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Comparing the effect of clozapine and risperidone on cue reactivity in male patients with schizophrenia and a cannabis use disorder: A randomized fMRI study

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ABSTRACT

Objective: Cannabis use disorders (CUDs) are highly comorbid in patients with schizophrenia and associated with poor outcome. Clozapine has been put forward as the first choice antipsychotic in this patient group. However, little is known about the mechanisms underlying the assumed superiority of clozapine.
Methods: A total of 38 patients with DSM-IV schizophrenia (30 with and 8 without a DSM-IV CUD) and 20 healthy comparison subjects were included between April 2009 and June 2012. Patients were randomized to antipsychotic treatment with clozapine or risperidone. At baseline and after 4 weeks of medication, brain response to cannabis-related, positive and neutral images was measured using functional MRI. Neural correlates of cue reactivity were assessed in the following regions of interest: amygdala, ventral striatum, insula, thalamus, orbitofrontal cortex and anterior cingulate cortex. Subjective craving was assessed using self-report questionnaires (OCDUS and MCQ).
Results: At baseline, patients with a comorbid CUD showed higher subjective craving and greater activation in response to cannabis-related images compared to patients without a CUD and healthy controls in most regions of interest. Clozapine treated patients reported a greater reduction in craving ($F(1,28) = 6.0, p = 0.04$) and showed a larger decrease in amygdala activation during cannabis-related images compared to risperidone treated patients ($T = 3.94$, pFWE $= 0.006$). In addition, significant correlations were found between subjective craving and thalamus and insula activation during cannabis-related images.
Conclusion: These findings provide evidence that clozapine is superior to risperidone in decreasing subjective craving and cue reactivity for cannabis-related images probably due to a differential effect on dopaminergic neurotransmission.
Trial registration: 'Nederlands trial register' (http://www.trialregister.nl), nr NTR1761, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1761

1. Introduction

Schizophrenia is highly comorbid with cannabis abuse or dependence(Regier et al. 1990; Machielsen et al. 2010) and comorbid cannabis use disorders (CUDs) are associated with poor outcome in these patients(Regier et al. 1990; Dixon 1999; Linszen et al. 1994; Moore et al. 2007; Zammit et al. 2008). Discontinuation of cannabis use may improve outcome, and is therefore an important target in the treatment of schizophrenia(Grech et al. 2005). Craving, the subjective urge to take a drug, is considered a key feature of substance abuse, contributing to its continuation and to relapse after a period of abstinence(Franken 2003; Robinson and Berridge 1993). Reducing craving could therefore help schizophrenia patients to stop cannabis use, thereby improving outcome. Clozapine has been put forward as the antipsychotic medication of first choice in the treatment of patients with schizophrenia and comorbid substance use disorder(Machielsen and de Haan 2009; Green et al. 2008; Machielsen et al. 2012; Brunette et al. 2011; Green et al. 2003; Kim et al. 2010). However, the mechanisms underlying clozapine's assumed superiority are insufficiently known.

The consumption of most illicit drugs results in a larger dopamine release than with natural rewards. Repeated drug use leads to increased salience of drug-related cues. Furthermore, chronic substance abuse is associated with a reduction of postsynaptic dopamine receptors in the mesocorticolimbic system coupled with a decreased sensitivity for natural rewards(Volkow et al. 2004). This hypodopaminergic state, which

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is also induced by antipsychotic medication, has indeed been found to be associated with increased substance abuse in patients with schizophrenia(de Haan et al. 2006). The assumed superiority(Machielsen and de Haan 2009; Green et al. 2008; Machielsen et al. 2012; Brunette et al. 2011; Green et al. 2003; Kim et al. 2010) of clozapine in diminishing craving in schizophrenia patients may thus reflect its low affinity to dopamine receptors. Clozapine and risperidone show a maximal difference in their affinity to dopamine D_2 receptors(Kuroki et al. 2008; Seeman 2002; Tauscher et al. 2004). Clozapine has a lower D_2 occupancy rate, a higher dissociation rate and a higher D_1/D_2 receptor occupancy ratio than risperidone(Kuroki et al. 2008; Seeman 2002; Tauscher et al. 2004), which may enhance responses to natural rewards while decreasing responses to drug rewards in clozapine compared to risperidone treated patients.

The current study was designed to (a) demonstrate differences in regional brain activity related to cannabis-related cues in patients with cannabis use disorder (CUD) compared to patients without cannabis use disorder (NCUD) and healthy controls (HC), and (b) investigate differences between clozapine and risperidone in their effect on subjective cannabis craving and associated regional brain activity. We hypothesized that CUD patients show more craving and greater regional brain activation in areas previously implicated in substance-related cue reactivity (ventral striatum, amygdala, insula, anterior cingulate cortex, thalamus and orbitofrontal cortex(Chase et al. 2011; Kuhn and Gallinat 2011; Naqvi and Bechara 2010) than NCUD patients and HCs; and that CUD patients treated with clozapine compared to risperidone would show decreased craving, a decreased neural response to cannabis related images (cue reactivity) and a stronger response to positive non-cannabis related images. We also hypothesized that subjective craving would be associated with regional brain activation following cannabis-related images.

2. Materials and methods

We conducted an open-label randomized controlled trial investigating the difference between clozapine and risperidone on subjective cannabis craving and brain activity following visual cannabis-related and non-cannabis related cues during fMRI scanning.

The medical ethics committee of the Academic Medical Centre of the University of Amsterdam approved the study.

2.1. Participants

Schizophrenia patients were recruited from inpatient and outpatient treatment settings of the Early Psychosis Department of the Academic Medical centre between April 2009 and June 2012. Inclusion criteria were male gender, age 18–30, DSM-IV diagnosis of schizophrenia, schizophreniform or schizoaffective disorder (for reasons of brevity this will be referred to as schizophrenia). Of the 38 patients included in the study 30 met DSM IV criteria of a cannabis user disorder (CUD: cannabis abuse or dependence) and 8 did not use cannabis (NCUD). Exclusion criteria were previous unsuccessful treatment with or a contra-indication for the use of risperidone or clozapine, using depot antipsychotic medication three months prior to inclusion, treatment with psychotropic medication other than biperiden or benzodiazepines, and the presence of non-removable metal objects as a contraindication for fMRI scanning.

Healthy controls were recruited through advertisements on schools and sport facilities. HC had a negative history of lifetime neurologic or psychiatric diseases, including substance use disorders. HC had used cannabis for a maximum of 50 times lifetime, last time at least 1 year prior to inclusion, and were matched for age and education.

After complete description of the study, written informed consent was obtained.

2.2. Study design

Patients were randomly allocated to receive either clozapine or risperidone. Patients started with a standard dose titration scheme in the evening after the first fMRI assessment directed at a dose of 3.5 mg risperidone or 350 mg clozapine. In some cases, emerging side effects resulted in slowing of dose titration and the target dose was reached later and subsequently scanning was postponed. In case of lack of antipsychotic effect the dose was adjusted as clinically applicable. In patients who already used antipsychotic medication, that medication was tapered down in the week before the first assessment. Concomitant psychotropic medication was restricted to benzodiazepines and biperiden. During the study patients received supportive treatment-as-usual.

Assessments (functional MRI and questionnaires) took place at baseline before the first dose of study medication, and at the end of four weeks of treatment. HC were assessed once.

All participants were asked to refrain from alcohol and drugs 24 h before testing, and patients did not smoke cigarettes at least 2 h before testing. Patients were instructed to refrain from cannabis use at least 3 days before testing. This was tested with quantitative tests in urine samples taken 3 days prior to scanning and the day of the scan. Although cannabis can be detected in urine even weeks after cessation, quantification of the difference between the two samples could confirm a decrease in detectable cannabis for all subjects. In addition, urine screens for amphetamines, benzodiazepines, opioids and cocaine were performed prior to all assessments. During the second assessment blood samples were taken to test compliance to the study medication.

2.3. Assessment of diagnosis and severity of symptoms

DSM-IV diagnoses of schizophrenia were established using diagnostic interviews based on the Comprehensive Assessment of Symptoms and History (CASH)(Andreasen et al. 1992) together with interviews with parents. The Composite International Diagnostic Interview (CIDI)(Robins et al. 1988) was used to assess the presence of (lifetime) substance use disorders. Craving during the past seven days and current craving were assessed with the cannabis version of the Obsessive Compulsive Drug Use Scale (OCDUS)(Dekker et al. 2012) and the short version of the Marijuana Craving Questionnaire (MCQ)(Heishman et al. 2009), respectively. The Positive and Negative Symptoms Scale (PANSS) was used to rate symptom severity(Kay et al. 1987).

2.4. Cue-reactivity task

During scanning, participants viewed cannabis-related ($n = 30$), neutral ($n = 30$), positive ($n = 30$) and target images ($n = 15$). Cannabis images were photos of cannabis, individuals smoking cannabis and cannabis use related paraphernalia previously used by Cousijn et al. (2012). Positive and neutral images were selected from the International Affective Picture System (IAPS) data base(Lang et al. 2008). These groups of images were visually matched on color and composition. To control for sustained attention, participants were asked to pay close attention to all images and to press a key on a response box when an animal (target image) was displayed. These target images were presented in a pseudo-randomized order within blocks. Each image was presented for 4 s and preceded by a fixation-cross for 1 s in five blocks consisting of 6 images and a target picture. Between blocks, a low-level baseline (fixation-cross) was presented for 15 s. Two different versions were used in a random order for each participant. Total task duration was 10 min.

2.5. Imaging parameters and data pre-processing

A 3 T MRI scanner (Philips Intera, Best, The Netherlands) with a phased-array SENSE RF eight-channel receiver head coil was used for image acquisition. In the first scanning session, a T1 structural image

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