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Amygdala Reactivity is Inversely Related to Level of Cannabis Use in Individuals with Comorbid Cannabis Dependence and Major Depression

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Abstract

Phan et al. (2008) recently reported that an acute dose of oral THC is associated with a decrease in threat-related amygdala reactivity during a social threat stimulus task. However, to date, those findings have not been replicated, and have not been extended to clinical studies involving smoked rather than oral cannabis. In this study, we hypothesized that level of cannabis smoked by participants in our treatment study would be inversely related to the level of threat-related amygdala reactivity. Subjects were recruited from among participants in our double-blind, placebo-controlled trial of fluoxetine in comorbid youth with cannabis dependence/major depression. The threat-related amygdala reactivity task used by Hariri et al. (2009) was completed during BOLD fMRI scans at study baseline and then again 12 weeks later at the end of the trial. Data are available from six subjects with pre-and post-treatment fMRI data. During the course of the study, five of the six subjects demonstrated a decrease in their level of cannabis use, with a mean decrease of 64%, and those persons all demonstrated an increase in their level of amygdala reactivity. One subject demonstrated an increase in their level of cannabis use (a 79% increase) during the treatment trial, and that person demonstrated a decrease in their level of amygdala reactivity. Thus, a higher level of cannabis use was consistently associated with a lower level of amygdala reactivity across all subjects (matched pairs $t=2.70$, $df=5$, $p<0.05$, two-tailed). These findings are consistent with the reports by Phan et al. (Phan et al., 2008) and Hariri et al. (Hariri et al., 2009) suggesting that cannabinoids have an inhibitory effect on threat-related amygdala reactivity.

1. Introduction

The amygdala plays a central role in the shaping of physiological and behavioral responses to environmental challenge, especially threat. The amygdala possesses a very high density of CB1 cannabinoid receptors (Perra et al., 2008). The endocannabinoid system has been shown to be associated with anxiety responses (Viveros et al., 2005). The amygdala is also implicated in

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the neurobiological mechanism of normal and pathological anxiety (Maldonado et al., 2006) as well as addiction (Perra et al., 2008). Recent evidence suggests that amygdala function is regulated by both exogenous and endogenous cannabinoid signaling. Using BOLD fMRI, Phan et al. (Phan et al., 2008) reported that an acute dose of oral THC is associated with a decrease in threat-related amygdala reactivity. Using a similar BOLD fMRI paradigm Hariri et al. (Hariri et al., 2009) reported that genetic variation associated with relatively increased endocannabinoid signaling is also associated with decreased threat-related amygdala reactivity. However, to date, those findings have not been replicated, and have not been extended to clinical studies involving smoked rather than oral cannabis or endocannabinoids. In the current study we examined the effect of cannabis use on threat-related amygdala reactivity assayed with BOLD fMRI. We hypothesized that level of cannabis use would be inversely associated with level of threat-related amygdala reactivity.

2. Materials and Methods

2.1 General Procedures

Before entry into the protocol, written informed consent was obtained after all procedures had been fully explained. The study was approved by the University of Pittsburgh Institutional Review Board. Inclusion criteria for this study included a current DSM-IV (SCID) cannabis use disorder and a DSM-IV (KSADS) diagnosis of major depressive disorder (MDD). Potential subjects were excluded if they were less than 18 years of age or over 25 years of age, if they had received psychotropic medication within the three months before the baseline assessment, if they demonstrated a DSM-IV dependence diagnosis involving any substance except cannabis or alcohol, or if they were identified as having paramagnetic material in their bodies.

The methodology of the treatment portion of the study have been described elsewhere (Cornelius et al., 2008). The fMRI scans were performed prior to starting study medications and again 12 weeks later after the completion of the treatment study. The fMRI scans were performed at the UPMC Health System Magnetic Resonance Research Center (MRRC) in Pittsburgh, Pennsylvania. For the fMRI task, the subject viewed objects on a screen via an angled adjustable mirror located inside the scanner (Hariri et al., 2009).

2.2 Threat-related amygdala reactivity paradigm

During this paradigm subjects viewed a trio of faces (expressing either anger or fear) and selected one of two faces (bottom) identical to a target face (top). Angry and fearful facial expressions can represent honest indicators of ecologically-valid threat, especially that related to conspecific challengers (Darwin et al., 1998). Within this context, we interpret the amygdala activation elicited by our task as being threat-related. Each face processing block consisted of six images, balanced for sex and target affect (angry or fearful) all derived from a standard set of pictures of facial affect (Ekman et al., 1976). During the sensorimotor control blocks, subjects viewed a trio of simple geometric shapes (circles, vertical and horizontal ellipses) and selected one of two shapes (bottom) identical to a target shape (top). Each sensorimotor control block consisted of six different shape trios. All blocks were preceded by a brief instruction ("Match Faces") lasting 2 seconds. In the face processing blocks, each of the six face trios was presented for 4 seconds with a variable inter-stimulus interval of 2-6 sec (mean = 4 sec) for a total block length of 48 seconds. The variable inter-stimulus interval within blocks allowed for the determination of expression-specific (i.e., anger or fear) amygdala reactivity.

2.3 BOLD fMRI Acquisition Parameters

Data were collected with a Siemens TRIO TIM 3T scanner optimized for functional brain imaging. An automated shim procedure was applied to minimize possible magnetic field inhomogeneities. In-plane T2 structural images were acquired for visualization and

normalization of functional imaging data. Blood oxygenation-level dependent (BOLD) functional images were acquired with a gradient echo EPI sequence oriented to the AC-PC line and encompassing the cerebrum and the majority of the cerebellum (TR/TE=2000/32, Matrix=128×128×29, Voxel size=2×2×3mm³, oblique axial acquisition (parallel to AC-PC), IPAT=2.

2.4 Statistical Methods of fMRI Image Analysis

We analyzed the imaging data using statistical parametric mapping (Friston et al., 2007). Images for each subject were first realigned to each other to correct for head motion, then normalized into a standard stereotactic space and smoothed with a Gaussian filter. We then performed a voxel-wise two-sample t-test for each subject, contrasting the “faces” blocks with the “control” blocks at $P < 0.05$ ($t > 1.7$), FDR corrected for multiple comparisons across the whole brain. The resulting t-map was then masked with a bilateral amygdala region of interest constructed using the WFU Pick Atlas and the associated AAL Atlas. The voxels surviving this masking and threshold were considered amygdala voxels exhibiting a significant main effect of task. For each participant, the number of above threshold amygdala voxels before and after treatment was then used as an index of relative activation. These activation levels were then compared relative to change in cannabis use with a matched pairs test, comparing amygdala activation at the time point when they had high cannabis use to amygdala activation at the time point when they had lower cannabis use.

3. Results

Data are currently available from six subjects with completed pre-and post-treatment fMRI. These six subjects all demonstrated current cannabis dependence in combination with current major depressive disorder. Those six subjects included five males (83.3%) and one female (16.7%), including 3 Caucasians (50.0%) and 3 African-Americans (50.0%). The subjects in this group ranged from 19 to 24 years of age, with a mean of 21.7 +/- 2.0 years, who used one to seven blunts of cannabis per day at baseline.

During the 12-week course of the treatment study, five of the six subjects demonstrated a decrease in their level of cannabis use, with a mean decrease of 63.6%, and those persons all demonstrated an increase in their level of amygdala reactivity. During the 12-week course of the treatment study, one subject demonstrated an increase in their level of cannabis use (a 79.0% increase), and that person demonstrated a decrease in their level of amygdala reactivity. Thus, across all six subjects, amygdala reactivity was inversely related to level of cannabis use (matched pairs $t=2.70$, $df=5$, $p<0.05$ two-tailed).

4. Discussion

This study provides what we believe is the first data relating levels of smoked cannabis determined in a controlled study with threat-related amygdala reactivity assayed with BOLD fMRI. In the study, amygdala reactivity was found to be inversely related to level of cannabis use. Thus, our hypothesis was confirmed. These findings are consistent with the reports of Phan et al. (Phan et al., 2008) and Hariri et al. (Hariri et al., 2009) suggesting that cannabinoids have an inhibitory effect on amygdala function.

It can be noted that major depression and anxiety disorders have been reported to be associated with increased reactivity of the amygdala (Drevets 2003), while treatment with antidepressant medications has been reported to reduce the reactivity (activation) of the amygdala in subjects with major depression (Sheline et al, 2001; Harmer et al., 2006; Fu et al, 2008). Importantly, amygdala reactivity increased rather than decreased in our comorbid subjects during the course of the treatment study, suggesting that the effects of the decreasing level of cannabis use

outweighed the effects of the decrease in depressive symptoms during the course of the study. Perhaps that finding is not surprising, since the mechanism of amygdala reactivity has been shown to involve the endocannabinoid system, which presumably would be affected more by level of cannabis use than by factors such as level of depressive symptoms.

Our current study is limited by its modest sample size, which limits the ability to control for factors such as level of depressive symptoms and the presence or absence of antidepressant medication. Future studies involving larger study samples are warranted to confirm or refute the findings of this paper, and to clarify the role of other factors that may affect amygdala reactivity.

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