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THE EFFECTS OF THE NEUROTENSIN-1 RECEPTOR AGONIST PD149163 ON VISUAL SIGNAL DETECTION TASK PERFORMANCE IN RATS

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Todd Michael Hillhouse, born on December 24, 1984

ABSTRACT

THE EFFECTS OF PD149163 ON VISUAL SIGNAL DETECTION TASK PERFORMANCE

By

Todd M. Hillhouse

Nearly 1 percent of Americans suffer from schizophrenia, a debilitating lifelong mental disorder. Cognitive impairments have been established as a core feature of schizophrenia, with attention appearing to be one of the most affected cognitive domains. Current antipsychotic drugs are effective for treating the positive, and to some degree negative, symptoms, but few antipsychotic drugs provide adequate gains in cognitive function. In preclinical animal models, neurotensin produces atypical antipsychotic-like behavioral and biochemical effects. In order to evaluate the effects of a neurotensin NT_1 receptor agonist on attention, the NT_1 receptor agonist PD149163 (0.0156-0.125 mg/kg) and the atypical antipsychotic drug clozapine (0.625-2.5 mg/kg) were tested in rats trained to perform a visual signal detection task. PD149163 produced a significant decrease in percent hit and correct rejections. A high dose (0.125 mg/kg) of PD149163 produced a significant increase in response latency and omissions. Clozapine (1.25 and 2.5 mg/kg) produced a significant decrease in percent hits and increase in response latency; however, clozapine failed to effect percent correct rejections and response omissions. Although PD149163 and clozapine produced a significant disruption in attentional performance, clozapine had a more detrimental effect on attention.

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LIST OF ABBREVIATIONS

Antipsychotic drug, APD

Dopamine, DA

Phencyclidine, PCP

N-methyl-D-aspartic acid, NMDA

Extrapyramidal side effects, EPS

Serotonin, 5-HT

Nucleus accumbens, NAC

Neurotensin, NT

Haloperidol, HAL

Prefrontal cortex, PFC

Ventral tegmental area, VTA

Prepusle Inhibition, PPI

Signal detection task, SDT

INTRODUCTION

1.1. Schizophrenia

Mental disorders are relatively common in the United States, affecting approximately 26 percent of American adults. Nearly 1 percent of Americans suffer from schizophrenia, accounting for an estimated 3 million individuals. The onset of the illness differs between males and females; approximately 18 to 25 years of age, and 25 to mid 30's, respectively (DSM-IV-TR, 2000). Evidence obtained from twin and relative studies suggests that schizophrenia is a biological illness. Compared to the general population, an individual's risk of being diagnosed with schizophrenia increases tenfold when a first-degree relative has the illness (DSM-IV-TR, 2000; Regier, Narrow, Rae, Manderscheid, Locke, & Goodwin, 1993). If both parents have schizophrenia, the individual's likelihood of developing the illness increases 50 percent. According to twin research, identical twins have a 50 percent chance developing schizophrenia if one twin is diagnosed with schizophrenia. While research suggests there are non-biological (environmental) factors that also play a role in the susceptibility of schizophrenia, the majority of evidence suggests that biological factors are a better predictor of the illness.

The defining features of schizophrenia are abnormal perceptions and ideas, as well as formal thought, emotional, motor and behavioral disorders. Examples of these include: hallucinations, delusions, disorganized speech and affective flattening or inappropriate responses (DSM-IV-TR, 2000). According to the DSM, schizophrenia

symptoms are divided into two groups: positive and negative. Positive symptoms are those that are present in addition to normal experiences, whereas negative symptoms are the loss of functions that would normally be present.

Positive symptoms consist of hallucinations, delusions and disorganization. Hallucinations may be present in auditory or visual forms; however, the auditory hallucinations are most common, which usually are voices distinct from the individual's thoughts (DSM-IV-TR, 2000). According to the DSM-IV-TR, delusions are erroneous beliefs that involve some kind of misinterpretation of perceptions. Two kinds of delusions are defined; Persecutory (most common), the belief that they are being tormented or followed and referential, the belief that certain gesture or comments are directed at them. Delusions can be bizarre if they are clearly implausible or allude to loss of control, for example; thought withdrawal, thought insertion and delusions of control (DSM-IV-TR, 2000). Lastly, disorganized thinking is argued by some to be atop the most important features of schizophrenia. These positive symptoms must be severe enough to considerably impair an individual's communication. These can vary in form including: loose associations (slips off one topic to the next), tangentiality (answers may be obliquely related), and incoherence (word salad, incomprehensible).

Negative symptoms mainly involve the loss of motivation and emotion, and are less dramatic than positive ones. The DSM-IV-TR defines affective flattening, alogia and avolition as negative symptoms. Affective flattening is relatively common in schizophrenia and consists of reduced body language, poor eye contact, and the face appearing immobile or unresponsive. Second, alogia (poverty of speech) is evident by brief empty replies. Lastly, avolition, the inability to initiate and continue in goal-

directed activities, plays an important role in functional and vocational outcome. Unfortunately, negative symptoms are difficult to evaluate because their presence ranges, are nonspecific and may be due to other factors, such as stress, depression or environmental stimulus (DSM-IV-TR, 2000).

Diagnostic criteria for schizophrenia are separated into five different groups: Paranoid, disorganized, catatonic, undifferentiated and residual. Paranoid schizophrenia is characterized by delusions that typically are persecutory or grandiose and organized around a coherent theme. According to the DSM-IV-TR, there is little to no cognitive impairments on neuropsychological testing associated with paranoid schizophrenia. Disorganized type is distinguished by disorganized speech, behavior and inappropriate or flattened affect. This disorganized behavior can lead to a disruption in the ability to perform normal everyday tasks or activities. The DSM-IV states there is an "impaired performance on neuropsychological and cognitive testing" associated with this type (DSM-IV-TR, 2000). Catatonic schizophrenia is differentiated from other types by its motor disturbance, which may involve excessive motor activity, immobility or extreme negativism. Undifferentiated type of schizophrenia does not have symptoms that are substantial enough to fulfill the criteria of the three previously discussed types. Residual type is characterized by a lack of prominent positive symptoms; conversely, it's indentified by the presence of negative symptoms.

The prevalence of suicide is exceedingly high among individuals with schizophrenia. Suicide has been found to be the number one cause of premature death in the schizophrenia illness (Fenton, McGlashan, Victor, & Blyler, 1997). The DSM-IV states, 20 to 40 percent of schizophrenia patients will make at least one attempt at suicide

during their life time (DSM-IV-TR, 2000), of which approximately 10 percent of these attempt will be successful (Miles, 1977). However, Palmer et al (2005) predicts a lower lifetime risk of suicide based a study using case fatality. Case fatality is determined by the percentage of the original sample that died due to suicide. This study found that case fatality is 5.6 percent and may be a more accurate approximation of lifetime suicide risk. When compared to older patients, younger patients in early stages of the illness are more likely to commit suicide. Additionally, first episode patients are more vulnerable to suicide attempts (Palmer et al., 2005; DSM-IV-TR, 2000).

1.2. Cognitive Impairments

Cognitive impairments are mentioned briefly by the DSM-IV but are not included as part of diagnosis criteria or as a negative symptom; however, cognitive impairments are generally considered an important feature of schizophrenia because of the affect on functional outcome. Over the past two decades, cognitive deficits in schizophrenia have been well established using a variety of neuropsychological battery tests. Approximately 20 percent of schizophrenia patients can be considered cognitively normal, which is one standard deviation within the population mean. The other 80 percent of schizophrenia patients perform 1.5 to 2 standard deviations below healthy controls in a wide variety of cognitive functions on neuropsychological tests (Gold, 2004; Keefe & Fenton, 2007; Keefe, 2008; Reichenberg, Harvey, Bowie, Mojtabai, Rabinowitz, Heaton, & Bromet, 2009). Not only has this been demonstrated in numerous studies, but it has been shown with large samples as well (Cohen, Forbes, Mann, & Blanchard, 2006; Gold, 2004; Heinrich & Zakzanis, 1998; Keefe & Fenton, 2007). When using Global Deficit Scores, 81.9 percent of schizophrenia patients were cognitively impairment and 84 percent were

identified as impaired accordingly to the Clinically Significant Cognitive Impairment scale (Reichenberg et al., 2009).

Cognitive impairments also have been shown to be associated with bipolar disorder and major depression as well; however, the cognitive impairments suffered by schizophrenia patients equal or exceed the degree of the deficits found in these other disorders. When compared to bipolar disorder and major depression, the deficits associated with schizophrenia are found at significantly higher rates and are more severe (Bora, Yucel, & Pantelis, 2009; Reichenberg et al., 2009). Patients with schizophrenia have larger deficits in nearly all cognitive functioning by 0.5 standard deviations, except for general verbal ability and visual processing (Bora et al., 2009; Keefe & Fenton, 2007; Reichenberg et al., 2009).

There are two major differences in the cognitive deficits associated with bipolar disorder and major depression; correlation with symptoms and improvements from baseline. First, the cognitive impairments in these two disorders are correlated with the patient's symptoms, which were assessed using the Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Negative Symptoms, Brief Psychiatric Rating Scale and Hamilton Depression Scale (Reichenberg et al., 2009). When symptoms are severe so are the cognitive impairments, and as the symptoms decline the impairments follow. As a result of this correlation, bipolar patients have the ability to improvement on their neurocogitive baseline scores. On the other hand, the cognitive impairments in schizophrenia are stable across the duration of the illness and are uncorrelated with symptoms (Gold, 2004; Keefe & Fenton, 2007; Keefe 2008). Cognitive impairments

vary depending on the cognitive domain; however, nearly all aspects of cognition are affected to some degree.

In 2002 the National Institute of Mental Health established the Measurement and Treatment Research to Improve Cognition in Schizophrenia program to stimulate the development of new drug treatments for cognitive impairments in schizophrenia. Another goal of this initiative was to establish a consensus of cognitive batteries for assessing cognitive impairments in the clinical settings (Marder & Fenton, 2004). The absence of standardized batteries has been a disadvantage of evaluating new possible treatments and the assessment of the cognitive deficits themselves. After numerous meetings, in April 2003 the Measurement and Treatment Research to Improve Cognition in Schizophrenia neurocognitive committee determined there were seven major domains of cognitive deficits that should be focused on: attention (vigilance), working memory, speed of processing, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition.

Attention appears to be one of the most affected cognitive domains identified by the Measurement and Treatment Research to Improve Cognition in Schizophrenia committee. Schizophrenia patients score 1.5 standard deviations below the normal mean on attention and speed of processing task, which included Trail Making Test (part A), Symbol Digit Modalities Test, and Wechsler Adult Intelligence Scale – Revised Digit Symbol Coding (Reichenber et al., 2009). When assessed by speed, advanced speed attention, basic speed attention, and non-speed attention, schizophrenia patients were 1.5, 1, and 0.5 standard deviations below the normal mean, respectively (Egeland, Rund, Sundet, Landro, Asbjornsen, Lund, Roness, Stordal, & Hugdahl, 2003). Additionally, on

the Continuous Performance Test, which assess selective and sustained attention, individuals with schizophrenia score approximately 1.25 standard deviations below the normal control group (Green, 2006).

Numerous studies have found a connection between these cognitive impairments and functional outcome (Cohen et al., 2006; Gold, 2004; Green, Kern, & Heaton, 2004; Keefe & Fenton, 2007; Keefe, 2008). This relationship is critical when evaluating new psychopharmacological treatments. Functional outcomes have been found to be poor in individuals with schizophrenia and are exceedingly hard to overcome. Studies have found that cognitive deficits (i.e. attention and working memory) are a better predictor than both positive and negative symptoms for poor functional outcome (Keefe & Fenton, 2007; Keefe, 2008). The seven domains MATRICS identified affect almost every aspect of everyday life including; community functioning, social functioning, and vocational outcome. Since the cognitive impairments in schizophrenia are stable across the illness, unlike in bipolar disorder and major depression, functional outcomes may begin to be hindered at the onset of the illness and continues throughout the illness.

Cohen at el (2006) found that the impairments in attention and vigilance are positively correlated with social functioning, which is the ability of an individual to interact in the normal or usual way in society. Moreover, social functioning becomes hindered as attention deficits become more apparent. Many of the cognitive deficits are affecting vocational outcomes as well. The inability to maintain successful and continuous employment is quite common in patients with schizophrenia. The cause for this struggle to maintain employment is partially due to the malfunction in attention and working memory. Impaired attention plays a crucial role in the inability to follow and

understand directions, job descriptions, and stay on task. Additionally, attention (vigilance) was linked to skill performance, while immediate memory was consistently related to skill acquisition (Green, Kern, Braff, & Mintz, 2000). Understandably, these disturbances in functional outcome are a crucial reason for the development novel treatments, which would presumably increase cognition in schizophrenia.

1.3. Antipsychotic Drugs

Prior to the development of antipsychotic drugs (APDs), the aims for schizophrenia treatment were quite diverse and had minimal, if any, improvements on positive and negative symptoms. In the 1930's, frontal lobotomy, non-specific sedation, and electroconvulsive therapy were the most common treatments for schizophrenia. The introduction of the first APD, chlorpromazine, revolutionized the outlook for treating schizophrenia. Chlorpromazine was originally synthesized for pre-anesthetic purposes. For patients with chronic psychoses, chlorpromazine was found to have a calming effect. Moreover, it was found to relieve positive symptoms in approximately 70 percent of schizophrenia patients; however, it failed to treat negative symptoms (Meyer & Simpson, 1997). The remaining 30 percent of schizophrenia patients are known as treatment resistant, meaning there was minimal or no improvements to chronic treatment with APDs.

The first APD chlorpromazine, and others with similar drug action, would eventually become known as typical or first generation APDs. Typical APDs are D_2 antagonists, which reduce the elevated levels dopamine (DA) activity in the limbic system. This blockade of DA release in the limbic system appears to be responsible for

the therapeutic effects, specifically the reduction of positive symptoms (Meyer & Simpson, 1997). However, typical APDs are largely ineffective for treating negative symptoms and cognitive impairments associated with schizophrenia (Meyer & Simpson, 1997). The most commonly prescribed typical APD, haloperidol (HAL), has minimal effects on the extracellular DA levels in the prefrontal cortex (PFC) (Kuroki, Meltzer, & Ichikawa, 1999), which is associated with its inability to improve cognitive impairments (i.e. attention, working memory) and negative symptoms. Unfortunately, D_2 antagonism has been found to produce undesirable neurological effects, which include both minor and more serious prolonged effects.

The adverse effects produced by typical APDs differ from those associated with atypical APDs. These differences are a result of receptor blockade and include sedation and weight gain (H_1 receptors), orthostatic hypotension ($alpha_1$ receptors), and dry mouth and blurred vision (muscarinic cholinergic receptors) (Meyer & Simpson, 1997). These less severe adverse effects are found to become more tolerable after chronic treatment, whereas the more serious adverse effects are debilitating motor disorders. The DA activity in the basal ganglia is found to be normal in individuals with schizophrenia; however, the D_2 antagonist action in the basal ganglia reduces the DA activity, which results in adverse motor activity called extrapyramidal side effects (EPS). EPS resembles Parkinson's disease, in that it consists of tremors, involuntary movements, and muscle rigidity. Atypical APDs do not exhibit these motor effects at therapeutically effective does; however, they still carry the risk for EPS. Additionally, long term treatment of typical APDs can produce tardive dyskinesia, a motor disorder affecting muscles around the mouth and other parts of the face. Approximately 20 percent of APD treated patients

develop tardive dyskinesia with symptoms that include facial tics and involuntary movements of the jaw, tongue, and lips (Owens, 1999). Unfortunately, in some patients tardive dyskinesia will persist for a months or even years after termination of APD treatment.

APDs are thought to mediate DA release (i.e. D_2 antagonist) in the brain, specifically in the limbic system, to relieve positive symptoms (Seeman, 2006). Ultimately, an APD's affinity for D_2 receptors is the single best predictor of effective clinical dosage, which is approximately 60-80 percent occupancy at the D_2 receptors (Seeman, 2006). In addition, amphetamine increases the levels of DA in the brain especially the limbic system, which are known to briefly produce positive-like symptoms in otherwise healthy individuals. These findings have led to the DA hypothesis for schizophrenia (Meltzer & Fang, 1976), which suggests the disorder results from hyperfunctioning dopaminergic pathways that result in too much DA activity in certain areas of the brain. In particular, the mesolimbic DA pathway, which starts at the ventral tegmental area (VTA) and terminates throughout the limbic system, appears to excessively release DA. DA has been found to signal target neurons in two ways – synaptically and extrasynaptic. Synaptic transmission has a level of specificity and targets a specific receptor. Extrasynaptic transmission diffuses neurotransmitters outside the synapse increasing the neurotransmitter concentration (Sesack, Carr, Omelchenk, & Pinto, 2003). In addition to a hyperfunctioning mesolimbic DA pathway, the revised DA hypothesis states that there is reduced DA activity in the PFC, which is believed to be responsible for the negative symptoms and cognitive impairments in schizophrenia. The mesocortical DA pathway, which originates in the VTA and terminates throughout the

cortex, is responsible for the reduced levels of DA released in the PFC. The reduced levels of DA in the PFC may account for the cognitive impairments (i.e. attention, working memory).

The glutamate hypothesis for schizophrenia suggests diminished levels of glutamate are being released at glutamate synapses, which lead to dysregulation of functioning throughout the brain, specifically in the PFC and limbic system (Paz, Tardito, Atzori, & Tseng, 2008; Sesack et al., 2003). The diminished levels of glutamate release may account for reduction of DA activity in the PFC and excessive DA activity in the limbic system. Excessive doses (e.g. overdose) and long-term use of the N-methyl-D-aspartic acid (NMDA) antagonists PCP and ketamine are found to produce drug effects that resemble both positive and negative symptoms of schizophrenia (Paz et al., 2008). These symptoms include auditory hallucinations, cognitive impairments (i.e. attention, working memory), out-of-body experience, emotional blunting, and thought disorder (Paz et al., 2008). The hypofunction of NMDA receptors throughout the PFC suggests a combination of DA receptor blockade and NMDA receptor activation may improve both positive and negative symptoms.

Developed in 1959, although not introduced to Europe until the early 1970's, clozapine transformed the attitude towards schizophrenia treatment. Clozapine became the model for a novel drug class (atypical or second generation APDs) due to its superiority over typical APDs. First, clozapine was effective in treatment resistant patients (Meyer & Simpson, 1997), which accounted for 1/3 of schizophrenia patients unsuccessfully treated with typical APDs. Secondly, unlike typical APDs, EPS were not found to be associated with clozapine. Also, atypical APDs typically do not produce

catalepsy, which is a predictor of EPS in animal models. Ultimately, if a drug is found to exhibit APD effects and does not produce catalepsy then it's considered an atypical APD. Although many atypical APDs have been developed, none have achieved a similar efficacy to clozapine (Paz et al., 2008). Clozapine's drug actions occur at postsynaptic Serotonin $(5\text{-HT})_{2A}$ receptors and D_2 receptors; it has strong affinity as a 5-HT_2 antagonist and considerably weaker affinity as a D_2 antagonist (Meyer & Simpson, 1997). Additionally, clozapine has been shown to bind to a variety of different receptors (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, α_1-adrenoceptors, α_2-adrenoceptors, and muscarinic receptors), some of which have been implicated in therapeutic properties. Researchers suggest the weaker D_2 receptor blockade, when compared to typical APDs, account for the lack of EPS and the slight improvement of negative symptoms.

Clozapine's remarkably high success rates for treating schizophrenia led to the development of novel atypical APDs, like olanzapine (Zyprexa) and risperidone (Risperdal). Atypical APDs appear to have two distinctive drug mechanisms that are important for their success - not producing EPS and the slight improvement of negative symptoms (e.g. cognitive impairments, avolition), which are due to weaker D_2 receptor blockade and increased DA levels in the prefrontal cortex, respectively. The weaker D_2 receptor blockade at the basal ganglia appears to be responsible for the lower risk of EPS. Unfortunately, atypical APDs can produce EPS at higher doses; however, the risks of EPS are lower than for typical antipsychotics. The D_2 fast-off theory suggests that atypical APDs occupy D_2 receptors long enough to relieve positive symptoms, then disengage before producing EPS (Seeman, 2002). Ultimately, D_2 antagonism is the

primary mechanism of action for typical APDs, and results in a longer action at these receptors and undesired EPS.

Atypical APDs produce an increase in DA levels in the PFC, which are suggested to account for the improvement, although modest, of negative symptoms and cognitive impairments. Kuroki and colleagues (1999) found a positive correlation between atypical APDs' ability to increase levels of extracellular DA in the medial PFC, as compared to the nucleus accumbens (NAC), and the differences in affinities at 5-HT_{2A} and D_2 receptors. Clozapine and olanzapine, when compared to haloperidol (most commonly prescribe typical APD), produce a greater increase in extracellular DA at the medial PFC, which is associated with HAL's inability to treat negative symptoms (Kuroki et al., 1999). Asenapine, a relatively new atypical APD, was found to increase extracellular DA levels in the medial PFC, NAC, and hippocampus, although the doses needed to produce an increase in the NAC were far greater than those needed to produce antipsychotic-like effects (Huang, Li, Dai, Shahid, Wong, & Meltzer, 2008). Atypical APDs produce a greater or comparable increase in DA release in the medial PFC compared to the NAC; however, typical APD increase extracellular DA in the NAC with minimal alteration in the medial PFC.

Current APDs are effective for treating the positive, and to some degree negative, symptoms, but few APDs provide adequate gains in cognitive function. Presumably, new APDs that may improve cognitive functioning will act in the brain in ways different than currently available APDs.

1.4. Neurotensin

Neurotensin (NT) is an endogenous tridecapeptide originally isolated from bovine hypothalamus (Carraway & Leeman, 1973). NT is found in the central nervous system and gastrointestinal tract (St-Gelais, Jomphe, & Trudeau, 2006). Additionally, NT interacts with multiple neurotransmitter systems including monoamines and catecholamines (Kasckow & Nemeroff, 1991). Three different NT receptors, known as NT_1, NT_2 and NT_3, have been identified (St-Gelais et al., 2006). NT_1 was found to have the highest-affinity, while NT_2 receptor affinity is 10 times lower for NT_1 receptors. Consequently, NT_3 has the lowest affinity for NT, which is 1000 times lower than NT_1 (Petrie, Bubser, Casey, Davis, Roth, & Deutch, 2004). Although NT is highly localized in the brain, it does not have the ability to cross the blood brain barrier.

NT interacts with a variety of neurotransmitter systems including; dopaminergic, cholinergic, serotonergic, noradrenergic, glutamatergic and GABAergic (Kasckow & Nemeroff, 1991; Ferraro, Tomasini, Fernandez, Bebe, O'Connor, Fuxe, et al., 2001; Sanz, Exposito, & Mora, 1993). As previously noted in the APD section, many of these transmitters systems have been implicated as the cause of symptoms and treatment of schizophrenia (i.e. DA, 5-HT, and glutamate). NT and DA are co-localized in the VTA and substantia nigra, which mediate the DA mesolimbic and nigrostriatal pathways, respectively (Binder, Kinkead, Owens, & Nemeroff, 2001b). Herve and colleagues (1986) found that a 6-hydroxydopamine lesion to the VTA significantly decreased the number of NT receptors in the VTA, substantia nigra, and striatum, which demonstrated a relationship between these neurotransmitters and their modulation. NT is found to increase DA release through an antagonist relationship by reducing D_2 receptor sensitivity and enhancing D_1 receptor sensitivity (Fuxe, O'Connor, Antonelli, Osborne,

Tanganelli, Agnati, etal., 1992). Additionally, NT increases DA release in the NAC by inhibiting the functions of the D_2 autoreceptors (Fawaz, Martel, Leo, & Trudeau, 2009).

In preclinical animal models, NT produces atypical APD-like behavioral effects, which provides further support that NT/DA have an antagonistic relationship. The two NT_1 receptor agonists, NT69L and PD149163, have primarily been evaluated for their APD-like effects. The NT_1 receptor agonist, NT69L, blocks apomorphine-induced climbing behavior (Cusack, Boules, Tyler, Fauq, McCormick, & Richelson, 2000), as well as amphetamine-, and cocaine-induced hyperactivity in rats (Boules, Warrington, Fauq, McCormick, & Richelson, 2001). NT69L (5 mg/kg) produced hypothermia in rats, which is consistent with other APD. Additionally, the same dose that produced hypothermia did not produce catalepsy, which suggests a low risk for EPS (Cusack et al., 2000). At low doses HAL produced catalepsy starting at 30 minutes and lasted for almost 6 hours. Moreover, the treatment of NT69L before or after the administration of HAL blocked or reversed catalepsy, respectively (Cusack et al., 2000). In a condition avoidance response task, PD149163 significantly reduced the percent avoidance compared for vehicle without producing escape failures and did not increase catalepsy, which is consistent with atypical APD (Holly, Enbrecht, & Prus, 2011). These findings on motor activity and catalepsy suggest that NTR1 agonists have APD-like properties low risk of EPS.

Another important preclinical model used to evaluate novel APD is the prepulse inhibition (PPI) task. The PPI task has been found to be a reliable measure of sensory gating. Individuals with schizophrenia have been found to have reduced sensory gating. Amphetamine and dizocilpine produced PPI deficits similar to schizophrenia,

presumably, any novel drug that can reverse these deficits are considered to have APD-like properties. Shilling and colleagues (2002) found systemic administration of NT69L dose dependently reversed dizocilpine- and d-amphetamine-induced PPI disruptions. When comparing wild-type and $NT^{-/-}$ null mice, NT null mice had a significantly greater pulse alone startle, as well as a disrupted PPI (Kinkead, Dobner, Egnatashvili, Murray, Deitemeyer, & Nemeroff, 2005). In wild-type mice, HAL and quetiapine significantly increased PPI; however, HAL and quetiapine failed to restore PPI in NT null mice (Kinead et al., 2005). Additionally, the NT antagonist, SR142948A, blocked both typical and atypical PPI restoration in isolation reared animals, which have PPI disruptions when compared to socially reared animals (Binder, Kinkead, Owens, Kilts, & Nemeroff, 2001a). Although amphetamine successfully disrupts PPI in normal mice, amphetamine produced no effect on NT null mice (Kinead et al., 2005). These data suggest that NT signaling may mediate PPI. Interestingly, clozapine was the only APD tested that restored PPI in both wild type and $NT^{-/-}$ mice (Kinead et al., 2005). NT not only produces APD-like behavioral effects, its biochemical effects are similar to atypical APDs.

The implication that NT plays a role in schizophrenia stems from NT's ability to mediate various neurotransmitter levers in a number of brain regions, as well as the effects that APDs have on NT levels. In a dose dependent manner, local perfusion of NT significantly increases glutamate concentration in the striatum and medial PFC (Ferraro et al., 2001; Sanz et al., 1993). According to the hypoglutamate hypothesis, this ability to increase glutamate should help relieve the symptoms, as well as the cognitive impairments associated with schizophrenia. Consequently, pretreatment with the NT

antagonist, SR48692, attenuated the increase of glutamate in the striatum (Ferraro et al., 2001). Radke and colleagues (1998) found chronic, but not acute, administration of HAL, clozapine, and olanzapine significantly increased NT concentration in the NAC; however, only HAL produced a significant increase in the striatum, which is associated with EPS. In addition, the inability of acute administration to produce the same increase supports the theory that APDs may take approximately 2 weeks to produce desired therapeutic effects, as well as NT interaction with neuropsychological disorders.

As discussed previously, atypical APDs produce a greater increase in DA release in the medial PFC, which may account for minimal cognitive improvements, when compared to the NAC. The NT_1 receptor agonist, NT69L (1.0 and 3.0 mg/kg), was found to dose-dependently increase DA concentration in the medial PFC; however, only 1.0 mg/kg produce a significant increase in the NAC (Prus, Huang, Li, Dai, & Meltzer, 2007). Ultimately, the results from preclinical models suggest that a NT_1 receptor agonist is a putative APD, while catalepsy and microdialysis studies demonstrate the profile is that of an atypical APD. Presumably, the ability to increase DA and glutamate in the medial PFC may produce cognitive improvements (e.g. attention and working memory), which needs to be an aim for novel APDs.

Recent research regarding NT analogs has focused on their ability to produce cognitive improvements in animal models. In a social discrimination paradigm, PD149163 reversed memory deficits in vasopressin-deficient Brattleboro rats (Feifel, Mexal, Melendez, Liu, Goldenberg, & Shilling, 2009). Additionally, intracerebroventricular administration of PD149163 improved memory-based performance by reversing scopolamine (a muscarinic receptor antagonist) - induced

deficits in novel object recognition (Azmi, Norman, Spicer, & Bennett, 2006), as well as improved trace conditioning in an aversive trace conditioning task (Grimond-Billa, Norman, G, & Cassaday, 2010). Furthermore, PD149163 reversed scopolamine-induced deficits in percent choice accuracy in a delayed non-match to position task (Prus, Goboly, & Rusch, unpublished.b). Moreover, the NT antagonist, SR48692, increased reference and working memory errors in a spatial learning task (Tirado-Santiago, Lazaro-Munoz, Rodriguez-Gonzalex, & Maldonado-Vlaar, 2006). Despite the growing literature on the effects of NT and NT_1 receptor agonists on cognitive functioning, no studies that have examined the effects of these NT_1 receptor agonists on attention. Thus, studies are needed to further characterize the cognitive profile of NT_1 receptor agonists.

1.5. Visual Signal Detection Task

The operant visual signal detection task (SDT) has been commonly used to assess attention in rats since the 1950's. In the SDT rats are required to discriminate between visual and non-visual signals (cues). Two types of trials are used - signal trials and blank trials. Signal trials and blank trials are presented an equal number of times during each testing session. Any intensity change (e.g. 0.9, 1.8, and 2.7 lux) from the signal light resulting in an increase above background illumination is defined as a signal trial. A blank trial (correct rejection) is defined as no stimulus change from the signal light.

The task is made more difficult by two variables; signal intensity and inter-trial delay. Signal intensity plays a crucial role in this task. At lower intensities it is more difficult for the rats to detect the change; whereas, the full intensity is more easily detected by the rats (Bushnell, 1999). Additionally, inter-trial delays are inversely related

to percent accuracy; that is, as the interval lengths increase, the percent accuracy decreases. The sequence of events for SDT is as follows; inter-trial delay, signal (or no change), post-signal interval, then levers extend, at which time the animal makes his choice for that trial.

Both typical and atypical APDs have been screened using the SDT to assess their effects on attention. As expected, typical APDs produce more detrimental effects on sustained attention than atypical APDs, which is most likely due to the inability of typical APDs to increase DA in the medial PFC. HAL (0.01 mg/kg), the most commonly prescribed typical APD, produced a significant decrease in percent hit; however, it had no effect on correct rejections (Rezvani & Levin, 2004). Higher doses (0.02 and 0.04 mg/kg) of HAL produced a significant disruption in behavioral activity that increased omissions and ultimately, percent hit and correct rejections could not be analyzed (Rezvani & Levin, 2004). This disruption in behavioral performance may be due to the increased DA blockade in the basal ganglia (mesostriatal DA pathway), which cause EPS in humans.

Surprisingly, both typical and atypical APDs disrupt percent hit accuracy; however, atypical APDs usually do not disrupt overall behavior or affect correct rejection accuracy. Clozapine dose-dependently decreases percent hits, which is more apparent at higher signal intensities (Rezvani, Kholdebarin, Dawson, & Levin, 2008a; Rezvani & Levin, 2004). Clozapines effects on correct rejections are less definitive than hit accuracy. A recent study has found 2.5 and 1.25 mg/kg of clozapine decreased correct rejections (Rezvani et al., 2008a), while a different study found that clozapine produced no effect on correct rejections (Rezvani, Getachew, Hauser, Caldwell, Hunter, et al.,

2008b). Additionally, the high dose produced an increase in omissions and response latency. Consistent with clozapine, risperidone significantly decreased percent hit, increased response latencies, and failed to effect correct rejections (Rezvani et al., 2008b; Rezvani & Levin, 2004). Although the difference between typical and atypical APDs may be subtle, it appears that atypical APDs are less disruptive for attention in this task.

RATIONALE

The brain penetrant NT_1 receptor agonist, PD149163, appears to be a putative atypical APD, based on results from a variety of preclinical models. NT_1 receptor agonists have shown APD-like behavioral effects in PPI, locomotor activity, and conditioned avoidance response tasks. Additionally, microdialysis studies provide evidence that NT agonists produce greater DA release in the PFC when compared to NAC, which is consistent with atypical APDs (Prus et al., 2007). Moreover, NT was shown to reverse innate or drug-induced memory deficits in social discrimination, aversive trace conditioning, object recognition, and delayed non-match to position tasks (Feifel et al., 2009; Grimond-Billa et al., 2008; Amzi et al., 2006; Prus et al., unpublished.b).

No previous studies have been reported on the effects of NT_1 receptor agonists on attention performance. In order to evaluate the effects of the NT_1 receptor agonist, PD149163 (0.0156-0.125 mg/kg) was tested in rats trained to discriminate visual and non-visual signals in the visual signal detection task. The goal of this study was to evaluate the ability of PD149163 to increase attention in the SDT as compared with the atypical APD clozapine.

METHODS

2.1. Subjects

The subjects used in this experiment were 12 adult, male Sprague-Dawley rats (Charles River, Portage, MI). All rats were housed individually in plastic cages in the colony room (rodent animal room). The colony room maintains a constant temperature of 20-22 ^{o}C under 12-hour light cycle (lights on 0700-1900 h). Testing and training sessions occurred during the light cycle (7:00-7:00pm). All rats were given restricted access to food to maintain 85% of their *ad libitum* weights. All rats had free access to water. All procedures were approved by the Institutional Animal Care and Use Committee at Northern Michigan University.

2.2. Apparatus

Rats were trained in six identical operant chambers enclosed within a sound attenuating cabinet (Med-Associates, St. Albans. VT). Each operant chamber was equipped with a signal (cue) light, a house light, two retractable levers, a food cup and a fan (i.e. white noise). The signal light was located directly above the food cup centered on the front panel of the chamber. There were two retractable levers on either side of the food cup. The background and signal illuminations were evaluated using a light meter (CEM, DT-1301, Metershack, Saratoga, CA) measured in lux, and expressed as a mean across all operant chambers. A signal consisted of a 300-ms mean illumination increase of 0.9, 1.8 and 2.7 lux above background illumination (10.00 lux). The fan was mounted

on the sound attenuating cabinet and generated background white noise of approximately 65 dBs. Signals and data collection were generated using computer controlled interface (Med PC, Version 4) running on a Windows Vista operating system.

2.3. Drug preparation

The NT_1 receptor agonist PD149163 (NIMH Drug Respository, Bethesda, MD, USA) was made fresh daily and dissolved in 0.9% physiological saline. Clozapine (Sigma-Aldrich) was not made daily and dissolved in sterile water with a few drops of 85% lactic acid. PH strips were used to maintain the PH balance at a safe level. All of the drugs were administered subcutaneously 30 prior to each session in a volume of 1ml/kg.

2.4. Procedures

Rats were trained to perform the visual signal detection task (Rezvani et al., 2008a; Rezvani & Levin, 2004; Bushnell, 1999).

Magazine Training

For acclimation purposes, day one was magazine training in which the animals were placed in the operant chamber with both the house and signal light on (at the background level, 10 lux), and received food pellets on a fixed ratio 1 schedule.

Lever Pressing Training

For day two training, the chambers were set up the same as day one except the assigned blank-lever was extended into the test chamber. Blank lever assignments were counterbalanced between subjects. The rats were required to perform 30 lever presses,

which resulted in food deliver for each lever press, before the session was completed. There was no time limit for day two training.

Errorless Training

Errorless training began on day 3 with 64 trials and the number of trials increased each day over approximately 4 days until reaching 256 errorless trials. In errorless training, only the correct lever was available for the corresponding trial (i.e. signal-lever on signal trial or blank-lever on blank trial). A signal consisted of full illumination of the stimulus light (2.7 lux above background illumination). A failure to respond within 10 seconds of the levers being extended was counted as a trial omission. The criterion for errorless training was successful completion of 256 trials with no more than 2 omissions. After completion of errorless training, the rats were introduced to "full signal vs. blank" training.

Full Signal vs. Blank Training

The "full signal vs. blank" training was conducted in a similar fashion to errorless training, except that both levers were extended after the signal period. Also, the response omission period was reduced to 5 seconds. The sequence of events for SDT is as follows; inter-trial delay, signal (or no change), post-signal interval, then levers extend, at which time the animal makes his choice for that trial.

There were two possible correct responses; hits or correct rejections. A hit was defined as a signal lever press on the signal trial. A correct rejection was defined as pressing the blank lever on a blank (no change) trial. All correct responses were followed by the delivery of a food pellet. There were two possible incorrect responses; misses or

false alarms. A miss was defined as pressing the blank lever on a signal trial. A correct rejection was defined as pressing the signal lever on a blank trial. Following an incorrect response the rat received a time out, 2 seconds of darkness. Full signal vs. blank training consisted of 128 trials, 64 blank and 64 signal trials, and 4 inter-trial delay, 1-24 seconds. Training criterion was as follows; choice accuracy needed to be 75% or higher on a 1 second delay, approximately 50% at the 24s delay, and approximately 40-60% at the 8s and 16s delays for 2 out of 3 consecutive sessions. After meeting these criteria, the number of trials per session was increased to 196 trials per session. The criterion was the same for previous training.

Trial type	**Inter-trial delays**			
	1s	**8s**	**16s**	**24s**
Blank (No Change)	75%	40-60%		50%
Full Intensity (2.7 lux)	75%	40-60%		50%

Table 1. Training criteria percent accuracy for trial type and inter-trial delay.

Testing

Test sessions were identical to training sessions except that additional signal intensities were used. The testing session consisted of 96 blank (no change), 32 one-third intensity (0.9 lux), 32 two-third intensity (1.8 lux), and 32 full intensity trials (2.7 lux).

Two days interceded each test session. On the day prior to a test session, a training session was conducted. After completing the dose response curve for one drug, the animals received 7 days off before the next drug was tested.

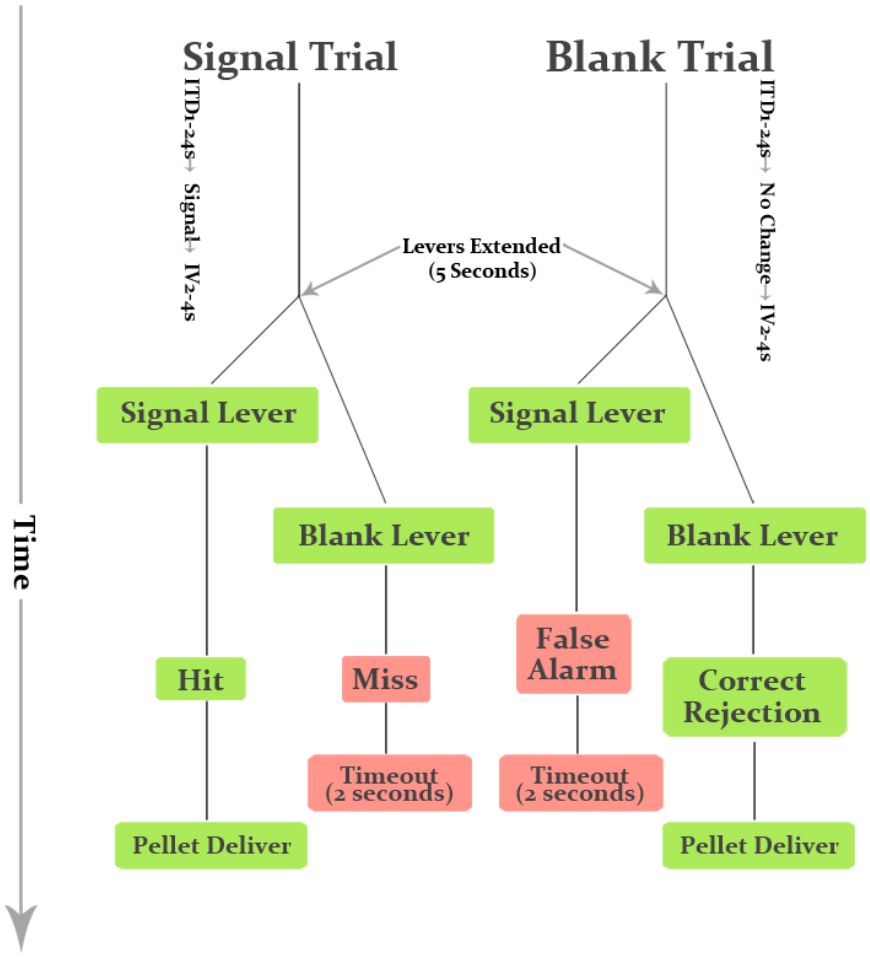

Figure 1. The visual signal detection task sequence of trials. This task will consist of two trial types, Signal and blank. Trial types only differ in that a signal will be presented during the signal trial and will be omitted during the blank trial. In each trial, rats will be required to press the appropriate lever for the designated trail (signal or blank). There are five possible outcomes for the task; Hit (correct lever on signal task), Miss (blank lever on signal trial), correct rejection (correct lever on blank trial), False alarm (signal lever on blank trial), and omission (no response before 5s elapse). Hits and correct rejections will be followed by the delivery of food; Misses, false alarms, and omissions will be followed by a time out (2s of darkness).

2.5. Data Analysis

Five dependent variables were used to measure the effects of the compounds: Percent hit, percent correct rejection, omissions, correct response latency, and incorrect response latency. A hit was defined as correct response on signal trial (signal-lever press on signal trial) and correct rejection is a correct response on blank trial (blank-lever press blank trial). An omission was defined as no lever press within 5 seconds of the lever being inserted into the testing chamber. Latency response is the lapse of time from the insertion of the lever and lever press. All dependent variables were subjected to a repeated measures two-way ANOVA. The threshold for significance is $p<0.05$. Two-way interactions were assessed using Tukey multiple comparisons test.

RESULTS

3.1. Training Criteria

After eight animals have successfully completed training criteria (see table 1), the number of training days until criterion was assessed. Any animals that failed to meet criteria within 2 standard deviations of the successfully trained rats were eliminated from the study.

Eight of the twelve rats met criterion in 61.88 +/- 4.52 (mean+/- SEM) training sessions. The remaining 4 rats failed to meet criteria within 85 trials and were eliminated from the study.

3.2. PD149163

Effects of PD149163 and inter-trial delays on signal performance

The percent hit accuracy data for PD149163 and inter-trial delay are shown in figure 2, top panel. PD149163 and inter-trial delay produced statistically significant effects on percent hits for main effect of PD149163 ($F[4, 28]=3.07$, $p<0.05$), and the main effect of delay ($F[3, 21]=15.35$, $p<0.001$);but not for the interaction effect ($F[12, 84]=1.47$; $p>0.05$). While a statistically significant main effect of PD149163 was shown, significant differences between doses were not revealed by post hoc multiple comparison

tests. Between trial delays, the 1 sec (Feifel, Goldenberg, Melendez, & Shilling, 2010)ond delay produced significantly lower percent hits than the 8, 16, or 24 second delay.

The correct choice latency (time in seconds) data for PD149163 and inter-trial delay are shown in figure 2, center panel. PD149163 and inter-trial delay produced statistically significant effects on correct choice latency for main effect of PD14913 ($F[4,28]=4.39$, $p<0.01$), and for main effect of delay ($F[3,21]=3.23$, $p<0.05$); but not for the interaction effect ($F[12, 84]=0.82$; $p>0.05$). A 0.125 mg/kg dose of PD149163 significantly increased correct choice latency compared to vehicle. While a statistically significant main effect of delay was shown, differences between delays were not revealed upon conducting Tukey post hoc multiple comparison tests.

The incorrect choice latency (time in seconds) data for PD149163 and inter-trial delay are shown in figure 2, bottom panel. PD149163 and inter-trial delay produced statistically significant effects on incorrect choice latency for main effect of PD14913 ($F[4,28]=6.15$, $p<0.001$), and for main effect of delay ($F[3,21]=7.18$, $p<0.01$); but not for the interaction effect ($F[12,84]=1.11$, $p>0.05$). A 0.125 mg/kg dose of PD149163 significantly increased incorrect choice latency compared to vehicle. Between trial delays, the 1 second delay produced significantly higher incorrect latency compared to 8 and 24 second delay; however, there was no difference between 1 and 16 second delay.

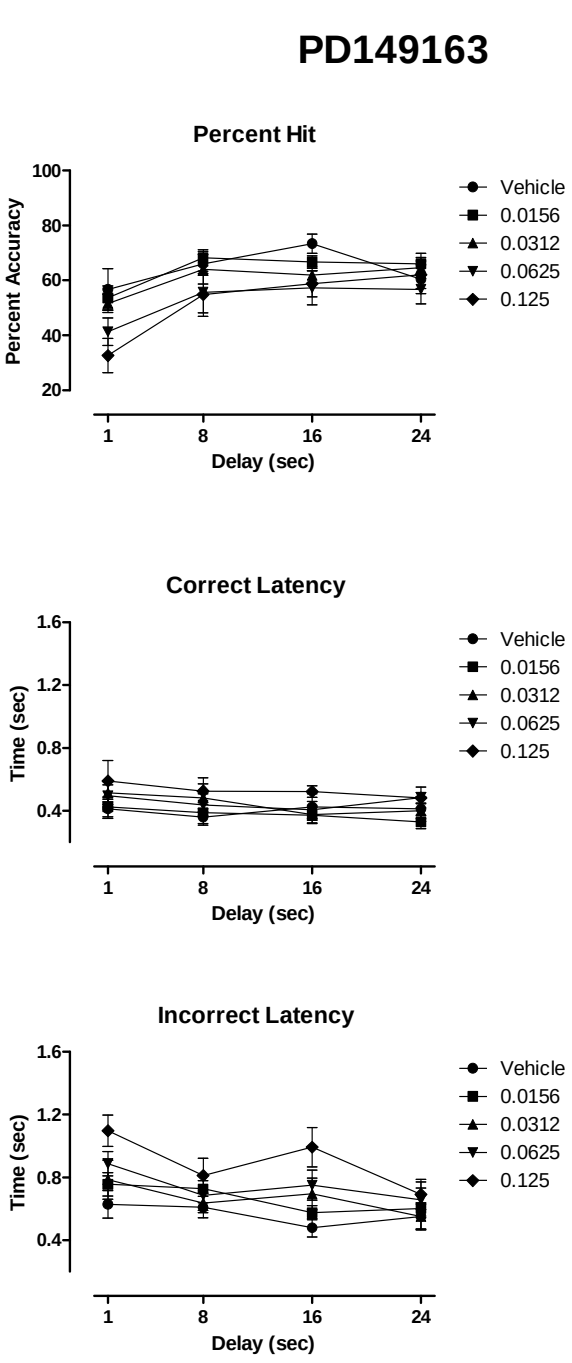

Figure 2. Effects of the neurotensin-1 receptor agonist PD149163 and inter-trial delays on the mean (+/- SEM) a) percent hit (top), b) correct choice latency (middle), and c) incorrect choice latency (bottom) *$p<0.05$ versus VEH.

Effects of PD149163 and inter-trial delay on correct rejection performance

The percent correct rejection accuracy data for PD149163 and inter-trial delay are shown in figure 3, top panel. PD149163 and inter-trial delay produced statistically significant effects on percent correct rejections for main effect of PD149163 ($F[4, 28]=2.93$, $p<0.05$), and the main effect of delay ($F[3, 21]=2.07$, $p>0.05$); but not for the interaction effect ($F[12, 84]=1.37$; $p>0.05$). While a statistically significant main effect of PD149163 was shown, significant differences between doses were not revealed within the Tukey post hoc multiple comparison test results.

The correct choice latency data for PD149163 and inter-trial delay are shown in figure 3, center panel. PD149163 and inter-trial delay produced statistically significant effects on correct choice latency for main effect of PD149163 ($F[4, 28]=9.19$, $p<0.001$), the main effect of delay ($F[3, 21]=7.69$, $p<0.01$), and for the interaction effect ($F[12, 84]=2.76$; $p<0.01$). Compared to vehicle, the high dose (0.125 mg/kg) significantly increased correct latency at all inter-trial delays. The dose 0.0625 mg/kg produced a statistically significant increase in correct latency for the 1 and 16 second delays compared to vehicle. The main of effect of dose on correct choice latency revealed 0.125 mg/kg significantly increased response latency.

The incorrect choice latency data for PD149163 and inter-trial delay are shown in figure 3, bottom panel. PD149163 and inter-trial delay produced statistically significant effects on incorrect choice latency for main effect of PD149163 ($F[4, 28]=6.25$, $p<0.01$); but not for the main effect of delay ($F[3, 21]=0.78$, $p>0.05$) or the interaction effect

(F[12, 84]=1.33; p>0.05). A 0.125 mg/kg dose of PD149163 significantly increased incorrect choice latency compared to vehicle.

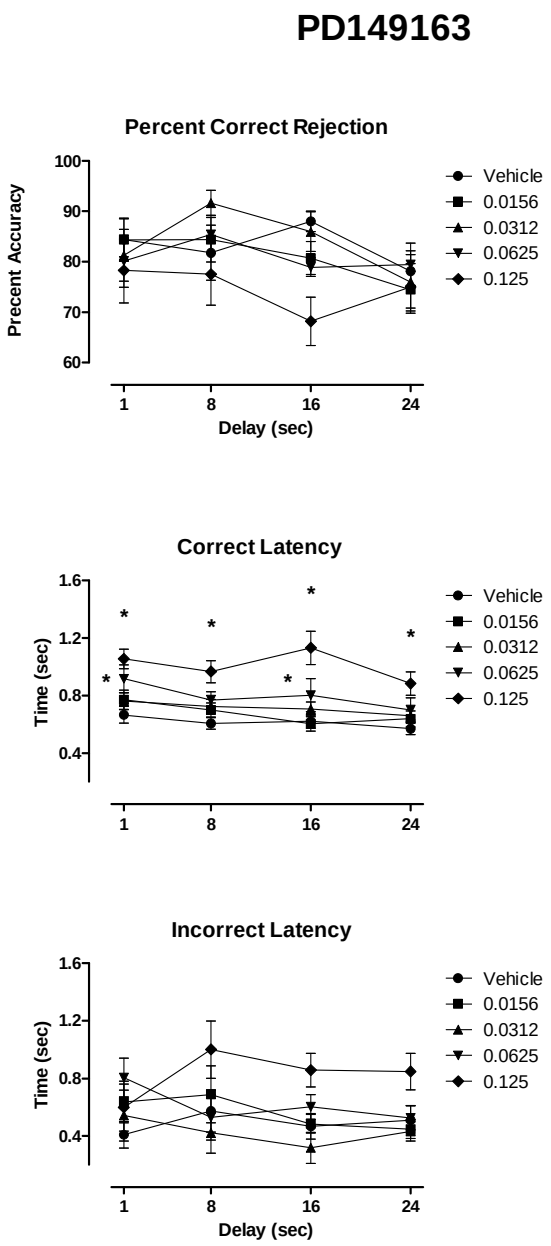

Figure 3. Effects of the neurotensin-1 receptor agonist PD149163 and inter-trial delays on the mean (+/- SEM) a) percent correct rejection (top), b) correct choice latency (middle), and c) incorrect choice latency (bottom) *p<0.05 versus VEH.

Effects of PD149163 and signal intensity on signal detection performance

The percent hit accuracy data for PD149163 and signal intensity are shown in figure 4, top panel. PD149163 and intensity produced statistically significant effects on percent hits for main effect of PD149163 ($F[4, 28]=2.99$, $p<0.05$) and for main effect of signal intensity ($F[2, 14]=75.13$, $p<0.001$); but not for the interaction effect ($F[8, 56]=1.55$; $p>0.05$). While a statistically significant main effect of PD149163 was shown, differences between doses were not revealed upon post hoc multiple comparison tests. Between signal intensities, the 1/3 intensity produced significantly lower percent hit than the 2/3 intensity. The 2/3 intensity produced significantly lower percent hit than the full intensity.

The correct choice latency data for PD149163 and signal intensity are shown in figure 4, center panel. PD149163 and signal intensity produced statistically significant effects on correct choice latency for the main effect of PD14913 ($F[4, 28]=4.39$, $p<0.01$), main effect of signal intensity ($F[2, 14]=10.70$, $p<0.01$), and the interaction effect ($F[8, 56]=2.13$; $p<0.05$). The high dose (0.125 mg/kg) produced a statistically significant increase in correct latency at the 1/3 intensity compared to 2/3 and full intensity. The main effect of dose failed to reveal a difference between doses. The main effect of signal intensities revealed the 1/3 intensity produced significantly lower percent hit than the 2/3 intensity. The 1/3 intensity produced significantly lower percent hit than the full intensity.

The incorrect choice latency data for PD149163 and signal intensity are shown in figure 4, bottom panel. PD149163 and signal intensity produced statistically significant

effects on incorrect choice latency for the main effect of PD14913 ($F[4, 28]=6.15$, $p<0.01$) and for main effect of signal intensity ($F[2, 14]=3.75$, $p<0.05$); but not for the interaction effect ($F[8, 56]=1.63$; $p>0.05$). Compared to vehicle, the 0.125 mg/kg dose of PD149163 significantly increased incorrect choice latency. Between signal intensities, 1/3 signal intensity produced a statistically significant increase in incorrect choice latency when compared to full intensity.

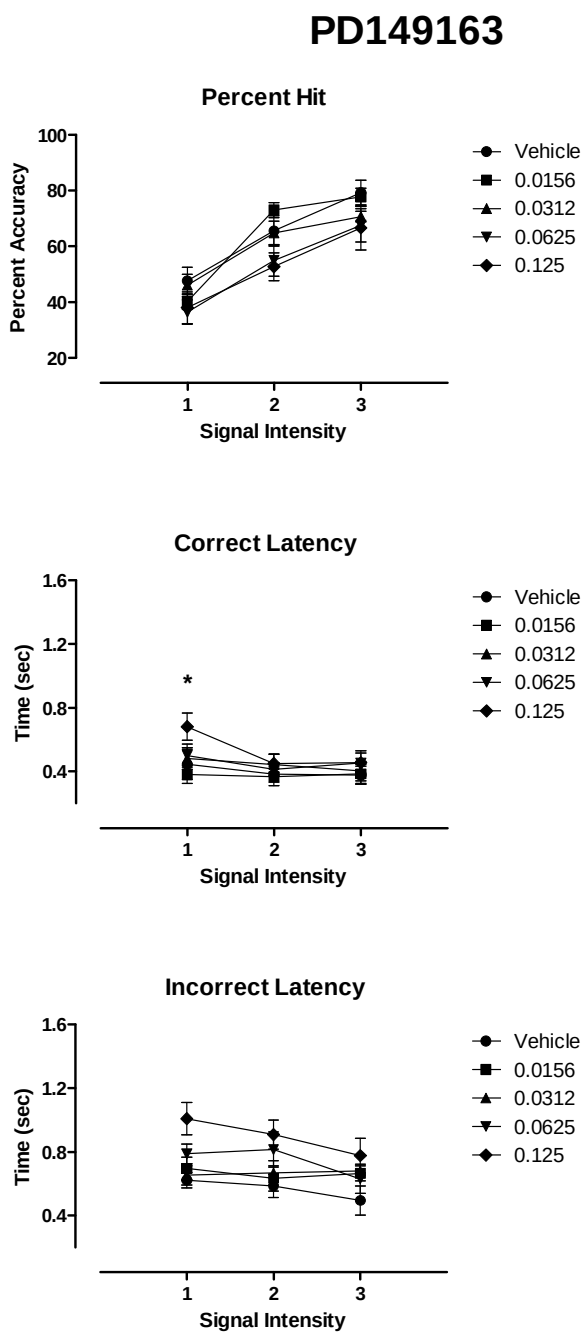

Figure 4. Effects of the neurotensin-1 receptor agonist PD149163 and signal intensity on the mean (+/- SEM) a) percent hit (top), b) correct choice latency (middle), and c) incorrect choice latency (bottom) *$p<0.05$ versus VEH.

Effects of PD149163 on trial omissions for signal and correct rejection performance

The trial omission data for PD149163 and trial type are shown in figure 5. The highest dose of PD149163 (0.125 mg/kg) produced a statistically significant increase on omissions for signal ($F[4,28]=3.36$, $p<0.05$) and blank trials ($F[4,28]=3.54$, $p<0.05$).

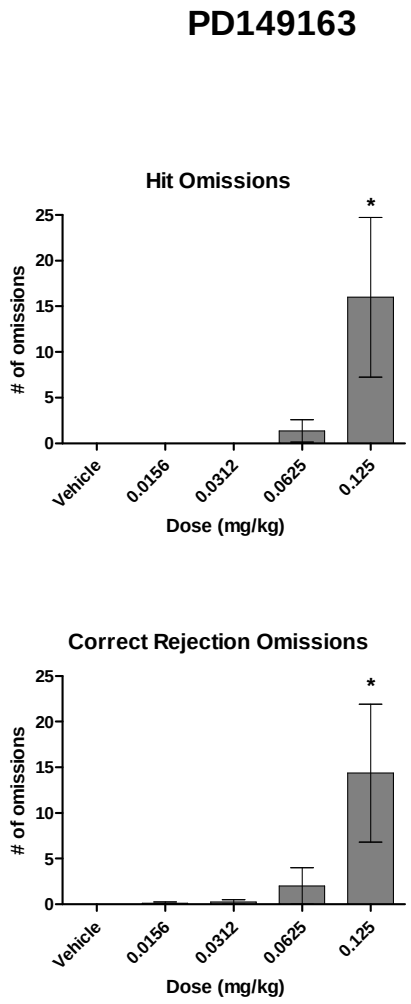

Figure 5. Effects of the neurotensin-1 receptor agonist PD149163 and trial omissions on the mean (+/- SEM) a) signal trials (top), b) correct rejection trials (bottom) *$p<0.05$ versus VEH.

3.3. Clozapine

Effects of clozapine and inter-trial delays on signal detection performance

The percent hit accuracy data for clozapine and inter-trial delay are shown in figure 6, top panel. Clozapine and inter-trial delay produced statistically significant effects on percent hits for the main effect of clozapine ($F[3, 21]=16.60$, $p<0.001$), main effect of delay ($F[3, 21]=7.12$, $p<0.01$), and interaction effect ($F[9, 63]=2.34$; $p<0.05$). Compared to vehicle, clozapine, 2.5 mg/kg, decreased percent hits at the 1 and 8 second delay. The 1.25 mg/kg produced a significant decrease in percent hit at the 8 second delay compared to vehicle. The main effect of dose revealed clozapine dose-dependently, 1.25 ($p<0.05$) and 2.5 ($p<0.001$) decrease percent hit compared to vehicle. The main effect of delays, the 1 second delay produced significantly lower percent hit than the 8, 16, and 24 second delay.

The correct choice latency for clozapine and inter-trial delay are shown in figure 6, center panel. Clozapine and inter-trial delay produced statistically significant effects on correct choice latency for the main effect of delay ($F[3, 21]=6.54$, $p<0.01$); but not for the main effect of clozapine ($F[3, 21]=2.61$, $p>0.05$) or interaction effect ($F[9, 63]=1.55$; $p>0.05$). Between trial delays, the 1 second delay produced significantly higher correct choice latency than the 8, 16, or 24 second delay.

The incorrect choice latency for clozapine and inter-trial delay are shown in figure 6, bottom panel. Clozapine and inter-trial delay produced statistically significant effects on incorrect choice latency for the main effect of clozapine ($F[3, 21]=11.74$, $p<0.001$), main effect of delay ($F[3, 21]=8.65$, $p<0.01$), and interaction effect ($F[9, 63]=3.47$;

$p<0.01$). Compared to vehicle, 1.25 and 2.5 mg/kg dose of clozapine increased incorrect latency at the 1 second delay. The main effect of dose revealed clozapine dose-dependently, 1.25 mg/kg ($p<0.05$) and 2.5 mg/kg ($p<0.001$) increased incorrect choice latency compared to vehicle. For the main effect of delays, the 1 second delay significantly increased incorrect choice latency compared to the 8, 16, and 24 second delay.

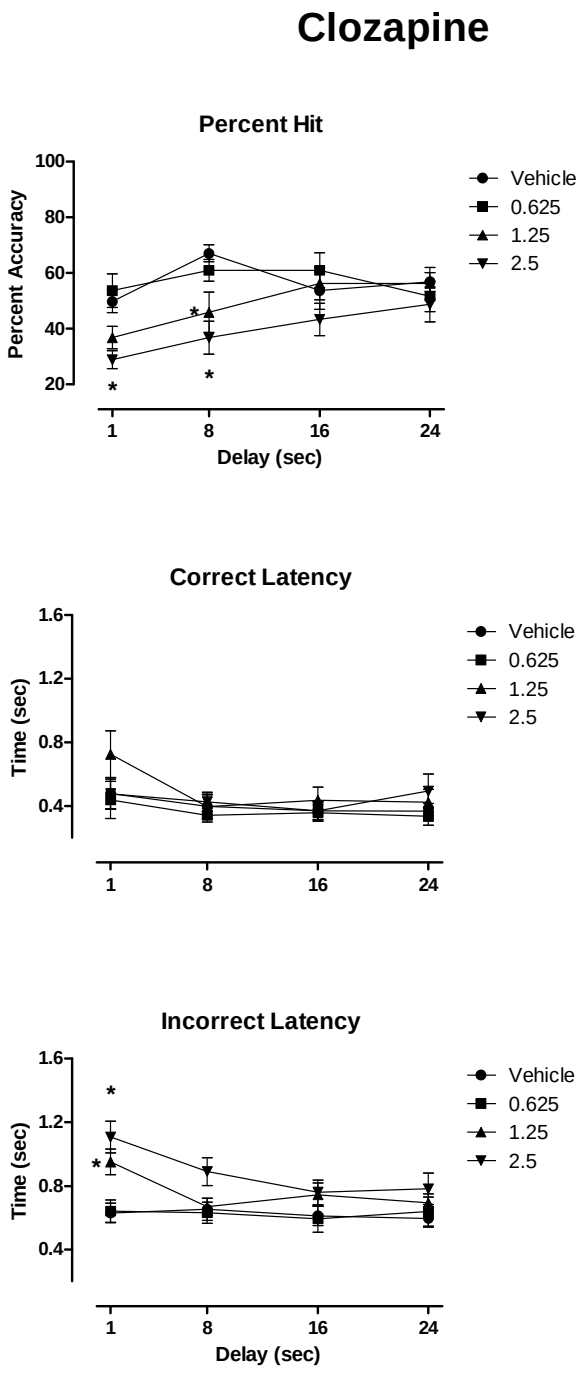

Figure 6. Effects of the atypical antipsychotic clozapine and inter-trial delays on the mean (+/- SEM) a) percent hit (top), b) correct choice latency (middle), and c) incorrect choice latency (bottom) *$p<0.05$ versus VEH.

Effects of clozapine and inter-trial delays on correct rejection performance

The percent correct rejection accuracy data for clozapine and inter-trial delay are shown in figure 7, top panel. Clozapine and inter-trial delay produced statistically significant effects on percent correct rejection for the main effect of clozapine ($F[3, 21]=4.16$, $p<0.05$), main effect of delay ($F[3, 21]=6.77$, $p<0.01$), and interaction effect ($F[9, 63]=2.47$; $p<0.05$). For vehicle, the percent accuracy at the 24 second delay was significantly lower than the 1 second delay; however, the Tukey post hoc failed to reveal a significant difference between simple effect means. The main effect of delays, the 24 second delay produced significantly lower percent correct rejections than the 1 second delay.

The correct choice latency for clozapine and inter-trial delay are shown in figure 7, center panel. Clozapine and inter-trial delay produced statistically significant effects on correct choice latency for the main effect of clozapine ($F[3, 21]=4.38$, $p<0.05$), main effect of delay ($F[3, 21]=11.01$, $p<0.001$), and interaction effect ($F[9, 63]=7.40$; $p<0.001$). Compared to vehicle, clozapine produced a significant decrease in correct latency at the 1 second delay. The main effect of dose revealed clozapine dose 2.5 mg/kg ($p<0.01$) decrease correct choice latency compared to vehicle. The main effect of delays, the 1 second delay produced significantly greater increase in correct choice latency than the 8, 16, and 24 second delay.

The incorrect choice latency for clozapine and inter-trial delay are shown in figure 7, bottom panel. Clozapine and inter-trial delay produced statistically significant effects on incorrect choice latency for the main effect of clozapine ($F[3, 21]=5.87$, $p<0.01$), main

effect of delay ($F[3, 21]=6.95$, $p<0.01$), and interaction effect ($F[9, 63]=3.38$; $p<0.01$). Compared to vehicle, the high dose (2.5 mg/kg) of clozapine produced a statistically significant increase in incorrect latency at the 1 second delay. The main effect of dose revealed clozapine 2.5 mg/kg decrease incorrect choice latency compared to vehicle. The main effect of delays, the 1 second delay produced a significantly greater increase in incorrect choice latency compared to 8, 16, and 24 second delay.

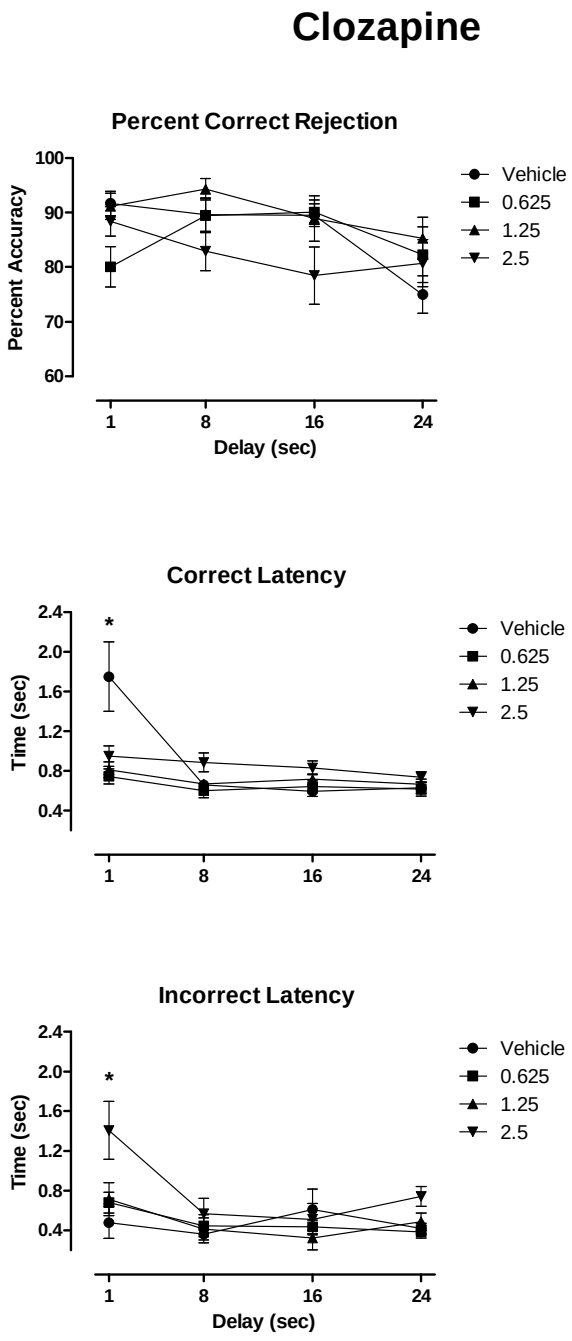

Figure 7. Effects of the atypical antipsychotic clozapine and inter-trial delays on the mean (+/- SEM) a) percent correct rejection (top), b) correct choice latency (middle), and c) incorrect choice latency (bottom) *p<0.05 versus VEH.

Effects of clozapine and signal intensity on signal detection performance

The percent hit accuracy data for clozapine and signal intensity are shown in figure 8, top panel. Clozapine and signal intensity produced statistically significant effects on percent hits for the main effect of clozapine ($F[3, 21]=16.63$, $p<0.001$) and main effect of signal intensity ($F[2, 14]=63.60$, $p<0.001$); but not for the interaction effect ($F[6, 42]=0.30$; $p>0.05$). Higher doses of clozapine (1.25 and 2.5 mg/kg) significantly decreased percent hit accuracy. The main effect of signal intensities revealed the 1/3 intensity produced significantly lower percent hit than the 2/3 intensity. The 1/3 intensity produced significantly lower percent hit than the full intensity.

The correct choice latency data for clozapine and signal intensity are shown in figure 8, center panel. Clozapine and signal intensity failed to produce statistically significant effects on correct choice latency for the main effect of clozapine ($F[3, 21]=2.61$, $p>0.05$), main effect of signal intensity ($F[2, 14]=0.35$, $p>0.05$), and interaction effect ($F[6, 42]=1.61$; $p>0.05$).

The incorrect choice latency data for clozapine and signal intensity are shown in figure 8, bottom panel. Clozapine and signal intensity produced statistically significant effects on incorrect choice latency for the main effect of clozapine ($F[3, 21]=11.74$, $p<0.001$); but not for the main effect of signal intensity ($F[2, 14]=1.84$, $p>0.05$) or interaction effect ($F[6, 42]=1.46$; $p>0.05$). A 1.25 and 2.5 mg/kg dose of clozapine significantly increased incorrect choice latency.

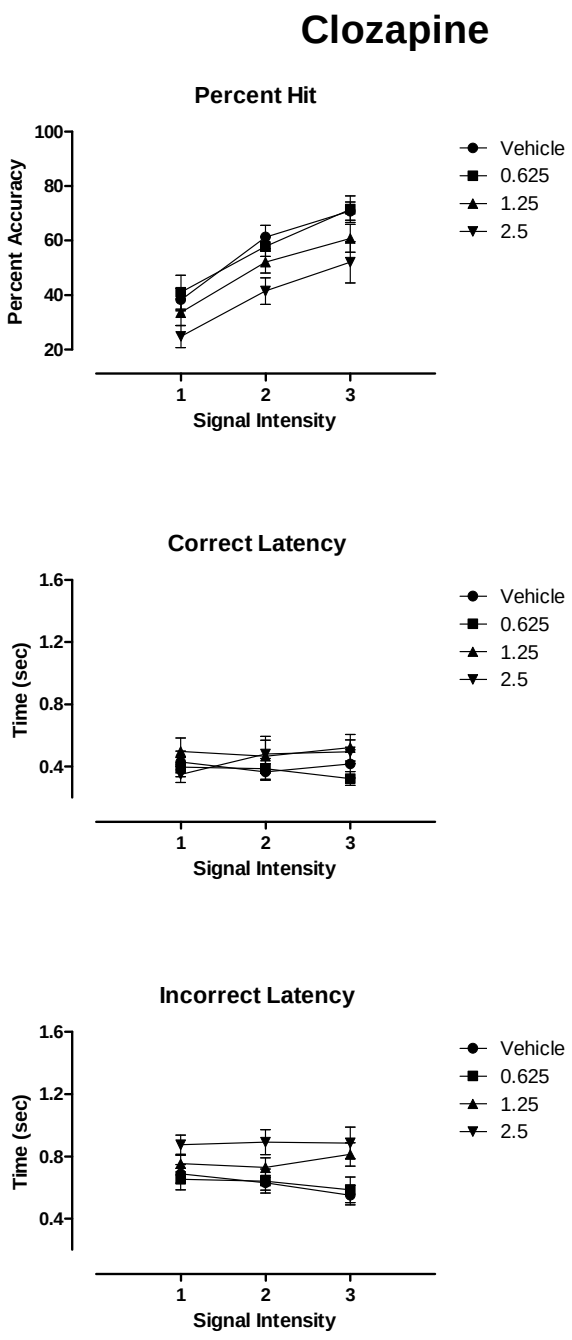

Figure 8. Effects of the atypical antipsychotic clozapine and signal intensity on the mean (+/- SEM) a) percent hit (top), b) correct choice latency (middle), and c) incorrect choice latency (bottom) *p<0.05 versus VEH.

Effects of clozapine on trial omissions for signal and correct rejection performance

The trial omission data for clozapine and trial type are shown in figure 8. Clozapine failed to significantly increase trial omissions.

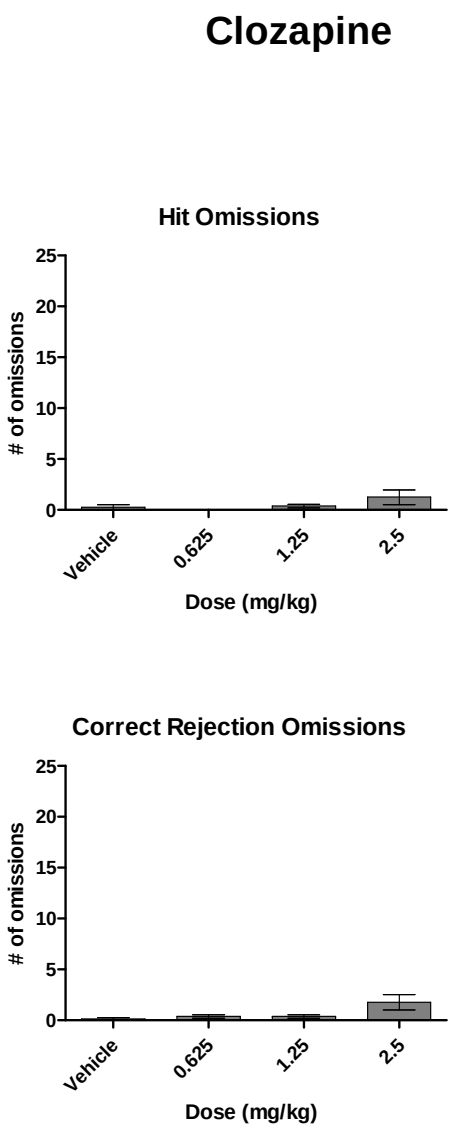

Figure 9. Effects of the atypical antipsychotic clozapine and trial omissions on the mean (+/- SEM) a) signal trials (top), b) correct rejection trials (bottom) *p<0.05 versus VEH.

DISCUSSION

The present study is the first to examine the effects of a NT_1 receptor agonist on attention in rats using the SDT. The primary findings for this study suggest that the NT agonist PD149163 and the atypical APD clozapine caused a significant disruption in attentional performance in rats; however, these impairments may be due to different mechanisms.

For both percent hits and correct rejections, a main effect of PD149163 was found, however the post hoc tests failed to reveal any statistical differences between vehicle and drug doses. The high dose of PD149163 (0.125 mg/kg) produced a significant increase in response latency (correct and incorrect). Moreover, a 0.125 mg/kg dose of PD149163 produced a significant increase in omissions on blank (14.38 +/- 7.55) and signal (16.00 +/- 8.73) trials, while no other doses produced a significant increase in omission. Together, the increase in response latency and trial omissions suggests that behavioral disruption may account for the decrease in percent accuracy rather than a disruption in attention.

Although a wider dose range (0.01-1.0 mg/kg) of PD1491763 can be used in aversive stimulation tasks without a decrease in motivation (Grimond-Billa et al. 2008; Holly et al., 2011; Prus, Hillhouse, & LaCrosse, In review; Shilling and Feifel, 2008), higher doses of PD149163 (0.25-1.0 mg/kg) are found to significantly decrease

responding in food motivated tasks (Norman, Grimond-Billa, Bennett, & Cassaday, 2010; Prus et al., unpublished.b). In a preliminary study, our laboratory found that a 0.25 mg/kg dose of PD149163 abolished behavior in the SDT and we were unable analyze the data due to the increase in omissions (mean +/- SEM) (Prus, Hillhouse, & Armes, unpublished.a). Further, in the present study 0.125 mg/kg PD149163 produced omissions on more than half the trials or produced non-specific effects (e.g. pressing one lever for the entire testing session). The reduction in behavioral responding for food motivated task, but not aversive stimulation, suggests loss of motivation rather than debilitating motor effects. Repeated administration of PD149163 (0.1, 0.25, and 1.0 mg/kg) has been shown to significantly reduce weight gain in rats, while 0.25 and 1.0 mg/kg significantly decreased food intake (Feifel, Goldenberg, Melendez, & Shilling, 2010; Prus et al., In review).

While PD149163, 0.125 mg/kg, produced a significant disruption in behavior, the two lowest doses (0.0156 and 0.0312 mg/kg) failed to produce an effect on percent hit, percent correct rejection, response latency, or omissions. Although PD149163, 0.0625 mg/kg, produced an interaction on correct latency for blank trials, it failed to produced an effect in percent hit, percent correct, or omissions. These data suggest low dose of PD149163 (0.0156-0.0625 mg/kg) may no longer be susceptible to the appetite suppressing effects of the NT_1 receptor agonist. To better understand the motivation factor, a future study needs to further elucidate the effects of PD149163 on weight gain and food intake.

Replicating previous studies, the atypical APD clozapine dose dependently (1.25 and 2.5 mg/kg) decreased percent hit (Rezvani & Levin, 2004; Rezvani et al., 2008b).

Clozapine had no effect on correct latency and trial omissions for signal trials. However, clozapine did produce a significant increase in incorrect latency. Although an interaction was found for clozapine on percent correct rejection, a Tukey post hoc analysis failed to reveal differences between doses of clozapine. Instead the interaction was found for vehicle between 1 and 24 second delays, leaving percent correct rejections unaffected by clozapine. Rezvani and colleagues have found that both a 1.25 and 2.5 mg/kg dose of clozapine produced a reduction in percent correct rejection (2008b); however, in another study only 2.5 mg/kg produced a deficit on correct rejections (2004). Further, in a study assessing the effects of chronic nicotine and dizocilpine on attention, clozapine failed to produce an effect on percent correct rejections (Rezvani et al., 2008b). The effects produced by clozapine also are consistent with the atypical APD risperidone, which reduced percent hit, increased response latency and produced no effect on trial omissions (Rezvani & Levin, 2004).

In the present study and previous studies clozapine produced a decrease in percent hits, while decreases in percent correct rejections are less consistent across studies. Unlike PD149163, clozapine-induced decreases in accuracy occur at non-behaviorally disruptive doses. The accuracy decreases by clozapine may be due to anticholinergic effects. Clozapine has a marked affinity for muscarinic cholinergic receptors ($m_1 – m_4$) in radioligand and *in vitro* binding studies (Bymaster, Calligaro, Falcone, Marsh, Moore, Tye, et al., 1996; Bymaster, Felder, Tzavara, Nomikos, Calligaro, & Mckinzie, 2003; Arnt, & Skarsfeldt, 1998). These affinities for muscarinic receptors are similar to those produced by muscarinic antagonist and cognitive disruptor scopolamine. Scopolamine and clozapine may share discriminative stimulus effects as well. In a drug discrimination

study, clozapine and scopolamine were found to cross generalized, meaning scopolamine fully substituted for clozapine trained rats and clozapine fully substituted for scopolamine trained rats (Kelley and Porter, 1997). Further, the m_1 antagonist trihexyphenidyl produced full substitution for the clozapine discriminative stimulus.

Similar to the effect of clozapine on attention, scopolamine has been shown to dose dependently decrease percent hit and increase omissions. However, scopolamine has failed to decrease percent correct rejections (McQuail and Burk, 2006). An extensive review by Levin and colleagues (2011) on attention found scopolamine reliably decrease percent hit, demonstrating the significant role muscarinic receptors play on attention.

For individuals with schizophrenia, attention appears to be one of the cognitive domains most affected by the disorder, with patients scoring 1.5 standard deviations below healthy individuals. The aim of new pharmacological agents for the treatment of schizophrenia should attempt to alleviate the cognitive impairments associated with the disorder, not further hinder cognition. Further, typical and atypical APDs are found to disrupt attention, which may result in reducing attention in already impaired individuals. In the present study, 0.125 mg/kg of PD149163 was found to impair attention; however, at this dose changes in motivation appeared to be a confounding variable as latency to complete the task was significantly increased. All other doses of PD149163 had no effect on attention, which is different from all other APD. It has been shown that intracerebroventricular administration of PD149163 reversed scopolamine-induced memory deficits in the novel object recognition task (Azmi et al., 2006) and 0.25 mg/kg of PD149163 increased trace conditioning in an aversive, but not food motivated, trace conditioning task (Grimond-bella et al., 2008). Taken together, the cognitive profile for

the NT1 receptor agonist, PD149163, is still unclear but is trending toward a cognitively safe drug as compared to other APDs.

In conclusion, the atypical APD clozapine and NT_1 receptor agonist PD149163 produced a significant disruption in attentional performance in rats using the visual signal detection task. Compared to PD149163, clozapine had more detrimental effects on attention. These findings suggest that NT_1 receptor agonists are unlikely to impair cognitive functioning in schizophrenia, and therefore, warrant further study as a new class of atypical APDs.

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APPENDIX A

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Continuing Education
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MEMORANDUM

March 17, 2010

TO: Dr. Adam Prus
Todd Hillhouse
Department of Psychology

FROM: Cynthia A. Prosen, Ph.D.
Dean of Graduate Studies & Research

RE: **Application to use Vertebrate Animals**
Application # IACUC 139
Approval Period: 03/15/2010-02/25/2012

The Institutional Animal Care and Use Committee have approved your application to use vertebrate animals in research, "Effects of PD149163 in the Visual Signal Detection Task".

If you have any questions, please contact me.

kjm

Telephone: 906-227-2103 ■ FAX: 906-227-2108
E-mail: conteduc@nmu.edu ■ Web site: www.nmu.edu/ce

APPENDIX B

Below is an alternative way to assess signal detection using D prime.

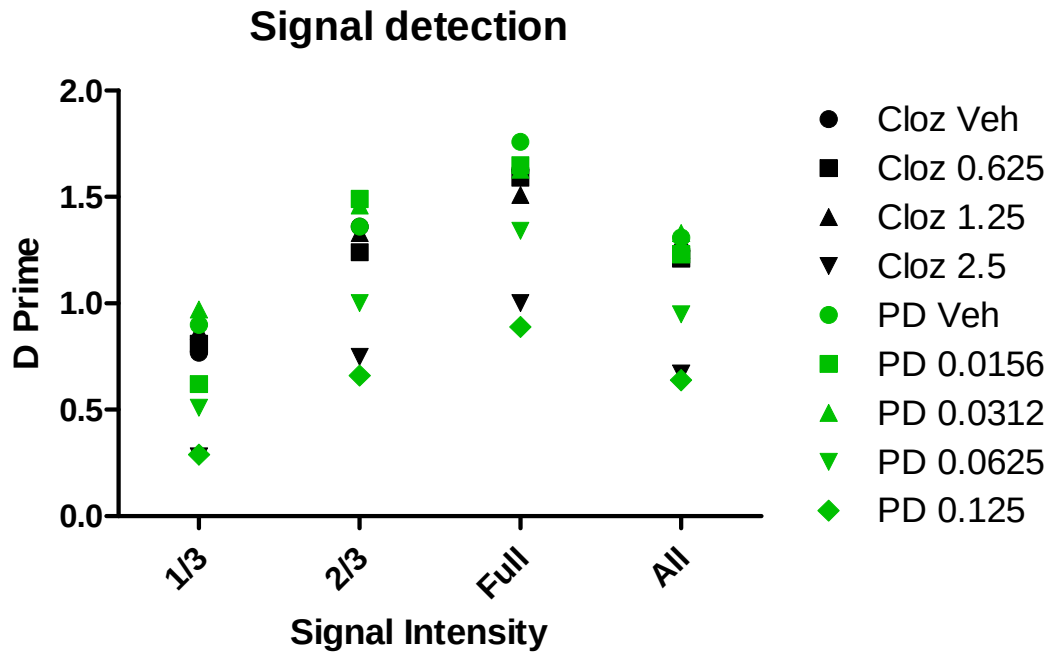

Figure 9. Effects of the atypical antipsychotic drug clozapine and neurotensin agonist PD149163 on D prime for signal intensity.