



The effects of synthetic cannabinoids (SCs) on brain structure and function

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Abstract

There is an increasing use of “Novel Psychoactive Substances” containing synthetic cannabinoids worldwide. Synthetic cannabinoids (SC) are highly addictive and cause severe adverse effects. The purpose of our study was to assess whether chronic use of SC alters brain volume and function. Fifteen SC chronic users and 15 healthy control participants undertook an MRI scan to assess brain volume and function while performing a working memory N-back task and a response-inhibition Go-No-Go task. SC users showed impaired performance on the N-back task but not on the Go-No-Go task. They also showed reduced total gray matter volume compared with control participants, as well as reduced gray matter volume in several cortical regions including the middle frontal gyrus, frontal orbital gyrus, inferior frontal gyrus, insula, anterior cingulate cortex and the precuneus. Moreover, SC users showed diminished brain activations in the precuneus, cuneus, lingual gyrus, hippocampus and cerebellum while performing the N-back task. No differences were found in brain activation while performing the response-inhibition task. This is the first study showing overall reduced grey matter volume and specific reduced grey matter volumes in chronic SC users. Furthermore, this study showed for the first time impairment in the neural brain mechanisms responsible for working memory in SC users. Our results of reduced grey matter density and diminished activation during a working memory task in SC users, may suggest vulnerability of the frontal-parietal network in chronic SC users.

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Introduction

There is an increasing worldwide use of new types of novel psychoactive substances (NPS) which contain various psychoactive compounds (Zawilska, 2011; Weinstein et al., 2017). Some of these NPS contain synthetic cannabinoid (SC) compounds that are marketed as a natural herbal mixture under different brand names (Fattore and Fratta, 2011). However, when consumed, they produce various adverse effects that are similar to the effects of cannabis (Seely et al., 2012). Moreover, SC drugs contain other psychoactive substances, of which some are unknown (Fattore and Fratta, 2011).

As the popularity of SC increased, their potentially harmful effects has been recognized, especially affective disorders, psychosis and paranoia, tachycardia, chest pain, tremors, seizures, loss of memory, sedation and higher risk for developing dependence after persistent usage (Castellanos and Thornton, 2012; Winstock and Barratt, 2013; Vandrey et al., 2012; Seely et al., 2012). Moreover, these undesired effects are considered as more intense either in terms of duration and severity than effects induced by non-synthetic cannabis products (Spaderna et al., 2013). The evidence for association between non-synthetic cannabis consumption and impaired cognitive function is mixed (Bossong et al., 2014; Eldreth et al., 2004; Jager et al., 2006). Preclinical studies showed that chronic consumption of SC resulted in impairment of cognitive function (Pattij et al., 2008; Castaneto et al., 2014). We have shown that chronic SC users had poorer performance on working memory, cognitive inhibition and a long-term memory task than non-users and recreational cannabis users in Israel and in Hungary (Cohen et al., 2017).

The purpose of the current study was to assess whether SC display changes in brain structure and neuronal activity associated with working memory and response inhibition. We hypothesized that chronic SC users will have smaller grey matter volume in brain regions associated with chronic cannabis use. We further hypothesized that SC users will show reduced brain activity in areas associated with working memory and response inhibition compared with healthy control participants.

Experimental procedures

Participants

A total of thirty-three participants were recruited and undertook an MRI scan. Fifteen SC chronic users were recruited from rehabilitation centers of the Ministry of Health in Israel and eighteen healthy controls were recruited from the community to participate in the study.

Inclusion criteria for SC users were chronic use of SC, age 18+ years and age at admission < 45 who had used SC for at least 1 year prior to enrollment in the study. Participants were diagnosed as having cannabis use disorder, based on DSM-V diagnosis (American Psychiatric Association, 2013) by a Psychiatrist. Participants who had another Axis-I psychiatric disorder, neurological disorders or a past or current substance use disorder other than cannabinoids, such as alcohol, cocaine or heroin, were excluded. Socio-

demographic data was collected including sex, age, marital status and years of education. The participants were excluded from the study if they had any use of other drugs detected in urine samples or psychotropic medication. They received counseling and pharmacological treatment in the rehabilitation center during their 3-4 week's stay before the study.

Healthy control participants (males, ages 18-43) with similar demographics were recruited from the community. Exclusion criteria for healthy control participants were history of significant neurological or psychiatric disorder and history or current substance use disorder.

Additional exclusion criteria for participants in MRI scanning were: claustrophobia; presence of metal in the body; or any pathology found on their MRI scan. The study was approved by the IRB Committee of Sheba Medical Center and the University of Ariel in Israel. All participants provided written informed consent prior to inclusion in the study.

Questionnaires

Depressive symptoms and anxiety symptoms of participants were assessed by the Beck Depression Inventory (BDI) (Beck et al., 1961) and Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983).

MRI data acquisition

SC users were scanned at the diagnostic imaging department, Sheba Medical Center. Scans were acquired on a 3 Tesla whole body MRI system (GE Signa HDxt, version 16 VO2) equipped with an eight-channel head coil.

Structural imaging Acquisition

High-resolution (1mm³, Matrix 256 × 256, FOV 25.6 cm) images of the entire brain were acquired, using a standard 3D inversion recovery prepared fast gradient echo pulse (FSPGR) T₁ weighted sequence with the following parameters: TR = 7.3 s; TE = 2.7; flip angle = 20°; TI = 450 ms.

Functional imaging Acquisition

N-back task: T₂*-weighted gradient-echo echo-planar images (GE-EPI) were acquired: TR = 3 s; TE = 35 ms; flip angle = 90°; matrix size 64 × 64, FOV 22 × 22 cm, 40 contiguous oblique axial slices covering the whole brain (slice width 3 mm, 0.4 mm gap) voxel size = 3.4 mm³.

Go-No-Go task: T₂*-weighted gradient-echo-planar images (GE-EPI) were acquired: TR = 2.5 s; TE = 35 ms; flip angle = 81°; matrix size 64 × 64, FOV 20 × 20 cm, 35 contiguous oblique axial slices covering the whole brain (slice width 3 mm, 0.3 mm gap) voxel size = 3.125 mm × 3.125 mm × 3.125 mm. fMRI paradigms were presented using E-prime 2.0 software (Psychology Software Tools, Inc) and Presentation software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA,

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