mg of THC intranasal administration might equal the condition of our experiment. However, it should be noted that because of the lack of a fixed experimental dose, the standard deviation in our study is considerably higher (1.5 vs 0.5).

Also because of our study design a placebo arm could not be included. However, the experienced participants would probably render this type of control ineffective. One way of tackling this issue could be to apply a low dosage of active cannabis or a can-

nabis sample with a low concentration of psychoactive ingredients, less discernible from an inactive cigarette.

Other factors should be taken into consideration. The cannabis withdrawal in frequent cannabis smokers might introduce additional bias to the results due to the adaptive changes that occur after a short period of abstinence (Filbey et al, 2018a; Lee et al, 2014). Since in both experimental sessions, the subjects had to stop consuming cannabis 1 week prior the assessment, the obtained differences between conditions cannot be explained by withdrawal effects.

One cannot also exclude the general effects of other substances such as alcohol and tobacco on the brain since the simultaneous use of alcohol and cannabis is very likely in recreant users (Schlienz and Lee, 2018). Indeed, Vergara et al. (2018) in between-subject design using dynamic FC connectivity approach, allocated various profiles of brain dynamic changes in different categories of alcohol, nicotine and marijuana users as well as in the subjects with co-usage of these substances. The authors described a state that was more common in marijuana users and was characterized by the higher connectivity strength in somatosensory cortex that corresponded to the dynamic state associated with THC intoxication in our study. Filbey et al. also identified the differences in the connectivity of posterior DMN, bilateral fronto-parietal network, dorsal attentional network and visual networks in a group of participants with concomitant cannabis and nicotine use as compared to only cannabis and only nicotine users (Filbey et al., 2018b). However, Wetherill et al. (2015) by examining the resting state functional connectivity in the individuals with cannabis dependence who smoked and who did not smoke tobacco, concluded no difference in the connectivity detected in the core nodes of the default mode network. The heterogeneity of the results might be due to the differences in the sample characteristics (recreational or chronic users), various connectivity approaches applied (whole-brain connectivity vs ROI analysis).

On the other hand, cannabis is oftentimes consumed together with tobacco, and one should not exclude a combined acute effect on the brain connectivity. Indeed, as suggested mostly by animal studies, due to the increase of nicotine acetylcholine receptor (nAchR) availability in the prefrontal cortex and thalamus (for review see Viveros et al., 2006) potentiates the acute pharmacological effect of THC. However, there are no studies that would employ such experimental design that allows disentangling the acute effects of cannabis and those of tobacco on cognitive processing.

All subjects in our study prepared their cigarette by mixing cannabis with tobacco. Although this is common practice in most countries and is therefore a further confirmation of the adherence of our study design to the real world, it has to be acknowledged that the combination of cannabis and nicotine might influence resting state FC. In our study the within-subject design and limited sample size prevented us to add confounders such as alcohol and nicotine use to the analyses.

As for the limitations in data analysis, within the dynamic functional connectivity approach, linear correlation was used to assess the functional connectivity between the extracted component time series for each temporal window. As an extension, more sophisticated nonlinear measures such as mutual information could be used to quantify FC, potentially providing a more accurate picture of the connectivity structure. On the other hand, it has been previously shown that at the level of average regional signals, the deviation of BOLD signals from Gaussianity is relatively minor, and the linear correlation is a sufficient measure of dependence for standard analysis (Hlinka et al., 2011) as well as advanced graph-theoretical characterization (Hartman et al., 2011). Concerning the group comparison, it has been previously reported that drug-induced alterations in behavioural or physiological states (such as the amount of head motion) could lead to state-related changes in signal artefacts, and therefore also fMRI-BOLD derived indices such as measures of the amplitude of the low-frequency signal fluctuations or even functional connectivity (Hlinka et al., 2010; see Power et al., 2015 for a recent review of the methodological issue). To minimize such effects, we carefully reviewed the acquired data and removed subjects with motion artefacts from the sample by means of mean frame-wise displacement that showed no differences between the groups. Moreover, apart from the standard motion correction and regressing motion parameters in the pre-processing step, extra robustness was achieved implicitly by extracting the time series by ICA, where only components without substantial artefactual contributions were used and others were removed from the data.

To define the transient brain states and assign them to segments of the data, we used one of the most prominent and recently developed methods, based on temporal clustering of signal segments based on the extracted functional connectivity matrices. To this end, a standard k-means clustering algorithm was used. There is an increasingly acknowledged danger in such heuristic approaches, in that clustering methods may lead to the discovery of distinct states even if the data were perfectly stationary, and the functional connectivity variations were solely due to noise (Hlinka and Hadrava, 2015). In milder cases, the particular data pre-processing and algorithm may bias the results towards specific patterns or temporal scales. However, extraction of fMRI states with the current methods has been relatively established by previous studies, and in our specific case the main result does not concern the detection of these particular states, but rather a clear statistical difference in their prevalence in the two conditions (intoxicated vs. non-intoxicated).

In conclusion, the study shows that THC intoxication in recreational users results in heterogeneous individually-driven dynamic changes in resting state brain connectivity. The patterns of the dynamic FC with the increased sensory cortical connections decoupled from subcortical structures correspond to the subjective experiences of cannabis users (Isbell, 1967) and the occurrence of sensations, possibly being synesthetic in nature (Dovern et al., 2012). Finally, with the use of a dynamic connectivity approach we found a transient connectivity state that specifically occurred during intoxication and was the only state to correlate with THC plasma levels and with the altered states of consciousness described by the subjects after smoking. To our knowledge, this state stands out as the first imaging biomarker of cannabis effect on the brain, and clearly needs confirmation through further research.

Acknowledgements

The authors wish to thank David Tomeček for carrying out motion detection analysis of the fMRI data and Craig Hampson for a proofread of the article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The study was supported by a project from the Ministry of Interior of the Czech Republic (grant number VG20122015080), by the project 'National Institute of Mental Health (NIMH-CZ)', (grant number ED2.1.00/03.0078), and the European Regional Development Fund, by the project 'Sustainability for the National Institute of Mental Health', (grant number LO1611), with the financial support of the Ministry of Education, Youth and Sports of the Czech Republic (NPU I programme). It was also supported by the Ministry of Health of the Czech Republic, by the project 'CZ - Conceptual development of research organization' (project NIMH-CZ, 00023752), from Charles University in Prague (grant number PRVOUK34); Norwegian Financial Mechanism 2009-2014 and the Ministry of Education, Youth and Sports of the Czech Republic under Project contract no. MSMT-28477/2014, project no. 7F14236; support by the Czech Science Foundation project No. 17-01251S.

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References

Allen EA, Damaraju E, Plis SM, et al. (2014) Tracking whole-brain connectivity dynamics in the resting state. *Cereb Cortex* 24: 663–676.

Allen EA, Erhardt EB, Wei Y, et al. (2012) Capturing inter-subject variability with group independent component analysis of fMRI data: A simulation study. *Neuroimage* 59: 4141–4159.

Androvicova R, Horacek J, Tintera J, et al. (2017) Individual prolactin reactivity modulates response of nucleus accumbens to erotic stimuli during acute cannabis intoxication: An fMRI pilot study. *Psychopharmacology (Berl)* 234: 1933–1943.

Anticevic A, Cole MW, Rapovs G, et al. (2014) Characterizing thalamocortical disturbances in schizophrenia and bipolar disorder. *Cereb Cortex* 24: 3116–3130.

Ashton CH (2001) Pharmacology and effects of cannabis: A brief review. *Br J Psychiatry* 178: 101–106.

Atakan Z, Bhattacharyya S, Allen P, et al. (2013) Cannabis affects people differently: Inter-subject variation in psychogenic effects of delta-9-tetrahydrocannabinol: A functional magnetic resonance imaging study with healthy volunteers. *Psychol Med* 43: 1255–1267.

Bhattacharyya S, Atakan Z, Martin-Santos R, et al. (2012a) Neural mechanisms for the cannabinoid modulation of cognition and affect in man: A critical review of neuroimaging studies. *Curr Pharm Des* 18: 5045–5054.

Bhattacharyya S, Crippa JA, Allen P, et al. (2012b) Induction of psychosis by Δ9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. *Arch Gen Psychiatry* 69: 27–36.

Bhattacharyya S, Falkenberg I, Martin-Santos R, et al. (2015) Cannabinoid modulation of functional connectivity within regions processing attentional salience. *Neuropsychopharmacology* 40: 1343–1352.

Bossong M, Jansma JM, van Hell HH, et al. (2013) Default mode network in the effects of delta9-Tetrahydrocannabinol (THC) on human executive function. *PLoS One* 8: e70074.

Bravermanova A, Viktorinova M, Tyls F, et al. (2018) Psilocybin disrupts sensory and higher order cognitive processing but not pre-attentive cognitive processing- study on P300 and mismatch negativity in healthy volunteers. *Psychopharmacology (Berl)* 2: 491–503.

Calhoun VD, Adali T, Pearlson GD, et al. (2001) A method for making group inferences from functional MRI data using independent component analysis. *Hum Brain Mapp* 14: 140–151.

Calhoun VD, Eichele T, Adali T, et al. (2002) Decomposing the brain: Components and modes, networks and nodes. *Trends Cogn Sci* 16: 255–265.

Chang C and Glover GH (2010) Time-frequency dynamics of resting-state brain connectivity measured with fMRI. *NeuroImage* 50: 81–98.

Cheng H, Skosnik PD, Pruce BJ, et al. (2014) Resting state functional magnetic resonance imaging reveals distinct brain activity in heavy cannabis users - a multi-voxel pattern analysis. *J Psychopharmacol* 28: 1030–1040.

Crean RD, Crane NA and Mason BJ (2011) An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *J Addict Med* 5: 1–8.

de Bruijn SEM, de Graaf C, Witkamp RF, et al. (2017) Explorative placebo-controlled double-blind intervention study with low doses of inhaled Δ9-tetrahydrocannabinol and cannabidiol reveals no effect on sweet taste intensity perception and liking in humans. *Cannabis Cannabinoid Res* 2: 114–122.

Damaraju E, Allen EA, Belger A, et al. (2014) Dymanic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia. *Neuroimage Clin* 5: 298–308.

Damoiseaux JS, Rombouts SA, Barkhof F, et al. (2006) Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A* 103: 13848–13853.

Dittrich A (1998) The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. *Pharmacopsychiatry* 31: 80–84.

Dovern A, Fink GR, Fromme CB, et al. (2012) Intrinsic network connectivity reflects consistency of synesthetic experiences. *J Neurosci* 32: 7614–7621.

Filbey FM, Asian S, Lu H, et al. (2018a) Residual effects of THC via novel measures of brain perfusion and metabolism in a large group of chronic cannabis users. *Neuropsychopharmacology* 43: 700–707.

Filbey FM, Gohel S, Prashad S, et al. (2018b) Differential associations of combined vs. isolated cannabis and nicotine on brain resting state networks. *Brain Struct Funct* 223: 3317–3326.

Fisher AS, Whitfield-Gabrielli S, Roth RM, et al. (2014) Impaired functional connectivity of brain reward circuitry in patients with schizophrenia and cannabis use disorder: Effects of cannabis and THC. *Schizophr Res* 158: 176–182.

Greicius MD, Krasnow B, Reiss AL, et al. (2003) Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A* 100: 253–258.

Grimm O, Löffler M, Kamping S, et al. (2018) Probing the endocannabinoid system in healthy volunteers: Cannabidiol alters fronto-striatal resting-state connectivity. *Eur Neuropsychopharmacol*. Epub ahead of print 7 June 2018. DOI: 10.1016/j.euroneuro.2018.04.004.

Handwerker DA, Roopchansingh V, Gonzalez-Castillo J, et al. (2012) Periodic changes in fMRI connectivity. *Neuroimage* 63: 1712–1719.

Hartman D, Hlinka J, Palus M, et al. (2011) The role of nonlinearity in computing graph-theoretical properties of resting-state functional magnetic resonance imaging brain networks. *Chaos* 21: 013119.

Herrero MT, Barcia C and Navarro JM (2002) Functional anatomy of thalamus and basal ganglia. *Childs Nerv Syst* 18: 386–404.

Himberg J and Hyvärinen A (2003) ICASSO software for investigating the reliability of ICA estimates by clustering and visualization. In: *Proceedings of the 13th Workshop on Neural Networks for Signal Processing, NNSP'03*, Toulouse, France, 2003, Espoo: IEEE, pp. 259–268.

Hlinka J, Alexakis C, Hardman JG, et al. (2010) Is sedation-induced BOLD fMRI low-frequency fluctuation increase mediated by increased motion? *Magn Reson Mater Phy* 23: 367–374.

Hlinka J, Palus M, Vejmelka M, et al. (2011) Functional connectivity in resting-state fMRI: Is linear correlation sufficient? *Neuroimage* 54: 2218–2225.

Hlinka J and Hadrava M (2015) On the danger of detecting network states in white noise. *Front Comput Neurosci* 6: 74.

Houck JM, Bryan AD and Feldstein Ewing SW (2013) Functional connectivity and cannabis use in hih-risk adolescents. *Am J Dru Alcochol Abuse* 39: 414–423.

Isbell H, Gorodetzsky CW, Jasinski D, et al. (1967) Effects of delta-9-tetrahydrocannabinol in man. *Psychopharmacologia* 11: 184–188.

Iversen I (2003) Cannabis and the brain. *Brain* 126: 1252–1270.

Jones DT, Vemuri P, Murphy MC, et al. (2012) Non-stationarity in the 'resting brain's' modular architecture. *PLoS One* 7: e39731.

Kiviniemi V, Starck T, Remes J, et al. (2009) Functional segmentation of the brain cortex using high model order group PICA. *Hum Brain Mapp* 30: 3865–3886.

Kiviniemi V, Vire T, Remes J, et al. (2011) A sliding time-window ICA reveals spatial variability of the default mode network in time. *Brain Connect* 1: 339–347.

Klumpers LE, Cole DM, Khalili-Mahani N, et al. (2012) Manipulating brain connectivity with delta-9-tetrahydrocannabinol: A pharmacological resting state fMRI study. *Neuroimage* 63: 1701–1711.

Langlois D, Sylvan C and Gosselin D (2010) An introduction to independent component analysis: InfoMax and FastICA algorithms. *Tutor Quant Methods Psychol* 6: 31–38.

Lee D, Schroeder JR, Karschner EL, et al (2014) Cannabis withdrawal in chronic, frequent cannabis smokers during sustained abstinence within a closed residential environment. *Am J Addict* 23: 234–242.

Loyd S (1982) Least squares quantization in PCM. *IEEE Trans Inf Theory* 28: 129–137.

Martin-Santos R, Fagundo AB, Crippa JA, et al. (2010) Neuroimaging in cannabis use: A systematic review of the literature. *Psychol Med* 40: 383–398.

Meszlényi RJ, Hermann P, Buza K, et al. (2017) Resting State fMRI functional connectivity analysis using dynamic time warping. *Front Neurosci* 11: 75.

Mitra A, Snyder AZ, Blazey T, et al. (2015) Lag threads organize the brain's intrinsic activity. *Proc Natl Acad Sci U S A* 112: e7307.

Musty RE, Reggio P and Consroe P (1995) A review of recent advances in cannabinoid research and the 1994 international symposium on cannabis and the cannabinoids. *Life Sci* 56: 1933–1940.

Northoff G, Heinzel A, de Greck M, et al. (2006) Self-referential processing in our brain – a meta-analysis of imaging studies on the self. *Neuroimage* 31: 440–57.

O'Hanlon E, Newell FN and Mitchell KJ (2013) Combined structural and functional imaging reveals cortical deviations in grapheme-color synaesthesia. *Front Psychol* 4: 755.

Orr C, Morioka R, Behan B, et al. (2013) Altered resting-state connectivity in adolescent cannabis users. *Am J Drug Alcohol Abuse* 39: 372–381.

Power JD, Schlaggar BL and Petersen SE (2015) Recent progress and outstanding issues in motion correction in resting state fMRI. *Neuroimage* 105: 536–551.

Pujol J, Blanco-Hinojo L, Batalla A, et al. (2014) Functional connectivity alterations in brain networks relevant to self-awareness in chronic cannabis users. *J Psychiatr Res* 51: 68–78.

Ramaekers JG, van Wel JH, Spronk D, et al. (2016) Cannabis and cocaine decrease cognitive impulse control and functional corticostriatal connectivity in drug users with low activity DBH genotypes. *Brain Imaging Behav* 10: 1254–1263.

Sakoğlu U, Pearlson GD, Kiehl KA, et al. (2010) A method for evaluating dynamic functional network connectivity and task-modulation: Application to schizophrenia. *Magn Reson Mater Phy* 23: 351–366.

Sayin U (2012) A comparative review of the neuropsychopharmacology of hallucinogen-induced altered states of consciousness: The uniqueness of some hallucinogens. *Neuroquantology* 10: 316–340.

Shao Y, Wang L, Ye E, et al. (2013) Decreased thalamocortical functional connectivity after 36 hours of total sleep deprivation: Evidence from resting state fMRI. *PloS One* 8: e78830.

Smith SM, Fox PT, Miller KL, et al. (2009) Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci USA* 106: 13040–13045.

Smith SM (2012) The future of FMRI connectivity. *Neuroimage* 62: 1257–1266.

Schlienz NJ and Lee DC (2018) Co-use of cannabis, tobacco, and alcohol in adolescence: Policy and regulátory implications. *Int Rev Psychiatry* 30: 226–237.

Studerus E, Gamma E and Vollenweider FX (2010) Psychometric evaluation of the altered states of consciousness rating scale (OAV). *PloS One* 5: e12412.

Tart C (1990) *Altered States of Consciousness*. 3rd ed. New York: Harpercollins.

Thijssen S, Rashid B, Gopal SM, et al. (2017) Regular cannabis and alcohol use is associated with resting-state time course spectra in incarcerated adolescents. *Drug Alcohol Depend* 1: 492–500.

van Hell HH, Vink M, Ossewaarde L, et al. (2010) Chronic effects of cannabis use on the human reward system an fMRI study. *Eur Neuropsychopharmacol* 20: 153–163.

van Hell HH, Bossong MG, Jager G, et al. (2011) Evidence for involvement of the insula in the psychotropic effects of THC in humans: A double-blind, randomized pharmacological MRI study. *Int J Neuropsychopharmacol* 14: 1377–1388.

Vergara VM, Weiland BJ, Hutchison KE, et al. (2018) The impact of combinations of alcohol, nicotine, and cannabis on dynamic brain connectivity. *Neuropsychopharmacology* 43: 877–890.

Vingerhoets WA, Koenders L, van den Brink W, et al. (2016) Cue-induced striatal activity in frequent cannabis users independently predicts cannabis problem severity three years later. *J Psychopharmacol* 30: 152–158.

Viveros MP, Marco EM and File SE (2006) Nicotine and cannabinoids: Parallels, contrasts and interactions. *Neurosci Biobehav Rev* 30: 1161–1181.

Vollenweider FX (2001) Brain mechanisms of hallucinogens and entactogens. *Dialogues Clin Neurosci* 3: 365–279.

Wang HL, Rau CL, Li YM, et al. (2015) Disrupted thalamic resting state functional networks in schizophrenia. *Front Behav Neurosci* 9: 45.

Wetherill RR, Fang Z, Jagannathan K, et al. (2015) Cannabis, cigarettes, and their co-occurring use: Disentangling differences in default mode network functional connectivity. *Drug Alcohol Depend* 153: 116–123.

Zhang J, Chen YC, Feng X, et al. (2015) Impairments of thalamic resting-state functional connectivity in patients with chronic tinnitus. *Euro J Radiol* 84: 1277–1284.