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Maternal immune activation alters sensitivity to action-outcome contingency in adult rat offspring

Jessica Millar, David K. Bilkey, Ryan D. Ward *

University of Otago, PO Box 56, Dunedin 9054, New Zealand

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ABSTRACT

Epidemiological studies have provided convincing evidence for a role of maternal immune activation in the pathogenesis of neurodevelopmental disorders such as autism and schizophrenia. In recent years, several research groups have capitalised on this discovery and developed animal models such as the maternal immune activation (MIA) model that emulates many phenotypes characteristic of disorders such as schizophrenia. In the present series of experiments we used the MIA model to examine motivation, a core component of the negative symptomatology in schizophrenia. Contrary to what we expected, in the progressive ratio task, which assesses an animals' willingness to work for a reward under increasing effort requirements, we found that MIA rats appeared more motivated than controls. Subsequent tests showed that this seemingly enhanced motivation was not due to an overall increase in responding, nor due to enhanced attribution of incentive salience to reward associated responses. Instead, we found that the increased willingness to work exhibited by MIA animals was due to an inability to detect changes in the contingency between their behaviour and the resulting rewarding outcome. With regard to motivation, the experiments reported here are the first to subject the MIA model to a rigorous experimental analysis of behaviour by parsing underlying processes that give rise to the overt symptoms in psychiatric disease.

1. Introduction

Deficits in motivation are one of the negative symptoms of schizophrenia and are important as they relate to functional outcomes but do not respond well to medication (Kirkpatrick et al., 2006). Motivational impairments could arise due to an inability to experience pleasure (anhedonia) or an inability or unwillingness to work purposefully to obtain a rewarding outcome (avolition) (Barnes et al., 2014; Gard et al., 2007). Research in both human participants (Cohen and Minor, 2010; Gold et al., 2008) and with animal models of schizophrenia favours the latter idea (Simpson et al., 2011). For example, Ward et al. (2012) used a transgenic animal model of the negative symptoms of schizophrenia in which mice over-express striatal dopamine (DA) D2 receptors (D2R-OE mice). Using a variety of operant paradigms, Ward et al. (2012) showed that the D2R-OE mice were less willing to expend effort to seek reward compared to control mice. The D2R-OE mice were shown to be just as responsive to rewarding stimuli as controls, for example no differences were shown in gustatory or taste reactivity testing (intact hedonia), however they were less inclined to keep working when task demands increased (deficit of volition).

Strauss and colleagues investigated motivational abnormalities in patients with schizophrenia. They used a progressive ratio procedure to examine whether the severity of negative symptoms was correlated with performance on this effortful task. They found that the point at which patients finally discontinued to work for a reward correlated with the severity of symptoms of avolition, lending further support for motivational impairments as one of the core features of negative symptoms in schizophrenia (Strauss et al., 2016).

Maternal immune activation (MIA) is a significant risk factor for development of schizophrenia and other neurodevelopmental disorders (Brown and Derkits, 2010; Mednick, 1988; Weinberger, 1987). Epidemiological evidence suggests that prenatal immune challenge activates a cascade of physiological changes in the maternal host that subsequently impacts the developing brain of the foetus and increases the incidence of schizophrenia in the offspring (Meyer et al., 2009; Meyer and Feldon, 2012; Smith et al., 2007; Uhlhaas and Singer, 2010; Zuckerman and Weiner, 2005).

Maternal immune challenge can be initiated in animal models by administering a synthetic viral RNA (Poly I:C) to the pregnant dam during mid-gestation. The offspring of mothers subject to Poly

* Corresponding author at: Department of Psychology, University of Otago, PO Box 56, Dunedin 9054, New Zealand.
E-mail address: rward@psy.otago.ac.nz (R.D. Ward).

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I:C injection subsequently mimic behavioural, cognitive and neurophysiological deficits that model the effects in human patients with schizophrenia (Dickerson and Bilkey, 2013; Giovanoli et al., 2013; Meyer, 2014; Wolff and Bilkey, 2010; Wolff et al., 2011). To our knowledge, however, the Poly I:C model of maternal immune activation has not yet examined the impact of immune challenge on tasks probing motivation in animal offspring.

In another animal designed to model one specific aspect of the pathogenesis of schizophrenia, increased striatal dopamine D2 activity, (Simpson et al., 2011) it has been shown that animals demonstrate a lack of motivation in operant paradigms such as the progressive ratio procedure, a task demanding increasing amounts of effort for a reward (Simpson et al., 2011). As MIA has been demonstrated to contribute significantly to neurodevelopmental dysfunction and disease development, we sought to examine the effect of MIA on the progressive ratio task. Contrary to our predictions, we found that MIA animals worked longer than controls on the progressive ratio schedule, seemingly being more willing to continue to work as the ratio requirement increased across trials. We then conducted further tests to assay the specific nature of the differences in performance between MIA and control rats. We found that the increased persistence in the progressive ratio schedule was not due to increased general activity or increased attribution of incentive salience to reward associated cues. Rather, increased persistence in this task appeared to be due to an inability of MIA rats to detect changes in the contingencies between their responding and the resulting outcomes.

2. Materials and method

2.1. Subjects

The generation of MIA rats has been described in detail previously (Dickerson et al., 2010). Briefly, female Sprague-Dawley rats were mated at three months of age. On gestational day 15 (GD15), pregnant dams were anesthetised with isoflurane and were administered either a single dose of Poly I:C (4 mg/kg i.v.) dissolved in saline, or vehicle. Dams were monitored for 24 h after the injection and weight changes were monitored for the following days of pregnancy. As we have previously shown, dams subject to Poly I:C displayed a transient decrease in weight in the 24 h following the injection (Wolff and Bilkey, 2010). Once weaned, litters of six males were group housed in standard plastic bottom/wire lid cages, three males per cage based on treatment group, i.e. three Poly I:C offspring or three saline offspring per cage until they were at least three months old at which point experimentation began. The colony room was on a 12 h light/dark cycle with lights on at 0700hours. All animals were food deprived to 85% of their free feeding weight to motivate them to earn rewards in the task. Standard rat chow was given to maintain their 85% weight as their home cage food and 45 mg grain-based rodent food pellets (Bio-Serv) were provided as reward in the operant chambers. All experimental procedures were approved by the University of Otago Animal Ethics Committee.

2.2. Apparatus

10 identical operant chambers (Med-Associates, St Albans, VT; model ENV-307w), measuring 22.5 × 18.5 × 12.5 cm were used. All operant chambers were within a light and sound attenuating cabinet with an exhaust fan which provided 72 dB of background noise. Chambers were equipped with two retractable levers, located on either side of the food hopper that was located centrally on the same wall to which the reward was delivered. An infrared photocell detector was used to record head entries into the food hopper. The floor of the chamber was comprised of metal rods spaced 0.87 cm apart. Each chamber contained a houselight which provided chamber illumination and an audio speaker, positioned 8.5 cm from the floor on the opposite wall to the food hopper. All output programming and data recording was completed using Med-PC IV.

2.3. Procedure

2.3.1. Prelimary training

2.3.1.1. Pellet training. Initially, rats were exposed to the food pellets that were used as rewards in their home cage during two ten-minute exposures across two days. Rats were then trained to retrieve pellets from the hopper in the operant chamber over three sessions of 32 trials each. By the end of this training, all rats retrieved all pellets during the session.

2.3.1.2. Lever press training. On each trial, either the right or left levers were presented and a response made within 10 s resulted in delivery of a reward. Failure to respond within 10 s resulted in lever retraction and no reward. Sessions lasted for 60 trials. Rats moved onto the next condition if they received rewards on more than 50 trials during the session. This occurred within 3 sessions for all rats. There was no inactive lever for this condition of training.

2.4. Experiment 1: progressive ratio

On each trial, a lever was extended and the houselight was turned on. Following a specified number of presses, the lever was retracted, the houselight was extinguished, and a reward was delivered. The criterion was set at one lever press for the first trial and then doubled with each successive trial (e.g., 2, 4, 8, 16, 32, 64...). Each session ended after either 2 h had elapsed or after 3 min without a lever press. Each rat's break point was defined as the last completed ratio. A total of 21 (MIA = 10, control = 11) animals from 10 litters (5 MIA, 5 control) were used for this experiment. There was no inactive lever for this experiment.

2.5. Experiment 2: random ratio

Immediately following progressive ratio training, rats received three sessions of training which were identical to the initial lever press training with the exception that both levers were presented during the session. Rats responded to at least 50 out of the 60 lever presentations within the three training sessions. During random ratio schedule testing, each session two levers were extended, one active and one inactive. Presses on the active lever produced a reward according to a random ratio (RR) schedule in which the number of lever presses per reward varied from trial to trial but the average number of lever presses for a reward stayed constant. The average response requirement was increased every two days from RR5, RR15, RR30 and finally RR60 over the course of several sessions. Presses on the inactive lever never produced a reward. Sessions ended after the delivery of 60 rewards. A total of 9 (MIA = 5, control = 4) animals which also participated in the progressive ratio were used for this experiment.

2.6. Experiment 3: autoshaping

A separate cohort of naive rats were trained to eat pellets from the hopper as described above. No preliminary leverpress training was given before the experiment proper. During each session, trials began with an intertrial interval (ITI; mean 30 s). Following the ITI, either the left or the right lever was extended for 10 s. One lever was designated S+, the other was designated S− (counterbalanced