Relation Among Potential Predictors Of Drug Abuse Risk In Rats

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INTRODUCTION

Animal models have been used to investigate behavioral processes and mechanisms that underlie addiction. A variety of measures have been developed for rats that are modest predictors of drug abuse risk. The purpose of this pilot study was to begin to assess whether several established or potential measures of drug abuse vulnerability were correlated.

Following drug administration, some animals manifest acute withdrawal and some do not. Correlations were used to provide clues regarding which type of animal might be a drug-vulnerable phenotype.

GENERAL METHOD

Subjects. The subjects were eight adult male Wistar rats.

Apparatus. The behavior of the animals was monitored in two different kinds of apparatus, including an elevated choice alley and open fields.

Procedures. The rats were run on procedures that yielded measures of excessive risk aversion (anxiety), sensation seeking, short-term responsiveness to acutely administered drug, and withdrawal from acutely administered drug. The latter is a potential new measure of drug abuse vulnerability.

GENERAL RESULTS

All measures produced considerable individual differences.
The following matrix shows the correlations that were obtained between measures.

	Risk Aversion	Sensation Seeking	Short-Term Response	Acute Withdrawal
Risk Aversion		0.188	-0.123	-0.249
Sensation Seeking			-0.527	0.311
Short-Term Response				0.256
Acute Withdrawal				

CONCLUSIONS AND IMPLICATIONS

On each measure, individual subjects showed a range of responses from low to high. Individual differences on these measures could reflect individual differences in vulnerability to drug.

While none of the correlations was significant—an outcome that was expected given the small sample size—the pattern of trends suggested that the drug-vulnerable phenotype may be the animal that is sensitive to acute withdrawal.

REFERENCES AND ACKNOWLEDGEMENTS

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- Campos AC, Fogaca MV, Aguiar DC, Guimaraes FS. Animal models of anxiety disorders and stress. Rev Bras Psiquiatr, 35 Suppl 2: S101-11, 2013.
- White W, White IM. Amphetamine and morphine may produce acute-withdrawal related hypoactivity by initially activating a common dopamine pathway. Physiol Behav, 165: 187-94, 2016.

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METHOD

Risk Aversion (Anxiety)

Each animal was placed, on one occasion, in the apparatus picture at the left for five minutes. The apparatus is a variant of the elevated plus maze, and it consists of one enclosed arm and one open arm. The time of each arm entry was recorded. The task assesses risk aversion. Animals higher in risk aversion spend a higher percentage of time in the closed arm, and highly risk-averse animals may be at greater risk for drug abuse.

Sensation Seeking

Each animal was placed in a novel open field, like the one pictured to the left, for 60 minutes. A field had an array of infrared emitters and detectors, and distance moved was quantified from the pattern of beam breaks. The procedure is one way to assess sensation seeking. Animals high in sensation seeking explore a novel context more thoroughly than non-sensation seeking animals, and they may be at higher risk for drug abuse.

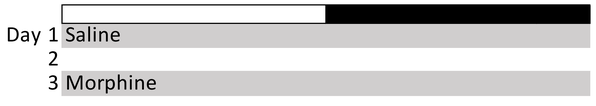
Short-Term Response to Acutely Administered Morphine and Withdrawal from Acutely Administered Morphine

This manipulation was conducted in Open fields of the type pictured above. A field was placed within a sound attenuating shell. A lamp within the shell arranged for a 12-12 hour light-dark cycle, with lights on at 10 AM and off at 10 PM. Chow blocks were placed in one corner of the floor, and a metal holder containing a water bottle was hung on one side wall.

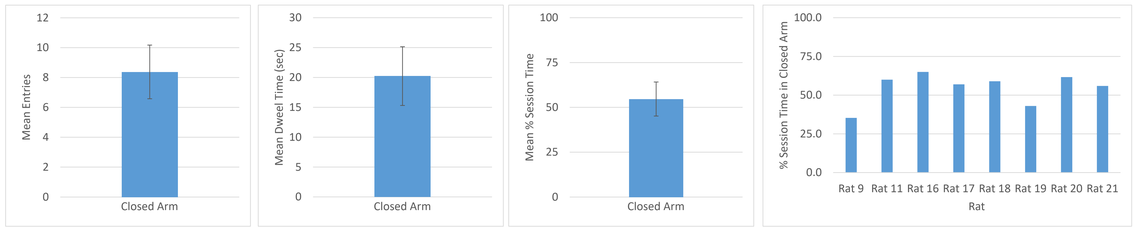
The manipulation consisted of several phases.
Open field habituation.
- Each animal was placed in an open field at 10 AM and was allowed to acclimate for 24 hours. Two days of acclimation were arranged, separated by a 24-hour period when an animal was in the colony.

Injection procedure habituation.
- To acclimate animals to the injection procedure, each animal was given a saline administration, and was then placed in an open field for a third 24-hour period.

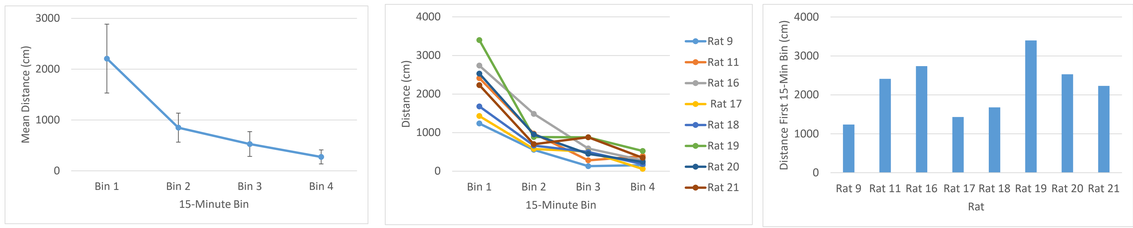
Test.
- The diagram below shows the test procedure. On Day 1 each animal received saline (1.0 ml/kg), and on Day 3 each animal received 5.0 mg/kg morphine. Administrations were given at light onset. Activity was monitored for 24 hours following each administration (gray). Effects of saline and morphine were compared. The short-term response to morphine (hours 1-6 post-treatment) and the acute withdrawal effects of morphine (hours 7-24 post-treatment) were assessed.



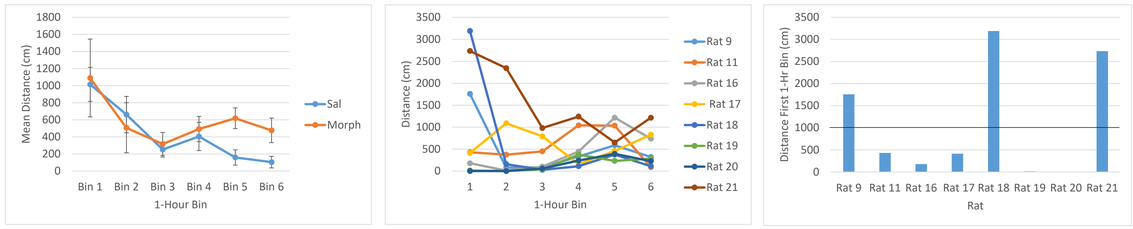
RESULTS



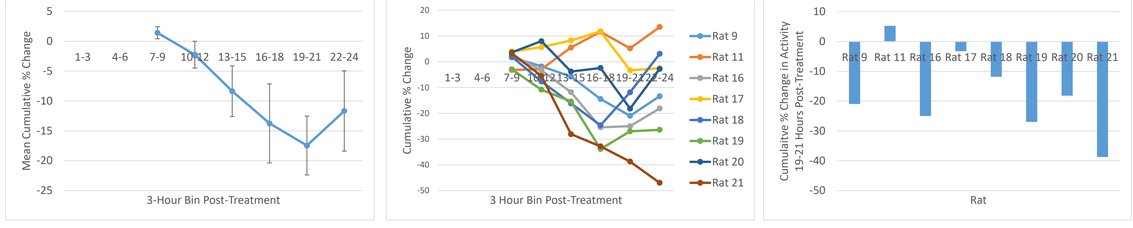
Figures above. Right. Risk aversion was operationalized as the % of total session time an animal spent in the closed arm. Considerable individual differences were observed. Higher risk aversion may predict lower morphine withdrawal. Values from figures in the right column were used in correlations.



Figures above. Left. On average, activity was highest during the first 15-min bin, and it decreased progressively afterwards. **Middle.** Animals varied in the amount of activity they showed during the 60-min session. **Right.** Sensation seeking was operationalized as the total distance each animal moved during the 15 minutes of the session. Considerable individual differences were observed. Higher sensation seeking may predict higher morphine withdrawal.



Short-Term Effect of Morphine. Figures above. Left. On average, morphine produced a rebound in activity 5-6 hours after treatment. **Middle.** Considerable individual variation occurred in the initial reaction to morphine and in aspects of the rebound. **Right.** The acute response to morphine was operationalized as the total distance moved during the first hour following drug. This varied considerably across animals. Higher short-term effect of morphine may predict higher morphine withdrawal.



Acute Withdrawal Effect of Morphine. Figures above. Left. On average, compared to saline, morphine produced a progressive decrease in mean cumulative % activity 7-24 hours after treatment. **Middle.** The effects of morphine on activity varied considerably across subjects: Some subjects showed a massive deficit, and others showed no effect or a positive rebound. **Right.** Acute withdrawal was operationalized as the % decrement in distance moved that had occurred by 19-21 hours post-morphine. This varied considerably across animals.