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The effects of environmental enrichment on nicotine sensitization in a rodent model of
schizophrenia

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Department of Psychology

Honors Thesis

ABSTRACT

Environmental enrichment, for more than fifty years, has shown to increase learning in behaviors and to alter some brain structures (Renner and Rosenzweig). Some brain changes that occur when environmental enrichment is implemented include the following: increases in cortical thickness, especially the occipital cortex, increases in size of neuronal cell bodies, number of dendrites and dendritic spines, increases in astrocyte branching, increases in the number of brain blood capillaries, and increases in mitochondria (an indication of higher metabolic activity) (Stairs and Bard). It has been shown in research studies that rats in the environmental enrichment group are less sensitive to nicotine effects, both repeated and acute, than rats in isolated situations (Green et al). This is so because enrichment changes the intensity of the acute administration of drugs of abuse. Rats are stimulated by the environment, rather than a particular stimulant.

Keywords: Environmental enrichment, nicotine, self-administration

INTRODUCTION

Smoking cigarettes is a convenient and legal form of drug self-administration that often begins in adolescence (Kelly). Approximately 80% of schizophrenics smoke cigarettes, which is 3-4 times that of the general population (Lang). Schizophrenia is a complex disorder that involves positive and negative symptoms. Factors of negative symptoms include affective flattening, alogia, avolition, anhedonia, and attentional impairment (Andreasen). Positive symptoms include auditory and visual hallucinations and delusions and visions of grandeur (Zimmermann et al). With the negative symptoms come depression, anxiety, and a high suicide rate. Thus, so many people with schizophrenia smoke to alleviate the stress associated with the disorder.

A hallmark of schizophrenia is increased dopamine D2receptor sensitivity in the brain, especially in brain areas that mediate reward. Research from our laboratory has shown that quinpirole, a dopamine D2/D3receptor agonist, administered to rats during the neonatal period produces long-term dopamine D2receptor supersensitivity consistent with psychosis (Perna). Studies have shown that nicotine sensitization is more robust in adolescence than adulthood (Elliott), age-dependent within adolescence (Belluzzi), less robust or non-existent in adulthood (Schochet). Research has shown that neonatal quinpirole results in more robust sensitization to nicotine in both adolescents and adults (Perna). Past work has also shown that environmental enrichment eliminates sensitization to psychostimulants, and reduces self-administration of psychostimulant drugs in rats. Further, isolated housing results in an enhancement of the response to psychostimulants (Stairs). In this current study, the researchers were interested in analyzing the effects of environmental enrichment on nicotine sensitization in adolescent rats that were neonatally treated with quinpirole. The researchers also wanted to look at isolation environments and stress.

PURPOSE AND HYPOTHESES OF THE PRESENT STUDY

For this study, the experimenters had several motives and hypotheses. The investigators wanted to learn more about how experience, in this case, environmental enrichment, plays a role in drug sensitization in a rodent model of schizophrenia.

It was originally hypothesized that animals housed in an enriched environment would eliminate enhanced sensitization of nicotine in rats neonatally treated with quinpirole, based on past studies done with psychostimulants. The experimenters also hypothesized that animals housed in an isolated environment would increase the sensitization of nicotine in rodents neonatally treated with quinpirole, because these animals would not have an enriched environment to decrease nicotine sensitization.

METHODS

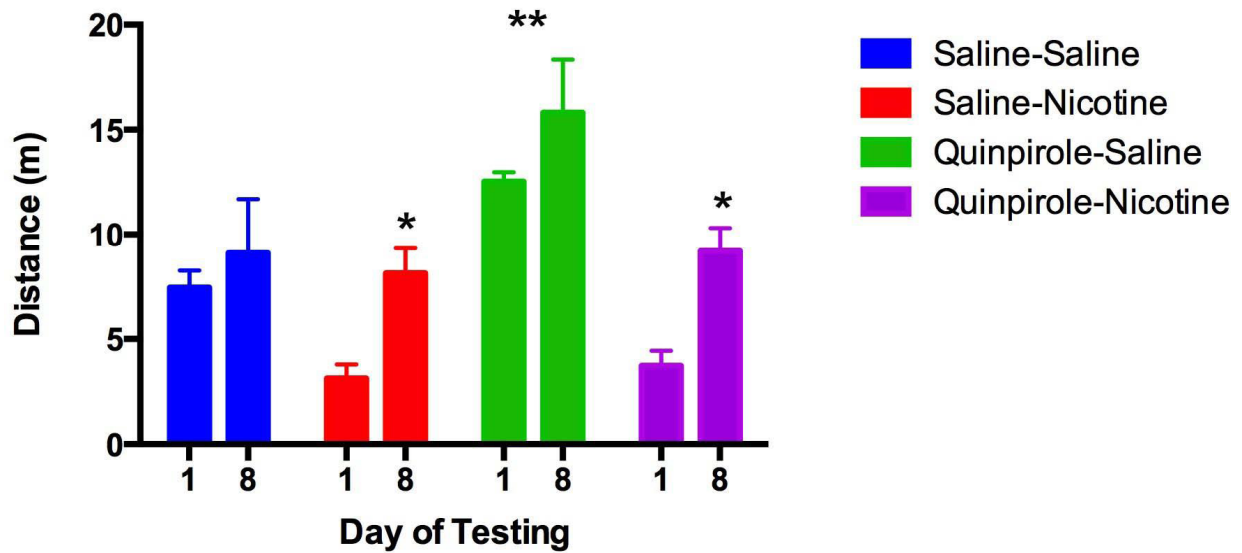
Neonatal drug treatment: Animals were given a single daily intraperitoneal (ip) injection of either quinpirole (1 mg/kg) or saline from postnatal day 1 to 21 (P1 to P21). After animals were weaned at P21, rats were randomly divided and placed into isolation or environmentally enriched housing and remained in these housing conditions throughout behavioral testing until brain tissue was harvested at P46.

Housing Conditions: Animals housed in the isolated condition were singly housed in wire hanging cages, and animals housed in the enriched condition were socially housed in a large wire cage (76.2 cm x 91 cm) with at least 4 other cagemates. The enriched housing contained several different objects animals could interact with, and one-half of these objects were replaced every two days and rotated into new positions daily for the entire study. Animals were also handled daily by an experimenter.

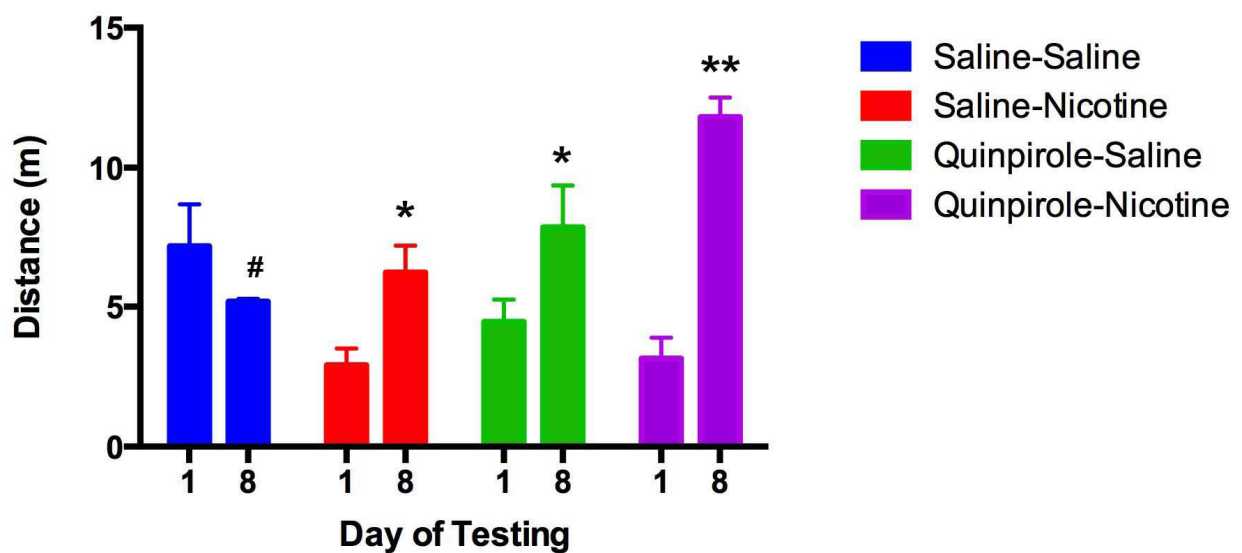
Adolescent drug treatment: Behavioral testing began on P35. Animals were habituated to square locomotor chambers (30 cm/side) for three consecutive days from P35-37, and began drug treatment on P38. On each behavioral testing day, animals were given an ip injection of either nicotine (0.5 mg/kg free base) or saline. Approximately 10 min later, all animals were placed into the locomotor chambers and behavior recorded using AnyMaze software (Stoelting Co, Wood Dale, IL). Behaviors recorded were locomotor activity (distance traveled) and number of entries to a defined central zone measuring 10 cm/side. There were 4-5 animals per group. Animals were tested for eight consecutive days from P38-45, and brain tissue was harvested on P46.

RESULTS

Isolated Condition: Locomotor Activity



Enriched Condition: Locomotor Activity



EXPLANATION OF THE CHARTS

Figure 1. Nicotine sensitization in adolescent males and females neonatally treated with quinpirole:

A three-way ANOVA revealed significant main effects of neonatal drug treatment $F(1,23)=0.6$, $p<.001$, adolescent drug treatment, $F(1,23) = 11.88$, $p<.002$, housing condition $F(1,23)= 10.71$, $p<.003$, and a three-way interaction of neonatal drug treatment x adolescent drug treatment x housing condition $F(1,23) = 6.64$, $p<.017$.

•**Isolated Condition:** Animals neonatally treated with quinpirole and given saline in adolescence demonstrated a robust increase in activity compared to all other groups (indicated by **, $p<.001$) and demonstrated a significant increase in activity over the 8 days of testing.

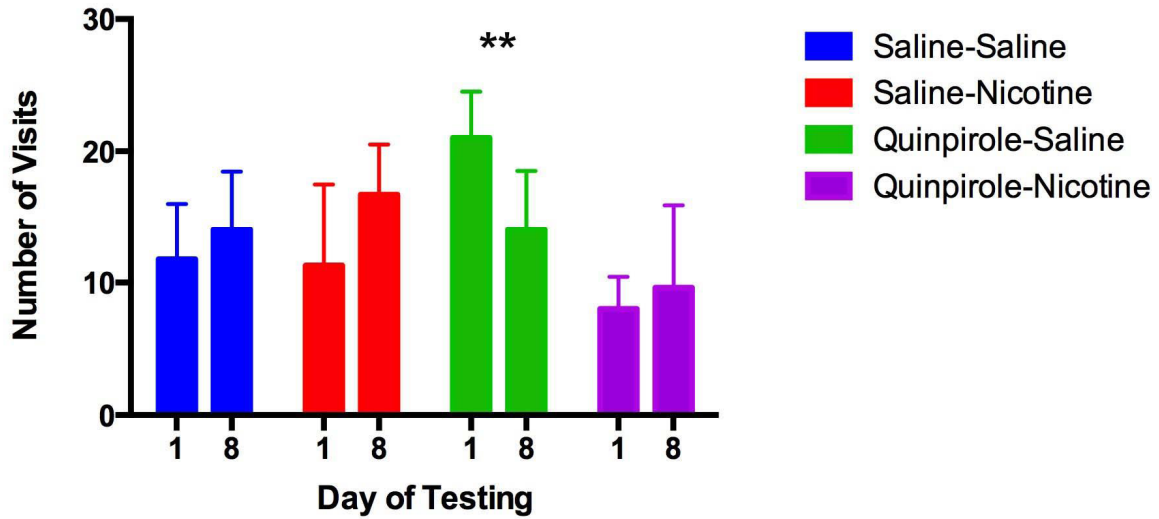
•**Isolated Condition:** Regardless of neonatal drug treatment, animals demonstrated sensitization to nicotine and increased distance traveled over days of testing (indicated by *, $p<.01$)

•**Enriched Condition:** Animals neonatally treated with quinpirole demonstrated more robust sensitization compared to all other groups (indicated by **, $p<.01$)

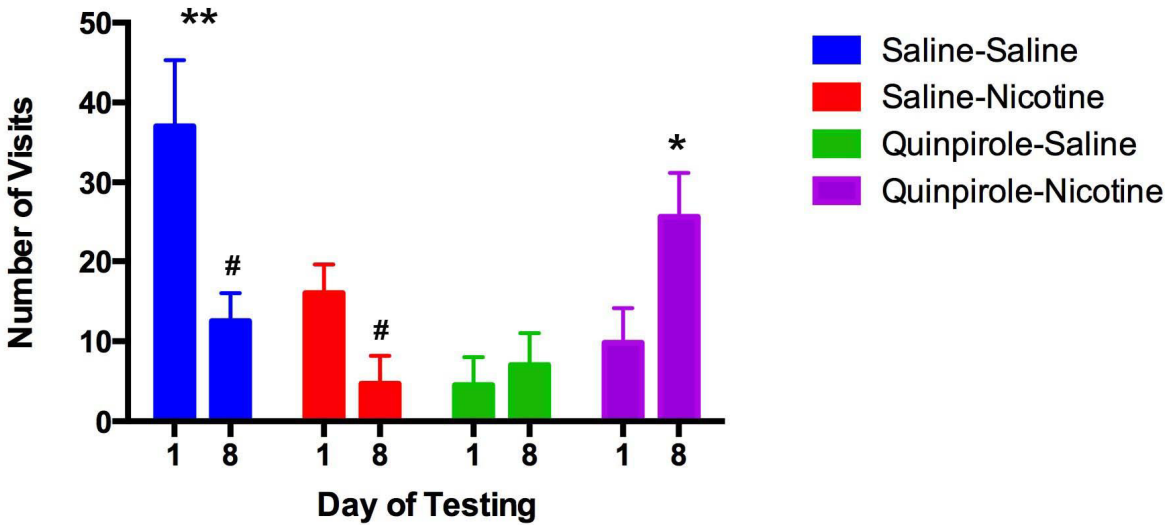
•**Enriched Condition:** Rats neonatally with saline and demonstrated sensitization to nicotine, and animals neonatally treated with quinpirole and treated with saline in adolescence demonstrated an increase in activity over days of testing (indicated by *, $p<.05$). Animals neonatally treated with saline and given saline in adolescence demonstrated a significant decrease in activity over days (#, $p<.05$).

RESULTS, continued.

Isolated Condition: Entries to Central Zone



Enriched Condition: Entries to Central Zone



EXPLANATION OF THE CHARTS

Figure 2: Entries to central zone during nicotine sensitization.

A three-way ANOVA revealed a significant three-way interaction of neonatal drug treatment x adolescent drug treatment x housing condition $F(1,23) = 7.19$, $p < .013$ and a significant two-way interaction of neonatal drug treatment x housing condition x day of testing $F(1,23) = 4.91$, $p < .037$.

Isolated housing condition: Rats neonatally treated with quinpirole and given saline in adolescence demonstrated a significant increase in number of entries to the central zone compared to all other groups (indicated by **, $p < .05$).

Enriched housing condition: Animals neonatally treated with saline and given saline in adolescence demonstrated a significant increase in number of entries to the central zone compared to all other groups (indicated by **, $p < .05$).

Enriched housing condition: Animals neonatally treated with saline and sensitized to nicotine decreased number of central zone entries over days of treatment (#, $p < .05$).

Enriched housing condition: Rats neonatally with quinpirole and sensitized to nicotine demonstrated an increase in number of entries to the central zone over days of treatment (*, $p < .01$).

CONCLUSIONS

From these results, the experimenters noted that animals housed in isolation, neonatally treated with quinpirole and given saline in adolescent demonstrated a robust increase in activity compared to all other groups tested. Interestingly, animals neonatally treated with quinpirole housed in isolation demonstrated **equivalent** sensitization to nicotine as isolated animals neonatally treated with saline and given nicotine. These data points show that nicotine alleviated the robust increase in activity observed in isolated animals neonatally treated with quinpirole.

Concerning enrichment, enriched animals neonatally treated with quinpirole demonstrated **more** robust sensitization to nicotine than all other groups. **Thus, environmental enrichment appears to enhance sensitization to nicotine in our model, not supporting our original hypothesis.**

Analyses of the entries to a defined central zone in the arena revealed that isolated neonatal quinpirole animals given saline in adolescence demonstrated an increased number of entries to the central zone, likely due to their increased activity. Nicotine decreased number of central zone entries in isolated neonatal quinpirole rats. For enriched animals, nicotine appears to increase number of central zone entries in neonatal quinpirole rats compared to all other groups. **In essence, environmental enrichment appears to enhance sensitization to nicotine in animals that have supersensitized dopamine D2 receptors, and isolation likely results in an increased stress response in these animals.**

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