



## Research report

## Sex differences in psychotomimetic-induced behaviours in rats

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## HIGHLIGHTS

- Studies using equal numbers of males and females are sparse in psychiatry research.
- We compared male and female Sprague-Dawley rats in two widely-used, validated models.
- Amphetamine-induced hyperlocomotion (distance travelled) was greater in female rats.
- Phencyclidine-induced hyperlocomotion was similar in male and female rats.
- There were no sex differences in drug-induced disruption of prepulse inhibition.

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## ABSTRACT

Animal model studies using equal numbers of males and females are sparse in psychiatry research. Given the marked sex differences observed in psychiatric disorders, such as schizophrenia, using both males and females in research studies is an important requirement. Thus the aim of this study was to examine sex differences in psychotomimetic-induced behavioural deficits relevant to psychosis. We therefore compared the acute effect of amphetamine or phencyclidine on locomotor activity and prepulse inhibition in adult male and female Sprague-Dawley rats. The results of this study were that: (1) amphetamine-induced distance travelled was greater in female rats than in male rats, (2) phencyclidine-induced locomotor hyperactivity was similar in male and female rats; (3) there were no sex differences in amphetamine- or phencyclidine-induced disruption of prepulse inhibition; (4) male rats had an increased startle response after amphetamine. These findings suggest that sensitivity to amphetamine, but not phencyclidine, differs between male and female rats, and that this sex difference is selective to locomotor hyperactivity and startle, but not prepulse inhibition. This study used two widely-used, validated preclinical assays relevant to psychosis; the results of this study have implications for psychiatry research, particularly for disorders where marked sex differences in onset and symptomatology are observed.

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## 1. Introduction

The use of animal models in psychiatric research is crucial to enhance our understanding of a human condition and to elucidate the relationship between changes in brain function and behaviour. Furthermore, the importance of using male and female animals in experiments focusing on behavioural changes is paramount as sex differences are observed in the onset and

severity of schizophrenia and other psychiatric conditions. For example, women with schizophrenia were found to have a later age of onset, better antipsychotic treatment response and a less severe clinical course as compared with men [1–3]. The most widely considered neurochemical hypotheses of schizophrenia are the dopamine and glutamate hypotheses [4,5]. In particular, overactivity in dopaminergic signaling is a core pathophysiological feature of psychotic illness and all clinically used antipsychotic treatments block dopamine D<sub>2</sub> receptors [6,7]. Specifically, recent evidence indicates a presynaptic hyperdopaminergic abnormality linked to psychotic symptoms of schizophrenia, which may result from multiple environmental or genetic insults [4,6]. Evidence supporting a role for glutamatergic hypofunction in the pathology of schizophrenia includes clinical challenge studies highlighting the

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similarity between glutamate NMDA receptor antagonist-induced behavioural deficits and the symptoms of schizophrenia [4]. Recent neuroimaging studies confirm earlier pharmacological and post-mortem studies, and further suggest an integrated hypothesis whereby glutamate dysfunction may underlie the dopamine dysfunction observed in schizophrenia [4].

Behavioural animal models of schizophrenia have been extensively used to mimic certain symptoms of the illness [8]. Here we focus on two of the most widely-used animal models of psychosis-like behaviours: psychotomimetic drug-induced locomotor hyperactivity and prepulse inhibition of the acoustic startle reflex (PPI). As pharmacological models, they have face, construct and predictive validity and their effects can be reversed by antipsychotic treatments [9,10]. Drug-induced locomotor hyperactivity is an animal model of psychosis, particularly psychotic agitation/excitement [8]. The quantification of rodent hyperlocomotion, which includes parameters such as distance moved or stereotypy movements, can be measured by automated photocell chambers [11]. Hyperlocomotion is generally linked to limbic-striatal modulation of brainstem motor circuits. The nucleus accumbens is an important regulatory interface between limbic and motor systems in driving such behaviour [12]. PPI measures sensorimotor gating and is considered to represent the interface of psychosis and cognition [8]. PPI is deficient in individuals with schizophrenia and various other psychopathologies, and can be disrupted in rodents or healthy humans using psychotomimetic drugs [13–16]. The key structures of brain circuitry mediating PPI include the prefrontal cortex, hippocampus, striatum, pallidum, and pontine tegmentum [17]. While there is some overlap, the brain circuitry involved in regulating locomotor hyperactivity and PPI is different.

As dopamine and glutamate play an important role in psychosis [5,18], psychotomimetic drugs targeting these systems, such as amphetamine and phencyclidine which model a hyperdopaminergic and hypoglutamatergic state, respectively, are extensively used in rodent behaviour studies. Primarily, amphetamine is considered a dopamine indirect agonist, and phencyclidine is a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist [19,20]. However, evidence suggests these drugs target multiple neurotransmitter-receptor systems in different brain regions of the circuitry regulating locomotor activity and PPI [8,17,21,22]. For example, amphetamine-induced locomotor hyperactivity is dependent upon intact dopamine activity in the nucleus accumbens [23–26] but also depends on noradrenaline and serotonin release from presynaptic terminals [27,28]. The effect of phencyclidine on behaviour involves NMDA receptor antagonism, but also glutamate efflux in frontal cortical regions, and potent inhibition of noradrenaline and serotonin uptake [29–32].

Some studies have examined sex differences in behaviour in animal models of altered dopaminergic and glutamatergic states. For example, male mice lacking the dopamine transporter (resulting in increased levels of dopamine) showed significant disruptions in PPI, whereas deficits in PPI were not found in female dopamine transporter knock-out mice [33]. Furthermore, female rats appeared to be more sensitive to the effects of acute phencyclidine administration by showing severe deficits in recognition memory when compared to male rats [34]. By contrast, in response to phencyclidine young male, but not female, rats displayed decreased sucrose preference, a correlate for anhedonia, but no sex difference was found in adult rats [35]. In the elevated plus maze, exposure to phencyclidine had an anxiogenic effect in male rats but anxiolytic effect in female rats [35].

While locomotor hyperactivity and disruption of PPI caused by acute administration of amphetamine and phencyclidine are commonly-used behaviours, the majority of previous studies have used male rats only (for example, [22,36–39]). While there are few studies using male and female rats [40–42], these measure only one

behaviour with one of the psychotomimetic drugs [43–45]; to the best of our knowledge, there are no studies comparing the effects of amphetamine and phencyclidine in locomotion and PPI in both male and female rats. For example, after acute or chronic treatment with amphetamine, female rats showed greater hyperlocomotion when compared to male rats [44], however, the effect of phencyclidine on locomotion was not examined. In terms of amphetamine or phencyclidine-induced PPI disruption in male and female rats, only one study examined sex differences. Phencyclidine-induced PPI disruption was similar in male and female rats, however this study did not use amphetamine, nor examine the effects of these psychotomimetic drugs in locomotor activity [45].

The aim of this study was to examine sex differences in amphetamine and phencyclidine-induced behavioural deficits relevant to psychosis, in order to provide a basis for which studies using these drugs can refer to. To achieve this, we compared the acute effect of different doses of amphetamine and phencyclidine on locomotor activity levels and PPI in adult male and female Sprague-Dawley rats.

## 2. Materials and methods

### 2.1. Animals

The experimental protocol was carried out using 32 male and 32 female adult Sprague-Dawley rats (Department of Pathology, University of Melbourne). The rats were housed in open-top cages under standard conditions in groups of 2–3, with free access to food and water. They were maintained on a 12 h:12 h light/dark cycle (lights on at 0700 h) at a constant temperature of  $21 \pm 2^\circ\text{C}$ . One week prior to experimentation, rats were handled each day over a five day period. At the time of the first locomotor experiment, body weights ranged from 300 to 400 g for male rats and 250 to 350 g for female rats. At the time of the first PPI experiment, body weights ranged from 400 to 500 g for male rats and 250 to 300 g for female rats. The experimental protocol was approved by the Animal Experimentation Ethics Committee of the University of Melbourne, Australia, and conducted in accordance with the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* (1990) set out by the National Health and Medical Research Council of Australia.

### 2.2. Experimental design

The study included 4 cohorts of  $n = 16$  rats ( $n = 8$  male and  $n = 8$  female rats per cohort): (1) male and female rats treated with amphetamine (0, 0.5 and 2.5 mg/kg) and tested for locomotor activity; (2) male and female rats treated with phencyclidine (0, 2.5 and 5.0 mg/kg) and tested for locomotor activity; (3) male and female rats treated with amphetamine (0, 0.5 and 2.5 mg/kg) and tested for PPI; and (4) male and female rats treated with phencyclidine (0, 0.5 and 2.5 mg/kg) and tested for PPI.

### 2.3. Drugs

The psychotomimetic drugs *D*-amphetamine sulfate (Sigma Chemical Co., St. Louis, MO, USA) and phencyclidine HCl (Sigma) were dissolved in 0.9% saline solution and injected subcutaneously (s.c.) in the nape of the neck in a volume of 1 ml/kg. In a randomized, cross-over protocol, all rats in each experiment received all doses, with 3–4 days allowed between each dose. The randomization procedure minimizes any possible effects of repeated exposure or dosing order. The cross-over protocol allows for within-animal statistical analysis and also reduced the total number of animals required.

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