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Cannabis use and brain structural alterations of the cingulate cortex in early psychosis

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ABSTRACT

As cannabis use is more frequent in patients with psychosis than in the general population and is known to be a risk factor for psychosis, the question arises whether cannabis contributes to recently detected brain volume reductions in schizophrenic psychoses. This study is the first to investigate how cannabis use is related to the cingulum volume, a brain region involved in the pathogenesis of schizophrenia, in a sample of both at-risk mental state (ARMS) and first episode psychosis (FEP) subjects. A cross-sectional magnetic resonance imaging (MRI) study of manually traced cingulum in 23 FEP and 37 ARMS subjects was performed. Cannabis use was assessed with the Basel Interview for Psychosis. By using repeated measures analyses of covariance, we investigated whether current cannabis use is associated with the cingulum volume, correcting for age, gender, alcohol consumption, whole brain volume and antipsychotic medication. There was a significant three-way interaction between region (anterior/posterior cingulum), hemisphere (left/right cingulum) and cannabis use (yes/no). Post-hoc analyses revealed that this was due to a significant negative effect of cannabis use on the volume of the posterior cingulum which was independent of the hemisphere and diagnostic group and all other covariates we controlled for. In the anterior cingulum, we found a significant negative effect only for the left hemisphere, which was again independent of the diagnostic group. Overall, we found negative associations of current cannabis use with grey matter volume of the cingulate cortex, a region rich in cannabinoid CB1 receptors. As this finding has not been consistently found in healthy controls, it might suggest that both ARMS and FEP subjects are particularly sensitive to exogenous activation of these receptors.

1. Introduction

The cingulum is a functionally heterogeneous region, involved in a range of behavioural domains (Vogt et al., 1992). It represents a key structure within the limbic system and is composed of several areas which differ in respect to structure and function: the different subdivisions play an important role in emotional, cognitive, attentional, nociceptive, and motoric processing (Bush et al., 2000; Vogt et al., 1992). The anterior cingulate cortex (ACC) represents a central component of those subdivisions that control affective and cognitive functions. The central task of this brain region is the modulation of inner emotional reactions. The ACC has anatomical connections to the dorsolateral prefrontal cortex, motoric areas and the thalamus, depending on the specialised subdivision. It is an essential component of social cognition and visualisation, and is mainly activated by emotional stimuli (Bush et al., 2000; Kopelman et al., 2005). The posterior cingulate cortex (PCC) is activated by both emotional and non-emotional stimuli, and it plays an important role in memory access, visual span and spatial orientation (Vogt et al., 1992, 2006; Vogt and Laureys, 2005).

Studies of individuals with genetic or clinical risk for psychosis have indicated that the cingulum might be involved in the pathogenesis of schizophrenia (for review, see Borgwardt et al. (2009), Fusar-Poli et al. (2008, 2011), Smieskova et al. (2010)). A recent study from our group reported that at-risk mental state (ARMS) (Yung et al., 2005) subjects had significantly reduced left caudal ACC volume compared to healthy controls; and, within ARMS, those who later made the transition to psychosis (ARMS-T) showed significantly reduced volume of the whole right cingulate cortex, right subgenual cingulate cortex, and right PCC compared

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to ARMS subjects who did not make the transition to psychosis (ARMS-NT) (Röthlisberger et al., 2012).

Cannabis use and abuse occurs much more frequently in patients with psychosis than in the general population (Koskinen et al., 2010) and is suspected to be a risk factor for psychosis (Drewe et al., 2004; Moore et al., 2007). Neurobiological models for this association postulate that delta-9-tetrahydrocannabinol (THC, the main psychoactive component of cannabis) causes dopaminergic imbalances by increasing the dopaminergic tone in striatal regions of the brain via activation of cannabinoid 1 (CB1) receptors and decreasing dopamine levels in prefrontal regions of the brain (Kuepper et al., 2010). However, most evidence supporting this stems from animal research (Kuepper et al., 2010) and has not been empirically investigated in humans. Nevertheless, there is persuasive evidence that there are associations between schizophrenia and alterations of dopamine levels (for review, see Howes and Kapur (2009)) as well as between schizophrenia and brain structural alterations (for review, see Steen et al. (2006)).

Another neurobiological explanation for the cannabis–psychosis association could be that cannabis contributes to abnormalities in the brain structure and therefore to the development of psychotic symptoms. Although studies investigating how cannabis affects the brain structure of healthy individuals have produced inconsistent results, the most consistent brain volume abnormalities associated with cannabis use in healthy controls were found in medial temporal regions (for review, see Lorenzetti et al. (2010), Martin-Santos et al. (2010)). It has been reported that cannabis may affect the integrity of white matter fibre tracts in the ACC (Gruber and Yurgelun-Todd, 2005). Functional MRI studies found that acute administration of THC or marijuana increases resting activity and activation of the ACC during cognitive tasks (Martin-Santos et al., 2010). There is only one structural MRI study with healthy controls that took into account the effects of cannabis on the cingulum volume. Specifically, Cousijn et al. (2012) reported negative associations between amygdala/hippocampus grey matter volume and amount of cannabis use but no associations of cannabis with ACC and striatum in a voxel-based morphometry study (Cousijn et al., 2012).

In contrast to studies in humans, animal studies have demonstrated that THC induced dose-dependent neurotoxic changes in brain regions rich in cannabinoid CB1 receptors (Downer et al., 2001; Landfield et al., 1988; Whitaker-Azmitia et al., 2000). However, this could also be due to the fact that in animal studies, the THC doses administered were high and THC was often not mixed with other cannabinoids. There are also studies which reported neuroprotective effects of cannabinoids in animals (e.g., Sagredo et al. (2011)).

We have recently reviewed studies comparing brain volumes of cannabis-using patients with psychosis with those of non-using psychosis patients and healthy controls (Rapp et al., 2012). The systematic review demonstrated that cannabis use is associated with the smaller volume of global and specific brain structures, particularly in CB1 receptor rich brain regions, such as the cingulate cortex (Bangalore et al., 2008; Szeszko et al., 2007), prefrontal cortices (James et al., 2011; Rais et al., 2010) and the cerebellum (James et al., 2011; Solowij et al., 2011). Furthermore, the associations between brain structural volume reductions and cannabis consumption were more pronounced in patients with psychosis and individuals at genetic risk for psychosis than in healthy controls, suggesting that these groups might be particularly vulnerable to brain volume loss due to cannabis exposure. Our literature review also revealed that, to date, only one study (Stone et al., 2011) investigated the effect of cannabis on brain structure in ARMS subjects. By analysing the interaction between the two diagnostic groups (ARMS/first episode psychosis (FEP)) and cannabis use, conclusions can be drawn as to whether cannabis use is associated with brain structure in a disease stage-dependent manner. To this end, associations between cannabis consumption and cingulum volume in both ARMS and FEP samples, that were obtained within the same study were investigated. We hypothesised that

(1) cannabis use is associated with lower grey matter volumes in the cingulate cortex in both diagnostic groups; and
(2) these associations are more pronounced in FEP than in ARMS subjects.

2. Methods

2.1. Setting and recruitment

This study was part of the Basel *FePsy* (*F*rüherkennung von *Psy*chosen) study, which aims to improve the early detection of psychosis. The *FePsy* study has been described in detail elsewhere (Riecher-Rössler et al., 2007, 2009). Subjects were recruited into the study via a specialised outpatient clinic at the Psychiatric Outpatient Department at the University Hospital Basel. This clinic was set up specifically to identify, assess, and follow up individuals in the early stages of psychosis. The study was approved by the Ethics Committee of Basel, Switzerland (EKBB), and written informed consent was obtained from each of the participants.

2.2. Screening procedure

For screening, the Basel Screening Instrument for Psychosis (BSIP) was used (Riecher-Rössler et al., 2008). Individuals were assessed and identified as ARMS, FEP, or "not at risk for psychosis" (i.e., other psychiatric diseases) subjects.

2.3. Participants

In this study, we present the data of 60 patients from the Basel *FePsy* study who agreed to participate in the imaging arm of the study. Twenty-three patients were identified as FEP and 37 as ARMS subjects. Data of this study overlap with our previous studies (Bühlmann et al., 2010; Röthlisberger et al., 2012; Walter et al., 2012) (overlapping $n=60$).

2.4. Cannabis, alcohol and other drug use

Cannabis, alcohol and other drug use was determined for both ARMS and FEP at study inclusion by using the Basel Interview for Psychosis (BIP) (Smith and co-workers, unpublished results), a structured and specifically developed interview for the assessment of psychosis development, which is much more detailed than the BSIP. The BIP contains two items assessing the frequency of past and present cannabis/alcohol/other drug consumption. Past drug consumption refers to lifetime consumption, and present consumption refers to the frequency participants reported to usually use cannabis during assessments. Frequency of substance use is assessed by these items on a five-point ordinal scale using the following response categories: daily, several times a week, several times a month, less than several times a month, and not at all. For the present analyses, only current substance use was considered. A dichotomous variable of cannabis use was created differentiating between current cannabis users (=daily, several times a week, several times a month and less than several times a month) and non-users (=no use at all).

In 60% of the included patients, cannabis use was additionally assessed by urine toxicology screens. Urine tests were considered positive when THC-COOH was present in the urine in a concentration of at least 10 μg/l, in order to infer a detection window of ≈1 month. Although urine tests were only available in a subset of our sample, the agreement between urine tests and the questionnaire item on current use was excellent. That is, all patients with cannabis-positive urine had responded to the questionnaire item measuring current cannabis use with a frequency of at least rarely and all patients with cannabis-negative urine had responded with a frequency less than several times per month. Hence, relying only on information of the BIP in those patients who did not have urine toxicology screens was considered well justified.

2.5. Structural MRI

2.5.1. Image acquisition

Subjects were scanned using a Siemens (Erlangen, Germany) Magnetom Vision 1.5 T scanner at the University Hospital Basel. Head movement was minimised by foam padding and velcro straps across the forehead and chin. A three-dimensional