

Chronic pubertal cannabinoid treatment as a behavioural model for aspects of schizophrenia: effects of the atypical antipsychotic quetiapine

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Abstract

Chronic pubertal cannabinoid treatment in rats has been suggested for modelling aspects of schizophrenia since it results in long-lasting behavioural alterations reflecting certain characteristics of schizophrenia symptomatology. Lasting deficits in sensorimotor gating, impaired short-term mnemonic processing, reduced motivation as well as inappropriate and deficient social behaviour have been reported after chronic cannabinoid treatment during pubertal development. In addition, sensorimotor gating deficits were able to be restored by acute injections of the typical antipsychotic haloperidol. The aim of this study was to examine possible acute as well as lasting beneficial effects of the atypical antipsychotic drug quetiapine in adult animals undergoing chronic treatment of the synthetic cannabinoid receptor agonist WIN 55,212-2 (WIN) (1.2 mg/kg) during puberty. Therefore, animals were tested repeatedly for their performance in social interaction and social recognition after acute and chronic quetiapine treatment. Chronic pubertal WIN treatment induced persistent deficits in social recognition and impaired social interaction. Acute quetiapine treatment was able to completely restore those deficits in social behaviour and social memory. Social recognition memory was affected again 1 wk after cessation of chronic quetiapine treatment; however, in social interaction persistent improvements could be detected. In conclusion, the results indicate that the atypical antipsychotic drug quetiapine is able to acutely restore deficits in social behaviour induced by developmental cannabinoid exposure and even exert some persistent beneficial effects. Furthermore, the present data give further support and validity for the suitability of chronic pubertal cannabinoid administration as an animal model for aspects of schizophrenia.

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Introduction

Global evidence indicates that cannabis use acts as a modest risk factor for the emergence of schizophrenia (Caspi *et al.* 2005). It is well known that cannabis or cannabinoid intoxication can lead to acute transient psychotic episodes in some individuals (Koethe *et al.* 2009) and it can produce short-term exacerbation, recurrences as well as an earlier onset of psychotic symptoms (Hall & Degenhardt 2000; Jockers-Scherübl *et al.* 2003; Veen *et al.* 2004). Acute cannabis use can induce attentional deficits in humans similar to those

observed in acute schizophrenia and is associated with schizotypal personality (Skosnik *et al.* 2001), and several reports have shown that cannabis consumption can induce schizophrenia-like symptoms in healthy individuals (Emrich *et al.* 1997; Koethe *et al.* 2009; Leweke *et al.* 1999*b*). Recent findings have even suggested that a dysregulation of the endogenous cannabinoid system may be associated with the pathogenesis of schizophrenia (Dean *et al.* 2001; Emrich *et al.* 1997; Giuffrida *et al.* 2004; Leweke *et al.* 1999*a*).

We have shown recently that chronic treatment with the synthetic cannabinoid full receptor agonist WIN 55,212-2 (WIN) during pubertal development leads to long-lasting behavioural disturbances in adulthood, resembling certain characteristics of schizophrenia symptomatology (Schneider & Koch,

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2003, 2005, 2007; Schneider *et al.* 2008). Therefore, chronic pubertal WIN administration has been proposed as a valid animal model for schizophrenia. Cannabinoid exposure during pubertal development in rats induces lasting short-term memory deficits (O'Shea *et al.* 2004; Quinn *et al.* 2008; Schneider & Koch 2003, 2007), impairs sensorimotor gating, and leads to deficient and inadequate social behaviour and anhedonia in adulthood (Schneider & Koch 2003, 2005, Schneider *et al.* 2008), thereby displaying high face validity with aspects from the positive and negative symptom cluster from schizophrenia patients. Furthermore, the construct validity of this animal model is quite high, since prospective studies were able to show that the use of cannabis preparations during adolescence increases the likelihood of experiencing symptoms of schizophrenia in adulthood (Arseneault *et al.* 2004; Caspi *et al.* 2005; Konings *et al.* 2008). Cannabis use has been associated with an increased risk of experiencing schizophrenia symptoms, which does not appear to be secondary to a pre-existing psychosis. Furthermore, early cannabis use entails a greater risk for schizophrenia outcomes than later cannabis use (by age 18 yr) (for detailed review see Arseneault *et al.* 2004; Moore *et al.* 2007), indicating the high susceptibility of the pubertal developmental period for the deleterious effects of cannabinoids. Finally, with respect to the predictive validity of chronic pubertal WIN administration, it has been shown that lasting deficits, found after chronic pubertal WIN administration in sensorimotor gating could be reversed by acute injections of the classical antipsychotic haloperidol (Schneider & Koch, 2003).

The aim of the present study was to investigate possible acute and long-term beneficial effects of the atypical antipsychotic drug quetiapine (Seroquel[®], AstraZeneca, Germany) on social behaviour in animals pre-treated with the cannabinoid agonist WIN during pubertal development. The focus of this study was on social skills, since inadequate and atypical social behaviour and social withdrawal are among the findings of patients with schizophrenia from the negative symptom cluster (APA, 1994). We therefore examined the effects of quetiapine in WIN-treated rats on social behavioural skills and short-term mnemonic processing in a social context, using the social interaction test and the recognition memory test for social partners. The antipsychotic quetiapine is a dibenzothiazepine derivative that is widely used in the treatment of schizophrenia and other psychotic disorders (Ellenbroek *et al.* 1996). Quetiapine has a modest effect on positive and negative symptoms, as well as cognitive impairments in schizophrenia. Negative

symptoms in schizophrenia are important in affecting the psychosocial and occupational functioning of patients, and atypical antipsychotic drugs play an important role in the treatment of negative symptoms, since they have been shown to be superior to conventional drugs in this regard (Kinon *et al.* 2006).

Methods

Subjects

A total of 37 first-generation offspring male Wistar rats from our own breeding colony were used for the present study. Adult male and female Wistar rats were imported from Harlan-Winkelmann (The Netherlands) and housed together in pairs under standard conditions on a 12-h light/dark schedule (lights on 07:00 hours). They received free access to tap water and were fed *ad libitum*. After 3 wk male rats were removed from the breeding cages. The litters were culled to eight pups directly after birth. In order to avoid litter effects we attempted to assign equal proportions of rats of each litter to the different treatment groups (Zorilla, 1997).

After weaning on postnatal day (PD) 21, male pups were housed in a different room in groups of 6 (Macrolon cage type IV) under standard conditions on a 12-h light/dark schedule (lights on 06:00 hours). They received free access to tap water and were fed *ad libitum*.

The experiments were performed in accordance with the ethical guidelines for the care and use of laboratory animals and were approved by the local animal care committee (Cologne, Germany).

Drugs

WIN 55,212-2 (WIN) (Sigma-Aldrich, Germany) was dissolved in 0.1% Tween-80 and diluted in saline (0.9%). The drug was administered intraperitoneally (i.p.) at a dose of 1.2 mg/kg.

Quetiapine (AstraZeneca) was dissolved in 0.3% tartaric acid and the pH was adjusted to 5.5 with 0.1 N NaOH. Quetiapine was administered i.p. at a dose of 7 mg/kg.

Injection volumes were 1 ml/kg. The experimenter was blind to the drug treatment of the animals.

Experimental design

The pubertal chronic treatment of either the synthetic cannabinoid agonist WIN or vehicle lasted 25 d from PD 40 to PD 65 throughout the rats' puberty (Fig. 1) (Schneider, 2008). During this period the rats received

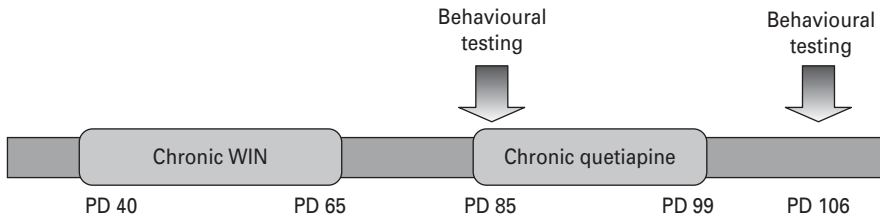


Fig. 1. Time schedule of pubertal cannabinoid treatment and subsequent behavioural testing and quetiapine administration.

20 injections which were not delivered regularly. Each day the rats received either 1, 2 or no injection (10 times one injection, 5 times two injections and 10 times no injection per day). This protocol was chosen in order to mimic the irregular consumption practice in humans (Schneider & Koch, 2003). Twenty rats received WIN and 17 rats received vehicle. At PD 85, 20 d after cessation of the cannabinoid treatment the animals were further divided into subgroups and received either a chronic quetiapine (Quet) or vehicle (Veh) treatment for 14 d (Veh-Veh: $n=9$; WIN-Veh: $n=11$; Veh-Quet: $n=8$; WIN-Quet: $n=9$). Behavioural performance was assessed during and after quetiapine treatment. First, the acute effects of quetiapine were investigated 30 min after the first quetiapine injection on PD 85. Additionally, the animals' behavioural performance was retested 7 d after the cessation of chronic quetiapine treatment on PD 106.

Behavioural testing took place between 8:00 and 16:00 hours and included the analysis of social interaction and the social recognition test. Behavioural performance was videotaped (digital handycam, Sony, USA) and evaluated offline by a trained experimenter blind to group assignment. Constant background noise was provided by a radio (65 dB) during behavioural testing.

Behavioural testing

Social recognition

Social memory was assessed using the social recognition test. For social recognition young male rats were used as social stimuli to exclude confounding effects of aggression and sexual behaviour (Everts & Koolhaas, 1997; Schneider & Koch, 2002). They were marked on the head and tail for later identification and were kept individually 1 h prior to and during testing to ensure a characteristic body odour. Juveniles received 10-min habituation to the test arena 24 h before testing. Experimental rats were placed in the open field and exposed to an unknown social partner (A) for 3 min during the first sample phase (P1). After the 15-min

inter-trial interval the familiar (A') and a novel (B) social partner were presented to the experimental animal in P2. Social investigation (anogenital exploration and non-anogenital exploration) was recorded during P1 and P2. Other social behaviours, such as grooming, crawling over or social play, were not scored as social investigation.

Social interaction

Social interaction was assessed in the open field during P1 of the social recognition test where the rat to be tested was exposed to an unfamiliar social partner for 3 min (Schneider *et al.* 2008). The following behavioural elements were quantified only for the experimental rats.

(A) *Social behaviour.* Contact behaviour, social exploration, tail manipulation and approach/following were scored as social behaviours (Pellis *et al.* 1997; Vanderschuren *et al.* 1997). (1) Contact behaviour: contact behaviour includes (a) grooming (chewing and licking the partner's fur) and (b) crawling over/under the partner; (2) social exploration: (a) anogenital investigation (sniffing or licking the anogenital area of the social partner) and (b) non-anogenital investigation (sniffing at any part of the partner's body, except the anogenital area); (3) approach/following: approaching or following the social partner in the test arena.

(B) *Evade.* Running, leaping or swerving away from the social partner. Evade, which is normally defined as a defensive behaviour in the context of social play (e.g. Pellis *et al.* 1992), was scored in the social interaction test as an active withdrawal from social contact. Social play behaviours (pinning, attack, defence) occurred so rarely during the 3-min social interaction period that they were not evaluated.

(C) *Self-grooming behaviour.* Licking or biting own fur and rubbing forepaws over the head (Robertson *et al.* 1999).

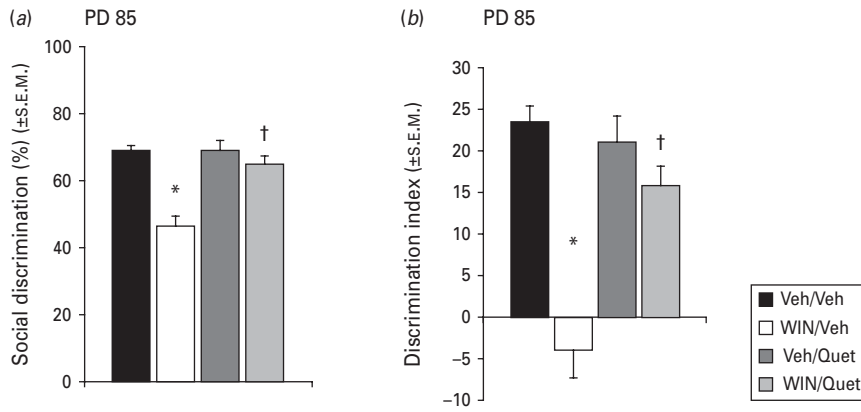


Fig. 2. Social recognition at PD 85 after acute quetiapine treatment in WIN pre-treated rats. Percentage social discrimination ($p < 0.001$) as well as discrimination index ($p < 0.001$) were significantly reduced after chronic WIN administration compared to vehicle (Veh/Veh)-treated controls (*). These deficits were completely restored in WIN pre-treated rats after acute quetiapine injection since they did not differ from controls (Veh/Veh and Veh/Quet) ($p > 0.05$) but showed a higher percentage social discrimination ($p < 0.001$) and discrimination index ($p < 0.001$) than WIN/Veh groups (†).

Statistical analysis

In the social recognition test the exploration time was recorded during P1 (A), and for the two conspecifics in P2 (A' and B). Besides the discrimination index ($B - A'$), social discrimination was also evaluated. Calculation of the social discrimination exploration time of the novel conspecific was expressed as percentage of the total exploration time of both conspecifics during P2 ($100 / (A' + B) \times B$).

Different social behaviours were quantified during social interaction testing. Since the occurrence of social grooming and crawling over was quite rare, these behaviours were expressed together as total contact behaviour. In addition, contact behaviour and social exploration were also summed and expressed as total social behaviour.

Effects of chronic WIN and chronic quetiapine treatment on behavioural performance in social recognition and social interaction were evaluated using a two-way ANOVA, followed by *post-hoc* Tukey *t* tests for pairwise comparisons. A value of $p < 0.05$ was considered to represent a significant effect.

Results

Social recognition

Acute quetiapine treatment

A two-way ANOVA revealed a significant drug interaction effect for chronic WIN and acute quetiapine administration for percentage social discrimination ($F_{1,33} = 12.7$, $p < 0.05$) and discrimination index

($F_{1,33} = 12.2$, $p < 0.05$) at PD 85 (Fig. 2). A significant reduction of social discrimination and discrimination index was only detected in WIN-treated rats that received acute vehicle injections. This social recognition deficit was completely restored in rats that received an acute quetiapine injection (percentage social discrimination: $p > 0.05$; discrimination index: $p > 0.05$). Neither chronic pubertal WIN nor acute quetiapine treatment affected the initial exploration of the social partner during P1 at PD 85 (values, Veh/Sal: 64.8 ± 5.7 ; Veh/Quet: 60.9 ± 6.1 ; WIN/Sal: 59.8 ± 5.2 ; WIN/Quet: 57.4 ± 5.7) (WIN treatment: $F_{1,33} = 1.1$, $p > 0.05$; quetiapine: $F_{1,33} = 0.7$; $p > 0.05$) (Veh-Veh: $n = 9$; WIN-Veh: $n = 11$; Veh-Quet: $n = 8$; WIN-Quet: $n = 9$).

Chronic quetiapine treatment

Chronic pubertal WIN treatment still significantly affected social recognition 1 wk after cessation of chronic quetiapine or vehicle treatment at PD 106 (Fig. 3). Two-way ANOVA revealed a WIN treatment effect for percentage social discrimination ($F_{1,33} = 25.6$, $p < 0.05$) and discrimination index ($F_{1,33} = 23.4$, $p < 0.05$). However, no effect of chronic quetiapine treatment was detected on either social discrimination ($F_{1,33} = 0.3$, $p > 0.05$) or discrimination index ($F_{1,33} = 0.2$, $p < 0.05$). The initial exploration of the social partner during P1 was unaffected by chronic WIN and chronic quetiapine treatment (values, Veh/Sal: 73.6 ± 6.1 ; Veh/Quet: 72.1 ± 6.5 ; WIN/Sal: 70.0 ± 5.5 ; WIN/Quet: 70.0 ± 6.1) (WIN treatment: $F_{1,33} = 0.2$, $p > 0.05$; quetiapine: $F_{1,33} = 0.02$, $p > 0.05$) (Veh-Veh: $n = 9$; WIN-Veh: $n = 11$; Veh-Quet: $n = 8$; WIN-Quet: $n = 9$).

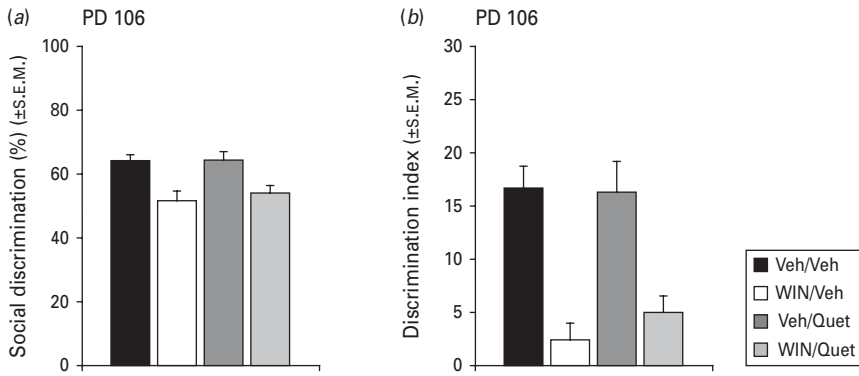


Fig. 3. Social recognition at PD 106 after chronic quetiapine treatment in WIN pre-treated rats. At PD 106 a general WIN treatment effect was still obtained for percentage social discrimination and discrimination index. However, no lasting effect of the chronic quetiapine treatment was detected and also no interaction effect.

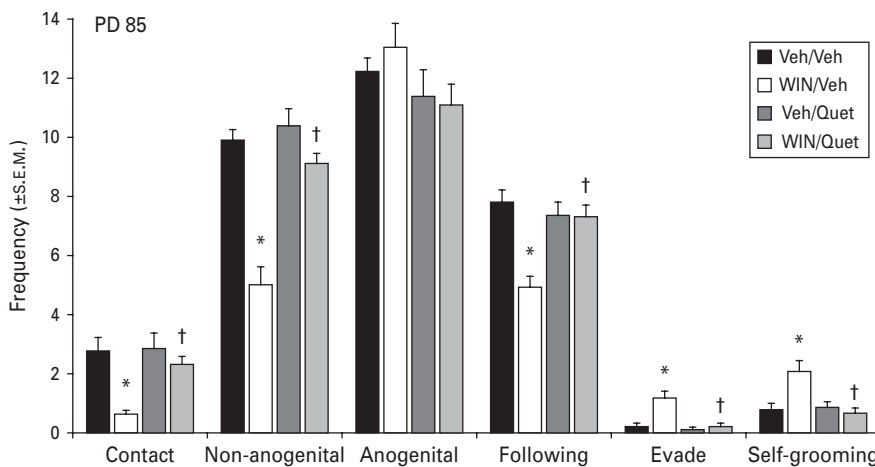


Fig. 4. Social interaction after acute quetiapine treatment at PD 85 in WIN pre-treated rats. Social contact behaviour ($p < 0.001$), following ($p < 0.001$), non-anogenital investigation ($p < 0.001$), social evade ($p = 0.001$) and self-grooming ($p = 0.007$) were significantly affected by chronic pubertal WIN treatment compared to vehicle (Veh/Veh)-treated controls (*). No such deficits were detected in WIN-treated rats that received an acute injection of quetiapine compared to controls (Veh/Veh and Veh/Quet) ($p > 0.05$). WIN pre-treated animals that received quetiapine differed significantly from those receiving WIN and vehicle (†) for social contact behaviour ($p = 0.006$), following ($p = 0.002$), non-anogenital investigation ($p < 0.001$), social evade ($p = 0.001$) and self-grooming ($p = 0.004$).

Social interaction

Acute quetiapine treatment

A significant drug interaction effect was detected by two-way ANOVA for chronic pubertal WIN and acute quetiapine treatment at PD 85 (Fig. 4) for social contact behaviour ($F_{1,33} = 4.2$, $p < 0.05$), following ($F_{1,33} = 7.4$, $p < 0.05$), non-anogenital investigation ($F_{1,33} = 8.0$, $p < 0.05$), total social behaviour (data not shown) ($F_{1,33} = 4.3$, $p < 0.05$), social evade ($F_{1,33} = 4.8$, $p < 0.05$) and self-grooming ($F_{1,33} = 5.2$, $p < 0.05$).

A significant reduction in contact behaviour by WIN was only observed in vehicle-treated animals at PD 85 compared to controls. No lasting WIN effect on

contact behaviour was found in quetiapine-treated rats ($p > 0.05$). Similar results were also obtained for the other social behaviours. Chronic pubertal WIN administration significantly reduced following, non-anogenital investigation and total social behaviour only in vehicle-, but not in quetiapine-treated rats. Similarly, social evade and self-grooming behaviour were significantly increased in WIN-treated rats receiving acute vehicle injections compared to controls. This effect was not found in WIN-treated animals that received acute quetiapine treatment.

Neither chronic pubertal WIN nor acute quetiapine administration affected anogenital investigation at PD 85 (WIN treatment: $F_{1,33} = 0.1$, $p > 0.05$;

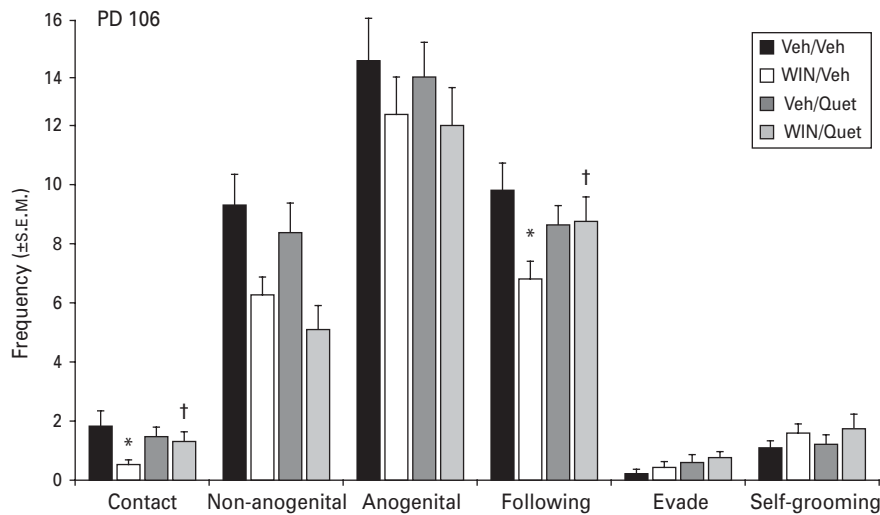


Fig. 5. Social interaction after chronic quetiapine treatment at PD 106 in WIN pre-treated rats. A general lasting effect of pubertal WIN treatment was still observed for contact behaviour, following, and non-anogenital exploration. In addition, drug-interaction effects for quetiapine and WIN were detected for social contact behaviour and following, with WIN/Veh animals showing a significant reduction of these behaviours compared to controls (*) ($p=0.005$ and $p=0.003$, respectively) and compared to animals receiving the chronic quetiapine treatment after WIN pre-exposure (†) (contact behaviour: $p=0.047$; following: $p=0.046$).

quetiapine: $F_{1,33}=1.9$, $p>0.05$) (Veh-Veh: $n=9$; WIN-Veh: $n=11$; Veh-Quet: $n=8$; WIN-Quet: $n=9$).

Chronic quetiapine treatment

One week after cessation of chronic quetiapine treatment a two-way ANOVA detected a significant drug interaction effect for WIN and quetiapine at PD 106 (Fig. 5) for social contact behaviour ($F_{1,33}=4.5$, $p<0.05$) and following ($F_{1,33}=4.2$, $p<0.05$). A significant reduction of contact behaviour and following compared to controls was only found in WIN-treated animals that had received chronic vehicle treatment. No lasting WIN effect was observed in animals that underwent chronic quetiapine treatment ($p>0.05$).

Lasting significant effects of pubertal WIN treatment were found at PD 106 for non-anogenital exploration ($F_{1,33}=16.3$, $p<0.05$) and total social behaviour (data not shown) ($F_{1,33}=7.9$, $p<0.05$). Chronic quetiapine treatment had no effect on either non-anogenital exploration ($F_{1,33}=2.2$, $p>0.05$) nor total social behaviour ($F_{1,33}=0.3$, $p>0.05$).

No effects were found for anogenital exploration (WIN treatment: $F_{1,33}=1.6$, $p>0.05$; quetiapine: $F_{1,33}=0.1$, $p>0.05$), social evade (WIN treatment: $F_{1,33}=0.8$, $p>0.05$; quetiapine: $F_{1,33}=2.9$, $p>0.05$) and self-grooming behaviour (WIN treatment: $F_{1,33}=2.1$, $p>0.05$; quetiapine: $F_{1,33}=0.1$, $p>0.05$) (Veh-Veh: $n=9$; WIN-Veh: $n=11$; Veh-Quet: $n=8$; WIN-Quet: $n=9$).

Discussion

In the present study we showed that social deficits observed in adult rats after chronic pubertal cannabinoid treatment can be completely restored by acute administration of the atypical antipsychotic drug quetiapine. Chronic treatment with the cannabinoid agonist WIN throughout the pubertal period induced persistent impairments in social behaviour and social memory, confirming our previous findings (Schneider & Koch, 2005; Schneider *et al.* 2008). Social deficits were even observed 40 d after treatment cessation. Social recognition memory was affected again 1 wk after cessation of chronic quetiapine treatment; however, in social interaction minor persistent improvements could be detected.

Chronic pubertal WIN treatment affected social behaviour during social interaction testing in adult rats 20 d after treatment cessation on PD 85. Social contact behaviours as well as exploratory behaviours (non-anogenital sniffing and following) and the total amount of social behaviours were reduced, while the anxiety-related behaviours (social evade and self-grooming) were enhanced compared to vehicle-treated controls. These findings confirm results of our previous study where social behaviour was tested at PD 75 (Schneider *et al.* 2008) and are partially in accord with earlier findings (O'Shea *et al.* 2004) that reported a persistent decrease in total social interaction after adolescent cannabinoid exposure. In addition, a clear

deficit was also observed in social recognition testing of WIN-treated rats, indicating that chronic pubertal WIN treatment leads to deficient olfactory social recognition and inadequate social behaviour in adulthood.

Acute quetiapine treatment at PD 85 completely restored the behavioural deficits observed in social interaction and social recognition after chronic WIN treatment. No differences were detected between WIN pre-treated rats that received an acute injection of quetiapine and those that received vehicle.

All animals were retested 21 d later for their social performance, 1 wk after cessation of chronic quetiapine treatment. It appeared that social recognition memory was affected again in all WIN-treated rats at PD 106, irrespective whether they had received chronic quetiapine or vehicle treatment. Similar results were found for total social behaviour as well as non-anogenital exploration during social interaction testing. However, the effects of pubertal WIN treatment on anxiety-related behaviours (e.g. increased self-grooming and evade) upon social contact were no longer observed at PD 106 and therefore did not depend on the quetiapine/vehicle treatment. Thus, it appears that this WIN-induced increase in anxiety-related behaviours is only a transient effect that wanes around 1 month after treatment cessation. Interestingly, some minor persistent positive effects on social interaction of the chronic quetiapine treatment could still be found 7 d later. Social contact behaviour and following were not affected at PD 106 in WIN pre-treated animals that underwent chronic quetiapine treatment.

We have shown previously that chronic pubertal WIN exposure might serve as a promising animal model with high face and construct validity for the aetiology and symptomatology of schizophrenia (Schneider & Koch, 2003, 2005; Schneider *et al.* 2008). The present findings additionally demonstrate a high predictive validity of this animal model, since it is shown that lasting behavioural deficits observed after pubertal cannabinoid administration can not only be restored by administration of first-generation antipsychotics like haloperidol (Schneider & Koch, 2003) but also by atypical antipsychotics such as quetiapine.

The finding that acute quetiapine treatment efficiently restored impairments in social functioning is in line with other studies showing similar positive effects of short-term and chronic quetiapine treatment on social behaviour. Quetiapine treatment has been associated with improvements in social competence and social functioning in schizophrenia patients (Harvey *et al.* 2006; Swartz *et al.* 2007; Tyson *et al.*

2006). Similar results were also found in animal studies. In an animal model for negative symptoms of schizophrenia in Java monkeys, quetiapine prevented the occurrence of amphetamine-induced social isolation (Ellenbroek *et al.* 1996). In addition, quetiapine significantly inhibited social isolation-induced aggressive behaviour in Wistar rats (Uchida *et al.* 2009).

Quetiapine shows affinity for multiple brain receptors, including serotonergic 5-HT₂ receptors and dopaminergic D₂ receptors. It has a greater affinity for 5-HT₂ than D₂ receptors, together with considerable activity at histamine H₁ receptors, α_1 - and α_2 -adrenergic receptors. Even though quetiapine alone is not able to activate these receptors, it behaves as a competitive antagonist and therefore prevents the effects of endogenous neurotransmitters at these sites. In addition, quetiapine has partial agonist activity at serotonin 5-HT_{1A} receptors (Ellenbroek *et al.* 1996; Orsetti *et al.* 2007). Interestingly, it has been shown that schizophrenia patients taking atypical antipsychotics with little or no affinity to 5-HT_{2A} receptors (quetiapine, amisulpride) performed better on a measure of social functioning than those on high-5-HT_{2A}-affinity antipsychotics (risperidone, olanzapine, clozapine). By contrast, splitting the patient group in terms of the dopaminergic properties of the antipsychotics yielded no group differences. These findings suggest that 5-HT_{2A} affinity may play an important role in the cognitive effects of the atypical antipsychotics, and that low or no affinity may be more beneficial for social function than high affinity (Tyson *et al.* 2006). Further studies will be necessary to identify the detailed mechanisms underlying the beneficial effects of acute and also chronic quetiapine treatment on social behaviour in WIN pre-treated animals.

Notably, no quetiapine effects on social interaction or social recognition were observed in vehicle pre-treated rats, indicating that quetiapine alone does not affect social functioning in male adult rats. This finding is valuable for a better understanding of the complete spectrum of possible side-effects of antipsychotics, since it has been shown before that quetiapine together with other typical and atypical antipsychotic drugs has a negative effect on maternal social behaviour in rats (Li *et al.* 2004).

In conclusion, the present results indicate that acute treatment with the second-generation antipsychotic drug quetiapine effectively restores behavioural deficits induced by developmental cannabinoid exposure and even exerts some minor longer-lasting beneficial effects on social behaviour. In addition, the present data further support the suitability of chronic pubertal cannabinoid administration as an animal model with

high validity for negative symptoms that resemble the characteristics of schizophrenia.

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Statement of Interest

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