NEGLIGBLE EFFECTS OF ACUTE ATOMOXETINE ADMINSTRATION ON VISUAL WORKING MEMORY IN THE MACAQUE MONKEY

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Abstract

Working memory (WM) is a basic cognitive process central to daily activities including communication and problem solving. This limited capacity system guides future behaviour through the short-term retention of information.

The neural basis of WM is thought to lie in the persistent activity of a network of prefrontal cortical neurons. This activity presents itself during the retention interval of behavioural tasks that probe WM and is reported to be influenced by catecholamines. Accordingly, catecholamine reuptake transporter inhibitors enhance neurotransmission of catecholamines and thus, are said to modulate WM performance. Atomoxetine (ATX) selectively inhibits the reuptake of dopamine and norepinephrine. Evidence of acute ATX effects on WM performance in healthy nonhuman primates or humans is currently lacking. Reports of ATX-induced improvements are equivocal because the majority of studies are sub chronic and the implemented tasks are often inadequate in their measure of WM.

Here we tested the acute effects of orally administered ATX on the performance of two female rhesus macaques in a delayed visual sequential comparison (VSC) task with a wide range of doses (0.03 – 3.0 mg/kg). This task reliably assesses both the limited capacity and short time interval of WM by implementing a memory load greater than 2 and a 1s retention interval. It is hypothesized that ATX improves WM performance on the delayed VSC task in a dose- and memory load-dependent manner.

Despite the reported contribution of catecholamines on cognition, there were no dose- or memory load-dependent effects observed on delayed VSC task performance following systemic ATX administration. In fact, all changes in performance were within the variability of the control data. While the findings failed to establish a role for catecholamines in WM, a potential modulatory role in motivation was revealed. An increase in task engagement was observed on the task, prompting the implementation of a visual progressive ratio task to further assess the potential motivational effects. These results reveal the need to re-evaluate the notion that catecholamines are capable of modulating WM and direct our attention to their contribution to motivation.

Co-Authorship

This thesis project was conducted under the supervision of the principal investigator, Dr. Martin Paré, who was responsible for the planning and implementation of the research protocols. I was responsible for the data collection with assistance from Catherine Crandell. Data analysis was completed through joint efforts from Dr. Paré and myself. I produced this thesis in its entirety with editing and revision provided by Dr. Paré.

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List of Abbreviations

AD	Alzheimer’s disease
ADHD	Attention Deficit/Hyperactivity Disorder
AMPA	Amino-3-hydroxy-5-methyl-4-isoxazole
ATX	Atomoxetine
BADDS	Brown Attention Deficit Disorder Scales
BRIEF	Behaviour Rating Inventory of Executive Function
CANTAB	Cambridge Neuropsychological Test Automated Battery
CNS	Central Nervous System
CYP2D6	Cytochrome P450 2D6
DA	Dopamine
DAT	Dopamine Transporter
DMST	Delayed Match-to-Sample Task
DNMST	Delayed Non-Match-to-Sample Task
EPSP	Excitatory Post-Synaptic Potential
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
HCN	Hyperpolarization-activated Cyclic Nucleotide-gated (channel)
HR	Heart Rate
IT	Inferior Temporal Cortex
LC	Locus Coeruleus
MPH	Methylphenidate
NE	Norepinephrine
NET	Norepinephrine Transporter
NHP	Nonhuman Primate
NMDA	N-methyl-d-aspartate
NRI	Norepinephrine Reuptake Inhibitor
ODR	Oculomotor Delayed Response Task

PD	Parkinson disease
PET	Positron Emission Tomography Scan
PFC	Prefrontal Cortex
PKA	Protein Kinase A
PPC	Posterior Parietal Cortex
PRM	Pattern Recognition Memory
SOPT	Self-Ordered Pointing Task
SRM	Spatial Recognition Memory
VSC	Visual Sequential Comparison (task)
WM	Working Memory
WMTB-C	Working Memory Test Battery - Children

Chapter 1 – Introduction

1.1 Working Memory

Dialing a telephone number, solving a simple mathematics problem, carrying out a conversation; all of these daily actions have one thing in common: working memory (WM). This basic cognitive function is necessary to complete problem solving, reasoning and communication tasks (Baddeley, 1992). Working memory is a limited capacity system that temporarily stores relevant information. This temporary storage differentiates WM from other forms of memory that require repetition to maintain information. WM is not limited to processing new stimuli, but also retrieves information from other memory stores (Goldman-Rakic, 1995). It is considered to connect the perception of information with long term memory storage and action (Baddeley, 2003); allowing us to act in the absence of the original stimuli (Arnsten, 1998). For example, when dialing a telephone number WM can acquire information from a new visual stimulus (reading a telephone number out of the phone book) or can retrieve previously stored information (a telephone number previously committed to memory).

Formally described as a mental sketchpad, information is only maintained in WM for a brief period of time and is “erased” once it loses relevance (Baddeley, 1992). As such, WM is an active system that is constantly updating (Baddeley and Hitch, 1974). Two key features that differentiate WM from long term memory are a short time interval and limited capacity. Both of these characteristics were described by Sperling (1960) who demonstrated that “more is seen than can be remembered” through several visual experiments conducted in humans. Participants were presented with a series of letters in rows on a screen and only instructed which row needed to be recalled at the end of the trial. In this particular experiment the instructive signal was delayed up to 1 second rather than occurring simultaneously with the disappearance of the stimuli. The introduction of this delay period, or retention interval, into the task demonstrated that the accuracy of WM declines as a function of time as the information available decays (Sperling, 1960).

The storage capacity of WM continues to be a topic of debate among researchers (see for review Fukuda et al., 2010a) with studies indicating its variability across individuals, age, and forms of WM (for review see Vogel and Machizawa, 2004). For instance, Gilchrist and colleagues (2008) reported an age-related decline in WM capacity on a task that tested the recall of spoken sentences. The majority of research on limited capacity challenges the initial work of Miller et al. (1956) who suggested humans could retain a total of 7 items at a time in their "immediate memory". Brief exposure experiments by Sperling et al. (1960) suggested that on average only 4 items could be retained at a time in WM. Replications of this work using different behavioural tasks agree that human WM capacity ranges from 3 to 4 items (Vogel et al., 2001; for review see Fukuda et al., 2010a; Hiebel & Zimmer, 2015). Presenting stimuli in 4 different colours and orientations, Luck and Vogel (1997) advanced this notion by showing that complex items are remembered as easily as simple or single-feature items; reporting the retention of up to 8 features at a time in 4 stimuli. The authors proposed that visual WM stores integrate items with many features rather than storing them individually (Luck and Vogel, 1997). Similarly, Awh et al. (2007) demonstrated that WM has a fixed capacity despite the complexity of the stimuli. However, Alvarez and Cavanagh (2004) argue that the storage capacity is around 4 items for simple stimuli, but as the details or features of the stimulus increase the number of items that can be stored declines.

The capacity of WM is said to correlate with overall cognitive ability (Engle et al., 1999; Fukuda et al., 2010b; Johnson et al., 2013) and is crucial for the execution of everyday tasks. In a healthy individual WM capacity can be a determinant of intelligence and reasoning ability (Fukuda et al., 2010b). Likewise, impairments in WM are present in a number of diseases such as schizophrenia, Parkinson's disease (PD), Alzheimer's disease (AD), and attention deficit hyperactivity disorder (ADHD). Memory impairment is a core cognitive symptom of schizophrenia with deficits appearing in all modalities of WM (Lee and Park, 2005; Fioravanti et al., 2005). In fact, recent work by Park and Gooding (2014) demonstrates how a WM deficit could indicate a predisposition for schizophrenia. While Parkinson's disease is better known for its motoric symptoms, executive function and memory are also commonly affected, including decline in WM capacity (Dubois and Pillon, 1997; Lewis et al., 2005; Lee et al., 2010). The presence of WM impairment in cases of Alzheimer's disease is inconsistent, some studies suggest deficits develop as the disease progresses, but are not present in the early stages (see for review Huntley and Howard, 2010; Kirova et al., 2015). ADHD, a condition that is common in school-aged children, is associated with impulsivity, difficulties in attention, and both verbal and spatial WM impairments (Martinussen et al., 2005; Kasper et al., 2012; Alderson et al., 2013). However, there has also been indication that WM does not differ between individuals with ADHD and healthy, age- and IQ-matched controls (Spronk et al., 2013). Many efforts have been made to ameliorate deficits in WM among children with ADHD through training programs thought to improve WM performance, incentives, and/or medications (Klingberg et al., 2002; Holmes et al., 2010; Strand et al., 2012). The broad range of clinical populations affected by deficits in WM highlights the need for development of appropriate therapeutics and thus, a better understanding of the neural basis of WM.

Initial observations of WM come from studies with humans; for example, Hunter (1913) conducted his early experiments on his own children. The nonhuman primate (NHP) provides an alternative model to humans due to a similarly developed prefrontal cortex (PFC), and close evolutionary connection with humans (Goldman-Rakic, 1987). Modifications have to be made to tasks for use with NHP, but WM performance is comparable. Research in NHP models, using similar methods as described above in human studies, estimates a WM capacity of at least 2 items (Heyselaar et al., 2011; Lara and Wallis, 2013). Additionally, NHP provide opportunity for neural recordings and lesion studies to accompany behavioural observations made in both NHP and humans (see for review Goldman-Rakic, 1987). A greater understanding of the neural basis of WM and the underlying mechanisms can then be directly applied to ongoing therapeutic research in humans.

1.2 Studying Working Memory

A variety of behavioural tasks have been designed to test WM performance without interference from other cognitive processes. To effectively capture WM processes the tasks should manipulate both the short time interval and limited capacity characteristics of WM. Below is a discussion of the more commonly used visual WM tasks that have been reported to effectively study WM in a range of species, particularly humans and NHP.

1.2.1 Delayed Response Task

The delayed response task was first implemented in 1913 by Walter Hunter as an assessment of intelligence in animals and children (Hunter, 1913). The original task consisted of 2 boxes in front of the subject; the experimenter places an item of food in one of the boxes and immediately blocks the closed boxes from sight by placing a screen between them and the subject. After a delay period the screen is removed and the subject must select the box that contains the food. If the subject selects the box containing the food on the first attempt the trial is considered correct and the food is obtained as reward (Figure 1). This task was adapted for use with several species including dogs and racoons (Hunter, 1913), pigeons (Blough, 1959) and species of NHP (Harlow et al., 1932). The difficulty of the task can be manipulated by increasing the retention interval (Arnsten and Jentsch, 1997) and by increasing the number of trays to choose between (Bartus et al., 1978). Furthermore, the task has been adapted into a visual version, the oculomotor delayed response (ODR) task, which permits simultaneous recording of neurons in behaving animals (Funahashi et al., 1989). This version requires the subject to fixate on a central point displayed on a television screen while a white cue appears in one of 8 positions in the periphery of the fixation point. After a delay period (1 to 6 seconds) the central fixation point disappears and the subject makes a saccade to where the cue appeared.

The delayed response task and adapted versions have been used for over a century to test WM in many different species. It appropriately targets the short time interval of WM through the manipulation of the retention interval; however, it typically only uses one item or stimulus, failing to address the limited capacity of WM.

1.2.2 Self-Ordered Pointing Task

The self-ordered pointing task (SOPT) was originally designed by Petrides and Milner (1982) in their work with individuals with frontal or temporal lobe lesions. For their purpose they had 4 different versions of the task that used words or images to assess verbal and nonverbal processing. In recent WM literature it is the abstract design version that is more commonly replicated (Ross et al., 2007). The task has 4 sets each with 6, 8, 10, or 12 items per page and the same number of pages as there are items. The participant is asked to point to one image per page

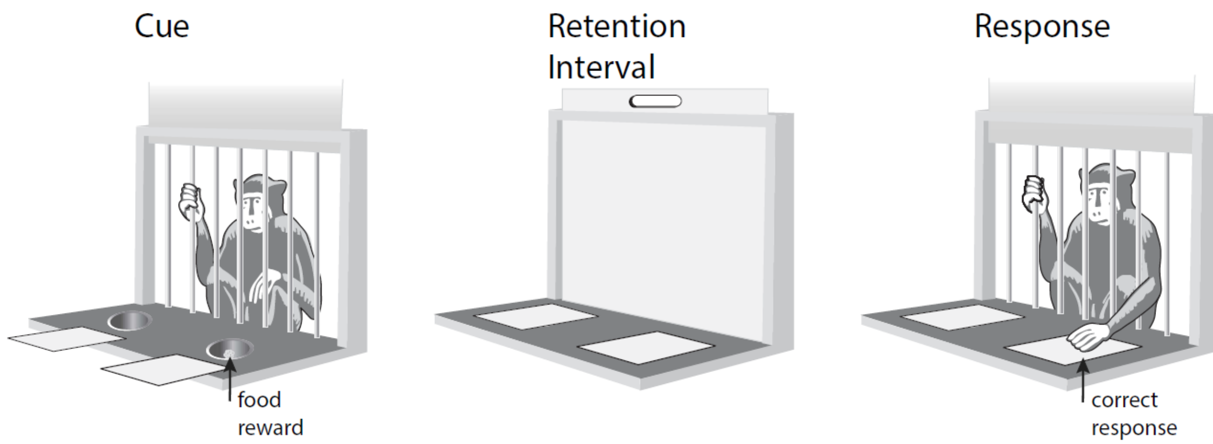

Figure 1: Delayed Response Task. Implemented with the Wisconsin General Test Apparatus for use with nonhuman primates; adapted from Tsujimoto and Postle (2012).

that they have not previously pointed to. The images remain the same in each set, but unlike the original task designed by Petrides and Milner (1982), the layout of the images is different on each page (Daigneault and Braun, 1993). The order in which the images are pointed to is left up to the participant, making up the “self-ordered” component of the task. A score on the SOPT is a tally of the number of errors or the number of times a participant touches an image they had previously touched (Ross et al., 2007). Unlike the delayed response task discussed above, the SOPT requires the maintenance of multiple items at a time; thus, performance on the task reflects WM’s limited capacity. That being said, the task has its own limitations. Ross et al. (2007) assessed the test-retest reliability of the SOPT in college students and found a statistically significant practice effect in performance. Taking an automated form, this task has been adapted for use with NHP using a touch-sensitive screen (Collins et al., 1998). This version of the task presented 2-5 coloured squares at a time for a NHP to touch in a self-ordered manner. However, inconsistent with other versions of the SOPT, the version implemented by Collins et al. (1998) did not change the location of the squares making the task prone to strategy development. Using a single page or display requires the subject to retain only one position in memory at a time, rather than previous positions, making it easy to obtain a perfect score on the task (Gillett, 2007). Due to this, NHP are able to develop strategies such as touching the items in a clockwise manner or following a proximity strategy (Collins et al., 1998; Taffe and Taffe, 2012). For these reasons it cannot be said with certainty that the SOPT measures WM performance exclusively.

1.2.3 Delayed (Non) Match-to-Sample

The delayed match-to-sample task (DMST) first appeared in research by Skinner (1950) using pigeons as subjects. His work was replicated using white and red light (Ferster, 1960) as well as flickering or steady light (Blough, 1959). The task has now been used to assess WM performance in a variety of species other than pigeons including hens (Weavers et al., 1998), rats (Leblanc and Soffie, 1999), capuchin monkeys (Etkin and D'Amato, 1969), baboons (Rodriguez et al., 2011), rhesus macaques (Mishkin and Delacour, 1975; Chelonis et al., 2014), and humans (children: Chelonis et al., 2000; 2014; adults: Critchfield and Perone, 1990). The task presents a 'sample' stimulus (a picture or light) that disappears and is followed by a delay period. In the testing phase of the trial two or more stimuli are presented: one identical to the first and one or more novel stimuli. A correct response on the DMST is the selection of the stimulus that matches the sample. Similar to the DMST is a delayed non-match to sample (DNMST) task. Rather than selecting the sample, the participant is asked to select the novel stimulus that does not match what they viewed before the delay.

The difficulty of this task has been reported to change by increasing the retention interval, but also by increasing the number of stimuli presented after the delay, which increases the amount of distractions, challenging cognitive processing. Adamson et al. (2000) used as many as 32 stimuli in a set in her study with adult humans; there was a decline in accuracy with the increase in stimuli up to 8, but no consistent changes were found for 16 or 32 stimuli. This is in agreement with WM capacity and work by Sperling (1960) showing that an increase in memory load causes a decline in performance. However, other studies testing the set size of the DMST have found no effect (Etkin and D'Amato, 1969; Mason and Wilson, 1974) or the opposite effect (Worsham, 1975; Mishkin and Delacour, 1975). The DMST cannot be solved with strategy; however the variable performance across studies raises questions of its reliability for assessing WM capacity.

1.2.4 Visual Sequential Comparison Tasks

The limited capacity storage is a crucial component of WM that is often overlooked in WM tasks despite evidence that performance declines as memory load increases (Sperling, 1960). The memory load of a visual sequential comparison (VSC) task, however, is able to manipulate the limited capacity with different set sizes, activating this memory load-dependent change in performance (Heyselaar et al., 2011). Egeth (1966) first used a form of the VSC task to analyze stimulus discrimination in humans. This version of the task had participants decide if two simultaneously presented visual representations were the "same" or "different". It wasn't until studies in 1971 that the visual representations were presented in sequence separated by a retention interval; this is the form of the task that is used today to assess visual WM in humans (Phillips and Baddeley, 1971; Cermak, 1971). The task presents two identical or very similar visual representations separated by a short delay period. The visual arrays in Phillip's (1974) design were displayed on a computer screen and were comprised of a matrix of cells that were randomly lit up varying from 4 by 4 cells to 8 by 8 cells. The second array was either identical or differed from the first by having one less or one more cell light up; again, the task objective was to indicate if the array was the same or different as the initial array. Adjusting the length of the retention interval allows the temporal limitation of WM to be investigated with this task. Shorter intervals ensure that WM is being assessed with little to no impact from long-term memory processes. Additionally, the variable matrix size manipulates the memory load of the task, appropriately assessing the limited capacity storage of WM.

A variant of the task, termed a change detection task, was used by Luck and Vogel (1997). The visual arrays consisting of 1 to 12 coloured squares were presented on a monitor.

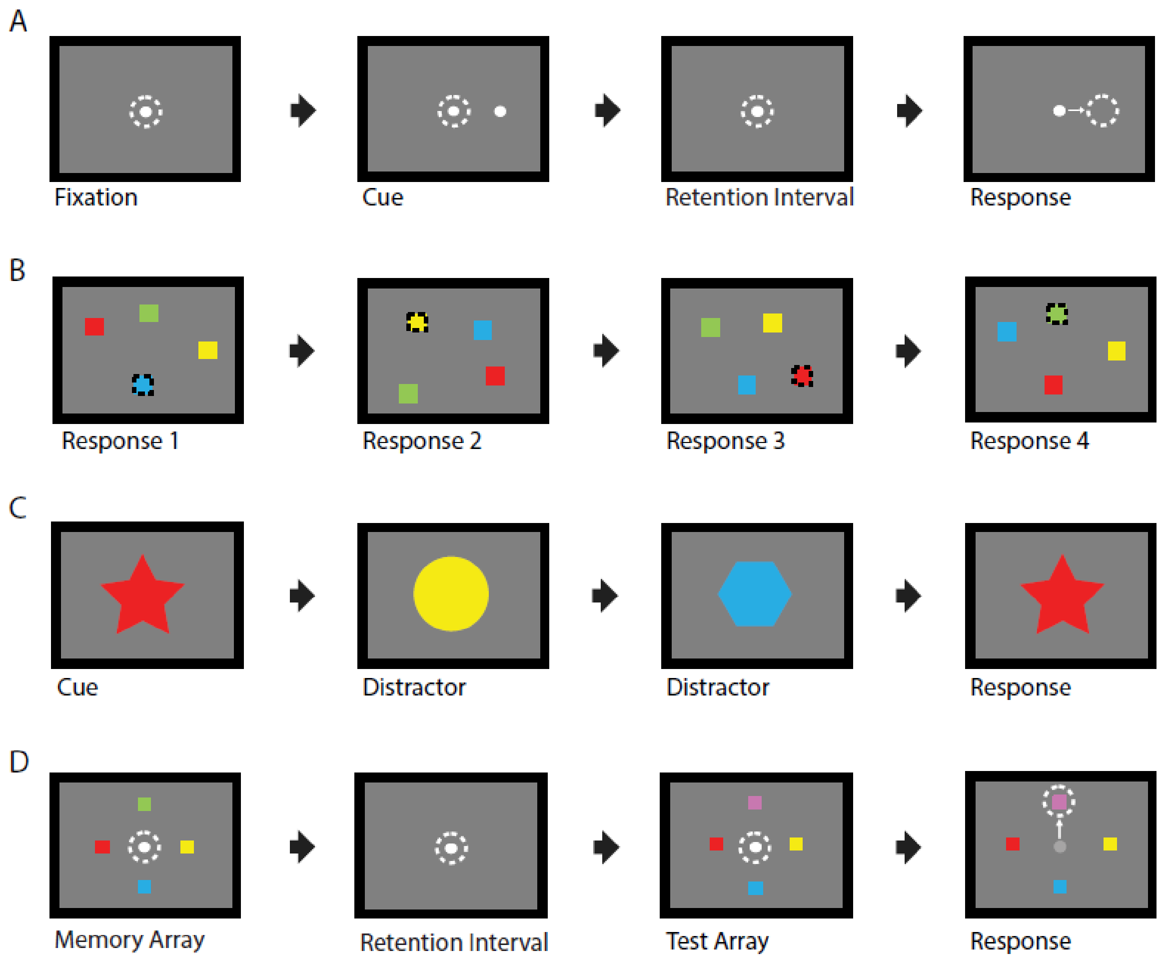

Figure 2: Various Tasks to Assess Working Memory. A: Oculomotor delayed response (ODR) task. Dotted circles represent eye position and arrows indicate eye movement to the remembered position. B: Self-ordered pointing task (SOPT). Dotted squares represent the individual's response in each trial. C: Delayed match-to-sample (DMST). D: Delayed visual sequential comparison (VSC) task. As in A, dotted circles represent eye position and arrows show a saccade to the response target.

Only one feature of the initial array would be changed in the test array on half of the trials. Changing the memory load and the length of the retention interval revealed memory load- and retention interval-dependent decreases in performance accuracy (Luck and Vogel, 1997). Furthermore, this design has been modified to assess WM performance in rhesus macaques (Heyselaar, 2011; Oemisch, 2012; Elmore, 2012) and pigeons (Elmore et al., 2012). The task performance of monkeys is comparable to that of humans on the delayed VSC task, showing a drop in accuracy with an increase in both memory load and retention interval (Heyselaar, 2011; Oemisch, 2012).

1.3 Neural Basis of WM

1.3.1 Persistent Activity

To date, the proposed neural correlate of WM is suggested to be the persistent activity of a network of neurons in the posterior parietal and prefrontal cortices. Evidence for the role of these regions in WM is collected from lesion studies and single unit neural recordings in NHP models. In rhesus macaques, prefrontal cortex (PFC) lesions produced revealed a drastic decline in performance on a delayed response task (Jacobsen, 1935) and a spatial memory task (Passingham, 1985) without the intact PFC. Such studies revealed that the animals were still able to complete the tasks if permitted to respond immediately, but performance declined with the introduction of a delay period (Passingham, 1985). Establishing the critical structures of WM provided an avenue to investigate the neural activity behind the cognitive process. The dorsolateral PFC is considered imperative to spatial WM (Goldman-Rakic, 1987), while more ventral regions have been reported to be more involved in processing non-spatial information such as colours and objects in WM (Wilson et al., 1993). Fuster and Alexander (1971) were among the first to make single unit neural recordings from the PFC of rhesus macaques performing a delayed response task. They found that the firing frequency of some neurons was increased during the delay period of the task. The increased firing carried on for the length of the retention interval when there were no stimuli present. Furthermore, the activity diminished when the delay period ended and the animal made its response. This persistent activity has been demonstrated during the retention interval of WM tasks in many similar studies in NHP (Kubota and Niki, 1971; Funahashi et al., 1989; 1991; 1993; 1997; see for review: Funahashi, 2013). The presence of the persistent activity after the stimuli have disappeared is suggested to be essential to temporarily maintaining relevant representations of the stimuli in WM (Rawley and Constantinidis, 2009) and considered necessary to correctly perform the task at hand (Goldman-Rakic, 1987). This theory is supported by three key features of persistent activity. Understandably, the first is the increased neural firing that occurs during the delay period. Secondly, the duration of the activity corresponds with the duration of the delay period; if the interval is shortened the length of the activity is also shortened (Funahashi et al., 1989; Fuster and Alexander, 1971). Finally, this persistent activity is weak or even absent on error trials compared to correct trials (Fuster 1973; Batuev et al., 1985; Funahashi et al., 1989) and has been suggested to be predictive of WM performance (Pessoa et al., 2002). Neural recordings that were taken while a NHP performed an ODR task showed an absence of neuronal activity when the animal made large saccadic errors (Funahashi et al., 1989). Similarly, fMRI studies in humans show large discrepancies in the BOLD signals of correct and incorrect trials when compared; significantly less BOLD signal is present during the delay period of incorrect trials (Sakai et al., 2002).

A number of studies in NHP and humans have found persistent activity exhibited in other regions of the brain during the retention interval of tasks. Berryhill and Olson (2008) studied two individuals with lesions to the posterior parietal cortex (PPC) to further investigate the parietal lobe's role in WM deficits. Using a variety of delay response tasks it was apparent that the retrieval process of visual WM suffered a deficit as a result of impairment to the PPC. Neurophysiological recordings in NHP have shown similar results (Gnadt and Anderson, 1988*;* Chafee and Goldman-Rakic, 1998; Quintana and Fuster, 1999), as well as neuroimaging studies in humans (see for review Wager and Smith, 2003). Quintana and Fuster (1993) used a cortical cooling technique to temporarily impair the PFC and PPC and demonstrated a resulting deficit in visual WM. However, evidence suggests that inactivation of the PPC by cooling does not interfere with WM performance to the same extent that inactivation of the PFC does (Quintana and Fuster, 1993; Chafee and Goldman-Rakic, 2000). Additionally, persistent activity has been reported in the inferior temporal cortex (IT) and is thought to be an integral player in WM processing (Miller et al., 1996; Ranganath, 2006). While persistent activity is present in other regions of the cortex, it is apparent that these regions interact with the more critical PFC to support WM processing (see for review Passingham and Sakai, 2004; Ranganath, 2006).

The majority of research on the neural basis of WM has been conducted in NHP. Translating this information for use with humans required the use of fMRI due to differences in neural anatomy (Courtney et al., 1998). Persistent activity present during the delay period of a spatial WM task was located in regions of the PFC in humans that corresponded with those in the primate brain (Courtney et al., 1998). Furthermore, several event related fMRI studies have shown sustained activity in the human PFC during the retention interval of delayed response tasks (Zarahn, 1999; Jha and McCarthy, 2000; Sakai et al., 2002; see for review Curtis and

D'Esposito, 2003; Rottschy et al., 2012). Compared to studies in rhesus macaques, fMRI studies conducted with humans show activity in the areas surrounding the PFC as well as the PFC itself. This allows the researcher to infer what connections are made between the PFC and other possible structures involved in the storing and processing of information.

1.3.2 Role of the NMDA Receptor

The precise processes behind WM are not yet understood; a number of models have been proposed, each attempting to encapsulate the various components of WM (see for review Barak and Tsodyks, 2014). For instance, to address the maintenance of multiple items models propose a balance of excitation and inhibition within the network to process several bouts of activity for features of a stimulus. Another model hypothesizes that persistent activity rests on the activation of N-methyl-d-aspartate (NMDA) receptors. NMDA receptors are ionotropic receptors with two specific requirements for complete activation. They are co-activated by the binding of the abundant neurotransmitters glutamate and glycine. However, the NMDA receptor is blocked by a magnesium ion that is only removed when the postsynaptic cell becomes depolarized. Full activation of the receptor permits the flow of calcium and sodium ions into the cell and potassium ions out of the cell; this fluctuation generates an excitatory post synaptic potential (EPSP). Moreover, NMDA receptors are characterized by their slow kinetics; this differentiates the NMDA receptor from another common glutamate receptor, amino-3-hydroxy-5-methyl-4-isoxazole (AMPA; Wang, 1999). Slow kinetics and voltage dependency creates the ideal mechanism to sustain persistent activity (Wang, 1999). It is postulated that the hypofunction of NMDA receptors fails to produce the necessary excitation needed for the maintenance of information in WM leading to the WM deficits observed in some clinical populations (Lisman et al., 1998). For instance, decline in performance on various WM tasks has been observed after the administration of NMDA antagonists. Antagonists bind to NMDA receptors preventing glutamate from binding and thus, inhibit activation of the receptor diminishing the neural activity. A deficit in WM performance as a result of blocking NMDA receptors has been produced with sub anesthetic doses of ketamine in rodents using a spatial delayed alternation task (Verma and Moghaddam, 1996) and rhesus macaques performing different WM tasks (Taffe et al., 2002; Roberts et al., 2010; Heyselaar et al., 2011), as well as humans (Krystal et al., 1994; 2005). More recently, Driesen et al. (2013) demonstrated a decline in spatial WM performance and reduced brain activation in fMRI scans following low dose ketamine administration to humans. Lastly, Seamans and colleagues (Seamans et al., 2003; see also Kroener et al., 2009) showed that NMDA antagonists reduce or eliminate the current underlying the network persistent activity of rodent PFC neurons during depolarized up-states. Importantly for this thesis, NMDA receptors are modulated by catecholamines as discussed in detail below (see for review Wang et al., 2013).

1.4 Catecholamine Modulation of Working Memory

Catecholamines are a class of monoamine neuromodulators that consist of a benzene ring with two hydroxyl side groups and a side-chain amine; epinephrine, norepinephrine, and dopamine are classified as catecholamines. It is suggested that persistent activity can be manipulated by modulating the concentration of catecholamines in the PFC (Wang & O’Donnell, 2001; Kroener et al., 2009; Dembrow et al., 2010; see for review Arnsten, 2011; Xing et al., 2016). Extensive work with the PFC of primates and rodents has revealed the structure’s sensitivity to its neurochemical environment (Arnsten, 1998). This review will focus on the two catecholamines thought to be most critical in WM performance, dopamine (DA) and norepinephrine (NE; Xing et al., 2016). It was Brozoski (1979) who first tested the influence of DA and NE on WM performance. By depleting the concentration of catecholamines in the PFC of NHP he was able to mimic the reduction in performance seen in monkeys with ablated PFC (Brozoski, 1979). Performance deficits have also been reported in aging animals where depletion of catecholamines is known to occur naturally (NHP: Bartus et al., 1978; rodents: Luine et al., 1990).

1.4.1 Dopamine

Dopamine is a neuromodulator important in the regulation of many functions throughout the body including motor, motivational, and cognitive functions of the central nervous system (CNS). In the primate brain, the PFC and PPC contain a high density of DA axons (see for review Melchitsky and Lewis, 2004). DA's role in WM processing was first proposed from the behavioural work conducted by Brozoski (1979). It was later shown that local application of DA enhanced PFC activity during the retention interval of a spatial WM task, but activity declined following application of a DA antagonist (Sawaguchi et al., 1988). Together, these studies suggested a modulatory role for DA in WM function. The influence of DA on the neural mechanisms and subsequent performance of WM has since been investigated thoroughly with a combination of behavioural and neurophysiological studies.

There are at least five subtypes of dopamine receptors that are more commonly categorized into D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors. In the primate PFC, including that of humans, the D1 receptor is more abundant than the other subtypes (Richfield et al., 1989; Goldman-Rakic et al., 1990). Administering D1/D2 and D2 agonists to humans, Muller et al., (1998) found that D1/D2 agonists enhanced WM performance, but D2 agonists did not. This suggested that D1 receptors, but not D2, are necessary in facilitating WM performance. Likewise, the involvement of D1 receptors in WM has been investigated using antagonists in behaving animals in a number of studies (Sawaguchi and Goldman-Rakic, 1991; 1994; Sawaguchi, 2001; Floresco and Phillips, 2001). Sawaguchi and Goldman-Rakic (1991) found a delay period-dependent deficit in performance on an ODR task after injection of D1 antagonists into the dorsolateral PFC of rhesus macaques. Trials without a delay period did not have a similar deficit inferring the necessity for DA in mnemonic processing (Sawaguchi and Goldman-Rakic, 1991; 1994). However, in a delayed alternation task performed by rats, Romanides et al. (1999) claimed that administration of D1 or D2 receptor blockers had no effect on task ability. Less research has been conducted on the contribution of D2 receptors in WM processing, but it has been reported that D2 receptor agonists enhance WM performance (Luciana et al., 1998). Likewise, administration of antagonists of this receptor have been reported to cause impairments in performance (Mehta et al., 2004; Von Huben et al., 2006) or to have no effect at all (Muller et al., 1998).

The precise neural mechanism that DA facilitates is not yet completely understood. Several studies suggest that persistent activity relies on an interaction between the D1 receptors and glutamate transmission (Jay et al., 1996; Seamans et al., 1998; O'Donnell et al., 1999). Levine and colleagues (1996) reported that D1, rather than D2, receptors modulate glutamatergic transmission by enhancing NMDA responses. Application of a selective D1 agonist and NMDA individually produced a dose-dependent increase in PFC pyramidal neuron activity in whole-cell recordings, as determined by the number of evoked spikes in a recording (Wang and O'Donnell, 2001). More importantly, the excitability increased synergistically when a D1 agonist and

NMDA were applied in combination (Wang and O'Donnell, 2001). This effect was blocked when protein kinase A (PKA) inhibitors were added to the bath suggesting that PKA, an important compound to D1 reception, is necessary for the observed excitability in PFC neurons (Wang and O'Donnell, 2001). Further experimentation found that addition of a Ca^{2+} chelator also diminished the synergistic effect (Wang and O'Donnell, 2001). Based on these results, it was proposed that an interaction between D1 receptors and NMDA was the cause of increased excitability in PFC cells. Accordingly, activation of D1 receptors in the nucleus accumbens has been reported to initiate a PKA-dependent pathway resulting in the phosphorylation of several ion channels (Snyder et al., 1998). Specifically, activating the D1 receptor may cause a PKA or Ca^{2+} signalling cascade resulting in an increase in Ca^{2+} current and enhanced NMDA receptor activity (Snyder et al., 1998). Further indication of an interaction between DA and NMDA comes from Seamans and colleagues (2001) who found that a low dose of a D1 agonist not only enhanced NMDA activity, but also decreased non-NMDA activity. It is possible that DA facilitates or maintains persistent activity in PFC neurons indirectly by activating NMDA receptors.

Due to the diversity of DA's actions in the PFC it is postulated that dopaminergic regulation varies by receptor and cognitive operation (see for review Floresco, 2013). For instance, D1 receptor-mediated actions are thought to follow an inverted-U curve in which too little or too much DA in the PFC impairs cognition, but the optimal concentration facilitates performance (see for review Cools and D'Esposito, 2011; Floresco, 2013). Murphy et al. (1996) mimicked what occurs when the body is under stress by increasing the DA turnover in the PFC of rats and NHP; this resulted in a significant decline in performance on a spatial WM task in both species. Dose-dependent responses have been reported from behavioural studies in humans

(Luciana et al., 1998; Gibbs and D'Esposito, 2005a), as well as behavioural and electrophysiological studies in rodents (Murphy et al., 1996; Zahrt et al., 1997) and monkeys (Cai and Arnsten, 1997; Vijayraghavan et al., 2007).

A baseline-dependent relationship between WM performance and baseline levels of DA has also been proposed (Cools and D'Esposito, 2011). For example, in aged monkeys with naturally occurring declines in WM ability in association with a prominent loss of DA in the PFC (Goldman-Rakic and Brown, 1981), administration of D1 agonists have been shown to improve delayed response performance (Arnsten et al., 1994; Cai and Arnsten, 1997). Interestingly, Arnsten et al. (1994) showed that the same D1 agonist that improved performance in aged monkeys did not affect WM performance in young monkeys. Alternatively, the opposite is observed when a D1 antagonist is administered to young versus aged monkeys (Arnsten et al., 1994). In young humans, a similar phenomenon is proposed with variance in WM capacity; individuals with a lower capacity fared better on a variety of WM tasks after DA agonist administration, whereas those with a high capacity experienced a decline in performance (Kimberg et al. 1997; Gibbs and D'Esposito, 2005b).

The above findings serve to better our understanding of the dopaminergic system not only in the healthy population, but also in aged and clinical populations. The therapeutic use of DA agonists has been developed for treatment of several mental illnesses including PD, schizophrenia and ADHD, all which have associated WM deficits.

1.4.2 Norepinephrine

There are 3 types of receptors that NE interacts with: α1, α2, and β type receptors. NE is released from noradrenergic neurons that are found projecting from the locus coeruleus (LC) in the brainstem throughout the cerebral cortex (Porrino and Goldman-Rakic, 1982; see for review Melchitzky and Lewis, 2004). NE axons are similarly distributed in the primate PFC as DA axons (Melchitzky and Lewis, 2004). It was initially understood that DA was essential for healthy WM function, with little or controversial evidence of a role for NE. This includes the work by Brozoski (1979) who found that greater depletion of NE than DA had minimal impact on WM performance. However, there is now substantial evidence to suggest that NE is as important as DA to WM processes. Blocking reception of NE in the PFC by administration of adrenergic receptor antagonists is suggested to produce deficits in WM (Li and Mei, 1994), likewise administration of α2 agonists are reported to improve or restore performance in aged and NE-depleted NHP (Arnsten and Goldman-Rakic, 1985; Cai et al., 1993; Rama et al., 1996; see for review Ramos and Arnsten, 2007). After experimental depletion of NE in young monkeys, administration of clonidine, an α2 agonist, improves delayed response performance (Cai et al., 1993). Likewise, clonidine improved performance in aged monkeys with natural NE depletion (Arnsten and Goldman-Rakic, 1985). At higher doses, α2 agonists were also reported to positively impact WM performance in young, healthy NHP (Franowicz and Arnsten, 1998). In electrophysiological experiments, neural recordings from the NHP dorsolateral PFC revealed an apparent increase in neural firing during the retention interval of an ODR task following α2 receptor stimulation induced by ATX administration (Gamo et al., 2010).

A multitude of work has compared the actions of the subtypes of NE receptors and suggests that α2 receptors are the critical receptor subtype for facilitating WM (Li and Mei, 1994; Arnsten and Jentsch, 1997; Mao et al., 1999; Arnsten et al., 1999). Stimulation of α2 receptors has been shown to improve performance on delayed response tasks (Li et al., 1999), whereas α1 receptor stimulation impairs WM performance in rats (Arnsten et al., 1999) and NHP

(Mao et al., 1999). Li et al. (1999) observed an improvement in delayed response performance of NHP with administration of guanfacine, an α2A agonist, and application of yohimbine, an antagonist of the same receptor, suppressed this persistent activity. Conversely, low doses of α1 agonists impaired performance on a delayed spatial WM task in aged NHP and was reversed by administration of α1 antagonists (Arnsten and Jentsch, 1997).

Studies in humans have had mixed results demonstrating the role of NE in facilitating WM performance (see for review Chamberlain et al., 2006). For instance, studies using α2-adrenergic receptor agonists in healthy humans have reported dose-dependent effects of NE; a lower dose of clonidine produced no effect, but a greater dose improved spatial WM (Coull et al., 1995). Further, low and high doses of clonidine were detrimental to WM performance in healthy humans, but a dose in the middle had no effect (Jakala et al., 1999). However, a study in healthy men reported no effects on WM following administration of guanfacine (Muller et al., 2005). From a clinical standpoint, adrenergic agonists have therapeutic potential; for example, administration of guanfacine was reported to improve delayed response performance in patients with frontal lobe epilepsy (Swartz et al., 2008). Further, individuals with PD, ADHD, and schizophrenia show improvement on WM tasks after administration of α2 agonists including clonidine (see for review Arnsten et al., 1996; Ramos and Arnsten, 2007; Arnsten, 2010).

The actions of NE on persistent activity and WM function require a particular neurochemical environment to operate. A number of multi-faceted studies have provided physiological and behavioural evidence for the proposed role of α2A receptors in WM modulation (see for review O’Donnell et al., 2012; Arnsten, 2010). Through a series of iontophoretic experiments in NHP, Wang et al. (2007) proposed an α2A receptor-cAMP-HCN signalling mechanism, whereby activation of α2A receptors inhibits the production of cAMP in

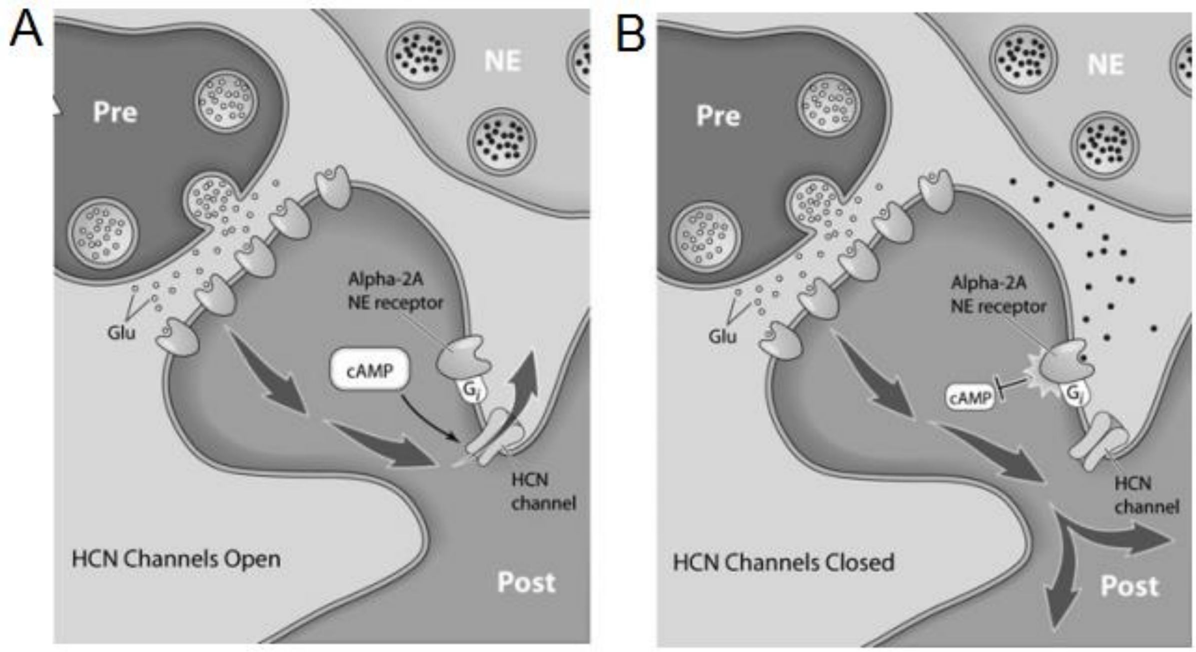

Figure 3: Proposed Mechanism of NE Transmission in WM. An α2A adrenergic receptor-cAMP-HCN interaction facilitates persistent activity in PFC neurons. A: The presence of cAMP opens HCN channels suppressing synaptic activity due to lowered membrane resistance. Activation of NE receptors inhibits cAMP production causing HCN channels to close; efficacy of synaptic input increases. Copied with permission from Wang et al. (2007).

the post-synaptic cell causing hyperpolarization-activated cyclic nucleotide-gated (HCN) channels to close (Figure 3; see for review Arnsten et al., 2012; O'Donnell et al., 2012; Arnsten and Jin, 2014). It is proposed that the opening of HCN channels lowers the resistance of the cell membrane and thus, diverts synaptic input. In NHP, co-iontophoresis of the HCN blocker ZD7288 with either an α2A antagonist or cAMP activator rescued a reduction in neural firing, such that blocking HCN restored the spatial mnemonic tuning (Wang et al., 2007). This hypothesized mechanism was further supported behaviourally in knockdown HCN rats, which were found to improve on a spatial delayed alternation task compared to controls (Wang et al., 2007). The independent rat electrophysiological study of Barth et al. (2008) also reported enhanced excitability in the rat PFC as a result of α2 receptor-mediated HCN channel inhibition. In contrast, the rat electrophysiological study by Carr et al. (2007) showed that the α2A receptor-mediated HCN channel inhibition results from the activation of a phospholipase C-PKC pathway, rather than being dependent on cAMP. Furthermore, Zhang and colleagues (2013) reported that NE-evoked persistent activity in rat PFC is indeed enhanced by postsynaptic α2A receptor-mediated HCN channel inhibition, but it appears to be mediated by the activation of presynaptic α1 receptors that facilitates glutamate release. Another study reported that the knockout of the HCN1 gene in mice reduces the intrinsic persistent activity of PFC neurons, but that deletion had no effect on the PFC network persistent activity (up states; Thuault et al., 2013). Unlike the finding of Wang et al. (2007), HCN1 deletion did not result in performance impairment in a delayed non-match to place task, but it was associated with a deficit in a version of that task in which proactive interference was prominent (Thuault et al., 2013). Lastly, other electrophysiology in rats suggested that α2A receptor activation is involved in a mechanism of excitatory suppression of PFC activity, rather than enhancement (Ji et al., 2008; Yi et al., 2013).

Overall, it is evident that further research is needed to determine the exact mechanism of actions of NE in persistent activity and WM.

1.5 Catecholamine Reuptake Transporter Inhibitors

The catecholamine concentration can be manipulated by introducing catecholamine reuptake transporter inhibitors into the system. These act indirectly to increase the extracellular concentration of certain catecholamines by blocking their respective transporters and preventing the catecholamines from being absorbed back into the presynaptic cell (Figure 4). ADHD therapeutics like methylphenidate (MPH) and atomoxetine (ATX) have been developed to block the transporters of DA and NE (MPH: Seeman and Madras, 1998; ATX: Bymaster et al., 2002). In a mouse model, acute administration of MPH and ATX caused increases in extracellular levels of DA and NE in the PFC (Koda et al., 2010). Both of these reuptake inhibitors are commonly prescribed to alleviate the core symptoms of ADHD (see for review Savill et al., 2015). MPH has a high binding affinity for the DA and NE transporters (DAT and NET, respectively; Han and Gu, 2006). The affinity values (K_i, inhibition constant) of MPH reported in rat PFC were 34 nM for DAT and 339 nM for NET (Bymaster et al., 2002). However, using PET imaging in humans to determine the effective dose 50 (ED_{50}) of MPH, it was reported that MPH has greater affinity for NET than DAT (Hannestad et al., 2010). Various research has indicated that a therapeutic range of doses of MPH successfully increases the concentration of these catecholamines in humans by blocking DAT and NET in a dose-dependent manner (Volkow et al., 2001; 1998). Atomoxetine has been shown to block DAT and NET in the rat brain, but is more specifically classified as a norepinephrine reuptake inhibitor (NRI) due to a greater binding affinity for NET (Wong, 1982; Tatsumi, 1997; Bymaster et al., 2002; for review: Garnock-Jones

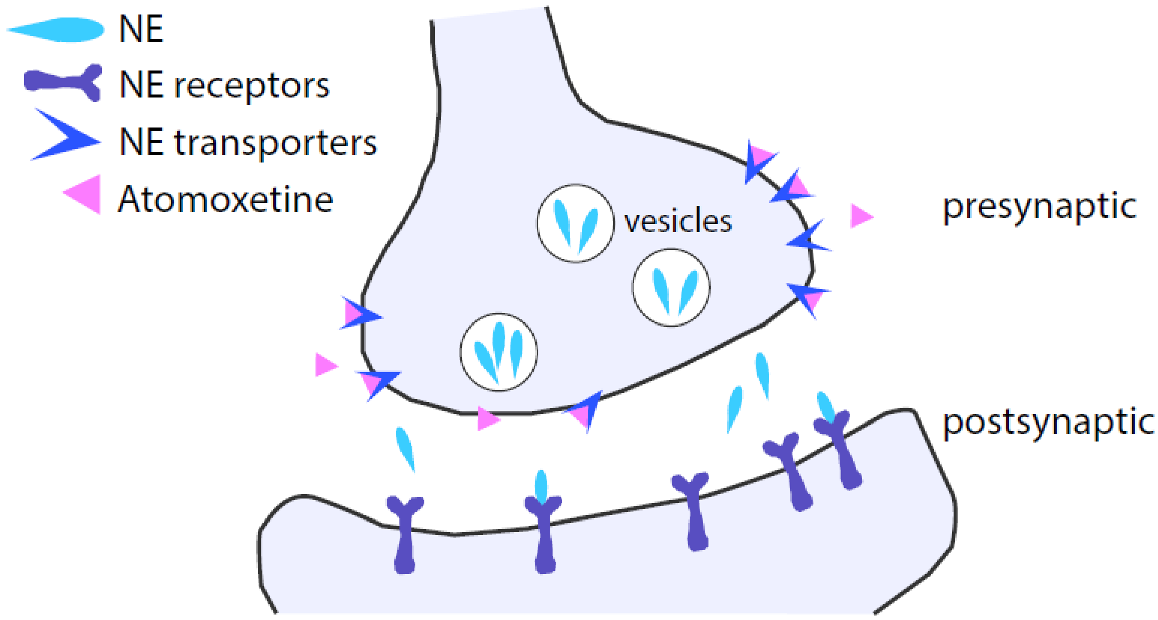

Figure 4: Schematic of ATX's effect on the synapse. An increase in NE in the synapse as a result of ATX increases the neurotransmission of the postsynaptic cell. NE is released into the synapse and binds to receptors. ATX prevents reabsorption of NE from the synapse by blocking NE transporters on the presynaptic cell. Figure recreated from adhd-institute.com.

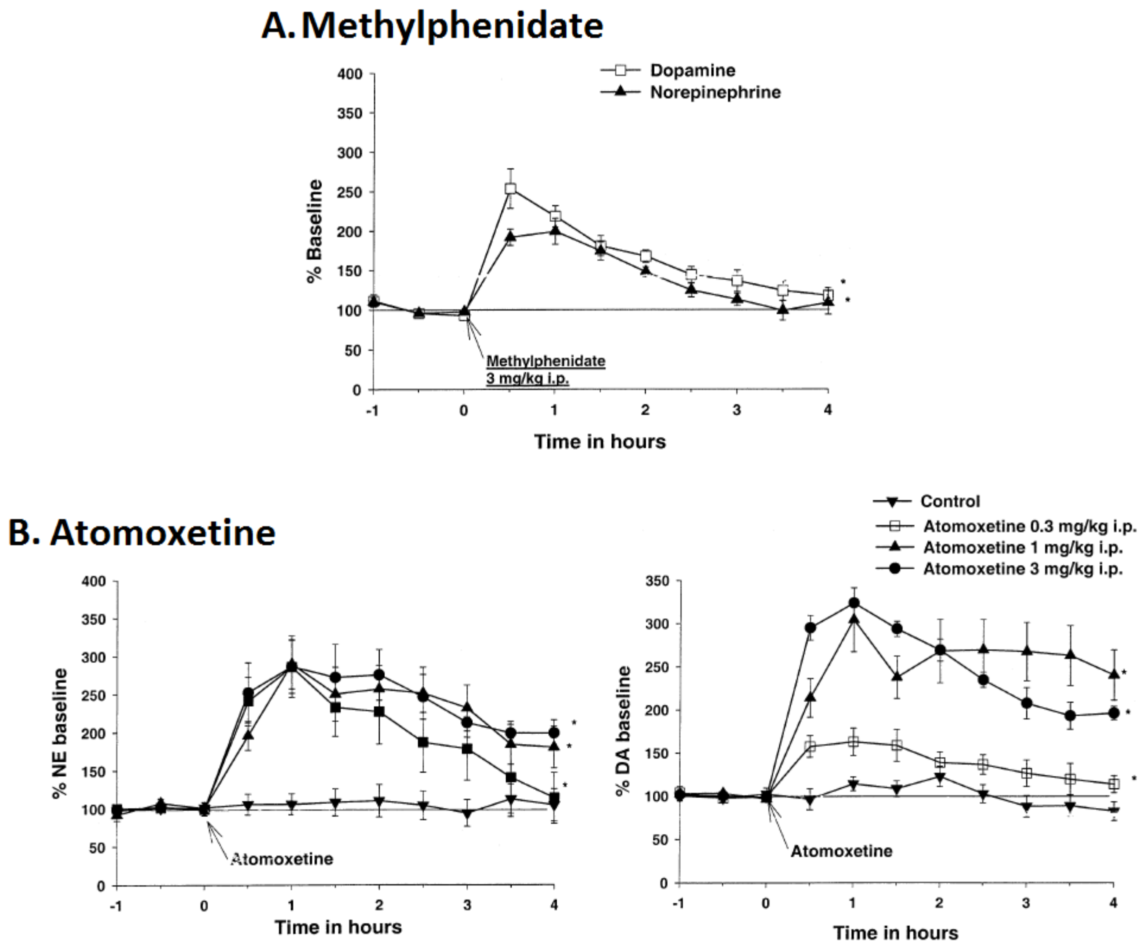

Figure 5: Effect of MPH and ATX on Catecholamine Levels. Measurement of extracellular catecholamine levels in the prefrontal cortex of freely-moving rats following intraperitoneal injection (i.p.) of MPH (A) and ATX (B). Arrows show time of injection. Asterisks indicate significant increase in dopamine and norepinephrine levels from baseline. Figures copied with permission from Bymaster et al. (2002).

and Keating, 2009). For example, Bymaster et al. (2002) reported an increase in both DA and NE concentrations in the rat PFC following atomoxetine (Figure 5), but reports very different values of K_i for DAT and NET (1451 nM and 5 NM, respectively). It is suggested that the affinity MPH has for NET is one order of magnitude greater than that of DAT (Hannestad et al., 2010), but the affinity of ATX for NET (K_i: 5 nM) is two orders greater than that of MPH (K_i: 339 nM; Bymaster et al., 2002).

PET scans from both NHP (Seneca et al., 2006) and humans (Logan et al., 2011) demonstrate ATX occupancy of NET in regions of the brain with high densities of the transporter. NET is widely distributed in the primate brain with high densities reported in the LC, the primary site of NE synthesis, and raphe nuclei (humans: Ordway et al., 1997; NHP: Smith et al., 2006). Systemic administration of ATX permits binding of NET throughout the brain causing increases of NE neurotransmission in areas like the LC. ATX is reported to dose-dependently modulate activity and enhance signalling of NE neurons in the LC which implicates its use as an attention-enhancing therapeutic (Bari and Aston-Jones, 2013).

1.5.1 Methylphenidate

Methylphenidate, better known by its brand name Ritalin®, is one of the more common treatments for ADHD due to its proven efficacy (Findling, 2008). It is a stimulant medication prescribed to alleviate the core symptoms of ADHD (see for review Van der Oord et al., 2008). In individuals with ADHD, it has been demonstrated with a number of different tasks that MPH effectively improves WM performance (see for review Martinussen et al., 2005; Nigg, 2005; Willcutt et al., 2005; Pietrzak et al., 2006; Kasper et al., 2012; Coghill et al., 2014). For instance, in a study using fMRI to compare neural activation in children with ADHD and a control group of healthy children, MPH was found to improve WM performance in the ADHD group; however, there were no detectable changes in the fMRI scans (Kobel et al., 2008). In contrast, the effect of MPH on performance in healthy subjects is equivocal with only marginal evidence of an enhancement on WM tasks (see for review Linssen et al., 2014; Ilieva et al., 2015). Despite equivocal literature, MPH is used recreationally as a cognitive enhancer in healthy individuals (see for review Linssen et al., 2014; Ilieva et al., 2015). Further, in healthy NHP acute administration of MPH had limited influence on performance in a delayed VSC task (Oemisch, 2012). The authors tested a wide range of doses of MPH, but found no significant changes in response accuracy or latency (Oemisch, 2012; Figure 6). While it is thought that MPH increases catecholaminergic concentration by inhibiting reuptake of DA and NE, it is not yet clear how this increase impacts behaviour in the non-disordered system.

1.5.2 Atomoxetine

ATX is a non-stimulant used to treat ADHD with similar efficacy to its psychostimulant counterparts (see for review Hanwella et al., 2011). Branded as Strattera®, ATX is a relatively novel alternative to MPH, often chosen because of a lower risk of abuse (Findling, 2008). There is ample literature on the efficacy of ATX, however it is often assessed as a daily medication rather than in an acute design. Like MPH, ATX is considered to be a cognitive enhancer in the treatment of ADHD (see for review Bidwell et al., 2011), but the evidence for this is equivocal. Studies assessing the effect of ATX on WM performance have had mixed results regardless of whether doses are given daily, twice daily, or acutely on the day of the lab visit. The variance in methodology across these studies limits our understanding of ATX (see Table 1). While each of the following studies investigates populations of ADHD participants, the populations vary

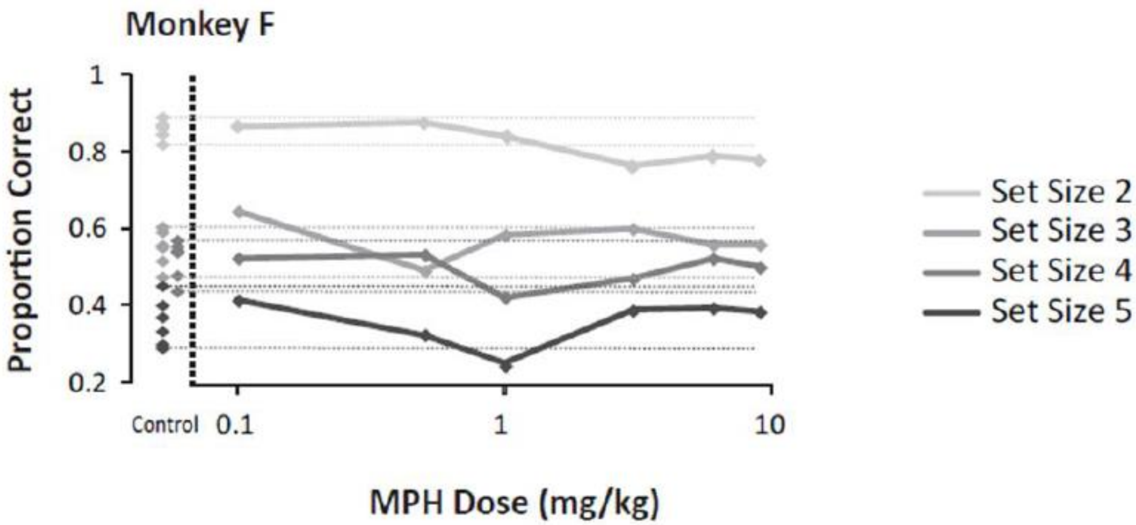

Figure 6: Response Accuracy in Healthy Nonhuman Primates after MPH. Performance on the delayed visual sequential comparison task following acute administration of MPH did not significantly alter response accuracy across set size. Dashed lines represent maximum and minimum values of vehicle control sessions. (Adapted from Oemisch, 2012).

including children with additional learning impairments (Reading disorder: de Jong et al., 2009; dyslexia: Sumner et al., 2009; Wietecha et al., 2013), drug naïve boys (Gau and Shang, 2010; Cubillo et al., 2013), and adults (Chamberlain et al., 2007a; Brown et al., 2009; Ni et al., 2013; Adler et al., 2014a; 2014b). The tasks implemented to assess WM performance in sub-chronic studies of ATX are inconsistent and are often limited in their assessment. Popular tasks include the Working Memory Test Battery for children (WMTB-C; Sumner et al., 2009; Wietecha et al., 2013) and the spatial WM portions of the Cambridge Neuropsychological Test Automated Battery (CANTAB; Gau and Shang, 2010; Ni et al., 2013). Also implemented are the digit span task and Rey complex figure test (Yang et al., 2012), the corsi block tapping task (de Jong et al., 2009; Yang et al., 2012), and the Wisconsin card sorting task (Tasdelen et al., 2015). More general assessments of executive function are made from self-report analyses using the Brown Attention Deficit Disorder Scales (BADDS; Brown et al., 2009) and the Behaviour Rating Inventory of Executive Function (BRIEF; Maziade et al., 2009; Yang et al., 2012; Adler et al., 2014a; 2014b); these assessments inadequately represent changes in WM due to the unreliable nature of self-reporting. Additionally, the use of BADDS or BRIEF in children often relies on reporting from parents and teachers rather than self-assessment (Yang et al., 2012). Marginal improvements in WM performance were reported to some degree in all of the above mentioned studies; however, these changes are often specific to the study and poorly reflect a general improvement in WM ability. For instance, Sumner et al. (2009) and Wietecha et al. (2013) reported improvement on the WMTB-C in children who have both ADHD and dyslexia, but not in children with only ADHD after administration of 1-1.4 mg/kg of ATX daily.

Studying the effects of ATX in individuals with ADHD using an acute study design is not as common and similarly difficult to compare. One study used the n-back WM task to assess the

Table 1: Assessment of Atomoxetine on WM Performance in Humans with ADHD. A demonstration of the variability in the current literature.

Authors	N (ATX)	N (Ctrl)	ATX dose	Acute	Age	WM Task	Retention Interval	Findings
Adler et al. (2014a)	266	258	80-100 mg	N	Adult	BRIEF-A	n/a	Significant improvement relative to placebo after 25 weeks
Adler et al. (2014b)	161	167	40-100 mg	N	Adult	BRIEF-A	n/a	Significant improvement relative to placebo after 12 weeks
Brown et al. (2009)	94	112	25-100 mg	N	Adult	BADDS	n/a	Significant improvement relative to placebo after 6 months
Chamberlain et al. (2007a)	22	20	60 mg	Y	Adult	SWM of CANTAB	n/a	No significant effect
Cubillo et al. (2013)	20	20	1 mg/kg	Y	Child	1,2,3-back	Inter-trial: 2s	No significant effect
de Jong et al. (2009)	16	26	1.06-1.14 mg/kg	N	Child	Corsi block tapping	n/a	No significant effect after 2 months
Gau and Shang (2010)	30	n/a	1.2 mg/kg	N	Child	SWM of CANTAB	n/a	Significant improvement relative to baseline after 4 or 12 weeks
Maziade et al. (2009)	16	16	1.4 mg/kg	N	Child	BRIEF	n/a	Significant improvement relative to baseline after 6 months
Ni et al. (2013)	32	n/a	0.5-1.2 mg/kg	N	Adult	SWM of CANTAB	n/a	Significant improvement relative to baseline after 8-10 weeks

Shang and Gau (2012)	30	n/a	0.5-1.2 mg/kg	N	Child	PRM; SRM	5s	PRM latency: significant decrease after 4 and 12 weeks PRM accuracy: increase after 4 weeks but not 12 SRM latency: significant decrease after 12 weeks SRM accuracy: no effect
Sumner et al. (2009)	20	n/a	1-1.4 mg/kg	N	Child	WMTB-C	n/a	Significant improvement of the central executive score relative to baseline after 16 weeks
Wietecha et al. (2013)	27	n/a	1-1.4 mg/kg	N	Child	WMTB-C	n/a	No significant effect after 32 weeks
Yang et al. (2012)	57	46	0.5-1.4 mg/kg	N	Child	BRIEF; RCFT; digit span	n/a	Significant improvement on BRIEF, RCFT, and digit span relative to baseline after 4-6 weeks
Taselen et al. (2015)	16	n/a	0.5-1.2 mg/kg	N	Child	WCST; VADS B	n/a	Significant improvement on WCST and VADS B scores relative to baseline after 13 weeks

Age ranged from 8-17 (child) and 18-54 (adult) across studies. PRM: pattern recognition memory; RCFT: Rey complex figure test; SRM: spatial recognition memory; SWM: spatial working memory; WCST: Wisconsin card sorting task; VADS B: visual auditory digit span B.

influence of a single therapeutic dose of ATX (1mg/kg) in drug naïve boys (Cubillo et al., 2013). There were no task improvements reported within ADHD participants, however fMRI scans showed greater activation in the dorsolateral PFC after ATX administration. This reveals a potential influence of ATX on neural activity in the PFC, but fails to draw the connection between sustained activity and behaviour. In adults, Chamberlain et al. (2007a) used the CANTAB to assess spatial WM, but found increased error in task performance in both the ATX group and the placebo group.

Research of ATX in healthy participants is scarce. In fact, one meta-analysis of noradrenergic modulation in healthy volunteers included ATX as a search term, but there were no studies available at the time that assessed the effects of ATX on WM (Chamberlain et al., 2006). Due to the available data using reboxetine, another SNRI, the author's concluded that effects on WM were inconsistent with the use of SNRIs (Chamberlain et al., 2006). More recently a study was conducted using fMRI activation as an indicator of WM activity (Marquand et al., 2011). The data suggested that doses of ATX do not have a significant effect on a delayed match-to-position task when compared to MPH (Marquand et al., 2011; Table 2). However, this research also reported no differences between reaction time and task accuracy between the two drug conditions (Marquand et al., 2011). Unfortunately there was no placebo control included in this study, so the effect of ATX on WM performance cannot be explicitly quantified.

In NHP it was reported that an optimal dose of ATX enhances WM performance on a manual delayed response task (Gamo et al., 2010; Table 3). This study orally administered a range of doses to rhesus macaques to find the dose that optimized performance in each animal individually. The authors suggested the effects followed an inverted-U dose response curve (Figure 7). Combining these optimal doses with DA or NE receptor antagonists was reported to

Table 2: Assessment of Atomoxetine on WM Performance in Healthy Humans.

Authors	N	ATX dose	Age	WM Task	Retention Interval	Findings
Marquand et al. (2011)	15	60 mg	Adult	Delayed match to location	8-10s	No significant differences in reaction time or accuracy between ATX and MPH conditions.

Table 3: Assessment of Atomoxetine on WM Performance in NHP. Animals are assumed to have natural catecholamine levels and doses are administered acutely.

Authors	N	ATX dose	Species	WM Task	Retention Interval	Findings
Bain et al. (2003)	5	0.01-1.0 mg/kg	Rhesus Macaque	DMTS, distractor DMTS	12-82 s (average)	No significant improvement in accuracy or latency
Gamo et al. (2010)	18	0.001-5.0 mg/kg	Rhesus Macaque	Delayed response task	2.5s	Improvement in accuracy at moderate doses; memory-related firing increased for preferred direction

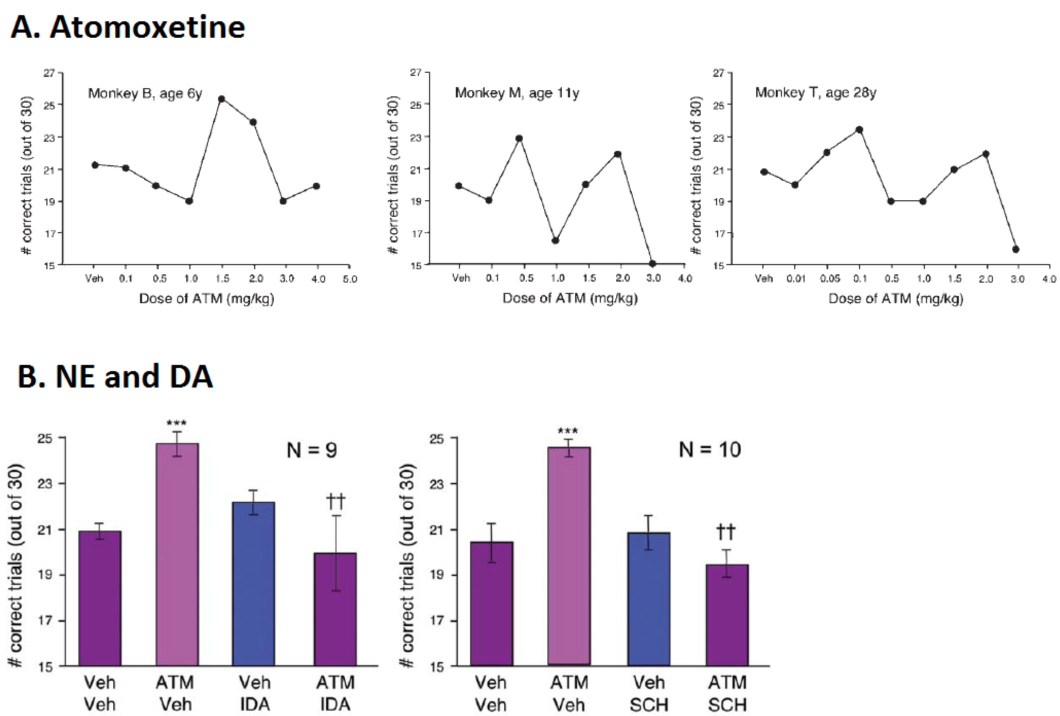

Figure 7: Working Memory Performance Following ATX (Gamo et al. 2010). A. Performance on a delayed response task compared in three NHP following administration of various doses of ATX. Dose-response curves suggest enhanced performance. Asterisk indicates the lack of higher doses being tested in Monkey B due to her use in another study. B. Application of IDA (α2-adrenoceptor antagonist) or SCH (D1 receptor antagonists) impaired drug-induced task improvement. ***p<0.001 compared with vehicle; ++ p<0.001 compared with ATX and vehicle. Veh: vehicle; ATM: atomoxetine. (Copied with permission from Gamo et al., 2010).

impair performance on the delayed response task suggesting that ATX acts via these receptors to enhance performance (Figure 7). In addition to the manual task, Gamo et al. (2010) utilized an ODR task to conduct electrophysiological recordings in the dorsolateral PFC of one monkey. Again, the authors claimed that spatially tuned neurons responded in an inverted-U manner following a range of doses of ATX (Gamo et al., 2010). Interpretation of the data suggested that delay-related firing of these neurons was enhanced following low doses of ATX and suppressed by high doses. Additionally, it was suggested that low ATX doses dose-dependently increased firing of the cell’s preferred direction, enhancing the signal-to-noise ratio of the neuron (Gamo et al., 2010). However, there are several limitations in this study. For one, the delayed response task is a weak assessor of WM performance because it often fails to challenge the limited capacity storage, as described in section 1.2.1., and the retention interval was altered on an individual basis, which introduces discrepancy between subjects. The study is also limited by sample size; while 10 animals were studied overall, the number of trials available for analysis was quite small (30 trials per dose). No statistical analyses on the performance of each animal was reported and the best dose analysis method used has been shown to yield false positives (Soto et al., 2013). Lastly, the electrophysiological experiments were conducted on 17 neurons in a single monkey. These limitations emphasize the need for a more comprehensive analysis of ATX effects on WM. On the contrary, Bain et al. (2003) found that performance on a computerised DMST task did not improve in NHP following a range of ATX doses (Table 3; Figure 8). Even administration of individual best doses did not cause a significant change in performance on the task (Bain et al., 2003). Both of these studies investigate the effects of acute ATX administration on NHP performing WM tasks, but have different results. This ambiguity emphasizes the need for further research to elucidate the effects of this drug on WM in healthy populations. It is

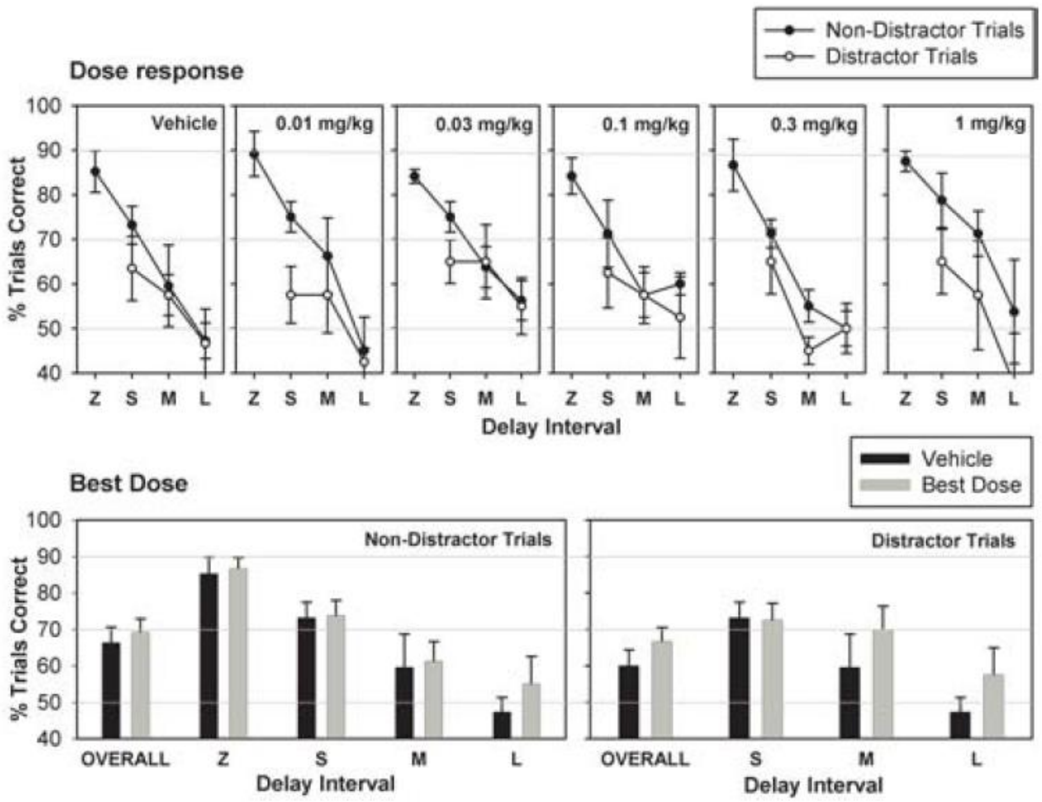

Figure 8: Working Memory Performance Following ATX (Bain et al., 2003). On a DMTS task 5 doses of ATX were assessed over zero (Z), short (S; average: 11.8s), medium (M; 36.9s), or long (L; 81.9s) delay intervals in 5 rhesus monkeys. ATX did not cause a significant change in accuracy compared to vehicle performance and an individualized best dose of ATX did not increase accuracy. (Copied with permission from Bain et al., 2003).

feasible that ATX differentially effects healthy individuals because of normal concentrations of catecholamines; thus, it is important to expound the inconsistencies in the effects of ATX on the healthy system.

1.6 Scope of Study

Decades of ground breaking research have enlightened our understanding of the neural mechanisms responsible for WM function. This includes the contribution of persistent activity and how this activity can be manipulated pharmacologically to amend the impaired PFC. That being said, there are still many unanswered questions. The above literature review challenges the extent to which catecholamines are involved in WM function and the effectiveness of current pharmaceuticals in the treatment of cognitive deficits. If previous evidence is accurate in proposing a mechanism for catecholamines in the modulation of cognition, then manipulation of catecholaminergic concentrations should be evident at the behavioural level. However, support for this is insubstantial. Furthermore, this review highlights the importance of implementing a task that manipulates the limited capacity of WM storage in future research through discussion of equivocal evidence gathered from tasks that are limited in their assessment of WM performance.

With this in mind, the current study continues the investigation of a catecholaminergic contribution to WM performance. It aims to elucidate the effect of catecholamine reuptake transporter inhibitors on visual WM performance through acute oral administration of a large range of ATX doses to two rhesus macaques performing a delayed VSC task. Both the short time interval and limited capacity characteristics of WM are adequately assessed using this task. It is hypothesized that an optimal dose of ATX improves response accuracy and shortens response latency in a dose- and memory load-dependent manner (Figure 9). This project aims to compliment previous work conducted in our lab that demonstrated the limited influence of MPH on performance in the same task (Oemisch, 2012). With a greater affinity for NE than MPH, investigating the effects of ATX on delayed VSC task performance will more directly address the influence of NE on WM. Together, these studies will provide a comprehensive investigation of catecholamine contribution on cognition.

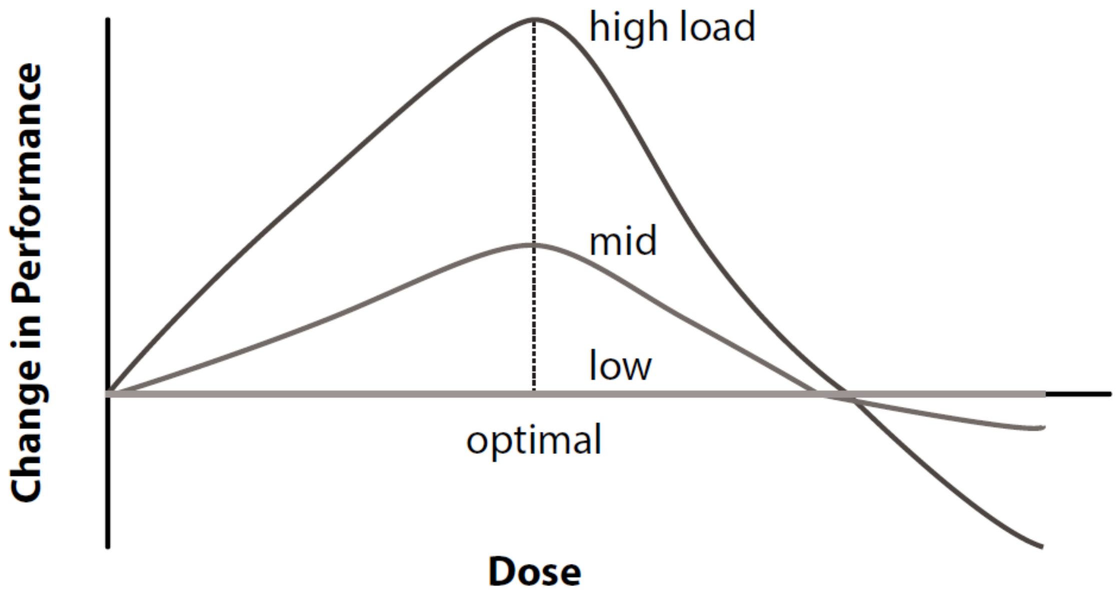

Figure 9: Project Hypothesis. Following the theory of inverted-U curves, performance varies in a dose-dependent and memory load-dependent manner; such that doses above or below the optimum impair performance with the greatest effect occurring at higher memory loads.

Chapter 2 – Methods

2.1 Subjects and Apparatus

Two female rhesus monkeys (*Macaca mulatta*) were used for the following experiments. Monkey B weighed an average of 6.3 kg and Monkey F weighed an average of 9.1 kg throughout the experiments; both animals were 17 years of age. NHP were a practical model for this project because they permit the control of potential confounding factors including, but not limited to, diet, hormone fluctuation, and environment. The animals were cared for and used under experimental protocols approved by Queen's University Animal Care Committee and in accordance with the Canadian Council on Animal Care guidelines. Animals underwent surgery in preparation for the experiments, in which a head restraint and subconjunctival search coils were implanted to monitor eye position (for details see Shen and Paré, 2006). They received both antibiotics and analgesic medications during the post-surgery recovery period. After recovery, the animals were trained with operant conditioning and positive reinforcement to perform fixation and saccade tasks for liquid reward until satiation. Water intake was controlled throughout the experiment allowing water to be used as a reward and motivator. In addition to unrestricted access to monkey chow, treats including fresh fruit and vegetables were made available daily. Body weights were recorded prior to every lab session to ensure health was not compromised by the experiments; animals were monitored closely by the experimenters, animal care staff, and university veterinarians.

The QNX-based Real-Time Experimentation Software (REX) system running on a Pentium III PC was used to control the visual displays, behavioural paradigms, and data acquisition of the experiments (Hays et al. 1982). The visual displays were created using MATLAB and the Psychophysics Toolbox (Brainard, 1997) and were run on a Power Mac G4 computer. The paradigm was presented at a viewing distance of 57 cm from the monkey on a 37" monitor (NEC MultiSync XP37 plus, 60-Hz non-interlaced, 800x600 resolution, 32-bit colour depth). To monitor eye positions the magnetic search coil technique was used *(*Robinson, 1963*)*. The field coils placed around the eye generate opposing horizontal and vertical magnetic fields, allowing the voltage generated from the scleral search coil to be recorded.

The implemented paradigm presents stimulus arrays consisting of two to five coloured squares; these measure 1.2° x 1.2°. Within each set size the position of the squares remains the same from trial to trial and all squares are presented 10° from the central fixation point. The stimuli are presented to the left and right of the central fixation point during the set size two trials. All other set sizes have one stimulus positioned directly above the central fixation point, with the remaining stimuli presented at equal distances from each other (Figure 8). The set size and colours of the stimuli are chosen at random for each trial. Each colour can only appear once in a given display and are chosen from six highly discriminable colours: red (CIE x = 0.633, y = 0.327, L = 9.8 cd/m^2), green (CIE x = 0.288, y = 0.602, L = 9.8 cd/m^2), blue (CIE x = 0.155, y = 0.063, L = 9.9 cd/m^2), magenta (CIE x = 0.345, y = 0.168, L = 9.9 cd/m^2), yellow (CIE x = 0.432, y = 0.485, L = 9.9 149 cd/m^2), and cyan (CIE x = 0.223, y = 0.337, L = 9.9 d/m^2). Luminance and chromaticity of the colours were measured using a Minolta CA 100-Plus photometer.

2.2 Behavioural Paradigm

The monkeys performed a delayed VSC task, which manipulates memory load with different set sizes (Figure 10). A trial begins with the presentation of a white fixation point (0.5°) at the center of the display monitor. The animal must fixate on this point within 1000 ms of its presentation and maintain fixation for 500-800 ms within a 2° x 2° window; this is considered initiation of a trial. During fixation, a memory array of a randomly determined set of 2 to 5 squares is presented for 500 ms. Previous work in this lab demonstrated that presenting the array for 500 ms was a sufficient amount of time for the animals to perform the task accurately (Oemisch, 2012). The memory array is followed by a 1000 ms retention interval in which no stimuli are shown except for the fixation point. This relatively short retention interval has been chosen to limit the impact of long-term memory storage on performance in this task. It corresponds with the interval length implemented in human studies using a change detection task (Luck, 2008; Luck and Vogel, 2013). Although longer intervals do not disrupt performance (Vogel et al., 2001; Jeneson et al., 2012), they may promote the influence of long-term memory processes. Patients with medial temporal lobe damage had impaired performance on change detection trials with long retention intervals (3-8 seconds), but WM remained intact as demonstrated by normal performance on trials with a 1000 ms retention interval (Jeneson et al., 2012). In the present task, fixation is maintained throughout the 1000 ms interval until the test array is presented. The test array consists of the same number and spatial configuration of stimuli as the memory array except one of the stimuli has changed colour. Simultaneously, the luminance of the fixation point is dimmed and the monkey has 500 ms to make a single saccade to the location of the stimuli that changed colour. To successfully complete the trial the monkey must remember the location and colour of each stimuli in the memory array. If successful, the monkey receives a liquid reward and the trial is marked correct. Incorrect trials occur when the monkey makes a saccade to the wrong location or does not respond within the 500 ms (omission); these trials do not receive a reward and are followed by a 3000 ms time out period. To prevent dark adaptation during the intertrial interval the monitor screen is illuminated with diffuse white light (1.5 cd/m^2). In addition to omissions,

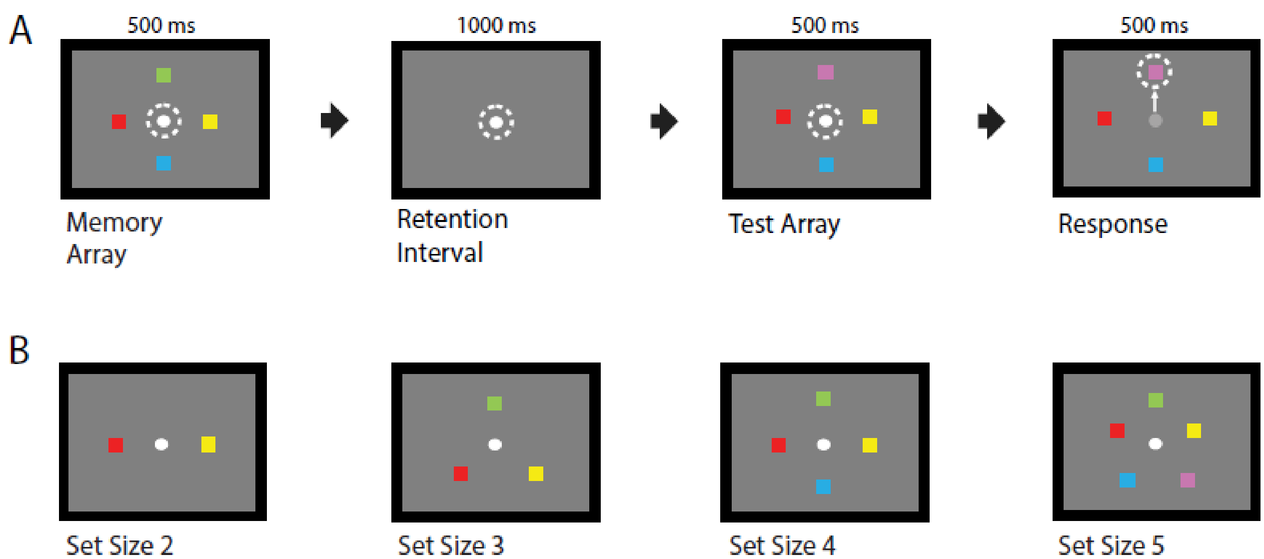

Figure 10: Delayed Visual Sequential Comparison Task. A: A schematic of task execution. Dotted circles represent eye position; arrows show a saccadic eye movement to the response target. B: Stimulus position for each set size (2-5).

there are three ways a monkey can abort a trial before it is completed; these include fixation, array, and retention breaks (Figure 11). A fixation break is classified as a saccade away from the fixation window before the memory array has been presented. If a saccade is made during the presentation of the memory array the abortion is considered an array break. Thirdly, a retention break occurs if fixation is not maintained during the retention interval of the trial.

2.3 Experimental Procedure

Prior to starting these experiments, all animals had previously demonstrated stable performance on this task in more than 10,000 trials and none had prior exposure to atomoxetine. Each treatment session was conducted a minimum of 13 days apart to ensure enough time for the previous dose to be eliminated from the system. The rate of metabolism in the rhesus macaque is not yet known for ATX. The average half-life in humans following oral administration of ATX differs in extensive and poor metabolizers as a result of the polymorphic expression of CYP2D6 metabolic enzyme (Sauer et al., 2005). The half-life is reported to be 5.2 hours and 21.6 hours, respectively (Sauer et al., 2005). However, it is not known if this metabolic difference is present in NHP. Atomoxetine was orally administered 30 minutes before the start of each treatment session to assess performance during peak blood concentration. According to its high water solubility and intestinal permeability, oral administration of ATX is rapidly absorbed (Sauer et al., 2003). In humans, the peak blood concentration varies by age and is again influenced by the activity of the CYP2D6 metabolic enzyme (Farid et al., 1985; Witcher et al., 2003; see for review Sauer et al., 2005). In extensive metabolizers, oral administration of a single 20 mg dose reached peak blood concentration at 1 hour in adults, but a 10 mg dose took 2 hours in children (for review see Sauer et al., 2005). Likewise, the maximum blood concentration in children with

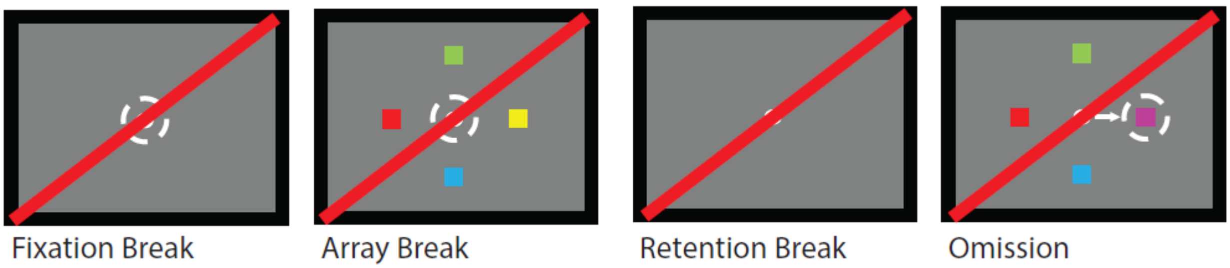

Figure 11: Different Trial Breaks. When the subject breaks fixation during the delayed VSC task before the response phase the trial ends, followed by a time out. Fixation breaks occur during the initial fixation period at the start of the trial. Array breaks are when fixation is broken during the presentation of the memory array. If fixation is broken during the retention interval it is considered a retention break. These are illustrated above with a red diagonal line indicating the abortion of the trial. An omission occurs when the subject fails to make a response after the presentation of the test array.

ADHD ranged from 1 hour to 4 hours (average 2 hours) following a single dose of 10 mg (Witcher et al., 2003). A study in rats and dogs, which lack the CYP2D6 metabolic enzyme, found that peak blood concentration was achieved at 2 hours and 1.3 hours, respectively (Mattiuz et al., 2005). Catecholamine concentrations recorded in the rat PFC were reported to increase 30 minutes following intraperitoneal injection of ATX, peaking at 60 minutes (Bymaster et al., 2002).

The therapeutic dose of ATX for children with ADHD approved by the FDA is between 0.5 and 1.4 mg/kg (Eli Lily and Company, 2015). In comparison, the best dose found in NHP varies between individuals, ranging from 0.01 to 1.0 mg/kg (Bain et al., 2003; Gamo et al., 2010). Accordingly, this experiment will test the following doses in each animal: 0.03, 0.056, 0.1, 0.18, 0.3, 0.56, 1.0, 1.8, and 3.0 mg/kg to appropriately assess ATX effects on WM. Immediately prior to oral administration the dose of ATX was combined with a 10 mL vehicle of juice. These treatment sessions were compared to vehicle control sessions collected one day prior to the respective treatment session. Similar to treatment sessions, 10 mL of juice was administered 30 minutes prior to control sessions to eliminate any variability between treatment and control data.

2.4 Data Analysis

The analysis of this experimental data was done using MATLAB (The MathWorks, Natwick, MA) and Microsoft Excel. Several hundred trials were collected over nine experimental and control sessions for each monkey permitting a large sample size for analysis. The first 600 trials of each treatment and control session were analyzed which is roughly equivalent to an hour of testing. Not only does this keep the number of trials consistent across animals, but also controls for waning motivation. On average, the number of trials performed per session did not greatly exceed 600; Monkey B performed 876 ± 163 trials per session and Monkey F performed 950 ± 145 trials. Task performance will be assessed with two measures: response accuracy and latency. Response accuracy is defined as the probability that the target is selected with the first saccade. While response latency is the time it takes for the first saccade to land on the target after presentation of the test array. The data from each session, either control or treatment, was combined. All of the data were then compared using a χ^2 test ($p<0.05$). Additionally, each treatment session was compared to the control session that preceded it in a pairwise manner (χ^2 test, $p<0.05$).

Correct and incorrect trials were analyzed for the evaluation of the response accuracy in control and treatment sessions. Omission trials were included in the analysis as incorrect trials; Monkey F had 2 omission trials between the treatment and control sessions and Monkey B had a total of 26 omission trials. If a trial was aborted before the test array was presented it was excluded from analysis. The response accuracy was compared to the mean control response accuracy for all set sizes and doses of ATX. A significant change in performance was assessed as greater than two standard deviations above or below the control average. Additionally, comparisons were made between control and treatment sessions across dose and set size to assess statistical significance (χ^2 test, $p<0.05$). Similarly, the standardized change in response latency from the mean control response latency was assessed for each dose of ATX. Further statistical analysis of response latency was completed by t-test ($p<0.05$).

In addition to day-before control sessions and treatment sessions, each experimental block included several “everyday controls” that followed the same vehicle control procedures, but were not associated with a treatment session. Analysis of these everyday control sessions provided additional strength to the day-before control data. There were 32 sessions of everyday control data collected for Monkey B and 42 sessions collected for Monkey F. However, Monkey B had a number of days of uncharacteristically poor performance; particularly striking was the number of omission trials committed in these sessions, which was as high as 101 in one session. Thus, a session was removed if there was more than 10 omissions committed; this decision was based on control data from Monkey B, which never had more than 9 omissions per session. Removal of these sessions was imperative to an accurate analysis with the everyday controls. In total, seven of the 32 everyday control sessions were omitted from analysis. A number of factors could cause this disruption in behaviour including changes in the environment (lab or pen) or health related changes (menses or illness). In fact, the omitted days occurred over two sequences suggesting external factors were the cause and not a change in motivation or compliance of the animal.

2.5 Assessment of Task Engagement

The proportion of trials aborted was computed to assess change in task engagement. We compared the proportion of total aborted trials between control and treatment sessions, as well as the proportion of total array, fixation, and retention breaks between the conditions. Statistical significance was determined by χ^2 test ($p<0.05$). Analysis of the proportion of trials the animal failed to initiate was done as an additional measure of task motivation. The animal initiates a trial by fixating on the central point for 500-800 ms; the number of initiated trials was compared against the number of times the fixation point appeared in a given session to obtain the proportion of trials that each animal did not initiate during a session of 600 trials. Statistical significance between control and treatment sessions was determined by χ^2 test ($p<0.05$).

In addition to the delayed VSC task, a modulated form of the progressive ratio task was implemented to assess the effects of ATX on motivation. The progressive ratio task was designed by William Hodos to assess the "attractiveness" of a reward under varying motivational conditions (Hodos, 1961). First implemented in rats, the progressive ratio task requires the subject to perform exponentially more trials to obtain the same volume of liquid reward. Hodos (1961) found that the number of trials completed varied with the concentration of the reward, as well as with daily food and water availability. Performance on the progressive ratio task is assessed by the final ratio attained by the subject and the amount of reward received overall (Spinelli 2004). Typically, addictive compounds, such as cocaine, are used as the reward in the task to assess their reinforcing or addiction properties (for example, Wee and Wolverton, 2004). However, it can also be used to assess how administration of certain compounds affects the motivation of a subject for a generic reward such as juice. For example, Von Huben et al. (2006) tested what effects D1 and D2 antagonists had on cognitive function including spatial WM and motivation; both antagonists reduced progressive ratio performance. Another study investigated the motivational properties of MPH using the progressive ratio task and reported an increase in performance (Chelonis et al., 2011). With this in mind, it is hypothesized that administration of ATX improves performance on the progressive ratio task.

The novel task implemented in this thesis is a visual variation of the original. Rather than requiring the animal to touch a stimulus presented on a screen the animal maintains fixation on a presented stimulus (Figure 12). The first target is presented in the centre of the screen; the animal must fixate on the target for 1000 ms to receive a juice reward. Following the progressive ratio schedule, the second trial presents two targets in sequence: the first in the centre of the screen

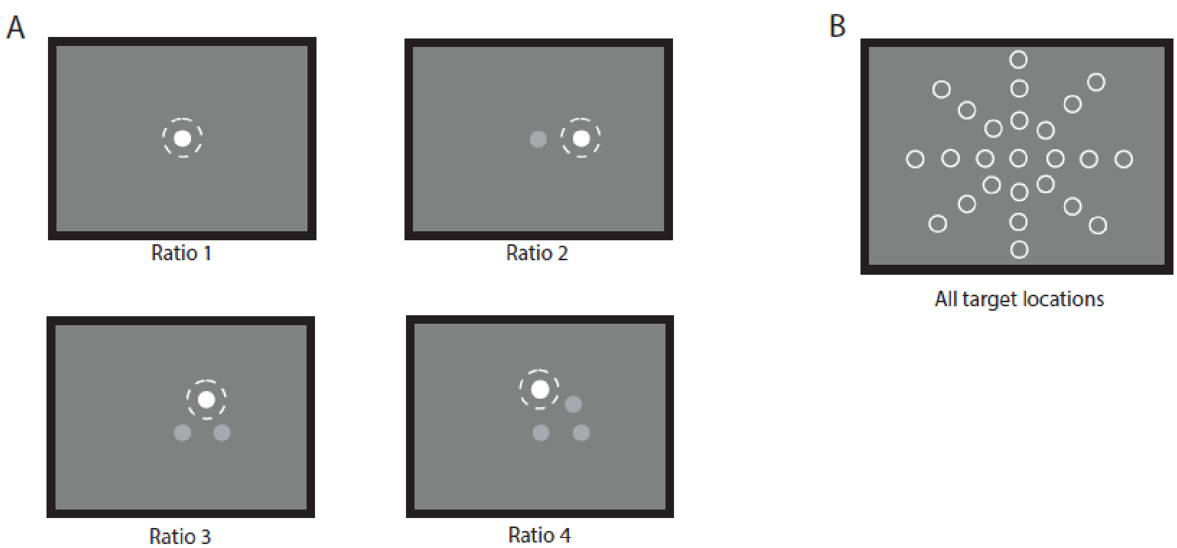

Figure 12: Visual Progressive Ratio Task. A: White circles show the final position of the target in each ratio that must be fixated on to receive reward. Grey circles indicate position of previous targets in the trial. B: Demonstrates all 25 target positions. The task always begins with the first target appearing in the centre of the screen. The target then appears counter clockwise around the inner ring before beginning counter clockwise around the second and third rings.

and the second to the right; the animal must fixate each one to receive the same volume of liquid reward. The ratio used in this experiment increases by an increment of one such that the animal must respond to one stimulus for the first trial, two stimuli for the second trial, three stimuli for the third trial, and so on. The targets appear counter-clockwise around the centre of the screen in three circles; eight target positions make up each circle for a total of 25 positions, including the centre position (Figure 11). The number of stimuli required in each trial continues to increase until the break point has been reached (Hodos, 1961). The breakpoint of the visual progressive ratio task is the final ratio attained by the animal. The block of trials ends if the animal attempts a ratio ten times and still does not complete it. Once the breakpoint has been reached the task is restarted from the beginning; one session consists of three attempts at the task. Again, performance on the visual progressive ratio task is determined by the final ratio achieved.

The progressive ratio task was performed by Monkey B and F as well as a third animal, Monkey D (7.8 kg, 8 years). Vehicle controlled baseline performance in all animals was collected prior to administration of a single, 1 mg/kg dose of ATX. Each animal performed the task at the beginning of the session to ensure the greatest motivation. If the task was implemented after performance on the delayed VSC task, then performance on the visual progressive ratio task would likely be hindered by the water received during the VSC task and thus, would be an inaccurate representation of the animal’s motivation. Therefore, the progressive ratio task began 30 minutes following administration of vehicle or ATX. The average breakpoint across the three trials in each session was used for analysis of progressive ratio performance.

Chapter 3 – Results

3.1 Control Performance

Both Monkey B and Monkey F have had extensive training on the delayed VSC task prior to use in this study. The animals worked five days a week for eighteen weeks over the course of this experiment. From these daily sessions there were nine day-before treatment sessions collected as controls. Peripheral to the nine day-before control sessions and nine treatment sessions are a collection of everyday controls that follow an identical, vehicle-controlled protocol; 32 and 42 everyday control sessions were collected in Monkey B and F, respectively. The average proportion of correct trials for the day-before control sessions of Monkey B were 0.89 ± 0.02, 0.76 ± 0.03, 0.63 ± 0.04, and 0.59 ± 0.04 for set sizes 2, 3, 4, and 5, respectively. For the same set sizes the performance averages for Monkey F were 0.85 ± 0.03, 0.72 ± 0.05, 0.58 ± 0.03, and 0.43 ± 0.06 (Figure 13). This performance in control sessions was well above chance performance for both monkeys across all set sizes (z-test, $p<0.0001$). Additionally, the proportion of correct trials declined as a function of set size in both monkeys (ANOVA, $p<0.0001$). There were no differences found between the response accuracy across set sizes of the day-before control sessions and the everyday control sessions that were collected (t-test, $p<0.05$), demonstrating the strength and reliability of our pool of control data. For instance, the average response accuracies for the everyday controls were 0.87 ± 0.03, 0.74 ± 0.04, 0.60 ± 0.05, and 0.55 ± 0.05 for Monkey B and 0.86 ± 0.03, 0.72 ± 0.04, 0.59 ± 0.04, and 0.44 ± 0.04 for Monkey F over set sizes 2, 3, 4, and 5, respectively. Further, this performance is comparable to previous records of rhesus macaque performance on the delayed VSC task (Heyselaar et al., 2011; Oemisch, 2012).

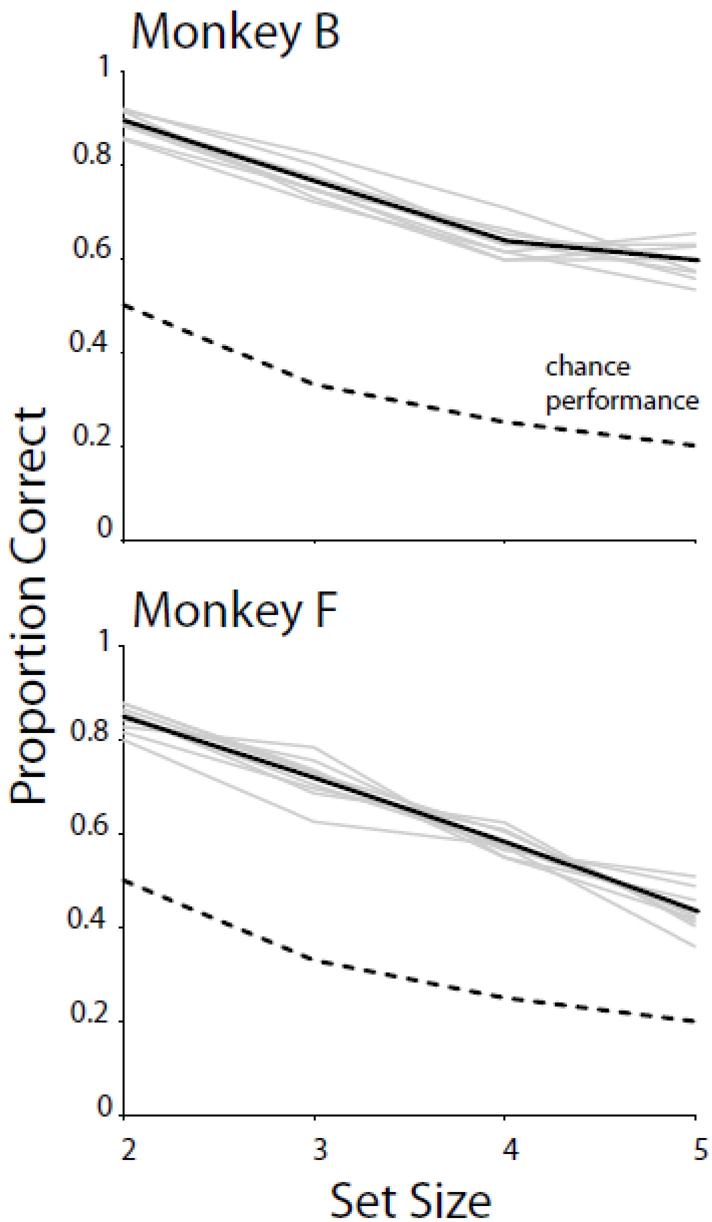

Figure 13: Response Accuracy of Control Performance. Proportion of correct trials for control sessions is plotted against set size for each animal. Average performance is shown by the solid black line with averages of the nine individual sessions plotted in grey. Dotted lines represent the chance performance across set size.

The response latency in correct control sessions for Monkey B averaged at 192 ± 5 ms across all set sizes. Monkey F had an average response latency of 197 ± 3 ms across all correct responses in control sessions. A two-way ANOVA using set size (2 to 5) and the outcome of the trial (correct or incorrect) as factors, shows that there is a significant interaction between response latency and trial outcome (Figure 14). Incorrect trials had significantly longer latencies than correct trials in both animals ($p<0.0001$). This is an important indication that the animals were not guessing on the trials, but were responding based on mnemonic information (Heyselaar et al., 2011). Furthermore, analysis between the everyday controls and day-before control sessions revealed no significant difference across set sizes in either animal (t-test, $p>0.05$).

3.2 Effect of Atomoxetine on Response Accuracy

Analysis of the effects of ATX on WM performance included comparison of the response accuracy following administration of the drug with response accuracy in day-before control sessions. Like control data, the response accuracy after ATX administration declined as a function of set size in both animals (ANOVA, $p<0.0001$). However, across the range of doses there was no consistent dose- or memory-load effects. In Figure 15 proportion correct is plotted as a function of ATX dose; each set size is compared across the 9 tested doses. The day-before session data for each set size is included for comparison in each monkey. It is evident that there is no optimal dose effect as predicted in the hypothesis; there is no single dose that similarly influences response accuracy across all of the set sizes. Rather, the treatment data falls within the variability of the control data. Further, Figure 16 depicts the response accuracy for each monkey as a change from the control average. Performance in treatment sessions generally fell within 2 standard deviations of the control average with the exception of a few data points. In Monkey B,

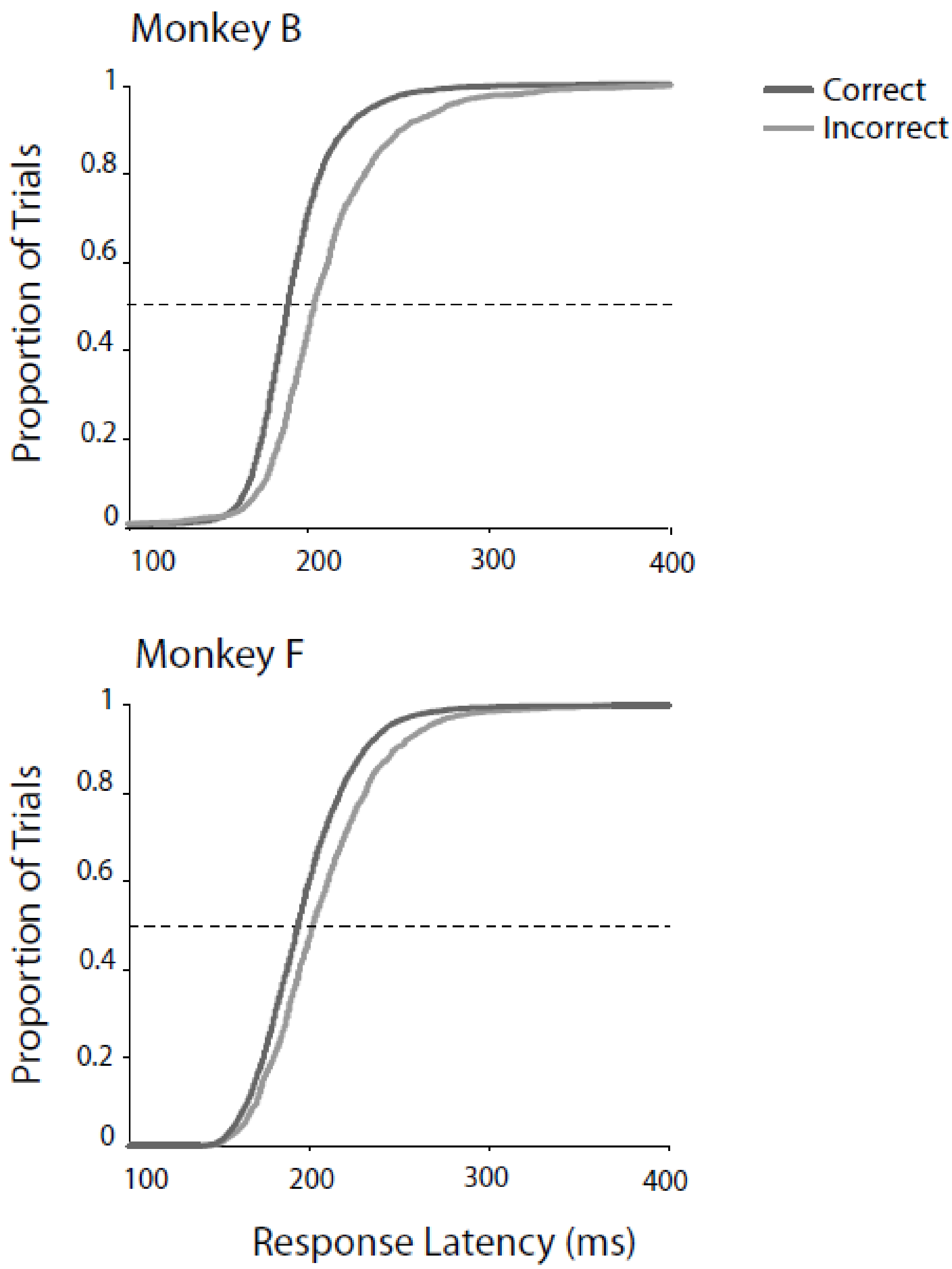

Figure 14: Response Latency of Control Performance. Response latency was shorter on correct control trials (dark trace) compared to incorrect control trials (light trace) in both animals.

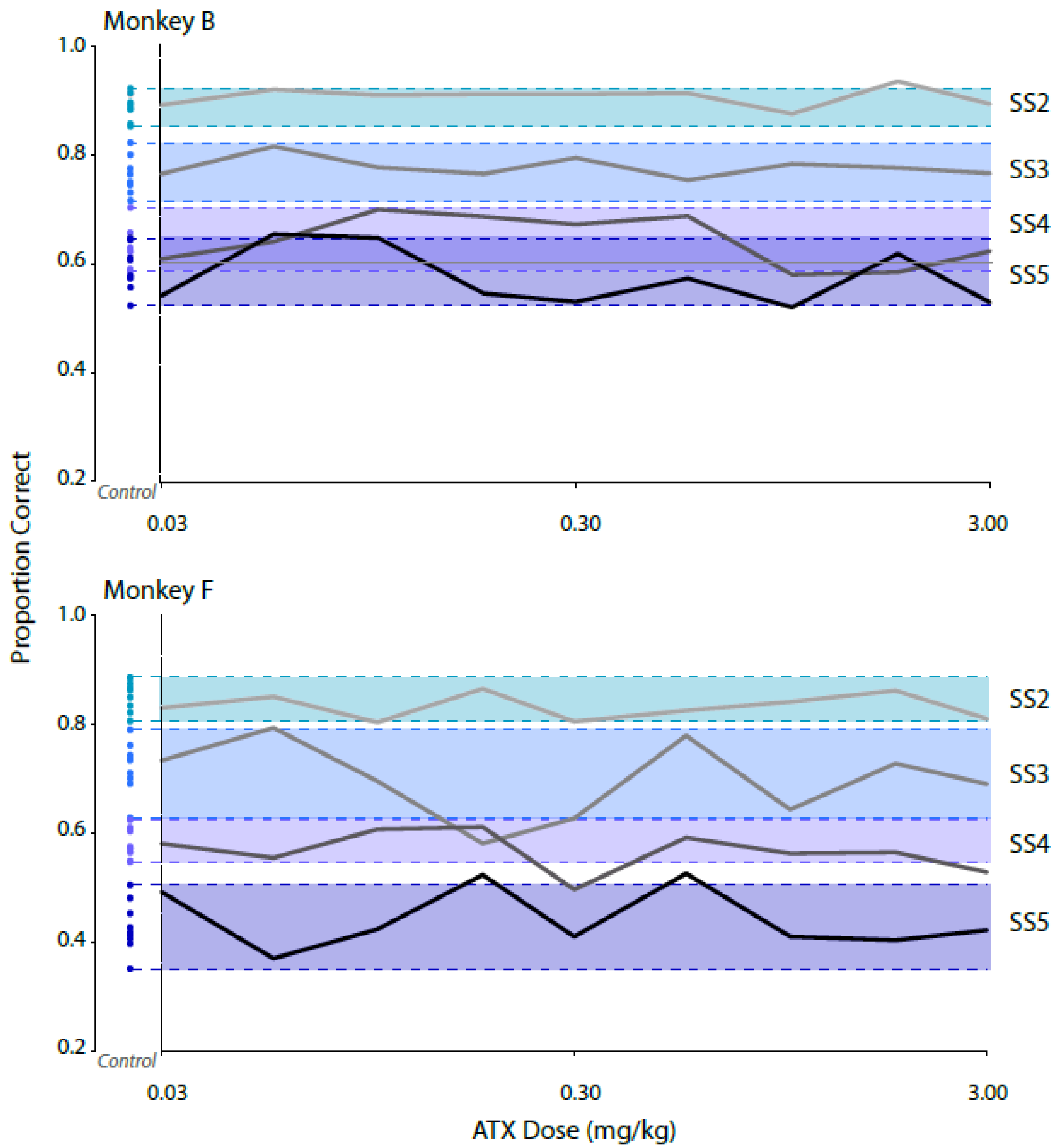

Figure 15: Proportion Correct Across Dose Following ATX. Solid traces show the average proportion correct obtained per dose of atomoxetine for set sizes 2 through 5. Coloured banners indicate range of average control performance for each set size (control averages per session shown to the left). Dotted traces represent minimum and maximum proportion correct obtained during control trials.

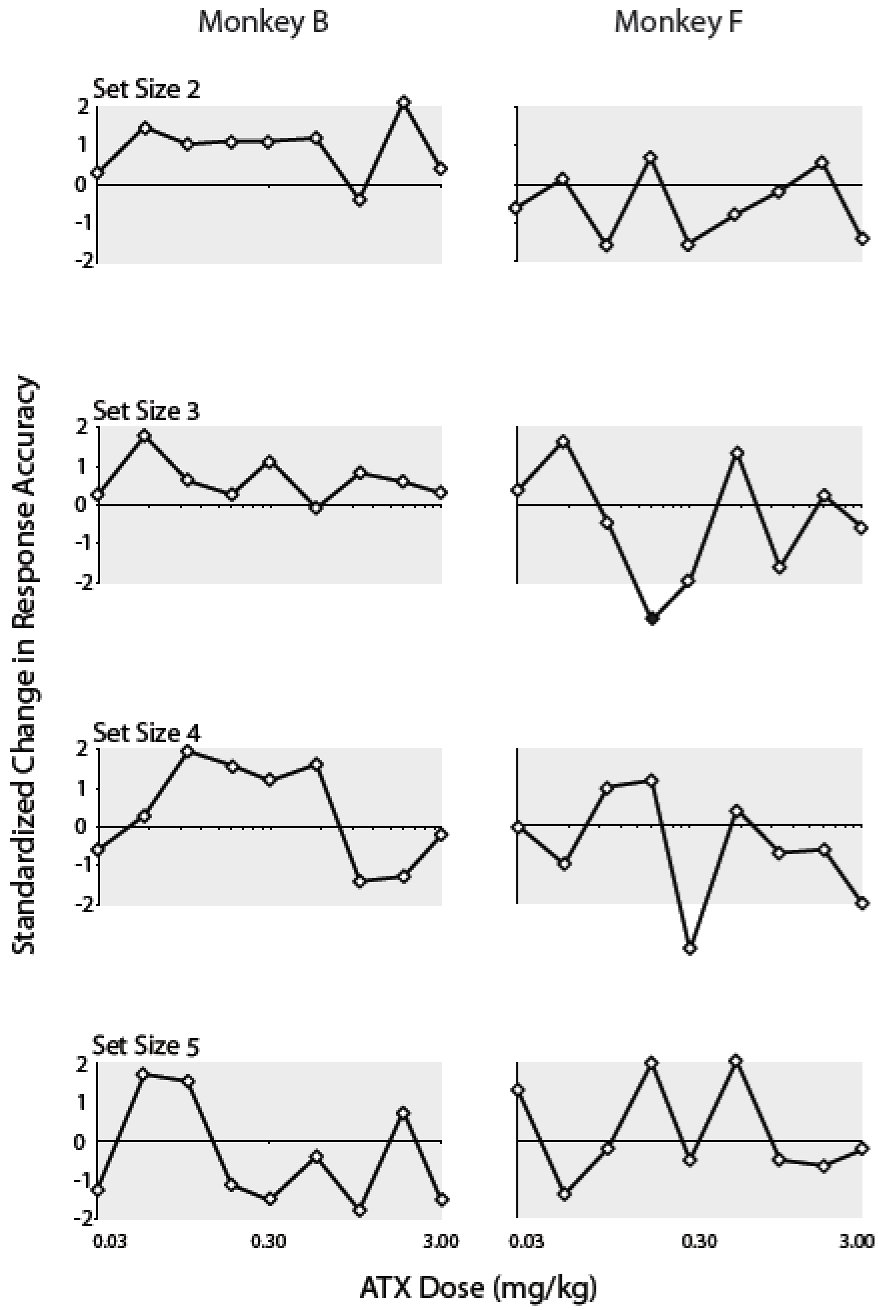

Figure 16: Response Accuracy per Set Size for Monkey B and F. Solid points indicate significant findings (χ^2, p<0.05). Grey boxes represent ± 2 standard deviations from the average control response accuracy.

response accuracy across all treatment sessions within each set size did not differ significantly from all control sessions (χ^2, p>0.05) and fell within 2 standard deviations of the control average. Although nonsignificant, a slight inverted-U trend can be observed when comparing response accuracy of Monkey B between set sizes especially if one excludes the highest doses. This trend appears consistent across all four set sizes, but is not specific to an optimum dose. For Monkey F there were no statistically significant differences across all control sessions, however response accuracy across all treatment sessions differed significantly in set size 3 (χ^2, p=0.00056). The control data of set size 3 was compared to the set size 3 treatment data in a pairwise manner, revealing significantly poorer response accuracy following an ATX dose of 0.18 mg/kg (χ^2, p=0.0053). No further statistically significant results were apparent in the other set sizes for this dose or the remaining doses. There was no significant difference found across any of the set sizes in a comparison of all control data and all treatment data (χ^2, p>0.05).

Overall, these data demonstrate a negligible effect of ATX on response accuracy in the delayed VSC task in these two monkeys. While the hypothesized trend is apparent in Monkey B, these changes failed to reach statistical significance. Response accuracy was minimally altered by ATX for all of the tested doses and set sizes in both animals. Furthermore, there was no significant dose-dependent or memory load-dependent effect on response accuracy following administration of ATX in this task.

3.3 Effect of Atomoxetine on Response Latency

Performance on the delayed VSC task was also quantified with response latency. According to the hypothesis, an optimal dose of ATX shortens response latency. The average response latency for the correct trials in each treatment session was calculated as a standardized change from the average correct control response latency (Figure 17). In Monkey B, significant changes in response latency were observed across set sizes following doses of 0.03, 0.10, and 1.80 mg/kg (t-test, $p<0.05$). Compared to control trials 0.10 mg/kg and 1.8 mg/kg shortened response latency, whereas 0.03 mg/kg lengthened it. Overall, the changes observed in Monkey B were within 2 standard deviations of the control average. Further, even changes in response latency compared across set sizes were within 2 standard deviations of the control average, with only a dose of 1.8 mg/kg producing a significantly shorter latency in set size 2 (t-test, $p=0.0034$). Regardless of set size, four doses of ATX produced significant changes in response latency of Monkey F (t-test, $p<0.05$). Of these four doses 0.18, 1.80, and 3.00 mg/kg lengthened response latency (t-test, $p<0.05$). Analysis across the individual set sizes revealed a shortened response latency in set size 3 following a dose of 1.0 mg/kg of ATX (t-test, $p<0.05$). Several lengthened response latencies were statistically significant as well (t-test, $p<0.05$; Figure 17), but did not demonstrate consistency across set sizes or a dose-dependent effect.

Following the administration of ATX, changes in response latency failed to yield any consistent dose-dependent effects. The majority of the treatment data fell within the variability of the control response latency and no common relationship could be established across monkeys.

3.4 Effect of Atomoxetine on Task Engagement

A further indication of ATX's influence on behaviour is change in motivation. The effect of ATX on motivation was estimated by comparing the proportion of aborted trials between the treatment sessions and the control sessions. The proportion of aborted trials is a combination of the fixation, memory array, and retention breaks made; it makes up 4.6% of the total trials conducted in both session conditions and monkeys. Overall, the total number of aborted trials for

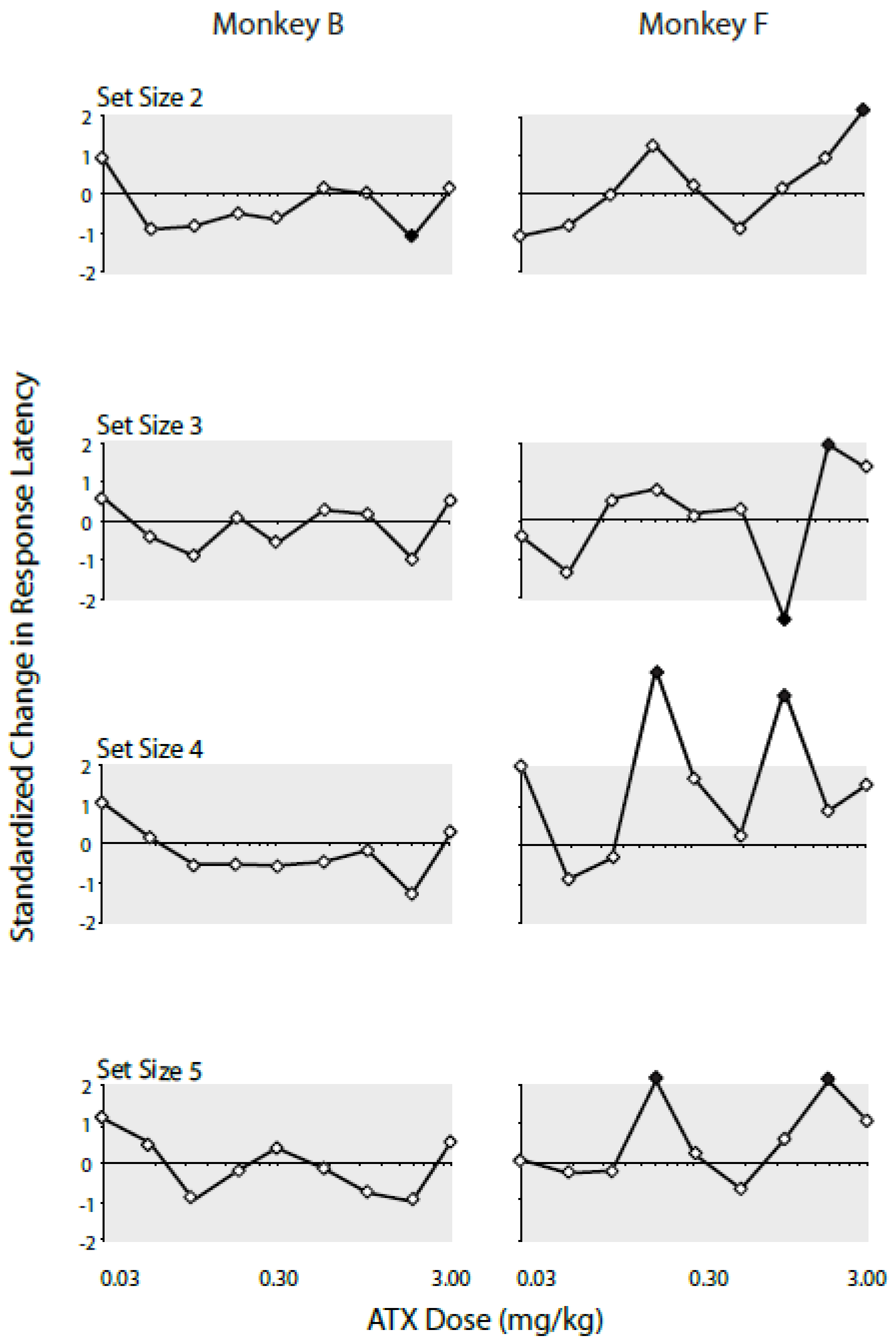

Figure 17: Response Latency per Set Size for Monkey B and F. Solid points indicate significant findings (χ^2, $p<0.05$). Grey boxes represent ± 2 standard deviations from the average control response latency.

each monkey was moderately decreased by ATX (Figure 18). Monkey B aborted 5.6% of trials following ATX administration compared to 7.4% in control sessions, reaching statistical significance (χ^2 test, p=0.00015, φ= 0.036). Monkey F aborted 2.5% and 3.1% of trials in treatment and control sessions, respectively. This difference in proportion just failed to reach statistical significance (χ^2 test, p=0.052, φ=0.019).

Similarly, the proportion of failed trial initiations was lower during treatment sessions than during control sessions in both monkeys. Monkey B failed to initiate 7.7% of control trials compared to 4.3% of treatment trials, reaching significance (χ^2 test, p<0.0001). In control sessions, Monkey F failed to initiate 8.7% of trials compared to 7.1% of trials in treatment sessions; this failed to reach significance (χ^2 test, p=0.10). These data indicate that ATX has a modest effect on motivation.

To supplement these data, performance on a visual progressive ratio task was assessed in both Monkey B and F, as well as Monkey D. Breakpoint scores varied considerably between the three animals, but were consistent on an individual basis across sessions. For each monkey, the average breakpoint score from eight control sessions was compared to the average score following a dose of 1.0 mg/kg of ATX. There were no distinct changes in these scores (Table 4). Administration of a range of ATX doses will be necessary to elucidate the parameters of this task. These results, in addition to the trial break and failed initiation analyses, provide a foundation for future research of ATX's effects on motivation in the NHP.

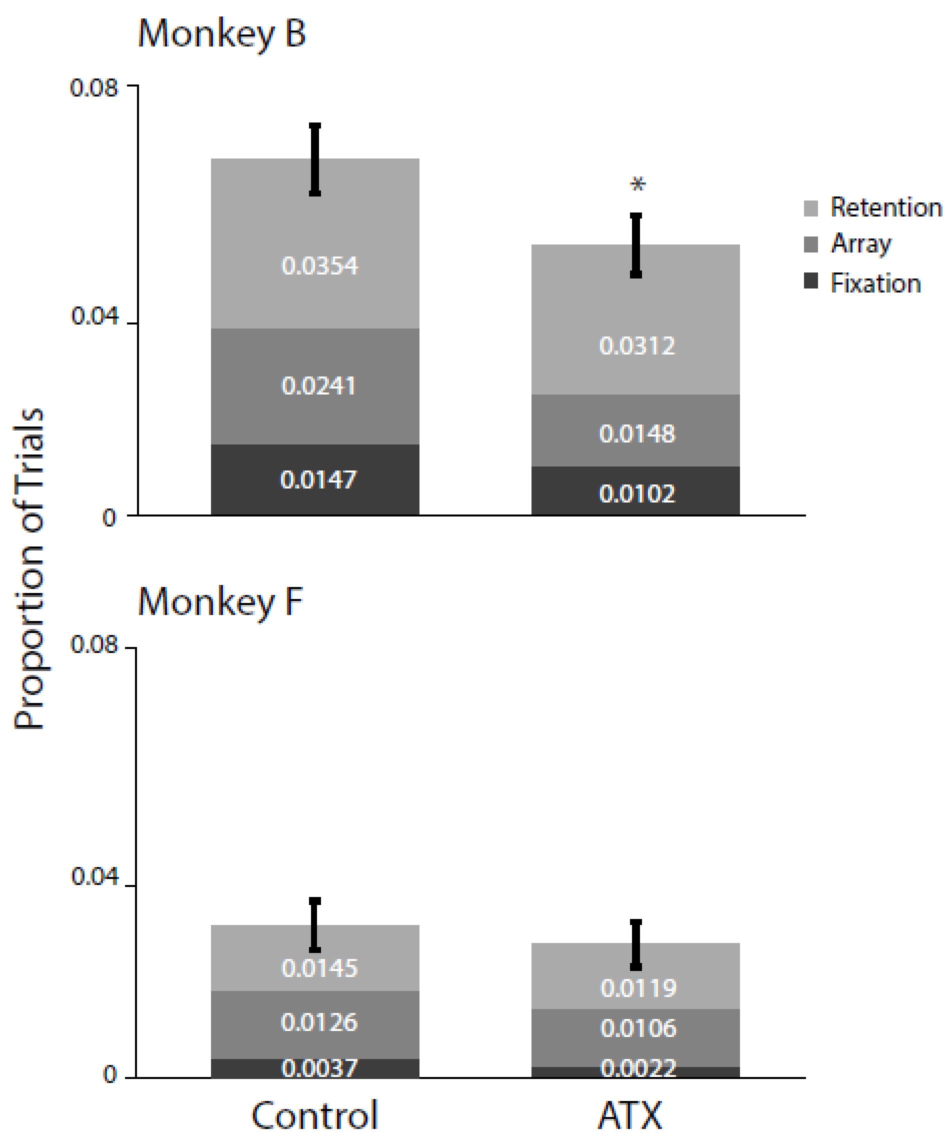

Figure 18: Proportion of Aborted Trials for Monkey B and F. The overall proportion of trials aborted per treatment and control session are plotted. Shading indicates the proportions of retention, array, and fixation breaks that make up each condition's total. Asterisk indicates significantly fewer breaks made in the treatment condition (χ^2, $p<0.05$).

Table 4: Visual Progressive Ratio Breakpoint Averages. The breakpoint average for 8 control sessions is shown with standard deviation (SD) for each monkey. The ATX column reports the average breakpoint value following a 1 mg/kg dose. Performance remained consistent within individuals.

	Control		**ATX**
	Average	SD	Average
Monkey B	12.5	2.8	13.7
Monkey D	9.9	4.0	9.3
Monkey F	4.8	1.3	5.3

Chapter 4 – Discussion

4.1 Results

Performance on a visual WM task was observed in two NHP following the acute administration of a wide range of doses of the catecholamine reuptake transporter inhibitor, ATX. Changes in performance on the delayed VSC task were within the variability of the control data and failed to present a dose- or memory load-dependent relationship. Both animals aborted fewer trials in treatment sessions, reaching statistical significance in one; this suggests a potential motivational effect of ATX. These results indicate that ATX does not directly influence WM ability in healthy subjects and introduce skepticism in the proposed catecholaminergic regulation of this cognitive process. Given data from catecholamine deficient models it is possible that the healthy model implemented in this thesis prevented an accurate analysis of ATX effects on cognition. Our control data shows that the animals' performance is variable and sub-optimal with room for improvement and yet, administration of ATX fails to maximize WM performance.

4.1.1 Effect of Atomoxetine on Response Accuracy

Atomoxetine did not have the hypothesized effect on delayed VSC task performance; the observed changes in response accuracy did not significantly improve accuracy relative to the control data. Varying the dose of ATX did not influence the performance on the task. Based on the therapeurtic application of ATX and its proposed influence on WM, ATX was expected to have an effect on WM in NHP. Our results are unexpected, but an interesting addition to the equivocal literature currently available.

Research assessing ATX's effects on WM performance in NHP models is limited. Preliminary work by Gamo et al. (2010) reported an improvement on a delayed response task in rhesus monkeys following optimal doses of ATX. Several doses were tested from 0.1-5.0 mg/kg and inverted-U shaped curves were reported in each animal. On the other hand, Bain et al. (2003) assessed the effects of a number of potential cognitive enhancers, including ATX, on NHP WM performance in a delayed match-to-sample task. Unlike the other drugs tested, ATX did not produce a significant change in accuracy on the task. Even administering the best doses of each individual did not appear to increase accuracy significantly (Bain et al., 2003). Both of these examples implement different WM tasks than what was used in the present experiment, possibly explaining the discrepancy across results. Additionally, the best dose analysis technique has been criticized; Soto et al. (2013) demonstrated that this method often leads to false positives. Thus, the above studies provide only equivocal evidence of ATX's effect on accuracy during WM tasks.

Due to its clinical application, a number of studies have assessed the efficacy of ATX in humans, both in individuals with ADHD and in healthy subjects. Again, these studies fail to agree on ATX's effect on WM ability. There are a number of inconsistencies across studies of humans with ADHD that makes comparison with this thesis challenging. Namely, the use of different tasks makes it difficult to draw parallels between studies because each task's assessment of WM is different and often incomplete. For example, Gau et al. (2010) and Ni et al. (2013) both used the spatial WM portion of the CANTAB and reported improvements in performance up to 10 and 12 weeks after daily ATX treatment, respectively, compared to the baseline performance collected at week 0. However, as this task specifically assesses spatial WM, studies using this task are not easily comparable to changes in performance on other WM tasks. For instance, tasks like the Rey complex figure test assess visual WM, while the WMTB-C uses 9 subtests to assess the central executive, phonological loop, and visuospatial sketchpad components of WM. Changes in visual WM following ATX administration are reported on a Rey complex figure test (Yang et al., 2012), while only changes in performance on the phonological loop subtests of the WMTB-C were reported in other studies (Sumner et al., 2009; Wietecha et al., 2013). The majority of these studies have reported an improvement in accuracy or a decrease in impairment on the various WM tasks implemented. Due to the inconsistency of these studies, their findings are difficult to apply beyond the ADHD population. Additionally, the majority of studies using individuals with ADHD are sub-chronic in design and implemented over inconsistent lengths of time. Improvements have been suggested after 6 months (Brown et al., 2009; Maziade et al., 2009) to as short as 4 weeks (Shang and Gau, 2012; Yang et al., 2012) after the start of ATX treatment. The administration of ATX in this thesis was acute, so while these examples suggest ATX enhances WM after a number of daily doses, it cannot be said that the present work falsifies this notion directly. Yet, an experiment by Chamberlain et al. (2007a) used an acute dose of ATX to assess WM in adults with ADHD and did not demonstrate an improvement in WM ability. On the contrary, an increase in error was reported in performance on a spatial WM task for both the ATX and placebo conditions compared to baseline. Adults with ADHD exhibited deficits in WM in comparison to the control group when given placebo; these deficiencies still remained after administration of ATX (Chamberlain et al., 2007a). Similarly, Cubillo et al. (2013) used fMRI in addition to an n-back WM task to assess performance in children with ADHD following an acute dose of ATX of 1 mg/kg. The study was placebo controlled and performance from treatment and placebo conditions was compared to an age-matched control group. An increase in dorsolateral PFC activation was observed, but this change did not transpire behaviourally within the children with ADHD (Cubillo et al., 2013). The data suggest the performance deficits were normalized relative to the healthy control group, but a dose of ATX did not significantly improve performance relative to the performance of the individual after placebo (Cubillo et al., 2013). It is possible that acute versus chronic administration is critical to the influence of ATX on WM ability; this distinction is likely implicated in the results of this thesis.

The studies mentioned above demonstrate an incomplete understanding of ATX in the disordered system, but the present thesis work investigates its effects in a healthy model. One study found that a single dose of ATX did not affect WM performance on a DMST in a group of healthy participants (Marquand et al., 2011). It should be noted, however, that the delay interval implemented in this particular study was 5 s; it is therefore possible that this task was not effective in assessing WM processing based on previous literature suggesting that a 1 s retention interval length is sufficient to assess WM (Luck, 2008; Luck and Vogel, 2013). The immense variability of the above research demonstrates the need for more, uniform. In particular, more research in healthy models would be valuable in elucidating WM processing.

4.1.2 Effect of Atomoxetine on Response Latency

The second measure of performance used to assess WM ability in this thesis was response latency on the delayed VSC task. The data revealed longer reaction times on incorrect trials in both control and treatment sessions, but a significant effect of ATX on response latency was not found. Thus, the hypothesis that an optimal dose of ATX shortens response latency on this task was not proven. Literature on ATX's effects on response latency is currently lacking, making it difficult to compare the data with previous findings. Bain et al. (2003) assessed the choice latency of NHP in a DMST task, which refers to the time it takes for the monkey to press the choice key after the presentation of the choice colours. There were no changes in choice latency observed in the ATX sessions (Bain et al. 2003). In children, Shang and Gau (2012) measured response latency on two memory tasks: a pattern recognition memory task (PRM) and a spatial recognition memory task (SRM). These tasks operate similarly to a DMST with a retention interval of 5s. Response latency was reported to shorten relative to baseline in both tasks during assessment 12 weeks later (Shang and Gau, 2012). The effect of ATX on response latency still requires attention; complete analysis of the present findings is limited given the lack of evidence to support or negate the data. However, given that the response latency data agrees with the response accuracy data it can be accepted that performance on the delayed VSC task was not influenced by ATX.

4.1.3 Effect of Atomoxetine on Task Engagement

Analysis of the number of aborted trials made by each animal provided supplementary data in the investigation of ATX effects; this reached statistical significance in one animal. A fewer number of trials were aborted in treatment sessions than in control sessions. Further, there were fewer failed trial initiations observed in treatment sessions than control sessions. Again, this reached statistical significance in one monkey. Our interpretation of the data suggests an increase in motivation following administration of ATX; however, these data could be representative of another process such as a decrease in impulsivity. Impulsivity can be described as behaving with little forethought or consideration of consequences and is associated with greater risk-taking behaviour. It is one of the core symptoms of ADHD, as well as neurodegenerative diseases (Stevens et al., 2002). In fact, ATX has been reported to improve performance on a response inhibition task in Parkinson’s patients (Ye et al., 2015) as well as in measures of impulsivity and risk-taking (Kehagia et al., 2014). While the VSC task does not test impulsivity specifically, making fewer trial abortions could be an indication of increased inhibition. To resolve this we implemented a novel variation of the progressive ratio task that is modified for use with our NHP to specifically assess motivation. An acute dose of 1 mg/kg did not influence performance on this visual progressive ratio task. This could be attributed to the novelty of the task, as discussed in section 4.3.3, or the lack of data as only one dose has been investigated thus far.

4.2 Variability between ATX and MPH

Previous work in this lab studied the effects of the catecholamine reuptake transporter inhibitor MPH on WM ability through the performance of three rhesus macaques on the delayed VSC task (Oemisch, 2012). The work presented in this thesis compliments this study by testing ATX, another catecholamine reuptake transporter inhibitor with similar actions as MPH. As mentioned in section 1.5, MPH has greater affinity for the NE receptors than for the DA receptors (Hannestad et al., 2010) and ATX has two-fold the affinity for the NE transporter than MPH does (Wong, 1989; Bymaster et al., 2002). Together, these studies build upon our understanding of the role of NE in WM processes.

Both of these drugs are commonly prescribed as treatment for ADHD; ATX has gained popularity as a non-stimulant alternative to the more common MPH. The differences in efficacy of these two drugs have been explored (Bymaster et al., 2002; Heal et al., 2004) as well as compared their effects on various cognitive processes. Gamo et al. (2010) suggested that both drugs enhance monkeys' performance on a manual delayed response task and exhibit dose-dependent relationships in an inverted-U manner. Despite the equivocality of the best dose analysis discussed earlier, the preliminary findings report an apparent improvement in performance compared to vehicle control performance. Using fMRI, Cubillo et al. (2013) imaged children with ADHD following administration of ATX, MPH, or placebo and compared this to images of a control group of healthy children. WM performance was assessed simultaneously on an n-back task. Performance accuracy did not differ significantly between the 3 conditions or from the performance of the healthy control participants. However, drug specific differences in activation during performance on the task were observed. An increase in right dorsolateral PFC activation was greater in the ATX condition than in the MPH condition, whereas MPH caused an increase in the left inferior frontal cortex relative to ATX and control conditions (Cubillo et al., 2013). These results imply that the drugs act differently on the catecholaminergic system underlying cognition (Cubillo et al., 2013). Furthermore, daily doses of ATX were reported to improve performance on a Stroop task and a Wisconsin card sorting task overtime, yet improvements observed following daily MPH administration were greater (Yildiz et al., 2011). ATX and MPH have been reported to similarly effect WM and cognition, but the means of achieving these effects appear to differ.

Similar to our findings of ATX, Oemisch (2012) found nonsignificant changes in response accuracy and latency following MPH administration; a dose-dependent relationship between MPH and performance on the delayed VSC task was not observed. Interestingly, there was a positive, dose-independent association between MPH and the proportion of aborted trials. Fewer trials were aborted following MPH administration, reaching statistical significance in one of three monkeys. In children with ADHD, Chelonis et al. (2011) compared performance on a progressive ratio task after a dose of MPH and without a dose; MPH significantly raised the breakpoint suggesting an increase in motivation. The current study introduced a visual adaptation of the progressive ratio task to supplement the findings of enhanced motivation. To further support the motivational effects observed in the work by Oemisch (2012), animals could be tested on this novel paradigm following MPH administration. The present findings and development of the visual progressive ratio task open the window for future research on the effects of ATX and MPH. It is imperative that the potential motivational effects of these drugs be considered in past and future experimental efforts because of the close link between motivation and greater cognitive processes. The motivation of an individual likely effects their willingness to complete a task at hand and thus, interpretation of WM performance needs to be cautious of motivational contributions. Testing motivation specifically, such as with the progressive ratio task, can provide insight on how great of an impact motivation may have on behaviour.

4.2.1 Catecholaminergic Influence on Working Memory

Various studies have demonstrated the contribution of DA and NE to WM ability in rodents, NHP, and humans. Increases in DA and/or NE have been suggested to improve performance on WM tasks, while decreases have been associated with a decline in performance. Administration of the catecholamine reuptake transporter inhibitors MPH or ATX is expected to influence WM performance in a dose-dependent manner by enhancing the neurotransmission of DA and NE. Despite a collection of research supporting these hypotheses, the data from this thesis and Oemisch (2012) did not reveal the expected inverted-U function or any dose-dependent relationships. The combination of the results from these projects put into question the long-held belief of a catecholaminergic contribution to cognition, specifically WM.

Previous research by Brozoski et al. (1979) established a role for catecholamines, specifically DA, in WM ability by chemically depleting the concentration of DA and NE in the NHP brain. This created an impairment in performance on a delayed alternation task akin to ablation of the PFC. Likewise, administration of receptor antagonists for DA and NE causes a decline in performance (Sawaguchi and Goldman-Rakic, 1991). From this came the presumption that performance can be improved by increasing the levels of these catecholamines. However, the majority of research that claims an improvement in WM performance following an increase in DA or NE neurotransmission are conducted in catecholamine-depleted models.

For instance, administration of the DA agonist L-DOPA was reported to reverse the depletion-induced impairment in WM performance (Brozoski et al., 1979). Interestingly, the agonist did not improve performance above baseline (Brozoski et al., 1979). Administration of α2 adrenergic agonists improved performance on a delayed response task in aged rhesus macaques (Arnsten and Goldman-Rakic, 1985; 1988). Yet, natural catecholamine depletion is reported in aged animals as a result of a significant reduction in catecholamine synthesis (Goldman-Rakic and Brown, 1981). Even an apparent improvement of delayed response task performance following administration of an α2 adrenergic agonist in young rhesus macaques is a demonstration of a depleted model as the animals first underwent chronic treatment of reserpine, a catecholamine-depleting agent (Cai et al., 1993). Mizoguchi et al. (2000) induced DA depletion in a rat model of stress and found that administration of a D1 receptor agonist rescued the induced spatial WM deficits. These models provide essential insight to the clinical population, but are not comparable to the healthy model implemented in this thesis and fail to address the extent of catecholaminergic contribution to cognition.

In healthy humans, Muller et al. (1998) reported an improvement in visuospatial WM performance on a delayed matching task following administration of a D1/D2 receptor agonist. However, there is also evidence that DA or NE agonists have no effect or the opposite effect on WM performance in healthy models. For instance, one study suggests an α2 adrenergic receptor agonist has no effect on various WM tasks in healthy humans (Muller et al., 2005). While over stimulation of DA receptors in the PFC impairs performance on a delayed alternation task in healthy rats (Zahrt et al., 1997). Administration of a D1 receptor agonist caused a dose-dependent impairment in task performance that was actually reversed by a D1 receptor antagonist (Zahrt et al., 1997). That being said, an improvement in delayed response performance was reported in young NHP following high doses of an α2 agonist, while low doses had no effect (Franowicz and Arnsten, 1998; 1999). Overall, there is evidence to suggest that WM impairment can be ameliorated by reversing catecholamine depletion; whether performance can be improved in a healthy model remains equivocal.

It is evident that ATX and MPH increase the concentrations of NE and DA in cognitively critical regions of the brain (Bymaster et al., 2002; Koda et al., 2010). However, if this does not translate into behavioural changes in WM performance, it could be an indication that increasing the concentration of DA and NE above healthy levels has little to no impact on cognition. The studies discussed bring into question the precise role of DA and NE in cognition and highlight discrepancies between healthy and impaired or depleted systems.

4.2.2 Clinical Applications

Due to its modulatory effects on DA and NE, ATX could be a potential treatment for PD, AD, Huntington disease, and schizophrenia, all of which can have accompanying WM impairments. These illnesses are associated with catecholamine impairment, namely depletion of DA and NE, such that administration of a catecholamine reuptake transporter inhibitor could potentially improve deficits of the disorders including WM.

However, few pilot studies have actually been conducted to investigate the potential therapeutic effects of ATX in these patient groups. One study administered an increasing dose of

ATX (25-100 mg/day) to individuals with PD and assessed behaviour on various scales of executive function over 8 weeks (Marsh et al., 2009). A decrease in executive dysfunction in 75% of individuals favoured the use of ATX as treatment for PD, but further study is necessary to establish the specifics of this apparent improvement (Marsh et al., 2009). Investigation of ATX's effects on the depressive symptoms of PD revealed an improvement in global cognition, but the assessment did not address WM specifically (Weintraub et al., 2010). Despite these clinical studies, amelioration of WM deficits in PD through ATX remains undefined (for review see Connolly and Lang, 2014). ATX is also a candidate for treatment of AD given the link between many of the symptoms of AD and NE deficiencies (Chalermpalanupap et al., 2013), however there is a lack of research investigating this. A placebo trial conducted in patients with mild-to-moderate AD assessed general cognitive performance with the Alzheimer's disease Assessment Scale – Cognitive Portion (ADAS-Cog) 6 months after daily doses of ATX (25-80 mg/day), but found no significant cognitive changes compared to baseline (Mobs et al., 2009). Similarly, a study in patients with Huntington disease failed to report any cognitive improvements, including WM, following a dose of 80 mg daily for 10 weeks (Beglinger et al., 2009). Literature in the schizophrenic population is equally as limited; daily doses of 80 mg over 8 weeks failed to improve WM or general cognition (Friedman et al., 2008; Kelly et al., 2009). fMRI analysis was implemented by Friedman et al. (2008) to investigate the neural mechanisms at play; this revealed an increase in WM-related activity, but was not supported behaviourally.

These initial investigations failed to support the therapeutic use of ATX in these clinical populations, despite its actions on DA and NE concentrations in the brain. The number of studies conducted in these patient groups is not sufficient enough to interpret ATX's effects. Interestingly, the doses administered in these trials were higher than those typically assessed in

ADHD studies (including those treating adults). Negative findings ceased investigations of ATX therapy in PD, AD, Huntington disease, and schizophrenic populations; however, implementation of wider dose ranges may provide powerful insight into the use and neural actions of ATX.

4.3 Limitations

Although similar conclusions were drawn using the catecholamine reuptake transporter inhibitor MPH, the negative results obtained from these experiments could have been influenced by several factors. Based on the discrepancies between this work and earlier studies, limitations in methodology and interpretation are present.

4.3.1 Methodology

Each treatment session in this study began with the oral administration of a randomly designated dose of atomoxetine. The precise pharmacokinetics of ATX in the rhesus macaque are not fully understood; because of this the design of the experiment is a combination of methods from previous ATX research in NHP and data collected in humans and rodents. One concern due to the limited pharmacokinetic data available is the uncertainty that ATX has effectively entered the system. The present study orally administered each dose of ATX in a 10 mL vehicle of juice, whereas other studies using animal models utilized more direct methods such as intravenous (Seneca et al., 2006; Takano et al., 2009), intramuscular (Bain et al., 2003), and intraperitoneal (Bymaster et al., 2002) injections. However, oral administration is better aligned with the clinical use of this medication as humans are prescribed ATX in capsule form. The concern with oral administration is that the animal will attempt to reject the bitter taste of the higher doses (1.0-3.0

mg/kg) making it challenging to ensure the entire dose is adequately ingested. In spite of the lack of effects on WM performance, the effect of ATX on task engagement in this thesis provide evidence that ingestion was successful. An important consideration of systemic administration is that ATX is distributed throughout the entire brain and not just in regions specific to WM processing. This causes an increase in catecholamine concentrations throughout the brain and as a result, it cannot be said that WM is studied exclusively; this is evident by the observed effects on task engagement.

Another methodological limitation is the 30 minutes between the administration of the dose and the start of the paradigm which was implemented to allow data to be collected during the peak blood concentration of ATX. However, the pharmacokinetics measured in humans indicate a C_{max} of ATX that ranges from 1-3 hours post-administration, averaging at 2 hours (Witcher et al., 2003; Sauer et al., 2005). Mattiuz et al. (2005) reported a peak blood concentration of 2 hours in rodents and 1.3 hours in dogs. In the literature, the period of time between testing and initial administration varies considerably. In some studies, human participants were asked to wait 1.5 hours before behavioural testing began following the acute administration of ATX (Cubillo et al., 2013; Chamberlain et al., 2007a). In rhesus macaques, Gamo et al. (2010) orally administered ATX 60 minutes before testing, while Bain et al. (2003) only waited 10 minutes following intramuscular injection. With a lack of data on the peak blood concentration of ATX in NHP, it is possible that data collection in the present study was premature; implementing a longer time between drug administration and task initiation may more accurately demonstrate the effects of ATX. If this were the case, ATX would be expected to cause a change in performance later in the session. However, we observed consistent performance overtime in the treatment sessions, suggesting that the timing chosen for our experiments was appropriate. In addition, data suggest that food intake may delay the maximum plasma concentration by 3 hours (Sauer et al., 2005). Unrestricted access to food poses a challenge to monitoring when animals are eating; coordinating feeding with experimental sessions may prove influential on the effects of ATX in NHP.

To rectify these discrepancies, we compared the heart rate (HR) of Monkey F during control sessions with the HR following administration of 1 mg/kg dose of ATX. It has been previously reported that a single dose of ATX produces a slight increase in HR in humans (Kelly et al. 2005; Chamberlain et al., 2007b). Other studies, however, have suggested no effect or a decrease in HR following ATX (see for review Awudu and Besag, 2014). Our HR experiment did not reveal a significant change in HR after administration of ATX. A blood plasma analysis would have provided conclusive evidence of the pharmacokinetics following oral administration, but was not a feasible option for this thesis project.

4.3.2 Age, Health and Sex Effects

It is also possible that ATX did not produce a perceivable change in performance because of the animal models used. It is assumed that these middle-aged monkeys have unimpaired catecholaminergic systems. It has been suggested that the efficacy of ATX is influenced by the concentration of catecholamines, whereby only the depleted system benefits from the actions of these drugs. For example, DA antagonists have been reported to reduce WM performance in juvenile monkeys, but had little or no effect in aged monkeys with natural catecholamine depletion (Arnsten et al., 1994). Additionally, DA agonists have been reported to enhance WM in a depleted model (Arnsten et al., 1994; Cai and Arnsten, 1997), but had little influence on juvenile or healthy models (Arnsten et al., 1994). Likewise, spatial WM performance reportedly improved in aged NHP with a lower dose than in young animals (Gamo et al., 2010). In this respect, the changes observed in studies of humans with ADHD compared to the lack of change in healthy human participants could be influenced by the catecholaminergic disruption that occurs with ADHD. Based on this literature it is possible that using healthy, middle aged NHP limited the outcome of the current experiment.

Furthermore, using all female animals introduces hormones as a variable. Some research suggests that there is an association between estrogen levels and cognition. In humans it has been claimed that higher levels of estrogen correlated with fewer errors on a spatial WM task (Luine, 2014). In rhesus macaques, exogenous estrogen was reported to improve spatial WM performance in adolescent females (Golub et al., 2004) as well as aged, ovariectomized females (Rapp et al., 2003). On the other hand, Baxter et al. (2013) found that hormone therapy did not improve performance in ovariectomized rhesus macaques. In the present study, control data were collected the day before treatment sessions providing a control for cycling hormone levels. Any shift in performance as a result of hormone changes would have also been evident in the control data. Since the changes in performance during treatment sessions were within the variability of the control sessions it is unlikely that cycling hormone levels influenced the data in this study.

4.3.3 Motivation

Determining the proportion of trials that the monkey attempts but does not complete is only suggestive of motivation. Typically, motivation research uses a specific task to assess motivational effects such as the progressive ratio task (Hodos, 1961). A modified form of the progressive ratio task was implemented in this thesis to support the reported findings from the delayed VSC task. The visual design makes it easier to compare the data with the aborted trial data obtained on the delayed VSC task. In this thesis project an acute dose of 1 mg/kg was administered to three NHP thirty minutes prior to performing the visual progressive ratio task. The lack of performance changes between conditions could be attributed to the peak concentration of ATX. As discussed above, the precise pharmacokinetics of ATX in NHP are not explicitly known. The visual progressive ratio task is completed in a short time span; therefore, it is possible that ATX had not reached its peak concentration during this period of time. On the other hand, an hour of performance on the delayed VSC task was analysed to procure the trial break data. Performing the task for longer, increasing the interval between drug administration and task initiation, and testing a range of doses could all influence the outcome of progressive ratio task performance.

Additionally, the use of this task is novel. There is no study to date that investigates the effects of ATX on performance on the spatial progressive ratio task, posing challenges in interpretation of the data. However, Von Huben et al. (2006) found that administration of D1 and D2 receptor antagonists reduced performance on a progressive ratio task suggesting that a decline in DA concentration impairs motivation for reward. Thus, it can be inferred that an increase in available DA would enhance performance on this task. Further experiments will be necessary to elucidate the effectiveness of this task in assessing motivation.

4.4 Final Thoughts

4.4.1 Future Directions

Given the weaknesses discussed above, the current model can be adjusted to extend the validity of the data. A future study may consider investigating the pharmacokinetics of ATX in the NHP model to better design future projects on catecholamine reuptake transporter inhibitors. Further analysis of blood pressure, heart rate, and especially blood plasma concentration would provide evidence that ATX has entered the system and would further support the current findings.

Extension of the motivation experiment should assess performance on the visual progressive ratio task following a range of MPH and ATX doses, supplementing the data collected by Oemisch (2012) and exploring the role that NE reuptake transporter inhibitors have on motivation. In addition, the progressive ratio task can be used to assess the limits of the motivational potential of a drug. Spinelli et al. (2004) described this assessment as a “filter test” whereby various doses of the drug are administered to reveal if a particular dose enhances or weakens motivation more than another. It is important to investigate the motivational potential of ATX and MPH to gain a better understanding of the processes these drugs act on.

It would be interesting to extend the temporal state of the current experimental design by administering a dose of ATX on a regular basis. The majority of ATX research conducted in humans uses daily doses to replicate the drug’s medical use making it difficult to compare the negative findings of this thesis project with the positive findings of daily doses. Is there a benefit from taking ATX daily that is unobservable after a single dose? Performance data from the same task and following the same experimental procedures would reveal the differences and similarities of these dosing schedules.

Likewise, it quickly became apparent that the majority of research on ATX is conducted in individuals with ADHD. Considering data that suggests the effects of ATX are greater in the impaired system, the use of a healthy animal model may be a disadvantage. A future study in rhesus macaques could deplete the system of DA and NE prior to administering ATX to mimic an impaired system. This can be established by administering antagonists for DA or NE receptors, or by conducting these experiments in aged animals with naturally depleted levels of catecholamines (Goldman-Rakic and Brown, 1981; Moore et al., 2005). Alternatively, blocking the mechanism further down the signal cascade by an NMDA receptor antagonist would also create a WM impaired condition. In fact, administration of the NMDA receptor antagonist ketamine has been shown to impair WM performance on the delayed VSC task in rhesus macaques (Heyselaar et al., 2011). Incorporating ketamine into our experiment to create a WM deficit could further explore ATX's ability to ameliorate performance deficits.

4.4.2 Conclusion

In brief, the above results do not support the proposed hypothesis of this thesis. Acute oral administration of atomoxetine failed to produce dose- and memory-load dependent changes in performance on a delayed VSC task. This task effectively tests working memory while limiting the interference of other cognitive processes; because of this, we are certain that WM has been successfully assessed and can conclude that ATX did not affect NHP performance in this task. Alternatively, our experiments revealed a potential increase in task motivation as a result of ATX administration. This observation led to the innovation of a visual progressive ratio task, a novel task designed to visually assess motivation using the same apparatuses implemented for the VSC task. The extent to which catecholamine reuptake transporter inhibitors correct or enhance cognition remains equivocal; the combined results of this thesis and that of Oemisch (2012) indicate that catecholamines play only an indirect role on WM in the healthy system. These results highlight the need for further research on the influence of catecholamines in both the functional and dysfunctional system and should encourage the continued investigation of the catecholaminergic properties of cognition, including working memory.

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