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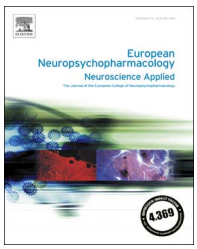

Cortical thickness, cortical surface area and subcortical volumes in schizophrenia and bipolar disorder patients with cannabis use

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Abstract
Cannabis is associated with increased risk for severe mental illness and is commonly used among individuals with schizophrenia or bipolar disorder.
In this study we investigated associations between cannabis use and brain structures among patients with schizophrenia or bipolar disorders. Magnetic resonance imaging scans were obtained for 77 schizophrenia and 55 bipolar patients with a history of cannabis use (defined as lifetime use >10 times during one month or abuse/dependence), and 97 schizophrenia, 85 bipolar disorder patients and 277 healthy controls without any previous cannabis use. Cortical thickness, cortical surface area and subcortical volumes were compared between groups. Both hypothesis-driven region-of-interest analyses from 11 preselected brain regions in each hemisphere and exploratory point-by-point analyses were performed. We tested for diagnostic interactions and controlled for potential confounders.
After controlling for confounders such as tobacco use and alcohol use disorders we found reduced cortical thickness in the caudal middle frontal gyrus compared to non-user patients and healthy controls. The findings were not significant when patients with co-morbid alcohol and illicit drug use were excluded from the analyses, but onset of cannabis use before illness onset was associated with cortical thinning in the caudal middle frontal gyrus.

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To conclude, we found no structural brain changes associated with cannabis use among patients with severe mental illness, but the findings indicate excess cortical thinning among those who use cannabis before illness onset. The present findings support the understanding that cannabis use is associated with limited brain effects in schizophrenia as well as bipolar disorder.

1. Introduction

Cannabis use is associated with risk of schizophrenia and bipolar disorder (Moore et al., 2007; van Laar et al., 2007) and is commonly used among patients with both disorders (Fergusson et al., 2006; Hunt et al., 2016). It has been suggested that cannabis use can precipitate psychosis onset in vulnerable individuals (McLaren et al., 2010) and animal studies have shown that cannabis use interferes with brain development (Rubino and Parolaro, 2015). Cannabis largely exerts its effect on brain function via binding to cannabinoid (CB) 1 receptors that are widely distributed in the brain, or modulates other neurotransmitter effects (Loberg et al., 2014). In schizophrenia and bipolar disorder, lower age at illness onset (De Hert et al., 2011; Helle et al., 2016; Lagerberg et al., 2014), more positive symptoms and higher frequency of hospitalizations (Large et al., 2014; Schmidt et al., 2011) are found in patients with cannabis abuse compared with patients without co-morbid cannabis abuse. Earlier illness onset and more severe illness in cannabis users can suggest that cannabis use have a negative impact on the brain, which may be reflected in the size of brain structures.

Structural magnetic resonance imaging (sMRI) allows for *in vivo* investigations of cannabis effects on brain structure. In healthy adults with regular cannabis use, the most consistent findings are brain tissue reductions of hippocampus, amygdala, prefrontal cortex and cerebellum (Lorenzetti et al., 2016).

Studies on cannabis associations with brain structure in schizophrenia are inconsistent (Cahn et al., 2004; Cunha et al., 2013; Schnell et al., 2012; Wobrock et al., 2009). The most consistently reported results are volume loss associated with cannabis use in the cingulate, the prefrontal cortex and the cerebellum (Rapp et al., 2012; Szeszko et al., 2007), which are CB1 receptor dense brain areas (Glass et al., 1997) indicating that cannabis drive these findings. Comparisons between studies are difficult due to methodological differences. The existing studies comprise both whole-brain and regions-of-interest (ROI) studies. The ROI studies use different measurement protocols, which may prevent comparisons between them. Since the numbers of cannabis-users in previous studies are low ($n \leq 52$), the analyses may not have had enough statistical power to detect associations if present. There is little evidence for cannabis use associations with brain structure in first-episode psychosis (FEP) (Malchow et al., 2013) and brain structure changes may not be present before illness onset, but findings from studies on chronic cannabis abuse indicate that continued consumption can alter brain morphology in schizophrenia (Habets et al., 2011). In keeping with this, regional cortical thinning in the left dorsolateral prefrontal, anterior cingulate and occipital regions (Rais et al., 2010) and ventricular volume enlargement (Rais et al., 2008) in cannabis users compared to non-users were reported in two 5 year follow-up studies of a FEP sample, pointing to potentially harmful brain effects of cannabis in psychosis patients (Rais et al., 2010).

Few studies have investigated brain effects from long-term cannabis use in chronic schizophrenia. A study of chronic schizophrenia patients ($n=88$) with cannabis use demonstrated reduced global cortical thickness and trends for thinning of the left frontal pole and bilateral parahippocampal cortex among heavy cannabis users (>40 times lifetime) (Habets et al., 2011). Higher frequency of cannabis use has also been associated with brain structure alterations in psychosis (Bangalore et al., 2008).

It is unknown if the cannabis-related structural alterations also occur in bipolar disorder. Cannabis use increase risk for mania symptoms independently of psychosis (Henquet et al., 2006), which suggests differential roles of cannabis in the pathophysiology of schizophrenia and bipolar disorder. However, MRI studies including cannabis users with bipolar disorder patients have not specifically investigated if brain changes in bipolar disorder differ from non-affective psychosis (Cunha et al., 2013) or have focused on adolescents with bipolar disorder (Jarvis et al., 2008).

There is evidence for cortical thinning, smaller hippocampi and larger ventricles (Arnone et al., 2009; Ellison-Wright and Bullmore, 2010; Rimol et al., 2010), as well as an overlap in symptomatology and cognitive deficits (Simonsen et al., 2011) between schizophrenia and bipolar disorder suggestive of a common neurobiology. Changes in regionally distinct brain structures may be related to the behavioural and cognitive deficits found in cannabis users as compared to non-user patients (Curran et al., 2016; Volkow et al., 2016). Also, there is increasing support for adverse effects of cannabis on the clinical phenotype of bipolar disorder, i.e. lower age at onset and greater illness severity (De Hert et al., 2011; Lagerberg et al., 2016; Lagerberg et al., 2014). Still, there are few studies on cannabis associations with brain structure on adults with bipolar disorder. No previous studies have investigated how cannabis is associated with brain structure across schizophrenia and bipolar disorder.

Based on previous findings, and the distribution of brain CB1 receptors, we hypothesized to find cortical thinning in fronto-temporal regions (Habets et al., 2011; Lopez-Larson et al., 2011), as well as abnormalities in ventricular, hippocampal, amygdala, thalamus, putamen, caudate, nucleus accumbens and cerebellar volumes in cannabis-using patients compared with non-using patients. Since the majority of studies have examined regions restricted to fronto-temporal brain areas and may have failed to detect changes in other regions, we also conducted an exploratory analysis.

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