The Development Of A Match To Sample Memory Task And Test Of Impulsivity To Investigate Rat Models Of Schizophrenia

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Abstract

Animal models of schizophrenia have been developed using chronic exposure to the dissociative anesthetics phencycladine (PCP) and ketamine to induce psychosis in rats. Preliminary research in our laboratory has shown marginal effects of low doses of PCP on the rat P300 event related potential (ERP) similar to those found in human male schizophrenics. As part of a broader program of research investigating the P300 ERP in a rat model of schizophrenia, we have been developing a battery of behavioral paradigms to test for memory deficits and impulsiveness that can be used to differentiate schizophrenic-like behavior from normal behavior in rats. The present research is directed toward developing a Y-maze match to sample (MTS) and a two lever MTS paradigm to screen for memory deficits. In these tests the rat receives a water reinforcer only if it chooses to run to the alley that was lighted or press the lever that was lighted during the sample phase. Memory is tested by inserting a delay interval during which the light cue disappears and the response is prevented. We are also developing a test of impulsivity in which the rat must inhibit a nose poke response until the third brief presentation of a light to obtain a water reinforcer. Early nose pokes result in a time out. Olin Hall construction delayed the initiation of this experiment. Accordingly preliminary results will be presented.

Experiment I

Rationale and Goals

Previous research in our laboratory has shown that rats quickly learn to use visual cues (e.g, run to the lighted maze arm) in Y-maze learning and that correct performance on this task can be disrupted by pharmacological manipulations. Last year we evaluated a delayed match to sample (DMTS) task using spatial cues that the rats learned quickly. However, their spatial memory is so well developed, based on species specific foraging behavior ,that their performance was nearly perfect even after long delays. Since the goal of the research is to develop a paradigm that establishes a normal range of short term memory (about 20 seconds) that can be disrupted by pharmacological interventions, the spatial DMTS task was unsatisfactory.

The present experiment uses the visual task of running to the lighted arm of the maze but introduces a delay interval before running can occur. The opaque doors of the maze were replaced with translucent plexiglas doors so that the rats could see which arm of the maze was lighted but not run until the doors were opened. By programming a delay interval during which the light in the correct arm was turned off before the door opened, we could establish memory intervals during which the rat must remember the location of the cue. To be effective in testing acute drug effects and chronic pharmacological manipulations designed to induce an animal model of schizophrenia , the paradigm must be able to generate similar memory effects after multiple assessments at different delay intervals.

The purpose of Experiment 1 was to evaluate the efficacy of a Y-maze Visual DMTS paradigm as a test of memory in rats.

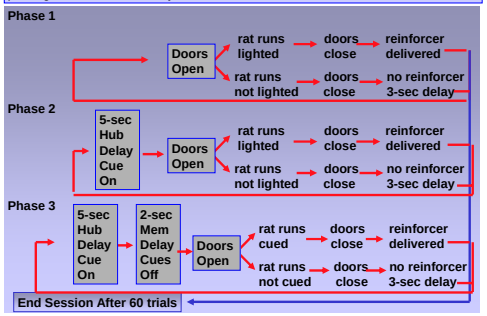

Figure 1: Flow chart of the contingencies in effect during daily training sessions

Figure 2: The Coulbourn Y-Maze system.

Figure 3: The nose poke module and water dipper

Methods Highlights

Subjects

Seven female blue spruce hooded rats with previous experience in the Y-maze served as subjects in this experiment. They were individually housed with free access to food and water except for 23.5-hours of water deprivation prior to each session to establish water as a reinforcer.

Apparatus

All training and testing was conducted in four Coulbourn automated Y-mazes equipped with photocells to monitor the rats position, automated doors to each alley and water dippers with cue lights at the end of each alley. (See Figure 2)

Procedures

In Phase I the rats were trained to run to the lighted arm of the maze for 4-sec access to water reinforcement. Each daily session terminated after about 60 trials. Following each session rats were given an additional 15-minutes free access to water.

After attaining stable correct performance (90% correct choices)Phase 2 began. In Phase 2, only the door to the alley they were currently in opened while the doors for the choice alleys remained closed ,with the correct alley cue light on (Hub Delay). After 5-seconds the choice doors opened. Following door opening the cue light remained on. In Phase 3 we introduced, after the hub delay, a 2-second memory delay interval during which the cue light was turned off and the doors remained closed. During this delay the rat was required to remember which alley was lighted to make the correct choice.

Figure 1 summarizes the contingencies in effect during daily sessions.

Results & Conclusions Summary

Figure 4 presents the total correct responses in each arm of the maze for the three phases of Experiment I across training session for each of the seven rats. Inspection of Figure 3 illustrates the following:

- *The rats learned the response of running to the lighted arm and relatively quickly achieved asymptotic levels of correct responding.*
- *The introduction of the 5-second hub delay disrupted performance briefly followed by a rapid recovery of asymptotic performance.*
- *The introduction of the 2-second memory delay with the cue lights off disrupted performance in all seven rats.*

At the present time we are continuing to run this experiment and anticipate the rats will return to asymptotic performance with the 2-second delay, at which time we will increase the delay. Once a delay from which they cannot recover asymptotic performance is determined we will begin pharmacological manipulations.

- While further data is needed based on the present findings it appears that the visual DMTS task will be an effective paradigm to test for memory deficits that can be used to differentiate schizophrenic-like behavior from normal behavior in rats.

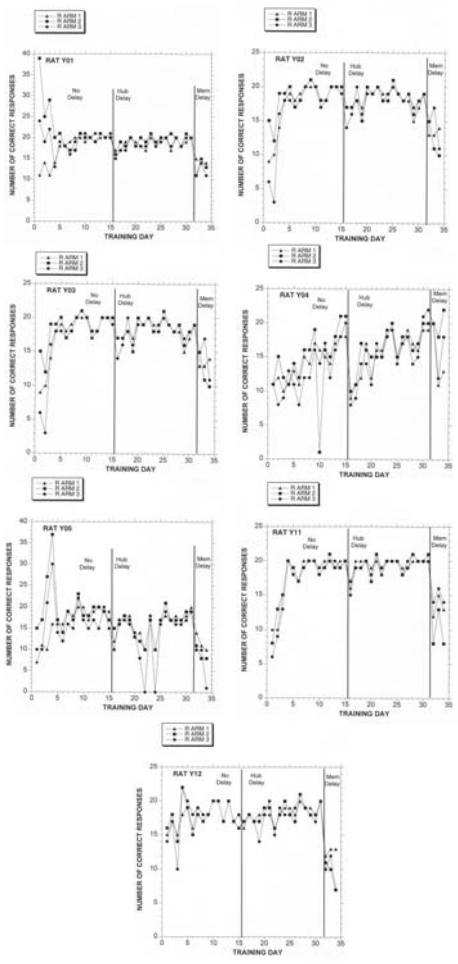

Figure 4: The total correct responses in each arm of the maze for the three phases of Experiment I across training session for each of the seven rats.

Experiment 2: Rationale and Goals

The purpose of Experiment 2 was to develop a test of impulsiveness that could be used in the battery of tests for the animal model of schizophrenia. The nose poke task has been used to test impulsiveness in a variety of other research paradigms. In the nose poke task the rat is required to attend to two brief (2-second) illuminations (cues) of a hole in the chamber wall (see Figure 3). It is trained to inhibit poking its nose in response to the first cue and to withhold the response until the second (terminal) cue. In this paradigm, the operational definition of impulsive behavior is nose poking during the first cue. This experiment is ongoing and only partially completed due to the construction delays in Olin Hall.

Methods Highlights

Subjects

Ten female blue spruce hooded rats with prior experience in an operant chamber served as subjects in this experiment. They were individually housed with free access to food and water except for 23.5-hours of water deprivation prior to each session to establish water as a reinforcer.

Apparatus

All training and testing was conducted in six Coulbourn automated operant chambers equipped with nose poke modules and water dippers. (See Figure 3)

Procedures

The rats were initially trained to poke their nose into a lighted nose pose module for 4-sec access to water. After this shaping, they were trained to emit the nose poke when the cue light was on. Cues were presented on a variable time 10-sec schedule. Nose pokes during light off produced no water reinforcer. In Phase 2 of the experiment a 2-second (First) cue was followed by a 2-second no cue period followed by the terminal cue presentation. The terminal cue stayed on until a nose poke occurred. Nose pokes to the first cue were followed by a 10 second blackout of the chamber and no reinforcer. Nose pokes to the terminal cue were followed by a 4-second water reinforcer. Sessions were run to a total of 60 reinforcer deliveries.

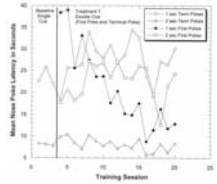

Figure 5: A graph of the mean number of nose pokes in the two seconds following first cue and terminal cue onset for the last three days of baseline (single cue) and all sessions of two cue training.

Preliminary Results and Implications

Figure 5 shows the mean number of nose pokes in the two seconds following first cue and terminal cue onset for the last three days of baseline (single cue) and all sessions of two cue training. Note the increase in short latency (1-sec) terminal cue pokes and the decrease in short latency (1-sec) first cue nose pokes during Phase 2. Although preliminary, these data suggest that the rats are learning to inhibit the impulse to make the first poke. Once the first cue nose pokes are reduced to a stable low asymptote, we can begin pharmacological manipulations to disinhibit nose poking, thereby showing impulsivity.