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The instrumental role of operant paradigms in translational psychiatric research: Insights from a maternal immune activation model of schizophrenia risk

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Rigorous behavioral analysis is essential to the translation of research conducted using animal models of neuropsychiatric disease. Here we discuss the use of operant paradigms within our lab as a powerful approach for exploring the biobehavioral bases of disease in the maternal immune activation rat model of schizophrenia. We have investigated a range of disease features in schizophrenia including abnormal perception of time, cognition, learning, motivation, and internal state (psychosis), providing complex insights into brain and behavior. Beyond simple phenotyping, implementing sophisticated operant procedures has been effective in delineating aspects of pathological behavior, identifying interacting pathologies, and isolating contributing mechanisms of disease. We provide comment on the strengths of operant techniques to support high-quality behavioral investigations in fundamental neuropsychiatric research.

Key words: operant, schizophrenia, maternal immune activation, animal model, rat

Animal models are crucial to the study of psychiatric disease. They utilize a wealth of genetic, physiological, and molecular methods to attempt to recapitulate aspects of clinical conditions and to elucidate fundamental neurophysiological dysfunction that precipitates onset and maintenance of disease states. Behavior analysis, and operant methods in particular, stand to contribute immensely to the characterization of genetic and other models of psychiatric disease, but this contribution has historically been small due to the divergence of theoretical accounts of the cause of behavior between behavior analysts, cognitive psychologists, and clinical psychiatrists (Ward et al., 2011). More recently, the utility of operant methods has begun to be more fully recognized in parsing subtle behavioral deficits in animal models with relevance to human clinical diagnoses. Operant methods provide a degree of control and specificity which lends itself well to in-depth examination of specific deficits with relevance to human conditions. In addition, due to the ability to keep many features of a task constant while manipulating specific aspects of interest, operant methods are particularly suited to examining the interaction of various cognitive and motivational processes in producing functional impairments (Ward, 2016).

Here we review our recent work using operant methods to dissect the behavioral and neurophysiological phenotype of a particular model of schizophrenia risk. We begin with a brief introduction to schizophrenia and the model we have examined. We then discuss results from experiments that have probed behavioral performances with relevance to deficits seen in patients with schizophrenia. This work, though still not a complete picture of this model, has uncovered aspects of dysfunction in behavior with relevance to negative, cognitive, and most recently, positive symptoms of schizophrenia. A summary of the results from these studies is shown in Table 1. We suggest that a thorough program of behavior analysis of animal models of psychiatric disease is critical to realizing truly translational outcomes. Models are only as good as their behavior. Genetic and molecular sophistication cannot compensate for shallow behavioral

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Table 1

Summary of Operant Findings in Rats Exposed to MIA in Early, Mid, and Late Gestation

INDEX	TASK	MODEL	BEHAVIOR	NEUROBIOLOGY	KEY CONCLUSIONS
Timing	Temporal Bisection	GD15	overestimation of time		• Perception of time is altered, and correlates with sustained attention capacity
		GD10/18	↑underestimation of time with ↓ sustained attention	GD10 ↑L-ornithine relates to timing, attention; GD18 ↓L-ornithine relates to timing	
Sustained attention	Two-choice discrimination	GD10/18	≈ sustained attention		• Timing, cognitive function corresponds with changes in PFC L-arginine metabolism
Working memory			↓working memory maintenance	↑L-citrulline, ↑putrescine relates to ↓working memory capacity	**(Deane et al., 2017, 2021a)**
Motivation	Progressive ratio	GD15	↑ willingness to work under increasing work requirement		• Increased responding
	Random ratio		≈ goal directed behavior, basal excitation, satiety		• No increases in locomotion behavior
Learning	Signaled probability sustained attention (SPSA)		≈ basic learning, sustained attention, or motivation-attention interactions		• Interaction between motivation and cognition not disrupted
	Autoshaping		≈ basic learning		• Intact learning, attribution of salience
	Reversal Learning		≈ basic learning, ↓reversal learning, ↑ perseveration		• Impaired ability to flexibly adjust goal-oriented learning
	Contingency Degradation		↓sensitivity to action-outcome contingency		• Impaired updating of goal-directed behavior
		GD10/18	≈ sensitivity to action-outcome contingency	Absence of a relationship between contingent learning and PFC MAPK	**(Bates et al., 2018; Fisken & Ward, 2019; Millar et al., 2016)**
Sensorimotor processing	Pre-pulse inhibition (PPI)*	GD10/18	≈ PPI	↑PFC MAPK in relation to ↓PPI	• MAPK signal transduction within PFC is important to learning and sensorimotor processing
					(Deane et al., 2021b)

Table 1

Continued

INDEX	TASK	MODEL	BEHAVIOR	NEUROBIOLOGY	KEY CONCLUSIONS
Internal state	Drug discrimination 7.5mg/kg ketamine/saline	GD15	↓ discrimination		• Impaired ability to discriminate ketamine
	Drug discrimination 1, 3, 10, 30mg/kg ketamine/saline		↓discrimination of 3,10 mg/kg doses		• Impaired ability to discriminate between baseline internal state and ketamine at psychomimetic levels
	Satiety protocol		≈ satiety		• Intact ability to discriminate satiety
	Drug discrimination 3.2mg/kg morphine/ saline		≈ discrimination		• Intact ability to discriminate between basal and morphine-induced internal states
	Locomotor assay* 1, 3, 10, 30mg/ kg ketamine		↑ locomotion at 3, 10mg/kg doses		• Discrimination differences not attributable to reduced ketamine sensitivity
					(Meighan et al., 2021)

Note. * non-operant measure; ↑ increase; ↓ decrease; ≈ no change.

analysis. We are heartened that in recent years, the utility of operant methods seems to have been realized by some working in animal models of psychiatric disease. We hope to see many more fruitful collaborations and contributions from behavior analytic methods, and theory, in the years to come.

Schizophrenia and the Maternal Immune Activation (MIA) Model

Prevalent in 0.28% of the global population (Charlson et al., 2018), schizophrenia is a developmental neuropsychiatric disorder arising from a complex interaction between genetic and environmental risk factors. The disease phenotype is considered broad and highly variable and is generally divided into three symptom categories: positive, negative, and cognitive. Positive symptoms describe features of psychosis, including hallucinations, delusions, and disorganized speech and behavior. Negative symptoms are characterized as social withdrawal, blunted or flat affect, anhedonia, and reduced initiative and energy. Finally, cognitive symptoms encompass a broad range of cognitive dysfunctions (Kahn et al., 2015). The pathophysiology of schizophrenia is heterogeneous, and includes dopamine, N-Methyl-D-aspartate (NMDA), and γ-aminobutyric acid (GABA) signaling impairments, among others. Critically, however, the disease mechanisms of schizophrenia are poorly understood (Kahn et al., 2015). Current pharmacotherapeutic options are largely targeted towards attenuating dopamine transmission. This clinical strategy manages positive symptoms, although efficacy is poor for negative and cognitive symptoms and results in substantial unmet need within the patient

population (McCutcheon et al., 2020). Future directions for improving treatment efficacy involve isolating the neurobiology underlying specific symptoms, or symptom clusters (Insel et al., 2010), requiring in-depth investigations into brain and behavioral changes and their functional relationships.

To this end, animal models of schizophrenia are an essential tool for elucidating disease processes. Within our lab we have used the maternal immune activation (MIA) rat model, which recapitulates the effects of prenatal exposure to inflammation through administration of a viral mimetic, polyinosinic-polycytidylic acid (polyIC). Substantial research has found that mid-gestation polyIC exposure in rats (gestational day [GD] 15) induces a range of positive, negative, and cognitive phenotypes in conjunction with neurobiological changes analogous to those observed in schizophrenia (Haddad et al., 2020). Early and late rat models (GD10 and GD18/19) are also being used to understand the gestational window of vulnerability to this risk factor, however investigations are preliminary (da Silveira et al., 2017; Deane, Potemkin, & Ward, 2021; Hao et al., 2019; Rahman et al., 2020). Overall, the MIA model exhibits high construct, face, and predictive validity (Haddad et al., 2020), and when used in combination with an array of operant analyses, we have found it to provide powerful insight into the functional impairment and pathophysiology of schizophrenia.

Timing and Cognition

A common yet understudied trait of schizophrenia is abnormal perception of time. In the case of prospective timing of interval durations (durations in the range of seconds to minutes), individuals with schizophrenia underestimate the passage of time, corresponding to a subjective quickening of time (Thoenes & Oberfeld, 2017). Changes to the timestamp of incoming sensory information has implications for how the external world is perceived, and in the case of schizophrenia, this is theorized to contribute to features of psychosis (hallucinations and delusions), in addition to learning deficits (Gómez et al., 2014; Roy et al., 2012).

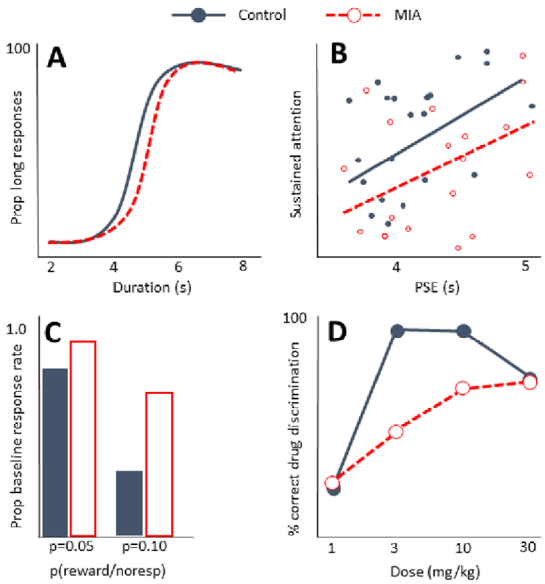
Current knowledge surrounding the biological instantiation of timing is limited, and as such, research exploring functional and mechanistic contributions to temporal pathology is needed. Functional studies indicate a substantial overlap of areas implicated in timing and in cognitively demanding tasks (Alústiza et al., 2017), with the likelihood of a region being activated during timing being dependent on the extent of cognitive demand (Gómez et al., 2014). Given cognitive impairment is a hallmark feature of schizophrenia (Insel, 2010), it is important to explore the extent to which general cognitive disfunction may be related to impaired timing. In addition, because accurate timing requires the accurate function of a number of cognitive processes, such as attention, working memory, and decision making, assessing timing can provide a window on the state of function of these processes in models of disease and can give clues as to further areas of study (Ward et al., 2009; Ward, Kellendonk et al., 2012).

The temporal-bisection task, originally created by Church & Deluty (1977), is a commonly used tool in patient studies and has been critical in our exploration of temporal perception differences in the MIA rat model. In this task, rats are trained to discriminate between two anchor cues of defined durations, differentiating 'short' (e.g, 2 s) and 'long' (e.g., 8 s) durations by responding on respective levers. Following this preliminary training, a range of unreinforced intermediate durations are presented to be categorized as being subjectively more like either the short or long anchor cue duration. Plotting the proportion of long responses as a function of sample duration generally produces an increasing sigmoidal function which can be quantitatively modeled to yield measures of multiple separable components of temporal processing, including accuracy (also known as the point of subjective equality; PSE) and precision (variability; Blough, 1996; Chiang et al., 2000; McClure et al., 2005; Ward & Odum, 2005; 2006; 2007; Ward et al., 2009).

Using the bisection task with 2 s and 8 s auditory anchor cues (intermediate cues: 2.6, 3.2, 4, 5, 6.4 s), our group has identified that exposure to MIA at GD10, GD15, and GD18 impairs accuracy of timing in rats (Deane et al., 2017; Deane, Liu et al., 2021). Both early and late exposure to MIA (GD10/18) resulted in animals underestimating the passage of time as observed in individuals with schizophrenia, indicating that the model is accurately recapitulating aspects of the disease (Deane, Liu et al., 2021, see Fig. 1A).

Figure 1

Key Outcomes of Operant Experiments



Note. (A) MIA rats exhibit abnormal perception of time (a subjective quickening of the passage of time relative to control animals). (B) Association of temporal accuracy (PSE = point of subjective equality) with sustained attention. Higher PSEs (indicative of impaired timing) corresponded with poorer sustained attention capacity (a greater value on the y axis). (C) MIA rats exhibit reduced sensitivity to action–outcome contingencies. When the probability of reward was increased to 0.10 for withholding lever presses, MIA rats continued to respond at a high rate relative to the notable reduction exhibited by control animals. (D) MIA rats show impaired discrimination of ketamine only at psychotomimetic doses.

To explore cognitive involvement in timing, we employed a simple two-choice visual discrimination paradigm. Rats were trained to discriminate between two lateralized LED light stimuli in the presence of the house light. Cue duration was systematically decreased across sessions (2, 1, 0.5, 0.25 s) to index sustained-attention capacity, and following retraining to a baseline 2 s cue, a delay between cue cessation and lever extension was systematically increased across sessions (2, 4, 8, 16 s; Kahn et al., 2012) to index working memory maintenance capacity.

Analysis of the two-choice visual discrimination data revealed that relative to control performance, exposure to MIA resulted in rats exhibiting poorer working-memory maintenance capacity, however basal sustained-attention capacity was not impacted. Data from these cognitive tasks were then correlated with temporal accuracy (PSE) data from the bisection task, in order to explore the functional relationship between these measures. We found that irrespective of treatment, temporal accuracy correlated with sustained-attention capacity, representing the first direct isolation of a timing–attention relation in rodents. In addition, greater temporal underestimation in MIA rats corresponded with poorer sustained-attention capacity (see Fig. 1B), supporting the previous work showing that the extent of cognitive deficits mediates the magnitude of timing impairment (Lee et al., 2009; Papageorgiou et al., 2013). Finally, despite previous work identifying working memory as a key contributor to temporal accuracy, no relation was found between working-memory capacity and temporal accuracy in either MIA or control rats. Rather than negating the importance of working memory in timing, we believe this result reflects that the short durations used in the bisection task (2 and 8 s) do not recruit working-memory function and as such we have not captured this relation. In another rodent model of schizophrenia risk, deficits in timing occurred only following longer duration temporal stimuli (10 s or greater; Ward et al., 2009), suggesting that a relation between working memory and timing may be more apparent if longer duration stimuli are used. Ultimately, these findings support the idea that temporal perception and attentional deficits in schizophrenia may have a common pathological mechanism, and commend the MIA model as a tool for elucidating this issue in future studies (Deane, Liu et al., 2021).

Timing, Cognition, and L-Arginine

Research has established a multitude of postmortem neurobiological changes in schizophrenia, however the functional consequences of many of these changes remain unexplored. L-arginine is a ubiquitous and metabolically versatile amino acid implicated in processes including neurotransmitter functioning, synaptic plasticity, and regulation of cellular health (see Liu et al., 2016, for review), and which is altered in the brains of individuals with schizophrenia (Pérez-Neri et al., 2006; Yuan et al., 2010). Using tissue from prefrontal cortex (PFC), we investigated

the role of arginine metabolism in timing and cognition in MIA via high-performance liquid chromatography (HPLC) and liquid chromatography–mass spectrometry (LC/MS). Neurochemical data was correlated with outcomes from the temporal-bisection task, as well as the two-choice visual discrimination task (sustained attention, working memory maintenance). We found evidence of changes in metabolites L-citrulline and putrescine in MIA rats, which correlated with impaired working-memory maintenance. In addition, glutamate levels were elevated in GD10 rats, and decreased in GD18 rats respective to controls, indicating that aspects of arginine metabolism may be differentially impacted depending on whether MIA is incited early or late in gestation. These outcomes replicate trends previously observed in brain tissue of patients (Liu et al., 2016; Pérez-Neri et al., 2006), and provide the first evidence that altered arginine metabolism has implications for cognitive functioning following exposure to an inflammatory risk factor for schizophrenia (Deane, Liu et al., 2021).

Outcomes from this study also implicate arginine metabolite L-ornithine in the timing-attention relation irrespective of disease. L-ornithine levels correlated with both temporal accuracy and sustained-attention capacity in GD10 MIA and GD18 controls, and exclusively correlated with timing in GD10 controls. This set of findings forms preliminary evidence to suggest that L-ornithine may be involved in timing or be regulated by a related mechanism. L-ornithine has previously been implicated in circadian timing however this is the first link to temporal perception shifts (Deane, Liu et al., 2021).

Motivation and Learning

Impaired motivation is a core negative symptom of schizophrenia associated with poor functional outcomes, and which responds poorly to treatment (Fervaha et al., 2015; Foussias et al., 2015). Traditional perspectives considered anhedonia (reduced intensity of pleasure) to be a driving factor in motivational impairment in schizophrenia (Strauss, 2013; Strauss et al., 2014), however, research into hedonic responses to reward suggests the anhedonia hypothesis of schizophrenia is erroneous. Findings from both animal models and patients indicate that consummatory pleasure is intact in the face of reduced engagement in motivated behaviors (Strauss & Gold, 2012; Ward, Simpson et al., 2012), indicating that avolition (diminished will to initiate or persist in goal-oriented tasks) may be a more likely contributing factor. In addition, a large body of work has found that dopamine transmission, which is compromised in schizophrenia, is related to motivation to engage in behavior, but not hedonic processes (Berridge and Robinson, 2016; Salamone et al., 2007; 2015; 2016). To explore this issue in MIA rats, we employed a multiparadigm approach to delineate the contribution of different domains to motivated behavior (Millar et al., 2016).

First, we explored basal motivation using a progressive-ratio paradigm. In this task the number of lever presses required to obtain reward is doubled over successive trials within an operant session, systematically increasing work requirements to index the motivational 'breakpoint' (maximum number of presses for a single reinforcement) for an individual. Contrary to the idea of decreased motivation, we found that MIA rats seemed more willing to work in the face of increasing work requirements. Relative to controls, MIA rats made more total responses, had higher breakpoints, and received more rewards, suggesting higher motivation levels. What was unclear, however, was the driving factor behind these putative motivational increases. One hypothesis was that MIA increases behavioral output, resulting in increased but non-goal-directed lever pressing.

To test whether increased willingness to work was attributable to increased behavioral output, we exposed the same cohort of rats to a random-ratio paradigm. In this task, both levers were extended, however one was 'active', delivering rewards on a random-ratio (RR) schedule, and the other 'inactive,' which did not deliver any rewards. The average response requirement for reward was increased every 2 days (RR5, RR15, RR30, RR60). We found that MIA and control performance did not differ in this task; animals targeted their responses to the active lever, and willingness to work increased with RR demands. This revealed that MIA lever pressing was not driven by a basal increase in activity, and that MIA behavior was goal-directed.

Another possible account for increased willingness to work in MIA rats is enhanced attribution of incentive salience to reward-associated responses (Berridge, 2007; Berridge and Robinson, 1998). To assess incentive salience, lever-press naïve rats completed an autoshaping experiment. During this experiment, rats were exposed to trials where one lever designated S+ was extended for 10 s, followed by reward, or the other lever designated S- was extended for 10s, without subsequent reward delivery. Progressive association of the S+ lever with food delivery results in predictive gnawing and pressing targeted towards the S+ lever, in the absence of such a response to the S- lever, ultimately indicating attribution salience. Lever pressing on the S+ lever did not differ between MIA and control rats, suggesting that enhanced attribution of incentive salience was not a driving factor in increased willingness to work.

Goal-oriented behavior is informed by an understanding that outcomes are contingent upon specific actions, however this is not a static process; rather, actions must be adaptively updated to achieve goals in an ever-changing environment. While we knew that MIA rats were able to engage in goal-directed behavior, the extent to which this behavior was flexible was unclear. To assess this, we used a contingency-degradation task. In this task, rats were trained to lever press at a steady rate on an RR20 reward schedule, where the probability of reward for each press was 0.05. Subsequent trials presented the RR20 schedule concurrently with noncued free rewards, which became available according to a specific probability for every second that no response was made. Free reward probabilities were set at 0.05 and 0.10 for five sessions each. Sensitivity to action–outcome contingency is represented in the magnitude of behavioral adjustment; response rate should decrease as increased benefit can be obtained through reduced effort. As seen in Figure 1C, we found that while lever pressing reduced for both groups in response to the free reward levels, MIA rats were lever pressing significantly more than controls at the 0.1 level, indicating that they were less sensitive to the contingency between their behavior and resulting outcome. Given this result, increased willingness to work in MIA animals can be attributed to a poorer ability to detect changes in action–outcome contingency, and not elevated motivation (Millar et al., 2016). It is important to note that the deficits seen here are subtle, and should not be interpreted as indicating a catastrophic failure in reward learning or some other related process. MIA rats still modulated their behavior in response to changes in contingencies, just not as adaptively as controls. These subtle differences mirror those seen in schizophrenia, and require nuanced parametric manipulation to uncover, further commending operant methods to this type of work.

Sensitivity to Action-Outcome Contingencies and the Mitogen Activated Protein Kinase (MAPK) Cascade

The MAPK signaling cascade is a ubiquitous feature of the brain implicated in signal transduction, synaptic plasticity, learning and memory (Sweatt, 2001). Altered MAPK expression has been found in the postmortem tissue of individuals with schizophrenia (Funk et al., 2012; Kyosseva et al., 1999), however the role of this disease feature in functional deficits is largely unexplored. Using GD10 and GD18 rats, we investigated PFC MAPK (ERK1/2) expression via western blotting in relation to sensitivity to action–outcome contingency (contingency-degradation paradigm), as well as prepulse inhibition (PPI), an index of sensorimotor gating, which displays a robust and canonical impairment in schizophrenia. MIA was not found to alter basal MAPK expression, however lower MAPK levels in controls corresponded with greater adaptive learning capacity, a relationship which was absent in MIA rats. We also found that higher MAPK levels corresponded with poorer sensorimotor gating exclusively in MIA rats, irrespective of time of MIA. With MAPK as a gross marker of signal transduction, these findings suggest that alterations in cellular communication within PFC are detrimental to sensory processing and learning, providing the first evidence that basal MAPK expression relates to functional outcomes following exposure to a risk factor for schizophrenia. On the basis of previous research, we believe that altered MAPK expression may be reflective of NMDA receptor dysfunction, however additional research is needed to explore whether MAPK may be independently contributing to pathology (Deane, Potemkin, & Ward, 2021).

Interaction of Motivation and Cognition

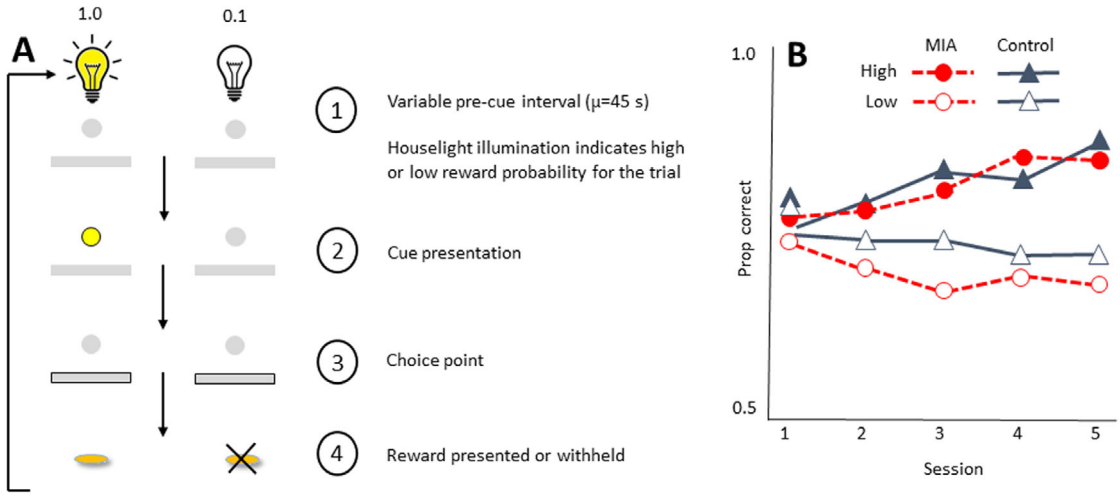
One aspect of functioning that is particularly compromised in patients is the ability of motivationally significant stimuli to modulate cognitive performance (Barch, 2005; Barch & Dowd, 2010; Gard et al., 2007). Thus, motivation–cognition interactions are particularly important to address in animal models of the disease. We recently developed a paradigm which explicitly assays one such motivation–cognition interaction. In our signaled probability sustained attention (SPSA) task (Ward et al., 2015; see Fig. 2A), we test the ability of cues which signal the probability of correct responses on a trial-by-trial basis to modulate attentional performance. We have demonstrated that intact rodents display increased accuracy on high-reward probability trials as compared to low-reward probability trials. We have interpreted this increased accuracy as indicative of increased recruitment of attentional resources on high probability trials. We have further shown through a number of experiments that areas which are crucially involved in attention are necessary for performance of this task (Hall-McMaster et al., 2017; Tashakori-Sabzevar & Ward, 2018; Ward et al., 2015).

As the deficient interaction of motivation and cognition is likely a critical component of functional deficits in patients, we recently tested MIA and control rats on our SPSA task (Bates et al. 2018). To our surprise, we found no impact of MIA on performance in the task. Both MIA and control rats showed normal learning of the task, and intact modulation of attention performance by signaled reward probability (Fig. 2B). We further showed no difference in performance during an extinction or reacquisition phase of this task. These results indicate that, in our hands, basic learning, extinction, sustained attention, and motivation–attention interactions are all intact in the MIA model.

These results highlight the importance of rigorous tests of behavior in animal models of psychiatric disease (Ward et al., 2011), but they were also surprising because they did not show any impairment in aspects of performance that have been shown to be impacted in schizophrenia. This negative result is likely due to the lack of the MIA model to reconstitute the full range of changes that produce schizophrenia. Although numerous behavioral deficits have been reported in this model, it does, in the end, only model one risk factor,

Figure 2

(A) Schematic of the Signaled Probability Sustained Attention Task, Adapted from Ward et al., 2015



Note. Trials were initiated with both levers retracted. (1) During a variable pre-cue interval, the houselight state (on or off) cued either a high or low reward probability for making a correct choice. (2) The cue light indicates which lever will be rewarded at the choice point. (3) Levers extend, requiring animals to make a choice. (4) Reward delivery is dependent on the animal selecting the cued lever. (B) Representative signaled probability sustained attention (SPSA) performance during acquisition for MIA and control rats.

and is therefore unlikely to be able to recapitulate all of the changes and deficits seen in the disease. Other studies have demonstrated that deficits relevant to disease states are much more likely to be seen following exposure to a second or multiple risk factors, known as "hits" (Abazyan et al., 2010; Giovanoli et al., 2013; Ibi et al., 2010; Meyer and Feldon, 2012). As predisposing factors coupled with other precipitating events are required to produce symptoms diagnosed as a disease, the more of these factors and events we can model, the better chance we have of observing disease-relevant phenotypes in our models. Thus, further work should assess the impact of multiple hits on the role of MIA in producing schizophrenia-relevant syndromes.

Behavioral Flexibility

Another aspect of functioning that is impaired in schizophrenia is behavioral flexibility (Everett et al., 2001; Pantelis et al., 1999; Prentice et al., 2008). Behavioral flexibility is the ability of an organism to adapt its behavior to changing situations. It is critical to adaptive functioning in an unpredictable world. Behavioral flexibility is often assayed using a reversal-learning task. In these tasks, rats are taught to behave according to a given rule. Following learning, the rule is reversed, and the subject must behave in a manner opposite to the initial learning. Deficits on this task are indicative of impaired behavioral flexibility and are seen in schizophrenia (Waltz and Gold, 2007).

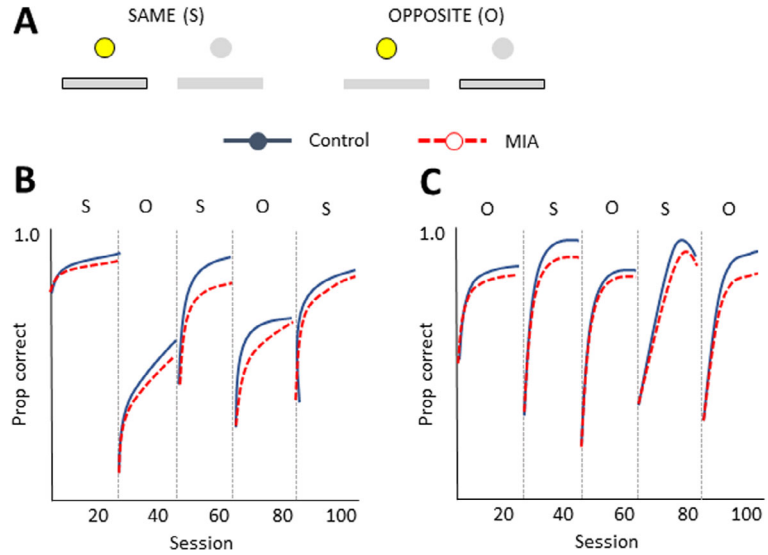
Kleinmans and Bilkey (2018) tested MIA rats in a T-maze reversal procedure and found no difference between control and MIA rats in acquisition of the learning rule, but impaired performance of MIA rats during the reversal. There are a number of aspects of performance in reversal learning that, if impaired, could lead to performance deficits. Most often, deficits in these paradigms are taken as indicative of some impairment in reinforcement learning. Of the multiple components involved in reinforcement learning, compromised function in any of them could impair performance. For example, in order to perform a reversal task, rats must first learn the initial relationship between the response and the reward. This presumably involves holding some representation of this information within working memory during execution of the task and updating this information with subsequently experienced relevant detail. In order to learn from rewards, rats must be able to form and hold some type of outcome representation which serves to guide future decisions. All of this must then be reversed during the reversal phase. New learning must take place. Another possibility is that it simply takes more cognitive resources to perform under the increased cognitive burden associated with the reversal phase (Kleinmans and Bilkey, 2018). According to this interpretation, reinforcement learning is intact, but rats are unable to marshal or recruit the necessary cognitive resources to perform the reversal phase because it involves learning a new rule, and this new learning may be interfered with by the initial learning. In other words, rats must remember not to perform the previously learned action, while executing the newly learned alternative.

We recently tested whether the reversal deficit shown in MIA rats could be replicated under conditions designed to assess the specific nature of the underlying processes which are affected during this task (Fisken and Ward, 2019). We were particularly interested in looking at the interaction between cognitive burden during the learning and reversal phases and performance. We trained control and MIA rats in a simple discrimination procedure in which they were rewarded for pressing a lever that had been cued at the beginning of the trial. There were two groups, group Same and group Opposite (Fig. 3A). As seen in Figure 3 B and C, these groups differed in the specific discrimination rule that was learned during the initial learning phase. Group Same learned to press the lever on the same side as the cue light (i.e., left cue, left lever), while group Opposite learned to press the lever on the opposite side of the cue light (i.e., left cue, right lever). These contingencies were then reversed over several phases.

The results showed that the group that learned the Opposite rule were slower to learn the task overall and had a significantly lower baseline accuracy than rats that learned the Same rule, but there were no differences between MIA and control rats, indicating that the rats are not impaired in the basic processes involved in learning the task. During the reversal phase, rats that learned the Same

Figure 3

Schematic and Results of Reversal Task



Note. (A) Schematic showing light and lever associations used in the reversal task (Fisken & Ward, 2019). MIA rats exhibit impaired reversal learning. Average learning trends can be observed for animals who started with (B) the Same discrimination rule, and (C) the Opposite discrimination rule.

discrimination rule experienced a massive performance decrement when reversed to the Opposite rule and were barely able to achieve chance accuracy by the end of the reversal. When reversed back to the Same rule, the rats' accuracy improved steadily until they were at baseline accuracy by the end of the reversal. In addition, MIA rats had significantly impaired reversal performance across reversals. By contrast, rats that learned the Opposite rule experienced a performance decrement when reversed to the Same rule, but quickly rebounded to their baseline level of accuracy. Differences between MIA and control rats were similar to those in group Same, though not significant, in this group as well. There were also significant differences in the number of perseverative errors (choice of a lever that had been correct in the previous reversal) between MIA and control rats.

Taken together, these results indicate that, notwithstanding the overall impact of discrimination difficulty on accuracy, MIA rats are impaired relative to control rats in a reversal procedure. The manipulation of discrimination difficulty in this experiment was meant to address the possibility that overall learning is intact, but the increased cognitive burden during the reversal phase taxes MIA more than control rats. Our results indicate that there is an additional impairment in MIA rats above and beyond the impact of cognitive burden introduced during the reversal phase. This impairment is not in learning the initial task, but is specific to the reversal phase. The similar rate of acquisition of the reversed rule between MIA and control rats in both the Same and Opposite groups suggested that learning of the new rule is not compromised either. Instead, it is the asymptotic performance that seems to be affected during reversals.

The results of this experiment, when considered in relation to the rather puzzling array of results from assays of cognitive performance in MIA rats, indicate that performance decrements are most likely to be observed when a learned contingency changes in some way. In most studies, basic learning is intact in MIA animals, but performance decrements are manifest when something about the situation changes, when a new rule must be learned which changes the situation in relation to the previously learned rule. We suggest that this highly specific deficit points to impaired function of orbitofrontal cortex, which is crucial in

the appreciation of new contingencies and in the formation of a "cognitive map" of the current task space (Stalnaker et al., 2015; Wilson et al., 2014).

Toward Modeling Psychosis

One of the most difficult aspects of schizophrenia to model in nonhumans is psychosis. This is because of the difficulty of ascertaining subjective internal state in nonhumans in a rigorous fashion (Canetta and Kellendonk, 2018; Ferreira et al., 2020; Ritskes-Hoitinga et al., 2020). Psychosis is considered a uniquely human aspect of the disease, and includes changes in subjective internal states, perceptual processing, and behavioral abnormalities. Current treatments are successful in ameliorating psychotic episodes in patients, but have significant side effects and produce functional impairments due to their blockade of a majority of D2 receptors in the brain. In order to develop less harmful treatments, specific mechanisms underlying psychosis need to be determined, which necessitates the use of nonhuman animal models which can creatively approach this problem. The key difficulty in assessing subjective internal state is figuring out how to ask a rat "how it feels" and obtain a rigorous response. If this problem could be solved, one might expect to be able to determine whether models that recapitulate specific aspects of disease risk produce subjective internal states that are analogous to aspects of human psychosis. If this could be shown, we would be one step closer to developing models in which mechanisms of psychosis could be isolated and therapeutic strategies pursued.

We recently combined the MIA model of schizophrenia risk with a classic operant paradigm to try an innovative new approach to this problem (Meighan et al., 2021). We took advantage of the drug-discrimination paradigm, a method that trains rats to respond on one lever in the presence of saline, and another lever in the presence of a drug (Stolerman et al., 2011). In this paradigm, the only stimulus available to the rat to give them information about which condition they are in is the subjective internal state generated by the drug. Decades of research has shown that this paradigm is exquisitely sensitive to variations in subjective internal state produced by various drugs, and doses of the same drug (Colpaert, 1999; Solinas et al., 2006; Stolerman et al., 2011). We reasoned that this paradigm would provide a sensitive measure for our purposes. In order to determine whether the subjective internal state of MIA rats might be similar to the internal state of psychosis as experienced in schizophrenia, we took advantage of the well-known fact that administering the NMDA antagonist ketamine in subanaesthetic doses in humans produces acute psychosis that is indistinguishable from that experienced in schizophrenia (Krystal et al., 1994). We reasoned that if the subjective internal state of MIA rats is similar to that experienced in schizophrenia, they would be impaired in their ability to discriminate a dose of ketamine that produces psychosis in humans. The neurobiological mechanism of ketamine in humans is conserved in rats, therefore we were confident that the effects of the particular dose could be interpreted in a similar fashion.

We trained MIA and control rats to discriminate 7.5 mg/kg ketamine from saline. We found that MIA rats were impaired in learning this discrimination. Fewer MIA rats acquired the discrimination overall, and the asymptotic level of performance by those who did acquire was lower than for controls. Ketamine has a unique dose-effect profile, with low doses producing qualitatively different effects than higher doses. In order to establish whether the impaired discrimination was specific to the psychotomimetic dose of ketamine, we tested our rats in a dose-effect phase in which daily sessions of the 7.5 mg/kg training dose were alternated with a testing dose. We tested the effects of 1, 3, 10, and 30 mg/kg. MIA and control rats showed equivalent discrimination of the 1 and 30 mg/kg doses, but MIA rats were impaired at discriminating the intermediate doses, those which correspond to psychotomimetic doses in humans (Fig. 1D). These results strongly suggest that the basal subjective internal state of MIA rats is similar to that produced by a psychotomimetic dose of ketamine.

Manipulations that model disease risk factors can have multiple and varied effects, and it is important to isolate the specific psychological mechanisms which underlie any observed effects, as outcomes can be confounded with unknown impacts of the manipulations. In our case, perhaps MIA rats were less able to

discriminate ketamine than control rats because the MIA manipulation renders them less able to discriminate their own subjective internal state generally. If this were the case, we would predict the results we obtained without needing to posit a psychosis-like subjective internal state.

In order to test this, we tested MIA and control rats in a satiety protocol in which rats were trained to press a lever for food reward. Before the satiety test, we gave rats free access to 20 g of the food pellets. Both control and MIA rats decreased their response rates during the session from baseline, but there was no difference between groups. These results indicate that MIA rats are just as able as control rats to discriminate their own subjective internal state.

Perhaps MIA rats are impaired at learning the drug discrimination procedure generally, in which case we may have obtained the impaired performance we saw. To test this, we trained MIA and control rats to discriminate 3.2 mg/kg morphine from saline. There was no difference in acquisition or asymptotic performance between MIA rats and controls, indicating that MIA rats are not impaired in learning to discriminate drug from saline generally.

Finally, we tested whether MIA rats were less sensitive to ketamine generally than control rats. We tested rats in a locomotor assay after injecting them with 1, 3, 10, or 30 mg/kg ketamine. We found that MIA rats only differed from control at the intermediate doses, as in our first study. However, MIA rats were *more* sensitive than controls to the locomotor enhancing effects of ketamine at these doses. These results indicate that the results from the ketamine discrimination experiment cannot be due to a decreased sensitivity to ketamine generally.

Together, the results of this study indicate that MIA rats are impaired at discriminating a dose of ketamine that produces psychosis in humans from saline. This impairment is not due to an impaired ability to discriminate subjective internal state generally, to impaired ability to learn the drug discrimination procedure, or to a decreased general sensitivity to ketamine. We suggest that our results strongly indicate that the subjective internal state experienced by MIA rats is similar to that experienced in human psychosis. These results provide a methodological basis for exploring the impact of MIA on subjective internal states and related behavioral phenomena such as human psychosis, and could provide means for better understanding neurobiological or molecular mechanisms of this phenomenon as it relates to schizophrenia (Kangas & Maguire, 2016).

The Utility and Necessity of the Operant Tradition in Research on Neuropsychiatric Disease

In the 90 years since its inception, operant methodology and theory have developed a wealth of resources for the study of neuropsychiatric disease, particularly with respect to translational work. Beyond fundamental disease phenotyping, behavioral metrics provide a functional readout of factors related to etiology and pathology, as well as enabling quantification of the impact of pharmacological agents or treatment manipulations.

The principal strength of operant work is the high level of control conferred by the operant environment. Using simple variations in stimuli and schedules of reinforcement, it is possible to index a broad range of behavior and thus present a complex picture of disease. Application of this approach within our lab has established the heterogeneous effects of prenatal MIA exposure by detecting impairments in learning, memory, and cognition, as well as perception and internal states.

Reliable isolation of effects is a common challenge within the field of behavioral sciences, however we have found that implementing well-designed operant paradigms produces robust and replicable behaviors. The strength of the operant approach is commended by its sensitivity in detecting small or nuanced effects present in the MIA model. It is now accepted that exposure to multiple risk factors, or 'hits,' are required for clinical symptoms of schizophrenia to manifest, however single hits, such as MIA, are still able to perturb brain development (Maynard et al., 2001). As such, we have found the operant environment has sufficient sensitivity to index single-hit pathology following MIA exposure. This sensitivity has also been essential in our exploration of the outer window of vulnerability to MIA, where we have observed that the disease profile is attenuated relative to mid-gestation insult.

An operant approach also offers superior insight into disease via its ability to delineate and quantify separable aspects of cognitive functions. The neuropathology incited by risk factors for schizophrenia has vast functional consequences. Functional pathology may directly impair interrelated processes or have down-stream repercussions. A stepwise training approach within an operant environment enables the progressive building of complex behavior as a functional index, however observing task acquisition across time also informs whether fundamental impairments within processes such as learning, memory, or attention may be related to disease features of interest. In addition, the ability to record trial-by-trial multisource feedback also contributes to a quantitatively rich contextualization of disease. Recording trial-by-trial lever press responses, head entry latency, an index of motivation, and choice response latency, an index of decision making, among others, provides numerous sources of information which can be gleaned to inform the dissection of the underlying processes and to rule out certain interpretations.

A central goal of translational work is to establish disease phenotypes via robust paradigms, thereby establishing rigorous baseline measures against which interventions can be assessed. Adoption of such standards supports the replication and generalizability of translational findings, strengthening the characterization of a given model. Operant paradigms provide a replicability and standardization that is crucial to this line of work and provide parametric manipulations that can distinguish subtle deficits in animal models that are not detected with more gross behavioral measures, allowing for further partitioning of behavioral processes into their functional aspects. This is particularly important in eliminating alternative explanations for behavior that are unrelated to the mechanisms and processes of interest, but can often drive behavioral changes and lead to spurious conclusions. This has led to a bottleneck in translational research from laboratory to clinic. Use of methods in animals that are directly analogous to those used in humans will help to ameliorate this disappointing trend. Furthermore, more widespread use of these paradigms will provide an empirical foundation from which to mine the rich theoretical work from the operant tradition, leading to further refinement in theory and methods to provide powerful and impactful insights into neuropsychiatric disease.

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