# CORRELATIONS OF DOPAMINE (D1, D2, D3) AND NMDA NR2A RECEPTOR SUBUNIT MRNA QUANTITIES WITH MORRIS WATER MAZE WORKING MEMORY AND SPATIAL LEARNING IN RATS

by

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# Correlations of Dopamine (D1, D2, D3) and NMDA NR2A Receptor Subunit mRNA Quantities with Morris Water Maze Working Memory and Spatial Learning in Rats

A Thesis submitted in partial fulfillment of the requirements for the degree of Master of Arts at George Mason University

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Dedication

This is dedicated to my family for allowing me the time and space to complete this paper. I am so grateful for their words of encouragement, understanding, and technical assistance.

Acknowledgements

I would like to acknowledge Laura Smith for the behavioral testing of the rats and allowing me to adopt them for this study, and for all her advice and support. I would also like to thank my committee, especially Susan Bachus and Bob Smith for their unrelenting support of this project.

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List of Abbreviations

| | |
|---|---|
| D1 PFC | Dopamine D1 mRNA in the Prefrontal Cortex |
| D1 Nac | Dopamine D1 mRNA in the Nucleus Accumbens |
| D1 NacC | Dopamine D1 mRNA in the Nucleus Accumbens Core |
| D1 NacS | Dopamine D1 mRNA in the Nucleus Accumbens Shell |
| D2 PFC | Dopamine D2 mRNA in the Prefrontal Cortex |
| D2 Nac | Dopamine D2 mRNA in the Nucleus Accumbens |
| D3 Nac | Dopamine D3 mRNA in the Nucleus Accumbens |
| D3 OFT | Dopamine D3 mRNA in the Olfactory Tubercle |
| mRNA | Messenger RNA |
| MWM | Morris Water Maze |
| NAC+S | Nucleus Accumbens |
| NMDA | *N*-methyl-D-aspartate |
| NR2A PFC | NMDA NR2A mRNA in the Prefrontal Cortex |
| NR2A Nac | NMDA NR2A mRNA in the Nucleus Accumbens |
| PFC | Prefrontal Cortex |

Abstract

CORRELATIONS OF DOPAMINE (D1, D2, D3) AND NMDA NR2A RECEPTOR SUBUNIT MRNA QUANTITIES WITH MORRIS WATER MAZE WORKING MEMORY AND SPATIAL LEARNING IN RATS

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Experimental manipulations have implicated dopamine and NMDA glutamate receptor activation as playing integral roles in the learning and memory process, but no research appears to have examined individual variability in the natural expression of dopamine and NMDA glutamate receptor levels. In this study, the naturally occurring variability of dopamine (D1, D2, D3) and glutamate NMDA NR2A receptor expression in the prefrontal cortex and nucleus accumbens, measured by in situ hybridization, in relation to individual differences in performance of spatial reference memory and spatial working memory tasks were examined. Spatial reference memory testing was conducted in the Morris water maze (MWM), utilizing the submersible Atlantis-style platform paradigm. Spatial working memory testing was conducted utilizing the MWM moving platform task. Significant correlations between mRNA values and behavioral values implicate the mRNA studies here in several aspects of learning. Dopamine D2 and D3, and NMDA NR2A in the nucleus accumbens is associated with memory consolidation in spatial reference memory. Dopamine D1 in the nucleus accumbens core is involved in the

acquisition and maintenance of a new strategy, whereas, D1 in the nucleus accumbens shell is involved in the consolidation process of spatial location in working memory task. The findings in this study are consistent with the substantial research using experimental manipulations that have identified dopamine and NMDA receptor activation as playing an integral role in the learning and memory process. Individual differences in both spatial reference and spatial working memory were correlated with individual differences in mRNA levels, suggesting that individual differences in mRNA expression are a determinant of individual performance differences in these aspects of behavior.

# 1. Introduction

Decades of research have identified some of the underlying components and neuronal mechanisms involved in learning and memory. Converging evidence implicates dopamine and NMDA glutamate receptor activation within the prefrontal cortex (PFC), striatum, limbic system and midbrain as playing an integral role in the learning and memory process (Brozoski et al., 1979; Goldman-Rakic, 1995; Kelly, Smith-Roe and Holahan, 1997; Watanabe, Kodama and Hikosaka, 1997; Zahrt et al., 1997; Floresco and Phillips, 2001).

The PFC contains dopamine and glutamate terminals that converge onto individual pyramidal cells and parvalbumin-containing interneurons (Goldman-Rakic, 1996; Lidow et al., 1998; Smiley et al., 1994; Kruse et al., 2009). Quantitative analysis revealed that 100% of the PFC neurons that expressed dopamine D1 receptors also expressed NR2A NMDA glutamate receptor subunits, with 65% being parvalbumin-containing interneurons (Kruse et al., 2009). The nucleus accumbens (Nac) receives glutamateric input from the PFC, amygdala, hippocampus, mediodorsal thalamus and dopaminergic input from the VTA (Baldwin et al., 2002; Goldman-Rakic, 1995). These fibers converge on the dendritic spines of medium spiny neurons found within the Nac that project out to various motor systems (Kelly et al., 1997). Together these components form a corticostriatal network of parts that differentially contribute to the learning and memory process (Baldwin et al., 2000).

Early studies provided evidence for the involvement of the PFC in working memory by measuring the electrical activity in the PFC in monkeys while they performed a classical delayed -response task (Fuster, 1973; Kubota and Niki, 1971). Distinct patterns of activity were observed relative to the cue, delay, and response phases of the task. Activity levels remained active during the delay period of the task until the initiation of a response was made. The sustained activity during the delay period is considered to be the neuronal correlate of the mnemonic processing component of working memory task.

Building upon these findings, researchers discovered that specific sets of neurons repeatedly responded to the presentation of specific target locations (Funahashi, Bruce and Goldman-Rakic, 1989). These same neurons did not become activated when another target location was presented. Based upon these findings, researchers concluded that the PFC contains "memory fields" similar to those found in the primary visual cortex in which different neurons encode for specific target locations. A decrease in the level of activity below baseline levels was detected in neurons opposite the memory field, suggesting the presence of 'opponent' memory fields.

D1 receptor expression is ten times greater than D2 receptors in the PFC (Lidow et al., 1998; Missale et al., 1998; Oak et al., 2000). Pharmacological studies have identified the dissociable effects of D1 and D2 receptor activation in the working memory process. D1 receptor activation selectively modulates the neuronal activity associated with the mnemonic processing component of working memory task, without affecting the cue and response related components (Sawaguchi and Goldman-Rakic, 1991; Williams and Goldman-Rakic, 1995). Neurons within monkey PFC memory fields increased their activity in response to low doses of a D1 antagonist, while higher doses completely disrupted neuronal activity. Neurons outside of

the memory field showed no activation, suggesting that memory fields contain a high density of D1 receptors. The resultant inverted "U" shaped dose-dependent response curve indicates that an optimal level of D1receptor activation is critical to the proper function of the working memory. Variant doses of a D2 antagonist had no effect on performance of the task.

D2 receptor activation selectively modulates the neuronal activity associated with the response component of working memory task without affecting the cue and mnemonic processing components (Wang et al., 2004). Response-related neurons showed a directional preference for a presented target, indicating the presence of D2 receptors in memory fields. Different subsets of response-related neurons selectively became active prior to the initiation of the response, while other neurons selectively became active after the completion of the task. The effects of D2 receptor activation are dose-dependent, as noted for D1 receptors. The balance between D1 and D2 receptor activation within the PFC is essential to facilitate the successful retention and manipulation of information necessary to select an appropriate response.

Behavioral studies show a strong relationship between dopamine levels and performance of a working memory task (Zahrt et al., 1997; Floresco and Phillips, 2001). Low levels of dopamine impair performance of a working memory task. Increasing levels of dopamine steadily improve performance, which ultimately plateaus. Continual increase in dopamine beyond optimal levels results in a steady decline in performance of the working memory task. When optimal levels of dopamine are restored, performance of the task returns to near perfect. This clearly illustrates a dose-dependent inverted "U" response curve indicating that an optimal level of dopamine is critical to the proper function of working memory.

Research has also shown that NMDA glutamate receptors also play a significant role in the learning process. Transgenic mice with enhanced hippocampal NMDA receptor subunits showed superior ability in the performance of a Morris water maze spatial learning task compared to their wild-type counterparts (Tsien,1996; Tang et al., 1999). Conversely, transgenic mice deficient of hippocampal NMDA receptor units showed inferior ability in the performance of a spatial learning task (Sakimura et al., 1995; Tsien, 2000).

Low doses of NMDA antagonist infused into the PFC had no effect. High doses of a NMDA receptor antagonist prevented acquisition, but had no effect on the performance of the lever pressing behavior in an appetitive instrumental learning task (Baldwin, Sadeghian and Kelley, 2002; Tsukada et al.,2005).

Molecular and electrophysiological studies confirm that the close proximity of the D1 and NMDA receptors in rat PFC and hippocampus not only facilitates interaction between the two receptors, but that D1 receptor activation mediates NMDA receptor activation (Kruse et al., 2009; Sarantus, Matsokis and Angelatou, 2009). Evidence supporting these findings shows that co-activation of dopamine D1 and glutamate NMDA receptors within the PFC of rats is necessary for successful acquisition and performance of an appetitive instrumental task, but not necessary once the task is learned (Baldwin, Sadeghian, and Kelly, 2002). Low doses of D1 and NMDA antagonist separately infused into the PFC had no effect on learning and performance, but co-infusion of low doses of D1 and NMDA antagonists impaired the ability to acquire the correct lever pressing response compared to controls. Reinfusion of D1and NMDA receptor anatagonists on the final day of the trial produced no effect from the drug treatment indicating that D1- NMDA receptor co-activation is not necessary once the task is learned. The D1- NMDA

co-infusion had no effect on locomotive or feeding behaviors, providing further support that the drug induced impairments are specific to learning.

D1 and NMDA receptor activation in the Nac also plays a significant role in the learning and memory process. High doses of the D1 receptor antagonist infused into the nucleus accumbens core(NacC) of rats prevented acquisition, but had no effect on the performance of the lever pressing behavior in an appetitive instrumental learning task (Smith-Roe and Kelley, 2000). High doses of the NMDA receptor antagonist infused into the NacC of rats produced the same effect in regards to acquisition, but reinfusion of the NMDA receptor antagonist on the final day of the trial produced no effect indicating that NMDA receptor activation is not necessary once the task is learned. High doses of the NMDA receptor antagonist infused into the nucleus accumbens shell (NacS) produced measureable, yet insignificant impairment in acquisition of the task (Kelley, Smith-Roe and Holahan, 1997).

Evidence supporting these findings shows that co-activation of D1 and NMDA receptors within the NacC of rats is necessary for successful acquisition and performance of an appetitive instrumental task (Smith-Roe and Kelley, 2000). Low doses of D1 and NMDA antagonist separately infused into the NacC had no effect on learning and performance, but co-infusion of D1 and NMDA antagonists impaired the ability to acquire the correct lever pressing response compared to controls. The D1-NMDA co-infusion had no effect on locomotive or feeding behaviors, providing further support that the drug induced impairments are specific to learning.

Decades of experimental manipulations have implicated dopamine and NMDA glutamate receptor activation as playing integral roles in the learning and memory process, but until recently, no research appears to have examined individual variability in the natural

expression of dopamine and NMDA glutamate receptor levels (Smith et al., 2004; Smith et al., 2005). The results of the Smith studies revealed significant correlations between rat brain neurochemistry and performance of working memory and spatial reference memory tasks. The purpose of the present study is to examine the naturally occurring variability in dopamine and NMDA glutamate receptor expression in the PFC and Nac in relation to individual differences in performance of a spatial reference memory and spatial working memory tasks.

## 2. Methods

*Subjects*

Sixteen (8 eight-month old) and (8 eleven-month old) female Sprague-Dawley rats were used in this study. Rats were individually housed and given access to food and water *ad libitum* under a 12 hour light/dark cycle. All testing was conducted during the light phase of the cycle.

*Apparatus*

The Morris water maze (MWM) apparatus is a circular pool, 1.8 meters in diameter, with black interior walls and floors, and a transparent, submersible platform. The pool is filled with water and the water temperature regulated at 23°C ± 1°. White curtains surround the pool, with black, distinctly shaped environmental cues hung at each of the four quadrants.

*Behavioral Testing (conducted by Laura Smith)*

Spatial reference memory testing was conducted in the Morris water maze (MWM), utilizing the submersible Atlantis-style platform. The platform remained fixed in the North-West quadrant throughout the testing period, except during probe trials. Testing consisted of three 60 second trials per day over eight days, with 45 seconds between trials. If the platform was not located within the 60 second period, the rat was physically guided to the platform, allowed to remain there for 15 seconds, then returned to her cage. If the platform was located during the

trial, the rat was allowed to remain on the platform for 10 seconds before being returned to her cage. Measurements of latency to locate the platform and thigmotaxicity were recorded. Probe trials to test memory were performed every sixth trial. During probe trials the platform was made unavailable, and the rat is allowed to swim for 60 seconds. Measurements of the number of times the platform position was crossed and percentage of time spent in the correct quadrant were recorded. Immediately following the probe trials, the submerged platform was raised with the rat still in the pool to prevent extinction of the task.

Spatial working memory testing was conducted in the MWM, during which the platform remained raised, but was moved to a different quadrant at the beginning of each testing day. Testing consisted of four 60 second trials per day over four days, with 45 seconds between trials. On day one the platform was placed in the North-East quadrant, moved to the South-West on day two, the South-East on day three, and North-West on day four. If the platform was not located within the 60 second period, the rat was physically guided to the platform, allowed to remain there for 15 seconds, then returned to her cage. If the platform was located during the trial, the rat was allowed to remain on the platform for 10 seconds before being returned to her cage. Measurements of latency to locate the platform and thigmotaxicity were recorded. Spatial working memory was assessed by performance on B trials, and (A- B) trials for each day.

*Tissue Preparation*

The rats were sacrificed by decapitation, brains were rapidly removed, and placed on fresh frozen dry ice, and stored airtight at -80°C until cryostat sectioning. Coronal sections were taken from the PFC and Nac at 16µm thickness, affixed to subbed slides, and returned to storage at -80°C.

*In Situ Hybridization*

In Situ hybridization and probe labeling were conducted following the method of Young (1992). Oligonucleotides were radioactively-labeled using $^{35}S$ and targeted against mRNAs for dopamine (D1, D2, D3) and NMDA NR2A subunits. Prepared slides and $^{14}C$ standards were placed in cassettes with X-omat (Kodak, Rochester, NY, USA) film and exposed for two weeks. Autoradiographic images of individual slides were digitized and converted to TIFF files using a flatbed scanner. Samples were taken from PFC and nucleus accumbens and quantitative analysis was performed using NIH Image (Rasband, NIH). Optical densities of the mRNA's were interpolated along the calibration curve established from the $^{14}C$ standards.

*Hypotheses*

The purpose of the present study was to examine the naturally occurring variability in dopamine and NMDA glutamate receptor expression in the PFC and Nac in relation to individual differences in performance of spatial reference memory and spatial working memory tasks.

*Specific Aims:*

1. To confirm the involvement of dopamine and glutamate in spatial reference and working memory learning processes. No published research appears to exist that directly compares the naturally occurring rat brain neurochemistry to individual measurements of spatial learning and memory. Significant correlations would add further support to the findings of experimental manipulation studies that results are specific to learning and memory.

2. To determine whether these neurotransmitters are expressed differentially in relation to individual differences in learning and memory abilities. Experimental studies involving the manipulation of dopamine and NMDA receptor activity conclude that an optimal

level of these neurotransmitters is necessary for the successful acquisition and performance of memory tasks. No published research enumerates the actual optimal levels of receptor activity. The quantification of naturally occurring receptor levels in relation to measures of learning and memory would provide insight into the range of optimal levels.

My hypothesis is that rats with higher dopamine and NMDA mRNA expression will be associated with better learning and memory ability as measured by performance of spatial reference and working memory tasks.

## 3. Data Analysis

*Atlantis-Style Platform*

Spatial reference memory abilities were examined using the Atlantis-style platform paradigm. Repeated measures analysis of variances (ANOVAs) were used to analyze behavioral measures previously outlined. Analyses were performed across days and trials, as well as between age groups. Since half of the C trials were probe trials, C trials were analyzed separately from A and B trials. Post hoc analyses were performed as appropriate when results were found to be significant ($p < .05$).

*Moving Platform*

Spatial working memory abilities were examined using the Moving platform paradigm. Repeated measures analysis of variances (ANOVAs) were used to analyze behavioral measures previously outlined. Analyses were performed separately for all trials (A, B, C and D), with special interest on B trials. B trials were considered separately from all other trials, since B trials are the best indicator of working memory ability (Frick, et al., 1995). The difference between the latency for the A and B trials (A-B) was calculated as a supplemental indicator of working memory ability. Since performance during A trials represents the time to find the new location of the platform at the beginning of each day, any decrease in latency from A to B trials within a single day can be attributed to working memory. Post hoc analyses were performed as appropriate when results were found to be significant ($p < .05$).

*mRNAs and Behavior*

Pearson's correlations were performed to investigate the relationships between mRNAs quantities, and the relationships between behavioral learning variables within individuals and mRNA quantities. Post hoc analyses were performed as appropriate when results were found to be significant ($p < .05$).

# 4. Results

## Behavioral Analyses

### *Atlantis-style Platform*

For A trials, results of a repeated measures ANOVA showed significant differences in latency scores across days, $F_{(6,84)} = 6.18$, $p = .00$. Results of a paired sample t-test showed a significant decrease in latency scores between Day 2 (M = 52.69, SE = 3.46) and Day 8 (M = 30.07, SE = 5.16), $t = 3.93$, $p < .01$, (Figure 1A). Subjects were able to locate the platform faster on the last day when compared to the second day, indicating positive learning of the task. Further analysis showed that the averaged latency score for the averaged Days 2-4 (M = 52.39, SE = 2.22) was higher when compared to the averaged latency score for Days 5-8 (M=33.75, SE = 3.14), showing that subjects located the platform significantly faster on Days 5-8, $t = 7.88$, $p < .01$, (Figure 1B).

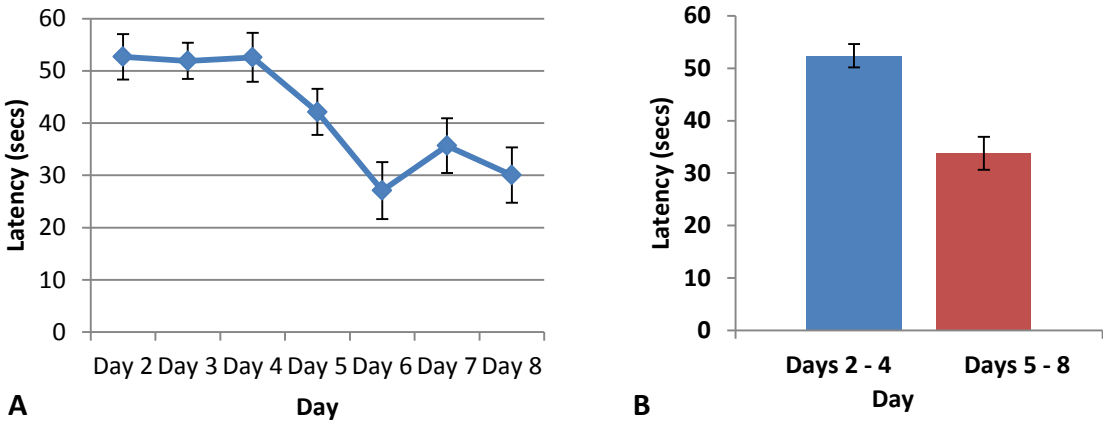


**Figure 1A**. Averaged latency scores for Atlantis A trials.
**Figure 1B**. Average latency scores for Atlantis A trials for days 2-4 and 5-8.

These findings held true for the percent of time spent in the correct quadrant. Results of a repeated measures ANOVA showed significant differences in the percent of time spent in the correct quadrant across A trials, $F_{(6,84)}$ =2.49, $p$ = .03. There was a significant increase in the amount of time spent in the correct quadrant between Day 2 (M = 28.79, SE = 1.86) and Day 7 (M =44.25, SE = 4.15), $t$ = 3.51, $p$ = .00. Subjects spent more time in the correct quadrant on Day 7 compared to Day 2, indicating positive learning of the task (Figure2A). Further analysis showed that the averaged percent of time spent in the correct quadrant for Days 2-4 (M = 30.83, SE = 1.68) was significantly lower compared to averaged time for Days 5-8 (M = 39.08, SE =2.62), $t$ = -2.70, $p$ = .02 (Figure 2B).

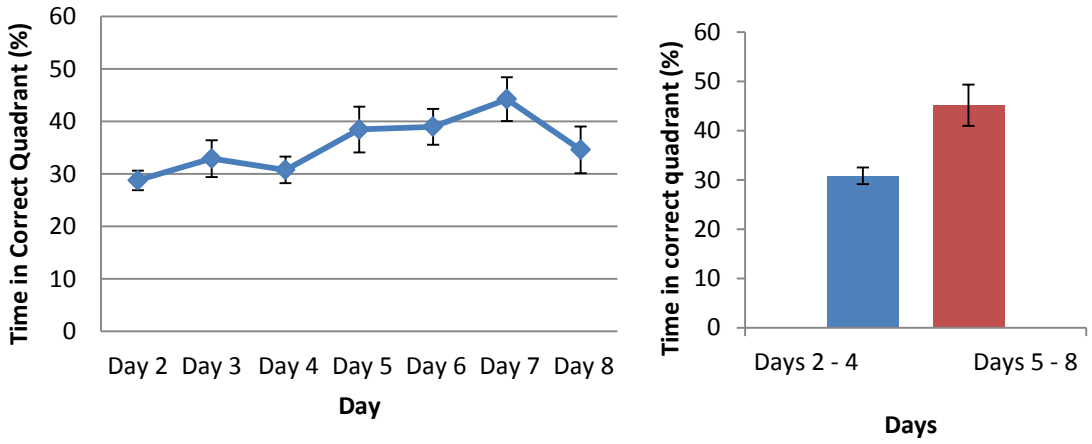


**Figure 2A**. Averaged percent of time spent in the correct quadrant for Atlantis A trials.
**Figure 2B**. Averaged percent of time spent in the correct quadrant days 2-4 and 5-8.

For probe trials, results of a repeated measures ANOVA showed significant differences in the percent of time spent in the correct quadrant across trials, $F_{(3,42)} = 4.03$, p = .01. Results of a paired samples t-test showed significant increases in the percent of time spent in the correct quadrant between probe trial 1 and probe trial 4 (M = 8.99, SE = 2.93), $t = 3.10$, $p < .01$, and probe trial 2 and probe trial 4 (M = 8.78, SE = 3.39), $t = 2.59$, $p < .05$ (Figure 3A). Results of a repeated measures ANOVA showed significant differences in the number of platform crossings between probe trials, $F_{(3,42)} = 4.35$, $p = .01$. Significant increases occurred in the number of platform crossings between probe trial 1 and probe trial 4 (M = 2.00, SE = 0.56), $t = 3.55$, $p < .01$, and probe trial 2 and probe trial 4 (M = 1.88, SE = 0.56), $t = 3.34$, $p < .01$ (Figure 3B). Increases in the amount of time spent in the correct quadrant and number of platform crossings between the first and last probe trial indicate positive learning of the task.

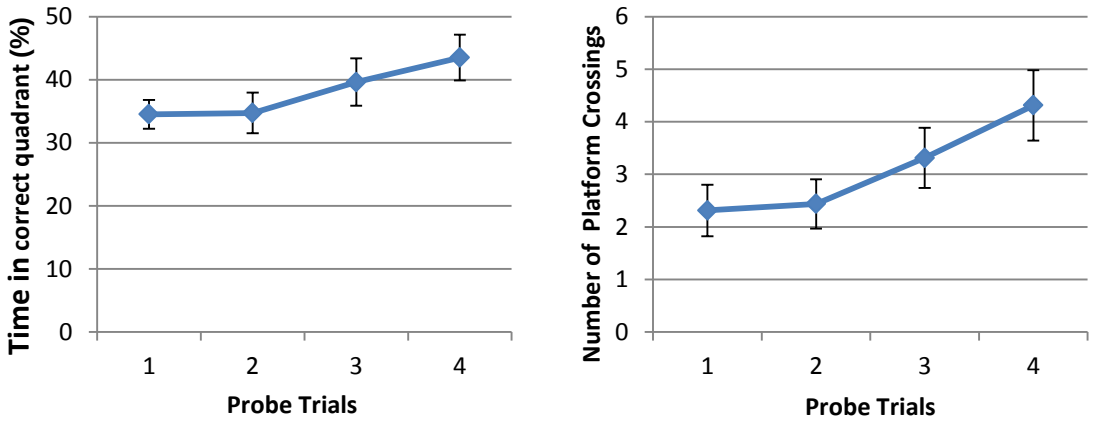


**Figure 3A**. Averaged percent of time spent in the correct quadrant for Atlantis Platform probe trials.
**Figure 3B**. Averaged number of platform crossing for Atlantis Platform probe trials.

*Moving Platform*

For A trials, results of a repeated measures ANOVA showed a trend for differences in latency scores across days, $F_{(3,42)}$ =2.20, $p$ = .10. Further analysis using a paired samples t test showed a significant decrease in time to find the new location of the platform between Day 1 (M = 41.32, SE = 4.90) and Day 4 (M = 24.22, SE = 4.55), $t$ = 2.45, $p$ = .03. Subjects were able to locate the new location of the platform faster on the last day of the trial when compared to the first, indicating positive learning of the task.

Repeated measures ANOVAs were conducted to examine the search strategy during A trials. Results showed significant differences in the percent of time spent searching in the previous days quadrant across trials, $F_{(3,45)}$ = 9.42, $p$ = .00. Results of a paired samples t-test show significant decreases in time spent in the previous days quadrant between trial Day 1 (M =3 7.08, SE =2.94) and Day 4 (M =22.62, SE =3.61), $t$ = 3.39, $p$ = .00, indicating positive learning of the task. The amount of time spent searching in the previous days quadrant significantly

decreased between day 2 and day 3, (M = 12.47, SE = 3.25),*t* =3.84, *p* = .00. Results of a repeated measures ANOVA showed significant differences in the percent of time spent searching in the correct quadrant across trials, $F_{(3,45)}$ = 2.82, *p* = .05. Although not significant, beginning on day 3, more time was spent in the correct quadrant of the new platform location, than in the previous day's platform location. A trend was found between time spent in the correct quadrant and time spent in the previous days quadrant for Day 4, *t* = 1.82, *p* = .09. The shift from searching in the previous day's quadrant to searching in the correct day's quadrant on day 3 demonstrates learning of the Moving Platform task (Figure 4).

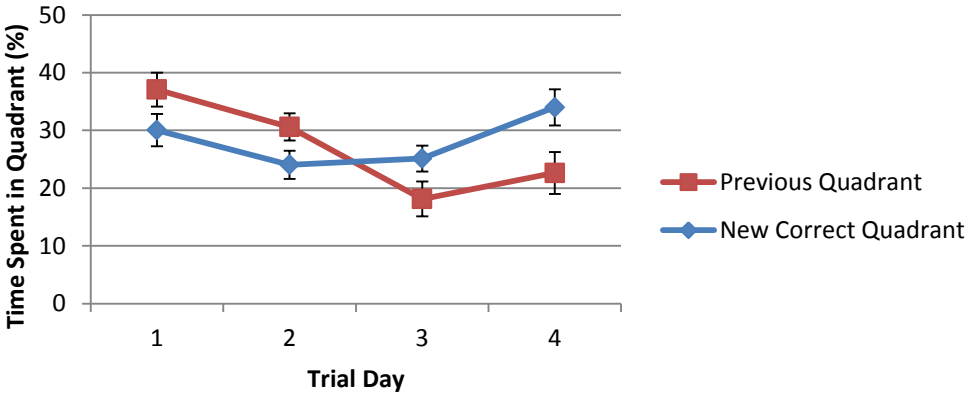


**Figure 4**. Time spent in previous day's quadrant vs. new correct platform quadrant for Moving Platform A trials.

For B trials, results of a repeated measures ANOVA showed no significant differences in latency scores across days, $F_{(3,45)}$ =.33, *p* = .81.

For A minus B latency difference scores, results of a repeated measures ANOVA showed no significant differences in latency scores across days, $F_{(3,45)}$ =1.41, *p* = .25. Results of a paired

samples t test revealed a significant decrease in latency from A to B trial on Day 1 (M = 17.95, SE = 4.63), $t$ = 3.88, $p$ = .00.

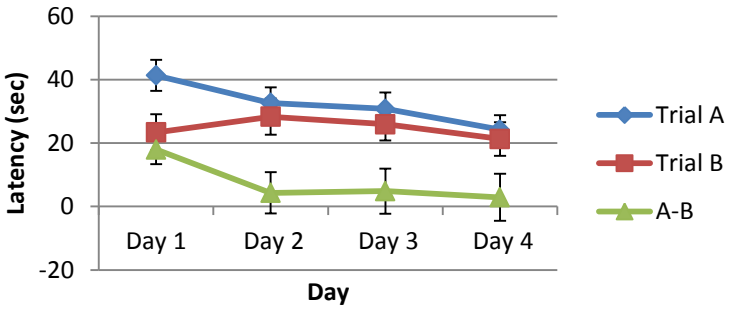


**Figure 5**. Average Latency Trial A, Trial B and (A-B) difference for Moving Platform

mRNA's

Pearson correlations were performed to examine the relationships between D1, D2, D3 and NR2A mRNAs within individual subjects. *r* values for significant results are shown in Table 1.

**Table1**. Pearson correlation r values between D1, D2, D3 and NR2A mRNA values within individual rats.

| | D1 PFC | D1 Nac | D1 Nas | D2 PFC | D2 Na | D3 Na | D3 OFT | NR2A PFC | NR2A Na |
|---|---|---|---|---|---|---|---|---|---|
| **D1 PFC** | | | | | | | .437 † | | |
| **D1 Nac** | | | .780** | -.668** | | | .740** | -.565 † | |
| **D1 Nas** | | | | -.534* | | | .797** | - .487 † | |
| **D2 PFC** | | | | | | | -.455 † | .537 † | |
| **D2 Na** | | | | | | -.336 † | | | .522* |
| **D3 Na** | | | | | | | | | |
| **D3 OFT** | | | | | | | | -.507 † | |
| **NR2A PFC** | | | | | | | | | .655* |
| **NR2A Na** | | | | | | | | | |

** $p < .01$, * $p < .05$, † $p < .10$, †* $p < .10$ one-tailed

One-way ANOVAs conducted to examine whether mRNA levels differ between age groups, showed that the younger group (M = .03426, SE= .00127) had significantly higher D2 mRNA in the Nac than the older group (M = .03067, SE = .00091), $F_{(1, 14)} = 5.28$, $p < .05$. No significant differences between age groups were found for any other mRNA locations (Figure 6).

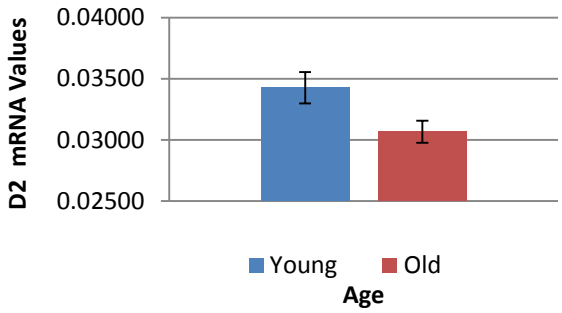


**Figure 6.** Differences in D2 mRNA values between young and old subjects.

mRNAs and Behavior

Pearson correlation coefficients were performed to examine the relationships between mRNA levels and behavioral performances. These correlations are shown in Table 2 and 3.

*Atlantis-style Platform*

**Table 2.** Pearson correlation r values between mRNA values and behavioral performance for Atlantis Platform.

| | ***D1 PFC*** | ***D1 Nac*** | ***D1 Nas*** | ***D2 PFC*** | ***D2* Na** | **D3 Na** | **D3 OFT** | **NR2A PFC** | **NR2A Na** |
|---|---|---|---|---|---|---|---|---|---|
| Probe 1 Correct Quadrant | | | | | | **- .515*** | | | |
| Probe 2 Correct Quadrant | | | | | | **- .504*** | | | |
| A Trials Platform Latency Avg Days 2-4 | | | | | **- .474†** | | | | **- .461†** |
| A Trials Correct Quadrant Avg Days 2-4 | | | | | **.546*** | **- .479†** | | | |

** $p < .01$, * $p < .05$, † $p < .10$

*D2 in Nucleus Accumbens (D2 Nac)*

For A trials, a significant positive correlation was found between D2 Nac mRNA levels and the average percent of time spent in the correct quadrant for the averaged days 2-4, $r = .546$, $p < .05$. Analysis using a one-way ANOVA showed that subjects with higher D2 Nac spent significantly more time in the correct quadrant for the averaged days 2-4 than those with lower D2 Nac , $F_{(1,14)} = 6.28$, $p = .03$. There was also a negative trend between D2 Nac mRNA levels and the average latency during A trials for the averaged days 2-4, $r = -.474$, $p = .06$. Further analysis showed a trend whereby subjects with higher D2 NA mRNA had lower latency scores than those with lower D2 Nac mRNA levels for the averaged days 2-4 during A trials, $F_{(1,14)} = 3.47$, $p = .08$). Individuals with higher D2 receptor expression in the nucleus accumbens spent more time in the correct quadrant and located the platform faster during the early stage of the trial period.

*D3 in Nucleus Accumbens (D3 Nac)*

A negative trend was found between D3 Nac mRNA levels and the average percent of time spent in the correct quadrant during A trials for the averaged days 2-4, $r$ = -.479, $p$ = .06. Lower D3 Nac was associated with a higher percent of time spent in the correct quadrant during Days 2-4 of the overall trial period. For probe trials, significant negative correlations were found between D3 Nac and the percent of time spent in the correct quadrant during Probe trial 1, $r$= -.515, $p$ <.05 and Probe trial 2, $r$ = -.504, $p$ < .05. Lower D3 mRNA levels in the nucleus accumbens is associated with more time spent in the correct quadrant during early probe trials.

*NR2A in Nucleus Accumbens (NR2A Nac)*

A negative trend was found between NR2A Nac levels and latency to reach the platform during A trials for the averaged days 2-4, $r$ = - .461, $p$ = .07. Higher NR2A mRNA levels in the nucleus accumbens were associated with faster times to locate the platform.

*Moving Platform*

Correlations between moving platform behavioral variables and mRNA levels are shown in Table 3.

**Table 3**. Pearson correlation r values between mRNA values and behavioral performance for Moving Platform.

| | D1 PFC | D1 NacC | D1 NacS | D2 PFC | D2 Nac | D3 Nac | D3 OFT | NR2A PFC | NR2A Nac |
|---|---|---|---|---|---|---|---|---|---|
| Avg A Trial Latency | | **- .527*** | **- .525*** | | | | | | |
| Avg (A-B) Difference | | **- .440†** | **-.657**** | | | | | | |
| Day 1 Correct Quadrant | | **. 494*** | | | | | | | |
| Day 3 A Trial Latency | | **- .611**** | | | | | | | |
| Day 3(A-B) Difference | | **- .695**** | **- .621**** | | | | | | |

** $p$ < .01, * $p$ < .05

Significant negative correlations were found between D1 NacS and D1 NacC mRNA levels and the average A trial latency score, $r = -.525$, $p < .05$, $r = -527$, $p < .05$, respectively. Higher D1 mRNA receptor expression in the nucleus accumbens shell and core is associated with less time to locate the new location of the platform at the beginning of each trial day. Results of a repeated measures ANOVA showed a significant main effect for D1 NacC mRNA levels across days, $F_{(1,14)} = 6.76$, $p = .02$. Subjects with higher D1 NacC had significantly lower A trial latency scores than those with lower D1 NacC mRNA levels, $t = 2.60$, $p = .02$. A significant negative correlation was found between D1 NacC and the A trial latency scores on Day 3, r = -.611, p = .01. Further analysis using an independent samples t-test showed that subjects with higher D1 NacC had significantly lower latency scores (M = 20.00, SE = 4.60), than those with lower D1 NacC levels (M = 44.64, SE = 7.75), for A trials on day 3, $t = -2.88$, $p = .01$. No significant effect was found for D1 NacS mRNA levels.

D1 NacC was significantly correlated with time spent in the correct quadrant for day 1 A trials, $r = .494$, $p < .05$, and a trend for day 2, $r = .416$, $p = .10$. Results of a repeated measures ANOVA showed a significant main effect for D1 NacC mRNA levels, $F_{(1,14)} = 4.39$, $p = .05$. An independent t-test showed that subjects with higher D1 NacC spent significantly more time searching in the correct quadrant (M = 30.37, SE = 1.33), than subjects with lower D1 NacC (M = 25.65, SE = 1.90), $t = 2.10$, $p < .05$.

For B trials, results of a repeated measures ANOVA showed a trend for an interaction between high vs. low D1 NacS mRNA levels and early (averaged Days 1 and 2) late (averaged Days 3 and 4) stages of the task, $F_{(1,14)} = 3.46$, $p = .08$. Subjects with lower D1 NacS took less

time to reach the platform than those with higher D1 NacS during the late stage of the task, $t = 2.22$, $p = .04$(Figure 7B).

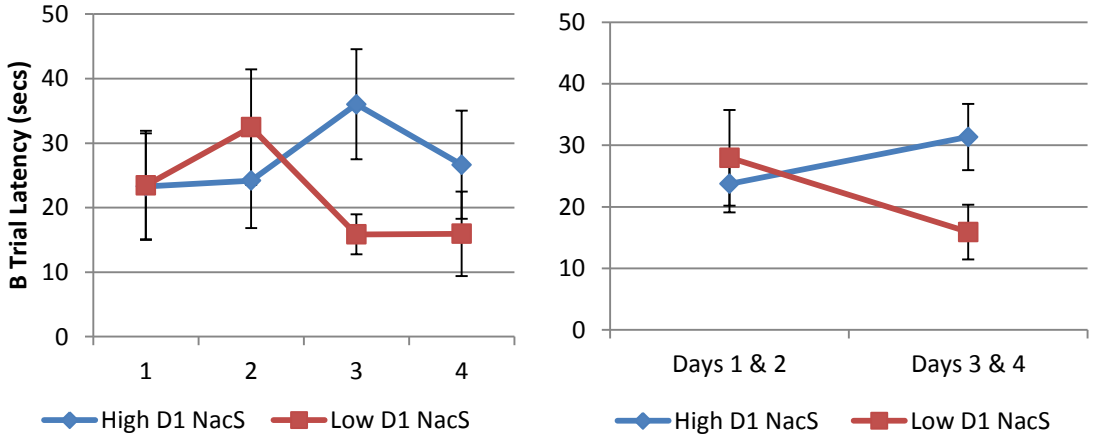


**Figure 7A.** Averaged latency for Moving Platform B trials for groups above or below the mean for D1 NacS
**Figure 7B**. Averaged latency for Moving Platform B trials for groups above or below the mean for D1 NacS for days 1-2 vs. 3-4

A significant negative correlation was found between D1 NacS and the average latency difference scores from A to B trials (A-B), $r = -.657$, $p < .01$. There also was a negative trend between D1 NacC and the average (A-B) latency score, $r = -.440$, $p = .09$. Results of a repeated measures ANOVA showed a significant main effect for D1 NacC mRNA levels, $F_{(1,14)} = 9.02$, $p = .01$. Subjects with lower D1 NacC mRNA receptor expression showed improved latency to locate the platform from A to B trials, a supplemental indicator of working memory.

A significant negative correlation was found between D1 NacC and D1 NacS mRNA levels and the latency difference score from A to B trials (A-B) on day 3, $r = -.695$, $p < .01$, $r = -.621$, $p < .01$. Individuals with lower D1 NacC and NacS mRNA receptor expression showed improved

latency to locate the platform from A to B trials, a supplemental indicator of working memory. Further analysis using separate independent samples t-test showed that subjects with lower D1 NacC mRNA levels had significantly higher latency difference scores from A to B trials on day 3 scores than those with higher D1 NacC levels (M = -20.08, SE = 9.28), $t$ = - 2.17, $p$ < .05. Also, subjects with lower D1 NacS mRNA levels had significantly higher latency difference scores from A to B trials on day 3 than those with higher D1 NacS levels (M = -32.25, SE = 11.92), $t$ = - 2.71, $p$ < .01.

## 5. Discussion

The purpose of this study is to examine the naturally occurring variability in dopamine and NMDA glutamate receptor expression in the PFC and nucleus accumbens in relation to individual differences in performance of a spatial reference memory and spatial working memory tasks. Significant correlations between mRNA values and behavioral values implicate the mRNA studied here in several aspects of learning.

Individuals with higher D2 receptor expression in the nucleus accumbens consistently spent more time in the correct quadrant and located the platform faster during A trials of the Atlantis-style Platform task. D2 Nac mRNA was only significantly correlated with behavior performance on Days 2-4, thus associating D2 Nac receptors with faster learning in the spatial reference memory process. These findings support one theory that suggests that nucleus accumbens D2 receptors are involved in memory consolidation and act indirectly as a modulator of memory storage in other brain regions (Setlow and McGaugh, 1998). Infusion of the D2 antagonist sulpiride into the nucleus accumbens immediately after training in a spatial water maze memory task, impaired memory retention, whereas, infusion 2 hours after training showed no impairment, supporting the involvement of D2 Nac receptors in memory consolidation. Control groups receiving saline infusions did not differ in behavioral performance of the task. Drug manipulation and lesions studies targeting the nucleus accumbens add further support to the hypothesis that memory storage for spatial memory involves in other brain regions. D2 antagonist infusions and lesions to the nucleus accumbens prior to training

prevented the acquisition of spatial memory tasks (Arnett, McGregor & Robbbins, 1989; Ploeger et al., 1994). D2 agonists administered post-training enhanced retention in water maze and radial arm tasks (Packard & McGaugh, 1994). In contrast, D2 antagonists administered post-training impaired acquisition (Ploeger et al., 1994). The correlation with early learning, but not later memory for platform location, support D2 involvement in the memory consolidation process acting as a modulator for memory storage elsewhere in the brain.

The only age-related differences in mRNAs were found in D2 mRNA values in the nucleus accumbens. Younger rats had significantly higher D2 Nac levels compared to older rats. Interestingly, this difference did not extend to behavioral performance for either the Atlantis or Moving Platform tasks. One possible explanation for lack of an age difference in behavioral performance is that the age difference between the groups was only three months. An ontological study conducted by Srivastava et al. (1992) investigated the postnatal development of D2 receptor expression in Sprague-Dawley rats from day 1 to 1 year of age. Specifically, in the nucleus accumbens, the D2 receptor is apparent on day 1, gradually increases, reaching maximum levels on day 28. After day 28, receptor expression sharply declines until 6 months of age, then steadily continues to decrease between 6 months and one year (Srivastava, 1992) The ages of the animals in this study (8 and 11 months), places them in the period where receptor expression is still decreasing at a steady rate, which explains the differences found between the groups; however, their ages place them in the same classification as being adult rats, where differences in learning ability would not be expected. Age-related impairment in spatial learning for the hidden-platform version (Atlantis), but not the cued version of the task, was found between (4-6 month) and (25-27month) Long-Evans rats. Younger rats exhibited significantly

superior performance during probe trials when compared to older rats (Gallagher, Burwell & Burchinal, 1993).

In contrast to D2, individual rats with lower D3 mRNA levels in the nucleus accumbens was associated with more time spent in the correct quadrant during early probe trials 1 and 2 of the Atlantis-style Platform task. There also was a similar trend for the percent of time spent in the correct quadrant during early A trials, thus associating D3 receptors in the nucleus accumbens with faster learning in the spatial memory process. The significant negative correlation between D2 Nac and D3 Nac establishes a relationship whereby higher D2 Nac expression is associated with lower D3 Nac expression. A similar relationship was found for the correlations between D2 Nac and D3 Nac mRNAs and behavioral performance measures during the early learning stage.

Substantial research indicates that memory consolidation is the result of the interaction between D2 and D3 receptors (Laszy, Laszlovsky & Gyertyan, 2005; Sigala, Missale & Spano, 1997; Xing et al., 2010; Xing, Meng & Wei, 2010). Genetically manipulated mice lacking the D3 receptor exhibited normal learning abilities when compared to their wild-type counterparts in a MWM spatial task (Xing et al., 2010). Aged D3 knockout mice exhibiting age-related memory impairment, performed better than their wild-type counterparts in a MWM spatial task, suggesting that antagonism of the D3 receptor improves age-related declines in memory (Xing, Meng & Wei, 2010).

Pharmacological experiments have shown that D3 antagonists had no effect on the behavioral performance of the unimpaired group in a step down passive avoidance and water labyrinth test (Laszy, Laszlovsky & Gyertyan, 2005;Sigala, Missale & Spano, 1997). D3

antagonism reversed behavioral deficits in the drug-induced memory impairment group for both tasks. Additionally, behavioral performance of the group that received co-administration of the D2 agonist and D3 antagonist was significantly better than the group that received the D2 agonist alone, concluding that D3 antagonism potentiates the effects of the D2 agonist (Sigala, Missale & Spano, 1997).

The relationship with lower D3 Nac in early behavioral performance may be related to the relationship between D2 and D3 in memory consolidation. Perhaps, D2 Nac and D3 Nac receptors are only involved in memory consolidation and no longer necessary for memory recall. Alternatively perhaps D3 Nac receptors differentially interact with the other brain regions involved in memory retrieval.

The negative trend between NR2A Nac and latency to reach the platform during A trials for the averaged days 2-4, establishes a relationship whereby higher NR2A receptor expression is associated with early learning processes. Antagonism of NMDA receptors in the nucleus accumbens core disrupts acquisition of an appetitive instrumental learning task (Smith-Roe and Kelley, 2000). Reinfusion of the NMDA receptor antagonist on the final day of the trial produced no effect on performance indicating that NMDA receptor activation is not necessary once the task is learned. High doses of the NMDA receptor antagonist infused into the nucleus accumbens shell produced measureable, yet insignificant impairment in acquisition of an appetitive instrumental learning task the task (Kelley, Smith-Roe and Holahan, 1997).

When behavioral performance was examined for the Moving Platform task, higher D1 mRNA in the nucleus accumbens core and shell was found to be associated with less time to locate the platform during A trials. This suggests that D1 receptors in the nucleus accumbens

shell and core positively contribute to acquisition of the working memory task. For B trials, lower D1 mRNA in the nucleus accumbens shell was associated with less time to reach the platform. This suggests that lower D1 mRNA in the nucleus accumbens shell is associated with working memory, since B trials are the best indicator of working memory ability (Frick, 1995). Additionally, lower D1 mRNA in the nucleus accumbens shell and core was found to be associated with improved latency to locate the platform from A to B trials, a supplemental indicator of working memory. The finding that only D1 Nac in the shell was found to be involved with performance on B trials suggests that D1 in the shell and core play different roles in the working memory process.

In an effort to tease out the different roles that D1 in the core and shell play, the search strategy during A trials was examined. For A trials on days 1 and 2, more time was spent in the quadrant where the platform was located on the previous day, than in the new correct platform location. Beginning on day 3, more time was spent in the quadrant of the new platform location, than in the previous day's platform location, indicating learning of the Moving Platform task.

Although more time was spent searching in the previous day's quadrant for days 1 and 2, higher D1 NacC was found to be associated with time spent searching in the new correct platform location. Subjects with higher D1 NacC mRNA spent consistently spent more time searching in the correct quadrant, than those with lower D1 NacC mRNA levels.

When latency measurements for day 3 were examined separately, the dichotomy between the core and shell was revealed. For A trials, higher D1 NacC was significantly correlated with less time to reach the platform. Additionally, subjects with higher D1 NacC had

significantly lower latency scores than those with lower D1 NacC levels on A trials on day 3. These findings suggest that high D1 NacC is associated with implementing a new strategy to successfully acquire the new platform location at the beginning of each trial day.

For B trials on day 3, lower D1 NacS was significantly correlated with less time to reach the platform. Subjects with lower D1 NacS mRNA had significantly lower latency scores than those with higher D1 NacS mRNA levels on day 3. During the late stage of the trial period, subjects with lower D1 NacS mRNA took less time to reach the platform than those with higher D1 NacS mRNA. These findings, together with performance on A trials, associate D1 receptors in NacS with the acquisition/learning and maintenance of the platform location from A to B trials in this working memory task.

The findings in the study reported here are consistent with those reported in the studies that use pharmaceutical manipulations involving D1 in the nucleus accumbens core and shell. Substantial research suggests that the core and shell in the nucleus accumbens differentially contribute to the learning and memory process (Floresco et al.; 2006; Nelson et al., 2010). Nelson (2010) examined the effect of lesions targeting the core and shell in the nucleus accumbens on object recognition and an object location tasks after 24 hour delay. Controls and animals with shell lesions showed a preference for the novel object. In contrast, animals with core lesions showed a preference for the familiar object over the novel object, suggesting that the core is involved in the process of memory consolidation or long term memory retrieval process. In the object location task, controls and animals with core-lesions easily located the new object location, whereas, those with shell lesions exhibited impaired ability in performance

of the object location task. These finding suggest that the shell is involved in the consolidation process of spatial location.

Floresco (2006) adds further support that the nucleus accumbens core is involved in acquisition of a maze-based set shifting task. Animals with lesions to the core had to learn to disregard a previously learned strategy and implement a new search strategy to receive a reward. In core-lesioned animals, the ability to implement the new search strategy was severely disrupted, implicating that the core is involved in the acquisition and maintenance of a new strategy.

Additional evidence shows that D1 receptors within the core and shell have dissociable roles in aversive memory using a one-trial inhibitory avoidance task. Antagonism of D1 receptors in the nucleus accumbens core immediately after training impaired latency in the step-down task 24 hours later. Antagonism of the D1 receptors in the shell had no effect on performance of the task. These findings further implicate D1 receptors in the shell in learning and D1 receptors in the core in memory consolidation (Manago, et al., 2008).

This is the first study to examine the relationship between naturally occurring variability in dopamine and NMDA receptor expression in relation to individual differences in behavioral performance. The findings in this study are consistent with the substantial research using experimental manipulations that have identified dopamine and NMDA receptor activation as playing an integral role in the learning and memory process. Individual differences in both spatial reference and spatial working memory were correlated with individual differences in mRNA levels, suggesting that individual differences in mRNA expression are a determinant of individual performance differences in these aspects of behavior.

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Curriculum Vitae

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