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GENETICS AND NEUROSCIENCE (C O'TUATHAIGH, SECTION EDITOR)

# Molecular Basis of Cannabis-Induced Schizophrenia-Relevant Behaviours: Insights from Animal Models

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**Abstract**
*Introduction* Cannabis use is a well-established component risk factor for schizophrenia; however, the mechanisms by which cannabis use increases schizophrenia risk are unclear. Animal models can elucidate mechanisms by which chronic cannabinoid treatment can induce schizophrenia-relevant neural changes, in a standardised manner often not possible using patient-based data.
*Methods* We review recent literature (within the past 10 years) using animal models of chronic and subchronic treatment with cannabinoids which target the cannabinoid 1 receptor [i.e. $\Delta^9$-tetrahydrocannabinol, CP55,940 and WIN55,212-2]. Schizophrenia-relevant behavioural consequences of chronic cannabinoid treatment are first briefly summarised, followed by a detailed account of changes to several receptor systems [e.g. cannabinoid, dopaminergic, glutamatergic, $\gamma$-aminobutyric acid (GABAe)rgic, serotonergic, noradrenergic], dendritic spine morphology and inflammatory markers following chronic cannabinoids. We distinguish between adolescent and adult cannabinoid treatments, to determine if adolescence is a period of susceptibility to schizophrenia-relevant molecular changes.
*Results* Chronic cannabinoid treatment induces behaviours relevant to positive, negative and cognitive symptoms of schizophrenia. Chronic cannabinoids also cause region- and subtype-specific changes to receptor systems (e.g. cannabinoid, dopaminergic, glutamatergic, GABAergic), as well as changes in dendritic spine morphology and upregulation of inflammatory markers. These changes often align with molecular changes observed in post-mortem tissue from schizophrenia patients and correspond with schizophrenia-relevant behavioural change in rodents. There is some indication that adolescence is a period of susceptibility to cannabinoid-induced schizophrenia-relevant neural change, but more research in this field is required to confirm this hypothesis.
*Conclusions* Animal models indicate several molecular mechanisms by which chronic cannabinoids contribute to schizophrenia-relevant neural and behavioural change. It is likely that a number of these mechanisms are simultaneously impacted by chronic cannabinoids, thereby increasing schizophrenia risk in individuals who use cannabis. Understanding how cannabinoids can affect several molecular targets provides critical insight into the complex relationship between cannabis use and schizophrenia risk.

**Keywords** Mouse model · Chronic cannabinoid treatment · $\Delta^9$-Tetrahydrocannabinol · WIN55,212-2 · CP55,940 · Glutamate receptor · Cannabinoid receptor · Dopamine receptor · $\gamma$-Aminobutyric acid receptor · GABA receptor · Dendritic spine morphology · Inflammation

## Introduction

Cannabis use increases the risk of developing schizophrenia [1, 2], particularly in individuals with genetic susceptibility for the disorder [3]. However, the precise mechanisms by which cannabis use increases schizophrenia risk are unclear. Elucidating these mechanisms in humans is difficult because of potentially confounding factors including the amount and

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frequency of cannabis smoked, cannabinoid composition, polydrug use, genetic predisposition, early life trauma and comorbid mental disorders. Rodent models of cannabis abuse provide an excellent opportunity to determine the molecular and cellular consequences of chronic cannabis abuse in a highly standardised manner and to relate these to behavioural impairments relevant to schizophrenia [for a review of cannabinoid-induced schizophrenia-relevant behaviour, see [4••]].

This review will present recent preclinical data (<10 years) to determine cannabinoid-induced changes in receptor expression and function, dendritic morphology and inflammatory markers and will relate brain pathology to schizophrenia-relevant behavioural changes in rodents. We will focus on the behavioural and molecular effects of cannabinoids targeting the $CB_1$ receptor ($CB_1R$), as the psychotic effects of cannabinoids are predominantly mediated by presynaptic $CB_1R$ activation [5••, 6]. Subchronic (3–7 days) and chronic (>7 days) administration paradigms will be discussed. These treatment designs are most relevant for modelling long-term cannabis use, which can precede the development of psychotic disorders in human patients [5••]. We will distinguish between adolescent and adult cannabinoid treatments, as adolescence appears to be a period of heightened susceptibility to cannabis-induced behavioural and brain changes [7•]. In this review, rodent adolescence will be broadly defined as post-natal day (PND) 21–60, which corresponds with preadolescence (8–10 years) until adulthood (18 years) in humans [8, 9].

## Behavioural Consequences of Chronic Cannabinoid Administration

Methodological details for references in this section are presented in Table 1.

### Positive-Like Behaviours

Positive symptoms of schizophrenia (e.g. hallucinations, delusions) are modelled in rodents through baseline and psychomimetic drug-induced locomotor activity, as this behavioural assay shares mechanisms of action with positive symptoms (i.e. enhanced prefrontal dopamine release) [58, 59•] and mimics elevated locomotor activity observed in patients with schizophrenia [60, 61].

Chronic cannabinoid treatment affects locomotor tolerance differently in adolescence and adulthood. The development of tolerance to the locomotor-suppressive effects of chronic or subchronic treatment with $\Delta^9$-tetrahydrocannabinol (THC, the main psychoactive component in cannabis) or CP55,940 (CP, a $CB_1R$ agonist) is present in adult rats [12, 17, 19, 22] but not adolescent rats [[14, 15, 21, 22] for mice, see [16, 20]]. Effects of chronic adolescent THC on locomotion appear to be modulated by genetic susceptibility to schizophrenia, e.g. mutation in the *Neuregulin 1* (*Nrg1*) and *catechol-O-methyltransferase* (*COMT)* genes [16, 18]. These genes regulate processes including neuronal migration, myelination, synaptic plasticity [*NRG1* [62]] and dopamine metabolism [*COMT* [63]], and polymorphisms in these genes are associated with increased cannabis abuse [*NRG1* [64]] or increased risk of psychosis following cannabis abuse [*COMT* [3]]. The $CB_1R$ agonist WIN55,212-2 (WIN) has different effects to THC and CP during chronic treatment, elevating locomotion at low doses [10] and suppressing locomotion at high doses [11]. Different effects of WIN on locomotion compared to THC and CP may arise from distinct $CB_1R$ affinities of these cannabinoids [65]. After an extended drug-free period, chronic cannabinoid treatment has no effect on drug-free locomotor activity at either age [[13, 14, 18, 23] although see [15]], but alters sensitivity to the locomotor-stimulating effects of psychomimetic drugs [12, 13, 23], suggesting that persistent neural adaptations occur within locomotor circuitry.

### Negative-Like Behaviours

Negative symptoms in schizophrenia include social withdrawal, emotional blunting, anhedonia, avolition and alogia, and can be modelled in rodents with for example tests of social interaction and social preference (modelling social withdrawal) and sucrose preference (modelling anhedonia) [66]. Chronic THC or WIN treatment in adolescence impairs social interaction when animals are tested during the treatment period [16, 25, 28] or drug free in adulthood [18, 23, 26–29, 31]. Gene mutations in *Nrg1* and *COMT* appear somewhat protective against adolescent cannabinoid-induced impairment in social behaviour [[16, 27] but see also [18]]. Chronic THC and WIN treatment in adolescence but not adulthood reduces preference for palatable food or sucrose, when animals are tested drug free in adulthood [adolescence: [24•, 29, 30]; adulthood: [24•, 29]]. These results suggest that adolescence is a period of increased susceptibility for cannabinoid-induced negative-like behaviours.

### Cognitive Impairment

Cognitive impairments in schizophrenia are characterised by deficits in attention, working memory, long-term memory and executive function, and rodent behavioural tasks can model some aspects of these domains [67••]. Chronic THC impairs spatial working memory, when animals are tested drug free during adolescence or in adulthood [[18, 23, 31, 44–47] but see [48]]. Chronic adolescent THC, WIN or CP also causes short-term recognition memory impairments up to 4 days after treatment cessation [19, 40] and in adulthood [[18, 23, 28, 29, 31, 33, 34, 40–43] but see [38]]. Subchronic THC in late adolescence

**Table 1** Behavioural changes following chronic or subchronic cannabinoid treatment

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Test age | Positive-like behaviours |
|---|---|---|---|---|---|---|---|
| Enayatfard et al. [10] | Rats | Male | WIN | 0.1 mg/kg twice daily for 10 days | Adult (no PND provided) | Days 1, 5, 10 of treatment and 2 days after treatment cessation | Chronic WIN treatment in adulthood causes locomotor sensitization when rats are tested under WIN treatment. Elevated locomotor activity is present in WIN-treated rats 2 days after treatment cessation. |
| Fanarioti et al. [11] | Rats | Male | WIN | 0.1, 0.3 or 1 mg/kg daily for 20 days | Adult (no PND provided) | Days 1, 10, 20 of treatment | Chronic WIN treatment in adulthood causes locomotor suppression when rats are tested under WIN treatment. |
| Ginovart et al. [12] | Rats | Male | THC | 1 mg/kg daily for 21 days | Adult (no PND provided) | Day 20 of treatment and 1 day after cessation of treatment | Chronic THC treatment in adulthood causes an acute reduction in locomotion (day 1 of treatment); tolerance to this effect develops by day 7 and is evident at day 21. Chronic adult THC treatment reduces locomotor activity to 2.5 mg/kg amphetamine and increases activity to 0.5 mg/kg quinpirole. |
| Gomes et al. [13] | Rats | Male | WIN | 20 injections of 1.2 mg/kg over 25 days | PND 40–65 | PND 85+ | Chronic adolescent WIN treatment enhances locomotor activity to 0.5 mg/kg amphetamine when rats are tested in adulthood. |
| Harte and Edwards [14] | Rats | Male + female | THC | 2 mg/kg daily for 19 days | PND 22–40 (juvenile/early adolescence) or PND 41–60) (late adolescence) | PND 22, 29 and 40 (juvenile/early adolescence) or PND 41, 48 and 60 (late adolescence) | THC reduces locomotor activity in male and female rats treated and tested in early adolescence; THC treatment reduces locomotor activity in females treated and tested in late adolescence, but not males. |
| Klug and van den Buuse [15] | Mice (WT and *BDNF* HET) | Male + female | CP | 0.4 mg/kg, 5× per week, for 3 weeks | PND 42–63 | PND 77+ | CP treatment in adolescence reduces locomotor activity in males and females when tested under CP treatment. Adolescent CP treatment reduces locomotor activity in males when tested 2 weeks after treatment cessation. |
| Long et al. [16] | Mice (WT and *Nrg1* TM HET) | Male | THC | 10 mg/kg daily for 21 days | PND 31–52 | PND 31, 43, 53 | THC treatment in adolescence reduces locomotor activity in WT mice are tested under THC on day 1 of treatment, but not on day 13 of treatment or 1 day after treatment cessation. THC treatment in adolescence reduces locomotor activity in *Nrg1* TM HET mice on day 1 of treatment and 1 day after treatment cessation. |
| O'Brien et al. [17] | Rats | Male | THC | 2.5 mg/kg daily for 14 days | Adult (no PND provided) | Days 1, 7, 14 of treatment | Chronic THC treatment in adulthood does not affect locomotor activity in a light-dark test. |
| O'Tuathaigh et al. [18] | | Male | THC | 4 or 8 mg/kg daily for 21 days | PND 32–52 (adolescent) or | | THC treatment in adolescent male *COMT* HET and *COMT* KO mice led to |

**Table 1** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Test age | Positive-like behaviours |
|---|---|---|---|---|---|---|---|
| | Mice (WT, *COMT* HET and *COMT* KO) | | | | PND 70–90 (adult) | PND 73+ (adolescent) or PND 111+ (adult) | elevated locomotor activity in adulthood; this effect was not present in adolescent female mice treated with THC or adult mice of either genotype treated with THC. |
| Puighermanal et al. [19] | Mice | Male | THC | 10 mg/kg, daily for 6 days | Adult (no PND provided) | During treatment and for 6 days after treatment cessation | Chronic THC in adulthood does not cause locomotor tolerance. |
| Tai et al. [20] | Mice | Male | THC, $CB_1$ agonists JWH-018 or JWH-073 | THC: 30 mg/kg daily for 4 days; JWH-018: 3 mg/kg daily for 4 days, JWH-073: 10 mg/kg daily for 4 days | Adult (no PND provided) | Adult (no PND provided) | Subchronic THC in adulthood causes locomotor tolerance. |
| Wiley and Burston [21] | Rats | Male + female | THC | 10 mg/kg 2× daily for 9.5 days | PND 30–39 | PND 40 | THC treatment in adolescence reduces locomotor activity in males and females, when rats are tested under THC treatment. |
| Wiley et al. [22] | Rats | Male | THC | 0.03, 0.1, 0.3 and 1 mg/kg daily for 10 days | PND 27–37 (adolescent) or PND 70–80 (adult) | PND 34–38 (adolescent) or PND 78–82 (adult) | THC reduces locomotor activity in male rats treated and tested in early adolescence; THC failed to reduce locomotor activity when rats were treated and tested in adulthood. |
| Zamberletti et al. [23] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | THC treatment in adolescence does not affect baseline locomotor activity when rats are tested in adulthood. Locomotor activity induced by acute phencyclidine (2.5 mg/kg) is greater in rats treated with THC in adolescence, compared to vehicle-treated rats. |
| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Test age | Negative-like behaviours |
| Bambico et al. [24•] | Rats | Male | WIN | 0.2 or 1 mg/kg daily, for 20 days | PND 28–48 (adolescent) or PND 50–70 (adult) | PND 70–100 (adolescent) or PND 90–120 (adult) | Chronic adolescent WIN treatment reduces sucrose preference when rats are tested drug free in adulthood, but chronic WIN treatment in adulthood has not effect on subsequent sucrose preference. |
| Klein et al. [25] | Rats | Male | THC | Escalating dose regime, daily, for 21 days (1 mg/kg for days 1–7, 3 mg/kg for days 8–14, 10 mg/kg for days 15–21) | PND 33–39 until PND 54–60 | PND 38–44 (1 mg/kg THC) and PND 45–51 (3 mg/kg THC) | Repeated adolescent THC treatment tends to reduce social interaction when rats are tested under 3 mg/kg THC treatment. |
| Leweke and Schneider [26] | Rats | Male | WIN | 1.2 mg/kg, 20 injections delivered over 25 days | PND 40–65 | PND 85+ | Chronic adolescent WIN treatment reduces social discrimination when rats are tested drug free in adulthood. |
| Long et al. [16] | Mice (WT and *Nrg1* TM HET) | Male | THC | 10 mg/kg daily for 21 days | PND 31–52 | PND 49 | Repeated adolescent THC treatment reduces social interaction when mice |

**Table 1** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Test age | Positive-like behaviours |
|---|---|---|---|---|---|---|---|
| | | | | | | | are tested under THC treatment; this effect is less pronounced in *Nrg1* TM HET mice. |
| O'Tuathaigh et al. [18] | Mice (WT, *COMT* HET and *COMT* KO) | Male | THC | 4 or 8 mg/kg daily for 21 days | PND 32–52 (adolescent) or PND 70–90 (adult) | PND 73+ (adolescent) or PND 111+ (adult) | Chronic THC administration in adolescence and adulthood reduces social novelty, but not social preference, in WT, *COMT* HET and *COMT* KO mice, irrespective of THC dose. |
| O'Tuathaigh et al. [27] | Mice (WT and *COMT* KO) | Male | WIN | 1 or 2.5 mg/kg daily for 20 days | PND 32–52 | PND 73+ | Chronic adolescent WIN treatment impairs social preference in WT mice, but not *COMT* KO mice. No effect of chronic adolescent WIN treatment on social novelty in either genotype. |
| Quinn et al. [28] | Rats | Male | THC | 1 mg/kg (first 2 days), 5 mg/kg on alternate days for 16 days (8 doses total), 1 final 5 mg/kg dose | PND 28 (adolescent) or PND 60 (adult) | Final treatment day (PND 55 or 87) and PND 70 or 102 (adolescent and adult, respectively) | Adolescent and adult THC treatment reduces social interaction in both age groups, when rats are acutely treated with THC (final treatment day) or 15 days following treatment cessation. |
| Realini et al. [29] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 (adolescent) or PND 75–85 (adult) | PND 75–85 (adolescent) or PND 115+ (adult) | Repeated THC treatment in adolescence reduces social interaction, as well as consumption of sucrose and palatable food, when rats are tested drug free in adulthood. Repeated THC treatment in adulthood does not reduce sucrose consumption when animals are tested drug free. |
| Rubino et al. [30] | Rats | Male + female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75–85 | Chronic adolescent THC treatment reduces sucrose preference in male and female adult rats. |
| Zamberletti et al. [23] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Chronic THC administration in adolescence reduces social interaction in adult rats. |
| Zamberletti et al. [31] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Chronic THC administration in adolescence reduces social interaction in adult rats. |
| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Test age | Cognitive behaviours |

**Table 1** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Test age | Positive-like behaviours |
|---|---|---|---|---|---|---|---|
| Abboussi et al. [32] | Rats | Male | WIN | 1 mg/kg, daily for 20 days | PND 27–30 until 47–50 (adolescent) or PND 54–57 until 74–77 (adult) | PND 67–70 (adolescent) or 94–97 (adult) | Chronic adolescent WIN treatment impairs acquisition and expression of spatial learning in the Morris water maze; this effect is not present following adult WIN treatment. No effect of chronic adolescent of adult WIN treatment on active avoidance in a shuttle box task. |
| Abboussi et al. [33] | Rats | Male | WIN | 1 mg/kg, 20 injections over 30 days | PND 27–30 until 47–50 | PND 67–70+ | Chronic adolescent WIN treatment impairs short-term recognition memory in the novel objection recognition task when animals tested drug free in adulthood; this is reversed following acute administration of the dopamine $D_3$ antagonist U-99194A. |
| Abush and Akirav [34] | Rats | Male | WIN | 1.2 mg/kg, daily for 14 days | PND 45–60 | PND 61, 70, 90 | Chronic WIN in adolescence impairs short-term spatial memory in the novel object location recognition task at 1, 10 and 30 days following treatment cessation, as well as novel object recognition for 1 and 10 days post-treatment cessation. Chronic WIN in adolescence impairs acquisition of platform location in the Morris water maze on day 1 of training (i.e. only 24 h after treatment cessation, but not at a longer washout). |
| Cha et al. [35] | Rats | Male + female | THC | 5 mg/kg daily for 21 days | PND 30 (adolescent) or PND 70 (adult) | PND 79 or 108 | Adolescent and adult THC acutely impairs acquisition of spatial learning in the Morris water maze in female rats, but only adolescent THC treatment acutely impairs acquisition of spatial learning in the Morris water maze in males. Chronic adolescent THC does not impair acquisition of spatial learning in the Morris water maze in male or female rats when tested drug free in adulthood. |
| Cutando et al. [36] | Mice | Male | THC | 1, 2.5, 5, 20 mg/kg, twice daily for 5.5 days | PND 49–70 | PND 55–76 | Subchronic THC in late adolescence slows acquisition of delayed eyeblink conditioning. Administration of the interleukin-1 receptor antagonist ameliorates impairment in eyeblink conditioning induced by chronic THC treatment. |
| Gleason et al. [37] | Mice | Male | WIN | 2 mg/kg, daily for 10 days | PND 30 (adolescent) or PND 63 (adult) | PND 120 (adolescent and adult) | Chronic WIN in adolescence impairs recall of contextual fear memory in adult drug-free rats, but chronic WIN in adulthood has no effect on fear learning in drug-free animals. |

**Table 1** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Test age | Positive-like behaviours |
|---|---|---|---|---|---|---|---|
| Gomes et al. [13] | Rats | Male | WIN | 20 injections of 1.2 mg/kg over 25 days | PND 40–65 | PND 85+ | Chronic adolescent WIN treatment impairs reversal learning and intra-dimensional shift when rats are tested in adulthood. |
| Higuera-Matas et al. [38] | Rats | Male + female | CP | 0.4 mg/kg daily for 11 days | PND 28–38 | PND 97 + | No effect of chronic adolescent CP treatment on short-term memory in the novel objection recognition task or working or reference memory in the Morris water maze when rats are tested in adulthood. |
| Irimia et al. [39] | Rats | Male | THC | One cycle: 0.3 or 3 mg/kg twice daily for 5 days, followed by 9 days behavioural testing. Cycles repeated 10 times | Adult (no PND provided) | Adult (no PND provided) | Subchronic THC in adult rats disrupts performance in the 5-choice serial reaction time task, causing motor impulsivity and behavioural disinhibition. These effects were persistent for 5 weeks of abstinence. |
| Kirschmann et al. [40] | Rats | Male | WIN | 1.2 mg/kg, daily for 20 days, or WIN self-administration for 11 days | PND 34–54 | PND 54 or 106 | Experimenter administered WIN in adolescence at PND 54 acutely impairs short-term memory in the novel object recognition test, but this effect is not present when rats are tested in adulthood, at PND 106. Unlike experimenter administered WIN, WIN self-administration in adolescence does not impair short-term memory. |
| Lovelace et al. [41] | Mice | Female | WIN | Escalating dose regime, twice daily, for 10 days (0.5 mg/kg, PND 35–36; 1 mg/kg, PND 37–41; 2 mg/kg, PND 42–45) | PND 35–45 | PND 70+ | Chronic WIN treatment in adolescence impairs short-term recognition memory in the novel object recognition test in adulthood. |
| O'Tuathaigh et al. [18] | Mice (WT, *COMT* HET and *COMT* KO) | Male | THC | 4 or 8 mg/kg daily for 21 days | PND 32–52 (adolescent) or PND 70–90 (adult) | PND 73+ (adolescent) or PND 111+ (adult) | Chronic adolescent or adult THC administration disrupts short-term recognition memory in the novel object recognition test. Chronic adolescent THC disrupts spontaneous alternation in the y-maze and impairs spatial memory of the location of a food reward; this effect was not present in adult THC-treated mice. |
| Puighermanal et al. [19] | Mice | Male | THC | 10 mg/kg, daily for 6 days | Adult (no PND provided) | During treatment and for 6 days after treatment cessation | Chronic THC in adulthood impairs short-term recognition memory during treatment and for up to 4 days after treatment, in mice. |
| Quinn et al. [28] | Rats | Male | THC | 1 mg/kg (first 2 days), 5 mg/kg on alternate days for 16 days (8 | PND 28 (adolescent) or PND 60 (adult) | Final treatment day (PND 55 or 87) and PND 70 or 102 (adolescent | Adolescent chronic THC exposure impairs short-term recognition memory in the novel object recognition |

**Table 1** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Test age | Positive-like behaviours |
|---|---|---|---|---|---|---|---|
| | | | | doses total), 1 final 5 mg/kg dose | | and adult, respectively) | test when animals are tested drug free in adulthood. |
| Raver et al. [42] | Mice | Male | WIN | 1 mg/kg, daily for 20 days | PND 35–55 | PND 100+ | Chronic adolescent WIN treatment impairs short-term reference memory in the novel object recognition test when mice are tested in adulthood. |
| Realini et al. [29] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 (adolescent) or PND 75–85 (adult) | PND 75–85 (adolescent) or PND 115+ (adult) | Adolescent chronic THC exposure impairs short-term recognition memory in the novel object recognition test when animals are tested drug free in adulthood. |
| Renard et al. [43] | Rats | Male | CP | Escalating dose regime, daily, for 21 days (0.15, 0.20 and 0.30 mg/kg for 7 days each) | PND 29–50 (adolescent) or PND 70–91 (adult) | PND 77 (adolescent) or PND 118 (adult) | Chronic adolescent CP exposure in rats causes impairment in novel object recognition and novel location recognition when animals are tested in adulthood. |
| Rubino et al. [44] | Rats | Male | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Chronic THC treatment in adolescence leads to spatial working memory deficits in the radial arm maze in adulthood, but not aversive learning deficits in the passive avoidance task. |
| Rubino et al. [45] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Chronic THC treatment in adolescence leads to spatial working memory deficits in the radial arm maze in adulthood, but not aversive learning deficits in the passive avoidance task. |
| Rubino et al. [46] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Chronic THC treatment in adolescence leads to spatial working memory deficits in the t-maze. |
| Steel et al. [47] | Rats | Male | THC | 6 mg/kg daily for 27 days | PND 28–54 | PND 28–54 (animals tested 17 h post-drug treatment) | Rats treated with THC in adolescence and tested 17 h after each drug treatment exhibit impaired learning in a radial arm maze. |
| Tantra et al. [48] | Mice | Male | THC | 7 mg/kg every second day for 28 days | PND 28–56 | PND 57 or PND 146 | Chronic THC administration in adolescence has no effect on working memory, reference memory or learning index in the hole board task in WT controls, when this test is conducted either immediately after treatment |

**Table 1** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Test age | Positive-like behaviours |
|---|---|---|---|---|---|---|---|
| | | | | | | | cessation or 3 months after treatment cessation. |
| Verrico et al. [49] | Monkey | Male | THC | 120 or 240 μg/kg, generally in an ascending order, 5 days per week for 6 months | Average age: 28.6 months (adolescent) | Monkeys tested throughout the 6 months of treatment, from age 28.6–-34.6 months, 23 or 71 h post-treatment | Chronic adolescent THC treatment impairs improvements in accuracy in a delay dependent manner in a spatial working memory task, but not in an object working memory task. |
| Weed et al. [50] | Rats | Male + female | THC | 5.6 mg/kg daily for 40 days | PND 35–75 | PND 76+ | Chronic THC administration in adolescence has no effect on acquisition or performance of an operant response sequence task when animals are tested drug free in adulthood. |
| Winsauer et al. [51] | Rats | Female (OVX and non-OVX) | THC | 5.6 mg/kg daily for 40 days | PND 35–75 | PND 76–190 | Chronic THC administration in adolescence has no effect on acquisition or performance of an operant response sequence task when animals are tested drug free in adulthood; chronic THC administration in adolescence does not interact with female hormone status. |
| Winsauer et al. [52] | Rats | Female | THC | 5.6 mg/kg daily for 40 days | PND 75–115 | PND 116 | Chronic THC administration in adulthood does not impair acquisition of an operant task; chronic THC administration does not interact with female hormone status. |
| Zamberletti et al. [23] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Chronic THC administration in adolescence impairs spatial working memory (novel object location recognition) and reference memory (novel object recognition). |
| Zamberletti et al. [31] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Chronic THC administration in adolescence impairs spatial working memory (novel object location recognition) and reference memory (novel object recognition). |
| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Test age | Sensorimotor gating impairment |
| Klug and van den Buuse [15] | Mice (WT and *BDNF* HET) | Male + female | CP | 0.4 mg/kg, 5× per week, for 3 weeks | PND 42–63 | PND 77+ | Chronic adolescent CP treatment had no effect on prepulse inhibition in male or female WT or *BDNF* HET mice. |
| Gleason et al. [37] | Mice | Male | WIN | 2 mg/kg, daily for 10 days | PND 30 (adolescent) or PND 63 (adult) | PND 120 (adolescent and adult) | Chronic WIN in adolescence impairs prepulse inhibition in adult drug-free |

**Table 1** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Test age | Positive-like behaviours |
|---|---|---|---|---|---|---|---|
| | | | | | | | rats, but chronic WIN in adulthood has no effect on prepulse inhibition in drug-free animals. |
| Long et al. [16] | Mice (WT and *Nrg1* TM HET) | Male | THC | 10 mg/kg daily for 21 days | PND 31–52 | PND 31, 51, 53 | Repeated adolescent THC treatment has no effect on prepulse inhibition in WT mice. Acute THC (day 1 of treatment) reduces PPI at the 74-dB prepulse in *Nrg1* TM HET mice, no effect of THC in *Nrg1* TM HET mice upon repeated THC treatment. |
| Llorente-Berzal et al. [53] | Rats | Male + female | CP | 0.4 mg/kg, daily for 15 days | PND 28–42 | Adulthood (PND not stated) | Chronic CP treatment in adolescence reduces prepulse inhibition in adult female rats when tested drug free in adulthood. This effect was not present in male rats. |
| Marusich et al. [54] | Rats | Male + female | THC | 30 mg/kg twice daily for 6.5 days | Adult (no PND provided) | Treatment day 7 | Chronic treatment with THC in adulthood does not affect prepulse inhibition when rats are not under THC treatment. |
| O'Tuathaigh et al. [27] | Mice (WT and *COMT* KO) | Male | WIN | 1 or 2.5 mg/kg daily for 20 days | PND 32–52 | PND 73+ | Chronic WIN (1 or 2.5 mg/kg) does not affect prepulse inhibition in adult drug-free WT mice, but chronic treatment with 2.5 mg/kg WIN reduces prepulse inhibition in adult drug-free *COMT* KO mice. |
| Silva et al. [55] | Rats | Male + female | THC | 3 mg/kg daily for 9 days | PND 29–38 | PND 39–40 | No effect of chronic adolescent THC treatment on prepulse inhibition in late adolescence. |
| Tournier et al. [56] | Rats | Male | THC | 1 mg/kg daily for 21 days | Adult (no PND provided) | Treatment days 1, 21 and 7 days after treatment cessation | Chronic treatment with THC in adulthood reduces prepulse inhibition under THC treatment; this effect was not present following treatment cessation. |
| Wegener and Koch [57] | Rats | Male | WIN | 1.2 mg/kg, 20 injections delivered over 25 days | PND 40–65 | PND 80–105 | Chronic WIN in adolescence impairs prepulse inhibition in adult drug-free rats. |

*COMT catechol-O-methyl transferase*, *CP* CP55,940, *KO* knockout, *Nrg1 TM HET Neuregulin 1* heterozygous transmembrane domain, *PND* post-natal day, *THC* $\Delta^9$-tetrahydrocannabinol, *WIN* WIN55,212-2, *WT* wild type like

**Table 2** Molecular changes following chronic or subchronic cannabinoid treatment

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Cannabinoid system effects |
|---|---|---|---|---|---|---|---|
| Behan et al. [69] | Mice (WT, *COMT* HET and *COMT* KO) | Male | THC | 8 mg/kg, daily for 20 days | PND 32–52 | PND 150–160 | Chronic adolescent THC treatment has no effect on $CB_1R$ expression in the prefrontal cortex or hippocampus after an extended drug free period; this is not modified by *COMT* mutation. |
| Cutando et al. [36] | Mice | Male | THC | 1, 2.5, 5, 20 mg/kg, twice daily for 5.5 days | PND 49–70 | PND 55–76 | Adult subchronic THC treatment reduces $CB_1R$ expression in mice in the cerebellum for up to 5 days post-treatment cessation. |
| Ginovart et al. [12] | Rats | Male | THC | 1 mg/kg daily for 21 days | Adult (no PND provided) | Day 20 of treatment and 1 day after cessation of treatment | Chronic THC treatment in adult rats decreases $CB_1R$ mRNA expression in the striatum and the substantia nigra/ventral tegmental area, 24 h post-treatment cessation. No effect of chronic THC treatment on cortical $CB_1R$ mRNA expression. |
| Gleason et al. [37] | Mice | Male | WIN | 2 mg/kg, daily for 10 days | PND 30 | PND 150 | Chronic adolescent WIN treatment increases protein expression of the metabolic enzymes for 2-arachidonoylglycerol and anandamide (monoacylglycerol lipase and fatty acid amide hydrolase, respectively) in the hippocampus of adult mice. No effect of chronic WIN on $CB_1R$ protein expression in the hippocampus of adult mice. |
| Klein et al. [25] | Rats | Male | THC | Escalating dose regime, daily, for 21 days (1 mg/kg for days 1–7, 3 mg/kg for days 8–14, 10 mg/kg for days 15–21) | PND 33–39 until PND 54–60 | PND 55–61 | Chronic adolescent THC treatment in male rats decreases $CB_1R$ binding in adulthood in the hippocampus, cingulate cortex, substantia nigra and caudate putamen. |
| Klug and van den Buuse [15] | Mice (WT and *BDNF* HET) | Male + female | CP | 0.4 mg/kg, 5× per week, for 3 weeks | PND 42–63 | PND 77+ | Chronic adolescent CP treatment elevates $CB_1R$ binding in the nucleus accumbens in male *BDNF* HET mice in adulthood, but not in the caudate. |
| Long et al. [16] | Mice (WT and *Nrg1* TM HET) | Male | THC | 10 mg/kg daily for 21 days | PND 31–52 | PND 53 | Chronic adolescent THC exposure reduces $CB_1R$ binding in the hippocampus, substantia nigra and ventral medial hypothalamus in WT and *Nrg1* TM HET mice and increases $CB_1R$ binding in the substantia nigra of *Nrg1* TM HET mice. No effect of adolescent THC treatment on $CB_1R$ binding in the prefrontal cortex or globus pallidus. |
| Lopez-Gallardo et al. [70] | Rats | Male + female | CP | 0.4 mg/kg daily for 15 days | PND 28–42 | PND 80 | Adolescent CP treatment reduces $CB_1R$ expression in the CA1 and dentate gyrus regions of the hippocampus in adult males, but $CB_1R$ expression is elevated in CA1 in adult females treated with CP in adolescence. |
| Lovelace et al. [41] | Mice | Female | WIN | Escalating dose regime, twice daily, for 10 days (0.5 mg/kg, PND 35–36; 1 mg/kg, PND 37–41; 2 mg/kg, PND 42–45) | PND 35–45 | PND 70+ | Chronic adolescent WIN treatment reduces $CB_1R$ co-localised with vesicular glutamate transporter 1 in the prefrontal cortex in adulthood; no effect of adolescent WIN treatment on monoglyceride lipase expression in the prefrontal cortex in adulthood. |
| Puighermanal et al. [19] | Mice | Male | THC | 10 mg/kg, daily for 6 days | | | |

**Table 2** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Cannabinoid system effects |
|---|---|---|---|---|---|---|---|
| | | | | | Adult (no PND provided) | During treatment and for 6 days after treatment cessation | Subchronic THC downregulates $CB_1R$ on GABAergic cells in the hippocampus, and mice lacking $CB_1R$ on hippocampal GABAergic cells do not exhibit THC-induced memory impairment. |
| Realini et al. [29] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 75–77; 5 mg/kg, PND 78–81; 10 mg/kg, PND 82–85) | PND 75–85 | PND 115+ | No effect of chronic THC in adulthood on $CB_1R$ binding in the nucleus accumbens, amygdala or ventral tegmental area or activation of G protein-coupled receptors when tissue is collected 30 days after treatment cessation. |
| Rubino et al. [30] | Rats | Male + female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 46 (adolescent) or PND 75–80 (adult) | Chronic adolescent THC treatment reduces $CB_1R$ binding in adulthood in female rats in the nucleus accumbens, amygdala and ventral tegmental area; in males, adolescent THC treatment reduces $CB_1R$ binding in adulthood only in the amygdala. CP-stimulated G protein activation is reduced in female rats treated with THC in adolescence in the nucleus accumbens and amygdala, in males in the hippocampus. |
| Rubino et al. [46] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 46, 60 and 75 | $CB_1R$ and anandamide binding in the prefrontal cortex is reduced during adolescence and into adulthood following chronic THC administration. THC treatment impaired cortical long-term depression, an effect dependent on $CB_1R$. |
| Silva et al. [71] | Rats | Male + female | THC | 15 mg/kg daily for 6 days | PND 35–41 | PND 42 and 56 | Adolescent THC treatment reduces $CB_1R$ expression in the CA1, CA2, CA3 and dentate gyrus of the hippocampus 24 h after treatment cessation in male and female rats. At 2 weeks post-treatment, $CB_1R$ binding is reduced in males in the CA2 region and in females in the CA1, CA2 and CA3 regions. |
| Silva et al. [55] | Rats | Male + female | THC | 3 mg/kg daily for 9 days | PND 29–38 | PND 39–40 | Adolescent chronic THC treatment increases $CB_1R$ mRNA expression but reduces G protein activation induced by CP in the central amygdala in late adolescence in female rats. No effect of chronic THC treatment on $CB_1R$ mRNA expression or G protein activation induced by CP in the central amygdala in male rats. |
| Tai et al. [20] | Mice | Male | THC, $CB_1$ agonists JW-H-018 or JW-H-073 | THC: 30 mg/kg daily for 4 days; JWH-018: 3 mg/kg daily for 4 days, JWH-073: 10 mg/kg daily for 4 days | Adult (no PND provided) | Adult (no PND provided) | Adult subchronic THC treatment reduces $CB_1R$ binding and activation of G protein signalling via $CB_1$ activation in the hypothalamus, but not the cortex. |
| Thibault et al. [72] | Rats | Male | CP | 0.75 mg/kg daily for 3 days | Adult (no PND provided) | Adult (2 h after last injection) | Subchronic THC treatment decreases $CB_1R$ protein levels and axonal labelling in the hippocampus and cortex. $CB_1R$ is upregulated in cholecystokinin-positive cells. |
| Weed et al. [50] | Rats | | THC | 5.6 mg/kg daily for 40 days | PND 35–75 | PND 76 | |

**Table 2** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Cannabinoid system effects |
|---|---|---|---|---|---|---|---|
| | | Male + female | | | | | Chronic adolescent THC in male and female rats does not change striatal or hippocampal $CB_1R$ protein levels when tissue is collected 24 h post-treatment cessation. |
| Winsauer et al. [51] | Rats | Female (OVX and non-OVX) | THC | 5.6 mg/kg daily for 40 days | PND 35–75 | PND 260 | $CB_1R$ protein is elevated in the hippocampus following chronic adolescent THC treatment in adult female non-ovariectomised rats. |
| Zamberletti et al. [31] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Chronic adolescent THC exposure reduces $CB_1R$ receptor expression in the prefrontal cortex in adult rats. |
| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Dopaminergic system effects |
| Behan et al. [69] | Mice (WT, *COMT* HET and *COMT* KO) | Male | THC | 8 mg/kg, daily for 20 days | PND 32–52 | PND 150–160 | Adolescent THC treatment reduced tyrosine-hydroxylase-positive cell density in the ventral tegmental area. Adolescent THC treatment reduced tyrosine-hydroxylase-positive + cell size in *COMT* KO, but not WT or *COMT* HET mice. |
| Fanarioti et al. [11] | Rats | Male | WIN | 0.1, 0.3 or 1 mg/kg daily for 20 days | Adult (no PND provided) | Days 1, 10, 20 of treatment | Chronic WIN treatment in adulthood causes decreased dopamine $D_2R$ mRNA expression in the substantia nigra and ventral tegmental area and increased dopamine $D_1R$ mRNA and protein levels in the nucleus accumbens. Dopamine transporter mRNA and protein levels were decreased in the substantia nigra. |
| Ginovart et al. [12] | Rats | Male | THC | 1 mg/kg daily for 21 days | Adult (no PND provided) | Day 20 of treatment and 1 day after cessation of treatment | Chronic THC treatment in adult male rats increases post-synaptic dopamine $D_{2/3}R$ binding in the dorsal striatum and increases dopamine $D_3R$ mRNA expression in the nucleus accumbens. Chronic THC treatment in adult rats decreases tyrosine hydroxylase mRNA expression in the substantia nigra/ventral tegmental area, 24 h post-treatment cessation. |
| Gomes et al. [13] | Rats | Male | WIN | 20 injections of 1.2 mg/kg over 25 days | PND 40–65 | PND 85+ | Chronic adolescent WIN treatment increases the number of spontaneously active dopaminergic neurons in the ventral tegmental area. |
| Higuera-Matas et al. [73] | Rats | Male + female | CP | 0.4 mg/kg daily for 11 days | PND 28–38 | PND 125 + | Adolescent CP administration reduces dopamine transporter binding in the caudate putamen in female rats, while dopamine $D_1R$ binding is increased in the nucleus accumbens shell of male rats. Both sexes show reduced dopamine $D_2R$ binding levels in the CA1 region of the hippocampus following adolescent CP treatment. |
| Lobo et al. [74] | Mice | Male | THC | 10 mg/kg twice daily for 7 days | | Adult (8 weeks +) | |

**Table 2** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Cannabinoid system effects |
|---|---|---|---|---|---|---|---|
| | | | | | Adult (8 weeks +) | | Subchronic THC increases ΔFosB expression in dopamine $D_1$ cells in the nucleus accumbens core and shell and dorsal striatum. |
| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Glutamatergic system effects |
| Fan et al. [75] | Mice | Male | THC | 10 mg/kg daily for 7 days | Adult (6–-9 weeks) | Adult (7–10 weeks) | Subchronic THC produced $CB_1$R-dependent decreases in the expression of hippocampal NMDAR subunits GluR1, NR2A and NR2B and the ratio of AMPAR/NMDAR-gated currents. |
| Gleason et al. [37] | Mice | Male | WIN | 2 mg/kg, daily for 10 days | PND 30 | PND 150 | Chronic adolescent WIN treatment reduces metabotropic glutamate receptor 5 protein levels in the hippocampus of adult mice. |
| Kirschmann et al. [40] | Rats | Male | WIN | 1.2 mg/kg, daily for 20 days, or WIN self-administration for 11 days | PND 34–54 | PND 118+ | WIN self-administration in adolescence increases phosphorylated NMDAR subunit N2RB expression in the infralimbic cortex, compared to sucrose self-administration. |
| Long et al. [16] | Mice (WT and *Nrg1* TM HET) | Male | THC | 10 mg/kg daily for 21 days | PND 31–52 | PND 53 | Adolescent THC treatment enhances NMDAR binding in the hippocampus, cingulate cortex and auditory cortex of *Nrg1* TM HET mice, but not WT mice. |
| Renard et al. [76] | Rats | Male | CP | Escalating dose regime, daily, for 21 days (0.15 mg/kg, PND 29–36; 0.2 mg/kg, PND 37–43; 0.3 mg/kg, PND 44–50) | PND 29–50 | PND 92–110 | Chronic CP in adolescence leads to reduced prefrontal cortex post-synaptic density protein 95 in adulthood, but not vesicular glutamate transporter 3 or synaptosphysin. |
| Rubino et al. [44] | Rats | Male | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Adolescent THC treatment reduces post-synaptic density protein 95 and NMDAR protein expression in the hippocampus in adulthood. |
| Rubino et al. [45] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Adolescent THC treatment reduces post-synaptic density protein 95 and synaptophysin protein expression in the prefrontal cortex. There is a non-significant reduction in post-synaptic density protein 95 in the hippocampus in adulthood. |
| Rubino et al. [46] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 46, 60 and 75 | Chronic adolescent THC treatment elevates prefrontal cortex levels of post-synaptic density protein 95 at PND 46 and 60, but not 75. Following chronic adolescent THC treatment, NMDAR subunit GluN2 was elevated at PND 60, while GluN2B and GluA1 were elevated at PND 75. |
| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | GABAergic system effects |
| Behan et al. [69] | | Male | THC | 8 mg/kg, daily for 20 days | PND 32–52 | PND 150–160 | |

**Table 2** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Cannabinoid system effects |
|---|---|---|---|---|---|---|---|
| | Mice (WT, *COMT* HET and *COMT* KO) | | | | | | Chronic adolescent THC treatment reduces parvalbumin soma size in *COMT* KO mice, but not WT, in the prefrontal cortex. |
| Fanarioti et al. [11] | Rats | Male | WIN | 0.1, 0.3 or 1 mg/kg daily for 20 days | Adult (no PND provided) | Days 1, 10, 20 of treatment | Chronic WIN treatment in adulthood decreases GABAR binding in the dorsal striatum and substantia nigra. |
| Kirschmann et al. [40] | Rats | Male | WIN | 1.2 mg/kg, daily for 20 days, or WIN self-administration for 11 days | PND 34–54 | PND 118+ | WIN self-administration in adolescence increases GABA-B2R expression in the prelimbic and infralimbic cortex of the medial prefrontal cortex, as well as GABAR transporter expression in the infralimbic cortex, compared to sucrose self-administration. |
| Zamberletti et al. [23] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Adolescent THC exposure reduces glutamate decarboxylase 67 and basal GABA levels within the adult prefrontal cortex. Glutamate decarboxylase 67 expression is reduced both in parvalbumin- and cholecystokinin-containing interneurons. |
| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Serotonergic system effects |
| Bambico et al. [24•] | Rats | Male | WIN | 0.2 or 1 mg/kg daily, for 20 days | PND 28–48 (adolescent) or PND 50–70 (adult) | PND 70–100 (adolescent) or PND 90–120 (adult) | Chronic treatment with WIN in adolescence, but not adulthood, reduces the neural firing rate of serotonin-expressing cells in the dorsal raphe. |
| Klein et al. [25] | Rats | Male | THC | Escalating dose regime, daily, for 21 days (1 mg/kg for days 1–7, 3 mg/kg for days 8–14, 10 mg/kg for days 15–21) | PND 33–39 until PND 54–60 | PND 55–61 | Chronic adolescent THC treatment in male rats has no effect on serotonin 1A receptor binding in the hippocampus, lateral septum or cingulate cortex. |
| Long et al. [16] | Mice (WT and *Nrg1* TM HET) | Male | THC | 10 mg/kg daily for 21 days | PND 31–52 | PND 53 | Chronic adolescent THC exposure reduces 5-$HT_{2A}$ receptor binding in the insula, cingulate and ventral pallidum and increases serotonin 2A receptor binding in the striatum in WT mice. *Nrg1* TM HET mice exhibit only increased serotonin 2A receptor binding only in the anterior insula following chronic adolescent THC. |
| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Noradrenergic system effects |
| Bambico et al. [24•] | Rats | Male | WIN | 0.2 or 1 mg/kg daily, for 20 days | PND 28–48 (adolescent) or PND | PND 70–100 (adolescent) or PND 90–120 (adult) | Chronic adolescent, but not adult WIN treatment dose dependently enhances burst firing of noradrenergic cells in the locus coeruleus in adulthood. |

**Table 2** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Cannabinoid system effects |
|---|---|---|---|---|---|---|---|
| | | | | | 50–70 (adult) | | |
| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Effects on dendritic spine density and morphology |
| Candelaria-Cook et al. [77] | Rats | Male | WIN | 3.5 mg/ml daily for 7 or 21 days | 6 months | 1 day after final WIN injection | Chronic THC treatment in adulthood reduces dendritic spine density in the dentate gyrus of the hippocampus. No effect of treatment duration (7 or 21 days) on reduction in dendritic spines. |
| Renard et al. [76] | Rats | Male | CP | Escalating dose regime, daily, for 21 days (0.15 mg/kg, PND 29–36; 0.2 mg/kg, PND 37–43; 0.3 mg/kg, PND 44–50) | PND 29–50 | PND 92–110 | Chronic CP treatment during adolescence reduces the number, length and complexity of basal dendritic spines of pyramidal neurons of the prefrontal cortex in adulthood. |
| Rubino et al. [44] | Rats | Male | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Chronic THC treatment in adolescence reduces dendritic spine length and number in the hippocampus. |
| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Effects on inflammatory markers |
| Cutando et al. [36] | Mice | Male | THC | 1, 2.5, 5, 20 mg/kg, twice daily for 5.5 days | PND 49–70 | PND 55–76 | Subchronic THC in adult mice increases mRNA expression of the neuroinflammatory markers interleukin-1β, tumour necrosis factor α, cyclooxygenase-2, integrin alpha M and chemokine (C-X-C motif) ligand 2, as well as protein expression of integrin alpha M, in the cerebellum 5 days after the completion of treatment. These effects were reversed following 5-day treatment with the immunosuppressant minocycline, which also inhibits microglial activation. |
| Enayatfard et al. [10] | Rats | Male | WIN | 0.1 mg/kg twice daily for 10 days | Adult (no PND provided) | Days 1, 5, 10 of treatment and 2 days after treatment cessation | Chronic WIN in adulthood enhances striatal nuclear translocation of peroxisome proliferator-activated receptor γ, as well as levels of tumour necrosis factor α and cyclooxygenase-2 during treatment; these levels return to control levels 2 days after treatment cessation. |
| Lopez-Gallardo et al. [70] | Rats | Male + female | CP | 0.4 mg/kg daily for 15 days | PND 28–42 | PND 80 | Chronic CP treatment in adolescence increases glial fibrillary acidic protein-positive cells in the polymorphic layer of the dentate gyrus. |
| Moretti et al. [78•] | Mice | Male | THC | Escalating dose regime, twice daily, for 10 days (5 mg/kg, days 1–3; 10 mg/kg, days 4–6; 15 mg/kg, days 7–10) | PND 33–42 (adolescent) or PND 80–89 (adult) | 24 h post-treatment cessation or 47 days post-treatment cessation | 24 h post-treatment cessation, tumour necrosis factor α and interleukin-1β protein levels are reduced, while interleukin-10 protein levels are increased in the hippocampus and hypothalamus (for both adolescent and adult treatment groups). Forty-seven days after treatment cessation, tumour necrosis factor α and interleukin-1β protein levels are increased, while interleukin-10 protein levels are reduced in the |

**Table 2** (continued)

| Reference | Species | Sex | Drug | Dosing regime | Treatment age | Age of tissue collection/cell recordings | Cannabinoid system effects |
|---|---|---|---|---|---|---|---|
| | | | | | | | hippocampus and hypothalamus, only in mice treated with THC in adolescence. |
| Rubino et al. [44] | Rats | Male | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Adolescent THC treatment reduces glial fibrillary acidic protein expression in the hippocampus in adulthood. |
| Zamberletti et al. [31] | Rats | Female | THC | Escalating dose regime, twice daily, for 10 days (2.5 mg/kg, PND 35–37; 5 mg/kg, PND 38–41; 10 mg/kg, PND 42–45) | PND 35–45 | PND 75+ | Chronic adolescent THC treatment increases prefrontal cortex expression of the proinflammatory markers, tumour necrosis factor α, inducible nitric oxide synthase and cyclooxygenase-2 and reduces prefrontal cortex expression of the anti-inflammatory cytokine, interleukin-10. This neuroinflammatory phenotype is associated with upregulation of $CB_2$ on microglial cells. Blocking microglia activation with ibudilast during THC treatment prevents the increases in tumour necrosis factor α, inducible nitric oxide synthase and cyclooxygenase-2 levels as well as the upregulation of $CB_2$ receptors on microglial cells. |

*AMPAR* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *$CB_1R$* cannabinoid receptor 1, *COMT catechol-O-methyl transferase*, *CP* CP55,940, *$D_{1/2/3}R$* dopamine receptor 1/2/3/, *KO* knockout, *GABA* γ-aminobutyric acid, *NMDAR N*-methyl-D-aspartate receptor, *Nrg1 TM HET Neuregulin 1* heterozygous transmembrane domain, *PND* post-natal day, *THC* Δ9-tetrahydrocannabinol, *WIN* WIN55,212-2, *WT* wild type like

slows acquisition of cerebellar-dependent delayed eyeblink conditioning [36].

Some cannabinoid-induced cognitive impairments are dependent on the type of cannabinoid administered. Chronic adolescent WIN impairs acquisition of spatial learning in the Morris water maze (MWM) [32, 34], recall of associative fear learning [[37] but see also [32]] and reversal learning and intra-dimensional shift in adult rats [13], but THC has no effect in these domains [[44, 45, 50–52] but see [35]]. THC only affects performance in operant tasks where cognitive load is high [[39], for non-human primates, see [49]]. WIN's more prominent effects may be due to WIN being a more potent $CB_1R$ agonist than THC [65], thus having stronger deleterious effects on performance.

### Sensorimotor Gating Disruption

Sensorimotor gating is a neural process of filtering out irrelevant stimuli and can be measured through tests of prepulse inhibition (PPI) of the acoustic startle response. PPI is considered an endophenotype for schizophrenia and appears associated with some aspects of cognition and global function, but should not be considered an indicator of cognitive function [68]. Chronic THC, CP and WIN treatment in adolescence impairs PPI in adulthood in rats, but not mice [15, 16, 37, 53, 54, 57]. Chronic cannabinoid treatment in late adolescence or adulthood does not impair PPI when animals are tested drug free [37, 55, 56]. Furthermore, chronic adolescent WIN impairs PPI in adult drug-free *COMT* knockout (KO) but not wild type (WT)-like mice [27].

## Neural Consequences of Chronic Cannabinoid Administration

Methodological details for references in this section are presented in Table 2.

### $CB_1R$ Changes

There are discrepancies in the direction of change for $CB_1R$ protein and messenger RNA (mRNA) expression in human schizophrenia imaging studies and post-mortem tissue [e.g. $CB_1R$ protein is up- or downregulated depending on the detection technique [79]]. Nonetheless, these changes in schizophrenia patients may indicate increased susceptibility to cannabinoid-mediated neural dysregulation. In rodent models, chronic adolescent and adult cannabinoid treatments impact on cannabinoid $CB_1R$ expression in several brain regions; mostly, a reduction in $CB_1R$ mRNA and protein expression is observed following chronic cannabinoid administration.

#### *Prefrontal Cortex*

Chronic cannabinoid treatment reduces $CB_1R$ binding in the prefrontal and cingulate cortices. Treatment with THC, WIN or CP in adolescence reduces prefrontal cortex (PFC) $CB_1R$ binding within a week of treatment cessation or after an extended drug-free period [[25, 31, 41, 46, 72] but see [16]]. Levels of the endogenous cannabinoid, anandamide, are also reduced in the PFC following chronic adolescent THC treatment [46]. Monoacylglycerol lipase (MGLL, which breaks down the endocannabinoid 2-arachidonoylglycerol; 2-AG) binding is unchanged in the PFC following chronic adolescent WIN [41]. These effects appear dependent on cannabinoid dose and treatment regime, as low doses do not alter $CB_1R$ protein expression in the PFC [12], and shorter, subchronic dose regimes (i.e. 3 days) also do not affect cortical $CB_1R$ protein levels [20]. There appears to be some recovery of $CB_1R$ expression after a prolonged drug-free period, as $CB_1R$ protein expression was not different to controls more than 100 days after cessation of THC treatment [69]. It is possible that reduced $CB_1R$ function in the PFC may contribute to cannabinoid-induced cognitive impairment, for in addition to $CB_1R$ effects, adolescent cannabinoid treatment also reduces endocannabinoid-mediated cortical long-term depression [46] and impairs short-term recognition and spatial memory in adulthood [41, 46]. Indeed, in human schizophrenia patients, cannabis use leads to cortical thinning in $CB_1R$-rich areas critical for cognitive function (e.g. DLPFC, anterior cingulate cortex) [80, 81].

#### *Hippocampus*

Chronic cannabinoid treatment has sex-specific effects on hippocampal $CB_1R$ protein and mRNA expression in rodents. In male rats and mice, adolescent or adult THC or CP treatment reduces $CB_1R$ protein levels and receptor binding in the hippocampus [16, 19, 25, 30, 70–72]; however, there are some reports of no change to $CB_1R$ expression or protein levels following adolescent THC treatment, particularly after an extended drug-free period [37, 50, 69]. Reductions in $CB_1R$ expression appear to occur on hippocampal γ-aminobutyric acid (GABA)ergic interneurons [19, 72]. The activation of G protein-coupled receptors by acute CP is also reduced in male rats following chronic adolescent THC treatment [30]; however, chronic adolescent WIN elevates protein expression of metabolic enzymes for 2-arachidonoylglycerol and anandamide [37]. Collectively, these data suggest decreased hippocampal $CB_1R$ function in male rodents following chronic cannabinoid treatment. In contrast, hippocampal $CB_1R$ function appears upregulated in female rats: $CB_1R$ protein and mRNA are elevated in the hippocampus following chronic adolescent THC treatment [51, 70]. Hippocampal $CB_1R$ may modulate cannabinoid-induced cognitive function in male rodents, as

male mice lacking $CB_1R$ on hippocampal GABAergic cells do not exhibit THC-induced short-term recognition memory impairment, where control mice do [19].

*Striatum and Substantia Nigra*

In the striatum and substantia nigra (SN), chronic adolescent and adult cannabinoid treatments reduce $CB_1R$ mRNA and protein expression immediately after treatment cessation; however, $CB_1R$ levels return to control levels when animals are drug free for an extended period. Chronic THC in adolescent male and female rats reduces $CB_1R$ receptor binding and mRNA expression in the striatum 24 h after treatment cessation [[12, 25, 30], but see [50]]. A similar acute reduction in $CB_1R$ mRNA and protein expression is observed in the SN after repeated adolescent THC [12, 16, 25]. With an interval of at least 2 weeks between treatment cessation and tissue collection, chronic adolescent or adult cannabinoid treatment does not change $CB_1R$ binding in male and female rodents [15, 29, 51]. This transient decrease in $CB_1R$ mRNA and protein expression suggests that acute downregulation of $CB_1R$ may be due to the acute effects of cannabinoid administration, rather than long-lasting effects on receptor function, which could have an enduring impact on schizophrenia-relevant behaviour. In addition, cannabinoid-induced changes to striatal and SN $CB_1R$ protein or mRNA expression have not yet been linked to any behavioural changes.

*Hypothalamus, Amygdala and Cerebellum*

There is some evidence for altered $CB_1R$ binding and function in other brain regions following chronic cannabinoid treatment. Chronic adolescent THC reduces hypothalamic $CB_1R$ binding 2 days after treatment cessation [16], while subchronic adult treatment with THC or the synthetic $CB_1R$ agonists JWH-018 or JWH-073 reduces $CB_1R$ binding and $CB_1R$-induced activation of G protein-coupled receptors in the hypothalamus [20]. Adult subchronic THC treatment reduces $CB_1R$ expression in the cerebellum for up to 5 days following treatment cessation [36]. Also, chronic adolescent THC treatment reduces $CB_1R$ binding, as well as $CB_1R$-induced activation of G protein-coupled receptors in the amygdala of adult rats [30, 55]; these effects are not present when animals are treated with THC in adulthood [29]. It is possible that the effects of adolescent THC treatment on $CB_1R$ function in the amygdala may affect social behaviour. Social withdrawal induced by chronic adolescent phencyclidine treatment is accompanied by reduced anandamide levels in the amygdala and cortex, and these social deficits are reversed following repeated adult treatment with URB597, an inhibitor of endocannabinoid degradation [82]. Chronic adolescent THC treatment also reduces social interaction and $CB_1R$ expression in the amygdala of adult female rats, and impairments in social interaction are reversed following URB597 treatment [29], suggesting that amygdala $CB_1R$ expression may contribute to social impairment in schizophrenia.

## Dopaminergic System Changes

The dopaminergic system is critically involved in expression of psychotic symptoms [e.g. antipsychotic drugs inhibit dopamine $D_2$ receptors ($D_2R$) to limit psychotic symptoms [83]], and in schizophrenia patients, there is dysregulation of dopaminergic receptor expression in a region- and receptor-specific manner. Dopamine receptor 2 expression is elevated in the striatum and PFC of schizophrenia patients, but decreased in other regions (e.g. thalamus) [84–86], whereas $D_1R$ expression is elevated in the parieto-temporal cortex, but reduced in the PFC [[85] but see also [87]]. There are no consistent changes to dopamine transporter (DAT) expression in schizophrenia patients [86, 88]. Some of these changes are observed in rodents following chronic cannabinoid treatment.

*Striatum and Hippocampus*

In the striatum and hippocampus, chronic treatment with $CB_1R$ agonists causes up- or downregulation of the dopaminergic system in a region- and receptor-specific manner. $D_1R$ binding and mRNA expression in the nucleus accumbens (NAcc) of male rats are elevated following chronic adolescent CP or adult WIN treatment [11, 73]. Similarly, chronic THC in adulthood increases ΔFosB expression in $D_1R$-expressing cells in the NAcc and dorsal striatum of male mice [74]. Effects of chronic cannabinoids on $D_2R$ binding are also region specific. Adult chronic THC increases post-synaptic $D_{2/3}R$ binding in the dorsal striatum [12], while adolescent CP treatment reduces $D_2R$ binding levels in the hippocampal CA1 region [73]. Finally, DAT expression in the striatum is reduced in female but not male rats following chronic adolescent CP [73]. The animal data show some similarities to human data and suggest an imbalance in dopaminergic system activity following chronic cannabinoid exposure. In particular, an imbalance between $D_1R$ and $D_2R$ subtype expression in the striatum may contribute to altered sensitivity to the locomotor-stimulating effects of dopaminergic agents in cannabinoid-treated rodents [12].

*Ventral Tegmental Area and Substantia Nigra*

Chronic cannabinoid treatment in adolescence or adulthood causes downregulation of dopaminergic cell expression in the ventral tegmental area (VTA) and SN. Adolescent or adult THC treatment reduces tyrosine hydroxylase-positive (TH+; a marker of dopaminergic neurons) cell density and mRNA expression in the VTA [12, 69], while chronic WIN in adulthood decreases $D_2R$ mRNA expression in the VTA [11].

Similarly, chronic adult WIN decreases $D_2R$ mRNA expression, as well as DAT mRNA and protein levels in the SN [11]. While chronic adolescent WIN increases the number of spontaneously active dopaminergic neurons in the VTA [13], this may be a compensatory mechanism to account for reduced dopaminergic cell or receptor density [13]. Interestingly, *COMT* KO mice show a greater reduction in TH+ cell size following chronic adolescent THC than control mice [69]. Considering that *COMT* KO mice exhibit higher basal levels of dopamine release, extracellular dopamine levels and dopamine metabolites in PFC [27], additional VTA dopamine release induced by chronic THC may have led to greater dopaminergic downregulation in these mice compared to controls. Importantly, downregulation of VTA dopaminergic function following chronic cannabinoid treatment appears associated with positive and cognitive behaviours in schizophrenia rodent models—changes in dopaminergic VTA cell activity impair cognitive tasks, including reversal learning and intradimensional shift and enhance locomotor activity to amphetamine challenge [13]. Furthermore, acute administration of the dopamine $D_3R$ antagonist U-99194A in adulthood reverses short-term recognition memory deficits induced by adolescent WIN [33]. Thus, it appears that dopaminergic downregulation in the VTA and SN following chronic cannabinoids may contribute to cognitive impairment and sensitivity to psychotomimetic agents in schizophrenia.

## Glutamatergic System Changes

Human imaging and post-mortem studies in schizophrenia patients generally report elevated tissue levels of glutamate in the medial prefrontal cortex (mPFC), basal ganglia and hippocampus [89, 90]. Despite substantial evidence supporting *N*-methyl-D-aspartate receptor (NMDAR) dysfunction in the pathophysiology of schizophrenia [89, 91], there are no consistent alterations of mRNA or protein expression of glutamate receptors across brain regions [92, 93].

### *Prefrontal Cortex*

Changes to prefrontal glutamatergic release, glutamate NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subunit receptor expression are present following chronic adolescent cannabinoid treatment. Chronic adolescent THC exposure elevates glutamate release in the PFC and dorsal striatum in response to acute phencyclidine treatment but not at baseline; this elevation of extracellular glutamate corresponds with an elevated locomotor response to acute phencyclidine [23]. There are conflicting reports on the direction of glutamate receptor expression changes following adolescent cannabinoid treatment. Chronic WIN increases phosphorylation of the NMDAR subunit N2RB in the infralimbic cortex of the PFC in adulthood [40], and chronic THC elevates cortical levels of post-synaptic density protein 95 (PSD95), as well as the NMDAR and AMPAR subunits GluN2, GluN2B and GluA1 up to 30 days post-treatment [16, 46]. However, chronic THC and CP have also been reported to reduce PSD95 and synaptophysin protein expression in the PFC in adulthood [45, 76], while chronic WIN treatment reduces expression of metabotropic glutamate receptor 2/3 in the mPFC in adulthood [41]. Despite these treatment protocols causing both up- and downregulation of glutamatergic receptor expression, these treatments produce spatial memory impairments [45, 76] and short-term recognition memory deficits [41, 76], when animals are tested drug free in adulthood. Thus, it appears that dysregulation of prefrontal glutamate contributes to cognitive impairment following chronic cannabinoid treatment. It is unclear whether these changes occur only following adolescent treatment, as no adult treatment studies have investigated glutamatergic changes to the PFC.

### *Hippocampus*

Glutamatergic receptor expression in the hippocampus is downregulated following chronic adolescent or adult cannabinoid exposure. Chronic adolescent WIN reduces expression of metabotropic glutamate receptor 5 in the hippocampus in adult mice [37], while chronic adolescent THC reduces PSD95 and NMDAR protein expression in hippocampus of adult rats [44]. Another study reports a non-significant reduction in PSD95 hippocampal protein expression in THC-treated adolescent rats [76], supporting a similar direction of change to markers of glutamatergic synaptic sites in the hippocampus. Conversely, mutation in *Nrg1* transmembrane domain elevates NMDAR binding in the hippocampus after chronic adolescent THC treatment, suggesting that *Nrg1* TM HET mutation modulates how THC affects hippocampal NMDAR expression [16]. Reductions in hippocampal glutamatergic receptor expression may only occur after an extended drug-free period—changes in glutamatergic receptor expression are observed more than a month after treatment cessation [37, 45], but not within a week, in control animals [16, 75]. Cannabinoid-induced reductions in hippocampal glutamatergic receptor expression are associated with spatial working memory impairment [44] and deficits in recall of fear-associated contextual memory [37]. This suggests that cannabinoid-induced hippocampal glutamatergic dysfunction may correspond with spatial learning and context recognition deficits.

## GABAergic System Changes

There is evidence for downregulation of the GABAergic system, particularly in the PFC and hippocampus, in human schizophrenia patients [e.g. reduced expression of glutamate decarboxylase 67 (GAD67), which converts glutamate to

GABA, reduced GABA reuptake transporter and altered GABAergic receptor subunit expression; see [94]].

Chronic cannabinoid administration in adolescence and adulthood reduces expression of GABAergic receptors and basal extracellular GABA levels in the forebrain. Adolescent THC reduces protein levels of GAD67 and basal GABA levels in the PFC, when tissue is collected in adulthood [23]. GAD67 expression is reduced both in parvalbumin- (PV) and cholecystokinin-containing interneurons [23]. Also, chronic adolescent THC reduces PFC PV soma size in *COMT* KO compared to WT mice, potentially indicative of reduced GABAergic function in PV-containing PFC cells in *COMT* KO mice [69]. Adolescent WIN self-administration increases expression of the GABA transporter in the infralimbic cortex of the mPFC [40], which could reduce extracellular GABA due to increased reuptake. Chronic WIN may have dose-dependent effects on GABAR subtype expression—when adolescent rats self-administer low-dose WIN, expression of mPFC GABA-B2R is elevated [40]; however, a higher dose in adulthood decreases GABA-AR binding in the dorsal striatum and SN [11].

Human and rodent studies suggest that prefrontal GABAergic dysfunction contributes to cognitive impairment in schizophrenia [reviewed in [95, 96]]; however, evidence supporting cannabinoid-induced impairment in GABAergic system function contributing to cognitive impairment is limited and mixed. The THC treatment regime which reduces PV soma size in *COMT* KO mice [69] also impairs short-term spatial memory in the Y-maze [18]. Also, while WIN-induced changes to GABA-B2R expression are correlated with performance on a delay-match-to-sample working memory task, WIN treatment improves cognitive performance in this task [40]. Finally, silencing GAD67 expression in the PFC using small interfering RNA, in a manner akin to that which occurs following adolescent THC treatment, does not affect short-term recognition memory in the NORT [23]. There appears some association between cannabinoid-induced changes in GABAergic receptor expression and cell-type characteristics, but more research is required to determine if chronic cannabinoid treatment alters GABAergic system function, in a manner which corresponds with cognitive impairment.

### Changes to Serotonergic and Noradrenergic Receptor Systems

Human post-mortem studies indicate that serotonergic and noradrenergic system changes in patients with schizophrenia—elevated PFC serotonin receptor subtype 1A (5-$HT_{1A}$R) binding, reduced PFC 5-$HT_{2A}$R binding [meta-analysis: [97]] and elevated brain noradrenaline concentration [98]—are observed in post-mortem tissue from patients with schizophrenia. These findings are similar to changes induced by chronic cannabinoids, although it should be noted there are a limited number of reports in this field.

Chronic adolescent THC treatment in rodents has distinct effects on serotonin receptor subtypes: chronic THC reduces 5-$HT_{2A}$R binding in the insula, cingulate and ventral pallidum and increases 5-$HT_{2A}$R binding in the striatum [16], but has no effect on 5-$HT_{1A}$R binding in the hippocampus, cingulate cortex and lateral septum [25]. Reductions in 5-$HT_{2A}$R expression may be due to a lower neural firing rate of 5-HT-expressing cells in the dorsal raphe following chronic cannabinoid treatment in adolescence, but not adulthood [24•]. Reduced serotonergic system function following chronic cannabinoid treatment is associated with behaviours representing negative symptoms, including anhedonia-like behaviour (i.e. decreased sucrose preference) [24•] and impaired social interaction [16]. Furthermore, *Nrg1* TM HET mice treated with THC in adolescence exhibit a less severe social interaction impairment and fewer THC-induced reductions in 5-$HT_{2A}$ receptor binding across several forebrain regions [16]. This suggests that cannabinoid-induced impairments in serotonergic function could contribute to negative-like symptoms in schizophrenia animal models.

There is limited evidence for noradrenergic system changes following chronic adolescent cannabinoid treatment. Chronic adolescent, but not adult, WIN treatment dose-dependently enhances burst firing of noradrenergic cells in the locus coeruleus (LC) in adulthood [24•]. Considering that $CB_1$R agonism stimulates LC noradrenergic activity [99], it is possible that the enhanced noradrenergic neural activity observed was due $CB_1$R upregulation in the LC [24•]. The elevation of noradrenergic activity in the LC following chronic WIN may correspond with elevated anxiety-like behaviour in the same treatment model—novelty suppressed feeding is inhibited following chronic high-dose, but not low dose, WIN [24•].

## Effects on Dendritic Spine Density and Morphology

Changes to dendritic spine density and morphology may contribute to schizophrenia aetiology, as developmental synaptic pruning and remodelling occur during a similar age bracket as the onset of schizophrenia (i.e. adolescence, early adulthood) [100]. Also, post-mortem brain tissue from schizophrenia patients exhibits reduced dendritic spine density and arborisation in the PFC [101].

Chronic cannabinoid treatment in adolescence and adulthood reduces dendritic spine density and complexity in the hippocampus and PFC. Chronic THC in adolescence reduces dendritic spine length and number in the hippocampus, for more than 30 days after treatment cessation [44].

Also, subchronic and chronic WIN in adulthood reduces dendritic spine density in the dentate gyrus of the hippocampus [77]. Similar effects of chronic cannabinoids on dendritic spine density are observed in the PFC—chronic adolescent CP reduces the number, length and complexity of basal dendritic spines of pyramidal neurons of the PFC for more than 40 days after treatment cessation [76]. Alterations to dendritic spine density in the hippocampus are associated with performance in a radial arm maze, such that having fewer dendritic spines is associated with a greater number of errors in a radial arm maze in adult rats [44].

## Effects of Chronic Cannabinoid Treatment on Inflammatory Markers

Increased neural inflammation during critical developmental periods may impair subsequent brain maturation (e.g. changes to structural connectivity, synaptic pruning) via processes such as excitotoxicity, oxidative stress, neuroinflammation and excessive activation of the hypothalamic/pituitary/adrenal axis [102, 103]. Indeed, expression of proinflammatory cytokines and markers of inflammation in blood and cerebrospinal fluid [e.g. tumour necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), IL-6, IL-8] [104] and reduced serum and plasma antioxidant markers [105] are observed in schizophrenia patients. Similar findings are reported in rodents: repeated cannabinoid administration in adolescence and adulthood generally increases protein and mRNA expression of inflammatory markers [10, 31, 36, 78•].

In the hippocampus, THC-induced expression of proinflammatory cytokines can change over time. Within 24 h of chronic THC treatment, there is an acute reduction of proinflammatory cytokine markers (e.g. TNF-α, IL-1β) in the hippocampus of mice treated in adolescence or adulthood with THC [78•], but 47 days after treatment cessation, elevation of proinflammatory cytokines in the hippocampus is observed only in adolescent-treated mice [78•].

There are also dose-dependent effects of cannabinoid administration on hippocampal astrocyte activation. Chronic adolescent treatment with a low dose of CP increases cells labelled with glial fibrillary acidic protein (GFAP, an astrocyte marker) in the dentate gyrus of the hippocampus in adulthood [70], while a moderate-to-high dose of THC in adolescence reduces GFAP protein expression in the hippocampus in adulthood [44].

Effects of cannabinoids on inflammatory markers are region dependent in the PFC and striatum. Effects of chronic WIN in the striatum during adulthood are transient—chronic WIN enhances striatal nuclear translocation of peroxisome proliferator-activated receptor γ (PPAR-γ), as well as receptor expression of TNF-α and cyclooxygenase-2 (COX-2) immediately after drug treatment cessation, but these effects return to control levels after 48 h [10]. Effects on inflammatory markers last longer in the PFC—chronic adolescent THC increases expression of the proinflammatory markers TNF-α, inducible nitric oxide synthase (iNOS) and COX-2, reduces IL-10 expression and upregulates $CB_2R$ expression on microglial cells when tissue is collected in adulthood [31].

In the cerebellum, subchronic THC in adult mice increases mRNA expression of the neuroinflammatory markers IL-1β, TNF-α, COX2, integrin alpha M (ITGAM) and chemokine (C-X-C motif) ligand 2, as well as protein expression of ITGAM for up to 5 days post-treatment [36].

Long-lasting (i.e. between 5 and 47 days) enhancement of proinflammatory markers following chronic cannabinoid treatment is associated with cognitive impairment. Chronic THC-induced increases in PFC expression of TNF-α, iNOS, COX-2 and $CB_2$ on microglia, as well as decreases in IL-10, are associated with impaired short-term recognition memory in adulthood [31]. Importantly, blocking microglial activation with ibudilast during THC treatment significantly attenuates short-term memory impairments in adulthood and prevents increased TNF-α, iNOS and COX-2 levels as well as the upregulation of $CB_2$ receptors on microglial cells [31]. In the cerebellum, subchronic adult THC increases mRNA expression of neuroinflammatory markers and impairs cerebellar-dependent eyeblink conditioning [36]; these impairments are reversed when animals are treated with the immunosuppressant and microglial inhibitor minocycline after THC treatment cessation [36]. These data indicate that upregulation of inflammatory markers following chronic cannabinoid treatment, particularly in the PFC and cerebellum, may contribute to cognitive impairment relevant to schizophrenia.

## Synthesis and Conclusions

Chronic cannabinoid treatment in adolescence and adulthood causes substantial changes to receptor expression and function across the brain, as well as marked changes to dendritic morphology and inflammatory markers. Changes in brain function and connectivity correspond with behavioural impairments relevant to schizophrenia and, indeed, indicate which symptom domains are particularly affected by chronic cannabinoid treatment.

Positive symptoms appear to correspond with cannabinoid-induced changes in dopaminergic system function—an imbalance of $D_1R/D_2R$ expression in forebrain regions and downregulation of dopaminergic cell function in the VTA and SN alters sensitivity to locomotor-stimulating dopaminergic agents. Behaviours corresponding with negative symptoms correlate with region-specific impairment

in $CB_1R$ expression and serotonergic system function: cannabinoid-induced impairments in social interaction and anhedonia correspond with reduced amygdala $CB_1R$ expression, impaired forebrain 5-$HT_{2A}$ receptor expression and reduced dorsal raphe 5-HT firing.

Cognitive impairment following chronic cannabinoid treatment appears dependent on altered receptor expression, dendritic morphology and increased inflammation; these effects often occur in the forebrain. Persistent downregulation of dopaminergic receptor expression in the VTA and SN, reductions in glutamatergic receptor expression in the hippocampus and lower PFC and hippocampal $CB_1R$ expression are associated with persistent cannabinoid-induced cognitive impairment. Reduced dendritic spine density in the PFC and hippocampus contributes to spatial memory and short-term recognition memory impairment. Long-lasting upregulation of inflammatory markers across the brain causes short-term recognition memory and cerebellar-dependent eyeblink conditioning impairment. It is presently unclear how chronic cannabinoid treatment causes persistent disruption of sensorimotor gating, but pharmacological manipulation of sensorimotor gating suggests that it may involve dysfunction in dopaminergic and glutamatergic systems [68].

From the animal data reviewed, there is some indication that adolescence is a critical period of susceptibility to cannabinoid-induced brain changes in rodents. Most of the research cited in this review examines how adolescent cannabinoid treatment affects neural function in adulthood, without comparison to an adult treatment group [studies with age comparison: [24•, 78•]]. Comparisons between studies using adolescent and adult treatment regimes [24•, 78•] demonstrate greater impairment in neural function following chronic adolescence cannabinoid treatment, compared to adult treatment; however, considering the small number of studies directly comparing the two age groups, it is clear that more research is required in this field. Finally, sex differences during adolescence and adulthood also require further investigation; most studies reviewed here examine responses in one sex only, and this is often males.

**Compliance with Ethical Standards**

**Conflict of Interest** The authors declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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