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REVIEW

Schizophrenia and drug addiction comorbidity: recent advances in our understanding of behavioural susceptibility and neural mechanisms

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Abstract

Schizophrenia is a severe psychiatric disorder which is worsened substantially by substance abuse/addiction. Substance abuse affects nearly 50% of individuals with schizophrenia, extends across several drug classes (e.g. nicotine, cannabinoids, ethanol, psychostimulants) and worsens overall functioning of patients. Prominent theories explaining schizophrenia and addiction comorbidity include the *primary addiction hypothesis* (i.e. schizophrenia susceptibility primes drug reward circuits, increasing drug addiction risk following drug exposure), the *two-hit hypothesis* (i.e. drug abuse and other genetic and/or environmental risk factors contribute to schizophrenia development) and the *self-medication hypothesis* (i.e. drug use alleviates schizophrenia symptoms). Animal models can be used to evaluate the utility and validity of these theories. Since this literature was last reviewed by Ng and colleagues in 2013 [*Neurosci Biobehav Rev*, 37(5)], significant advances have been made to our understanding of schizophrenia and substance abuse comorbidity. Here we review advances in the field since 2013, focussing on two key questions: 1) Does schizophrenia susceptibility increase susceptibility to drug addiction (assessing the primary addiction hypothesis), and 2) Do abused drugs exacerbate or ameliorate schizophrenia symptoms (assessing the two-hit hypothesis and the self-medication hypothesis). We addressed these questions using data from several schizophrenia preclinical models (e.g. genetic, lesion, neurodevelopmental, pharmacological) across drug classes (e.g. nicotine, cannabinoids, ethanol, psychostimulants). We conclude that addiction-like behaviour is present in several preclinical schizophrenia models, and drugs of abuse can exacerbate but also ameliorate schizophrenia-relevant behaviours. These behavioural changes are associated with altered receptor system function (e.g. dopaminergic, glutamatergic, GABAergic) critically implicated in schizophrenia and addiction pathology.

Key words: Schizophrenia; Drug Addiction; Drug Abuse; Rodent Model; Behaviour; Molecular

1. Introduction

Schizophrenia is a severe psychiatric illness affecting approximately 1% of the population worldwide [1], and is characterised by a combination of positive symptoms (e.g. delusions, hallucinations, conceptual disorganisation), negative symptoms (e.g. apathy, social withdrawal, emotional blunting) and cognitive impairment (e.g. impaired executive function, working memory and attention) [2]. Sex differences are evident in schizophrenia: males have a higher incidence rate and an earlier onset of schizophrenia (although females show an increased incidence of schizophrenia following menopause), males present with worse negative symptoms and do not respond as well to antipsychotic treatment as females; several of these differences have been attributed to protective effects of estrogen in females [3].

Drug abuse and addiction (used interchangeably) is very common in patients with schizophrenia, occurring up to five times more frequently than in the general population, and affecting nearly 50% of patients (excluding nicotine dependence, which affects nearly 90% of patients with schizophrenia) [4, 5]. For example, cannabis abuse occurs in 50% of patients with schizophrenia, compared to 1% of the general population, nicotine abuse occurs in 29% of patients, compared to 13% of the general population, and alcohol abuse occurs in 43-65% of patients, compared to 5% of the general population [5].

Drug abuse causes significant problems for patients by worsening symptoms, limiting treatment compliance, increasing psychotic relapse and hospitalisation, and increasing suicide risk [6–11]. Some drugs, such as cannabis and methamphetamine, increase risk for developing psychosis and schizophrenia; however, chronic drug abuse can also develop after disease onset, indicating a complex bidirectional relationship [12]. Several drug classes are abused in schizophrenia, including cannabis, psychostimulants (e.g. methamphetamine, cocaine), alcohol and nicotine [5]. To the authors' knowledge, sex differences in the prevalence of substance abuse in patients with schizophrenia has not been reported. Despite high rates of substance abuse in schizophrenia and the significant problems it causes, the causes of comorbidity are unclear.

1.1 Theories of schizophrenia and drug abuse comorbidity

Several theories have been developed to help explain the high rate of substance abuse in schizophrenia (see [13]). The *self-medication theory* suggests that individuals with schizophrenia abuse substances to ameliorate symptoms of the disease [14]; however, this has received limited empirical support (e.g. [15, 16]). The *primary addiction hypothesis* purports that schizophrenia and drug addiction share similar pathophysiology in mesocortolimbic circuitry, and thus individuals predisposed to schizophrenia also have an elevated propensity for addiction [17]. In the primary addiction hypothesis, drug addiction can occur prior to, but also after developing schizophrenia. The *two-hit hypothesis* claims that genetic or environmental vulnerabilities (first hit) for schizophrenia interact with additional genetic or environmental factor/s (second hit), such as substance abuse, resulting in the development of psychotic symptoms and schizophrenia [18]. In the *two-hit hypothesis* drug abuse both contributes to and exacerbates schizophrenia symptoms. Related to this is the *shared susceptibility hypothesis*, which suggests that poor functioning and the presence of poverty, victimization and toxic social environments in patients with schizophrenia accumulate to increase risk for developing substance abuse [19]. Due to the similarities between the two-hit hypothesis and the shared susceptibility hypothesis, we will evaluate environmental influences on substance abuse risk as part of the two-hit hypothesis. Clinical evidence mostly falls in favour of the primary addiction hypothesis and the two-hit hypothesis [12]; however, determining cause and effect can often be difficult in clinical samples due to the ethical implications of administering substances which increase psychotic symptoms to individuals with schizophrenia. Preclinical rodent models can thus facilitate our understanding of causative factors for substance abuse and schizophrenia comorbidity.

1.2 Rodent models of schizophrenia

Preclinical rodent models of schizophrenia can be used to better understand aspects of schizophrenia aetiology, pathophysiology, symptomology and neural function. While no model can encompass the full spectrum of neurological change within this uniquely human disorder, models can help us understand how specific genetic and environmental factors contribute to, and also interact to bring about the development of schizophrenia. Furthermore, rodent models allow us to more precisely investigate different hypotheses for substance abuse comorbidity in schizophrenia. This review will examine comorbidity between drug abuse and schizophrenia in the following classes of model:

Genetic models

Genetic models are generated by inserting, knocking down, deleting or mutating genes relevant to schizophrenia into the rodent genome [20]. Many genetic risk factors for schizophrenia are cumulative and explain a small amount (e.g. 1–2% of variance) in terms of risk for schizophrenia; thus combinations of risk genes or gene-environment combinations can improve on these models. Nonetheless, these models often possess good construct validity for schizophrenia, as causal factors associated with schizophrenia risk are reproduced in these models [20].

Neurodevelopmental models

Schizophrenia can be conceptualised as a neurodevelopmental disorder [21], and manipulations during gestation, birth and early postnatal development are used to produce irreversible changes in central nervous system development. Examples of manipulations include lesions, disruption of neurogenesis during critical gestational periods, post-weaning social isolation and maternal immune activation [20]. Due to the high volume of data on the neonatal ventral hippocampal lesion (NVHL) model, we will address this separately to other neurodevelopmental models.

Pharmacological models

In patients with schizophrenia, biochemical aberrations of the dopamine, γ-amino-butyric acid (GABA), glutamate [e.g. abnormalities of n-methyl-d-asparate (NMDA) receptors], and nicotinic receptor systems, as well as functional and structural changes in the brain are present [22]. Repeated administration of substances which disrupt these neurotransmitter systems including phencyclidine (PCP), ketamine, dizocilpine (MK-801), amphetamine and methamphetamine produces behavioural and brain abnormalities which resemble symptoms of schizophrenia [20]; however, the construct validity (i.e. the relevance of these pharmacological models to schizophrenia pathology) of these models is limited.

1.3 Schizophrenia-relevant behaviour in rodents

Schizophrenia-relevant behaviour can be modelled in rodents, and below we briefly describe behaviours modelling positive, negative and cognitive symptoms, as well as sensorimotor gating. For a more detailed review of this topic, see [20, 23, 24].

Positive symptoms of schizophrenia are modelled by tests of locomotor activity and sensitivity to effects of psychomimetic drugs on locomotion and stereotyped behaviours. Locomotor behaviour is considered a proxy measure for psychosis, as both locomotion and psychosis are elevated by increased dopamine transmission in the mesolimbic pathway, and both psychosis and hyperlocomotion in schizophrenia rodent models can be reduced by antipsychotic treatment [24]. Also, patients with schizophrenia are sensitive to the psychosis-inducing effects of psychomimetic drugs (e.g. amphetamines, the NMDA antagonist MK-801) [25], and these drugs can also increase locomotor behaviour. However, locomotion is a complex and non-specific behaviour, and should be interpreted with caution, as compounds can reduce locomotor activity by mechanisms that may not be related to antipsychotic efficacy [24].

Negative symptoms of schizophrenia, such as anhedonia, social withdrawal and loss of motivation are measured through tests such as sucrose preference (modelling anhedonia), social interaction/social preference (modelling social withdrawal) and operant progressive ratio testing for food rewards (modelling loss of motivation) [23, 24]. Sucrose preference measures voluntary consumption of a palatable food reinforcer (i.e. sucrose) as well as water, and a reduction in preference for sucrose over

water may indicate a limited ability to feel pleasure from a normally enjoyable activity. The social interaction test measures a range of behaviours exhibited when two unfamiliar rodents interact freely (e.g. sniffing the conspecific, following, climbing over/under etc). The social preference test assesses 1) preference for investigating an unfamiliar conspecific in a cage compared to an empty cage, and 2) preference for a novel conspecific over a familiar conspecific. While these social tests assess social behaviours, as well as the preference for socialisation and social novelty, the degree to which these directly correspond with social withdrawal in schizophrenia is not clear. Operant progressive ratio testing examines the motivation to obtain a food reward. Animals engage in an operant response (e.g. lever press, nose poke) to receive a food reward (e.g. sugar pellet), and throughout the session, the response requirements for the reward are increased, requiring more effort from the animal to obtain the food reward. This test is considered a measure of avolition, which can be impaired in schizophrenia [23, 24].

Cognitive impairment in schizophrenia, for example, deficits in working memory, attention, and executive function, are modelled through an array of rodent cognitive tasks. Most cognitive behavioural tasks reported in this review assess short- and long-term memory function, using tasks such as fear conditioning (animals learn to associate a tone and/or context with a footshock), the Morris Water Maze (animals learn to locate a platform submerged in water over successive days using either egocentric or environmental cues), novel object recognition test (animals investigate a novel object more than a familiar object) and Y-maze (animals investigate a novel arm in a Y-shaped maze more than familiar arms). However, there are more complex tests of cognitive ability which may better reflect cognitive impairment in schizophrenia. These include the 5 choice serial reaction time task, where animals in an operant chamber need to identify which of five apertures has been briefly illuminated, via a nose poke, to receive a food reward; this assesses attention and inhibitory control [24]. In the set shifting task, animals learn to dig for a food reward which is associated with specific cues. When tested, animals need to respond to relevant cues associated with a food reward (e.g. digging medium), and ignore cues which do not predict a food reward (e.g. odour); this assesses rule learning and discrimination [24]. Rodent touchscreen technology, in which rodents need to respond to 'target' visual pattern stimuli and to withhold responses to 'non-target' stimuli, permits assessment of perceptual discrimination, object-place associative learning, attention, impulsivity, compulsivity, extinction and other domains [26, 27].

A related domain is prepulse inhibition (PPI), a measure of sensorimotor gating, which is a pre-attentional process to facilitate stimulus filtering and limit sensory overload [28]. PPI is the reduction in startle to an auditory or tactile stimulus, by the prior presentation of a non-startling stimulus [28]. PPI is measured in rodents assessment of the whole body flinch to auditory (i.e. tone/white noise) or tactile (i.e. air puff) stimuli, and can be disrupted by administration of psychomimetic drugs [28]. PPI is impaired in patients with schizophrenia, but PPI deficits are also observed in other disorders e.g. obsessive-compulsive disorder, Tourette's syndrome; thus, PPI is not specific to schizophrenia alone [29].

1.4 Addiction-relevant behaviour in rodents

Here we briefly outline the behavioural assessment of addiction-relevant behaviour in rodents; however, further information on these tests can be found in the following reviews for conditioned place preference [28–31], behavioural/locomotor sensitization [32–34], and drug self-administration [35, 36].

Conditioned Place Preference (CPP): CPP is an indirect measure of drug reward, based on context-drug associations. The CPP apparatus contains two distinct environments (i.e. drug-paired and vehicle-paired environments), created by a combination of wall patterns, floor textures and/or scent cues. Animals are tested for their baseline preference between these two compartments, in a pre-test baseline session. Then, across several days, animals are given vehicle- and drug-environment pairings (i.e. animals are given a vehicle injection and confined to the vehicle-paired environment in the morning, and then in the afternoon or the next day, animals are given a drug injection and confined to the drug-paired environment). This process is repeated several times (e.g. normally 3-5 vehicle and drug pairings for each animals). At Test, animals are given free access to both compartments, and if they spend more time in the drug-paired environment than the vehicle-paired environment, this indicates the drug was rewarding. The place preference score is often presented as the difference between pre- and post-test scores.

Behavioural/Locomotor Sensitization: Behavioural/locomotor sensitization is defined by the augmented motor-stimulant response that occurs with repeated, intermittent exposure to a drug, and is considered a marker of neural adaptations that can facilitate future drug taking [32]. Briefly, animals are intermittently administered a drug in a specific context (e.g. an open field apparatus). Repeated administration of the same drug dose over successive days/weeks leads to an increase in the behavioural response to the drug, termed the development of sensitization. These behaviours can include locomotion and/or stereotyped behaviours (e.g. sniffing, grooming, head weaving). Expression of sensitization is evident when animals are given a low-dose drug prime and they exhibit higher levels of these behaviours than in response to vehicle treatment (i.e. the behaviours have sensitized).

Intravenous drug self-administration: Rodents can self-administer drugs of abuse freely within operant chambers, allowing control over the amount and frequency of the drug administered. Animals can engage in an operant response (e.g. lever press, nose poke, head movements detected by infra-red beams), which will provide a drug infusion. Drug reward can occur in the presence of cues (e.g. light, tone), and other discriminative stimuli (e.g. scents, wall and floor textures). An inactive operant response (e.g. lever press on the 'inactive' lever or nose poke in the 'inactive' hole) permits assessment of discrimination within the task. Rodents learn to self-administer abused drugs according to reinforcement schedules e.g. Fixed Ratio (FR) schedules require a fixed number of operant responses to obtain a drug reward (e.g. FR2 requires 2 lever presses for 1 drug reward), while a Progressive Ratio (PR) schedule requires an increasing number of operant responses to obtain a drug reward. After a period of self-administration (often 2-3 weeks), animals can be put into abstinence (e.g. kept in home cage with no exposure to operant chambers) or undergo extinction training, where the drug is no longer available in the operant chambers, and animals need to learn to inhibit their responding on the active lever. Extinction can also be conducted in a different context, mimicking the change in context which can occur in rehabilitation centres. Drug-associated cues may also be omitted during extinction. Relapse-like behaviour can be modelled in reinstatement and renewal tests, where animals are returned to the operant chambers and drug-associated cues are presented (i.e. cue-induced reinstatement), or a low dose drug-prime is administered (i.e. drug-primed reinstatement), or the animals experience a stressor (i.e. stress-induced reinstatement). Renewal of drug-seeking occurs when an animal is extinguished in a different context, but is then returned to the original drug-

taking context, which facilitates drug-seeking. Resumption of drug-taking can also be modelled after extinction; this is termed reacquisition.

Intracranial Self-Stimulation: In the intracranial self-stimulation (ICSS) paradigm, rodents are implanted with intracranial electrodes that target specific brain regions [e.g. medial forebrain bundle of the hypothalamus, ventral tegmental area (VTA)], and performance of an operant response results in the delivery of electrical stimulation to that target [37, 38]. ICSS is rewarding as it promotes dopamine release in nucleus accumbens, it is enhanced by drugs that increase extracellular dopamine in nucleus accumbens, and it is blocked by drugs that deplete dopamine or block dopamine receptors [37, 38]. Rodents learn to stimulate the target brain region over several training days, and ICSS rates levels can modified by parameters such as pulse frequency, pulse amplitude, stimulus train duration and schedule of reinforcement [37]. In ICSS paradigms, ICSS rates are lower at low frequencies (e.g. 56-71 Hz) and increase with higher frequencies (110 Hz+) [37]. The abuse potential of drugs can be assessed in ICSS: once animals have established baseline responding, administration of an abused drug can shift their baseline ICSS responding e.g. responding at low frequencies at baseline can be elevated by drug treatment [37]. The facilitation of ICSS responding is indicative of abuse potential; this may be due to ICSS and drug administration producing additive effects on mesolimbic dopamine release and transmission, thus facilitating the operant behaviour which maintains ICSS [37].

1.5 Methods and literature

During the course of writing this review, we noticed that interactions between abused substances and schizophrenia rodent models tended to target two major, yet distinct research questions. One question explored how rodent models of schizophrenia respond to drugs of abuse in addiction behavioural paradigms (e.g. conditioned place preference, locomotor sensitization, self-administration). This question evaluates the primary addiction hypothesis (i.e. that schizophrenia and drug addiction share similar pathophysiology in mesocortolimbic circuitry) and investigates *if addiction behaviour is elevated* in rodent models of schizophrenia, suggesting that risk for schizophrenia also elevates risk for substance abuse.

The other component of the literature addresses if animal models of schizophrenia *are more susceptible to the effects of abused drugs on schizophrenia-relevant behaviour*, including whether schizophrenia-like behaviour is exacerbated by abused drugs in rodent models of the disorder. This component addresses the two-hit hypothesis, and evidence in favour of this hypothesis suggests the development of schizophrenia may be facilitated by drug exposure. Alternatively, some studies also examine the possible therapeutic effects of some abused drugs in these models, potentially supporting the self-medication hypothesis.

To provide a structured overview, each component of the review is divided into the model used and the drug investigated. In 2013, Ng and colleagues reviewed the existing literature on rodent models of schizophrenia targeting dual diagnosis [39], and we refer readers to this review for an in-depth examination of substance abuse comorbidity in rodent models of schizophrenia prior to 2013. However, since then a large body of literature has examined this topic further, providing novel insights into the behavioural and molecular underpinnings of comorbid substance abuse in schizophrenia. Here, we present literature since 2013 on this topic; yet, where relevant (e.g. when limited information is available on a topic), we refer to older studies to help inform our conclusions. Literature searches were conducted using PubMed. Our search terms are provided in Table 1.

1.6 Definitions

Here we outline several definitions used within this review.

Developmental periods: Susceptible periods of rodent development include the neonatal period [gestational day (G) 1-18/21] and postnatal period [postnatal day (PND) 1-21], as well as adolescence (PND 22-60), young adulthood (PND 60-90) and adulthood (PND 90+). While there is discussion over the duration of adolescence in rodents [40], we have adopted these broad definitions, based on a review of the rodent adolescent literature [40], to provide consistency for the reader.

Drug administration: Drug administration is described as acute (once-off drug administration, often within 1 hour before or after experimental manipulation), sub-chronic (3-10 days drug administration; drugs are often administered 1-2x every 24 hours) or chronic (1-2 administrations per day for more than 10 days).

Schizophrenia-relevant behaviour: Schizophrenia-like behaviour can be modelled in rodents using tests to assess positive and negative symptoms, as well as cognitive impairment and sensorimotor gating deficits. These are described above in section 1.3 (reviews: [24, 41, 42]).

Addiction-relevant behaviour: We refer extensively to behavioural tests of addiction-relevant behaviour (described above in section 1.4), including conditioned place preference (CPP), behavioural/locomotor sensitization, and drug self-administration.

2. Addiction-relevant behaviour in rodent models of schizophrenia

All preclinical studies reviewed in section 2 are summarised in Tables 2, 3 and 4.

2.1 Genetic models

Addiction-like behaviour in genetic models of schizophrenia has been examined only for the psychostimulants cocaine and amphetamine, which increase dopamine release and transmission in the mesocorticolimbic pathway [43, 44].

Psychostimulants: cocaine and amphetamine

Dopamine metabolism and signalling are critically linked schizophrenia symptoms, whereby elevated dopamine release in the mesolimbic pathway is hypothesized to contribute to positive symptoms, whereas reduced dopamine in the mesocorticolimbic pathway appears to contribute to negative symptoms of the disorder [45, 46]. Altered dopamine signalling may be linked to dopamine receptor expression, and several studies indicate D_2 receptor expression is elevated in the striatum but reduced in thalamic regions of unmedicated patients with schizophrenia (review: [47]). Interestingly, mice overexpressing dopamine D_2 receptors in the paraventricular nucleus of the hypothalamus (PVT) (i.e. the opposite of what is observed in patients with schizophrenia) show attenuated locomotor sensitization to a cocaine challenge, compared to mice which do not overexpress PVT D_2 receptors [48], suggesting reduced susceptibility to cocaine-induced neural adaptations. These effects on cocaine sensitization occur in the absence of altered schizophrenia-relevant behaviours in PVT D_2 overexpressing mice [48]. The PVT may modulate cocaine sensitization via dense projections to critical reward regions such as the medial prefrontal cortex (mPFC), nucleus accumbens (NAcc),

Table 1. Search term keywords used in PubMed.

Keyword 1	Boolean operator	Keyword 2	Boolean operator	Keyword 3
Schizophrenia [Title/Abstract]	AND	Mouse [Title/Abstract]	AND	Alcohol [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Mouse [Title/Abstract]	AND	Nicotine [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Mouse [Title/Abstract]	AND	Cannabis [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Mouse [Title/Abstract]	AND	Cocaine [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Mouse [Title/Abstract]	AND	Methamphetamine [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Rat [Title/Abstract]	AND	Cannabis [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Rat [Title/Abstract]	AND	Nicotine [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Rat [Title/Abstract]	AND	Alcohol [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Rat [Title/Abstract]	AND	Cocaine [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Rat [Title/Abstract]	AND	Methamphetamine [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Mouse [Title/Abstract]	AND	Addiction [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Mouse [Title/Abstract]	AND	Substance Abuse [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Rat [Title/Abstract]	AND	Addiction [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Rat [Title/Abstract]	AND	Substance Abuse [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Rodent [Title/Abstract]	AND	Addiction [Title/Abstract]
Schizophrenia [Title/Abstract]	AND	Rodent [Title/Abstract]	AND	Drug abuse [Title/Abstract]

amygdala and bed nucleus of the stria terminalis (BNST). The effects of D_2 receptor knockdown/knockout in the PVT have not yet been examined; however, it would be interesting to observe whether reduced PVT D_2 expression increases cocaine sensitization and other addiction-relevant behaviours, potentially providing a mechanism for elevated drug abuse susceptibility in patients with schizophrenia.

The *DISC1* gene is a rare genetic risk factor for schizophrenia that codes for several proteins involved in dopamine signalling (e.g. cAMP-specific 3',5'-cyclic phosphodiesterase 4B, serine/threonine protein kinase Akt and glycogen synthasekinase-3 (GSK-3) [49, 50]). Several lines of transgenic mice designed to model *DISC1* mutations have been created, many of which exhibit schizophrenia relevant behaviours, including hyperactivity, decreased social behaviours, anhedonia in the sucrose preference test and sensorimotor gating impairment (review: [51]). Recent evidence suggests *DISC1* gene alterations can regulate addiction-relevant behaviour for cocaine in rats [52]. *Disc1* knockdown in the NAcc of rats increases cocaine self-administration under higher reinforcement schedules [i.e. FR4-10, but not FR1-2] [52]. Also,*DISC1* protein levels are elevated in the NAcc of sham control rats after 12 days of cocaine self-administration, compared to sham control rats which self-administer saline [52]. This suggests *Disc1* can regulate motivation for cocaine, and upregulation of *DISC1* protein may be a compensatory mechanism following repeated cocaine self-administration. Importantly, this provides a link between genetic risk for schizophrenia and drug addiction susceptibility, supporting the primary addiction hypothesis.

Epidermal growth factor (EGF) is involved in cellular proliferation, differentiation, and survival, and a functional single nucleotide polymorphism (SNP) in the *EGF* gene which increases *EGF* transcription is associated with lower age of onset of schizophrenia [53, 54]. *EGF* overexpression in mice facilitates acquisition of cocaine behavioural sensitization, such that cocaine sensitization is much stronger in mice overexpressing *EGF*, compared to wildtype-like (WT) controls where sensitization did occur but was not very prominent [55]. These behavioural effects are accompanied by changes in dopamine metabolites in mice overexpressing *EGF*: striatal extracellular levels of tyrosine hydroxylase (TH) are decreased and catechol-O-methyl-transferase (COMT) increased, whereas dopa-decarboxylase in the NAcc and frontal cortex are increased, and extracellular dopamine and DOPAC are elevated in the NAcc [55]. These findings link increased *EGF* function with elevated cocaine sensitivity via increased dopamine metabolism, and also supports the primary addiction hypothesis.

NMDA receptors regulate glutamate signalling which appears to be dysregulated in schizophrenia, and NMDA dysfunction is observed in post mortem brain tissue of patients with schizophrenia [56]. Changes to NMDA function can be modelled using glycine transporter 1 heterozygous knockout mice to model NMDA hyperfunction, and serine racemase knockout to model NMDA hypofunction [57]. Glycine transporter 1 heterozygous knockout in the forebrain (i.e. forebrain NMDA hyperfunction) enhances cognitive performance in mice [58, 59], while serine racemase knockout mice (i.e. NMDA hypofunction) exhibit hyperlocomotion, sociability deficits and greater ventricular volumes [60–62], all of which are relevant to schizophrenia. In terms of drug abuse potential, both NMDA hyper- and hypofunction mouse models express place preference for cocaine [57]. However, NMDA hypofunction facilitates extinction of cocaine place preference (i.e. NMDA hypofunction reduces drug seeking), whereas NMDA hyperfunction enhances drug-primed reinstatement of cocaine place preference (i.e. NMDA hyperfunction increases drug seeking) [57]. In addition, NMDA hypofunction reduces sensitivity to the threshold-lowering (i.e. rewarding) and the performance-elevating (i.e. stimulant) effects of cocaine in an intracranial self-stimulation paradigm [63]. NMDA hypofunction also attenuates cocaine locomotor sensitization [57]; this may be due to blunted cocaine-induced dopamine and glutamate release in the NAcc [63]. Note also that a previous study reported that NMDA hypofunction reduces expression of context-specific sensitization and conditioned hyperactivity for amphetamine, while NMDA hyperfunction facilitates acquisition of amphetamine sensitization [64]. Together, this suggests that NMDA receptor hypofunction decreases the rewarding responses of cocaine, and higher doses of cocaine are required to achieve a hedonic response, while NMDA hyperfunction increases cocaine reward and necessitates lower doses of cocaine for a hedonic response. Considering NMDA receptors appear downregulated in schizophrenia, particularly in reward-relevant regions such as the striatum and prefrontal cortex (review: [56]), it seems that individuals with schizophrenia may require higher doses of cocaine to achieve a rewarding state, increasing the risk of developing severe physiological dependency and withdrawal [63].

Together, these studies demonstrate addiction-like behaviour in genetic models of schizophrenia risk. In particular, genetic models with construct validity for schizophrenia e.g. *Disc1* and *EGF* transgenic mice, exhibit enhanced addiction-like behaviour, providing support for the primary addiction hypothesis. Furthermore, *EGF* transgenic mice exhibit elevated

Table 2. Addiction-relevant behaviour in genetic and pharmacological rodent models of schizophrenia

Author, date [Reference]	Model	Drug	Results - Behaviour (↓decrease, ↑increase, ~no effect)	Results - Brain (↓decrease, ↑increase, ~no effect)
Clark et al 2017 [48]	DA D_2 receptor overexpression in the PVT of mice	Cocaine	↓cocaine sensitization.	n/a
Gancarz et al 2016 [52]	*Disc1* knockdown in the Nacc of rats	Cocaine	↑ cocaine self-administration.	↑Nacc *DISC1* protein levels after cocaine self-administration in shams.
Eda et al 2013 [55]	*EGF* overexpressing mice	Cocaine	↑cocaine sensitization.	in *EGF* overexpressing mice: ↓striatal extracellular tyrosine hydroxylase, ↑catechol-O-methyl-transferase. ↑ dopa-decarboxylase in Nacc and FC. ↑Nacc extracellular dopamine and dopamine metabolites.
Puhl et al 2015 [60]	Glycine transporter 1 HET knockout mice	Cocaine	~ cocaine CPP and CPP extinction. ↑ Cocaine-primed reinstatement.	n/a
Puhl et al 2015 [60]; Puhl et al 2019 [63]	Serine racemase knockout mice	Cocaine	~ cocaine CPP. ↑ cocaine CPP extinction. ↓ cocaine sensitization. ↓sensitivity to cocaine ICSS.	↓cocaine-induced dopamine and glutamate release in NAcc.
Benneyworth et al 2012 [64]	Glycine transporter 1 HET knockout mice	Amphetamine	↑amphetamine sensitization. ~expression of amphetamine sensitization.	n/a
Benneyworth et al 2012 [64]	Serine racemase knockout mice	Amphetamine	↓Amphetamine sensitization and ↓expression of amphetamine sensitization. ↓Extinction of amphetamine sensitization.	↑NAcc spine density after extinction.
Fletcher et al 2018 [110]	Chronic amphetamine treatment in rats	Nicotine	~Acquisition and maintenance of nicotine self-administration.	n/a
Fletcher et al 2018 [110]	Chronic PCP treatment in rats	Nicotine	~Acquisition and maintenance of nicotine self-administration.	n/a

Abbreviations: CPP, conditioned place preference; DA, dopamine; Disc1; Disrupted in Schizophrenia 1; EGF, epidermal growth factor; FC, frontal cortex; HET; heterozygous; ICSS, intracranial self-stimulation; NAcc, nucleus accumbens, PCP, phencyclidine.

dopamine metabolism in forebrain regions, and considering the critical role of dopamine in reward signalling, these models provide a potential mechanism for elevated addiction propensity in individuals with schizophrenia. Future research will examine addiction-relevant behaviours in other genetic models of schizophrenia, to non-psychostimulant drugs.

2.2 Lesion models

The neonatal ventral hippocampal lesion (NVHL) is a widely used neurodevelopmental animal model, in which an excitotoxin infusion is made into the ventral hippocampus during the first postnatal week, a time point roughly comparable to the third trimester of human development [65]. This lesion causes neurodevelopmental interruptions hypothesised to be relevant to schizophrenia susceptibility [66]. The NVHL model develops behavioural and neurobiological dysfunction relevant to schizophrenia e.g. social interaction and cognitive impairment, prepulse inhibition deficits, and an enhanced locomotor response to stress [67, 68].

Psychostimulants: amphetamine and methamphetamine

In a brain stimulation paradigm in young adult rats, reward thresholds following acute amphetamine are similarly elevated in NVHL and sham controls, yet this elevation drops off more rapidly in NVHL rats, indicating increased tolerance for amphetamine [69]. In a drug self-administration paradigm, NVHL rats show higher motivation for methamphetamine self-administration under a progressive ratio schedule, but no differences in responding under a fixed ratio schedule of reinforcement [70].

Psychostimulants: cocaine

Cocaine-induced locomotor activity during sensitization, as well as locomotion following a cocaine challenge is enhanced in adult NVHL rats compared to sham controls [71, 72]. However, when examining gene expression in the caudate-putamen and mPFC using genome-wide microarrays, there is no overlap in the direction of gene expression change induced by NVHL and cocaine sensitization i.e. NVHL mostly downregulates gene expression in these regions, whereas cocaine sensitization mostly upregulates gene expression, compared to sham controls [71]. This analysis included genes associated with neuropsychiatric conditions (e.g. psychosis, bipolar disorder), *such as Estrogen receptor 2, Glial fibrillary acidic protein, CD 40 molecule TNF receptor Superfamily 5*, and several Zinc finger protein genes. There were a limited number of genes (17% of total genes) impacted on by NVHL-cocaine interactions, and there was no overlap in the direction of gene expression change for these interactions [71]. The rarity of convergence of NVHL and cocaine sensitization effects on individual genes suggests that the NVHL model and cocaine treatment may interact on the neural network level, rather than being reducible to one or a few molecular interactions [71].

Cocaine self-administration under fixed ratio responding is

intact in NVHL rats, yet lesioned rats demonstrate prolonged extinction and exaggerated cue-induced reinstatement of cocaine seeking, suggesting impaired prefrontal control over cue-induced drug-seeking or a general impairment in new action-outcome learning [73]. Supporting this, working memory deficits in the radial arm maze in adult NVHL rats predict subsequent cocaine behavioural sensitization, suggesting a link between cognition and addiction-relevant behaviours in this model [72]. However, incubation of cocaine craving is not altered in NVHL rats, suggesting specific addiction-relevant behavioural domains are altered following NVHL lesions [73]. Collectively, this suggests NVHL rats model several aspects of increased susceptibility to psychostimulant abuse observed in individuals with schizophrenia, and suggest changes in gene expression may interact at a neural network level to facilitate drug-seeking behaviour.

Nicotine

Nicotine abuse is very common in schizophrenia – up to 90% of patients smoke cigarettes compared to approximately 26% of the general population [5]. Animal models have the potential to unravel this high level of susceptibility to nicotine.

Neonatal ventral hippocampal lesions enhance the rewarding effects of nicotine. Adult NVHL rats demonstrate faster acquisition of nicotine self-administration and higher nicotine intake during self-administration ([74] but see also [72, 75]), modelling the higher levels of smoking observed in schizophrenia patients. Adult NVHL rats are also resistant to reducing nicotine use, exhibiting slower extinction of nicotine seeking and elevated drug-primed reinstatement compared to sham controls [72, 74, 75].

Increased susceptibility to nicotine may be age-dependent, occurring only in adult NVHL but not adolescent NVHL rats. Nicotine sensitization in adolescence is similar between NVHL and sham controls [74]. Furthermore, prior nicotine sensitization does not affect acquisition or extinction of nicotine self-administration, suggesting adolescent nicotine treatment does not facilitate later nicotine consumption [74]. While nicotine sensitization increases responding for a high nicotine dose (30 μg/infusion, dose-response study), this is unaffected by NVHL [74]. Together, this data suggests that schizophrenia pathology may precipitate vulnerability to nicotine addiction later in life, but early nicotine exposure does not modulate this relationship.

Interestingly, when both ethanol and nicotine are available in a self-administration paradigm, NVHL rats display greater consumption of both ethanol and nicotine compared to sham controls [75]. During extinction, when both ethanol and nicotine are unavailable, NVHL rats exhibit elevated responding for these two drugs, compared to sham controls [75]. Drug-primed reinstatement of nicotine-seeking is greater in NVHL rats compared to sham controls, but this is unaffected by ethanol availability [75]. These findings indicate vulnerability of NVHL rats to both substances when they are concurrently available.

Ethanol

Alcohol abuse is also observed at higher rates in schizophrenia (43-65% of patients experience alcohol dependence) than in the general population (approximately 5%) [5]. Adolescent alcohol use is associated with elevated use in adulthood in healthy controls [76]; however, susceptibility to the effects of adolescent alcohol use on brain reward dysfunction is unknown in schizophrenia. NVHL rats can be used to model this relationship. Indeed, NVHL rats are susceptible to adolescent ethanol exposure: NVHL rats given chronic voluntary ethanol access during adolescence demonstrate higher rates of ethanol consumption in two-bottle free choice in adulthood compared to sham controls given voluntary ethanol access in adolescence. NVHL rats with adolescent ethanol access also show escalation of ethanol self-administration, delayed extinction of ethanol-seeking and higher rates of drinking during reacquisition compared to sham controls with adolescent ethanol access [77]. These effects occur despite similar levels of adolescent ethanol intake between NVHL and sham rats, and importantly, addiction-like phenotypes (e.g. escalation of intake, resistance to extinction) are only present in NVHL rats which experience adolescent exposure to ethanol [77]. These findings indicate that NVHL lesions do not have an impact on the immediate effect of ethanol in adolescence but increase later susceptibility for addictive-like behaviour, supporting a two-hit model of addiction susceptibility i.e. early drug exposure and schizophrenia/addiction susceptibility increases risk for addiction in later life.

For a natural reinforcer (e.g. sucrose), in a self-administration paradigm, NVHL rats show intact extinction learning, and reacquisition of responding is similar to controls [77]. NVHL rats do however exhibit impaired acquisition and maintenance of autoshaping for a food reinforcer following latent inhibition, and impaired extinction of autoshaping behaviour [78], suggesting select cognitive deficits in this model. Interestingly, these cognitive deficits may contribute to the ethanol addiction-relevant phenotype of NVHL rats, as the degree of latent inhibition in NVHL rats predicts future ethanol drinking [78], suggesting a link between cognitive impairment and elevated ethanol consumption in this model.

Cannabinoids: CB_1 receptor agonists WIN 55,212-2 and Δ^9-tetrahydrocannabinnol

CB_1 cannabinoid receptor agonists are of particular relevance to schizophrenia because CB_1 receptors mediate the psychoactive and rewarding properties of cannabis [79], and there is strong evidence linking adolescent cannabis use with increased risk for schizophrenia, particularly in individuals with genetic predisposition for the disorder (reviews: [80, 81]). In addition, cannabis abuse is 3-4x higher in patients with schizophrenia than in healthy populations [5]. Assessing addiction-relevant behaviours for CB_1 receptor agonists in schizophrenia rodent models can provide insights into why cannabis use is so common in schizophrenia. It should be noted that in many rodent studies, CB_1 receptor agonists fail to produce rewarding and reinforcing effects [82–84], or only do so under specific experimental conditions, which may be due to concurrently occurring aversive properties of these drugs mediated by effects of cannabinoids on other receptors (e.g. in mice, κ-opioid receptors mediate aversive effects of THC); see discussion in [84].

NVHL rats exhibit an age-specific susceptibility to the CB_1 receptor agonist WIN 55,212-2 (WIN) [85]. While acute WIN treatment has no effect on locomotion in adolescence in NVHL rats, WIN increases locomotor activity in young adult NVHL rats, compared to sham controls [85]. In addition, young adult but not adolescent NVHL rats exhibit a greater aversion to WIN in a conditioned place preference paradigm compared to controls, yet the opposite effect occurs for CB_1 receptor agonist Δ^9-tetrahydrocannabinnol (THC), where sham controls demonstrate an aversion for THC, which is not present in NVHL rats [85]. These findings are mirrored in a brain stimulation reward paradigm, where THC produces a weak attenuation of reward in sham controls, but not NVHL rats, and WIN has the opposite effect, attenuating reward in NVHL rats but enhancing it in controls [69]. The different effects of THC and WIN may be due to different pharmacokinetics between the two drugs (e.g. WIN has a higher CB_1 receptor affinity than THC [86]), and/or cannabinoid receptor expression in reward regions [(e.g. striatum, VTA] in NVHL rats, but this has not been assessed. Nonetheless, together this suggests NVHL alters the sensitivity

of the endocannabinoid system to reward, in a manner specific to the reinforcer used (e.g. NVHL increases sensitivity to WIN, but decreases sensitivity to THC).

2.3 Non-lesion neurodevelopmental models

Non-lesion neurodevelopmental models of schizophrenia induce a pre- or post-natal insult via maternal cytokine elevation [e.g. administration of mitotoxin methylazoxymethanol acetate (MAM), lipopolysaccharide (LPS), polyinosinic-citidilic acid (Poly I:C) or quinpirole], prenatal stress or rearing environment manipulations during the post-natal period. Pups tested in adolescence and/or adulthood show altered addiction-relevant behaviour to several drugs of abuse. It should be noted that the timing of maternal infection and the infectious agent chosen can influence behavioural and neurological outcomes, and the current lack of consistency across research groups in the implementation of maternal infection may cause differences in the outcomes [87, 88].

Psychostimulants: amphetamine

Altered dopaminergic function is observed in the Poly I:C model, where prenatal Poly I:C treatment in mice enhances locomotor sensitization and stereotyped behaviour to repeated amphetamine administration, compared to control offspring [89]. Also, amphetamine CPP is greater in Poly I:C offspring compared to control offspring, suggesting heightened reward for amphetamine [89]. Similarly, prenatally MAM-treated rats show a greater stereotyped behavioural response to an amphetamine challenge dose than controls, suggesting greater expression of amphetamine sensitization following prenatal MAM treatment [90]. This suggests maternal infection can increase sensitivity to the rewarding and locomotor stimulating effects of psychostimulants, and may suggest heightened dopaminergic system function.

Psychostimulants: cocaine

Mice prenatally exposed to Poly I:C exhibit enhanced cocaine reward in CPP, indicating stronger cocaine context-reward associations [91]. Despite elevated cocaine context-reward associations, Poly I:C treated mice exhibit reduced cocaine-induced locomotor activity, which may indicate lower dopamine transporter or dopamine receptor availability in brain regions such as the VTA or striatum [91]. Prenatal Poly I:C treatment in rats also enhances cross-sensitization to cocaine after behavioural sensitization to amphetamine, suggesting elevated susceptibility to other stimulant drugs following repeated amphetamine administration [89]. Interestingly, Poly I:C mice do not exhibit place preference for a natural reward, sucrose, where control mice do, yet learning about an aversive stimulus (i.e. fear conditioning) is intact, suggesting impaired processing of appetitive reward in this model [91]. Collectively, this suggests increased susceptibility to stimulant reward in Poly I:C treated animals, but disrupted reward processing for natural rewards, which may reflect distinct neuronal changes (e.g. within the PFC-NAcc glutamate pathway and/or downstream in medium spiny neurons) that occur following exposure to drug *vs* natural rewards [92].

In rats which experience early life adversity [i.e. limited bedding and nesting (LBN) during PND 2-9], cocaine sensitization is unaffected. However, acute cocaine administration increases c-Fos expression in reward regions such as the NAcc core, central amygdala and lateral habenula of LBN rats, compared to controls [93]. c-Fos expression in orexin/hypocretin neurons following acute cocaine in LBN rats is decreased in the lateral, dorsomedial and perifornical regions of hypothalamus, suggesting reorganization of drug reward and stress circuitry following early life stress [93].

Despite elevated neuronal activity in reward regions following acute cocaine [93], cocaine self-administration behaviours are mostly unaltered in neurodevelopmental models of schizophrenia. While LBN rats initially acquire cocaine self-administration faster than controls, LBN rats self-administer similar amounts of cocaine as controls after 10 days of training, and exhibit similar sensitivity to different cocaine doses [93]. Cocaine extinction and reinstatement of cocaine-seeking are also unaltered in LBN rats [93]. Interestingly, the hedonic set point for cocaine is reduced, such that LBN rats prefer to self-administer lower doses of cocaine under low effort conditions but demonstrated similar levels of motivation to self-administer cocaine under higher effort conditions [93]. This suggests either a degree of cocaine anhedonia in LBN rats or that LBN rats reach cocaine satiety faster than controls, and suggests limited bedding and nesting does not increase cocaine addiction-like behaviours.

In the MAM neurodevelopmental model of maternal infection, there are no differences in cocaine self-administration under fixed and progressive schedules of reinforcement, nor in extinction or drug-induced reinstatement for cocaine [94]. Similarly, offspring of dams treated with LPS show unaltered cocaine self-administration, dose-response curves and extinction, despite working memory and sensorimotor gating impairment in this model [95]. Acute locomotor activity in response to various doses of cocaine is unaltered in MAM rats, compared to controls [94].

Together, this demonstrates sensitivity to cocaine addiction-relevant behaviours is highly dependent on the neurodevelopmental model used, for while Poly I:C treatment seems to increase cocaine reward and cross-sensitization, other neurodevelopmental models e.g. LBN, MAM, prenatal LPS, do not exhibit a cocaine addiction-like phenotype, or demonstrate a phenotype which suggests reduced susceptibility to cocaine (e.g. LBN show cocaine anhedonia).

Psychostimulants: methamphetamine

There are limited effects of prenatal MAM treatment on methamphetamine responses in offspring. Prenatal MAM treatment does not affect methamphetamine self-administration under an FR1 schedule of reinforcement, or cue-induced reinstatement after abstinence, in male or female rats [96]. Dose-response, schedules of reinforcement and extinction behaviour for methamphetamine have not yet been examined in MAM rats. However, MAM offspring are less susceptible to the suppressing effects of low dose ketamine on methamphetamine self-administration than control rats, and the authors suggest this may be due to impaired PFC glutamatergic signalling in MAM rats [97]. Further research into the effects of neurodevelopmental insults on addiction behaviour for methamphetamine are warranted.

Nicotine

Developmental stress appears to increase sensitivity to nicotine. Adult rats which experienced prenatal stress exhibit greater nicotine reward in CPP than offspring of non-stressed rats [98]. Also, rats reared in isolation during adolescence show behavioural sensitization to repeated nicotine administration during adolescence, where rats reared in an enriched environment do not [99]. LPS treatment during gestation facilitates intravenous nicotine self-administration at higher reinforcement schedules (i.e. FR5, not FR1/FR2), but has no subsequent effects on dose-response responding or motivation for nicotine under a progressive ratio [100]. Similarly, in the MAM rat model of schizophrenia, Weeks and colleagues found no differences between MAM rats and controls in nicotine self-administration [101]. This was observed across a range of doses

Table 3. Addiction-relevant behaviour in neonatal ventral hippocampal lesion rat models of schizophrenia

Author, date [Reference]	Model	Drug	Results - Behaviour (↓decrease, ↑increase, ~no effect)	Results - Brain (↓decrease, ↑increase, ~no effect)
Gallo et al 2014 [69]	NVHL rat	Amphetamine	↑tolerance for amphetamine in ICSS.	n/a
Brady et al 2008 [70]	NVHL rat	Methamphetamine	~ methamphetamine self-administration (dose range).	n/a
Chambers et al 2013 [71]; Rao et al 2016 [72]	NVHL rat	Cocaine	↑Cocaine sensitization and ↑expression of cocaine sensitization.	~ gene expression change in striatum and mPFC after cocaine sensitization in NVHL.
Karlsson et al 2013 [73]	NVHL rat	Cocaine	~Cocaine self-administration. ↓Extinction and ↑cue-induced reinstatement for cocaine. ~Incubation of cocaine craving	n/a
Rao et al 2016 [72]; Berg et al 2014 [74]; Sentir et al 2018 [75]	NVHL rat	Nicotine	~Nicotine sensitization. ~Nicotine sensitization on acquisition or extinction of nicotine self-administration. Nicotine sensitization in NVHL ↑'s nicotine self-administration, ↓extinction and ↑nicotine-primed reinstatement.	n/a
Sentir et al 2018 [75]	NVHL rat	Nicotine	↑Ethanol and nicotine self-administration (when available together). ↓Extinction of nicotine and ethanol. ↑Nicotine-primed reinstatement.	n/a
Jeanblanc et al 2015 [77]	NVHL rat	Ethanol	Following adolescent ethanol exposure, NVHL show ↑ethanol free consumption, ↑escalation of ethanol self-administration, ↓extinction and ↑reacquisition of ethanol.	n/a
Jeanblanc et al 2015 [77]; Khokhar et al 2018 [78]	NVHL rat	Sucrose	~Extinction and ~reacquisition for sucrose. ↓acquisition and maintenance of autoshaping following latent inhibition. ↓Impaired extinction of autoshaping behaviour for sucrose.	n/a
Gallo et al 2014 [69]; Gallo et al 2014 [85]	NVHL rat	WIN	In NVHL, ↑WIN-induced locomotion in young adulthood. ↓WIN CPP in young adult NVHL. WIN ↓ICSS reward in NVHL.	n/a
Gallo et al 2014 [69]; Gallo et al 2014 [85]	NVHL rat	THC	↓THC CPA in early adult NVHL. ~THC CPP in adolescent NVHL. ~THC ICSS in NVHL.	n/a

Abbreviations: CPA, conditioned place aversion; CPP, conditioned place preference; ICSS, intracranial self-stimulation; mPFC, medial prefrontal cortex; NVHL, neonatal ventral hippocampal lesion; WIN, WIN 55,212-2.

and schedules of reinforcement, in both standard 1-hr self-administration sessions and 23-hr extended access sessions, and this was not different between the sexes [101]. Interestingly, MAM animals responded less for sucrose or reinforcing visual stimuli alone or when paired with nicotine, suggesting potential deficits in reinforcement learning in this model [101]. Thus, it seems that developmental stress can increase susceptibility to nicotine addiction-like behaviour in adulthood, but this is not the case following maternal infection.

NAcc dopamine D_2 receptor mRNA expression levels are elevated in adult rats which are prenatally stressed [98], while chronic postnatal quinpirole treatment, which increases D_2 receptor sensitivity, enhances sensitization during adolescence to nicotine [99]. This suggests elevated D_2 receptor function may underlie effects of prenatal stress on nicotine reward. Importantly, elevations in D_2 mRNA expression induced by prenatal stress are reduced by sub-chronic (8 day) nicotine treatment during adulthood [98], suggesting this effect may be reversible and potentially supporting the self-medication hypothesis.

Chronic nicotine treatment also increases glial cell line-derived neurotrophic factor (GDNF) levels in the NAcc, and neonatal quinpirole reduces elevated GDNF levels induced by nicotine in isolation-reared rats [99]. Considering GDNF is critical for dopaminergic plasticity in reward-relevant brain regions [102], it is possible that elevated sensitivity to nicotine in neurodevelopmental rodent models of schizophrenia may be due to altered dopamine receptor function in reward regions (e.g. NAcc).

Ethanol

Recently, Ruda-Kucerova and colleagues found no differences in ethanol consumption using a voluntary consumption procedure or resumption of ethanol drinking after abstinence in male or female rats exposed to MAM prenatally [96]. However, other preclinical studies (pre-2013) have shown that early

Table 4. Addiction-relevant behaviour in neurodevelopmental rodent models of schizophrenia

Author, date [Reference]	Model	Drug	Results - Behaviour (↓decrease, ↑increase, ~no effect)	Results - Brain (↓decrease, ↑increase, ~no effect)
Borcoi et al 2015 [89]	Poly I:C mice	Amphetamine	↑Amphetamine sensitization and ↑Amphetamine CPP.	n/a
Chen et al 2014 [90]	Prenatal MAM treated rats	Amphetamine	↑Amphetamine sensitization challenge.	~regulation of afferent VTA DA neurons (from HPC and pedunculopontine tegmental area).
Labouesse et al 2015 [91]	Prenatal Poly I:C treated mice	Cocaine	↑Cocaine CPP, ↓Cocaine locomotor activity.	n/a
Borcoi et al 2015 [89]	Prenatal Poly I:C treated mice	Amphetamine then cocaine	↑cocaine cross-sensitization after amphetamine sensitization.	n/a
Labouesse et al 2015 [91]	Prenatal Poly I:C treated mice	Sucrose	No CPP for sucrose. ~Fear conditioning.	n/a
Bolton et al 2018 [93]	Limited bedding and nesting rats	Cocaine	~Cocaine sensitization. ↑acquisition of cocaine self-administration. ~cocaine self-administration (dose range). ~Cocaine extinction and reinstatement ↓cocaine hedonic set point.	Cocaine ↑'s c-Fos in NAcc core, central amygdala and lateral habenula after acute cocaine. Cocaine ↓'s c-Fos in orexin/hypocretin neurons in the lateral, dorsomedial and perifornical hypothalamus.
Featherstone et al 2009 [94]	Prenatal MAM treated rats	Cocaine	~Cocaine self-administration, ~cocaine motivation, ~cocaine sensitization.	n/a
Santos-Toscano et al 2016 [95]	Prenatal LPS treated rats	Cocaine	~cocaine self-administration acquisition and dose response, ~extinction of cocaine self-administration.	n/a
Ruda-Kucerova et al 2017; [96] Ruda-Kucerova et al 2017 [97]	Prenatal MAM treated rats	Methamphetamine	~Methamphetamine self-administration, ~cue-induced reinstatement for methamphetamine. ↓Ketamine suppression of methamphetamine self-administration.	n/a
Said et al 2015 [98]	Prenatally stressed rats	Nicotine	↑Nicotine CPP	↑NAcc DA D_2 receptor mRNA expression. Nicotine ↓Nacc D_2 mRNA in prenatally stressed rats.
Brown et al 2018 [99]	Isolation rearing vs environmental enrichment in rats	Nicotine	↑Nicotine sensitization. Chronic postnatal quinpirole ↑nicotine sensitization.	Neonatal quinpirole reduces elevated Nacc glial cell line-derived neurotrophic factor levels induced by nicotine in isolation-reared rats, but not in rats reared in an enriched environment.
Waterhouse et al 2018 [100]	Prenatal LPS treated rats	Nicotine	↑Nicotine self-administration acquisition. ~Nicotine dose-response or nicotine motivation.	n/a
Weeks et al 2019 [101]	Prenatal MAM treated rats	Nicotine	~Nicotine self-administration (dose range, reinforcement schedules).↓sucrose responding, ↓responding for reinforcing visual stimuli alone or paired with nicotine.	n/a
Ruda-Kucerova et al 2017 [96]	Prenatal MAM treated rats	Ethanol	~Ethanol consumption, ~ethanol resumption after abstinence.	n/a

Abbreviations: CPP, conditioned place preference; DA, dopamine; HPC, hippocampus; LPS, lipopolysaccharide; MAM, mitotoxin methylazoxymethanol acetate; NAcc, nucleus accumbens; Poly I:C, polyinosinic-citidilic acid; VTA, ventral tegmental area.

life stress (e.g. social isolation stress, chronic variable stress) can increase adult ethanol intake (e.g. [103–107], see also reviews: [108, 109]). Elevated ethanol intake in other neurodevelopmental models may be linked to molecular changes such as decreased firing of dopaminergic VTA neurons in an LPS model [103], and may be related to altered anxiety-like states, as ethanol consumption in two-bottle free choice can be reduced by administration of anxiolytic adrenergic drugs [105]. Together, this suggests a critical role of the schizophrenia-relevant model on ethanol intake and ethanol-seeking behaviour.

2.4 Pharmacological models

Nicotine

Only one study has examined how pharmacological models of schizophrenia respond to nicotine addiction-relevant behaviours. In models of reduced dopamine sensitivity (i.e. chronic adult amphetamine treatment) or glutamatergic dysfunction (i.e. chronic adult PCP treatment), acquisition and maintenance of intravenous nicotine self-administration is unaffected [110]. It should be noted that prior research demonstrates reduced brain stimulation reward and sucrose consumption in chronic PCP models, suggesting altered addiction-like phenotypes in this model [111, 112]. Considering this, further investigation into how pharmacological schizophrenia models respond in addiction behavioural paradigms is warranted.

2.5 Interim Summary

From the literature reviewed, it is clear that susceptibility to addiction-like behaviour depends on the model assessed and also the drug tested. The NVHL rat in particular exhibits elevated addiction-like behaviours to many abused drugs, including psychostimulants, nicotine, ethanol and cannabinoids. Some genetic models (e.g. *Disc1* knockdown and *EGF* transgenic) also exhibit addiction-relevant behaviour for psychostimulants; however, other drugs of abuse have not been assessed in these models, and this is an area of critical further study. Similarly, pharmacological models of schizophrenia remain practically unexplored in their addiction-like behaviour. In non-lesion neurodevelopmental models, addiction-like phenotypes appear dependent on the drug tested, with several models showing elevated addiction-like behaviour for nicotine, but not methamphetamine or ethanol, and only one model exhibiting addiction-like behaviour for cocaine. Cannabinoids have not been assessed in non-lesion neurodevelopmental models. Addiction-like behaviours for opioids have not yet been assessed in any rodent model of schizophrenia, and this is an interesting area of future research, as recent research suggests patients with schizophrenia abuse opioids less than the general population [113]. The reasons for why some models show addiction-like phenotypes and some do not is currently unclear; however, there appear links to altered dopaminergic signalling in models which do show addiction-like phenotypes e.g. *EGF* overexpressing mice, prenatally stressed rats. The mechanisms driving the presence of addiction-like phenotypes in different models is an area of critical further research.

The type of research reviewed above is critical for understanding which genetic and environmental schizophrenia risk factors influence addiction susceptibility. This is particularly important for genetic risk factors e.g. *DISC1*, *EGF*, as this could facilitate future genetic counselling for patients carrying these mutations about their elevated risk for addiction, providing a personalised medicine approach. Furthermore, these studies have started to shed light on molecular changes linked to elevated addiction propensity in schizophrenia models e.g. changes in dopamine metabolism and D_2 receptor function, increasing our understanding of potential mechanisms of comorbidity between these disorders. So far, the examination of mechanisms underlying addiction propensity in schizophrenia models has been limited, and has focused mostly on dopaminergic function; future research can examine other changes to other addiction-relevant neurotransmitter systems (e.g. glutamatergic, serotonergic) as well as plastic and epigenetic changes in mesocorticolimbic regions.

3. Susceptibility of schizophrenia rodent models to effects of drugs on schizophrenia-relevant behaviour and brain function

All preclinical studies reviewed in section 3 are summarised in Tables 5 - 9.

3.1 Genetic models

Psychostimulants – amphetamine, methamphetamine, dopamine agonists

Brain derived neurotropic factor (BDNF) is critical for hippocampal synaptic plasticity and the regulation of learning and memory [114, 115]. BDNF protein is reduced in first episode, drug naïve patients with schizophrenia [116, 117] and is increased after antipsychotic treatment [118]. BDNF mRNA expression is reduced in post-mortem PFC tissue from patients with schizophrenia [119], and BDNF is implicated in neural responses to psychostimulants [120]. Heterozygous *BDNF* mice (i.e. *BDNF* HET mice) exhibit prepulse inhibition deficits at baseline [121], similar to that observed in patients with schizophrenia [122].

Adult male *BDNF* HET mice are more sensitive to the disruptive effects of acute amphetamine on PPI compared to WT mice, but this sensitivity is not observed in female *BDNF* HET mice [121]. However, adult male or female *BDNF* HET mice do not exhibit differential sensitivity to the disruptive effects of acute apomorphine, a dopamine D_1 and D_2 partial agonist on PPI, suggesting drug-specific effects on PPI disruption, which may be linked to the pharmacodynamics of each dopaminergic drug (e.g. amphetamine reverses monoamine transporters, while apomorphine is a dopamine D_1 and D_2 partial agonist) [121].

In *BDNF* HET mice (sexes collapsed), chronic adolescent methamphetamine administration reduces cross-sensitization of locomotion to acute amphetamine, suggesting an attenuation of behaviours relevant to psychosis in methamphetamine-treated *BDNF* HET mice [123]. However, chronic adolescent methamphetamine administration does not alter other schizophrenia-relevant behaviours, such as social preference, social novelty, baseline prepulse inhibition or short-term memory in the Y-maze in *BDNF* HET males or females, compared to WT littermate controls [121, 124]. Methamphetamine-induced locomotion during the adolescent administration period is also similar between *BDNF* HET and WT mice, in both sexes [121]. This suggests that chronic adolescent methamphetamine in *BDNF* HET mice affects cross-sensitization to amphetamine, but has no effect on some schizophrenia-relevant social and cognitive behaviours.

In a mouse model of *DISC1* with the L100P amino acid substitution in exon 2 in *Disc1*, acute methamphetamine-induced locomotion is not different to WT controls [125]. The effect of methamphetamine on other schizophrenia-relevant behaviours in this model has not been assessed. Considering other *Disc1* models (e.g. *Disc1* knockdown, *Disc1 dominant neg-*

ative mutation, discussed below) exhibit greater susceptibility to addiction-like behaviour for cocaine and the cognitive impairing effects of THC, further work on this mouse model is warranted.

Together, these data suggest a limited effect of psychostimulants on schizophrenia-relevant behaviour in genetic models; however, PPI is disrupted by amphetamine and cross-sensitization to methamphetamine is reduced in *BDNF* HET mice.

Nicotine

A schizophrenia genetic susceptibility model, the *Snap-25* KO mouse, has a heterozygous deletion of the presynaptic protein SNAP-25, which is a critical component of the SNARE protein-protein complex responsible for action-potential triggered release of neurotransmitters [126]. *Snap-25* KO mice do not exhibit schizophrenia-relevant behaviours in adolescence at baseline e.g. locomotor hyperactivity, social withdrawal; however, there is a gene * *in utero* interaction, whereby locomotor hyperactivity and social withdrawal in adolescence are evident following prenatal nicotine exposure in *Snap-25* KO mice, but not WT controls [126]. Prenatal nicotine treatment in *Snap-25* KO mice also impairs striatal D_2 receptor dependent long-term depression (LTD) and reduces striatal D_2 receptor affinity, but leaves striatal CB_1 receptor regulated plasticity intact, compared to *Snap-25* KO mice without prenatal nicotine exposure [126]. This suggests that intact expression and function of *Snap-25* may be protective against the effects of prenatal nicotine on schizophrenia-like behaviour, as well as striatal D_2 receptor expression and function.

SNPs in the human *CHRNA5* gene, which encodes the $\alpha 5$ nicotinic acetylcholine (nACh) receptor subunit, increases risk for both smoking and schizophrenia [127]. Mice which express a human $\alpha 5$ SNP (i.e. $\alpha 5$-SNP-expressing mice) show impaired social behaviour and sensorimotor gating, as well as lower activity of vasoactive intestinal polypeptide (VIP) interneurons, which results in increased somatostatin interneuron inhibitory drive over layer II/III pyramidal neurons [128]. Importantly, the decreased activity observed in $\alpha 5$-SNP-expressing mice resembles the hypofrontality observed in patients with schizophrenia and addiction [128]. Chronic nicotine administration reverses this hypofrontality, supporting the self-medication hypothesis when alterations to nACh subunit $\alpha 5$ are present [128].

G72 is a gene from schizophrenia-associated genetic region SCZD7 on chromosome 13q32-q33, and elevated *G72* transcript levels are observed in forebrain structures in post-mortem tissue of patients with schizophrenia [129]. In transgenic mice overexpressing *G72*, chronic adult nicotine administration reverses impairments in social memory, working memory and PPI, compared to vehicle *G72* transgenic mice [130]. Chronic nicotine also reverses the upregulation of oxytocin receptor binding in the central amygdala observed in vehicle treated *G72* transgenic mice, which may relate to improvements in social memory in nicotine-treated *G72* transgenic mice [131]. The *G72* mutation is also protective against operant associative memory deficits caused by chronic nicotine, but long-term spatial learning in the Morris Water Maze is worsened by chronic nicotine treatment in *G72* mice [130], suggesting domain-specific effects of chronic nicotine in this model.

Reelin is a large extracellular matrix protein critically involved in brain development and neural plasticity. Reelin deficits have been observed in schizophrenia [132], and heterozygous *reeler* mice exhibit hyperlocomotion, PPI and cognitive deficits, and perseverative behaviour [133–135], as well as a loss of Purkinje cells of the cerebellum, which is also observed in patients with schizophrenia [136, 137]. In adolescent heterozygous *reeler* mice, subchronic (6 day) nicotine free choice drinking ameliorates hyperlocomotion, perseverative behaviour and cognitive impairment [138, 139]. Furthermore, in heterozygous *reeler* mice, subchronic nicotine restores mRNA levels of reelin and GAD67 in the cortex, hippocampus, striatum and cerebellum to WT-like levels [138, 139]. Together, this suggests protective effects of subchronic nicotine in the heterozygous *reeler* mouse.

Neuregulin 1 is a well-established risk gene for schizophrenia, involved in processes such as axon guidance, synapse formation and synaptic plasticity, as well as excitatory glutamatergic and inhibitory GABAergic transmission [140, 141]. Alternative splicing leads to >30 NRG1 isoforms, and several mouse models have been developed to study altered Nrg1 function with reference to schizophrenia. *Type III Neuregulin 1* heterozygous knockout (*Type III Nrg1* HET) mice exhibit social interaction impairment and PPI deficits at baseline. *Type III Nrg1* HET mice are also less sensitive to the effects of acute nicotine on theta-burst stimulation elicited long-term potentiation (LTP) in cortical-basolateral amygdala (BLA) synapses, such that in WT mice, nicotine reduces the threshold for the activation of LTP in cortical-BLA synapses, but this effect is absent in *Type III Nrg1* mutant mice [142]. This effect in *Type III Nrg1* HET animals is dependent on $\alpha 7$ nicotinic receptors [142]. Interestingly, chronic (6 weeks) nicotine consumption in drinking water improves PPI in *Type III Nrg1* transgenic mice [143]. Considering that the ameliorative effects of nicotine on PPI deficits involve $\alpha 7$ nicotinic receptors [144], and type III NRG1 backsignalling regulates $\alpha 7$ nicotinic receptor surface expression [145], it is possible that chronic nicotine treatment in *Type III Nrg1* mutant mice may restore $\alpha 7$ nicotinic receptor surface expression in the cortex and BLA to WT levels.

Together, these studies indicate that sensitivity to the effects of nicotine on schizophrenia-relevant behaviour and brain function depends on the model used, with most models showing protective or ameliorative effects of nicotine (e.g. *G72* transgenic, heterozygous *reeler*, *Type III Nrg1* transgenic mice), but some models showing development of schizophrenia-relevant behaviours only following nicotine administration (e.g. *Snap-25* KO mice). Considering several models show ameliorative effects of nicotine, this provides support for the self-medication hypothesis, whereby nicotine improves schizophrenia-relevant behaviour and brain function, which may help explain high usage rates in patients. Nicotine administration is accompanied by a range of neural changes, including reduced striatal LTD, increased oxytocin receptor binding in the central amygdala, increased reelin and GAD67 mRNA expression in the hippocampus, striatum, cortex and cerebellum, and a reduced threshold for LTP activation in cortical-BLA synapses, The timing of nicotine administration (e.g. neonatal *vs* adolescence *vs* adulthood) may impact on potential ameliorative effects of nicotine, but this has not yet been investigated.

NMDA antagonists

A novel *Type III Nrg1* overexpression mouse (i.e. *Nrg1 III tg*), which models the elevated Type III NRG1 mRNA detected in postmortem dorsolateral PFC tissue of patients with schizophrenia [146], exhibits sex-specific cognitive, social and prepulse inhibition impairment, but no changes to locomotor activity in either sex [147]. However, acute hyperlocomotor activity in response to the NMDA antagonist MK-801 is blunted in adult female *Nrg1 III tg* mice [147]. Interestingly, this effect is not observed in adult male *Nrg1 III tg* mice, where hyperlocomotion following MK-801 is similar to WT mice [148]. This may suggest a reduced number of available NMDA receptors in *Nrg1 III tg* female mice, in alignment with the NMDA receptor hypofunction theory of schizophrenia [56]. However, in *BDNF* HET mice, acute MK-801 does not differentially affect prepulse inhibition in male or female *BDNF* HETs compared to

Table 5. Susceptibility of schizophrenia genetic rodent models to effects of psychostimulant drugs (including nicotine) on schizophrenia-relevant behaviour and brain function

Author, date [Reference]	Model	Drug	Age at Drug Treatment / Age at Behavioural Testing	Results - Behaviour (↓decrease, ↑increase, ~no effect)	Results - Brain (↓decrease, ↑increase, ~no effect)
Manning et al 2013 [121]	*BDNF* HET mice	Acute amphetamine	Adult / Adult	↑sensitivity to amphetamine-induced PPI disruption in male but not female *BDNF* HET mice.	n/a
Manning et al 2013 [121]	*BDNF* HET mice	Acute apomorphine	Adult / Adult	~sensitivity to apomorphine-induced PPI disruption in male or female *BDNF* HET mice.	n/a
Manning et al 2013 [123]	*BDNF* HET mice	Chronic methamphetamine	Adolescence / Adult	↓Cross-sensitization to amphetamine after methamphetamine in adolescence.	n/a
Arime et al 2014 [125]	*DISC1* L100P mouse model	Acute methamphetamine	Adult / Adult	~Methamphetamine-induced locomotion	n/a
Baca et al 2013 [126]	Snap-25 HET mice	Chronic nicotine given to dams during gestation and after birth	Prenatal / Adult	↑Locomotor hyperactivity and social withdrawal after prenatal nicotine exposure *Snap-25* KO mice.	↓DA D_2 receptor-dependent LTD in nicotine-exposed *Snap-25* HET mice. Prenatal nicotine exposure altered affinity and/or receptor coupling of DA D_2 receptors in Snap-25 HET mice.
Koukouli et al 2017 [128]	α5-SNP-expressing mice	Chronic nicotine	Adult / Adult	n/a	↓Activity of VIP interneurons, reversed by chronic nicotine administration.
Hambsch et al 2041 [130]	*G72* overexpressing mice	Chronic nicotine	Adult / Adult	Chronic nicotine ↑social recognition memory, ↑PPI and ↑Y-maze working memory in *G72* transgenic mice. Chronic nicotine ↓ MWM spatial memory in *G72* mice. *G72* mutation protects against nicotine-induced associative memory deficits.	n/a
Zanos et al 2018 [131]	*G72* overexpressing mice	Chronic nicotine	Adult / Adult	n/a	↓oxytocin receptor binding in CeA after chronic nicotine in *G72* mice.
Romano et al 2013 [138]	*Reeler* HET mice	Subchronic nicotine	Adolescence / Adolescence	Nicotine ↓homecage locomotion in *Reeler* HET mice.	Nicotine ↑Reelin and GAD67 gene expression in FC, HPC, CB not striatum.
Romano et al 2014 [139]	*Reeler* HET mice	Subchronic nicotine	Adolescence / Early adulthood	Nicotine ↓hyperlocomotion, ↑holeboard exploration, ↑T-maze acquisition in *Reeler* HET mice. ~Nicotine on anxiety in either genotype.	Nicotine ↑Reelin and GAD67 cDNA levels in FC and HPC in *Reeler* HET mice.
Jiang et al 2013 [142]	*Type III Nrg1* HET mice	Acute nicotine applied to brain slices	Pre-weaning / Pre-weaning	n/a	*Type III Nrg1* HET mice less sensitive to nicotine effects on theta-burst stimulation elicited LTP in cortical-BLA synapses, such that in WT mice; this effect is dependent on α7 nicotinic receptors.
Chen et al 2008 [143]	*Type III Nrg1* HET mice	Chronic nicotine	Adult / Adult	Nicotine ↑PPI in *Type III Nrg1* HET mice.	n/a

Abbreviations: BDNF, brain derived neurotrophic factor; BLA, basolateral amygdala; CB, cerebellum; DA, dopamine; FC, frontal cortex; HET, heterozygous; HPC, hippocampus; KO, knockout; LTD, long-term depression; PPI, prepulse inhibition; VIP, vasoactive intestinal polypeptide.

WT mice [121], indicating model-specific effects of MK-801 on schizophrenia-relevant behaviour.

Cannabinoids: Cannabidiol

Spontaneously hypertensive rats (SHR) are a model of schizophrenia, exhibiting behaviours including hyperlocomotion, sensorimotor gating deficits, associative memory impairment and reduced social behaviour [149]. Cannabidiol (CBD) is a non-intoxicating cannabis plant compound which is a weak CB_1 receptor negative allosteric modulator [150], and is being investigated as a potential anti-psychotic [151]. In SHR, acute CBD treatment does not reverse hyperlocomotion and social withdrawal [152]. However, chronic low dose (i.e. 0.5 – 5 mg/kg) CBD treatment during adolescence dose-dependently reverses locomotor hyperactivity, sensorimotor gating deficits and fear-associated cognitive impairment in SHR [153]. Chronic adolescent CBD treatment also increases the ratio of 5-HIAA/serotonin tissue levels in the PFC in adulthood in both SHR and controls, but CBD has no effect on serotonin levels in the dorsal striatum or BDNF levels in the PFC or dorsal striatum [153], suggesting that CBD ameliorates schizophrenia-relevant behaviours in SHR by a different mechanism (e.g. increasing anandamide levels [154]).

Similarly, in a different Neuregulin 1 mouse model of schizophrenia (i.e. the *Neuregulin 1 transmembrane domain* heterozygous mouse, *Nrg1 TM* HET), which exhibits hyperlocomotion, impaired social behaviour and PPI deficits at baseline [155, 156], acute treatment with higher doses of CBD (i.e. 50 – 100 mg/kg) reverses PPI deficits, compared to vehicle treated *Nrg1* mutants [157]. Also, chronic treatment in this dose range increases social behaviour and increases GABA-A receptor binding in the granular retrosplenial cortex in adult *Nrg1 TM* HET mice [157]. However, chronic CBD does not reverse locomotor hyperactivity, sensorimotor gating deficits or reduced 5-HT_{2A} receptor binding density in the substantia nigra of these mice [157]. While this indicates CBD can have ameliorative effects on schizophrenia-relevant behaviours, it also shows that the effects of CBD can depend on the model used, the age targeted (e.g. adolescence vs adulthood) and the dose used.

Cannabinoids: Δ^9-Tetrahydrocannabinol

Several models of genetic risk for schizophrenia are more sensitive to behavioural and neural effects of THC. The dominant negative *Disc1* (*DN-Disc1*) mutant mouse is more susceptible to the effects of adolescent THC treatment than WT controls [158]. Chronic THC in adolescence increases anxiolytic behaviour and impairs short-term memory in *DN-Disc1* mutant mice, where these effects are not apparent in WT controls [158]. The cognitive impairment induced by THC in *DN-Disc1* mice may be linked to hippocampal CB_1 receptor and BDNF levels, as chronic THC selectively increases hippocampal CB_1 receptor and BDNF protein levels in WT mice but not in *DN-Disc1* mice [158]. Interestingly, overexpression of hippocampal BDNF in *DN-Disc1* mice prevents THC-induced cognitive impairment in these mice, suggesting that BDNF upregulation may be a homeostatic response designed to maintain proper cognitive function following exogenous insult [158].

In the *Nrg1 TM* HET model of genetic risk for schizophrenia, *Nrg1 TM* HET males are more sensitive to the locomotor suppressing and PPI enhancing effects of acute THC than are THC-treated WT controls [159]. Female *Nrg1 TM* HET mice do not exhibit this elevated sensitivity to THC in terms of locomotion and PPI, and are even less susceptible than WTs to the supressing effects of THC on some social behaviours [160]. The Nrg1 gene mutation assessed also impacts on susceptibility to THC, as male mice from a different Nrg1 mutant model, i.e. *Nrg1 III tg* mice do not exhibit altered THC-induced locomotion, social behaviour or prepulse inhibition, compared to THC-treated WT controls [161].

In adolescence, the *Nrg1 TM* HET mutation protects against inhibiting effects of chronic THC on investigative social behaviours in male mice [162]. However, adolescent *Nrg1 TM* HET mice continue to demonstrate locomotor suppression after 2 days washout from THC where WTs do not, suggesting increased susceptibility to locomotor, but not social effects of THC in adolescent *Nrg1 TM* mutants [162].

There are complex effects of chronic adolescent THC treatment on receptor expression across the brain in *Nrg1 TM* HET mice. Chronic adolescent THC increases CB_1 receptor binding in the substantia nigra in *Nrg1* but not WT mice [162]. Considering the role of CB_1 receptors in controlling dopamine release in the basal ganglia direct pathway, this elevation in CB_1 receptor binding may reflect continued suppression of locomotion following chronic THC in adolescent *Nrg1* mutant mice [162]. In addition, the elevation in NMDA receptor binding in the hippocampus, auditory cortex and cingulate cortex in THC-treated adolescent *Nrg1 TM* HET but not WT mice may also contribute to the continued locomotor suppression in *Nrg1* mutants, as NMDA receptor antagonism induces hyperlocomotion, and increased NMDA receptor binding may reflect reduced locomotion ([162] see also [163]). Finally, adolescent THC treatment increases 5-HT_{2A} receptor binding in the agranular insular cortex in *Nrg1* mutants, whereas in WTs, THC treatment reduces 5-HT_{2A} binding in the agranular insular cortex, ventral pallidum and cingulate cortex, and increases 5-HT_{2A} binding in the caudate-putamen [162]. In patients with schizophrenia, reduced 5-HT_{2A}R density is observed post-mortem in prefrontal and other cortical regions [164, 165], and may relate to social withdrawal and social anxiety observed in patients. The elevation of 5-HT_{2A} receptor binding in *Nrg1* mutants may reflect the protective effect of the *Nrg1* genotype on the social behaviour-suppressing effects of THC [162].

Using a proteomics approach, Spencer and colleagues [163] demonstrated that adolescent *Nrg1 TM* mutants chronically treated with THC show an altered profile of proteins which affect synapse formation and dendritic spine dynamics [163]. Chronic adolescent THC in *Nrg1* mutants induces changes in several proteins involved in intracellular trafficking and stabilization of NMDA receptors at the synapse (e.g. FLOT1, APOA1, GPSM2) [163]. Interestingly, THC treatment caused proteomic changes in WT mice suggestive of greater oxidative stress and neurodegeneration than in *Nrg1* mutant mice, again suggesting a degree of protection against some effects of THC in *Nrg1 TM* HET mice [163]. These findings may help to explain the altered behavioural responses of *Nrg1 TM* HET mice to cannabinoid treatment.

Clinical data indicates a complex relationship between cannabis use and schizophrenia susceptibility between the sexes [166–169]. It is possible risk genes modulate this relationship, e.g. BDNF Val66Met genotype when coupled with cannabis abuse modulates risk for psychosis onset in females, but not males [167]. The preclinical data presented above suggests complex interactions between cannabinoid treatment, schizophrenia genetic susceptibility and sex, where cannabinoids can both protect against and worsen schizophrenia-like behaviour. Further investigation into sex differences in these cannabis-gene interactions is warranted.

3.2 Lesion models

Psychostimulants: amphetamine

In NVHL rats, acute amphetamine-induced locomotion is enhanced compared to sham controls [72, 77, 85]. The effects of NVHL on amphetamine-induced locomotion may be age-dependent, as rats in early adolescence (i.e. PND 35) do not

Table 6. Susceptibility of schizophrenia genetic rodent models to effects of drugs (NMDA antagonists and cannabinoids) on schizophrenia-relevant behaviour and brain function

Author, date [Reference]	Model	Drug	Age at Drug Treatment / Age at Behavioural Testing	Results - Behaviour (↓decrease, ↑increase, ~no effect)	Results - Brain (↓decrease, ↑increase, ~no effect)
Olaya et al 2018 [147]; Olaya et al 2017 [148]	*Type III Nrg1* overexpressing mice	Acute MK-801	Adult / Adult	↓MK-801-induced locomotion in female *Nrg1 III tg* mice (vs WT). ~MK-801-induced locomotion in male *Nrg1 III tg* mice (vs WT).	n/a
Manning et al 2013 [121]	*BDNF* HET mice	Chronic methamphetamine, acute MK-801	Adult / Adult	~MK-801-induced PPI disruption in *BDNF* HET mice (vs WT).~Chronic methamphetamine on MK-801-induced PPI disruption in *BDNF* HET (vs WT).	n/a
Almeida et al 2013 [152]	SHR	Acute CBD	Adult / Adult	~CBD on hyperlocomotion and social withdrawal in SHR.	n/a
Peres et al 2018 [153]	SHR	Chronic CBD	Adolescence / Adult	CBD ↓hyperlocomotion ↑PPI and ↑cognitive impairment in SHR.	~CBD on ratio of PFC 5-HIAA/serotonin levels between SHR and controls. ~CBD on serotonin levels in dorsal striatum or *BDNF* levels in PFC or dorsal striatum.
Long et al 2012 [157]	*Nrg1 TM* HET mice	Acute and chronic CBD	Adult / Adult	Acute CBD ↑PPI in *Nrg1 TM* HET mice. Chronic CBD ↑social behaviour in *Nrg1 TM* HET mice. ~Chronic CBD on hyperlocomotion or PPI deficits in *Nrg1 TM* HET mice.	CBD ↑GABA-A receptor binding in the granular retrosplenial cortex in *Nrg1 TM* HET mice. ~CBD on CB_1 receptor, NMDA or 5-HT1A receptor binding across several forebrain regions in WT or *Nrg1 TM* HET mice.
Segal-Gavish et al 2017 [158]	Dominant negative *Disc1* mice	Chronic THC	Adolescence / Early adulthood	THC ↑anxiolytic behaviour and ↓short-term memory in *Disc1* mutant mice,. ~THC on locomotion in *Disc1* mutant mice. HPC *BDNF* overexpression in *Disc1* mutant mice ↑cognition.	THC ↑HPC CB_1 receptor and *BDNF* protein levels in WT but not *Disc1* mice.
Boucher et al 2007 [159]	*Nrg1 TM* HET mice	Acute THC	Adult / Adult	THC ↓locomotion, ↑anxiety and ↑PPI in *Nrg1 TM* HET mice.	n/a
Long et al 2010 [160]	*Nrg1 TM* HET mice	Acute THC	Adult / Adult	~THC-induced locomotion, PPI, anxiety, cognition between *Nrg1 TM* HET vs WT. THC ↓social behaviours in WT but not *Nrg1 TM* HET mice	n/a
Lloyd et al 2018 [161]	*Nrg1 TM* HET mice	Acute THC	Adult / Adult	~THC-induced locomotion, social behaviour or PPI between Nrg1 type III overexpressing mice vs THC-treated WT controls.	n/a
Long et al 2013 [162]	*Nrg1 TM* HET mice	Acute and chronic THC	Adolescence / Early adulthood	*Nrg1 TM* HET mutation protects against THC-induced ↓in social behaviour. ↓Locomotion in *Nrg1 TM* HET mice after THC washout. ~THC-induced anxiety or PPI between *Nrg1 TM* HET vs WT.	THC ↑CB1 receptor binding in SN of *Nrg1 TM* HET mice, THC ↑NMDA receptor binding in the HPC, auditory cortex and cingulate cortex in *Nrg1 TM* HET mice. THC ↑5-HT2A receptor binding in the agranular insular cortex in *Nrg1* mutants. THC ↓5-HT2A binding in the agranular insular cortex, VP and cingulate cortex, and ↑5-HT2A binding in the striatum.
Spencer et al 2013 [163]	*Nrg1 TM* HET mice	Acute and chronic THC	Adolescence / Early adulthood	n/a	THC alters profile of proteins which affect synapse formation and dendritic spine dynamics in *Nrg1 TM* mutants.

Abbreviations: 5-HT, serotonin; CB_1, cannabinoid receptor 1; CBD, cannabidiol; Disc1, disrupted in schizophrenia 1; GABA; Gamma Aminobutyric Acid; NMDA; N-methyl-d-aspartate; Nrg1, Neuregulin 1; PFC; prefrontal cortex; PPI, prepulse inhibition; SHR, spontaneously hypertensive rats; SN, substantia nigra; THC, Δ^9-tetrahydrocannabinol; tg, transgenic; WT, wild-type like.

exhibit altered acute amphetamine-induced locomotion compared to controls, where NVHL rats in late adolescence/young adulthood (PND 56) do [85]. This indicate an age * drug interaction in NVHL rats, potentially reflecting late adolescent developmental changes in the mesolimbic pathway, relevant to the development of schizophrenia at this age.

Nicotine

NVHL rats exhibit deficits in learning and memory in the radial arm maze [72, 74, 170]. Unlike some genetic models (e.g. *G72* transgenic mice, *reeler* mice, *Type III Nrg1* HET mice, detailed above), chronic nicotine treatment in adolescence or adulthood does not reverse cognitive impairment in the radial arm maze in NVHL rats [72, 74, 170]. Chronic adolescent or adult nicotine treatment also does not differentially affect nACh receptor binding in mPFC or ventral striatum in NVHL rats compared to sham controls [170]. These studies suggest limited effects of nicotine on learning and memory, as well as nACh receptor binding in NVHL rats. The effects of nicotine on other schizophrenia-relevant domains e.g. hyperlocomotion, social behaviour, sensorimotor gating are yet to be examined.

3.3 Non-lesion neurodevelopmental models

Psychostimulants: amphetamine

Offspring of maternal LPS-treated rats are more sensitive to amphetamine in early adulthood, displaying a reduced breakpoint for a food reinforcer under amphetamine treatment, and greater amphetamine-induced locomotion than controls [171]. However, these effects depend on the gestational day (G12 vs G16) at which LPS is administered, suggesting age-specific effects of LPS on brain development and subsequent drug reward susceptibility [171]. Embryonic midbrain dopaminergic neurons are reduced 48 hr after LPS treatment at E16 but this recovers by adolescence, while midbrain dopaminergic neurons are unaffected by LPS treatment at E12 [171]. This suggests altered dopaminergic function following maternal LPS treatment, which is protocol dependent and shows a degree of recovery with time. Considering the recovery of dopaminergic midbrain neurons following LPS treatment, it is possible sensitivity to amphetamine in LPS rats is mediated by dopaminergic neurons in a different brain region e.g. forebrain regions such as the dorsal and ventral striatum.

Nicotine

Cognitive deficits in rats prenatally treated with LPS are ameliorated by chronic nicotine self-administration, compared to LPS rats which self-administer saline [100]. This may indicate a restoration of deficits in nicotinergic $\alpha 7$ and $\alpha 4\beta 2$ receptor subtype function in LPS treated rats; however, this has not been assessed experimentally [100]. The effects of acute or chronic nicotine in neurodevelopmental models (e.g. MAM, Poly I:C, LBN) have not yet been assessed. However, considering interactions between the immune system and nicotine [172, 173], this is an interesting area of future research.

Cannabinoids: CBD, WIN, fatty acid amide hydrolase inhibitors

Osborne and colleagues examined the effects of CBD in a rat Poly I:C model of maternal infection, which exhibit cognitive deficits and social interaction impairment [174]. In males, chronic CBD treatment in early adulthood rescued deficits in short term working memory in the novel object recognition test and rewarded t-maze, as well as social interaction deficits in Poly I:C rats, with no effects of CBD in non-Poly I:C treated rats [174]. Chronic CBD treatment in early adulthood attenuated Poly I:C-induced deficits in CB_1 receptor binding in the PFC as well as GAD67 binding in the hippocampus [175]. CBD also increased protein levels of the interneuron marker parvalbumin in the hippocampus, irrespective of maternal infection, but did not affect NMDA or GABA-A receptor binding or protein levels of fatty acid amide hydrolase (FAAH), the enzyme which degrades anandamide, in the PFC or hippocampus. Overall, these findings suggest that in male rats, CBD may reverse schizophrenia-relevant negative and cognitive behaviours by restoring cannabinoid/GABAergic signalling deficits.

Similarly, in female Poly I:C rats, chronic CBD in early adulthood attenuates recognition memory and social interaction deficits, and reverses the Poly I:C induced reduction in NMDA receptor binding in the PFC [176]. Poly I:C also increases GAD67 and parvalbumin interneuron protein levels in the hippocampus [176]. Interestingly, CBD administration control rats (i.e. no Poly I:C treatment) reduces social interaction, as well as cannabinoid CB_1 receptor and NMDA receptor binding in the PFC, suggesting that CBD administration to healthy rats may have negative consequences on social behaviour and brain maturation in adulthood [176]. Together, this supports the antipsychotic potential of CBD for the treatment of cognitive and negative symptoms in schizophrenia but not healthy controls (review: [151]), and suggests CBD could be acting by reversing PFC CB_1 and NMDA receptor dysfunction and increasing GABA receptor function in the hippocampus, in a sex-specific manner.

In another model of maternal infection, the MAM model, chronic adolescent treatment with the CB_1 receptor agonist WIN prevents amphetamine-induced hyperlocomotion, but does not reverse deficits in a set-shifting task in MAM treated rats [177]. Interestingly, the effect of WIN on amphetamine-induced locomotion in MAM rats occurs in the absence of changes to dopaminergic neuron firing in the VTA [177], although cell activity in other brain regions relevant to locomotor sensitization (e.g. NAcc) were not assessed in this study. These findings are surprising as CB_1 receptor agonists often exacerbate schizophrenia symptoms [178]. The authors suggest that pubertal exposure to WIN may have changed the expression of components of the endocannabinoid system in brain structures related to motivation and motor control, thus limiting amphetamine-induced hyperlocomotion in MAM rats [177].

In a novel rodent model of schizophrenia susceptibility, the F2 methylazoxymethanol acetate (F2 MAM) rat, where only a proportion (40%) of rats display a schizophrenia-relevant phenotype (i.e. hyperdopaminergic phenotype characterized by increased dopamine neuron activity in the VTA), subchronic adolescent WIN treatment increases the proportion of F2 MAM rats with a schizophrenia-like phenotype (i.e. hyperdopaminergia) in early adulthood (i.e. from 36% to 71%), with no corresponding increase in schizophrenia-like phenotypes in WT controls [179]. Adolescent WIN treatment also increases sensitivity to acute amphetamine locomotor activity in early adulthood in F2 MAM rats, compared to WT controls [179]. Similarly, increasing endogenous cannabinoid signalling via the FAAH inhibitor URB597 also increases the proportion of F2 MAM rats with a schizophrenia-like phenotype in early adulthood (i.e. from 40% to 80%), but unlike WIN treatment, has no effect on amphetamine sensitivity [179]. This data mirrors clinical observations of increased risk for developing schizophrenia following cannabis abuse in individuals with genetic risk for the disorder [180–182], and will facilitate further investigation of the molecular and genetic mechanisms driving this susceptibility.

3.4 Pharmacological models

Psychostimulants: amphetamine

In a rat model of dopamine supersensitivity (i.e. withdrawal from chronic haloperidol), amphetamine treatment increases

Table 7. Susceptibility of schizophrenia neurodevelopmental rodent models to effects of drugs on schizophrenia-relevant behaviour and brain function

Author, date [Reference]	Model	Drug	Age at Drug Treatment / Age at Behavioural Testing	Results - Behaviour (↓decrease, ↑increase, ~no effect)	Results - Brain (↓decrease, ↑increase, ~no effect)
Gallo et al 2014 Behav Brain Res [85]; see also Rao et al 2016 [72], Jean-Blanc et al 2016 [77]	NVHL rat	Acute amphetamine	Early and late adolescence / Early and late adolescence	~Amphetamine-induced locomotion in early adolescence between NVHL and controls. ↑Amphetamine-induced locomotion in late adolescence in NVHL vs controls.	n/a
Berg et al 2014 [74]	NVHL rat	Chronic nicotine	Adolescence / Adult	~Chronic nicotine on cognitive impairment in the RAM in NVHL rats. Chronic nicotine ↓cognition in the RAM in WTs.	n/a
Berg et al 2015 [170]	NVHL rat	Chronic nicotine	Adolescence or adulthood / Late adolescence or adulthood	~Chronic nicotine on cognitive impairment in NVHL rats. Chronic nicotine ↑food reward consumption in RAM in NVHL.	Nicotine ↓NACh receptor binding in mPFC not striatum in NVHL rats.
Straley et al 2017 [171]	Prenatal LPS-treated rats	Acute amphetamine	Early adulthood / Adolescence and early adulthood	↓Breakpoint for food under amphetamine in LPS rats. ↑Amphetamine-induced locomotion in LPS rats.	↓Embryonic midbrain dopaminergic neurons 48 hr after LPS treatment at E16; this recovers by adolescence. ~LPS at E12 on midbrain dopaminergic neurons.
Waterhouse et al 2018 [100]	Prenatal LPS treated rats	Chronic nicotine	Adult / Adult	Nicotine ↑ cognitive impairment in latent inhibition and delayed non-matching to sample tasks in LPS rats.	n/a
Osbourne et al 2017 [174]; Osbourne et al 2019 [175]	Prenatal Poly I:C treated rats	Chronic CBD	Late adolescence / Early adulthood	CBD ↑short term working memory in NORT and T-maze, and ↑social interaction in Poly:IC rats	in Poly:IC rats, CBD ↑CB_1 receptor receptor binding in PFC and ↑GAD67 receptor binding in HPC. CBD ↑parvalbumin protein levels in HPC in Poly:IC rats and controls. ~CBD on NMDA, GABA-A or FAAH protein in PFC or HPC.
Osbourne et al 2019 [176]	Prenatal Poly I:C treated rats	Chronic CBD	Late adolescence / Early adulthood	CBD ↑social recognition memory and social interaction in female Poly I:C rats, but ↓social interaction in control rats.	CBD ↑NMDA binding in PFC in Poly I:C rats. CBD reduced CB_1 and NMDA binding in PFC in controls.
Gomes et al 2014 [177]	Prenatal MAM treated rats	Chronic WIN	Adolescence / Adult	WIN ↓amphetamine-induced hyperlocomotion in MAM rats. ~WIN on set-shifting task deficits in MAM rats.	↑Spontaneous dopaminergic cell firing in the VTA in MAM rats. ~WIN on dopaminergic cell firing in VTA in MAM rats.
Aguilar et al 2018 [179]	F2 methylazoxymethanol acetate (F2 MAM) rat	Chronic WIN or FAAH inhibitor URB597	Adolescence / Adult	WIN ↑amphetamine-induced locomotion in F2 MAM rats. ~FAAH inhibitor URB597 on amphetamine-induced locomotion in F2 MAM rats.	WIN and FAAH inhibitor URB597 ↑proportion of F2 MAM rats with hyperdopaminergic phenotype in VTA.

Abbreviations: CB_1, cannabinoid receptor 1; CBD, cannabidiol; E, embryonic day; FAAH, fatty acid amide hydrolase; GAD67, glutamate decarboxylase 67; HPC, hippocampus; LPS; lipopolysaccharide; MAM, mitotoxin methylazoxymethanol acetate; NACh, nicotine acetylchloline; NMDA; N-methyl-d-aspartate; NORT, novel object recognition; NVHL, neonatal ventral hippocampal lesion; PFC, prefrontal cortex; RAM, radial arm maze; VTA; ventral tegmental area; WIN; WIN 55,212-2.

the pursuit of food-based reward cues more vigorously in dopamine supersensitive rats than control rats [183–185]. This effect does not appear mediated by NAcc function, as intra-NAcc amphetamine injections or NAcc inhibition via GABA receptor agonists does not alter pursuit of food-based cues [185]. Baseline food-seeking, however, is unaltered by dopamine supersensitivity [183]. Amphetamine-induced locomotion as well as c-fos mRNA in the caudate putamen is also elevated following chronic haloperidol, compared to vehicle-treated controls [184]. While further research needs to be conducted in this field, these results suggest altered reward could be present in schizophrenia-relevant pharmacological models of altered dopamine function.

Nicotine

Information processing, in particular 40 Hz steady-state auditory evoked responses, is deficient in patients with schizophrenia [186], and assessment of auditory evoked responses in rodents can be used to model this in the laboratory. Acute MK-801 impairs auditory-evoked neural responses in anaesthetised rats [187], and MK-801 also exacerbates psychotic symptoms in patients with schizophrenia [188]. Interestingly, MK-801 induced impairment in auditory-evoked responses is ameliorated by acute nicotine administration [187]. Similarly, acute MK-801-induced memory impairments in mice are improved by acute nicotine administration [189], while chronic nicotine reverses heightened impulsivity in a mouse chronic PCP model [190]. Finally, systemic and intra-orbitofrontal cortex administration of nicotine or the nAChR agonist ABT-418 dose-dependently ameliorates chronic ketamine-induced impairments in a multisensory integration task, and this effect is blocked by GABA-A receptor antagonism [191]. These effects appear dependent on parvalbumin interneurons in the orbitofrontal cortex, as silencing parvalbumin interneurons impairs multisensory integration task performance, and this is reversed by ABT-418 administration [191]. Collectively, this suggests acute and chronic nicotine can improve cognitive impairment in an MK-801 schizophrenia rodent model, an effect which may depend on parvalbumin interneuron function in the PFC.

Cannabinoids: THC, WIN, FAAH inhibitors

PCP treatment, either neonatally or in adulthood, increases behavioural and brain responses to cannabinoids. A single neonatal PCP administration at G7 increases vulnerability to chronic adolescent THC-induced deficits in memory performance and sensorimotor gating [192]. Neonatal PCP also induces hyperlocomotion in adult mice which are chronically treated with THC (n.b. mice were tested for locomotor activity after at least 27 days of THC treatment, reducing the sedative effects of THC [192]). These behavioural effects are associated with reduced NMDA NR1 receptor protein in the cortex, reflecting a reduction in glutamatergic signalling which is hypothesised to contribute to schizophrenia pathophysiology [192].

When rats are treated subchronically in adulthood with PCP, this increases mPFC firing rates in response to the FAAH inhibitor URB597, suggesting increased susceptibility to elevated levels of endocannabinoids in PCP-treated rats compared to vehicle-treated controls [193]. Conversely, PCP-treated animals are unaffected by THC, where THC treatment decreases mPFC firing rates in saline treated animals [193]. Subchronic PCP treatment does not modulate firing rates in response to URB597 or THC in the ventral hippocampus, suggesting an mPFC-specific effect [193]. Considering neural oscillations are disrupted in schizophrenia, and cannabinoids can acutely decrease the power of neural oscillations [194], these findings can start to shed light on how cannabinoids affect mPFC neural firing in schizophrenia.

Interestingly, cannabinoids may have protective effects when administered prior to PCP. In rats which either self-administer or are treated chronically with the CB_1 receptor agonist WIN, the sensitized locomotor response to a PCP challenge is decreased in WIN-treated animals, compared to vehicle controls [195]. WIN self-administration also increases exploratory behaviour (i.e. rearing) and reduces anxiety-like behaviour in an open field arena in response to acute PCP administration [195]. Interestingly, PCP-induced social withdrawal and reduced anandamide levels in the PFC and amygdala can be reversed by elevating endogenous cannabinoids via the FAAH inhibitor URB597, or by increasing cannabinoid signalling via the cannabinoid agonist CP55,940 [196, 197]. This suggests PCP-induced social withdrawal and sensitized locomotor activity may result from deficient endocannabinoid transmission [196].

In a rat model selectively bred following social isolation housing and ketamine treatment in adolescence, WIN-induced G-protein activation is reduced in the cerebellum, cortex and in subcortical regions [198]. CB_1 receptor binding is also reduced in the cerebellum, cortex and subcortical regions in this rat model of schizophrenia, compared to controls [198]. These reductions in cannabinoid receptor binding and function correspond with similar endocannabinoid system changes and elevated susceptibility to cannabinoids in patients with schizophrenia (e.g. [199–201]).

Together, these results suggest cannabinoids generally worsen positive-like and cognitive behaviours, and cause altered receptor binding (e.g. cannabinoid, glutamatergic) and mPFC firing in pharmacological models of schizophrenia. This reflects clinical data, which demonstrates cannabis use can worsen symptoms in patients with schizophrenia, and in first episode patients, recent cannabis use is associated with decreased grey matter volume in the posterior cingulate cortex (review: [202]). Interestingly, in rodent models, the timing of cannabinoid administration can modulate this effect; cannabinoid administration prior to PCP treatment appears protective against schizophrenia-relevant behaviours.

3.5 Interim Summary

In Section 3, we summarised how abused drugs can exacerbate or alleviate schizophrenia-relevant behaviours in several rodent models of schizophrenia. Interestingly, there are some fairly consistent findings across models and drug classes. Nicotine, for example, often ameliorates schizophrenia-relevant behaviours, as observed in most genetic models, one neurodevelopmental model and one pharmacological model. Cannabinoids have bidirectional effects on schizophrenia-relevant behaviours, with CB_1 agonists (e.g. THC, WIN) mostly worsening these behaviours in genetic, neurodevelopmental and pharmacological models (although there are some exceptions), and CBD ameliorating schizophrenia-like behaviours in genetic and neurodevelopmental models. There is limited data available on the effects of psychostimulants on schizophrenia-relevant behaviour; however, lesion and pharmacological models show elevated sensitivity to psychostimulants, which can be age-dependent. The effects of nicotine, cannabinoids and psychostimulants mirrors what is observed in clinical literature, e.g. nicotine improves attention and processing speed in individuals with schizophrenia [203, 204], cannabis worsens schizophrenia symptoms and clinical prognosis [205], CBD has antipsychotic-like effects [206], and there is recent evidence of increased susceptibility to effects of amphetamine on sensorimotor gating in schizophrenia [207]. Importantly, this provides predictive validity to these models, and facilitates the use of these models to better understand brain changes associ-

Table 8. Susceptibility of schizophrenia pharmacological rodent models to effects of psychostimulant and antipsychotic drugs on schizophrenia-relevant behaviour and brain function

Author, date [Reference]	Model	Drug	Age at Drug Treatment / Behavioural Testing	Results - Behaviour (↓decrease, ↑increase, ~no effect)	Results - Brain (↓decrease, ↑increase, ~no effect)
Bédard et al 2011 [183], Bédard et al 2013 [184], El Hage et al 2015 [185]	Adult rat model of dopamine supersensitivity (i.e. withdrawal from chronic haloperidol). Rat model of chronic olanzapine treatment.	Acute amphetamine	Adult / Adult	Amphetamine ↑pursuit of food reward cues in dopamine supersensitive rats. ~NAcc amphetamine or NAcc GABA agonist on pursuit of food cues. ↑Amphetamine-induced locomotion in dopamine supersensitive rats. ~Olanzapine on amphetamine-induced locomotion or cue-seeking.	↑Amphetamine-induced c-fos mRNA in striatum in dopamine supersensitive rats. ~Olanzapine on amphetamine-induced c-fos mRNA in striatum.
Sivarao et al 2013 [187]	MK-801 induced impairment in auditory-evoked responses in rats	Acute nicotine	Adult / Adult	n/a	Nicotine ↑auditory-evoked neural responses, after MK-801 administration.
Brown et al 2014 [188]	Acute MK-801 in mice	Atypical antipsychotics: clozapine, risperidone, olanzapine. Sodium channel blockers: lamotrigine, carbamazepine. Cognitive enhancers: nicotine, donepezil, modafinil, and xanomeline. All drugs acutely administered.	Adult / Adult	Nicotine, donepezil, modafinil, carbamazepine and xanomeline attenuated MK-801-induced memory impairment. ~Clozapine, risperidone and olanzapine on MK-801-induced memory impairment.	n/a
Scott et al 2014 [189]	Chronic PCP in adult mice	Acute or chronic nicotine	Adult / Adult	Chronic, not acute nicotine ↓impulsivity in a mouse PCP model. ~Nicotine on locomotor activity in PCP mice.	n/a
Cloke et al 2016 [191]	Chronic ketamine in rats	Acute nicotine or ABT-418 (α4-β2-nicotinic-acetylcholine receptor agonist)	Adult / Adult	Nicotine or ABT-418. ↑cognition in ketamine rats; this effect was blocked by GABA-A receptor antagonism. Silencing OFC parvalbumin interneurons ↓cognitive performance; reversed by ABT-418	↓OFC GABAergic currents in ketamine rats, normalized by ABT-418. Parvalbumin OFC immunoreactivity decreased in ketamine rats.

GABA; Gamma Aminobutyric Acid; OFC, orbitofrontal cortex; NAcc, nucleus accumbens; PCP, phencyclidine.

Table 9. Susceptibility of schizophrenia pharmacological rodent models to effects of cannabinoid drugs on schizophrenia-relevant behaviour and brain function

Author, date [Reference]	Model	Drug	Age at Drug Treatment / Behavioural Testing	Results - Behaviour (↓decrease, ↑increase, ~no effect)	Results - Brain (↓decrease, ↑increase, ~no effect)
Rodriguez et al 2017 [192]	Single neonatal PCP administration at G7 in mice	Chronic THC	Early adulthood / Adult	Chronic THC ↑locomotion in neonatal PCP mice. THC ↓cognition in PCP mice. ~THC on PPI deficits in PCP mice.	THC ↓CB_1 receptor binding in FC of PCP mice. PCP ↓NMDA NR1 receptor binding in FC. THC ↓NMDA NR1 receptor binding in the FC in PCP mice and controls.
Aguilar et al 2016 [193]	Subchronic adult PCP treatment in rats	Acute FAAH inhibitor URB597 or THC	Adult / Adult	n/a	FAAH inhibitor URB597 ↑mPFC firing rates in PCP rats. ~THC on mPFC firing in PCP rats, where THC ↓mPFC firing in control rats. ~PCP on URB597 or THC-induced firing rates in ventral HPC.
Spano et al 2013 [195]	Chronic WIN treatment or WIN self-administration in rats	Acute or chronic PCP	Adult / Adult	↓PCP-sensitized locomotion in WIN-treated and WIN self-administering rats. WIN self-administration ↑exploration and ↓anxiety in PCP rats.	n/a
Seillier et al 2013 [196]; Matricon et al 2016 [197]	Subchronic adult PCP treatment in rats	Acute FAAH inhibitor URB597, cannabinoid agonist CP55,940, CB_1 antagonists AM251 and SR141716, TRPV1 antagonist capsazepine CPZ, cholecystokinin antagonist LY225910 LY	Adult / Adult	URB597 ↑social behaviour in PCP rats; this is CB_1 receptor but not TRPV1 receptor dependent. URB597 ↓social interaction in vehicle controls; this is CB_1 receptor dependent. LY225910 blocks acute PCP- and AM251-induced social withdrawal, but not URB597-induced social withdrawal.	Subchronic PCP ↓anandamide levels in amygdala and PFC; reversed by URB597. URB597 ↑c-fos protein expression in OFC, CeA and dorsomedial bed nucleus of the stria terminalis in PCP rats.
Szűcs et al 2016 [198]	27th generation of selectively bred male rats with social isolation and ketamine treatment	Chronic ketamine	Adult / Adult	n/a	↓WIN-induced G-protein activation and ↓CB_1 receptor binding in CB, FC, subcortical regions in ketamine-treated isolated rat model.

CB, cerebellum; CeA, central amygdala; FAAH, fatty acid amide hydrolase; FC , frontal cortex; G, gestational day; HPC, hippocampus; mPFC, medial prefrontal cortex; NMDA, N-methyl-d-aspartate; PCP, phencyclidine; PPI, prepulse inhibition; THC, Δ^9-tetrahydrocannabinol; WIN; WIN 55,212-2.

ated with drug susceptibility. The research reviewed above indicates that chronic nicotine has a range of effects on the brain in schizophrenia models, including reducing striatal D_2 receptor mediated LTD in *Snap-25* KO mice, increasing GAD67 and reelin mRNA in the cortex, hippocampus, striatum and cerebellum of *reeler* mice, and differential theta burst stimulated LTP in cortico-BLA synapses in *Type III Nrg1* HET mice. Chronic THC alters CB_1 receptor binding in the substantia nigra and CB_1 protein levels in the hippocampus in genetic models (i.e. *Nrg1 TM* HET and *DN-Disc1*). Chronic THC also alters protein binding of NMDA and $5\text{-}HT_{2A}$ receptors in the cortex and hippocampus of *Nrg1 TM* HET mice, potentially reflecting genotype-specific effects of THC on locomotion and social behaviour. Endocannabinoid signalling (e.g. firing rates following FAAH inhibitor administration, WIN-induced g-protein activation or anandamide levels) are also altered in the PFC and amygdala and cerebellum in pharmacological (e.g. PCP) and two-hit models (e.g. ketamine and social isolation), suggesting changes to endocannabinoid function potentially reminiscent of endocannabinoid system changes in patients with schizophrenia [199–201]. The antipsychotic-like effects of CBD may be mediated by reversing changes to PFC CB_1 and NMDA receptor dysfunction and increasing GABA receptor binding in the hippocampus and PFC in schizophrenia models. Finally, while there has been limited examination of how psychostimulants affect neural function in schizophrenia models, elevated c-fos mRNA expression in the caudate-putamen following chronic haloperidol suggests sensitized dopaminergic function in reward regions and may also contribute to drug-seeking susceptibility.

4. Conclusions

There has been a vast addition to the preclinical literature investigating schizophrenia and drug abuse comorbidity since 2013, and it is becoming increasingly apparent that drug addiction behaviours and susceptibility to effects of abused drugs exist in many schizophrenia models. This is an exciting development, and suggests a burgeoning new field which could lead to breakthroughs in our understanding of comorbidity between schizophrenia and addiction. Importantly, in this review we have highlighted how *often* addiction-like behaviour is observed in different models of schizophrenia, particularly in genetic and neurodevelopmental models. We also found significant support for each hypothesis to explain drug susceptibility in schizophrenia: neurodevelopmental and some genetic models support the primary addiction hypothesis; genetic, neurodevelopmental and pharmacological models support the two-hit hypothesis, particularly for cannabinoids and nicotine, while genetic models often support the self-medication hypothesis for nicotine. Interestingly, this review found that the susceptibility of schizophrenia models to drug abuse appears to often implicate altered dopaminergic function (e.g. increased dopamine D_2 receptor expression and dopamine metabolism), particularly in reward relevant regions such as the PFC and NAcc. This is relevant as changes in dopamine receptor expression are observed in drug abuse patients [5], and alterations to the dopaminergic system is consistent finding in schizophrenia, suggesting that schizophrenia susceptibility may alter drug reward pathways to elevate risk for drug abuse. It is interesting to note that cognitive impairment in some models (e.g. NVHL model) correlates with drug abuse susceptibility; investigating this in other models would be of considerable interest.

Furthermore, when examining susceptibility of schizophrenia models to abused drugs, there are effects on several neurotransmitter systems highly relevant to schizophrenia and addiction, primarily in mesocorticolimbic structures. Nicotine treatment has ameliorative effects on schizophrenia relevant behaviour in several models (e.g. genetic and pharmacological models, but not the NVHL model), and this may be dependent on actions at $\alpha 7$ nicotinergic receptors. Several models are more susceptible to the effects of cannabinoids such as THC and CBD on schizophrenia-relevant behaviours, and this is accompanied by complex changes in cannabinoid, glutamatergic, serotonergic and GABAergic receptor systems. Considering changes to these systems have all been reported in schizophrenia [208, 208–211], these findings not only validate the models used, but indicate how changes in these systems are relevant to both schizophrenia and drug susceptibility. Changes to specific receptor systems and subunits indicates which targets are specifically affected by drug exposure in schizophrenia, increasing our understanding of interactions between these disorders and potentially providing targets for future pharmacotherapies specifically designed to treat addiction in schizophrenia.

However, there are still several gaps in the literature which need to be addressed. To date, there has been very limited investigation into the molecular correlates of susceptibility to abused drugs. Also, most research has examined the response of schizophrenia models to effects of nicotine and cannabinoids on schizophrenia-like behaviours, yet behavioural and neural responses to other drugs of abuse (e.g. alcohol, psychostimulants, opioids), remains mostly unexplored. Other critical areas of future research include investigating addiction-like behaviour for non-psychostimulant drugs in genetic and pharmacological models of schizophrenia, as well as investigating potential sex-specific effects in terms of addiction-relevant behaviour. Poly-drug use has rarely been examined (but see a recent example: [75]), yet considering that poly-drug use is common in schizophrenia [212, 213], this is another research area with incredible potential. Addressing these gaps in the literature will thoroughly advance our understanding of the complex relationship between schizophrenia and drug abuse, and eventually help to better treat addiction in schizophrenia.

Declarations

Author's Contributions

RC conceptualised the review scope, VM and RC researched the topic and wrote the review, VM, JCO and RC edited the review, VM and RC approved the review prior to submission.

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This review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Editorial Notes

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- Plagiarism: Plagiarism detection software found no evidence of plagiarism.
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Peer Review

The review process for this paper was conducted double-blind because one of the authors is a member of the committee of management of the publisher, Episteme Health Inc. During review, neither the authors nor the reviewers were aware of each other's identities.

For the benefit of readers, reviewers are asked to write a public summary of their review to highlight the key strengths and weaknesses of the paper. Signing of reviews is optional.

Reviewer 1 (Anonymous)

This review aims to update the field on recent advances in our understanding of co-occurring schizophrenia and substance use disorders. The review focuses heavily on preclinical findings that have been published after 2013, and aims to address important questions related to how schizophrenia impacts vulnerability to substance use and how substance use alters the course of schizophrenia. The review is thorough (for the timepoints assessed), but sometimes the language is not specific.

Reviewer 2 (Steven Simmons, Childrens Hospital of Philadelphia, United States.)

This well-written and scholarly review discusses the complex interactions between substance use disorders (SUDs) and schizophrenia. It provides a major update to the field since a prior review published in 2013. Contained within are thorough descriptions of behavioral tests and measures used in animal studies that model both psychiatric conditions. The review frames studies through the lens of multiple theories attempting to account for the high comorbidity between SUDs and schiophrenia, including the "self-medication theory" (individuals with schizophrenia use drugs to manage symptoms of schizophrenia), the "primary addiction hypothesis" (predisposition to both psychiatric conditions are linked by common pathophysiology), and the "two-hit hypothesis" (genetic/environmental factors [first hit] initially predispose an individual to develop schizophrenia, and substance use [second hit] enables the manifestation of schizophrenia symptomatology). The review considers the underlying neurotransmitter systems and circuits that underlie behaviors associated with each disorder.

Reviewer 3 (Anonymous)

The authors of the review aim to summarise the literature surrounding the relationship between drugs of abuse and schizophrenia, in particular focusing on various rodent models, concentrating on studies published since 2013.

Drug addiction and abuse rates in the schizophrenia population is much higher than that of the general population, adding burden to an already highly burdensome disease. Given that both schizophrenia and drug addiction are complex disorders, many fundamental understanding is in flux. The review organises itself with two important and fundamental questions in mind - 1) whether schizophrenia primes individuals towards drug addiction and/or 2) whether drugs of abuse cause/exacerbate schizophrenia. The authors systematically review various types of rodent models and studies examining different drugs and molecular pathways, highlighting inconsistencies and areas that require further clarification.

The review is well constructed and laid out. It is a thorough summary and critique of the area of research. The review is well written and clear in its expression and offers a useful guide towards the future research in this field.

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