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*East Tennessee State University*

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Nicotine Sensitization in a Rodent model of Schizophrenia:  
A Comparison of Adolescents, Adults, and Neurotrophic factors

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A thesis presented to  
the faculty Department of Psychology  
East Tennessee State University

In partial fulfillment  
of the requirements for the degree  
Master of Arts in Psychology

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Marla K. Perna

May 2007

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Russell Brown, Ph.D., Chair

Otto Zinser, Ph.D

Michael Woodruff, Ph.D

Keywords: schizophrenia, quinpirole, nicotine, dopamine, BDNF, adolescent, adult, rat

## ABSTRACT

Nicotine sensitization in a rodent model of schizophrenia:

A comparison of adolescents, adults, and neurotrophic factors

by

Marla K. Perna

The behavioral effects of nicotine on locomotor activity in a rodent model of psychosis were analyzed. This model is based on neonatal quinpirole treatment (a dopamine D2/D3 agonist) which causes increased D2 receptor sensitivity, a phenomenon known as D2 priming that is common in schizophrenia. D2-primed adolescent rats did not demonstrate nicotine-induced hypoactivity early in training, and males demonstrated more rapid sensitization to nicotine as compared to controls administered nicotine. D2-primed females administered nicotine demonstrated increased stereotypic behavior. D2-primed adult rats given nicotine demonstrated significantly more robust sensitization to nicotine than controls given nicotine. Brain-derived neurotrophic factor (BDNF) was analyzed in the nucleus accumbens. BDNF was significantly increased in nicotine treated adolescent females but was not affected in males. Nicotine alleviated BDNF deficits in D2-primed adults. These results suggest that sensitization to nicotine in D2-primed rats is age dependent, and nicotine induced changes in BDNF that is age and sex-dependent.

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## CHAPTER 1

### INTRODUCTION

Schizophrenia is a debilitating disorder that affects approximately 1% of the population. The symptoms of schizophrenia involve a combination of positive and negative symptoms accompanied by impairment in social and/or occupational function according to the DSM-IV-TR (2000). Positive symptoms may be described as a loss of contact with reality, delusions, hallucinations, and bizarre behaviors. Hallucinations include auditory, visual, tactile, and olfactory hallucinations. The most common hallucinations are auditory, including hearing voices and sounds that are not shared by others (American Psychiatric Association Diagnostic and Statistical Manual, 2000; Mueser & McGurk, 2004 ). Negative symptoms of the disease include flattened affect (lack of emotion, monotonous voice tone, and immobile facial expression), anhedonia (the absence of pleasure and the inability or lack of motivation to follow through on plans), low goal-oriented behavior, and alogia (a reduced amount of speech or content of conversation). The DSM-IV-TR further lists impairment of social and occupational functions that include an inability to retain social relationships in personal and professional settings, as well as an inability to care for oneself.

#### *Psychostimulant Abuse in Schizophrenia*

Research has shown a significantly higher incidence of drug abuse in schizophrenics as compared to the general population, (Cuffel, 1992; LeDuc & Mittleman, 1993), and the incidence of drug abuse in schizophrenics has been steadily increasing in recent years. In 1965, 4.5% of schizophrenics reported use of psychostimulants. In 1990, 25.3% reported use of psychostimulants (Cuffel), and by 1999, 50% reported use of psychostimulants. Among psychostimulants, nicotine is used most often. Approximately 90% of the schizophrenic

population smokes cigarettes as compared to only 20% of the general population (Levin, Wilson, Rose, & McEvoy, 1996). Recent research suggests that schizophrenics may be using nicotine to self-medicate or to possibly relieve the unpleasant side effects of prescribed medications.

(Friedman, Adler, & Davis, 1999; Leonard & Giordano. 2002)

### *Dopamine Dysfunction in Schizophrenia*

Increased dopamine (DA) activity has been found in several psychiatric disorders including obsessive-compulsive disorder, attention-deficit hyperactive disorder, bipolar disorder, and schizophrenia. Research has shown that increased dopamine function is a key element in the etiology of schizophrenia. For example, dopaminergic receptors have been shown to have an increased sensitivity in schizophrenia (Kegeles et al., 2000) and all antipsychotic drugs used to treat schizophrenia block dopamine D2 receptors with some affinity (Tollefson, 1994). Research has shown that increased DA function in the prefrontal cortex and the nucleus accumbens may be involved in positive symptomology of the disease (Drew, Derbez, & Werling, 2000).

Therefore, it appears that the dopamine neurotransmitter system is hyperactive in schizophrenia.

### *Dopamine Function in the Brain.*

Dopaminergic cell bodies are primarily located in the ventral tegmental area (VTA) and project to several different brain areas including the basal ganglia, nucleus accumbens, with less major projections to the olfactory tubercle, hippocampus, and cerebral cortex. An important dopamine projection that plays a major role in positive reinforcement and drug addiction originates from DA cell bodies in the VTA and projects to the nucleus accumbens and frontal cortex. The projection from the VTA to the nucleus accumbens (Nacc) has been hypothesized to be the primary drug reinforcement pathway in the brain and is referred to as the mesolimbic dopamine pathway. Blockade of dopamine receptors either in the VTA or Nacc blocks self-

administration of reinforcing drugs such as nicotine, cocaine, and amphetamine (Adinoff, 2004; Badanich & Kirsteina, 2004; Maldonado, 2003), and dopamine receptor blockade also alleviates locomotor sensitization to drugs known to activate this pathway (Hsu, Tsou, Chiu, & Chau, 2005; Pierre & Vezina, 1998; Pudiak & Bozarth, 1997). Additionally, animals will work for stimulation of this brain pathway via an electrode that is activated by a lever press from the animal (Suto et al., 2003; Suto, Tanabe, Austin, Creekmore, & Vezina, 2002). Thus, it is apparent that the mesolimbic dopamine pathway is involved in mediating reinforcing effects of stimuli.

### *Drug Abuse Mechanisms in the Brain*

The two main theories of addiction focus on dopamine depletion and sensitization. Addiction stems from activation of the mesolimbic dopamine system causing increases in dopamine response and pleasurable feelings that are associated with drug reward. Discontinuation of drug use causes a dopamine-depleted state that has been referred to as the *dopamine depletion hypothesis* or also the general anhedonia model. Behavioral studies with cocaine show that dopamine depleted animals exhibit higher self-administration of cocaine than subjects with normal levels of dopamine, suggesting involvement of dopaminergic systems in the Nacc and the reinforcing and motivational effects of addictive drugs (Gerrits & Van Ree, 1996). Additionally, subjects with higher levels of dopamine exhibit lower levels of self-administration of cocaine. These behaviors are inversely correlated to extracellular levels of dopamine in the nucleus accumbens. Findings have shown that the use of dopamine agonists to treat cocaine addiction did not lower self-administration of cocaine, suggesting that the reinforcing properties of cocaine may not be related to dopamine but instead to the serotonergic system (Adinoff, 2004).

Although reward and addiction are mediated by different systems, these systems do overlap, therefore, creating a connection between the two behaviors (Adinoff, 2004).

The *sensitization hypothesis* suggests that repeated exposure to a drug causes heightened sensitivity of the dopamine system because of use of the drug. Behavioral studies have shown sensitization to cocaine is a causal link to cocaine addiction. The prediction of this hypothesis says that use of dopamine antagonists would decrease the use and self-administration of cocaine. However, double-blind placebo testing showed that dopamine antagonists did not decrease the use and self-administration of cocaine by those who were previously sensitized to the drug. This finding suggests that addiction may be controlled by more than just an increase or decrease in absolute levels of dopamine (Badanich & Kirsteina, 2004) and may be because of changes at the receptor level, as both D1 and D2 antagonists are known to produce a significant increase in dopamine receptor number (Ahmed & Koob, 2004).

#### *Dopamine, Schizophrenia, and Addiction: A Common Tie?*

Interestingly, addiction to certain drugs such as alcohol and amphetamine as well as prenatal exposure to particular drugs such as cocaine have also been shown to increase sensitivity of dopamine receptors. The discovery of changes in dopamine receptor function points to a shared underlying mechanism in both drug addiction and psychoses (Cuffel, 1992). It is known that the occurrence of cigarette smoking is more than four times as prevalent in the schizophrenic population than in the general population, which has been suggested to be because of nicotine's ability to reduce the negative side effects of neuroleptic medication, likely because of its effects on the dopaminergic system (Dalack, Healy, & Meador-Woodruff, 1998).

The positive reinforcing effects of nicotine are mediated primarily by the mesolimbic dopamine system. Research has shown that nicotine increases extracellular dopamine in the

nucleus accumbens through its action on presynaptically located nicotinic receptors on dopaminergic neurons (Wilkie, Hutson, Sullivan, & Wonnacott, 1996). Nicotine acts by binding to ionotropic nicotinic receptors located on the presynaptic side of the neuron, opening these receptors, and increasing release of dopamine through entry of calcium into the terminal. Calcium enters through these nicotinic receptors and binds to the protein calmodulin that subsequently acts to bring synaptic vesicles containing neurotransmitter to the membrane surface and release neurotransmitter (Julien, 2004).

This increase of dopamine release induced by nicotine has been hypothesized to play an important role in the reinforcing and locomotor stimulation effects of nicotine. For example, nicotine has been shown to increase locomotor sensitization when locally injected into the VTA (Leikola-Pehlo & Jackson, 1992). The ability of nicotine to induce increased locomotion and also conditioned place preference (Badanich & Kirsteina, 2004) suggests that nicotine has psychostimulant and addictive properties (Picciotto & Wickman, 1998). The increase in behavioral responding to nicotine has been shown through a number of behaviors including increased locomotion and increased vertical rearing behavior, as well as dopaminergic related behaviors such as paw treading and grooming. It is understood that other neurotransmitter systems are also involved in this phenomenon, but this may be attributed to modulation of other systems because of increased release of dopamine in the VTA-nucleus accumbens pathway (Church, Cotter, Bramon, & Murray, 2002; Crook, Tomaskovic-Crook, Copolov & Dean, 2001; Leonard & Giordano, 2002).

#### *Psychostimulant Abuse and Schizophrenia*

Two hypotheses have been proposed to explain the higher incidence of substance abuse in schizophrenics. The first hypothesis is that schizophrenics use psychostimulants as a form of

self-medication because of the processes of the disease. It has been suggested that schizophrenics use nicotine to alleviate sensory gating abnormalities and attentional deficits caused by the disorder. (Adler et al., 1998; Adler, Friedman, Ross, Olincy, & Waldo, 1999; Le Duc & Mittleman, 1995).

The second hypothesis suggests that schizophrenics may be using psychostimulants to alleviate the negative side effects (depression, anhedonia, apathy, and lethargy) of chronic neuroleptic treatment. Schizophrenic patients report similar reasons for smoking as do normal smokers. These include reduction of stress, anxiety, and agitation. They also report similar withdrawal symptoms as compared to normal smokers, with the addition of some patients reporting an increase of psychiatric symptoms during withdrawal (Dalack, 1996; Healy & Meador-Woodruff, 1996). Research has shown that use of certain neuroleptics causes an increase in cigarette smoking in schizophrenic patients because of dopamine D2 receptor blockade. For example, Dawe, Gerada, Russell, and Gray (1995) showed that the typical antipsychotic and potent dopamine D2 receptor antagonist haloperidol administered to normal non-schizophrenic smokers caused an increase in smoking as compared to baseline. It is believed that this is because of a decrease in function of dopamine receptor sites, namely the D2 receptor, producing an increase in nicotine intake to compensate for a lack of dopamine-related reward.

It has also been suggested that schizophrenic smokers extract more nicotine from a cigarette than do non-schizophrenic smokers, possibly increasing nicotine's addictive properties. Research by Olincy, Young, and Friedman (1997) has shown that schizophrenics have an increased amount of cotinine, a metabolite of nicotine, over non-schizophrenic smokers. It is believed that schizophrenics have a different pattern of inhalation, allowing increased amounts of nicotine to be extracted from each cigarette (Olincy et al.). Schizophrenics increase the intensity

of inhalation, rate of inhalation, and depth of inhalation to hypothetically increase the amount of nicotine delivered to the system, allowing the user to control the amount of nicotine absorbed (Hukkanen, Jacob, & Benowitz, 2005). Increased amounts of nicotine may target the low affinity alpha 7 receptor, which is associated with sensory deficits in schizophrenia, providing an increased ability for selective attention and possibly alleviating cognitive dysfunction (Leonard et al., 2001).

Atypical antipsychotic drugs cause schizophrenic patients to experience decreased feelings of reward (Green, Salomon, Brenner, & Rawlins, 2002; Green, Zimmet, Strous, & Schildkraut, 1999) as they reduce the amount of dopamine in the brain because of D2 receptor antagonism. Blockade of the D2 receptor has been shown to produce significantly reduced motivation, goal-oriented behavior, emotion, and anhedonia. The use of antipsychotic drugs has also been shown to cause upregulation of the D2 receptors in the brain, possibly explaining potential abuse of antipsychotics by schizophrenic patients, because the increase in receptors may lead to increased drug craving or may be synergistic to a patient's current drug addiction (Joyce, 2001; McEvoy, Feudenreich, Levin, & Rose, 1995). Reinforcement pathways in the brain have also been shown to be affected by drugs of abuse and are stimulated by drugs that produce a sense of euphoria. Stimulation of this system reduces anhedonia, increases goal-oriented behavior, and alleviates depression like symptoms (Di Chiara et al., 2004). Based on research that has prevalently shown schizophrenics have increases in sensitivity of the dopaminergic system, a possible mechanism for increased psychostimulant use in this population is that these drugs are increasing dopaminergic activity in an already sensitized dopaminergic system, that results in a significant increased euphoric reaction within the schizophrenic population (Leonard et al., 2001).

### *Nicotine Addiction*

Nicotine's addictive properties are thought to be a result of nicotine's effects on the dopamine system. Evidence suggests that nicotine may act directly at presynaptically located ionotropic nicotinic receptors located on dopaminergic neurons. When these receptors are bound, they allow for calcium to enter the presynaptic terminal, which acts to increase dopamine release in the drug reinforcement pathway (Srinivasan & Thara, 2001). By smoking cigarettes, the schizophrenic patient receives rapid reinforcement of the drug via rapid activation of the dopamine system. Because of rapid absorption of nicotine and the drug readily entering through the blood-brain barrier, behavioral reinforcement is strengthened through smoking cigarettes versus alternative forms of administration of nicotine, which also increases dependence of the drug (Hukkanen et al., 2005).

#### *Why are Schizophrenics More Likely to Smoke Cigarettes Than the Normal Population?*

Several hypotheses have been proposed to explain why schizophrenics are more likely to smoke cigarettes than the normal population. It has been shown that schizophrenics have an altered acetylcholinergic system as compared to normal non-schizophrenics, in that schizophrenics have been shown to have fewer nicotinic receptors, with the largest deficit found in the hippocampus (Hernandez & Terry, 2005). Deficiency of nicotinic receptors may cause increased anhedonia and a decrease in the rewarding effects of nicotine. Because of the deficiency of nicotinic receptors, it has been hypothesized that schizophrenic patients smoke cigarettes in an effort to self medicate by increasing stimulation to nicotinic receptor sites that may alleviate side effects caused by neuroleptic use (Leonard et al., 1998). Other hypotheses have suggested that nicotine may be used by this population to alleviate cognitive impairment (Elvevag & Goldbeg, 2000) or sensory gating deficits known to exist in schizophrenia (Braff,

Geyer, & Swerdlow, 2001; Geyer et al., 2001;). However, this research is speculative at this point, and there is no widely accepted mechanism for the significant increased use of nicotine in the schizophrenic population.

#### *Modeling Schizophrenia in Rodents: Rodent Models of Neurological Disease*

Rodent models of neurological disease are useful for studying components of specific diseases, but not necessarily for an entire disease itself. Animal models may be used to study the cause of a disease or to compare treatments for a particular disease but may not be able to predict the progression of the disease over a lifetime. Animal models may be useful for development and discovery of new and more effective treatments for neurological disorders (Woodruff & Baisden, 1994). In most cases, animal models of neurological disease and dysfunction are used to model one aspect of the disorder: behavioral, neurochemical, or neuropathological. This can be extremely useful because it can be informative about the contribution of this behavioral or neurochemical abnormality to the disease or disorder, although the entire disorder is not modeled in the animal. Additionally, animal models have been used extensively for testing antipsychotic drugs because of the high genetic homology between rodents and humans, therefore supporting the use of animals to model neurological disease (Gainetdinov, Mohn, & Caron, 2001).

#### *Past Rodent Models of Schizophrenia*

Schizophrenia is a difficult disorder to model because of its complexity and because it affects several neurotransmitter systems and brain areas. Therefore, most rodent models of schizophrenia have focused on one particular neurochemical or neuropathological abnormality produced by the disease. Several rodent models of schizophrenia have been used to test different behavioral deficits and the effects of drugs on these behavioral deficits as well as on neurochemical changes produced by the pathology of the disorder.

### *Latent Inhibition Model*

The amphetamine-haloperidol latent inhibition model of schizophrenia was proposed by Solomon et al. (1981) and Weiner et al. (1981) and has since been replicated by many other researchers. Latent inhibition (LI) is a learning phenomenon first described by Kamin (1968) that demonstrated pre-exposure to a conditioned stimulus (CS) produces a deficit in acquisition of a CR when the same CS is temporally paired with an unconditioned stimulus (US). Results have shown that amphetamine also disrupts conditioning of the CS thus producing a similar phenomenon as LI. The LI deficit is then reversed through use of atypical and typical antipsychotic drug pretreatment (Weiner, Schiller, & Gaisler-Salomon, 2002) given before amphetamine administration. This model is said to mimic the positive symptoms of the disease with face, construct, and predictive validity because these symptoms are also seen in humans with schizophrenia and schizotypal disorder and in normal subjects being exposed to antipsychotic drugs. This model focuses on the nucleus accumbens and dopamine innervation from circuitry involved in LI, which are involved in the conditioning phase of the model.

### *Phencyclidine (PCP) Model*

Hersco-Levy, Silipo, and Gavit (1996) have used a rodent model of schizophrenia through acute administration of phencyclidine (PCP). This model suggests that use of the drug PCP induces schizophrenia-like symptoms in normal subjects. This drug acts by blocking the PCP binding site located on the glutamatergic N-methyl-D-aspartate (NMDA) receptor, acting as an inverse agonist. This model focuses on blockade of NMDA receptors as a way of inducing schizophrenia-like symptoms because schizophrenics have also been shown to demonstrate hypoactivity of the NMDA receptor (Hersco-Levy et al.; Millan, 2002, 2005). By binding to noncompetitive NMDA sites, this model is able to produce both positive and negative

symptomology, whereas the amphetamine-LI model induces primarily positive symptoms of the disease. Findings with this model suggest that targeting the NMDA receptor site may lead to alleviation of both positive and negative symptoms of schizophrenia. Behavioral studies have shown that use of agonists at the NMDA receptor, such as a glycine agonist or D-serine, resulted in alleviation of positive and negative cognitive symptoms (Heresco-Levy et al.).

#### *Neonatal Hippocampal Lesion Model*

One of the more often used and well-validated rodent models of schizophrenia is the neonatal ventral hippocampal lesion model developed by Lipska and Weinberger (Lipska, Jaskiw, & Weinberger, 1993; for review see Lipska, 2004). This model is based on hippocampal dysfunction because schizophrenics show a significant increase in size of the lateral ventricles and significantly smaller hippocampi than normal subjects (Eastwood & Harrison, 1999). In this model, animals are given neonatal ventral hippocampal lesions at postnatal day 7 (P7). Several studies have shown that ablation of the ventral hippocampus during development leads to abnormalities in adulthood of numerous dopamine-related behaviors specific to schizophrenia. For example, rats with neonatal lesions exhibit faster cocaine self-administration and have a greater incidence of binge-like cocaine intake than control subjects, suggesting a higher susceptibility to psychostimulant abuse (Lipska et al.). Additionally, this model mimics the effects of changes in DA and GABA markers of mRNA in various regions of the brain that are also seen in human schizophrenics. The neonatal lesion has shown a significant reduction in expression of dopamine transporter (DAT) mRNA in the substantia nigra and VTA as adults. However, adult lesions do not show changes in expression (Lipska, 2003). Behaviorally, neonatal hippocampal lesions produce several behavioral deficits consistent with schizophrenia

including hyperlocomotion, pre-pulse inhibition deficits, social withdrawal, and isolation (Sams-Dodd, 1997) as well as cognitive impairment (Chambers, Moore, McEvoy, & Levin, 1996).

#### *Weaknesses of Past Rodent Models of Schizophrenia*

There are two primary weaknesses of past rodent models of schizophrenia. First, several models have used high doses of drugs that produce neurochemical abnormalities that are similar to schizophrenia. These animal models of dopaminergic hyperactivity do not effectively reproduce the effects of long-term increases in dopaminergic activity as is observed in schizophrenia. In the neonatal hippocampal lesion model, the primary weakness is that there has not been definitive evidence of cell death in the hippocampus in human schizophrenics (Harrison, 1999; Harrison & Eastwood, 2001, 2004). Therefore, there are some weaknesses in this model that may not be accurate relative to the neuropathology in schizophrenia.

#### *A New Rodent Model of Schizophrenia*

Studies from this laboratory have shown that neonatal quinpirole treatment in rats produces a marked D2 supersensitization that lasts throughout the animal's lifetime. Dopamine D2 supersensitization, a phenomenon also known as 'priming,' is manifested behaviorally through hyperlocomotion, increased vertical rearing, increased horizontal activity, and increased yawning. Past research has shown that acute nicotine treatment produces a partial or total block of the effects of the ontogenetic quinpirole treatment on spatial memory tasks (Brown et al., 2002; 2004a; 2004b; 2005) and dopamine-related behaviors (Tizabi, Copeland, Brus, & Kostrzewa, 1999).

#### *Why This is a Valid Rodent Model of Schizophrenia*

The D2 priming model as induced by neonatal quinpirole treatment is an accurate model of schizophrenia for several reasons. Certain physical aspects of schizophrenia suggest that the

disease is not because of neuropathology, or cell death in the brain, but because of a neurodevelopmental abnormality (Domino, Mirzoyan, & Tsukada, 2004). This model exemplifies the developmental change because neonatal quinpirole treatment takes place during the developmental stages of dopaminergic pathways. This model exhibits several key behaviors that are also seen in human patients including prepulse inhibition (PPI) deficits (Maple et al., 2007, manuscript in preparation), increased dopamine response to amphetamine (Nowak, Brus, & Kostrzewa, 2001; Nowak, Brus, Oswiecinska, Sokola, & Kostrzewa, 2002), cognitive deficits (Brown et al., 2004a, 2004b, Green et al., 2002), and significant decreases of neurotrophic factors such as NGF and BDNF in the hippocampus (Brown, Perna, Schaefer, & Williams, 2006; Durany et al., 2001; Toyo'oka, 2002). Pretreatment with the atypical antipsychotic olanzapine (trade name: Zyprexa) has been shown to alleviate deficits in cognitive performance in this model (Thacker et al., 2006).

### *Gender Differences*

Schizophrenia affects both men and women equally, with a later onset of symptoms in women than in men. Women experience less hospitalization because of schizophrenia and function better socially than men. Reasons for later onset of the illness for women are hypothesized to be because women have higher social functioning before the onset of the illness than men, and that estrogen can reduce the sensitivity of the D2 receptors in the central nervous system (McGurk & Mueser, 2004).

### *Gender Differences in Schizophrenia and Nicotine Abuse.*

Past research has shown gender differences in the course and manifestation of schizophrenia. Schizophrenic women demonstrate a later age onset and higher premorbid and overall functioning (Bardenstein & McGlashan, 1990; Goldstein & Kreisman, 1988; Symanski et

al., 1995). Women more often express affective symptomology and are differentially vulnerable to paranoia and hallucinations (Andia et al., 1995). Men more frequently exhibit flat affect and suffer from other negative or deficit symptoms (Symanski & Hertz-Picciotto, 1995). Although there is ample research that demonstrates gender differences in schizophrenia, there is very little information concerning whether there are gender differences in the impact of nicotine abuse in the schizophrenic population. Results suggest higher overall functioning observed in women, and that women schizophrenics smoke less often and are less likely to be substance abusers, fitting with the lower probability of anhedonia present in women schizophrenics (Gearon & Bellack, 2000; Leung & Chue, 2000). Little research that has been done on gender differences in schizophrenia and how gender differences and schizophrenia may interact with the use of nicotine.

*The Estrus Cycle in Female Rats and the Effects of Psychostimulants.*

The estrus cycle of the female rat has three stages, recurs every 4 days (Finch, Felicio, Mobbs, & Nelson, 1984), and is functionally equivalent to the menstrual cycle in humans. The stage of the estrus cycle can be determined by swabbing cells from the vaginal lumen after sterile wash (lavage) and then examining these cells microscopically. Vaginal estrus lasts 36 hours, and cornified epithelial cells are present. Vaginal estrus is followed by a period during which cornified cells become reduced in number, and this stage is called vaginal diestrus with a duration of 48 hours. The first day of diestrus is referred to as diestrus I, and the second day is referred to as diestrus II. The next phase is characterized by the presence of many nucleated epithelial cells and this stage is vaginal proestrus, which lasts for approximately 12 hours. It is important to understand that *behavioral* estrus coincides with vaginal proestrus, and there is elevated estrogen secretion during this period as well as estrous behavior.

Past studies have shown that psychostimulants given during certain stages of the estrous cycle enhance dopamine release in the striatum and produce an exaggerated locomotor response. Becker and colleagues have shown that during behavioral estrus in female rats, amphetamine-induced striatal dopamine release and amphetamine-induced behaviors are greater than on other days of the estrous cycle (Becker, 1999; Becker & Cha, 1989; Becker, Robinson, & Lorenz, 1982). Additionally, female rats show a greater behavioral response when the striatal dopamine system is stimulated during behavioral estrus, which is 6-12 h after the surges of estrogen and progesterone, than they do 24 h later on diestrus and show enhanced sensorimotor function on behavioral estrus compared to diestrus (Becker et al., 1982; Becker & Cha, 1989; Robinson, Camp, Jacknow, & Becker, 1982). During proestrus, striatal dopamine uptake sites are the highest, suggesting a presynaptic effect of gonadal hormones during this phase. Therefore, coincident with the endogenous surges of estrogen and progesterone during behavioral estrus, there is enhanced dopaminergic activity, as indicated by enhanced dopamine release, metabolism, and reuptake (Becker, 1999). Although it appears that there is an increase in dopamine release in females in response to nicotine and some behavioral and metabolic gender differences that exist, there is little evidence that the stage of the estrous cycle is critical to this gender difference. Stage of the estrous cycle was not found to affect nicotine self-administration as compared to males nor affect the rate of acquisition of nicotine self-administration (Donny et al., 2000).

#### *Gender Differences and Nicotine Sensitization*

There have been complex and sometimes contradictory findings relative to gender differences in the response to nicotine. Nicotine has been found to produce more robust locomotor sensitization in female rats than male rats (Booze et al., 1999; Harrod et al., 2004), but

this does not appear to be related to stage of the estrous cycle (Kuo et al., 1999). Additionally, recent findings have shown that nicotine administered iv (50 ug/kg) does not affect normal cycling in females (Harrod et al.) although there is contradictory evidence indicating that a higher dose of chronic nicotine administered via an osmotic minipump (5mg/kg/day) extends the proestrus stage of the cycle (Miyata, Meguid, Varma, Fetissoff, & Kim, 2001).

Several studies have shown that females are more sensitive to the effects of nicotine. Rosecrans (1971 1972) reported that female rats are more chemically and behaviorally sensitive to nicotine than males, and female rats have demonstrated significantly higher endogenous levels of nicotine in the brain as compared to males, suggesting gender differences in response to nicotine (Rosecrans, 1972). More recent work has shown that the increase in NAcc dopamine release is higher in female rats than in males following systemic nicotine treatment (Faraday, O'Donoghue, & Grunberg, 2003). This result may be related to findings that have shown estrogen enhances nicotine-induced dopamine release in striatal slices prepared from ovariectomized rats (Dluzen & Anderson, 1999). However, other findings have shown that this increase in dopamine release related to the estrogen surge does not correlate with nicotine-induced increases of activity in females (Harrod et al., 2004; Kuo et al., 1999).

#### *Gender Differences in Dopamine Receptor Sensitivity*

Several studies have shown gender differences in dopamine receptor sensitivity, as manifested in changes in locomotor behavior. For example, Schindler and Carmona (2002) have reported that although females demonstrate a higher sensitivity to the locomotor activating effects of the dopamine D1 receptor, males demonstrate a higher sensitivity to the locomotor depressing effects of dopamine D2 receptor activation. In a different study, male and female rats administered a dopamine D1 agonist were shown to exhibit an initial inhibitory effect followed

by an increase in activity, and results showed that males were more sensitive to the locomotor inhibitory effect of the D1 agonist than females, whereas the later hyperactive response was greater in females (Hejitz et al., 2002). Regarding the D2 receptor, the locomotor stimulatory effects of quinpirole have been shown to be greater in females than males (Frantz and Van Hartesveldt, 1999; Szumlinski, Goodwill, & Szechtman, 2000). These results appear to show gender differences in dopamine receptor sensitivity in that females demonstrate increases of sensitivity to locomotor stimulatory effects to dopamine agonists and males demonstrate increases of sensitivity to the locomotor inhibitory effects of dopamine agonists. However, it is not known how gender differences in the response to nicotine may interact with long-term increases in sensitivity of dopamine receptors, specifically increases in D2 receptor sensitivity.

*Gender Differences in Yawning Behavior, a Dopamine D2 Receptor Mediated Event*

Although locomotor activity data may suggest an increased sensitivity of dopamine receptors in females, we have demonstrated a reverse pattern in yawning behavior in adult rats. Recent data from this laboratory have shown that males and females neonatally treated with quinpirole both demonstrate a significant increase in yawning as compared to saline controls when tested for 1 hour after an acute quinpirole injection as adults, but males show approximately a three-fold increase in yawning compared to females (Brown et al., 2006a). Additionally, early postnatal male rats demonstrate a more severe deficit in cognitive performance as compared to females when administered a dopamine D2 antagonist immediately before training (Brown et al., 2005). These observations suggest that the sensitivity of the D2 receptor in males is increased in its relationship to cognitive function as compared to females. Regardless, it is very important to realize that locomotor sensitization, yawning, and cognitive function are three different behaviors that involve distinctly different brain areas and pathways, and clearly it appears that

the relationship of gender differences in dopamine D2 receptor sensitivity may affect these behaviors in very different ways.

#### *Age differences: Adolescent vs. Adult Drug Addiction*

Adolescent exposure to drugs of abuse has been shown to have a different outcome from exposure in adulthood. Special consideration has recently been given to nicotine addiction in adolescents. This research has shown that adolescent drug exposure leads to greater addiction, higher consumption, and a decreased rate of quitting as compared to adults (Chen et al., 1998). Age-related changes have also been found in gene expression and in cell number, along with a long term change in the reward pathway of adolescents (Kelley & Middlaugh, 1999). Trauth, McCook, Siedler, and Slotkin (2000) have shown that adolescent nicotine exposure produces significantly decreased cholinergic activity in the hippocampus during drug treatment but not in other regions of the brain, and these changes persist for up to 1 month posttreatment. This supports the hypothesis that this is a critical time period for change in certain brain areas of the adolescent rat.

#### *Dopamine System Differences in the Adult vs. the Adolescent Brain*

Research by Haycock et al. (2003) suggests that the difference between the dopamine system between adolescents and adults can be explained by neural organization and development. In humans, during the first 2 years of life, the dopamine system is undergoing significant growth, which continues until about the age of 30, where growth tends to taper off and eventually, in later adulthood, dopaminergic growth declines and cells begin to die in advanced age. However, during adolescence, the growth of the dopamine system is more rapid and elaborate because of reorganization and remodeling of the innervation of the dopamine

system. During this time, growth is especially observed in the prefrontal cortex and in the mesolimbic pathways, including the growth of dopaminergic pathways in all areas (Spear, 2000).

Badanich and Kirsteina (2004) have reported behavioral and neurochemical differences because of nicotine exposure in adult versus adolescent rats. Animals were treated with acute or chronic nicotine exposure during early adolescence, late adolescence, or early adulthood. Acute nicotine exposure in adult animals showed an increase in the dopamine release in the nucleus accumbens in response to a nicotine challenge, while adolescents did not demonstrate a significant increase in dopamine release. Interestingly, chronic exposure did not increase the dopamine response in adolescents or adults. These results suggest that acute exposure to nicotine in adults may cause a significant increase in dopamine response that is not apparent after repeated exposures because of tolerance to the drug. Additionally, other behavioral studies have shown that adolescent animals exposed to nicotine in a conditioned place preference paradigm prefer the drug paired chamber to the non-drug paired chamber, whereas adults do not show this preference for the drug paired chamber (Torella et al., 2004). All of these results suggest different organization of the dopamine system in the adolescent versus the adult.

#### *Nicotine's Effects on Adolescent Behavior and Importance*

Because adolescence is a critical time for the reorganization of neuronal pathways, these individuals are more susceptible to the addictive effects of drugs of abuse (Adriani et al., 2004). During adolescence, individuals are more likely to seek out new situations, sensations, and risks making them more likely to try new things, including drugs. Research has shown that drug exposure and drug use in adolescence may contribute to drug use and addiction later in life. Two explanations for this early exposure effect are that early exposure may alter the development of critical brain areas at that time, and that novelty seeking behavior in adolescence may predict

later abuse. Barron et al. (2005) has shown that pre-teen exposure to nicotine is predictive of alcohol abuse.

Research by Trauth, Siedler, Ali, and Slotkin (2001) and Slotkin et al. (1999) has shown that adolescent exposure to nicotine produces an overall change in the structure and upregulation of nicotinic receptors that differs from what is observed during adult exposure to nicotine. Robust receptor upregulation has been shown in both adolescents and adults, but there were major differences in the regional specificity and persistence of effect. In adolescents, upregulation was uniform across all regions during the infusion period, whereas in adults, there was a distinct regional hierarchy: midbrain < cerebral cortex < hippocampus. Accordingly, receptors in the adolescent midbrain were upregulated far more than with adult exposure. In addition, adolescent nicotine treatment produced long-lasting effects on the receptors, with significant increases still apparent in male rats 1 month after the termination of drug exposure, whereas this was not the case in adults. Additionally, evidence for hippocampal cell damage has been shown in adolescent female rats exposed to nicotine, characterized by increases in total membrane protein concentration indicative of a decrease in overall cell size. Adolescent nicotine exposure thus elicits region- and gender-selective effects that differ substantially from those in adults, effects that may contribute to increased addictive properties and lasting deficits in behavioral performance. Other research has shown that brain areas rich in dopamine, mainly the prefrontal cortex and the mesolimbic regions of the brain, show marked changes and development during adolescence (Spear, 2000).

#### *Competing Theories of Differences in Adolescent and Adult Responses to Drugs of Abuse*

There are two competing theories for the underlying mechanisms of adolescent addiction to drugs of abuse. The first theory states that adolescents have underdeveloped neural circuitry

that may underlie impulsivity and addiction vulnerability. According to this theory, adolescents are less likely to consider the negative repercussions of behavior, more likely to base decisions on proximal outcomes rather than distal outcomes, and may be better motivated by reward than by punishment. During this time, the activation of the ventral striatum is disproportionately higher than the influence of the inhibitory circuits (Kelley, Schochet, & Landry, 2004).

The second theory states that risky behavior in adolescence results from a relatively overactive ventral striatal motivational circuit that readily approaches salient appetitive cues (Cardinal, Winstanley, Robbins, & Everitt, 2004) Behavioral studies have shown that adolescents are more motivated by immediate rather than delayed reinforcement. Because of underdeveloped circuits, adolescents do not maintain motivation for gain between performing a behavior and waiting for the reward, making them more motivated by immediate reinforcement (Badanich & Kirsteina, 2004).

### *Neurotrophic Factors*

Neurotrophic factors in the brain were originally thought only to control the growth and differentiation of cells in the brain during development but are now known to play a major role in regulating plasticity and survival of adult glia and neurons (Shoval & Weizman, 2005). Recently, Hashimoto, Shintani, and Baba (2006) showed that alteration of neurotrophic factors during different stages in development may lead to pathological disorder. In schizophrenia, it has been shown that size abnormalities in the entorhinal, cingulate, and prefrontal cortex stem from disruptions in proliferation in early corticogenesis causing marked damage to these areas. In development, there are increased levels of neurotrophic factors in the hippocampus as compared to other brain areas. Also, findings show that schizophrenics have a reduced amount of neurotrophins in brain tissue supporting the hypothesis of their involvement in the

neuropathology of the disease (Durany et al., 2001, 2004; Shoval & Weizman, 2005). Reductions in the prefrontal cortex and entorhinal and cingulate cortex areas of the brain lead to alterations in the synthesis and release of certain neurotrophic factors, namely nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (McGurk & Meuser, 2004). Reductions in these areas are also found in the brains of schizophrenic patients.

Research has shown that chronic drug exposure causes changes in neurotrophic factors, typically NGF and BDNF, which may lead to psychostimulant addiction. Nicotine has been shown to produce a significant increase of both NGF and BDNF in the hippocampus and in frontal cortex (Brown et al., 2006b; French et al., 1999). Although other psychotimulants, such as cocaine and amphetamine have been shown to produce a significant increase in BDNF in the nucleus accumbens, there is no information relative to the effects of nicotine on this important brain area in drug reward. However, Brown and Kolb (2001) have shown that exposure to nicotine produces a 35% increase in spine length and density of dendrites in the nucleus accumbens, suggesting the possibility of changes in neurotrophic factors in the nucleus accumbens.

### *Research Problem*

Research has shown that there is a significant increase in dopamine (DA) function in schizophrenia, especially at the dopamine D<sub>2</sub> receptor (Nissel, Marcus, Nomikos, & Svensson, 1997). Kostrzewa et al. (1995) have shown that neonatal quinpirole (a dopamine D<sub>2</sub>/D<sub>3</sub> agonist) treatments produce long-term increases in D<sub>2</sub> receptor sensitivity that persists throughout the animal's lifetime. Koeltzow, Austin, and Vezina (2003) have shown that blockade of DA receptors block increases of locomotor activity and that chronic treatment of quinpirole produces locomotor sensitization. In addition, nicotine produces increases in locomotion, which can also

be blocked by blocking the D2 receptor (Clarke, Fu, Jakubovic, & Fibiger, 1988). Brown et al. (2006) have shown that neonatal quinpirole treatment produces decreased levels of nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) in the hippocampus, and that this deficit is alleviated by nicotine treatment in adulthood.

There is little information on the difference between adolescent and adult rats on sensitization to nicotine, and there is no information as to how this variable may interact with priming of the D2 receptor, gender differences in behavior, nor how this may be manifested in differences in BDNF in brain areas known to mediate drug reward in D2-primed and non D2-primed rats. In Experiment 1, both male and female rats will be neonatally treated with quinpirole, a dopamine D2/D3 agonist, which has been shown to prime the dopamine D2 receptor. We will sensitize both D2-primed and non D2-primed male and female adolescent and adult rats to nicotine. Postmortem, the NAcc will be assayed for BDNF.

The aim of this thesis is two -fold: 1) To measure behavioral differences, namely increases or decreases in locomotor activity, in D2-primed and non-primed male and female adolescent and adult Sprague-dawley rats; 2) Analyze differences in brain derived neurotrophic factor (BDNF) in the nucleus accumbens, a brain area important in the rewarding effects of nicotine. We hypothesize that: Animals neonatally treated quinpirole (D2-primed) will show increased activity as compared to animals neonatally treated with saline and D2-primed animals administered nicotine will show more robust sensitization as compared to all other groups. Female animals will show more increased sensitization than males, with D2-primed females administered nicotine demonstrating the most robust sensitization over all groups. As for BDNF, we hypothesize that neonatal quinpirole treatment will cause a decrease in BDNF in the nucleus accumbens and that adolescent or adulthood nicotine treatment will alleviate the deficit.

## CHAPTER 2

### METHODS

#### *Subjects*

Adolescent animals were 35 days old and were randomly assigned to drug groups by gender and neonatal treatment. Animals were derived from eight litters and were assigned as follows (the first drug represents neonatal treatment and the second drug represents adolescent drug treatment): Quinpirole-Nicotine, four females and seven males; Quinpirole-Saline, five females and eight males; Saline-Nicotine, four females and seven males; Saline-Saline, four females and seven males.

Adult animals were 60 days old and were randomly assigned to drug groups by gender and neonatal treatment. Animals were derived from seven total litters and were assigned as follows (the first drug represents neonatal treatment and the second drug represents adult drug treatment): Quinpirole-Nicotine, six females and seven males; Quinpirole-Saline, five females and five males; Saline-Nicotine, five females and seven males; Saline-Saline, six females and five males.

#### *Neonatal Drug Treatment*

Animals were given a single daily intraperitoneal (i.p.) injection of either quinpirole (1mg/kg) or saline from postnatal day 1-21 (P1-21). All animals were administered 1mg/kg quinpirole based on body weight. Different groups of male and female rats were raised to adolescence (P30) or adulthood (P60).

#### *Habituation to the Locomotor Arena*

The day following the yawning test (which is used to verify D2 supersensitivity), all animals were given i.p. injections of saline for the next 3 testing days and all animals were

placed in the locomotor arena (30 cm on a side) covered by a grid of white lines. This task provided a baseline activity measure and habituated the animal to the locomotor apparatus. There were four groups, with the first treatment administered neonatally and the second treatment administered in adolescence or adulthood: Saline-Saline, Saline-Nicotine, Quinpirole-Saline, Quinpirole-Nicotine.

#### *Locomotor Sensitization*

Following habituation, half of the animals were given i.p. injections of nicotine tartarate (0.5 mg/kg free base) and the other half were given saline every second day. Fifteen minutes after each injection the animals were placed in the locomotor arena for 10 minutes and the number of grid line crossings were recorded by an experimenter, which served as a measure of horizontal activity. Testing was performed for 9 days in all groups.

#### *Procedure, Research Design, and Analysis*

Animals were randomly assigned to each drug condition, with one animal per drug condition from each litter to control for across litter variability. For initial analyses of locomotor activity, a four -way ANOVA was used. The independent variables were two between groups of neonatal drug treatment (Quinpirole or Saline), adolescent or adulthood drug treatment (Between: Nicotine, Saline), sex (Between: Male, Female), and trial block (Three within levels: Trial block 1, 2, and 3). The dependent variable was the number of horizontal line crossings. The trial block measure was the average of three daily training sessions. Fisher's LSD tests were used for the post hoc test (alpha level = .05).

#### *BDNF Procedure*

Twenty-four hours after testing, the brains were harvested and flash frozen in cold isopentane (-20°C) and stored at -80°C. Nucleus accumbens (Nacc) was dissected from the

tissue samples and homogenized in a RIPA cell lysis buffer. After homogenization, tissue samples were analyzed using a BDNF sandwich ELISA kit purchased from Promega (Madison, WI). For the BDNF assay, 10  $\mu$ l of the anti-BDNF monoclonal antibody (mAb) was added to 9.99 ml of carbonate coating buffer (pH 9.7). To each well of the ELISA plate, (Nunc, MaxiSorp, 96 well polystyrene plate) 100 $\mu$ l of the carbonate coating buffer was added and incubated overnight at 4° C to coat the plate. All wells were washed with PBS-T and incubated at room temperature for 1 hour. Nonspecific binding was blocked with 1x block and sample buffer and incubated at room temperature for 1 hour. The BDNF standard curve was prepared using serial dilutions of the BDNF standard supplied by the manufacturer (1 $\mu$ g/ml). The standard was diluted 1:2,000 to achieve a concentration of 500 pg/ml. The Nacc was further diluted 1:2 prior to being assayed. The standards and samples were incubated with shaking at room temperature for 2 hours. Anti-Human BDNF pAB was then added to each well plate, incubated at room temperature for 2 hours, which was followed by incubation (1hour) with Anti-IgY horseradish peroxidase (HRP) conjugate. Finally, 100  $\mu$ l of TMB one solution was added to each well and incubated at room temperature to achieve color transformation. The reaction was stopped by adding 1N hydrochloric acid and read within 30 minutes using a Biorad plate reader. Optical density was measured using a Biorad 96-well plate reader.

## CHAPTER 3

### RESULTS

#### *Gender Differences in Adolescents*

##### *Horizontal Activity for Adolescent Females*

Horizontal activity is presented as a function of week of testing in Figure 1. A 2 x 2 x 3 repeated measures ANOVA revealed a significant two-way interaction of Neonatal Drug Treatment x Adolescent Drug Treatment  $F(1,22) = 9.95, p < .009$  and Adolescent Drug Treatment x Week of Testing  $F(2,22) = 5.42, p < .01$ . The Fisher's LSD post hoc test revealed a significant decrease in activity in D2-primed and non D2-primed animals receiving nicotine in week 1. D2-primed animals demonstrated a significant increase in locomotion as compared to saline animals in week 2, but not in weeks 1 or 3; however, the decrease in activity in the Q-N group in week 3 was because of increases in stereotypic behavior (notated by #). Nicotine induced a decrease in activity in both D2-primed and non D2-primed animals as compared to saline controls in the first week of testing.

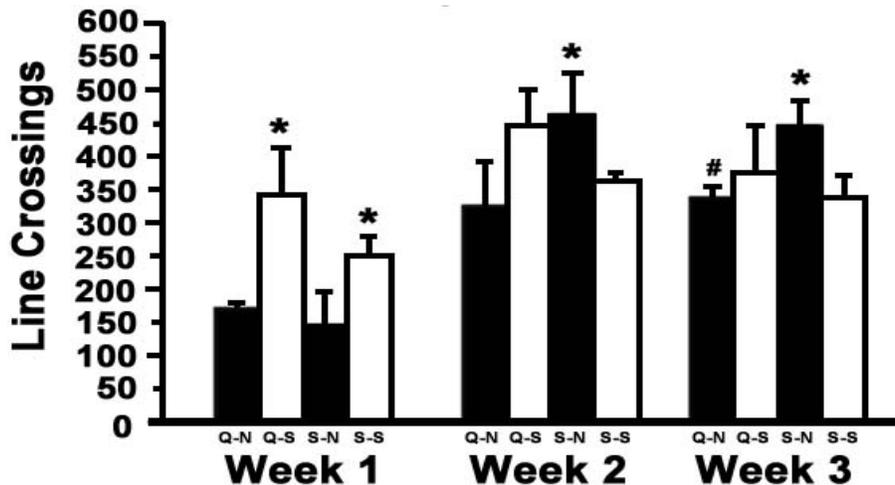
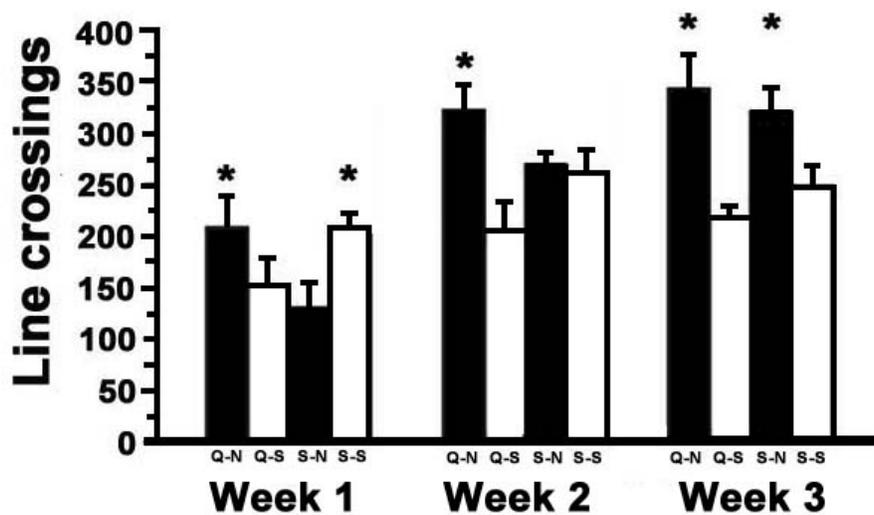


Figure 1. Horizontal Activity for Adolescent Females

### *Horizontal Activity for Adolescent Males*

Horizontal activity is presented as a function of week of testing in Figure 2. A 2 x 2 x 3 repeated measures ANOVA revealed a significant main effect of adolescent drug treatment  $F(1,25) = 10.34$ , week of testing  $F(2,25) = 46.88$ ,  $p < .001$ , a significant two-way interactions of Neonatal Drug Treatment x Adolescent Drug Treatment  $F(1,25) = 8.14$ ,  $p < .009$  and Adolescent Drug Treatment x Week of Testing  $F(2,25) = 13.47$ ,  $p < .001$ . The Fisher's LSD post hoc test revealed that D2-primed males receiving nicotine did not show a decrease in week 1 as compared to non D2-primed males receiving saline. However, non D2-primed males receiving nicotine did show a decrease in activity in week 1. In week 2, D2-primed males receiving nicotine showed a significant increase in activity as compared to all other groups. In week 3, D2-primed and non D2-primed animals receiving nicotine showed increased activity as compared to animals receiving saline, but these two groups were equivalent. Interestingly, D2-primed males receiving saline did not show increased activity over non D2-primed animals receiving saline.



*Figure 2.* Horizontal Activity for Adolescent Males

## *Gender Differences in Adults*

### *Horizontal Activity for Adult Females*

Horizontal activity is presented as a function of week of testing in Figure 3 for adult females. A 2 x 2 x 3 repeated measures ANOVA revealed a significant main effect of neonatal drug treatment  $F(1,18) = 4.74, p < .04$ , a significant main effect of week of testing  $F(2,18) = 67.15, p < .001$ , a significant interaction of Neonatal Drug Treatment x Week of Testing  $F(2,18) = 5.71, p < .007$  and a significant interaction of Adulthood Drug Treatment x Week of Testing  $F(2,18) = 21.88, p < .001$ . The separate analysis of estrous cycle revealed no significant main effects or interactions involving the stage of the estrous cycle (all effects  $p > .01$ ). This is consistent with past data that have shown stage of the estrous cycle in female rats does not interact with nicotine behavioral sensitization (Booze et al., 1999). Fisher LSD post hoc tests revealed D2-primed females administered nicotine demonstrated a significant increase in activity relative to all other groups in week 3. Nicotine induced a significant decrease in initial activity in both D2-primed and non D2-primed rats compared to controls administered saline. D2-primed females demonstrated a significant increase in activity relative to controls and statistically equivalent levels of activity compared to controls administered nicotine in week 3 (notated by #). D2-primed females administered saline showed a significant increase in locomotor activity as compared to non D2-primed animals administered saline. This significant increase in locomotion persisted throughout the 3 weeks of training.

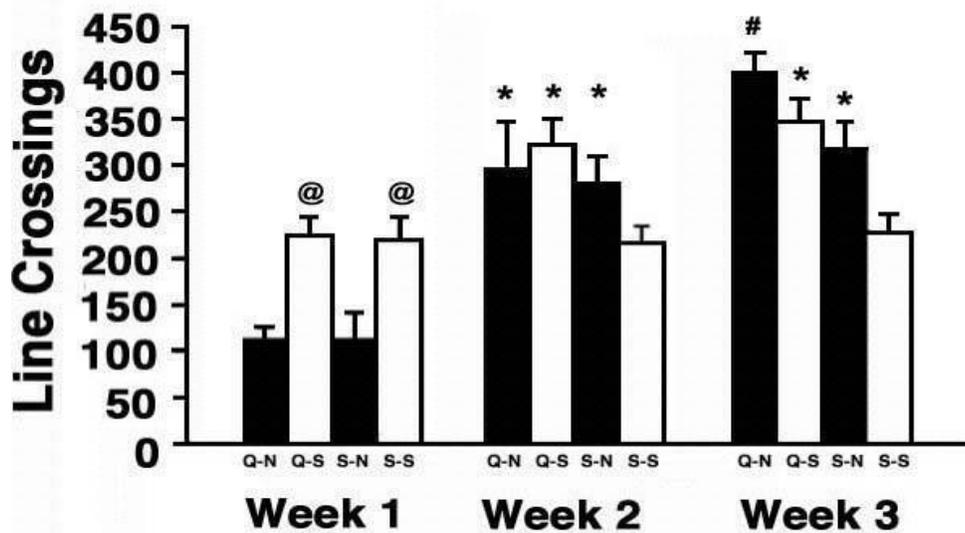


Figure 3. Horizontal Activity for Adult Females

*Horizontal Activity for Adult Males*

Horizontal activity is presented as function of week of testing in Figure 4 for adult males. A 2 x 2 x 3 repeated measures ANOVA in males revealed a significant main effect of adulthood drug treatment  $F(1,20)=13.47$ , week of testing  $F(2,20)=32.48$ , and a significant interaction of adulthood drug treatment x week of testing  $F(2,20)=19.06$ ,  $p<.001$ . Fisher LSD Post hoc tests revealed: D2-primed males administered nicotine demonstrated a significant increase in activity relative to all other groups in week 3 of testing. Male rats administered nicotine did not demonstrate the typical initial nicotine-induced hypoactivity in week 1 of testing, but nicotine produced a significant increase of activity in males at weeks 2 and 3. Control animals administered nicotine demonstrated a significant increase in activity relative to D2-primed and non D2-primed animals given saline at weeks 2 and 3. Unlike females, D2-primed males treated with saline did not demonstrate a significant increase in horizontal activity over the 3 weeks of testing.

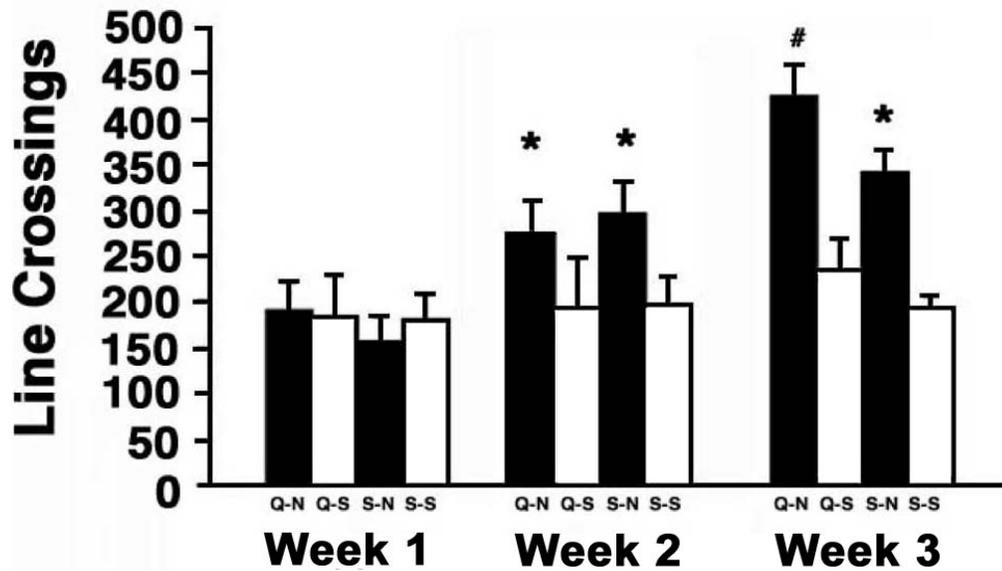


Figure 4. Horizontal Activity for Adult Males

#### *BDNF Results*

##### *Adolescent BDNF Results*

A two-way ANOVA revealed a significant main effect of sex  $F(1,21) = 8.32, p < .009$ , drug  $F(1,21) = 5.67, p < .027$ , and an age main effect  $F(1,21) = 4.77, p < .027$ . For adolescents, there was no significant main effect of neonatal drug treatment on BDNF levels (Figure 5), as was seen in adults (see Figure 6). However, there was a significant main effect of gender that was not seen in adults. Females administered nicotine during adolescence showed increased BDNF levels over all groups, while male animals administered nicotine during adolescence did not show an increase over male animals administered saline during adolescence.

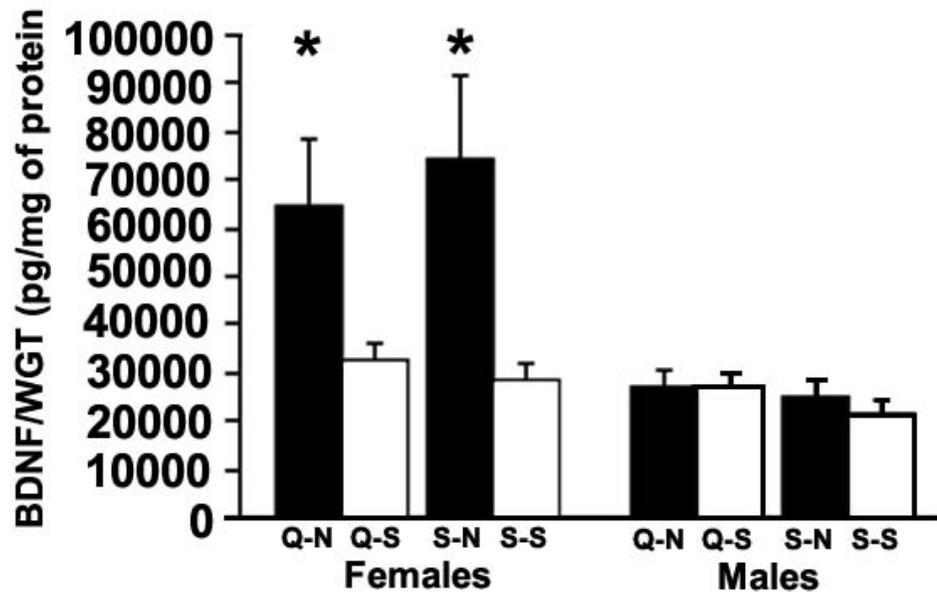


Figure 5. Adolescent BDNF Results

*Adult BDNF Results*

A two-way ANOVA revealed no significant main effects of neonatal drug treatment nor adulthood drug treatment, but the interaction of Neonatal Drug Treatment x Adulthood Drug Treatment was significant  $F(1,28) = 6.35, p < .017$ . Fisher's LSD tests revealed that D2-primed animals administered saline demonstrated a significantly lower level of BDNF relative to all other groups, demonstrating that nicotine treatment reversed the decrease in BDNF produced by neonatal quinpirole treatment.

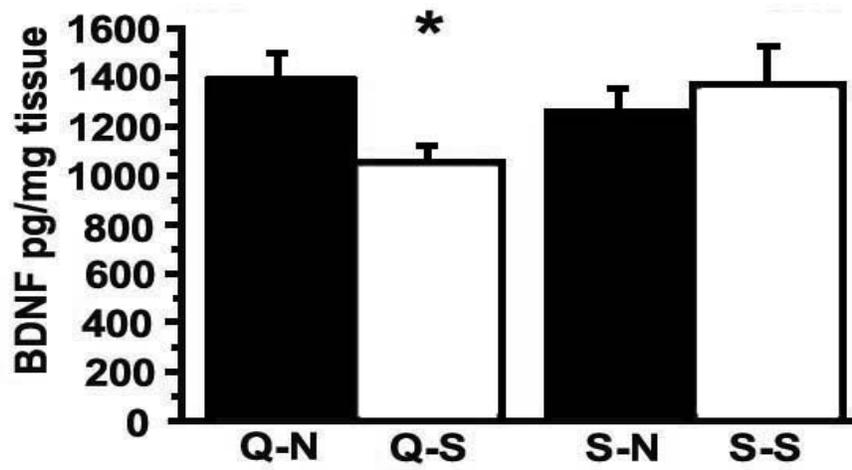


Figure 6. Adult BDNF Results

## CHAPTER 4

### DISCUSSION

These results suggested that neonatal treatment with the dopamine D2/D3 agonist quinpirole resulted in dopamine D2-receptor priming that resulted in more robust behavioral sensitization to nicotine in both adolescent and adult rats. Previous studies have shown that nicotine increases dopaminergic neurotransmission through its agonist action at nicotinic receptors located presynaptically on dopamine terminals (Marshall, Redfem, & Wonnacott, 1997). Because nicotine acts to increase dopamine release on primed postsynaptically-located D2 receptors, a significantly increased dopaminergic response to nicotine explains the more robust sensitization to nicotine observed in the present study. However, there were significant age and gender differences in response to neonatal, adolescent, and adulthood drug treatment, and these will be discussed below.

#### *Adolescent Results*

Overall, D2-primed male and female adolescent rats administered saline showed a significant increase in activity as compared to non D2-primed animals, consistent with previous reports from Frantz and Van Hartesveldt (1999), which showed increased locomotor activity because of repeated exposures to quinpirole. However, D2-primed females administered saline showed a significant increase over all groups in the first week of testing but did not show a significant increase in locomotion over the 3 weeks of testing. Interestingly, D2-primed adolescent male rats administered saline demonstrated a slight but significant increase over the 3 weeks of testing, although not equal to the magnitude of the females. This finding appears to be consistent with past findings showing that there are sex differences in the D2 receptor that are manifested in changes in activity, and adolescent females demonstrated both increased D2

sensitivity and significant increases in activity (Frantz & van Harestveldt, 1999; Schindler & Carmona, 2002).

Both D2-primed and non D2-primed adolescent males and females treated with nicotine showed a significant increase in locomotor activity over the 3 weeks of testing as compared to saline treated control animals, with the most robust increase in locomotor activity observed during the third week of testing. This is consistent with past data by Adriani et al. (2006) that showed increased behavioral effects of nicotine in adolescent animals, with increased locomotor activating effects occurring because of repeated nicotine administration.

During the first week of testing, D2-primed males did not demonstrate a hypoactive response to nicotine, whereas D2-primed and non D2-primed females as well as non D2-primed males all demonstrated a hypoactive response to the drug. This result appears to show that neonatal quinpirole blocks the hypoactive response to nicotine in adolescent males but not in female adolescents. Faraday, O'Donoghue, and Grunberg (2003) have shown that the hypoactive response to nicotine is dose-dependent in adolescent males, and a 0.5 mg/kg free base dose produces a hypoactive response in male adolescents, but neither a lower dose, 0.1 mg/kg, nor a higher dose, 1.0 mg/kg, produced the same effect. This suggests that adolescent males may be more sensitive to the locomotor activating effects of the dopamine system because neonatal quinpirole treatment blocks the hypoactive response to nicotine in this group. This effect may be because of the receptor sensitivity differences in males as compared to females but also may suggest that nicotine does not attenuate the hyperlocomotion effects in adolescent males as has been shown in adult animals (Schindler & Carmona, 2002). Although a past study by Tizabi et al (1999) using ontogenetic quinpirole treatment has shown that nicotine blocks the locomotor activating effect of quinpirole in young adolescent rats, Tizabi, et al (1999) used only acute

nicotine treatment and did not analyze subchronic nicotine treatment across adolescence as in the present study.

Dopamine D2-primed adolescent females appear to demonstrate a significant *decrease* in locomotor activity after subsequent nicotine administrations in weeks 2 and 3. This decrease in locomotor activity appears on the surface to be paradoxical, as presumably dopamine activity is increasing with subsequent nicotine administrations, and locomotor activity should positive correlate with this action. However, upon further observation, we have found that these D2-primed female adolescent rats administered nicotine appear to increase stereotypic behaviors related to increases in dopamine activity, including paw treading, vacuous chewing, and stereotypic motor movements. Several studies have shown a significant increase in stereotypic behaviors when the dopamine system is significantly elevated (Szechtman, Sulis, & Eilam, 1998; Tizabi et al., 2002), and this significant increase in stereotypic activity resulted in an overall decrease in locomotor activity. Thus, we hypothesize the dopamine system may be further elevated in D2-primed female adolescents as compared to D2-primed male adolescents, which could be related to sex differences in dopamine D2 receptor sensitivity in adolescents (Frantz & Van Hartesveldt, 1999) or possibly related to increases in the dopamine system in response to psychostimulants in females as compared to males (Becker, 1999). This issue is currently under investigation in our laboratory, as we have recently collected microdialysis samples from the nucleus accumbens core of both D2-primed and non D2-primed male and female adolescent rats that were sensitized to nicotine identical to this study, and those samples will soon be analyzed.

#### *Adult Results*

Adult D2-primed females administered saline demonstrated a significant increase in locomotor sensitization that persisted throughout training, an effect that was not observed in

adult male animals. This effect again may be related to sex differences in dopamine D2 receptor function in adults. Interestingly, D2-primed female adult rats administered saline demonstrated a significant *increase* in locomotor activity as compared to the first week of training, but this did not occur in D2-primed male adult rats nor in D2-primed adolescent rats. This appears to indicate an age and gender difference in the dopamine system that appears to be related to locomotor activity (Frantz & Van Hartesveldt, 1999; Schindler & Carmona, 2002). The adult female Q-S group demonstrated an increase in locomotion by week three that was not mimicked in adult males. The adolescent female Q-S group also showed increased activity as compared to female controls, but this effect was not as robust as observed in adults. This appears to indicate that an increase of D2 receptor sensitivity produces a significant increase in activity in females, which is a different pattern of activity as compared to males. This result is consistent with past findings by Schindler and Carmona (2002) that have shown increases in locomotor activity in adult female rats when the D2 receptor is activated as compared to males.

Dopamine D2-primed adult males and females administered nicotine demonstrated more robust sensitization to nicotine in week 3 of testing as compared to non D2-primed animals administered saline. Both groups also significantly increased locomotion across weeks. We hypothesize that this increase in locomotor sensitization is because of the increase in dopaminergic activity at D2-primed synapses (Nowak et al., 2001, 2002). Additionally, D2-primed females showed significantly increased levels of locomotion as compared to males in the current study. This is consistent with past results by Booze et al. (1999) who showed that repeated i.v. administration of nicotine to resulted in an overall increase in activity in females as compared to males. Although there are little data comparing the locomotor effects of nicotine on males versus females, similar effects are found with administration of the psychostimulant

cocaine. Cocaine administration caused significant increases in locomotor activity in all animals with females exhibiting a heightened effect of the drug as compared to males. Females showed a greater sensitivity to the D1 antagonist SCH 23390, but both groups showed equal sensitivity to the D2 antagonist eticlopride.

Non D2-primed adults administered nicotine also demonstrated a significant increase in locomotor activity at week 3 as compared to non D2-primed adults administered saline, with a more robust increase in sensitization between weeks 1 and 2 as compared to the differences in activity between weeks 2 and 3. This is consistent with past work by Faraday et al. (2003) that demonstrated a more robust increase in activity in the first six exposures to nicotine, with activity levels tapering off over the last six exposures to nicotine. Interestingly, in both past studies and the current study, a hypoactive response to nicotine was observed in the first exposure to the drug (Bevins & Palmatier, 2003; Dwoskin et al., 1999; Faraday et al., 2003), an effect that was seen in both male and female adult animals, but not in D2-primed adolescent male animals.

#### *A Comparison of Adolescent Versus Adult Results*

In fact, past studies by Schindler and Carmona (2002) and Frantz and Van Hartesveldt (1999) have shown a significant sex difference in dopamine D2 sensitivity in adolescent rats. These studies have shown that male adolescents have a heightened response to quinpirole that tapers off in adulthood. Contrary to results observed here, Cruz, Delucia, and Planeta (2005) showed that adult but not adolescent males show locomotor sensitization because of repeated exposure to nicotine. However, this study used a lower dose of nicotine (.4mg/kg) and a different route of administration (subcutaneous) than the current study, which may contribute to contradictory results.

### *Proposed Mechanism*

We hypothesize that the significant increase in activity as observed in both D2-primed adolescent and adult rats observed in the present study is because of the action of nicotine at dopaminergic synapses. Nicotine acts to increase dopamine (DA) release by acting at presynaptically located nicotinic receptors (nAChRs), which are presynaptically located on dopaminergic terminals in the nucleus accumbens (Barik & Wonnacott, 2006). When nicotine binds to the nAChR, calcium enters the cell and binds to the protein complex calmodulin that carries synaptic vesicles containing dopamine to the cell membrane. Dopamine is then released, diffuses across the synapse, and binds to primed (indicated by the '+' in Figure 7) dopamine D2 receptors, increasing the overall dopaminergic response in D2-primed rats given nicotine. Further, it is now known that nicotine blocks the action of dopamine on the presynaptically located D2 autoreceptor, increasing the dopaminergic response (Barik & Wonnacott, 2006). Therefore, an increased dopaminergic response to nicotine explains the more robust nicotine sensitization observed in the present study. However, it is likely, that the D1 receptor is playing the more important role in locomotor sensitization to nicotine. Essentially, the primed D2 receptors may produce an overall increased dopaminergic response, but the action of dopamine at D1 receptors is responsible for the increased locomotor sensitization, based on the several studies that have shown that the D1, and not the D2 receptor, plays a more important role in sensitization to psychostimulants (Vezina & Stewart, 1989) Additionally, females demonstrate a significant increased locomotor response because of increases of sensitivity in the dopaminergic system, and females have shown a significant increase in dopamine release in response to nicotine as compared to males in a past study (Faraday, O'Donoghue, & Grunberg, 2003).

### *Alternative Explanations for This Proposed Mechanism.*

Nicotine has been shown to have substantial effects on other neurotransmitters, thus, there are alternative explanations for the phenomena shown here. For instance, several studies have shown that pretreatment with glutamatergic NMDA antagonists block nicotine sensitization (Domino, 2001; Kelsey, Beer, Wagner, et al., 2002; Shoaib, Benwell, Akbar, Stolerman, & Balfouret, 1994; Shoaib, Schindler, Goldberg, & Pauly, 1997; Shoaib, Shippenberg, Goldberg, & Schindler, 1995;). Other results have confirmed that glutamate transmission may control dopamine-dependent locomotor function and synergistically combine with D2 receptor activation (David et al., 2002). If this is the case, glutamate may be acting on primed D2 receptors ultimately resulting in an increased dopamine response. Relevant to this explanation, Carlsson et al. (2000) have proposed that glutamate and dopamine functionally antagonize each other when stimulating the striatal GABA-ergic projection neurons, resulting in overall depressed neuronal activity. Smoking may counteract this functional antagonism through increasing the activity of both dopamine and glutamate. Regardless, the majority of the evidence has shown that nicotine increases dopamine release in the NAcc core through direct agonist action at nicotinic receptors, and this increased dopamine release plays a primary role in nicotine locomotor sensitization (Di Chiara et al., 2004; Shim, et al., 2001; Shoaib et al., 1994).

### *BDNF Results: Adolescents*

BDNF analyses revealed that nicotine produces a significant increase in BDNF in the nucleus accumbens in adolescent females but not adolescent males. Interestingly, neonatal quinpirole treatment did not produce any significant effect in adolescents. This increase in BDNF in females actually is consistent with findings that shown increases of BDNF activity in the nucleus accumbens produces a significant increase in activity (French et al., 1999), and

several studies have shown overall significant increases in activity in females as compared to males, and this sex difference is especially prevalent in adolescent females (Durany, 2001; French et al, 1999). The mechanism by which this occurs is unknown but is presumably because of the increases in dopamine system that have been shown to be heightened in females after psychostimulant administration (Becker, 1999).

Another issue here is that brain tissue was taken from these females when they were 50 days of age, and female rats begin estrus cycling around 42 days of age. Thus, these females have only been cycling for roughly a week when this tissue was taken, and surges in estrogen may be especially robust at this age, which may have affected our results. As discussed below, there was not a sex difference observed in adults, so this increase in BDNF produced by nicotine appears to be an age-related effect.

#### *BDNF Results: Adults*

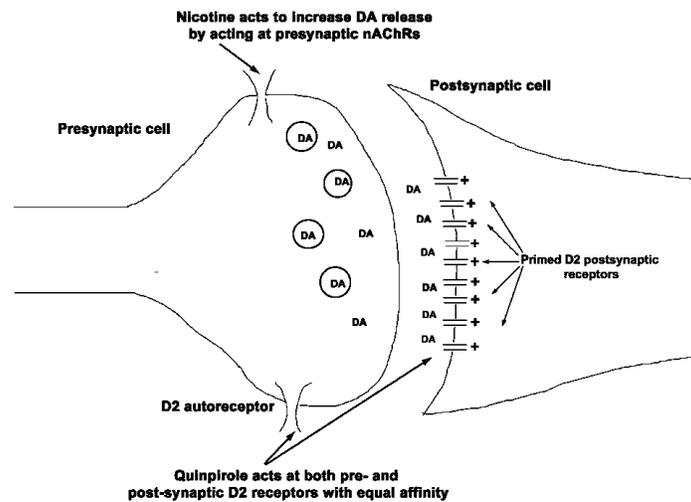
BDNF analyses revealed that neonatal quinpirole treatment produced a significant decrease in BDNF in the nucleus accumbens that was alleviated by adulthood nicotine treatment. Interestingly, nicotine treatment alleviated significant decreases in NAcc BDNF of D2-primed animals, similar to past reports from this laboratory demonstrating that subchronic nicotine administration alleviates significant decreases of BDNF levels in the hippocampus (Brown et al. 2006). These similar findings may be because of a similar mechanism, or it may indicate a relationship in dopaminergic activity between these two brain areas. For example, increased activity in the hippocampus because of amphetamine may be because of modulation of the hippocampus by the nucleus accumbens (White, Whitaker, & White, 2006) However, recent research from this laboratory has shown that nicotine treatment produces a significant decrease in BDNF levels in the hippocampus of non D2-primed adult female animals but not in males

(Brown et al. 2006). This clearly shows that there may be sex differences in BDNF activity in response to nicotine that appears to produce differential changes depending on the brain area analyzed.

One possibility is that dopamine D2-primed adolescent and adult males administered saline do not show significantly increased locomotor activity over time, possibly because of the fact that they are deficient in BDNF; however, nicotine increases BDNF, therefore producing an increased locomotor sensitization response. This effect may be purely correlational, or may be indicative of a change in neurochemistry rather than a change in behavior related to BDNF. Conversely, D2-primed adolescent and adult females administered saline both demonstrated significant increases in activity over days of testing, yet female adults showed decreased levels of BDNF, and female adolescents showed no change in BDNF levels as compared to control animals. There were no sex differences in BDNF levels in adults, suggesting that BDNF either is not related to locomotor activity, or that BDNF plays a role in locomotor sensitization in adult males but not in adult females. Other studies have shown that BDNF appears to play a role in locomotor sensitization, but to date, no study has examined the relationship between locomotor sensitization and BDNF protein levels in rat brain tissue. Interestingly, there has also been no study to examine sex differences in BDNF levels. Past studies that examined BDNF levels have found increases in mRNA levels of BDNF in the nucleus accumbens because of nicotine treatment (Le Foll, Diaz, & Sokoloff, 2005), but this was shown in male rats and female rats were not analyzed. These results support past findings of increased dopaminergic activity because of nicotine's ability to induce locomotor sensitization (Marshall et al., 1997).

### *Synaptic Effects of Quinpirole and Nicotine*

Nicotine acts to increase dopamine (DA) release by acting at presynaptically located nicotinic receptors (nAChRs). Dopamine diffuses across the synapse, binding to primed (indicated by the '+') dopamine D2 receptors, increasing the overall dopaminergic response in D2-primed rats given nicotine (see Figure 7). Therefore, an increased dopaminergic response to nicotine explains the more robust nicotine sensitization described in this study. Additionally, females demonstrate a significant increase in dopamine release in response to nicotine as compared to males in both past studies (Marshall et al., 1997) and the current study.



*Figure 7. Synapse Diagram*

### *Limitations of the Current Study*

Although the dose of nicotine used in the current study is clinically relevant to approximately 14-16 cigarettes per day in humans (Hieda et al., 1999), a dose response curve for nicotine was not examined. According to the literature, doses of .01 mg/kg and 1.0 mg/kg nicotine produce drastically different results between adult and adolescent males and may also

have different effects in adult and adolescent females (Faraday et al., 2003). Because of major differences in behavioral responses with different doses of nicotine, it may be worthwhile to examine other doses of nicotine in future studies.

#### *Suggestions for Future Research*

The current study examined the locomotor enhancing properties of nicotine using systemic administration of the drug. However, the use of alternative routes of administration may give a better understanding of nicotine's effects on locomotion and brain function. For example, intracranial administration of the drug may give insight as to brain areas that may be mediating these effects, as the drug could be applied directly to different brain areas and underlying mechanisms in these brain areas identified.

The use of microdialysis to investigate the locomotor activating effects of nicotine would also be pertinent to this study. It is known that nicotine's agonistic effects on the dopamine system cause an increase in dopamine release at the terminal. This would be useful because it would allow us to look at the changes in dopamine release that occur while the animal is under the influence of nicotine. A study is currently underway in our laboratory to investigate nicotine and microdialysis.

In past research, others have shown a dose response to the effects of nicotine as well as quinpirole, which was not examined in this study. Frantz and Van Hartesveldt (1999) showed differences in age and gender in dose responses to quinpirole, and Faraday et al. (2003) showed differences in dose response to nicotine in adult and adolescent male animals. However, methodology (use of neonatal quinpirole treatment versus adulthood quinpirole treatment) may alter the outcome of a dose response to quinpirole. Methodology would also affect the dose-response to nicotine that is shown by Faraday et al., who showed a hypoactive response to

nicotine in adolescent males in response to 0.1 mg/kg and 1.0 mg/kg but not 0.5 mg/kg nicotine treatment. Our study also did not show a hypoactive response to 0.5 mg/kg nicotine in D2-primed adolescent males, suggesting that D2-priming blocks the hypoactive response to nicotine. D2-priming may also block the hypoactive response to nicotine at different doses.

To date, no study has looked at a dose response to quinpirole and its interaction with nicotine. The current study showed that neonatal quinpirole treatment blocks the hypoactive response to nicotine in adolescent males but no other group. By using a dose response with quinpirole, it is likely that a lower or higher dose may not attenuate the hypoactive response to nicotine in adolescent males. Additionally, a dose response may show that quinpirole blocks the hypoactive response to nicotine in females or other pretreatment groups.

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## VITA

MARLA K. PERNA

- Personal Data: Date of Birth: September 1, 1980  
Place of Birth: Tiffin, Ohio  
Marital Status: single
- Education Public schools, Tiffin, Ohio  
Ohio Wesleyan University, Delaware, Ohio, 1999-2000  
B.A. Psychology, Heidelberg College, Tiffin, Ohio, May, 2003  
M.S. Psychology, East Tennessee State University, May 2007
- Professional experience Independent study, Bowling Green State University, Department of Psychology, Summer, 2002  
Graduate assistant, East Tennessee State University, Department of Psychology, 2003-2006
- Publications Brown, R.W., Perna, M.K., Schaefer, T.L., & Williams, M.T. (2006). The effects of adulthood nicotine treatment on D2-mediated behavior and neurotrophins of rats neonatally treated with quinpirole. *Synapse*, 59, 253-259.
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- Honors and Awards 1<sup>st</sup> place poster presentation, First and second year graduate students division, Student Research Forum (2004), East Tennessee State University, Johnson City, TN
- 2<sup>nd</sup> place poster presentation, Second year + graduate students division, Student Research Forum (2006), East Tennessee State University, Johnson City, TN