Communication breakdown: delta-9 tetrahydrocannabinol effects on pre-speech neural coherence

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Synchronised neural oscillations preceding speech generation are reduced in patients with schizophrenia, this deficit being implicated in symptom formation. We measured synchronisation of neural oscillations preceding vocalisation in the presence of delta-9 tetrahydrocannabinol (THC) and found they were significantly disrupted. Furthermore, the degree of disruption was related to THC-induced symptoms, suggesting THC may modulate a similar neural substrate to schizophrenia.

Self-generated actions are preceded by synchronised neural oscillations thought to be associated with preparation for movement.[1, 2] These oscillations may be involved in forming an internal representation (efference copy) of the actions, allowing subsequent sensory inputs to be correctly identified as originating from the self.[2, 3] This process may be impaired in patients with schizophrenia, leading to a failure to generate a sense of agency, and giving rise to delusions and hallucinations.[3, 4]. For example, patients with schizophrenia do not display the normal pattern of frontal neural oscillatory synchronisation (intertrial coherence [ITC]) in the 150ms preceding the onset of self-generated speech as measured by electroencephalography (EEG).[2] This disruption of ITC, is related to auditory hallucinations.[2]

Acute intravenous (IV) administration of delta-9 tetrahydrocannabinol (THC) – the main psychoactive component of cannabis – may induce perceptual disturbances some of which resemble positive symptoms of schizophrenia.[5-7] Here, we test the hypothesis that IV THC administration disrupts ITC in the 150ms prior to the onset of self-generated vocalisation, over the same region of frontal cortex previously studied in patients with schizophrenia (EEG lead FCz) [2] and that the level of disruption is associated with the degree of THC-induced psychopathology.

Methods are fully described in supplemental materials. We administered 1.25mg THC or placebo to 16 healthy volunteers prior to a self-generated vocalisation task during EEG acquisition. Volunteers completed a self-rated 24-item questionnaire on cannabis effects before and 30 minutes after the infusion (see supplemental materials). THC led to a significant increase in self-rated measures of salience (t=2.69, df=15, p=0.01), ipseity disturbance (t = 2.73, df = 15, p=0.015), anxiety (t=2.50, df=15, p=0.02), paranoid persecutory ideation (t=2.97, df = 15, p=0.01) and perceptual abnormalities (t = 4.16, df = 15, p=0.0008).

THC administration attenuated pre-speech ITC in the 150ms prior to the onset of self-generated speech, primarily at 3.9Hz, but also at 7.8Hz (3.9Hz: t = 4.78, df = 15, p=0.0002; 7.8Hz: t = 2.63, df = 15, p=0.02, figure 1). The ITC reduction was specific to speech generation as there was no difference in ITC between THC and placebo conditions prior to the onset of the visual cue used in the task at frontal or occipital electrode sites. At 11.7Hz, THC led to a modest increase in ITC (t = 2.29, df = 15. p = 0.04), and there was a trend for increase in ITC at 15.6Hz (t = 1.96, df = 15, p = 0.07).

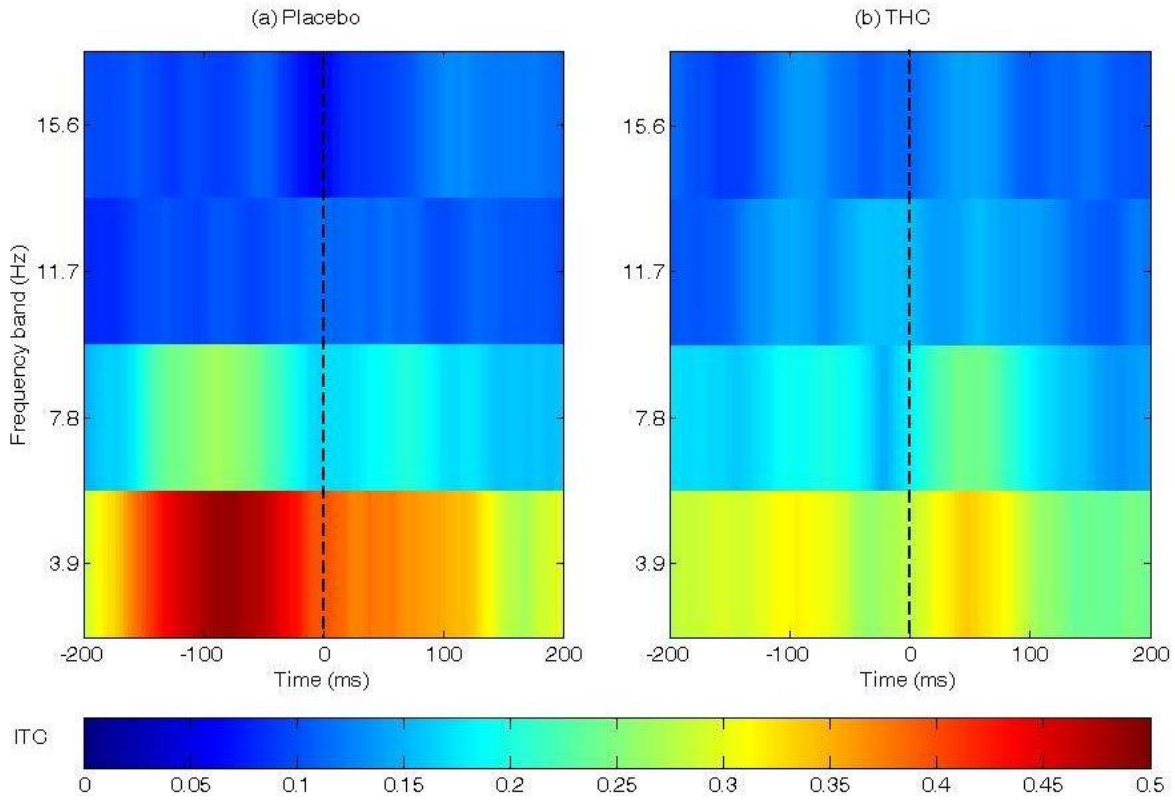
The degree of reduction in 3.9Hz ITC 150-0ms before onset of vocalisation was related to increasing self-rated measures of salience, simplifying to a single term - “my thoughts are more special or significant than usual” ($F_{1,14}$ = 4.69, p=0.048). It was also related to increasing self-rated measures of ipseity disturbance, simplifying to a single term - “I believe my mind is being read” ($F_{1,14}$ = 7.871, p=0.014). There was no relationship between ITC changes in any other frequency band with self-rated measures of cannabis effects.

These results provide the first evidence that THC disrupts ITC prior to the onset of self-generated vocalisation, and that the degree of disruption is related to THC-induced psychological effects. The

findings show considerable overlap with previously reported data in patients with schizophrenia,[2] although the frequency changes reported here are in a lower frequency band. This may reflect the lower frequency resolution used in the schizophrenia study, where changes in theta and alpha range ITC would have contributed to the lowest resolvable frequency at 15.6 Hz. However, it is also possible the ITC pre-vocalisation changes in schizophrenia have a different frequency composition to those found under THC, pointing to a difference in efference processing dysfunction in the two conditions. Whether the effect of THC is the same or closely related to that found in schizophrenia, our findings indicate modulation of ITC by THC may be a useful biomarker for the development of novel antipsychotic drugs.

Figure 1:

Time-frequency analysis of ITC EEG data acquired from FCz prior to the onset of vocalisation (time 0) following IV injection of placebo (a) or delta-9 THC (b).



DISCLOSURE

The authors declare no conflict of interest.

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Methods

The present study formed part of a series of experiments. Details of recruitment and demographics have been published elsewhere.[1, 2] Sixteen healthy volunteers (26 +/- 5 yrs; 9 females) with previous exposure to cannabis received either intravenous THC (1.25mg) or placebo (normal saline) on two separate occasions in a randomised order.

Symptoms were self-rated using a 5-domain, 24-item subjective effects of cannabis questionnaire (table 1), derived from the most commonly self-reported phenomena in 2 previous intravenous THC studies involving 32 individuals.[3, 4] Ratings were taken at baseline and at 30 minutes post-injection (pi).

At 15 minutes pi subjects vocalised the phoneme represented in English as “Aah” following the presentation of a visual cue (an X) on the computer screen, having previously been trained to vocalise with the minimum of jaw, tongue and throat movement. EEG data were acquired as previously reported,[2] (Neuroscan system, 64 electrode cap, linked mastoid reference, ground at AFZ, sample rate 2000Hz, high pass filter 0.05Hz, low pass filter 200Hz). The data was divided into 900ms epochs, time-locked to the onset of each vocalisation (400ms before to 500ms after vocalisation) and baseline corrected (400 to 250ms before vocalisation). Vocalisation events were detected using in-house software that sent an event marker to the EEG amplifier when a predefined amplitude threshold was reached in the microphone input. To take into account the computational time required to process the auditory signal and send the event marker to the EEG amplifier, a delay was introduced such that the marker was sent 200 ms after the threshold was detected. Timings were adjusted in the subsequent offline analysis such that 0 ms corresponded to the onset of vocalisation. The influence of THC on the visually evoked ITC was examined using the same parameters but epoching the data in relation to the X cue instead of vocalisation.

Analysis of inter-trial coherence (ITC) was performed using EEGLAB.[5] ITC values were calculated using a fast Fourier transform window (256 ms wide without zero padding) moving across 200 time points (EEGLAB finds the closest time point for each increment with an average increment of 3.22 ms). Note the time window used is of longer duration than that used in the Ford et al 2007 study (64 ms) allowing resolution of theta and alpha frequencies. A Hanning window was applied to each 256 ms window to reduce leakage from adjacent frequencies. ITC for each session was calculated for 4 linearly spaced frequencies (3.9 Hz, 7.8 Hz, 11.7 Hz and 15.6 Hz) in the same electrode (FCz) studied by Ford et al.[6] As in the Ford et al. study, ITC was examined in the 150ms prior to the speech onset (the time range believed to reflect efference copy generation). Placebo and THC sessions were compared using paired t-tests and the relationship between subjective effects of cannabis grouped by symptom domain (table 1) and ITC reduction in the pre-speech period investigated using stepwise multiple regression.

Table 1: Subjective Effects of Cannabis Questionnaire. All items are self-rated according to intensity on a scale of 0-5 (No, Minimal, Moderate, Strong, Extreme). The scale comprises 5 distinct phenomenological domains – salience (s), ipseity disturbance (id), anxiety (a), paranoid persecutory ideation (p) and perceptual disturbances (per).

1 Currently I'm interested in objects in the environment, more than usual	s
2 This experience is frightening.	a
3 This feels like a set up.	p
4 My perception of time is altered.	per
5 My thoughts are more special or significant than usual.	s
6 My thoughts or movements seem to have a life of their own	id
7 I'm worried for my mental or physical health	a
8 I'm paranoid about the researchers	p
9 My perception of objects is altered.	per
10 I feel agitated	a
11 I'm experiencing profound insights	s
12 There is an unusual delay between my thinking and speaking.	per
13 I'm worried this state of mind won't end.	a
14 I believe I'm being made a fool of.	p
15 Sounds are distorted.	per
16 People are are saying things with 'hidden' or double meanings	p
17 I am unsure if I have just been thinking a thing or have actually said it out-loud.	id
18 I feel I'm making a fool of myself	a
19 I believe my mind is being read.	id
20 I (or others) can hear my inner thoughts outside in external space.	per
21 Currently, events are more significant than usual.	s
22 My thoughts or movements are being controlled by something or somebody else.	id
23 I feel threatened by the researchers.	p
24 My perception of my own body is altered.	per

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