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Discrimination difficulty, cognitive burden, and reversal impairments in a maternal immune activation model of schizophrenia risk

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ABSTRACT

Reversal-learning impairments in the maternal immune activation (MIA) model of schizophrenia risk have been interpreted as being indicative of deficits in reinforcement learning. Here we sought to assess the specific role of cognitive burden in discrimination learning and reversal performance in this model. Control and MIA rats were trained on a visual discrimination task in which responses on either a left or right lever were rewarded depending on the location of a cue light at the beginning of the trial. Groups of MIA and control rats differed in the difficulty of the discrimination rule they initially learned (pressing the lever on the same side vs the opposite side of the cue light). Once the discrimination was learned, performance was tested across four reversals. Across all phases of the experiment, rats in Group Same performed better than rats in Group Opposite. There was no difference in performance of control and MIA rats during acquisition or baseline, but MIA rats displayed impaired performance across reversals, with performance decrements manifesting later in reversals after the new discrimination rule had been learnt. Across reversals, MIA rats also made more perseverative errors than control rats. These results are consistent with others that have shown reversal learning impairments in MIA rats. The results further suggest that impaired behavioural flexibility in the MIA model is not due to a deficit in reinforcement learning, but due to an impaired ability to organize information gained from experience into an accurate and stable representation of the current task requirements.

1. Introduction

Behavioural flexibility, the ability to adapt behaviour in the face of changing contingencies, is critical to adaptive functioning, and is compromised in schizophrenia (Everett et al., 2001; Pantelis et al., 1999; Prentice et al., 2008). One assay of behavioural flexibility that is impaired in schizophrenia is reversal learning (Waltz and Gold, 2007). In a reversal-learning paradigm, subjects must learn to behave according to one rule. The rule is then reversed, such that the previously-correct response is incorrect, and the previously-incorrect response is correct.

Activation of the maternal immune system during pregnancy in rats (MIA) produces cognitive and behavioural deficits in offspring that are similar to those seen in schizophrenia, including reversal-learning impairments (Han et al., 2011; Kleimans and Bilkey, 2018; Wallace et al., 2014; Savanthrapdian et al., 2013; Lins et al., 2018; but see Ballendine et al., 2015; Wolff et al., 2011; Zuckerman and Weiner, 2005), linking this identified risk factor with this canonical impairment. Reversal-learning impairments are generally interpreted as indicative of a deficit in some aspect of reinforcement learning, such as inaccurate representation of outcomes, an inability to learn the contingency between behaviour and consequences (Millar et al., 2017), or an impaired ability to learn from rewarded choices (Wallace et al., 2014). An alternative explanation is that reversal-learning deficits are the result of differences in the ability to engage available cognitive resources under the increased cognitive burden introduced during the reversal phase (Kleimans and Bilkey, 2018). These distinctions are important, as different neural circuits subserve different aspects of cognitive and behavioural flexibility.

In the present study, we trained control and MIA rats in a prefrontal-dependent visual-discrimination procedure in which they were rewarded for responding on either a left or right lever depending on the location of a cue light that was presented at the beginning of the trial (Ward et al., 2015a,b; Bates et al., 2018; Kahn et al., 2012; Tashakori-Sabzevar and Ward, 2018) and then assessed behavioural flexibility across several reversal phases. Cognitive burden was manipulated by varying the discrimination rule of the initial discrimination task (rewarded for choosing the same side vs opposite side as the cue light). Our goal was to explicitly assess the impact of cognitive burden on discrimination learning and reversal performance and to see whether

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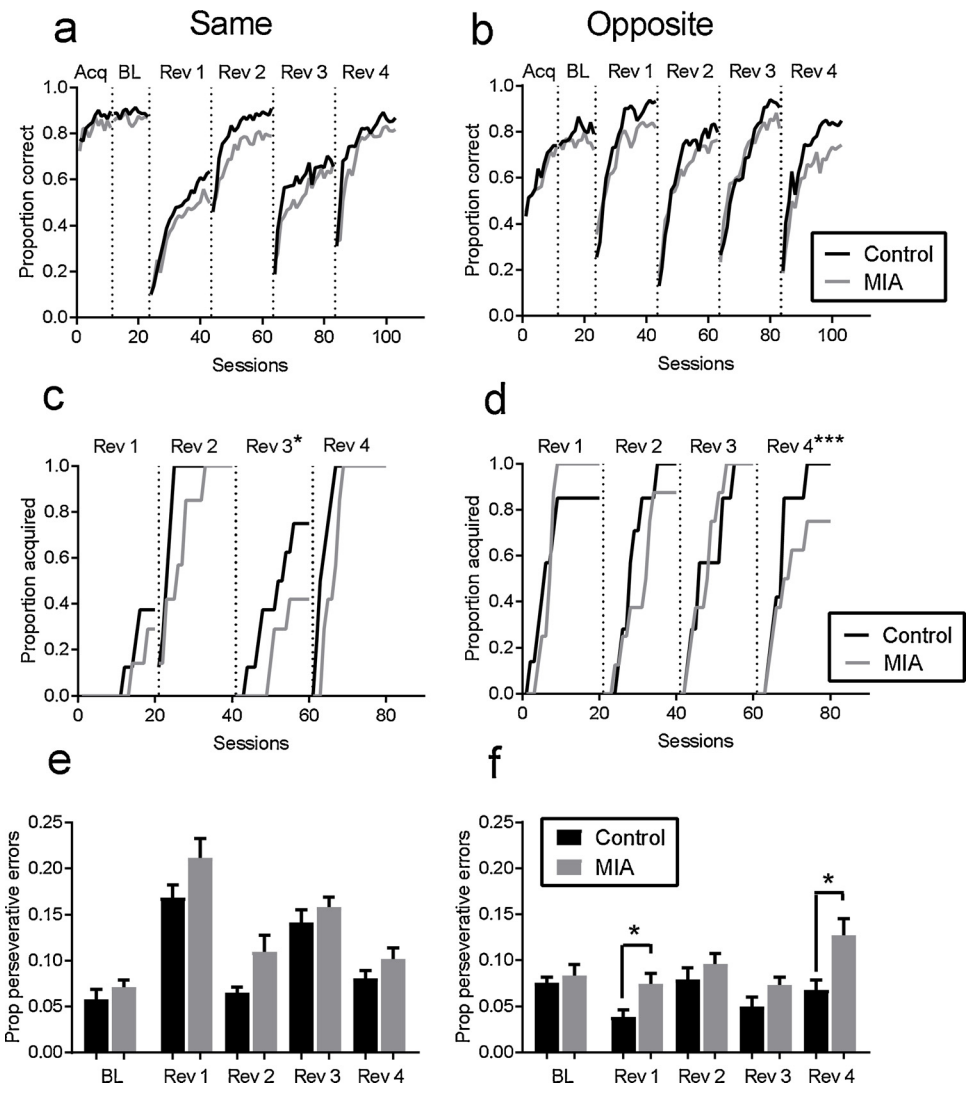

Fig. 1. Performance of control and MIA rats in a visual discrimination reversal task. A. Proportion correct across training, baseline, and reversal phases for group "same" (see text for detail). B. Proportion correct across training, baseline, and reversal phases for group "opposite" (see text for detail). C. Proportion of rats who acquired greater than 0.7 proportion correct across reversal phases as a function of sessions for group "same". D. Proportion of rats who acquired greater than 0.7 proportion correct across reversal phases as a function of sessions for group "opposite". E. Proportion of perseverative errors during baseline and across reversal phases for group "same". F. Proportion of perseverative errors during baseline and across reversal phases for group "opposite". *p < .05, ***p < .0005.

any impacts differed across MIA and control rats.

2. Methods

2.1. Subjects

Thirty male Sprague-Dawley rats (15 MIA, 15 control), 90 days old at the beginning of the experiment (approximately 250–300 grams at the beginning of the experiment; 350–450 grams at experiment's end), from multiple independent litters (see below for litter contribution to different experimental groups) were used as subjects. Rats were maintained at 80–90% of their free-feeding weight. Generation of and maintenance of MIA rats was as previously described (Bates et al., 2018; Millar et al., 2017). On gestational day 15 (GD15) pregnant females were anesthetised with isoflurane and injected with either a mixture of saline and poly I:C (4 mg/kg, i.v.) or a vehicle solution. The females were monitored for 24 h afterward, and weight was monitored for the remaining duration of gestation. Rats were group housed (two or three to a cage) in a temperature-controlled room with a constant 12 -h light/dark cycle. Water was available ad libitum. All procedures were approved by the University of Otago Animal Ethics Committee.

2.2. Apparatus

Experimental sessions were conducted in 10 standard Med Associate operant chambers. These consisted of a plastic walled box (internal dimensions 30.5 × 24.1 x 21 cm) with two levers, three LED cue lights located above the levers, and a food hopper along one wall. Chambers were located in a light- and sound-attenuating cabinet with a fan to mask back-ground noise. MedPC interfacing equipment and software (Version IV Fairfax, VT) installed on a PC computer controlled and recorded experimental events.

2.3. Procedure

2.3.1. Initial training and discrimination task

Rats were taught to retrieve pellets, press response levers, and learn the initial discrimination according to our previously-published protocol (Bates et al., 2018). During each trial, the cue was illuminated for five seconds. The correct lever was then extended. If the rat responded within 10 s, a reward was delivered, otherwise no reward was given, and a new trial began. For half of the rats, (Group Same; rats from 8 litters, 4 each for control and MIA) pressing the lever which was on the same side as the cue light was rewarded. For the other half (Group Opposite; rats from 12 litters, 6 each for control and MIA), pressing the lever on the opposite side was rewarded. Sessions lasted for 68 trials.

2.3.2. Reversals

Following establishment of a stable baseline, the discrimination rule was reversed such that the opposite discrimination rule was in effect

(i.e., Group Same rats now had to press the lever opposite the cue light, while Group Opposite rats had to press the lever on the same side as the cue light). Reversals were conducted for 20 sessions. Rats experienced a total of four reversals.

2.4. Data analysis

We calculated proportion correct across all phases of the experiment. Separate repeated measures ANOVAs were conducted on the data from the acquisition, baseline, and reversal phases, and performance was further analysed according to the discrimination rule that rats were initially trained on (Same vs Opposite). We also analysed the proportion of trials in which rats made an error by pressing a lever which had been rewarded on the previous trial (perseverative errors). To mitigate the possible influence of litter effects, data were analysed using one averaged value per litter as the effective statistical *N* (see Zorrilla, 1997). Data analysis and statistics were completed using GraphPad Prism and SPSS software.

3. Results

3.1. Acquisition and baseline

For acquisition (see Fig. 1), a three-way repeated measures ANOVA (group x discrimination rule x percent choice) found a significant main effect of discrimination rule [$F(1,16) = 88.086$; $p < 0.0001$] and percent choice [$F(2,32) = 24.139$; $p < 0.0001$], with a significant interaction [$F(2,32) = 4.023$; $p < 0.0001$]. No other main effects or interactions were significant [$Fs < 1.0$]. For baseline, a repeated measures ANOVA (group x discrimination rule x sessions) revealed only a significant main effect of discrimination rule [$F(1,16) = 10.913$; $p = 0.004$].

3.2. Reversal phase

When data from all groups were considered together (Figs. 1A and 1B), a repeated measures ANOVA (group x discrimination rule x reversal x session) found significant main effects of group [$F(1,15) = 7.722$; $p = 0.014$], discrimination rule [$F(1,15) = 9.957$; $p = 0.007$], reversal [$F(3,45) = 14.371$; $p < 0.0001$], and session [$F(19,285) = 157.833$; $p < 0.0001$]. There were also significant reversal x discrimination rule and session x discrimination rule interactions ($ps < 0.0001$) as well as a significant reversal x session x discrimination rule interaction [$F(57,855) = 1.685$; $p = 0.002$].

We conducted separate repeated measures ANOVAs on the data from groups that initially learned the same or opposite discrimination rule. For Group Same rats (Fig. 1A), significant main effects of group [$F(1,6) = 8.049$; $p = 0.03$], reversal [$F(3,18) = 88.082$; $p < 0.0001$], and session [$F(19,114) = 79.438$; $p < 0.0001$] were found, as well as a significant reversal x session interaction [$F(57,342) = 1.956$; $p < 0.0001$].

For Group Opposite rats (Fig. 1B) significant main effects of reversal [$F(3,27) = 5.805$; $p = 0.003$], and session [$F(19,171) = 99.266$; $p < 0.0001$] were found. Contrary to the results from Group Same above, the main effect of group was not significant [$F(1,9) = 3.111$; $p = 0.112$].

Figs. 1C-1D show that, in general, acquisition of the reversed rule (defined as the number of sessions to achieve greater than 0.7 proportion correct; not all rats acquired according to this criterion in some cases) was for the most part similar, although there were some notable exceptions (Group Same for Reversal 3 and Group Opposite for Reversal 4). These differences were statistically significant as demonstrated by Kolmogorov-Smirnov tests of the maximum difference between the cumulative acquisition distributions ($D = 0.45$; $p = 0.03$ and $D = 0.65$; $p = 0.0004$, for "same" Reversal 3 and "opposite" Reversal 4, respectively). Aside from these exceptions, these data indicate that differences in performance tended to emerge following acquisition of the new discrimination rule.

3.3. Perseverative errors

When all of the perseveration data (incorrect choice of a previously correct lever) from the different groups were considered together (Fig. 1E and F) a repeated measures ANOVA (group x discrimination rule x reversal) found significant main effects of group [$F(1,16) = 13.402$; $p = 0.002$], discrimination rule [$F(1,16) = 40.121$; $p < 0.0001$], and reversal [$F(3,48) = 11.422$; $p < 0.0001$], with a significant reversal x discrimination rule interaction [$F(3,48) = 46.395$; $p < 0.0001$]. Separate analyses of the data from rats initially trained with either "same" or "opposite" discrimination rules found significant main effects of group (MIA vs control) for opposite rats [$F(1,10) = 9.397$; $p = 0.012$], while the effect of group for rats initially trained on the "same" rule approached significance [$F(1,6) = 5.144$; $p = 0.064$]. The ANOVA also found significant effects of reversal for both same [$F(3,18) = 42.417$; $p < 0.0001$] and opposite [$F(3,30) = 8.955$; $p < 0.0001$] rats.

4. Discussion

The present results have clarified the specific nature of reversal-learning impairments in the MIA model. Across reversals, MIA rats performed more poorly than control rats, replicating previous results. In addition, the manipulation of cognitive burden (which discrimination rule was learned initially) had a profound effect on performance, affecting the asymptotic level of acquisition, as well as the character of performance during the reversals. For rats in Group Same, reversal to the opposite rule produced massive decrements in accuracy, with terminal reversal performance not much greater than chance. By contrast, rats in Group Opposite experienced a dramatic decrease in accuracy at reversal outset, but achieved close to their baseline accuracy by the end of the reversal.

The increased difficulty of the "opposite" discrimination rule likely has to do with the suppression of the prepotent tendency to respond to the lever on the same side as the visual cue required by this arrangement. It was not uncommon for our rats to approach the stimulus cue upon illumination, which in the "same" discrimination rule facilitates pressing of the lever on the ipsilateral side. Performance during the "opposite" condition requires disengaging from the cue to move to the other side of the chamber when the levers are presented, an act of inhibition that is likely difficult given the proximity to the ipsilateral lever.

There have been few studies that have explicitly assessed the effect of task difficulty on reversal learning in rodents. Most have inadvertently assayed this variable by comparing discrimination between different types of modalities (e.g., visual vs odor). Not surprisingly, rodents are better at learning odor than visual discriminations (Broadbent et al., 2007; Rozin & Kalat, 1972), although reversal learning is similar once the initial discrimination is learned (Brushfield et al., 2008). One early study also found no difference in reversal of a difficult visual task or an easier spatial task (Sweller, 1973). The results from the present study suggest some benefit from initial training with a more difficult task in terms of subsequent reversal performance, both in terms of overall performance and susceptibility of MIA rats to disruption during reversals. Given the paucity of studies that have explicitly manipulated task difficulty within the same stimulus modality within the context of reversal learning, further work is needed before conclusions can be drawn regarding the role of specific cognitive mechanisms in the performance observed here and how these may interact with MIA in producing impaired performance.

Notwithstanding the profound overall impact of discrimination difficulty on overall accuracy, the performance deficit displayed by MIA rats was similar across difficulty groups. This result indicates that

results from previous reversal experiments (Han et al., 2011; Kleimans and Bilkey, 2018; Wallace et al., 2014; Savanthrapdian et al., 2013; Lins et al., 2018) cannot be explained simply by appealing to difficulties produced by increased cognitive burden. In addition, the general lack of a difference in initial learning, notwithstanding the manipulation of task difficulty, and the similar rate of initial learning across sessions within each reversal, compliments results from other studies that have found no difference between MIA and control rats during discrimination training (Bates et al., 2018; Lins et al., 2018; Kleimans and Bilkey, 2018; Wallace et al., 2014; Wolff et al., 2011; Zuckerman and Weiner, 2005) or initial learning during reversals (Amodeo et al., 2019; Lins et al., 2018), and further indicates that reinforcement learning per se is not compromised in MIA rats. In addition, the increased proportion of perseverative errors (incorrect choice of a previously correct lever) committed by MIA rats is consistent with an analysis of perseverative errors in an odor-discrimination reversal task (Wallace et al., 2014; but see Amodeo et al., 2019). While our results support and expand those from previous studies, further work will be needed to specify the precise nature of the deficits observed here. It would be useful for future studies to manipulate cognitive burden in other types of tasks to further define the nature and boundaries of its interactions with maternal immune activation.

When the present data are considered in the context of previous results from the MIA model, it is clear that behavioural deficits are seen predominantly when reward contingencies change, rendering previously adaptive behavioural strategies unsuccessful. Put another way, the machinery that supports the learning of contingencies between actions and outcomes appears intact, but the information that is gained as a function of feedback for choices cannot be organized into an accurate representation of the current task requirements. This interpretation would explain the rather puzzling array of negative and positive results from MIA studies of learning, which often show intact basic learning but impaired behavioural flexibility when contingencies change. Further support for this interpretation is found in the present result that overall reversal performance did not improve across successive reversals, suggesting a fundamental dysfunction in the ability to organize information and learn from experience.

Recent work points to the importance of the orbitofrontal cortex (OFC) as an organizer of information gained from experience into an abstract “cognitive map” of the current task space (Stalnaker et al., 2015; Wilson et al., 2014). When contingencies change, the new relationships between actions and outcomes must be deduced through experience accumulated over the course of trials and sessions. Evidence suggests that the OFC, with its reciprocal connections with critical reinforcement-learning areas, such as the striatum, hippocampus, ventral tegmental area, and amygdala, plays a fundamental role in this process (see Stalnaker et al., 2015; Wilson et al., 2014, for reviews). Although prior work has shown dysfunction of other cortical areas (Amodeo et al., 2019), predominantly medial prefrontal cortex (Canetta et al., 2016; Meyer et al., 2008; Paylor et al., 2016; Roenker et al., 2011), to our knowledge, no one has specifically assayed OFC function in the MIA model. The specific nature of the deficits in the present study, together with the rather idiosyncratic character of cognitive deficits in the MIA model in general, point towards the OFC as a critical area for future research into impaired behavioural flexibility in the MIA model.

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