



# The endocannabinoid system and emotional processing: A pharmacological fMRI study with $\Delta 9$ -tetrahydrocannabinol



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Received 3 December 2012; received in revised form 5 June 2013; accepted 24 June 2013

## KEYWORDS

Endocannabinoid system;  
Emotional processing;  
Functional MRI;  
 $\Delta 9$ -tetrahydrocannabinol (THC)

## Abstract

Various psychiatric disorders such as major depression are associated with abnormalities in emotional processing. Evidence indicating involvement of the endocannabinoid system in emotional processing, and thus potentially in related abnormalities, is increasing. In the present study, we examined the role of the endocannabinoid system in processing of stimuli with a positive and negative emotional content in healthy volunteers. A pharmacological functional magnetic resonance imaging (fMRI) study was conducted with a placebo-controlled, cross-over design, investigating effects of the endocannabinoid agonist  $\Delta 9$ -tetrahydrocannabinol (THC) on brain function related to emotional processing in 11 healthy subjects. Performance and brain activity during matching of stimuli with a negative ('fearful faces') or a positive content ('happy faces') were assessed after placebo and THC administration. After THC administration, performance accuracy was decreased for stimuli with a negative but not for stimuli with a positive emotional content. Our task activated a network of brain regions including amygdala, orbital frontal gyrus, hippocampus, parietal gyrus, prefrontal cortex, and regions in the occipital cortex. THC interacted with emotional content, as activity in this network was reduced for negative content, while activity for positive content was increased. These results indicate that THC administration reduces the negative bias in emotional processing. This adds human evidence to support the hypothesis that the endocannabinoid system is involved in modulation of emotional processing. Our findings also suggest a possible

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role for the endocannabinoid system in abnormal emotional processing, and may thus be relevant for psychiatric disorders such as major depression.

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## 1. Introduction

Accurate processing of emotional information is an essential aspect of appropriate social interactions and interpersonal relationships. Abnormalities in emotional processing are among the most important characteristics of psychiatric disorders such as major depression, bipolar disorder and schizophrenia, with significant consequences for social functioning and subjective well-being of patients (Leppanen, 2006; Phillips et al., 2008). Evidence is accumulating for involvement of the endocannabinoid (eCB) system in emotional processing (Lafenetre et al., 2007). Additionally, a possible role for the eCB system in abnormalities in emotional processing related to psychiatric disorders has been suggested (Ashton and Moore, 2011; Hill et al., 2009).

The eCB system is a retrograde messenger system that regulates both excitatory and inhibitory neurotransmission, and consists of cannabinoid receptors and accompanying endogenous ligands (Heifets and Castillo, 2009). Modulation of the eCB system changes emotional responses and processing of emotional information. In humans, for example, smoking cannabis can produce a euphoriant effect, with feelings of intoxication and decreased anxiety, alertness and tension (Ashton, 2001). Administration of  $\Delta^9$ -tetrahydrocannabinol (THC), the main psychoactive component in cannabis and partial agonist of the cannabinoid CB1 receptor, has been shown to reduce perception of fearful facial emotions in healthy volunteers (Ballard et al., 2012), whereas both acute and long-term administration of the eCB antagonist rimonabant appear to induce a bias away from positive emotions on a memory recognition task (Horder et al., 2009, 2012). In animals, low doses of cannabinoid agonists or drugs that enhance levels of endogenous cannabinoids reduce anxiety-like behavior (Kathuria et al., 2003; Marco et al., 2004; Valjent et al., 2002; see for a review Hill et al. (2009)), while disruption of eCB-mediated synaptic regulation produces anxiety- or depressive-like states (Griebel et al., 2005; Martin et al., 2002; see for a review Lafenetre et al. (2007)).

Cannabinoid receptors are highly expressed in many of the key regions for emotional processing (Herkenham et al., 1991; Katona et al., 2001), such as the occipital and temporal lobes, which are involved in perceptual emotional processing, the amygdala and orbital frontal cortex, which are involved in emotion recognition and generation of emotional reactions (LeDoux, 2003), and the anterior cingulate and prefrontal cortex, which are involved in regulation of emotional reactions (Adolphs, 2002; Phillips et al., 2008). Based on this widespread involvement, the purpose of the present study was to examine network-wide interaction effects of the eCB system with emotional content of stimuli. For this purpose, we conducted a pharmacological functional MRI (fMRI) study with healthy volunteers, measuring the effects of THC administration on

brain function related to stimuli with either a negative ('fearful faces') or positive ('happy faces') emotional content.

So far, the role of the eCB system in human emotional processing has been investigated in a limited number of functional neuroimaging studies with administration of THC (Fusar-Poli et al., 2009; Phan et al., 2008). Specifically examining the effects of THC in the amygdala region with an identical task as used in the present study, Phan et al. (2008) found reduced amygdala reactivity for processing of stimuli with a negative emotional content. Fusar-Poli et al. (2009) reported less consistent effects, as THC increased activity in precuneus and primary motor cortex, and reduced activity in bilateral middle frontal gyrus and posterior cingulate cortex during a gender discrimination task with stimuli with a negative emotional content.

On the basis of recent neural models, we expected that processing of emotional stimuli would activate a wide network of brain regions, including amygdala, orbital frontal gyrus, prefrontal cortex, anterior cingulate cortex, and temporal and occipital lobes (Adolphs, 2002; Phillips et al., 2008). Based on both the study of Phan et al. (2008), in which a similar design was used as in the present study, as well as on the reported alterations in processing of emotional information after administration of cannabinoids (Ballard et al., 2012; Horder et al., 2009; Horder et al., 2012), it was hypothesized that THC would reduce the negative bias in emotional processing, and shift it towards a positive bias. We expected this to be reflected in reduced brain activity after THC administration when stimuli with a negative emotional content are processed, and increased activity after THC administration when stimuli with a positive emotional content are processed.

## 2. Experimental procedures

This study is part of the Pharmacological Imaging of the Cannabinoid System (PhICS) project, the design and objectives of which are provided in a methodological paper (van Hell et al., 2011).

### 2.1. Subjects

Fourteen healthy male right-handed subjects were recruited through flyers, posters and internet advertisements. All subjects used cannabis on an incidental basis, defined as having used cannabis at least four times but at most once a week in the year before inclusion in the study. All subjects were in good physical health as assessed by medical history and physical examination, and were screened for axis I psychiatric disorders using the Dutch version of the Mini International Neuropsychiatric Interview for DSM-IV clinical disorders. Subjects were asked to refrain from cannabis for at least two weeks before the first study day until study completion. Illicit drug use other than cannabis was not allowed within six months prior to inclusion. Compliance was tested by means of a urine sample at the beginning of each test day. For further details on inclusion and exclusion criteria we refer to van

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