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THE ROLE OF ACETYLCHOLINE IN ATTENTION AND LAPSES IN ATTENTION IN RATS USING THE MODE AND DEVIATION FROM MODE OF REACTION TIME LATENCY

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ABSTRACT

Attention Deficit-Hyperactivity Disorder (ADHD) is currently the neurodevelopmental disorder most commonly diagnosed in children in the United States, and one of the defining characteristics of ADHD is inattention. Inattention is marked by increased lapses in attention, and when assessed clinically, it has been highly correlated with reaction-time variability (RTV). Evidence from the human/clinical literature has shown an inherently higher RTV to be the primary quantitative indicator of an ADHD diagnosis.

Reaction-time distributions are characterized by an asymmetrical rightward skew, and because of the prevalence of this presentation, it has been theorized that the distribution peak and skew represent separate phenomena, or attention and lapses in attention respectively. By separating out the motor component of reaction time and employing parameters that closely parallel those used in clinical assessments of attention, the two-choice serial reaction time task (2-CSRTT) yields a measure in rodents, initiation time (IT), akin to human reaction time. Similar to the analysis of human reaction time using an ex-Gaussian approach, the peak and skew of IT distributions can be dissociated and separately analyzed using the mode and deviation from mode (distribution mean minus the mode), thus rendering a rodent variability measure indicative of lapses in attention.

The effects of attentional stress are cumulative and can be induced via manipulations of both environmental and external factors. The current studies utilized both by decreasing signal salience and blocking the neurotransmitter, acetylcholine. Additionally, in order to separate high performing rats from low performers, a median split based on training IT devmode was

introduced as a third independent variable. Lapses significantly increased when salience was reduced but remained unaffected by scopolamine HBr for all rats, as no main effect of baseline performance was observed following the median split. However, a three-way interaction effect was observed and under less salient conditions, lapses in attention increased for low performing rats following the blockade of acetylcholine transmission. The current findings, therefore, implicate acetylcholine in the facilitation and regulation of higher order attentional processes, such as sustaining attention and maintaining vigilance, and indicate an increased sensitivity to attentional stress in low performers.

DEDICATION

"We will get there when we get there." Well, Slothy, it looks like we've arrived. You are my world, Parker, and having you here with me to see this through has meant more to me than you will ever know. I love you.

LIST OF ABBREVIATIONS AND SYMBOLS

2-CSRTT	Two-choice serial reaction time task
5-CSRTT	Five-choice serial reaction time task
ACh	Acetylcholine
ADHD	Attention Deficit-Hyperactivity Disorder
CPT	Continuous performance test of attention
DevMode	Deviation from mode
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FC	Foot-candle
HV	High variability
IIV	Intra-individual variability
IP	Intraparietal
IT	Initiation time
LV	Low variability
Mg/kg	Milligrams per kilogram
MT	Movement time
PVC	Polyvinyl chloride
RT	Reaction time
RTV	Reaction-time variability
SC	Subcutaneous

Scop HBr	Scopolamine hydrobromide
Scop MBr	Scopolamine methylbromide
SDT	Signal detection tasks

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I. INTRODUCTION

Mechanisms of attention have evolved as a means to filter out irrelevant information and focus energy on signals most relevant to immediate and ongoing goals (Chun et al., 2011). Attention, or more specifically visual-spatial attention, is operationally defined as the processes by which sensory input is organized and actively processed, and the manner in which motor control output behavior is coordinated and executed (Robbins et al., 1998; Arnold et al., 2003). Attention is not a singular mechanism, but rather it is the sum of sensory-perceptual, executive, and motor functions that work in parallel from both the bottom-up (exogenous) and the top-down (endogenous). When attention is activated, afferent events such as sensory transduction, lens adjustment, and lens accommodation occur peripherally. Central sensory events, such as detection and discrimination, then align or direct attention towards stimuli via the visual cortices. Once sensory processing of the signal occurs, information concerning both the stimulus and the environment is integrated with existing knowledge to determine relevance, resulting in an appropriate response formation. This response formation is dependent on executive functions such as working memory, attentional modulation, and vigilance (Arnold et al., 2003). Finally, the response is processed through central motor cortices and carried out via efferent projections to muscle targets. When successful, attention allows for the dynamic routing of sensory and environmental information to guide decisions and behavior, and successful completion of all events yields quantifiable measures indicating the ability to direct attention (i.e., how quickly and accurately a single response can be executed (Rosenblith & Vidale, 1962).

Visual-Spatial Attention

The study of attention helped birth and define the field of experimental psychology, and these early studies proposed two independent but parallel types of processing, external (exogenous) and internal (endogenous), which serve to direct and focus attention. Exogenous attention is an involuntary, reflexive system that is driven from the bottom-up and is dependent on the parameters of a given stimulus or environment, while endogenous attention is a volitional process that reflects to the ability to consciously monitor and transiently refine information at a given location (Carrasco, 2011). Endogenous attention is voluntary, cognitive, and goal-driven, and it occurs from the top-down in order to continuously update processing systems of attention. Although these attentional controls operate independently, they are inherently interdependent, since information about the signal or environment cannot be modulated endogenously until it is first detected, filtered, and passed along from the bottom-up. In return, top-down attentional control facilitates sensory processing throughout cortex, even changing the qualia of how attended objects are perceived (Carrasco et al., 2004).

Exogenous Attention

Exogenous or bottom-up attention is transient and dependent on the parameters of a given signal, and it serves to facilitate early attentional processes, such as detection, discrimination, and covert orienting. Collectively, this facilitation is referred to as "signal processing, and it represents the average neural conduction velocity including synaptic delays in the sensory and association pathways of the cerebral hemispheres. Signal detection is defined as the entry of information concerning the presence of a signal into a system that allows the subject to report its existence by an arbitrary response indicated by the experimenter (Posner, 1980, Bushnell, 1998). The ability to distinguish between the target signal from background

information or between the target and a secondary signal is known as discrimination. The final stage of signal processing, covert orienting, is defined as the unconscious aligning of sensory and central attentional systems with an input source and indicates that the signal has been detected (Posner, 1980; Bushnell, 1998). Orienting is the shifting of focus from one location to another, and when covert, it occurs in the absence of eye movement(s). For example, when eye focus is forward and a target stimulus is presented within the visual field. By governing attention to particular locations, covert orienting can potentially affect the output of perceptual processes; however, it does not influence the information that is processed by the senses (Posner et al., 1980).

Together, these processes determine the subsequent control the signal has on continuous cognitive and behavioral activity (Posner et al., 1980). It should be noted that, within the experimental literature, "signal detection" and "signal processing" are often used interchangeably (Bushnell, 1998). Also, when measured behaviorally, signal processing includes a motor response but excludes higher-cognitive functions associated with endogenous attention (Hasselmo & Sarter, 2011).

Endogenous Attention

Acting as a gating mechanism endogenous or top-down attention assesses and filters cues in order to ascertain importance and, in concert with sensory processes and bottom-up control, limits what information is further processed. Endogenous attention is driven from the "top-down" by individual and situational, rather than by environmental signal-driven factors. Attentional processing operates in a flexible and dynamic manner, and it is endogenous processing that allows for the conscious direction and maintenance of attention. Once a signal has been selected and attended, higher-order cognitive functions such as motivation, allocation,

modulation, vigilance, and working memory operate in parallel to continuously update information concerning the signal, environment, and individual state in order to maintain attention (Posner, 1980).

Selective Attention. Allocation, or focus, is the ability to consciously direct attention in order to achieve a goal, which is necessary in order to orient to and select where attention will be paid. Since it is common for multiple stimuli to simultaneously compete for attention, selection is critical to the success of attention. Whereas orienting is covert when attention is driven from the bottom-up, overt orienting guides selection from the top-down and aides in the facilitation of decision making by biasing attention towards the most relevant stimuli. Overt orienting is the conscious act of selectively attending to a specific location, as indicated by controlled eye movements, which are relatively slow and voluntary. These differ from reflexive eye movements, which are fast and activated by the sudden appearance of stimuli (Posner et al., 1980).

Because top-down processing is an executive-based function, other higher-order processes and behaviors, such as inhibition, motivation, and working memory influence selection indirectly via endogenous control. For example, if more than one possible response option exists, behavioral inhibition stops competing responses from interfering with the execution of the correct response. Selecting a memory from competing memories also facilitates the biasing of allocation. When tasks or environments are more complicated, working memory holds information concerning the signal, environment, and response for comparison to new information, which allows for the adjustment of attention and subsequent behaviors in real time (Posner, 1980; Bushnell, 1998). Motivation helps to determine the relevancy and value of a signal. Subjects who are uninterested in the environment or apathetic will not be as vigilant as

those with high motivation (Robbins et al., 1998; Oken et al., 2006). Performing a task with a high value reward for performance will engage the attentional system stronger and with longer duration than performing the same task with no overt reward for performance; therefore, conceptually, effort and motivation are related.

Sustained Attention. Another top-down process, vigilance, is dependent on the successful modulation of attention and refers to the ability to focus attention over extended periods of time. When vigilance is successfully maintained, it functions to resist distractions, both internal and external, and keep attention focused on the goal (Muir, 1996; Sarter et al., 2001; Hasslemo, 2011). In an experimental setting, vigilance is relevant to a single trial and is maintained trial-by-trial in order to consciously direct a response towards a reward (Robertson et al., 2003; Carrasco, 2011). The collective success in the execution and maintenance of attentional processing, including vigilance, is known as sustained attention. It includes the ability to focus and maintain visual-spatial attention over a relatively long period of time, and it represents the degree to which distractions, both experimental and non-experimental, can be resisted as indicated by a continuous behavioral response (Muir, 1996).

It is important to note that definitions of attention and attentional subcomponents vary within and across individual psychological disciplines. For example, the definition of "sustained attention" varies substantially between studies, even in the same literature, and it is not uncommon for the terms "sustained attention" and "vigilance" to be used interchangeably, and when they are, the ability to sustain attention is brief and relevant only to the immediate goal (Oken et al., 2006). However, other the studies define sustained attention as the ability to repeatedly direct and maintain attention over a testing session or repeated trials (Bushnell, 1998, 2009; Chudasama, 2011). For the proposed dissertation, sustained attention is operationally

defined as the process of maintaining conscious stimulus processing and readiness over a period of time. While vigilance is the transient focus of attention, sustained attention operates on a longer time course. Based on these criteria, a failure in vigilance will always result in a failure to sustain attention, but a failure to sustain attention may not necessarily be attributed to failed vigilance.

Limiting Factors

Attentional control and processing are limited by factors such as resource competition, resource availability, biasing, and capacity (Chun et al., 2011; Tamm et al., 2012). Complex behaviors and/or higher order cognitive processes such as attention are not determined by a single brain region that is clearly defined and whose sole function is a specific cognitive domain; rather, they are initiated by the synchronized activity of a widespread neuronal networks (Hasselmo & Sarter, 2011). The same cortical region can be used for multiple cognitive functions, so if a particular area or system is needed for attention and that system is previously engaged by another function, resource competition will slow attention-specific processing. Slowing will also occur once the processing capacity is reached and/or central cognitive resources have been depleted, resulting in a breakdown of attentional functioning. When attention is no longer directed towards the goal, a detectable signal will not be perceived or perception will be delayed, and a failure to sustain attention or a lapse in attention will be observed.

The endogenous facilitation of attention depends on the ability to internally represent information about the signal, such as location, timing, and brightness (Posner, 1980). Existing knowledge, beliefs, goals, and expectations are collectively known as “attentional sets”, and these sets define the representations involved in the selection of goal relevant stimuli and

responses. They create bias, which can in turn alter the speed and accuracy of the processes that select meaningful or desired information. Attentional sets can be subdivided into perceptual and motor components. Perceptual sets consist of all that is known about the task, environment, and cognitive requirements. These sets aid in modulation and the efficiency of processing via selection by updating and maintaining mental representations of relevant information regarding immediate goals. Motor sets consist of all this is known about necessary movements required for successful responding, and a response is more likely to be executed quickly when the needed movements are known in advance (Corbetta & Shulman, 2002; Thiele & Bellgrove, 2018).

Exhaustion is not an "all or nothing" event, but rather a fluid process with a gradual decline, and once either or both are sufficiently stressed, decrements in performance will be observed (Castellanos et al., 2005; Buzy et al., 2009). This is known as the overload or resource depletion hypothesis, and it is theorized to occur because individuals expend resources for maintaining attention at a rate faster than they can be replenished (Parasuraman et al., 1987). When resources become too low, there is insufficient attention directed toward the task, resulting in a reduced ability to detect critical target events. Capacity, however, varies between individuals, so, although a lower inherent processing capacity may be reflected in vigilance decrements, experimental effects are not always universally observed (Castellanos et al., 2005; Tamm et al., 2012). Another theory of load attribution posits that performance decline is the result of a lack of stimulation, resulting in an unconscious drift of attention away from the perceptual input. This is known as the "mindlessness hypothesis". Often times, situations in which attention must be sustained for long periods are often monotonous and under stimulating. When this is the case, attention will begin to wander from the perceptual input from the incoming stimulus and the likelihood of distraction increases.

The ability to maintain focus over the course of time is inherently challenging and requires a considerable amount of mental effort. Sustained attention has been shown to be a function of task duration, with attentional performance deteriorating as the time needed for vigilance increases (Parasuraman, 1979). Additionally, the cognitive load, or attentional effort required for success, and inherent limitations of processing capacity have been shown to also affect performance (McGaughy et al., 1996, Parasuraman et al., 1987). This phenomenon, known as vigilance decrement, is formally defined as "deterioration in the ability to remain vigilant for critical signals with time, as indicated by a decline in the rate of the correct detection of signals" (Parasuraman, 1979), and due to the relationship between time and performance, decrements will occur more often towards the end of a long testing session (Parasuraman, 1979; McGaughy & Sarter, 1995; Robbins, 2002). Capacity varies between individuals, however, so effects are not always universally observed even under identical conditions (Castellanos et al., 2005; Tamm et al., 2012).

Lapses in Attention

At any given moment, the amount of environmental information available for processing far outweighs the amount that can be effectively processed, and while internal factors ceaselessly compete for control, countless stimuli must be detected and sorted in order to successfully navigate daily situations and environments. Failures in the complete processing of this information are commonly referred to as absentmindedness, daydreaming, or "zoning out", but formally they are defined as "short-term changes in behavior that signal moment-to-moment fluctuations in task performance and impair goal directed behaviors" (Cheyne et al., 2006; Buzy et al., 2009). Lapses are infrequent failures in endogenous attention that, because of a momentary

failure to attend to task relevant features, result in actions that are intended but not executed (Buzy et al., 2009).

II. LITERATURE REVIEW

Within a given environment, there are a multitude of stimuli that can potentially be perceived, and it is attention that allows for their filtration and assessment. Attention is not a singular function, but rather an aggregate of interdependent external and internal sub-processes that serve to optimize stimulus detection, discrimination, processing, and responding. Information about the world is transduced by the nervous system and is processed by salience filters that respond differentially to infrequent or important stimuli. Attention also serves to facilitate the processing of stimulus characteristics that are deemed important, such as location and modality, via "top-down tuning" of sensory systems. Cognitive and neural representations in various hierarchies encode information about movements, memories, emotional states, and goals. These help establish biases and expectancies, which allow for more efficient processing. A competitive, bottom-up process selects the representation with the highest signal strength for entry into the circuitry that underlies attention and related cognitive processes (Knudson, 2007). In turn, these processes then direct top-down bias signals that modulate the sensitivity of the representations that are being processed. When all attentional functions are successful, an environmental cue can be detected, assessed, and processed, which in turn allows attention to be directed and focused. Attention is also a crucial step in the successful transfer of stimulus information to higher cognitive processing, such as learning and memory (Arnold et al., 2003).

It is theorized that the capacity to sustain attention over a period of time is limited. Therefore, if a task requirement places higher demands on attentional processes, the less time will be needed to exhaust attentional resources and a decrement in attentional performance will be observed more quickly. It is also generally agreed upon that attention is sustained through the allocation of processing resources, and these resources are theorized to be limited (Kruschke, 2003*)*. Based on the assumption that there are limited capacities for attention, factors that increase attentional load or effort will deplete attentional resources and result in attentional lapses.

Attention Deficit-Hyperactivity Disorder (ADHD)

For most people, lapses in attention occur infrequently, and the consequences are usually harmless and benign with a minimal impact on daily life. However, for some individuals, such as those with attention deficit-hyperactivity disorder (ADHD), lapses occur more frequently and can become cognitively debilitating and significantly interrupt daily life (Robertson et al., 2003; Weissman et al., 2006; DiFrancesco et al., 2019). ADHD is currently the most commonly diagnosed neurodevelopmental psychiatric disorders, affecting an estimated 8-11% of children aged 4-17 in the United States. This is a marked increase from the approximately 3-5% diagnosed as of 1994. Additionally, an average diagnosis rate increase of 3% per year was reported from 1997 to 2003 and a 5% increase reported between 2003 and 2011 (cdc.gov/ncbddd/adhd/ data.html). Often times persisting through adolescence and into adulthood, ADHD is estimated to affect approximately 5% of the US adult population as well (http://www.nimh.nih.gov/health/ publications/attention-deficit-hyperactivity-disorder/index.shtml). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) defines ADHD as “a persistent pattern of inattention and/or hyperactivity-impulsivity

that interferes with functioning or development." Symptoms include difficulty staying focused and organizing tasks, difficulty controlling behavior, and hyperactivity or an inability to sit still. Often characterized by inattention, they are easily distracted, and as a result, children with ADHD struggle to succeed in school and get along with other children or adults (nimh.nih.gov/health/publications/attention-deficit-hyperactivity-disorder/index.shtml).

Behavioral Indicators

To date, there is no singular diagnostic tool for the clinical assessment of ADHD and other attention related disorders. Instead, an array of qualitative and quantitative tools is implemented. Diagnosis is based on self-reports, parent and/or teacher interviews, and performance on neuropsychological tests, such as continuous performance tests of attention (CPTs). CPTs are repetitive, operant-based tasks in which participants must sustain visual-spatial attention in order to continuously respond to behaviorally relevant signals (Conners, 2000). CPTs provide quantitative and objective scores for a number of performance measures, including reaction-time (RT) latency, reaction-time variability (RTV), response accuracy, omitted trials, premature responses, and perseverative responses. Performance, particularly RTV, has emerged as the strongest indicator of an ADHD diagnosis (Conners, 2000; Epstein et al., 2003; 2010). Children diagnosed with ADHD reliably show a greater amount of variability in their reaction-time latencies during clinical assessment compared to non-ADHD children (Leth-Steenson et al., 2000). This differential difference in variability suggests that children diagnosed with ADHD do not processes sensory information at a slower rate, but rather they are more prone to longer moments of inattention or lapses in attention (Leth-Steenson et al., 2000; Spencer et al., 2009; Tamm et al., 2012; Antonini et al., 2013).

In an attempt to better understand the degree of representation between these behavioral measures and attentional dysfunction, a study by Epstein and colleagues (2003) examined the relationship between three defining characteristics of ADHD and attentional performance. Correlating inattention, impulsivity, and hyperactivity with reaction-time variability, accuracy, omissions, and errors of commission (premature and perseverative responses), it was reported that increased reaction-time variability was highly indicative of behaviors associated with inattention, such as lapses, and moderately correlated with impulsivity and hyperactivity. Response accuracy was correlated with inattention as well but only moderately. Errors of commission were highly correlated with impulsivity and hyperactivity and showed a low correlation with inattention. The correlation between errors of omission and inattention was reported low to moderate, and while some studies have reported omissions to be of indicative inattention, Epstein and colleagues reported them to be most related to hyperactivity/ impulsivity. (Conners, 2000; Epstein et al., 2003).

Intra-Individual Variability

Reaction time is formally defined as "a time interval with boundaries marked off by an initiating stimulus event and a terminating motor response" (Antonini et al., 2013). It represents a convolution of exogenous attention (signal processing) and endogenous attention and includes the time needed to detect, select, and orient towards the signal. Additionally, it includes the time necessary to sort and decode the incoming sensory information, as well as formulating a decision and executing a response. The variability of an individual's reaction-time latencies over time is known "intra-individual variability (IIV)", and within the clinical and cognitive neuroscience literature, IIV has emerged as the leading indicator for a diagnosis of ADHD (Antonini et al., 2013).

Dissociation of Attention and Lapse

Response latencies taken over time will yield a distribution, and even under normal circumstances, these distributions will present with pronounced unidirectional variance when observed over time, marked by a rightward skew that rises rapidly and trails off slowly (Luce, 1986; Douglas, 1999). This is attributed to the disproportionately infrequent number of slow compared to fast responses, and this pattern holds true for all individuals within a given population and across species (Douglas, 1999; Sabol et al., 2003; Richards et al., 2011). Because this skew presents so consistently, it has been theorized that latency distributions may not represent a singular component, but rather they are the sum of a normal and exponential function with each representing independent attentional components (Douglas, 1999; Leth-Steenson et al., 2000; Spencer et al., 2009). Following this assumption, these distributional components have been dissociated, and when separately measured, the normal component of the distribution represents sensorimotor processing time when in an attentive state, while the exponential component, or variability, represents lapses in attention (Douglas, 1999; Leth-Steenson et al., 2000; Sabol et al., 2003).

Due to the consistent, non-normal distribution, analysis using normal, parametric statistics can yield unreliable results. Ordinarily, when performing statistical analysis of a data set, it is common practice to exclude extreme outliers, as they will skew certain measures of central tendency, in particular the mean and variance. However, evidence suggests that the skew of reaction-time distributions may represent a separate attentional component, so disregarding outliers could compromise the validity of results if the construct of interest is sustained visual-spatial attention (Hohle, 1967; Douglas, 1999; Leth-Steenson et al., 2000; Sabol et al., 2003; Hausknecht et al., 2005, Spencer et al., 2009). Therefore, some researchers have instead analyzed

a parametric description of the sample that provides a summary of the shape of the distribution (Luce, 1986). Using this method, data does not need to be fit or transformed since the assumption of normality needed for parametric testing refers only to the normality of the measures actually being used in the analysis and not to the distribution normality of observations from which the measures are actually obtained (Douglas, 1999; Leth-Steensen et al., 2000). Within these models, the normal component or peak of the RT frequency distribution is theorized to represent attention or attentional processing time, which includes receptor activation, the neural conduction of sensory processes, top-down processes, and central motor processing, while the skew is theorized to represent lapses in attention or other factors not contributing to attention (Richards et al., 2011). Within the clinical literature to date, this has been accomplished using two methods, the exponential-Gaussian and the mode/devmode method of analysis.

Exponential-Gaussian

The exponential (ex)-Gaussian method analyzes RT latency distributions using three parameters: mu (μ), sigma (σ), and tau (τ), or the mean of the normal component, standard deviation of the normal component, and mean of the exponential component, respectively. Sigma (σ) represents the rise in the left distributional tail, and tau (τ) represents the fall in the right distributional tail (Heathcote et al., 1991). When an ex-Gaussian model is used the mean of the normally distributed portion of the distribution (mu) can be measured and analyzed separately from the skew (tau), allowing the examination of the differential processing of children with ADHD (Buzy et al., 2009). In the ex-Gaussian model, it is proposed that tau represents lapses in attention (Leth-Steenson et al., 2000). The relationship between the distributional mean (E (X)),

the distributional variance (Var (X)), and these components can be expressed mathematically as the following equations:

- $E(X) = \mu + \tau$
- $Var(X) = \sigma^2 + \tau^2$

To date only a handful of studies have applied ex-Gaussian modeling in the examination of IIV in ADHD (Epstein et al., 2010; Geurts et al., 2007; Hervey et al., 2006; Leth-Steensen et al., 2000; Hwang, 2013). Of these studies, tau was found to be a sensitive measure of group differences between ADHD and normal controls (Epstein et al., 2010; Hervey et al., 2006; Leth-Steensen et al., 2000). However, one study using a short duration RT task reported no differences between ADHD participants and controls on tau. Since increased lapses in attention are seen towards the end of a testing session, it was suggested that the task was too short to exhaust attentional resources and allow differences on IIV to emerge (Geurts et al., 2007). Additionally, another study using ex-Gaussian parameters reported significant differences between ADHD and control groups in the fast portion of the RT distribution (mu), but reported a small effect size (0.08) (Williams et al., 2007). This was difference was attributed to different causal mechanisms for the multidimensional construct of RT variability. When a standard ANOVA was used for RT analysis, it was shown that the mean reaction time in children with ADHD differed from the age-matched controls, suggesting overall slower responding. By using an analysis based on the mean, it is assumed the data is normally distributed and the variance will exert influence on the mean. This can create an artificially inflated mean, especially given the inherent skewedness of RT data. However, when the corresponding ex-Gaussian parameter of mu was analyzed, no difference was reported.

Mode-Deviation From Mode

Although the ex-Gaussian method separates the peak and the skew for reaction-time latency, the peak is still quantified using a variation of the mean, which will inherently be influenced by outliers (Richards et al., 2011). Therefore, some have employed a simpler approach using the mode of the distribution and the average deviation from the mode (devmode = mean - mode) to quantitatively characterize the peak and skew, respectively (Sabol et al., 2003; Hausknecht et al., 2005). The mode represents the most frequently occurring IT when an attentive state is being maintained, while the deviation from mode represents the skew of the distribution and is theorized to represent a phenomena separate from attention, such as lapses (Sabol et al., 2003; Hausknecht et al., 2005; Richards et al., 2011).

Calculating a mode estimator based on intervals rather than a true modal value can reduce asymptotic bias and can provide a truer estimation of the normal function (Bickel, 2003). One such method of estimation is the "half-range method" (HRM), which is calculated by computing intervals within intervals, where each modal interval has a width equal to half the range of the observations within the previous modal interval. Estimation begins with a modal interval containing the entire sample (Bickel, 2002; Sabol et al., 2003; Hausknecht et al., 2005; Spencer et al., 2009).

Characteristics of Reaction-Time Variability

Although all behavior and related indices of performance fluctuate from moment to moment to some degree, the common observation that such fluctuations are larger and more common in children with ADHD has led to the recent suggestion that increased intra-individual variability might represent a ubiquitous and etiologically important characteristic (Castellanos et al, 2005; 2006). In light of this suggestion, studies began examining the relationship between

high variability responding and other markers indicating impairments in attentional control (Acheson & de Wit, 2008).

In order to introduce variability as an independent variable, a median split has been used to assess the behavioral effects of attention related drugs specifically on reaction-time variability independent of an ADHD diagnosis (Acheson & de Wit, 2008; Robinson, 2012; Avila & Lin, 2014). For example in 2008, Acheson and colleagues examined the clinical effects of bupropion, a smoking cessation aid with attentional indications, and d-amphetamine, a stimulant and currently the drug most prescribed for the treatment of ADHD. For the study, participants received placebo, bupropion (150 or 300 mg), or d-amphetamine (20 mg) in capsules. It was reported that bupropion reduced lapses in attention, and d-amphetamine decreased both sensorimotor processing time and lapses in attention for all participants. During analysis, it was found that there was a wide inter-individual variability across participants under placebo conditions. Therefore, to further explore the effects of bupropion and d-amphetamine on variability, two groups were formed by a median split of the deviation from mode data from placebo sessions (low deviation & high deviation groups). In the low deviation group, there were no effects of bupropion or d-amphetamine on reaction-time mode and deviation from mode. In contrast, the high deviation group showed significant improvements with bupropion or d-amphetamine on the mean and deviation from mode but not the mode. This suggested that the observed drug effects could be attributed, specifically, to a decrease in attentional lapses in the high deviation group (Acheson & de Wit, 2008).

Summary/Discussion

The recognition and measuring of individual characteristics found within reaction times has provided information pertaining to the nature of ADHD. That is, reaction-time latencies

associated with ADHD are not overall slower, but their frequency distributions present with a larger skew. Although lapses in attention have become a defining characteristic of ADHD, only a handful of studies have examined the importance of intra-individual variability as a stand-alone experimental variable (O'Connell et al., 2009; Epstein et al., 2011; Antonini et al., 2013). These studies comparing the distributional patterns of high versus low variability responders have provided insight, based on an estimation of intra-individual variability, into typical response patterns shown to be indicative of inattention. However, given the importance of differences in intra-individual variability outcomes and the supposition that reaction-time variability in and of itself may be indicative of attentional lapses, further examination of variability as a neurobehavioral indicator of attentional characteristics would provide the opportunity to increase the understanding of varied response patterns and behaviors associated with inattention (Douglas, 1999; Leth-Steenson et al., 2000; Spencer et al., 2009; Antonini et al., 2013)

Neural Substrates of Lapses in Attention

Evidence from rodent studies has provided a wealth of information concerning the underlying neural attributions of attentional processing and dysfunction in general, but focus within the clinical and cognitive literature has shifted towards more specific sub-processes, such as lapses in attention that have come to define ADHD. This shift is a recent development, and the rodent literature has lagged behind, so to date no studies exist that have investigated the neural substrates of lapses in attention using intra-individual variability in a way that is comparable to human investigations. Therefore, in order to attempt to identify possible neural analogues of lapses in attention between species, cognitive neuroscience evidence will be reviewed.

The development of in-vivo methods for the study of the underlying neural substrates of human cognition has allowed for the study of pathophysiology involved in psychiatric disorders

and associated mental phenomena, such as ADHD associated lapses in attention. For example, functional magnetic resonance imaging (fMRI) is a neuroimaging procedure that measures brain activity by detecting changes associated with blood flow (hemodynamic response) using blood-oxygen-level dependent contrast. Cerebral blood flow and neural activity are coupled, so when neurons become active, blood flow to those regions increases (Logothetis, 2001). With clinical evidence supporting a behavioral representation of attentional lapse(s) by intra-individual variability mounting, studies using fMRI to investigate neural activity during a momentary lapse in attention have followed. By investigating trial-by-trial relationships between neural activity and reaction time, observations of system-based contributions to the successes and failures of attention in real time has been possible, and these studies have lent support to the relevance of intra-individual variability in attentional processing and behavioral control dysfunction. Evidence from the fMRI literature suggests that visual-spatial attention as a whole is controlled by partially segregated, interdependent ventral and dorsal corticocortical neural systems (Corbetta & Shulman, 2002; Corbetta et al., 2008). Although both systems are specialized for specific attentional subprocesses, evidence suggests that depending on the demands of a given task, flexible attentional control can only be implemented by dynamic interactions of both systems (Vossel et al., 2014, Thiele & Bellgrove, 2018).

Ventral Frontoparietal System

The ventral frontoparietal system is centered on the temporoparietal and ventral frontal cortex. Evidence suggests that the ventral network is specialized for exogenous processes, engaged independent of task expectations or preparations, and recruited during signal processes such as detection and discrimination, particularly when signal is highly salient and unexpected (Posner et al., 1980; Corbetta & Shulman, 2002; Corbetta et al., 2008; Vossel et al., 2014). It is

also passively involved in the top-down regulation of attention and due to the interdependency of attentional systems, responds along with the dorsal network when behaviorally relevant stimuli are detected (Corbetta & Shulman, 2000; Corbetta et al., 2008). For example, when a signal is presented within the visual field, areas in the occipital lobe respond transiently and most likely reflect the sensory analysis of the signal (Corbetta & Shulman, 2002; Corbetta et al., 2008).

Dorsal Frotoparietal System

The dorsal frontoparietal network, whose core neuroanatomical regions include dorsal parietal and frontal cortices, mediates top-down mechanisms of attention and is active in the conscious selection of sensory information and responses (Desimone & Duncan, 1996). Increased levels of activity in the cortical regions associated with the dorsal network have been shown to be necessary for maintaining a state of high sensitivity to incoming stimuli and critical for detection that is not signal-driven (Critchley et al., 2002; Weissman et al., 2006). This network is theorized to be involved in the preparation and application of goal-directed selection by linking stimuli and responses. Additionally, the dorsal network has been linked to decision-making factors, which aid in the resolution of conflict between possible responses (Posner, 1980). These factors are associated with, but not limited to, information specific to the individual responder, such as memories, prediction of goals and events, and the value of reward (Wolfe, 1994).

Evidence suggests that the dorsal system generates and maintains endogenous signals based on current goals and pre-existing information about likely contingencies and sends out top-down signals that bias the processing of appropriate stimulus features and locations in sensory cortex. This conclusion is based on evidence that the dorsal network is pre-activated by the expectation of seeing an object at a particular location or with certain features (Hopfinger et al.,

2000; Corbetta et al., 2008), and/or by the preparation of a specific response (Astafiev et al., 2003; Connolly et al., 2002). Under some conditions, the preparatory activation of the dorsal frontoparietal network extends to visual cortex, presumably reflecting the top-down modulation of sensory representations (Giesbrecht et al., 2003; Silver et al., 2007; Sylvester et al., 2007). Areas in the dorsal posterior parietal cortex and in the frontal cortex show more of a sustained response and most likely indicate endogenous control, since they not related to either visual stimuli or motor responses (Corbetta & Shulman, 2002; Corbetta et al. 2008).

Intra-Individual Variability

The orienting/re-orienting of attention involves the coordinated action of the ventral frontoparietal network the dorsal frontoparietal network. At rest, each network is distinct and internally correlated, but when attention is focused, the ventral network is suppressed to prevent reorienting to distracting events (Corbetta et al., 2008). It has been theorized that the neural basis of increased reaction-time variability may be due to a lack of synchronization between these cortico-cortical regions, specifically the anterior cingulate, ventromedial prefrontal, and posterior cingulate regions (Corbetta & Shulman, 2002; Corbetta et al., 2008).

When attending to visual stimulation at a given location, attention is biased in favor of the neurons encoding information for that location, and stimuli presented in the visual field activate populations of neurons that engage in competitive interactions (Weissman et al., 2006). Frontal regions of the brain that control attention bias sensory regions to favor the processing of behaviorally relevant stimuli over that of irrelevant stimuli. This biasing increases sensory cortical activity that is evoked by the most behaviorally relevant stimuli, resulting in high-quality perceptual representations that can be fed forward to other brain regions that determine behavior. Thus, neurons with receptive fields at that location either remain active or become more active,

while others are suppressed, and this results in task-induced deactivation specific cortical and sub-cortical regions (Desimone & Duncan, 1996). When a behaviorally relevant stimulus is presented, processing resources need to be allocated/reallocated toward behaviorally relevant processes. During a brief attentional lapse, however, this may not be the case (Weissman et al., 2006). Therefore, lapses theoretically result in lower-quality perceptual representations being fed forward to downstream regions that identify and respond to behaviorally relevant stimuli. These regions should then need to work harder, resulting in positive relationships between longer reaction times and stimulus-triggered fMRI activity (Weissman et al., 2006).

In 2006 a findings from a study examining the correlation between neural activity and lapses in attention, as indexed by increased reaction-time variability, were published (Weissman et al., 2006). Although a number of studies have investigated activity during attentional testing, this was the first study that looked exclusively at the trial-by-trial relationship between brain activity and reaction-time variability. During this study, healthy participants were given a continuous performance task (CPT) while neural activity was recorded in real-time on a trial-by-trial basis in an attempt to system-wide view of the neural basis of momentary lapses in attention.

Observations were consistent with biased-competition models of attention and lapses began with reduced pre-stimulus activity in anterior cingulate cortex (ACC) and prefrontal regions, including the inferior frontal gyrus (IFG) and middle frontal gyrus (MFG). The ACC has been implicated in the detection and resolution in processing conflicts. The IFG is theorized to participate in stimulus-triggered reorienting of attention, while the MFG is theorized to maintain task goals in working memory. Less efficient stimulus processing during attentional lapses was additionally characterized by reduced stimulus-evoked sensory activity, signaling the failure of

attention to enhance the formation of behaviorally relevant perceptual representations (Weissman et al., 2006). At the same time increased activity was reported in the parietal cortex, specifically the precuneus and the middle temporal gyrus (Weissman et al., 2006). Parietal brain areas including the superior parietal lobe and the temporal parietal junction are crucial for orienting, both overt and covert, and the selection of information from sensory input (Posner, 1980; Corbetta & Shulman, 2002). This pattern of activity was theorized to reflect attentional lapses that had occurred before trial presentation, indicating greater control is needed to process stimuli that are presented during these momentary lapses. It was also suggested that trial-to-trial variability in the efficiency of these executive processes is a major determinant of momentary lapses in attention.

Summary/Discussion

Attentional mechanisms operate throughout the brain and are involved in every stage of processing, from sensory and perception to decision-making and consciousness, and much effort has been put into understanding the substrates of each individual level. Evidence from the cognitive literature suggests that separate but interdependent neural systems are involved in the facilitation and maintenance of processing, and the success or failure of processing can be indicated by the temporal activation of these systems (Weissman et al., 2006).

When a signal is distinguished and selected from competing options, the current and immediate effects of attention determine how quickly and accurately the target information is processed and response is executed (Chun et al., 2011; Carrasco, 2011). The influence of attention increases along the hierarchy of the cortical visual areas, resulting in a neural representation of the visual world affected by behavioral relevance of the information (Noudoost et al., 2010; Carrasco, 2011). Bias and expectancies allow for dynamic routing of information to

further guide decisions and behavior by provided a means of selecting specific representations for additional processing. The processing of sensory input is facilitated by knowledge and assumptions about the world, by the current behavioral state, and by the relevancy of information in the environment. Evidence from fMRI studies has indicated that increased reaction-time variability may be due to a lack of synchronized activity between cortico-cortical regions, particularly the anterior cingulate cortex, prefrontal cortex (dorsolateral, ventromedial, and orbital frontal), and posterior cingulate cortex (Critchley et al., 2002; MacDonald, 2006).

Perceptual, cognitive, and neural mechanisms do not always operate at peak levels, but instead, activation levels and processing efficiency ebb and flow. It has been theorized that lapses occur during the downturns in activation and reflect a low readiness for input processing, resulting in a slowed or incorrect response (Robbins, 2002; Parikh et al., 2007; Carrasco, 2011). Which neural mechanisms are active during attention and the extent of activation depends on numerous factors, including but not limited to: demands placed on processing, complexity of the situation, requirements for success, and interaction with other cognitive mechanisms.

Modeling of Attention & Lapse in Rodents

From behavioral to cellular, and across species, attention has been modeled at all levels. This has allowed for systematic investigation into the substrates underlying individual, parallel, and collective processes. In order to correctly infer attention and make effective conceptual comparisons within- and between-species, valid models are needed. Validity, or more specifically construct validity, is defined as the accuracy with which a test measures the construct that it is intending to measure.

Parametric Factors

Methods for establishing validity include effect comparisons of experimental factors, which are introduced to theoretically disrupt attentional performance. For example, the experimental assessment of sustained visual-spatial attention has investigated the effects of varied signal salience, signal event rate, and spatial predictability (Sarter, 2004). Systematically varying these factors has helped to establish across species relationships between cognitive processes and experimental procedures (Bushnell, 1998).

Signal Salience. Saliency refers to the noticeability of a signal within a given environment, and it is defined by parameters such as brightness and intensity. (Parasuraman et al., 1987; McGaughy & Sarter, 1995). Attentional performance is a function of signal strength, and when a signal is highly salient and background noise is weak, detection is one of the simplest acts of perception, orientation is unconscious, and the attentional effort required for success is minimal (Posner et al., 1980). Therefore, exogenously, signal driven processes can be taxed by introducing external noise by increasing the ambient, environmental light (Sabol et al., 2003; Richards et al., 2011).

Varying the saliency of the signal will primarily stress attention via sensation and perception. As a signal becomes less salient, increased detection times increase the overall attentional processing time. However, due to the interdependent nature of exogenous and endogenous attention, it can also stress vigilance since the required effort to maintain readiness is increased (Parasuraman, 1979; Parasuraman et al., 1987; Robbins, 2002; Warm et al., 2008). When a signal is less noticeable, effort must be allocated at a higher rate in order to maintain the same focus. Evidence suggests this effort is modulated via top-down or endogenous attention (Posner, 1980; McGaughy & Sarter, 1995; Dalley et al., 2004).

Temporal Predictability. Events that are spatially and temporally unpredictable are known to tax attentional resources (Bushnell & Strupp, 2009). Temporal unpredictability can be accomplished by varying the inter-trial interval (ITI) (McGaughy & Sarter, 1995; Robbins, 2002). The ITI is the time between separate trials, and it is usually measured from the beginning of a trial to the beginning of the following trial (Arnold et al., 2003). Varying the ITI is commonplace in attentional testing, and although rarely employed as a stand-alone variable, some studies have quantified its effects on attention. For example, in a 2013 study, Antonini and colleagues reported that a varied inter-trial interval (ITI) significantly moderated the relationship between inattention and on-task behavior during clinical attentional testing, whereby during long ITI trials, the negative relationship became stronger and higher rates of inattention were observed (Antonini et al., 2013). If performance impairments are only observed on conditions where the signal timing is unpredictable, deficits are more likely to reflect attentional rather than simple sensory functions (Robbins, 2002). Additionally, the event rate should have a range that includes relatively long and short intervals (Bushnell et al., 1997; Bushnell, 1999). A rarely occurring event will stress vigilance by increasing the time required to maintain attentiveness, while a signal that presents too frequently will tax processing capacity (Bushnell & Strupp, 2009).

Studies have also reported performance decrements resulting from either substantial increases or decreases in event rate. Increasing the event rate means that within a given testing session, the stimulus target will be presented more frequently. When the event rate is significantly increased, the animal must maintain, detect, and respond to a larger number of stimuli for a decreased period of time in order to receive a reward (McGaughy & Sarter, 1995). Oppositely, when the event rate is significantly decreased, the animal must sustain attention for a longer period of time in the absence of stimuli presentation, and thus becomes more susceptible

to distraction (Echevarria et al., 2005). For example, an ITI or foreperiod of three seconds will result in a high event rate, whereas an ITI or foreperiod of 30 seconds will result in a low event rate, but similar decrements in performance may be seen as result of either.

When the rate of presentation, or event rate, is varied, occurrence of the signal becomes unpredictable, which places stresses on endogenous attentional processing. Varying the event rate also ensures that a correct response was due to attention being paid rather than inadvertent temporal conditioning to the signal.

Spatial Predictability. Assessment of the role of endogenous attentional control can be accomplished by varying the location of the signal presentation as well. When the signal location is spatially unpredictable, attention must be allocated across an array of possible presentation locations rather than focused on at single location. If a stimulus is spatially predictable, the rat can disregard the array of possible target locations and formulate a correct response prior to the target onset. Because attention has a limited spatial locus, the effectiveness of attention is reduced when it is split across multiple locations or spread across space (Chun et al., 2011). Observers are better are better at detecting an object in a visual scene when they know in advance something about its features, such as location, motion or color (Eriksen & Hoffman, 1973). When a presentation location is unpredictable, automatic processing cannot be relied upon to respond at a particular time, so vigilance must be monitored on a continual basis (Bushnell & Strupp, 2009).

Behavioral Tasks and Measures

In an attempt to gain insight into clinical disorders of attention and to better understand the neurobiological substrates underlying attentional function and dysfunction, as well as assess the efficacy and side effects of pharmacotherapies, rodent models of sustained visual-spatial

attention were developed. Designed to parametrically emulate clinical assessment tools, these rodent tasks assess sustained attentional performance by establishing the effects of factors deduced from attentional theory performance, such as signal saliency, varied event rates, and spatial unpredictability, on (Sarter, 2004; Echevarria et al., 2005). This institutes a stable baseline performance under conditions that are theoretically specific to a given aspect or function of attention. By using a rodent model and inferring across-species function(s), the attentional effects of neurotransmitter depletions, including transient, permanent, specific, and global, can be assessed through drug or neurochemical manipulations (Arnold et al., 2003).

Forced choice, serial reaction-time tasks are by far the most often reported rodent tasks of attention. These tasks introduce spatial unpredictability and were specifically designed to measure endogenous and sustained visual-spatial attention (Carli et al., 1983; Robbins et al., 1989; Richards et al., 2011). They are operant-based, forced-response tasks with relatively few higher-cognitive demands and are able to model attention using numerous variations, including but not limited to signal salience, signal duration, spatial and temporal unpredictability, and a varied inter-trial interval (Robbins, 2002). The five-choice serial reaction-time task (5-CSRTT) is the most often cited of these tasks (Carli et al., 1983; Robbins et al., 1989; Robbins, 2002). A substantial amount of experimental evidence exists supporting the validity of serial reaction-time tasks in the measuring of sustained visual-spatial attention, with attentional impairments inferred from a reduction in choice accuracy, an increase in the number of omitted trials, and/or an increase in reaction-time latency (Bushnell & Strupp, 2009; Arnold et al., 2003).

Less often reported are signal detection tasks, which were designed to assess signal processing and attention by testing the detectability and discriminability of a spatially predictable signal over time (Parasuraman et al., 1987; Bushnell, 1995; McGaughy & Sarter, 1995).

Signal Detection Tasks (SDT). Signal detection tasks require a rat to monitor a single location and determine whether or not a signal event occurred. Following a varied inter-trial interval, either a signal is presented (signal trial) or no event occurs (blank trial). After a period of seconds, two response levers are extended into the chamber (McGaughy & Sarter, 1995). The assignment of the levers is counterbalanced to ensure any performance deficits can be attributed to attention and not sensory neglect (Bushnell, 1998). If a signal event occurred, a response to the signal-lever produces a reward (hit), while a response to the blank-lever results in a short timeout period and no reward (miss). If a signal event did not occur, a blank-lever press is rewarded (correct rejection), while a signal-lever press results in a time-out and no reward (false alarm). Levers are retracted following a response or if neither lever is pressed following a specified period of time (omission). Animals are presented with an equal number of signal and non-signal trials, which are pseudo-randomly distributed throughout each session in order to avoid the emergence of side or lever bias, as rats readily adopt such biases (McGaughy & Sarter, 1995). Although this is the basic design of the task, variations using nose-poke response ports have been reported in the literature. The behavioral measures for SDTs are as follows:

- *D' (d-prime)*: hits/misses (detectability rate)
- *P (hit):* hits/ hits + misses (accuracy for signal)
    - *Hits*: Correct response on signal trial
    - *Misses*: incorrect response or failure to respond on signal trial
- *P (fa):* false alarms/false alarms + correct rejections (accuracy for blank)
    - *Correct Rejections*: correct response on non-signal/blank trial
    - *False Alarms*: incorrect response or failure to respond on non-signal/blank trial
- *Reaction-Time Latency:* time between lever insertion into the chamber and response

Signal Processing. Calculated using signal trials alone, the measure d-prime (D') provides an index of perceptual sensitivity, or the detectability rate of the signal. D' is a function of signal strength, so it should be near the guess rate when the signal is weak and near 1.0 when the signal is strong. The proportion of correct detections should increase with increasing signal strength, so a predictable decrease in D' should be observed as signal processing is stressed (Bushnell & Strupp, 2009).

A wide range of signal strength values allows the differentiation between effects on attention and visual function (Rezvani & Levin, 2003). The measure P (hit) indicates accuracy on signal trials alone, so the signal strength should be adjusted so that the weakest signal produces a P (hit) about equal to the guessing rate, and the strongest signal produces a P (hit) of about 1.0. The guessing rate is given by the proportion of errors on blank trials, or false alarms, and should be independent of signal strength and range from about 0.10–0.20. In contrast, a change in the ability of the rat to see the signal should produce a horizontal shift in the P (hit) by signal strength gradient, so that P (hit) is altered only for signals of intermediate intensity; in addition, P (fa) should not change.

Attention. If a signal was presented on every trial, D' could be artificially inflated by simply responding to signal-lever every time, even when the signal is not detectable. Therefore, blank-trials, or trials in which no signal event occurs, are presented throughout a given testing session. This provides a "false alarm" measure independent from signal intensity and allows for the assessment of attention (McGaughy & Sarter, 1995; McGaughy et al., 1996; Arnold et al., 2003; Bushnell & Strupp, 2009). When a signal is detectable and a readiness to respond is maintained, attention should be observed as a high P (hit) and low P (fa) rate, and impairments in attention should be observed as a decreased P (hit) and increased in P (fa) at all signal strengths

where the former exceeds the latter (Bushnell & Strupp, 2009). Shortening the duration of stimulus places stress on attention, which McGaughy and Sarter (1995) used as a means of validating their model. They found that well-trained rats were able to respond correctly on non-signal trials 65 - 80% of the time when the signal duration was 500ms, and performance declined as the signal length shortened, such that correct rejections dropped to 50% at 50ms and 35% at 25ms signal durations (McGaughy & Sarter, 1995).

Other. In practiced subjects that exhibit high P (hit) and low P (fa) rates, reaction-time latency may become a critical measure in helping to determine the performance effect following behavioral, drug, and/or neuronal manipulations, and analysis of the data can be useful in delineating the behavioral and/or cognitive mechanisms mediating changes in performance (Burk, 2008). However, reaction times can be potentially confounded by a multitude of sensorimotor variables and competing behavioral activities, which is why it is often used as a secondary measure (Bushnell & Strupp, 2009). Rats typically choose which lever to press during the time interval after the signal by positioning themselves in front of one of the levers and pressing it during its insertion into the chamber. Reaction time typically does not vary with signal intensity, but does tend to be shorter for hits and false alarms than for misses and correct rejections (Bushnell, 1999).

Five-Choice Serial Reaction-Time Task (5-CSRTT). The 5-CSRTT was developed as a means to examine the behavioral patterns and neurobiological underpinnings of attention and dysfunction associated with clinical disorders such as schizophrenia, neural trauma, and ADHD, as well as to assess the effects of pharmaceutical treatments (Carli et al., 1983; Robbins et al., 1989; Robbins, 2002). Modeled after clinical tests of attention, the 5-CSRTT assesses the ability to sustain visual-spatial attention across five locations over a large number of trials (~100).

Currently, the 5-CSRTT is the task most commonly used to assess sustained visual-spatial attention in the rat, and much of what is known about the neurobiology of attention has come from these studies (Robbins, 2002).

During the 5-CSRTT, a rat is placed in a test chamber facing five openings arranged horizontally along the curved wall, and a food or reward magazine is located on the opposite wall. Nose-poking the reward magazine serves to both end the current trial and initiate a new trial. Following a short delay or inter-trial interval (ITI), a visual stimulus or signal is presented in one of the five openings along the curved wall. These locations must be continuously monitored to ensure a correct response, which is recorded with nose poke through a hole below the target signal. If the correct decision is made in an appropriate amount of time (~5 sec), the animal is rewarded in the food magazine, and the next trial begins (Carli et al., 1983; Bushnell & Strupp, 2009). The goal is to present a signal that, when combined with task parameters, elicits stable baseline levels of accuracy at ~80% and omissions at ~15%, with low within and between-subject variance. The behavioral measures for the 5-CSRTT are as follows:

- *Accuracy*: Percent correct of total completed trials (excluding omissions)
- *Omissions*: Responses made after a predetermined amount of time (~ 5 sec)
- *Perseverative Responses*: Additional lever presses after the initial response
- *Premature Responses*: Completed response prior to signal presentation
- *Decision Latency:* Time between signal onset and response
- *Reward Latency*: Time between response and reward collection

Attention/Lapses in Attention. Studies using the 5-CSRTT report an aggregate of behavioral measures to infer almost all aspects attention, and clues as to the nature of the dysfunction or attributable taxonomy can be provided by categorizing the types of errors and

evaluating each error type as a function of signal and/or task parametric variations (Carli et al., 1983; Robbins, 2002). Accuracy and omissions are the most commonly reported performance measures indicating sustained visual-spatial attention, and depending on experimental conditions, both have been attributed to lapses or not "paying attention" (Bushnell & Strupp, 2009; Robbins, 2002). When an inaccurate response is given, the animal is aware that a signal event has or should have occurred but has incorrectly guessed the location. When an omission occurs, the subject is unaware that a signal event has or should have occurred, so a response is not given within the appropriate amount of time

With respect to the 5-CSRTT, attention may be stressed by varying signal salience (intensity and duration), the inter-trial interval, and/or the event rate. When this is the case, effects to both accuracy and omissions have been reported, with impairments in attention being observed as a decrease in the former and increase in the latter. Additionally, pharmacological or neurochemical manipulations can be introduced once baseline performance has been established under a given condition. For example, a study investigating the role of cortical ACh in attention presented a signal of varying intensity levels (0, 10, 33, and 100%) in a pseudorandom order equally throughout a given testing session. Following selective cholinergic depletions, it was reported that performance accuracy decreased and omission rates increased as a function of signal salience (Risbrough et al., 2002).

Increased omission rates have also been reported in the absence of a change in performance accuracy. This pattern suggests that the signal is detectable, as measured by accuracy, so the increase should not be sensory in nature, and omissions are attributed to lapses in attention (Risbrough et al., 2002; Echevarria et al., 2005). For example, when the inter-trial interval was reduced from 7-seconds to 2-seconds during testing on the 5-CSRTT, a marked

increase in omissions was observed while no change in accuracy was reported (Dalley et al., 2004). This pattern suggests that when the rats were focused and attending, they had no problem detecting the stimulus and signal processing was unaffected. Lastly, because accuracy is independent from omissions and calculated using only completed trials, an attentional effect not detected by accuracy may be observed in omissions.

Other. Although referred to as a "reaction-time task", the 5-CSRTT is not actually sensitive to reaction time as a reliable measure of attention. Although the location of the signal presentation is predetermined, there is no way to control the position of the rat at the onset of the signal, so a large amount of variability in the latency measurement will exist. Reaction-time latencies will be longer when the starting position is further from the signal location. Therefore, it is most often reported as a secondary measure used to evaluate motor dysfunction or decreased motivation (Robbins, 2002). Some studies, however, have reported latency measures to be informative with respect to certain aspects of attention (Dalley et al., 2004). Decision latency on correct trials may provide a measure of signal processing speed, while reward latency may provide a measure of motivation. It is important therefore to determine the way in which each latency measure is affected. For example, if correct reaction-time latency is slowed but food retrieval latency is not altered, interpretation may be that information processing speed is slowed, and the fact that food retrieval latency is normal allows the exclusion of an impairment of motor function (Bushnell & Strupp, 2009).

The interpretation of omissions as a measure of attention, or as affected by motivational, sedative, or motor factors, depends on the pattern of changes in other variables. Therefore, It is important to rule out any possible confounds that may explain any observed effects. Differing interpretations can often be disambiguated by considering other control measures taken during

performance, and by taking into account the overall profile or pattern of effects for measures on the task as a whole (Robbins, 2002).

It has been argued that premature responses can be an active representation of inattention on the five-choice serial reaction-time tasks and can underlie the occurrence of maladaptive behaviors via poor stimulus control (Richards et al., 2011). This argument is supported by data from the clinical literature that has shown a moderate correlation between premature responses and inattention (Epstein et al., 2003). However, premature responses are most correlated with impulsivity/hyperactivity, so experimental effects on inattention versus impulsivity/ hyperactivity have not been reliably disentangled (Robbins et al., 1998, Robbins, 2002).

Two-Choice Serial Reaction-Time Task (2-CSRTT). For this task, three nose-poke ports are located along a single wall and monitored with photocell beams. A trial is initiated when the rat places its head in the center port and holds a fixed-position for a varied period of time. This varied time, known as the foreperiod, ends when a visual signal is presented on either side of the center port. This signal remains illuminated for the duration of the trial, and the animal must respond correctly in a given amount of time in order to earn a reward. The trial is terminated following a response choice and, if correct, immediate reward collection at the response location (Sabol et al., 2003; Hausknect et al., 2005; Richards et al., 2011). The 2-CSRTT requires only covert orienting, since the head is in a fixed-position and the signal is always presented within the animal's peripheral vision. The behavioral measures for the 2-CSRTT are as follows:

- *Initiation-Time Latency (IT):* Time between signal onset and removal of head from center port
    - *IT Mode:* Normal component of IT latency
    - *IT Deviation From Mode (devmode):* Exponential component of IT latency

- *Movement-Time Latency (MT)*: Time between removal of head from center port and nose poke at response location
- *Omissions*: Responses made after a predetermined amount of time (2-sec)
- *Accuracy*: Percent correct of total completed trials, including unrewarded but accurate responses
- *Premature Initiations*: Removal of head from center point prior to signal onset
- *Premature Responses:* Completed response prior to signal onset

Attention. The normal component or peak of initiation-time frequency distributions is theorized to represent attention or sensorimotor processing time when the animal is attentive. This includes receptor activation, the neural conduction of sensory processes, top-down processes, and central motor processing (Richards et al., 2011). Using this method of analysis, the differential effect(s) of stress on attentional processing can be assessed independently of lapses. When attentional processing is stressed, slowing should be frequent and consistent. For example, decreasing the salience of the signal should uniformly increase detection time, which will affect a "typical" response (mode).

Lapses in Attention. Lapses in attention can be inferred from the exponential component or skew of the distribution and are quantified by the deviation from the mode, which is calculated by subtracting the initiation-time mode from the initiation-time mean (Sabol et al., 2003; Hausknecht et al., 2005; Acheson & de Wit, 2008: Richards et al., 2011). During the 2-CSRTT, cognitive functions such as working memory are minimized so that attentional processing and vigilance can be isolated and evaluated (Hohle, 1967; Douglas, 1999; Sabol et al., 2003). The foreperiod of this and other similarly measured reaction-time tasks may be considered a miniature vigilance situation where alertness must be developed rapidly and maintained over a relatively brief interval (Posner, 1980). If endogenous control is not optimized

at the end of the foreperiod and immediately prior to the signal presentation, vigilance will fail and detection will be delayed, resulting in a lapse of attention (Richards et al., 2011).

Other. Accuracy can indicate whether or not a signal can be detected. If detection is not possible or if the signal cannot be discriminated from background noise, accuracy will be approximately the same as the guess rate or 50%. Because the signal remains illuminated for the duration of the trial, near perfect accuracy should be observed when the signal is detectable. For the 2-CSRTT, omissions can also indicate inattention since they are essentially attentional lapses that are longer in duration, but they can also indicate a possible motivation, motor, or sensory effect (Sabol et al., 2003; Hausknecht et al., 2005; Richards et al., 2011). Therefore, omissions are not reported as a primary measure of attentional lapse, but rather used secondarily to provide confirmation of impairment attribution.

Summary/Discussion

Although the aforementioned tasks can all indicate attention, the sensitivity to which they measure individual functions differs substantially. Therefore, determining which task to use when assessing attention in the rat ultimately depends on the experimental question being asked and the type of equipment available for testing (Bushnell & Strupp, 2009). Tasks using signal detection derived behavioral measures have been reported as valid indices of sustained visual-spatial attention; however, they are best suited for measuring sensory and perception related attentional processes, since these tasks are able to provide an assessment of detection (D') separate from attention. For these tasks, the duration, brightness, and timing of the signal can be varied, and these tasks also introduce the possibility of no signal event occurring.

Forced choice reaction-time tasks have historically been the benchmark for indicating attention, and parametric variations to the location, brightness, duration, and timing of the

stimulus can be varied. Of the forced choice reaction-time tasks, the 5-CSRTT is the most widely reported attentional task, with performance accuracy and omissions being the primary measures. Although the analysis of choice-accuracy converts scores into a percentage, it is inherently a dichotomous measure, as it is scored as either correct or incorrect. It may therefore not be sensitive enough to pick up slight differences in performance required to measure lapses in attention. The 5-CSRTT also relies on omissions as an indication of lapses of attention; however, correlations between omissions and inattention have been low to moderate and not always domain specific. In fact, it was reported that omissions were most associated with impulsivity in clinical ADHD assessment (Epstein et al., 2003; Antonini et al., 2013).

More recently, a two-choice variant (2-CSRTT) capable of measuring initiation-time latency, which is not a dichotomous measure, was introduced (Sabol et al., 2003; Richards et al., 2010). The parameters of this variant make it capable of providing a measure representing not only how often lapses in attention occur, but also the duration of each lapse. This is an important distinction, because ADHD-associated inattention has been shown to be a function of both the frequency of occurrence and duration of attentional lapses. In the 2-CSRTT, the rat must hold a fixed position prior to the stimulus onset, and this provides a uniform starting point for initiation time comparisons. Therefore, due to the design of the 2-CSRTT and the sensitivity of latency as a dependent measure, it is possible to then assess not only attention but also lapses in attention. However, due to its relative novelty, the 2-CSRTT has been implemented in only a handful of studies reporting lapses in attention (Sabol et al., 2003; Hausknecht et al., 2005; Redding et al., 2019). While all tasks speak to lapses in attention in some way, it is reaction-time latency that has come to the forefront of the ADHD literature. Evidence has shown that latency can provide

separate indices for attention and lapses, while the differentiation is less clear in models that use other measures (Risbrough et al., 2002; Bushnell, 1998; Echevarria et al., 2005).

Role of Acetylcholine and Stimulus Salience in Visual-Spatial Attention

The purpose of this dissertation is to examine the effects of manipulating stimulus salience and the neurotransmitter acetylcholine (ACh) on attention and lapses in attention. Prior to reviewing the literature directly related to the proposed experiments, a brief recap of key attentional concepts and animal models will be presented.

Attentional Concepts Summarized

The two major categories of attention are exogenous (bottom-up) attention and endogenous (top-down) attention. Exogenous attention governs signal related processes, such as detection and discrimination, while endogenous attention includes processes such as selection and sustained attention. Both exogenous attention and endogenous attention can be stressed experimentally, and because attention relies on success of both, a failure in either will result in a failure overall. As was stated earlier, lapses in attention are infrequent failures in endogenous attention that, because of a momentary failure to attend to task relevant features, result in actions that are intended but not executed (Buzy et al., 2009). While they are a related phenomenon, lapses differ from impairments in endogenous attention. Lapses are infrequent and dynamic, whereas impairments are static. When examined experimentally, impairments in exoogenous attention will be observed similarly across subjects, while lapses will differ between subjects due to individual differences (Robertson et al., 2003; Weissman et al., 2006).

Factors that stress endogenous attention do so by increasing the attentional effort needed in order to successfully complete a given task. For example, ACh is important in signal processes such as detection and discrimination. When brightness is diminished, the signal becomes more

difficult to process (exogenous attention). This results in an increased effort requirement, which in turn impairs sustained attention (endogenous attention).

Animal models, including signal detection tasks, the 5-CSRTT, and the 2-CSRTT, can all measure attention. Across all rodent tasks, the most often cited behavioral indices of attention are performance accuracy, omission rate, and depending on the protocol requirements, reaction-time latency. When a signal is detectable and a readiness to respond is maintained, successful attending should be represented behaviorally by high accuracy, consistently fast responding, and a high rate of completion.

On signal detection tasks, exogenous attention is indicated by P (hit) on signal trials, and endogenous attention is indicated by both P (hit) on signal trials and P (fa) on non-signal trials. Additionally, when P (fa) is unaffected but omissions are increased along with a change in P (hit), an effect on endogenous attention is assumed. Although it is possible that these tasks demonstrate lapses in attention when P (hit) decreases and P (fa) increases, lapses in attention and impaired endogenous attention have the same indicators. Therefore, signal detection outcomes will only be used for impaired attention, and not lapses, in the discussion below (Bushnell, 1999; Bushnell & Strupp, 2009; Sarter & Mcgaughy, 1998; Sarter et al., 2001; Sarter, 2004).

On the 5-choice serial reaction-time task, endogenous attention and the ability to maintain successful processing is measured by performance accuracy and rate of omissions, and each has been theorized to indicate both attention and lapses of attention (Bushnell, 1998; Bushnell & Strupp, 2009; Chudasama & Robbins, 2004; Blokland, 2005). However, lapses of attention have been theorized to occur when an increase in omissions is observed without a change in accuracy (Jakala et al. 1992; Shannon & Eberle, 2006).

In the 2-CSRTT, reaction time is broken down into initiation time (IT) and movement time (MT). IT is the measure of interest for the proposed experiments, and it is broken down into mode and devmode. IT mode is theorized to reflect sensory motor processing time when the animal is capable and ready to attend, and devmode is theorized to represent lapses of attention (Sabol et al., 2003; Richards et al., 2011). Devmode parallels the reaction-time variability measures used in humans to help diagnose lapses in attention in individuals with ADHD (O'Connell et al., 2009; Epstein et al., 2011; Antonini et al., 2013).

Acetylcholine and Attention

Within the rodent literature, the research question has historically been whether or not acetylcholine plays a role in attention and whether or not that role is in exogenous processing, endogenous processing, or both. It is theorized that ACh facilitates attention by enhancing characteristics of behaviorally relevant stimuli, which aids in exogenous attentional processes, such as signal detection and discrimination. The modulation of attention facilitates sensory processing across the cortical mantle by causing the influence of attention to increase along the hierarchy of sensory areas (Arnold et al., 2002; Dalley et al., 2004). This results in a neural representation of the visual world that is continuously affected by behavioral relevance of the signal. This in turn facilitates endogenous attentional processes, such as selection and sustained attention, by reducing the amount of effort needed to direct and maintain attention, resulting in fewer moments of inattention (Dalley et al., 2004; Sarter et al., 2005).

Acetylcholine Activity (In-Vivo)

Acetylcholine activity during attentional processes can be inferred at a millisecond resolution using in-vivo methods, such as choline-sensitive microelectrodes, which allows for the monitoring of changes in extracellular ACh levels in conscious, freely moving rats during

behavioral tests. The cholinergic role in recruitment and facilitation of signal processing, specifically detection and covert orienting (exogenous), is supported by findings from studies in which ACh release was associated with specific task events or behavioral responses related specifically to the presentation of a signal (Dalley et al., 2004; Himmelheber et al., 2000; 2001; Arnold et al., 2002; Parikh et al., 2007). When cortical samples of ACh were taken during performance on both the 5-CSRTT and SDT, an efflux was reported with spikes of cholinergic activity observed when the stimulus was accurately detected. These increases were not observed in animals performing behavioral procedures that controlled for non-cognitive performance variables, such as lever pressing and reward rates, or the presentation of stimuli and distractors in contexts that did not require attention (Himmelheber et al, 1997; Arnold et al., 2002). Since the efflux lessened when signal parameters were varied and increased when a signal was detected, results would indicate that ACh is associated with the exogenous attention (Himmelheber et al., 2000; 2001; Parikh et al., 2007).

This cholinergic efflux was recorded throughout the frontal cortex when a relevant cue was detected on a signal detection task, which was in contrast to no increase when rats were simply exposed to the testing chamber or performed a non-attentional task (Himmelheber et al., 2000). A relationship between signal processing (exogenous attention) and ACh was further supported by reported increases in cortical ACh levels when the brightness of the signal was increased and decreased levels when brightness was reduced (Passetti et al., 2000; Himmelheber et al., 2000; 2001; Parikh et al., 2007). This indicates that levels of ACh release in attentional task-performing animals vary as a function of the demands on attention, or attentional effort, but do not correlate with levels of attentional performance, as a decreased in accurate performance did not always correlate with decreased ACh activity (Dalley et al., 2004).

The collective evidence suggests that ACh facilitates attention by aiding signal detection, signal discrimination, and sustained attention. It is theorized that ACh modulates attention by facilitating sensory processing across the cortical mantle, causing the influence of attention to increase along the hierarchy of sensory areas and thereby enhancing the characteristics of behaviorally relevant stimuli (exogenous). This results in a neural representation of the visual world that is continuously adjusted by the behavioral relevance of the signal. This modulation facilitates sustained attention by reducing the amount of effort needed to direct and maintain attention, which results in fewer impairments in attention (endogenous) (Dalley et al., 2004; Passetti et al., 2000; Himmelheber et al., 2000; 2001; Parikh et al., 2007).

Scopolamine HBr (Systemic)

ACh dependent processing can also be examined experimentally by peripherally injecting a cholinergic antagonist that crosses the blood brain barrier, such as scopolamine hydrobromide (scopHBr), which demonstrates a high affinity for the M1 (muscarinic) receptor subtype (Blokland, 2005).

Attention. In a 1997 study, Bushnell and colleagues examined the role of ACh in attentional processing using a signal detection task (Bushnell et al., 1997). In this study, the duration of the signal was held steady at 300-milliseconds and the brightness was varied, with seven conditions ranging from slightly brighter (~2%) to more than twice as bright (~102%) compared to the chamber light. Scopolamine was administered peripherally at doses of 0.03, 0.056, 0.1 mg/kg (SC), and trials were randomly presented by type, signal or non-signal, in equal number and counterbalanced. Scop HBr was reported to affect exogenous attention, as indicated by a decreased P (hit) rate at all doses compared to saline controls. Additionally, this effect became more pronounced as signal brightness increased, and P (hit) was reduced by scopolamine

more at high intensities than at low intensities. At the highest dose (0.1 mg/kg), an increased P (fa) rate was observed compared to saline controls, which indicated an effect on endogenous attention and was further supported by an increased omission rate at 0.1 mg/kg. Unlike the exogenous effect, the effect on endogenous attention was similarly observed across all signal intensities.

In a more recent study, Mcquail and Burk evaluated the effects of scopolamine by administrating escalating doses (0.05, 0.1, 0.3, 0.5, and 1.0 mg/kg, IP) (Mcquail & Burk, 2006). Additionally, signal salience was also introduced as an experimental variable and testing was undertaken using varied signal durations (25, 100, 500-milliseconds). Compared to saline controls, a decrease in P (hit), or impaired accuracy on signal trials alone, was reported at doses of 0.3 and 1.0 mg/kg, but only at the longest signal duration of 500-milliseconds. This suggests that scop HBr and a shorter signal duration both affected exogenous attention. However, the effects of scop HBr were not observed until the signal duration was lengthened sufficiently enough to no longer affect exogenous processing. The P (fa) rate, or accuracy on non-signal trials, remained unaffected by both scop HBr and signal duration, while an increase in omissions was reported only at the highest dose (1.0 mg/kg) and independent of signal duration. Due to the lack of change in P (fa) across all dose levels, an effect on endogenous attention could not be confidently asserted; therefore, the increased omission rate observed at highest dose, as well as overall performance across signal durations was taken into consideration. It was ultimately concluded that scop HBr affected the ability to detect and process signal information (exogenous) at all doses but was dependent on signal duration, and the ability to sustain attention (endogenous) was impaired at the high dose 1.0 mg/kg dose level and occurred independent of signal duration.

In a study using a 5-CSRTT protocol, scopolamine doses of 0.03, 0.075, and 0.1 mg/kg (SC) were administered, and attention was tested using a signal duration of 0.5-seconds, a signal brightness of 575 lux, and a trial length of 5-seconds (Jones & Higgins, 1995). An effect on endogenous attention, as indicated by a decrease in accuracy, was reported only at the highest dose level of 0.1 mg/kg. These findings were later supported in a similar study that utilized a signal duration of one-second, a signal brightness of 2.8-watts (lux unspecified), and a trial length of 5-seconds. Following systemic scop HBr injections of 0.01, 0.03, and 0.1 mg/kg (IP), an endogenous effect was reported at a dose of 0.1 mg/kg as decreased accuracy was observed compared to saline treated animals (Mirza & Stolerman, 2000).

In a more recent study using the same task, scop HBr was systemically administered at doses of 0.003, 0.01, 0.03, 0.1, 0.3 mg/kg (SC), but in this study, a varied signal duration was introduced as an additional experimental variable (Shannon & Eberle, 2006). Signals were presented randomly at either a short duration (0.2-seconds) or long duration (2-second) with equal probability, and the trial duration was held constant at 5-seconds. Under these conditions and compared to saline treated animals, a decrease in accuracy was observed at the highest doses (0.1 & 0.3 mg/kg) but only at the short stimulus duration (0.2-seconds). This outcome indicates that scop HBr did affect endogenous attention, but only at the higher doses and only when additional stress was placed on attentional processing.

In a 2011 study, Klinkenberg and colleagues used a variant of the two-choice task protocol in which a signal was presented on either the left or right side of a central reward tray and two corresponding response levers were inserted simultaneously following signal termination (Klinkenberg et al., 2011). The duration of each trial was 3-seconds, and signals were presented at a varied duration (0.3, 1, 3-seconds). Following the systemic administration of

scop HBr at doses of 0.1, 0.3, and 1.0 mg/kg (IP), a decrease in accuracy and slowed choice reaction- time latency were observed at the dose levels of 0.3 mg/kg compared to saline treated animals. Additionally, the rate of omissions was increased at the same dose level, and for all three measures, effects were observed independent of stimulus duration condition. It should be noted that data for the 1.0 mg/kg dose was not analyzed due to the high number of animals that were unable to complete testing. Lastly, no published studies to date have reported on the effects of reduced global ACh transmission and signal salience on attention using a 2-CSRT task and the mode/devmode method of analysis set forth by Sabol and colleagues (2003) and detailed by Richards (2011). The only indication comes from unpublished data from the Sabol Lab, which observed no effect on initiation time (IT) mode following doses as high as 0.1 mg/kg IP (Damico and Sabol, unpublished honors thesis).

Analysis. Evidence across all tasks supports the theory that ACh plays a role both exogenous and endogenous attention. Using a signal detection task, Bushnell and McQuail both reported a decrease in P (hit) (Bushnell et al., 1997; McQuail & Burk, 2006). Because the P (hit) ratio takes into account performance on signal trials alone, this decrease suggests an effect of decreased ACh on exogenous attention and signal detection. Supporting the argument of a role of ACh in endogenous attention, Bushnell also reported impaired performance on non-signal trials, as indexed by an increase in P (fa). Citing an increase in omissions in the absence of a change in P (fa), evidence from McQuail also provides support for a cholinergic role in endogenous attention. Although the conclusions from these studies came about using different behavioral measures and scop HBr dose levels, the pattern of effects was similar, with a lower scop HBr dose affecting exogenous attention compared to endogenous attention. Studies employing choice reaction-time tasks also support the assertion that ACh plays a role in endogenous attention.

Evidence reported from each of the reviewed 5-CSRTT studies showed that scop HBr affected the ability to sustain attention, as indexed by a decrease in performance accuracy in the higher dose range of 0.1 mg/kg or higher (Jones & Higgins, 1995; Mirza & Stolerman, 2000; Shannon & Eberle, 2006). Finally, using a two-choice variant, Klinkenberg and colleagues reported decreased accuracy, decreased choice reaction time, and increased omissions at the high scop HBr dose of 0.3 mg/kg.

Findings from studies that have investigated the effects of scop HBr on attention when the attentional load has been increased via reductions in signal salience (e.g., duration and brightness) have been contradictory between tasks, leading to an inconsistent attribution of effect. With respect to signal detection tasks, the effects of scop HBr became either evident or exacerbated when the salience of the signal was increased (Mcquail & Burk, 2006; Bushnell et al., 1997). Conversely on the 5-CSRTT, the effects of scop HBr were only observed when the salience of the signal decreased (Shannon & Eberle, 2006). While this discrepancy between models with regards to signal salience has yet to be addressed in the literature, it may be explained by the parametric differences between models and measures.

In sum, the systemic administration of scop HBr has been shown to impair both exogenous and endogenous attention (Jones & Higgens, 1995; Bushnell et al., 1997; Mirza & Stolerman, 2000; Mcquail & Burk, 2006; Shannon & Eberle, 2006; Klinkengerg et al., 2011). While impairments were reported over a wide dose range, the pattern of effects stayed consistent, with exogenous attention being impaired at doses lower than those that affected endogenous attention. When the salience of the signal was decreased and attentional load increased, effects were inconsistent (Bushnell et al., 1997; McQuail & Burk, 2006; Shannon & Eberle, 2006). An

unpublished study provides useful information regarding the dose determinations that will be used in the proposed experiments (Damico and Sabol, unpublished honors thesis).

In the above reviewed studies, the minimal effective dose of scop HBr on attention ranged from 0.03 mg/kg to 1.0 mg/kg, with the most cited dose being 0.1 mg/kg. Impairments on signal processing were observed at a dose range of 0.03 – 0.3 mg/kg, while impairments on sustained attention were observed at a dose range of 0.1 – 1.0 mg/kg. Despite these wide dose ranges, the pattern of effects was consistent with exogenous attention being impaired at doses lower than those that impaired endogenous attention. While no attentional effects of scop HBr were observed at a dose 0.1 mg/kg using the 2-CSRTT and mode/devmode method of analysis, the collective evidence indicates that this is a reasonable scop HBr starting dose for the proposed studies.

Lapses in Attention. When considering evidence for lapses in attention, the most commonly reported indication is a change in the omission rate that occurs in the absence of a change in accuracy on the 5-CSRTT. For example, in a 1992 study Jakala and colleagues administered scop HBr at doses of 0.05, 0.1, 0.15, and 0.2 mg/kg (IP) (Jakala et al., 1992). For testing, the length of an individual trial was 3.5-seconds; the duration of the signal was 0.5-seconds, and the brightness of the signal was 3-watts (lux luminance unspecified). All factors were held constant. While no change in performance accuracy was reported under any drug condition, an increase in omissions was reported at all doses compared to saline treated animals. Another example is a more recent study in which testing conditions consisted of a two second signal duration, a trial length of 5-seconds, and a signal brightness of 100 lux. Following systemic doses of 0.1, 0.2, 0.3 and 0.4 mg/kg (IP), an increase in omissions was reported for all

doses compared to saline treated animals, while performance accuracy remained unaffected at all doses (Hodges et al., 2009).

In a follow-up to the aforementioned Jones & Higgins study, scop HBr was administered at doses of 0.01, 0.03, and 0.075 mg/kg (SC) and both signal brightness and duration were varied in order to increase attentional load, with varied salience conditions presented randomly and counterbalanced (Jones et al., 1995). The duration of each trial was 5-seconds; the signal was presented at varied brightness levels (16, 45, 82, or 575 lux), and the signal was presented varied durations (0.05, 0.15, 0.25, or 0.5 seconds). While no effect of scop HBr was observed on accuracy at any dose and under any salience condition, a signal brightness dependent increased omission rate was reported at the mid and high doses (0.03 and 0.075 mg/kg) compared to saline treated animals. Further analysis showed that this increase occurred at all brightness levels for the high dose group, but only the lowest three brightness levels (16, 45, and 82-lux) for the mid dose group. No effect of duration was reported on omissions.

The findings reported by Shannon and colleagues also suggest an effect on lapses in attention, but do so in a less straightforward manner. Unlike the other reviewed studies that reported no effect on accuracy, Shannon reported that accuracy and omissions were both affected at doses of 0.1 and 0.3 mg/kg (SC), but only when the signal duration was 0.2-seconds. When the duration of the signal was increased to 2-seconds, performance accuracy was recovered for both dosing groups compared to saline treated animals while the increase in omissions persisted (Shannon & Eberle, 2006). Finally, as was the case in regards to attention, no studies have reported on the effects of reduced global ACh transmission and signal salience on lapses in attention using a 2-CSRT task and the mode/devmode method of analysis. However, the same

unpublished data observed no effect on IT devmode, or lapses in attention, following doses as high as 0.1 mg/kg IP (Domico, 2004).

Analysis. Collectively, these patterns suggest that lapses in attention are modulated at least in part by ACh, and this modulation is subject to the influence of attentional load. The most common indication of lapses of attention on the 5-CSRTT is an increase in omissions with no change in accuracy, which was the outcome reported by Jakala (1992). While all task and signal parameters were held constant, peripheral administration of scop HBr resulted in an increase in the omission rate at all doses (0.05, 0.1, 0.15, and 0.2 mg/kg IP) with no change in accuracy observed. Similar outcomes were reported in a later study in which the upper limit of the scop HBr dose range was increased (0.1, 0.2, 0.3 and 0.4 mg/kg IP) (Hodges et al., 2009). This study also held the signal and task parameters constant throughout testing; however, both the signal and trial durations were slightly longer compared to those employed by Jakala.

While these studies demonstrate effects of scop HBr on lapses in attention in a static environment, others have shown how reduced ACh interacts with variations in attentional load. Similar to the aforementioned studies, Jones also reported that scop HBr increased omissions, albeit at a lower dose range (0.01, 0.03, and 0.075 mg/kg SC), without affecting accuracy (Jones et al., 1995). In this study, however, the increase in omissions was dependent on the dose level and brightness of the signal. At the highest dose, scop HBr increased the omission rate regardless of signal brightness, and when the attentional load was increased via reductions in signal brightness, the increase in omissions was elicited at the mid dose. Finally, the findings reported by Shannon and colleagues also suggest an effect on lapses in attention, even though both accuracy and omissions were affected. In this case, omissions were selectively affected when the

attentional load was decreased and the effort required for sustain attention was lessened as the signal duration increased (Shannon & Eberle, 2006).

In sum, although there have been conflicting theories regarding the representation of behavioral measures and specificity of effect, there is evidence suggesting that the omission rate on the 5-CSRTT is representative of lapses in attention. Evidence from these studies has shown an increase in the rate of omissions following the systemic administration of scop HBr at doses lower than those that have been reported to affect performance accuracy. Additionally, some have reported the effects on omission rate to occur independently of signal duration but not signal intensity (Jones et al., 1995; Shannon & Eberle, 2006).

Methylscopolomine

The cholinergic system is diffuse and has pathways outside of the central nervous system, so it is important to differentiate the central and peripheral effects following systemic drug administration. Since ACh also serves to regulate the PNS at muscle targets receptor subtypes, disruption in motor control can present an unwanted confound. The peripheral effects of systemic scop HBr appear to be mediated by M3 (muscarinic) receptor subtypes at smooth muscle and blood vessel targets. Although physiological effects, such as lens accommodation or pupil dilation, have been reported at doses as low as .01 mg/kg, behavioral deficits are rarely reported at doses lower than 0.5 mg/kg (Drinkenburg et al., 1995). Additionally, impaired motor functioning and increased locomotor activity have both been reported at doses as low as 0.5 mg/kg (Drinkenberg et al., 1995). Therefore, attentional studies in rats rarely administer doses higher than 0.25mg/kg.

Some studies have included a drug group given methylscopolamine, or scopolamine methylbromide (scop MBr), which is a quaternary form of scopolamine that has the same

receptor binding characteristics but does not readily cross the blood–brain barrier (Klinkenberg & Blockland, 2010). If performance impairments are seen at a given dose of scop HBr, and an equivalent dose of methylscopolamine does not produce the same impairments, it can be assumed that the effects are mediated by a mechanism within the CNS. For example, Jones and Higgins (1995) reported an increased distractibility following SCOP HBr could not be reproduced by similar doses of methylscopolamine, thus excluding possible peripheral actions. However, central effects following the administration of methylscopolamine have been reported (Andrews et al., 1994; Dunnett et al., 1990; Jones & Higgins, 1995). Because of this, it is commonplace to not include a separate group as a peripheral control, but rather have at least one performance measure that is sensitive to motor, sensory, and other non-attentional impairments. For example, on most attentional tasks, the motor contribution to the individual latencies has approximately the same motor requirements; however, on the 2-CSRTT, the motor requirements of movement time are far greater than those needed for initiation time. Peripheral motor impairments can therefore be measured by comparing MT (Richards et al., 2011).

Predictions/Hypotheses

While omission rates on the 5-CSRTT are the most commonly referenced indicators of attentional lapse within the rodent literature, the most reliable indicator of lapses across species is reaction-time variability. ADHD is currently the most commonly diagnosed neurodevelopmental psychiatric disorders, affecting an estimated 8-11% of children aged 4-17 in the United States (cdc.gov/ncbddd/adhd/ data.html), and the variability of RT latency, as measured on continuous performance tests of attention, has emerged as the strongest indicator of an ADHD diagnosis by specifically quantifying lapses in attention (Conners, 2000; Epstein et al., 2003; 2010). Within the human attentional and ADHD literature, the most often cited method of

analysis for RT latency is the Ex-Gaussian method, which separates latency distributions into mu (μ), sigma (σ), and (τ), or the mean of the normal component, standard deviation of the normal component, and mean of the exponential component, respectively (see p.15) (Luce, 1986; Leth-Steensen et al., 2000; Spencer et al., 2009; Tamm et al., 2012). In doing so, the measure of attention (mu) and the measure of lapses (tau) can be reliably dissociated and analyzed separately. The mode/devmode method of RT distribution analysis provides a similar dissociation of attention and lapses in attention but eliminates the influence of any potential outliers (Richards et al., 2011). This method of RT distribution analysis has been used in conjunction with the 2-CSRTT to study attention in a rodent model; therefore providing an investigational starting point for the proposed experiments (Sabol et al., 2003; Damico, 2004; Hausknecht et al., 2005).

Although evidence of lapses in attention is abundant in the human literature, it has not carried over to a rodent model due to the inherent parameter restraints of signal detection tasks and the 5-CSRTT. The reliable assessment of lapses in attention calls for the precise measurement of RT latency. While human subjects can be verbally instructed to remain engaged in the task and vigilant to the presentation of a stimulus, there is no way to ensure the same for rodents. In fact, it is commonplace for behaviors such as grooming, sleeping, and exploring to be observed at the time of the signal presentation (Robbins, 2002). Of the current rodent models, the 2-CSRTT most closely emulates human continuous performance tasks. A trial can only be initiated when the animal's head is in a fixed position, thus ensuring that the signal presentation will always be within the peripheral field of vision and orienting will be covert (Richards et al., 2011).

The proposed experiments will use the above-described 2-CSRTT to measure RT latency and the mode/devmode method of analysis to examine the differential effects of scop HBr and attentional stress on attention and lapses in attention. For the first experiment, performance will be evaluated under five conditions of varied signal salience, with the signal intensity being held constant and house light intensity being varied. For the second experiment, the number of signal salience conditions will be reduced to three and scop HBr will be administered peripherally at doses of 0.1 and 0.25 mg/kg (IP).

Table 1: Experimental design matrices

Independent Variable
Salience

Experiment 1					
	1	2	3	4	5
IT Mode					
IT DevMode					
Omissions					
Pre Initiations					
Pre Responses					

Independent Variables
Scopolamine HBr
Salience

Experiment 2									
	Saline			0.1 mg/kg			0.25 mg/kg		
	High	Mid	Low	High	Mid	Low	High	Mid	Low
IT Mode									
IT DevMode									
Omissions									
Pre Initiations									
Pre Responses									

Hypotheses (Attention)

Salience. Attentional performance has been shown to be a function of signal salience and influenced by parameters such as brightness and duration, and when signal salience is reduced, the time and effort requirements needed for attentional success are increased (Posner, 1980; Parasuraman et al., 1987; McGaughy & Sarter, 1995). This holds true across all rodent models of

attention. With respect to signal intensity, two studies using the 2-CSRTT and the mode/devmode method of analysis reported an increase in IT mode following reductions in signal salience, and using a signal detection task, Bushnell and colleagues reported a signal intensity dependent decrease in the P (hit) rate (Bushnell et al., 1997; Sabol et al., 2003; Hausknecht et al., 2005). Similar effects have also been reported in the 5-CSRTT literature, as evidenced by Risbrough and Shannon who both reported a signal intensity dependent decrease in performance accuracy, as well as signal duration dependent effects, with decreased accuracy observed between the longest and shortest signal durations (Risbrough et al., 2002; Shannon & Eberle, 2006). Similarly, Mcquail and colleagues reported a signal duration dependent decrease in the P (hit) rate using a signal detection task (Mcquail & Burk, 2006; Shannon & Eberle, 2006).

The proposed experiment examined the effects of decreased signal saliency on IT mode by varying the intensity of the chamber light while holding steady the signal intensity, and in addition to the two salience levels reported in the Sabol and Hausknecht studies (0% and 100% salience), this experiment introduced salience conditions of 25%, 50%, and 75% . We hypothesized that IT modes would increase as the salience of the signal decreases and that effects would be most pronounced when the signal was most salient.

Scopolamine HBr. The ability to sustain attention has been shown to be impaired in rodents following the administration of systemic scopolamine HBr; however, the evidence has been inconsistent across attentional models. With respect to both effect and dose, the most congruent findings come from the 5-CSRTT literature wherein decreases in performance accuracy have been consistently reported at a dose level of 0.1 mg/kg (Jones et al., 1995; Mirza & Stolerman, 2000; Shannon & Eberle, 2006). Similarly, Bushnell and colleagues reported a decreased P (hit) rate at the same dose level using a signal detection task, while Mcquail and

Burk reported a decreased the P (hit) rate following IP injections of scopolamine HBr but only at a dose level of 0.3mg/kg (Bushnell et al., 1997; Mcquail & Burk, 2006).

Attentional impairments have not been shown across all models of attention, as no effects were observed on IT mode at a dose of 0.1 mg/kg using the 2-CSRTT and mode/devmode method of analysis (Damico, 2004). This lack of an effect may be due to the inherent differences between measures, as reaction-time latency is a continuous variable, whereas performance accuracy and P (hit) are calculated as dichotomous measures. It may also be possible that the construct representations differ from what is currently argued in the rodent attentional literature and are therefore not comparable between models. Lastly, it is possible that the lack of an observed effect may be a matter of dosing, similar to the Mcquail study, and a higher dose is necessary in order to elicit an attentional impairment. Therefore, the current study increased the highest administered dose of scopolamine HBr from 0.1 mg/kg to 0.25 mg/kg and testing occurred under three levels of signal intensity (0, 50, & 75% salience), as experiment one showed no difference in IT mode between 75% and 100% saliency. We hypothesized that an increase in IT modes will be observed at the 0.25 mg/kg dose compared to 0.1 mg/kg and saline treated animals.

Hypotheses (Lapses in Attention)

Salience. Reducing the intensity of a signal presentation has been shown to increase lapses in attention. It has been theorized that, in rodents, lapses are indicated by changes in omission rates that occur independently of changes in accuracy on the 5-CSRTT and changes to IT devmodes on the 2-CSRTT. Evidence also suggests that these measures of lapses are more sensitive to the effects of decreased signal salience compared to the measures that are theorized

to be indicative of attention (Jones et al., 1995; Sabol et al., 2003; Risbrough et al., 2002; Damico, 2004; Hausknecht et al., 2005; Shannon & Eberle, 2006; Antonini et al., 2013).

The proposed experiment introduced five conditions of varied signal intensity (0, 25, 50, 75, and 100% salience), which provided multiple opportunities to examine the effects of decreased signal salience on IT devmode and allowed for a comparative examination of measures between models. We hypothesized that incremental decreases in signal intensity would increase IT devmode, and we hypothesized that an effect would be observed between all conditions.

Scopolamine HBr. Studies from the 5-CSRTT literature have reported an increase in omission rates in the absence of a change in accuracy following the systemic introduction of scopolamine HBr at a dose range of 0.05 to 0.1 mg/kg (Jakala et al., 1992; Jones et al., 1995; Shannon & Eberle, 2006; Hodges et al., 2009). Similar to the attentional effects of scopolamine HBr, evidence has not been congruent across rodent models. For example, a dose of 0.1 mg/kg scopolamine HBr failed to elicit a change in the IT devmode on the 2-CSRTT (Damico, 2004). The reasons for this inconsistency may be the same as those discussed previously in the scopolamine HBr and attention hypothesis. Therefore, for the current study, scopolamine HBr dosing began with the maximum ineffective dose reported by Domico (0.1 mg/kg) and the highest dose level was increased to 0.25 mg/kg IP. We hypothesized that an increase in IT devmodes would be observed at the highest dose of 0.25 mg/kg compared to the 0.1 mg/kg and saline treated animals.

Salience x Scopolamine HBr. Omissions on the 5-CSRTT have been shown to be sensitive to the additive attentional effects of decreased signal intensity and reductions in global ACh transmission (Jones et al., 1995). Therefore, as was mentioned earlier, testing occurred

under three levels of signal intensity (0, 50, & 75% salience), and IT devmode was measured for all drug conditions under all signal intensity levels. We hypothesized that the predicted scopolamine induced increase in IT devmodes would perhaps be observed under the mid and low salience conditions for the 0.1 mg/kg dose compared to saline treated animals, while increases would be observed under all salience conditions for the 0.25 mg/kg group compared to the 0.1 mg/kg and saline treated animals.

III. METHODS

Animals

Experiments used mature Sprague-Dawley rats (Harlan) weighing 250-300g upon arrival to the animal housing facility. Rats (N=20) were pair-housed in plastic cages with filtered tops, and lights were on in the colony room from 7:00 AM to 7:00 PM. Rats were water restricted compared to age-matched, ad lib controls and were only allowed access to water 20-minutes per day for the duration of training and testing, as well as a 24-hour period of unrestricted water access every Friday - Saturday. Experiments were conducted in accordance to the standards of NIH and the Institutional Animal Care and Use Committee of the University of Mississippi (protocol 13-031, approval date 6-17-2013).

Drug Information

Scopolamine Hydrobromide (Sigma-Aldrich, USA) was dissolved in saline and injected i.p. (0.1 and 0.25 mg/kg) 30-minutes prior to testing. Doses were calculated using freebase concentration from salt, and control animals were given injections of saline at an equivalent volume (1 ml/kg).

Apparatus

Animals were trained and tested in four operant chambers constructed of Plexiglas, aluminum, and stainless steel with overall dimensions of L 22.5 x W 20 x H 20 cm. Access to the chambers was gained through a hinged front panel, which was latched for duration of each training and testing session. Each chamber had a house light mounted on the back wall 13 cm

above the floor with a maximum illumination intensity of 6.0 fc. A center nose-poke hole was located opposite on the front wall, which served as the testing panel, 5.0 cm above the floor withresponse nose-poke holes located 5.5 cm to either side. Stimulus lights were located above each response port. When the animal was positioned in the center nose-poke hole, the left and right stimulus lights were in the same horizontal line with the eye line. Chambers were individually housed inside dark, sound attenuating containers. Dispensers located behind each response port delivered water into a small, recessed Plexiglas bowl at volume of 50uL. Each dispenser consisted of a 28-V solenoid valve attached to a separate 600 ml reservoir (Thermo-Scientific Nalgene) by 20 mm PVC tubing. Water dispensers were calibrated by adjusting the amount of water in the reservoir prior to beginning the training sequence and volume was confirmed prior to each session. All ports were monitored with infrared photocell beam detectors located 0.5 cm behind the front panel. Experimental contingencies and data collection were controlled using MED-PC software. Chamber lights and stimulus lights were calibrated prior to the onset of training, and brightness was verified weekly throughout training and testing. For calibrations, a photometer with sensor was placed directly in front of each light. With the room lights on, the Plexiglas chamber doors were shut but not latched, and the exterior container doors were shut and latched.

Signal Salience

The stimulus light was maintained at a maximal brightness of 6.0 fc (foot candles) in each chamber throughout testing for all experiments. Manipulations to saliency involved changes to the chamber light only, with its maximum brightness being equal to that of the stimulus light (6.0 fc). Signal salience conditions are shown in the following table:

Table 2: Signal salience conditions

Salience 1	Chamber light held at 0% of max brightness (most salient)
Salience 2	Chamber light held at 25% of max brightness
Salience 3	Chamber light held at 50% max brightness
Salience 4	Chamber light held at 75% of max brightness
Salience 5	Chamber light held at 100% of max brightness (least salient)

Reaction-Time Training

All phases of training were performed in the salience 1 condition with the chamber light off and the signal light illuminated. The first phase of training introduced the animals to the task requirements. A water drop was placed into the center port and both feeder holes at the start of the session on the first day. Collection of water in the center port triggered the onset of the stimulus following a foreperiod of 0.1s, with the likelihood of presentation to either the right or left side being equal. The stimulus light remained on until the collection of water in the response port directly under the illuminated signal. If the animal had not yet begun to respond by the second day, behavioral shaping was introduced. This phase of training continued until all rats had completed 100 trials within 45-min with 70% or greater correct responses. Once this performance criterion had been reached, the duration of the foreperiod was lengthened by one second each day until a maximum hold time of 6s was reached. Keeping all other parameters the same, this continued until all rats completed 100 trials within 45-min with 70% or greater correct responses.

Final parameters

Maintaining the 6 s max foreperiod requirement, the final phase of training introduced a response time requirement for reward into the overall performance criteria. A response time criterion of 0.71s was placed on all rats for the first trial, and for every two rewarded responses made subsequently, the criterion was reduced. Oppositely, for every unrewarded response, the

criterion was increased. The reward determination schedule in seconds was as follows: 2700, 10, 5, 2.5, 1, 0.89, 0.79, ***0.71***, 0.63, 0.56, 0.50, 0.45, 0.40, 0.35, 0.32, 0.28, 0.25, 0.22, 0.20, 0.18, 0.16, 0.14, 0.13, 0.12, 0.11, 0.01. Training ended when all rats had met the criteria for performance stability, which was defined as a difference in initiation time mean (see below) of no more than 4% for five consecutive sessions. Training occurred at 100-trials per day, five days per week.

Behavioral Measures

Initiation time is defined as the time occurring between the onset of the stimulus light and the removal of the nose from the center port. *Movement time* is defined as the time occurring between the removal of the nose from the center port and insertion of the nose into the response port. Initiation time and movement time collectively constitute *reaction time*, which is defined as the time occurring between the onset of the stimulus light and insertion of the nose into the corresponding response port. For initiation time and movement time, the *mode* was the measure of central tendency analyzed, and it was computed by grouping reaction times into 50-ms bins and computing a running frequency for bins: 0–50 ms, 10–60 ms, 20–60 ms, and so on. The midpoint of the 50-ms bin with the highest frequency of reaction times provided the estimate of the mode. In order to measure the direction and degree of distributional skew, *deviation from the mode* (DevMode) was computed by subtracting the modal time from the mean time. Trials in which a response was made to the incorrect port were not included in the analysis of initiation time and movement time.

Omissions were defined as an initiation time equal to or greater than 2s. A *premature initiation* occurred when the nose was removed from the center port prior to the onset of the stimulus light but a response was not completed. A *premature response* occurred when the nose

was removed from the center point prior to the onset of the stimulus light and the head was inserted into a response port. Because longer foreperiods provided more opportunities for premature initiations and premature responses, data for each was computed as a rate measure. Data were divided into three foreperiods: 0 – 200s, 200 – 400s, and 400 – 600s, and the number of premature initiations and premature responses was divided by the duration of the foreperiod calculated in seconds For each categories.

Procedure

Following arrival, rats were allowed to acclimate to the facility for one-week and had unrestricted access to water during this time. Water restriction began at the onset of the second week, with experimental rats allowed access to water 20-minutes at the end of every day, as well as a 24-hour period of unrestricted water access every Friday. Training began the Monday of the third week.

For both training and testing, a trial commenced when the rat placed and held its nose in the center port. After a variable amount of time, ranging from 0.3 to 6 s, a stimulus light was presented to either the right or left side and remained illuminated until a response was made. This variable period of time, known as the foreperiod, was cumulative, so if the animal did not wait the full duration following initial entry into the center port, time was added when the rat returned its head back to the center port. A response was rewarded with a 50uL water drop when, following the onset of the stimulus, the photocell beam located directly under the illuminated stimulus light was broken by a nose-poke and the response time criteria described above were met. For each experiment, testing was conducted daily with each rat running one session per day. Each session ended after 30-minutes or 100 trials, whichever came first.

Experiment One

Experiment one examined the effects of signal salience on attentional performance. Testing occurred five-days per week. Each rat ran a single session per day under a single condition and was tested under every condition each week. Signal salience was introduced as the within-subjects factor at five levels. As was stated earlier, manipulations to saliency involved changes to the chamber light only. Following task acquisition under the most salient condition with a maximal foreperiod of 6s, training concluded and testing began. For testing, rats were subject to a maximum foreperiod of 6s, which was cumulative, and the administration of reward was dictated by the aforementioned determination schedule (see *final parameters*). Condition order was determined using a Latin Square. We were interested in determining if performance would improve over time, so each rat was tested under each condition a total of four times and testing lasted a total of four-weeks.

Following the completion of experiment 1, rats were given a three-week rest period with unrestricted access to water. Restrictions were reinstated on Monday of the fourth week, and sessions resumed at the onset of the following week. At this time, the third phase of training was re-introduced and ran until rats had again met the performance criterion of an initiation-time mean difference of no more than 4% for five consecutive sessions. It took twelve days for all rats to meet criteria, and testing for experiment 2 began the following day. Rats were again subject to a maximum, cumulative foreperiod of 6s, as well as to a response time requirement for reward as set by the reward determination schedule.

Experiment Two

Experiment two examined the effects of scopolamine HBr and signal salience on attentional performance in high and low variability responders. Signal salience was again used as

a within-subjects factor; however, performance was tested only under conditions one, three, and four. Determination as to which conditions were carried over was based on the preliminary analysis of data from experiment 1, as an effect on IT DevMode but not IT Mode was observed between salience conditions three and four. Scopolamine HBr was introduced as a second within-subjects factor at three dose levels (saline, 0.1 & 0.25 mg/kg). Daily assignments were determined using two 3x3 orthogonal Latin Squares, one for the three signal salience conditions (1, 3, & 4) and the other for the three drug conditions (A, B & C) (Gao, 2005). Subject number determined daily condition assignment. Each rat ran a single testing session per day under a single drug/salience condition, and testing ran for nine-days.

Table 3: Testing schedule for experiment 2

Rat #	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
1	1_A	3_B	4_C	3_C	4_A	1_B	4_B	1_C	3_A
2	3_B	4_C	3_C	4_A	1_B	4_B	1_C	3_A	1_A
3	4_C	3_C	4_A	1_B	4_B	1_C	3_A	1_A	3_B
4	3_C	4_A	1_B	4_B	1_C	3_A	1_A	3_B	4_C
5	4_A	1_B	4_B	1_C	3_A	1_A	3_B	4_C	3_C
6	1_B	4_B	1_C	3_A	1_A	3_B	4_C	3_C	4_A
7	4_B	1_C	3_A	1_A	3_B	4_C	3_C	4_A	1_B
8	1_C	3_A	1_A	3_B	4_C	3_C	4_A	1_B	4_B
9	3_A	1_A	3_B	4_C	3_C	4_A	1_B	4_B	1_C

As a between-subjects factor, animals were assigned, according to baseline performance, to either the high variability group or low variability group. Assignment was determined using a median split based on IT DevModes collapsed across the final week of training. Animals that fell below the median were assigned to the low variability group, and those that fell above were assigned to the high variability group.

Data Analysis

For experiment one, each dependent variable was analyzed using a one-way, repeated measures ANOVA, with the within-subject factor of signal salience assessed at five levels. Where a significant main effect was observed, post-hoc comparisons were made between individual conditions using a Bonferroni adjusted alpha level in order to determine the source of the effect.

For experiment two, each dependent variable was analyzed using a three-way, mixed-factors, repeated measures ANOVA. The within-subject factors were signal salience assessed at three levels and scopolamine HBr assessed at three levels. The between-subjects factor was baseline performance (high and low variability). Where a significant main effect or interactions were observed, post-hoc comparisons were made between individual conditions and/or groups using a Bonferroni adjusted alpha level in order to determine the source of the effect.

IV. RESULTS

Experiment One

A repeated-measures ANOVA was run in order to better to understand the effects of signal salience on reaction-time latency. For analysis, reaction time was separated into initiation time latency (IT) and movement time latency (MT), and two components, mode and DevMode, were analyzed for each.

IT Mode

There was a significant main effect of signal salience condition on IT mode, $F(4,76) = 31.853$, $p < .0005$. Mauchly's test indicated that sphericity was assumed, $\chi^2 = 13.649$, $p = .137$. Pairwise comparisons were run between all signal salience conditions at a Bonferroni adjusted alpha level.

Post hoc analysis indicated that there were statistically significant mean differences between conditions one and two ($p = .003$); condition one and three ($p < .0005$); conditions one and four ($p < .0005$); conditions one and five ($p < .0005$); conditions two and three ($p = .006$); conditions two and four ($p = .001$); conditions two and five ($p < .0005$); and conditions three and five ($p = .009$) There were no significant differences between conditions three and four ($p = 1.0$) and conditions four and five ($p = .373$) (Figure 1).

IT DevMode

There was a significant main effect of signal salience condition on IT DevMode, $F(2.430, 46.162) = 65.028$, $p < .0005$. Mauchly's test indicated that sphericity could not be assumed, $\chi^2 =$

24.175, p =.004, so a Greenhouse-Geisser correction was applied. Pairwise comparisons were run between all signal salience conditions at a Bonferroni adjusted alpha level.

Post hoc analysis indicated that there were statistically significant mean differences between conditions one and two (p <.0005); conditions one and three (p <.0005); conditions one and four (p <.0005); conditions one and five (p <.0005); conditions two and three (p <.0005); conditions two and four (p <.0005); conditions two and five (p <.0005); conditions three and four (p = ,012); conditions three and five (p <.0005); and conditions four and five (p = .030) (Figure 2).

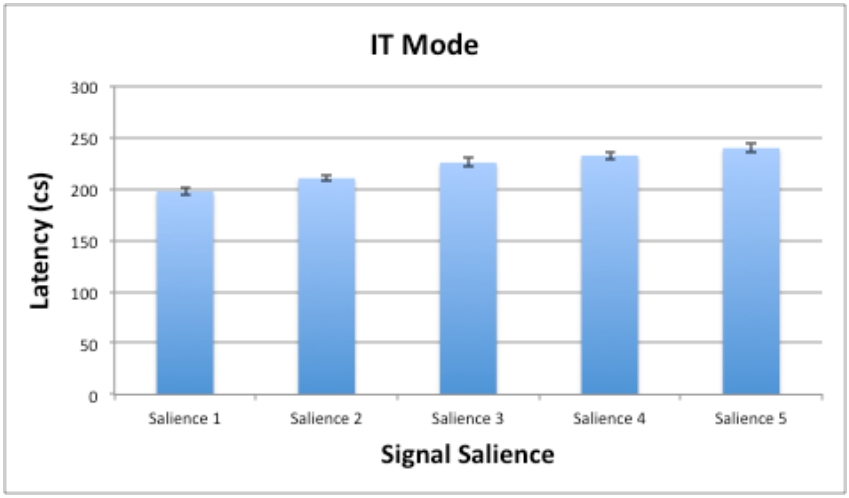


Figure 1: Effects of signal salience on IT Mode. Repeated-measures ANOVA (*Mean* ± *SEM*). Main effect of signal salience: F(4,76) = 31.853, *P*< 0.0005. Post hoc comparisons (Bonferroni correction of *P*< 0.005). 1 vs 2, 1 vs 3, 1vs 4, 1 vs 5; 2 vs 3, 2 vs 4, 2 vs 5; 3 vs 5

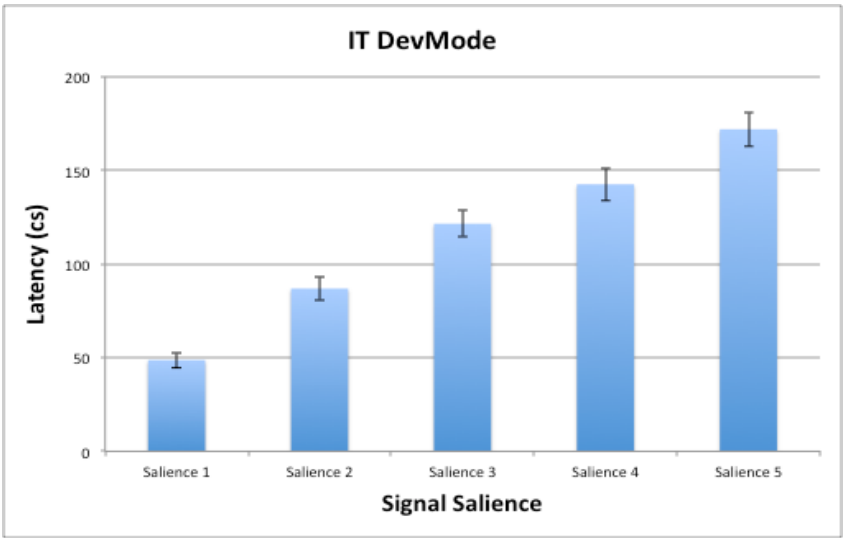


Figure 2: Effects of signal salience on IT DevMode. Repeated-measures ANOVA. Main effect of signal salience: F(2.430, 46.162) = 65.028, *P*< 0.0005. Post hoc comparisons (Bonferroni correction of *P*< 0.005). 1 vs 2, 1 vs 3, 1 vs 4, 1 vs 5; 2 vs 3, 2 vs 4, 2 vs 5; 3 vs 4, 3 vs 5; 4 vs 5

MT Mode

There was a significant main effect of signal salience condition on MT mode, F(4,76)= 3.784, p =.007. Mauchly's test indicated that the assumption of sphericity was met, χ^2 = .14.881, p = .096. However, when pairwise comparisons were run between conditions at an adjusted Bonferroni alpha level, no significant differences between conditions were reported (Figure 3).

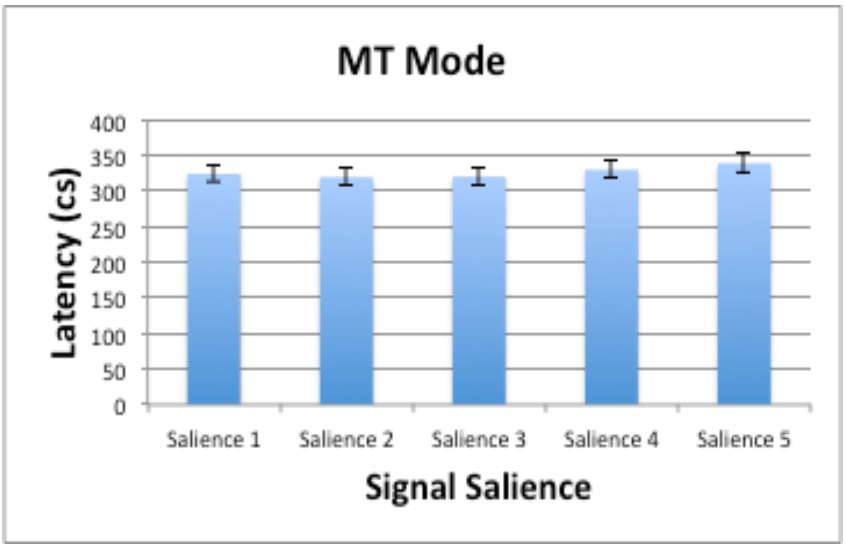


Figure 3: Effects of signal salience on MT Mode. Repeated-measures ANOVA. Main effect of signal salience: $F(4,76) = 3.784$, $P = 0.007$. Post hoc comparisons (Bonferroni correction of $P < 0.005$). No differences between conditions

Omissions

There was a significant effect of signal salience condition on the number of omissions, $F(4,72) = 32.423$, $p < .0005$. Mauchly's test indicated that the assumption of sphericity was met, $\chi^2 = 15.422$, $p = .081$. Pairwise comparisons were run between conditions at a Bonferroni adjusted alpha level.

Post hoc analysis indicated that there were statistically significant mean differences between conditions one and three ($p = .005$); conditions one and four ($p < .0005$); conditions one and five ($p < .0005$); conditions two and four ($p = .003$); conditions two and five ($p < .0005$); conditions three and four ($p = .005$); and conditions three and five ($p < .0005$) (Figure 4).

Premature Initiations

There was a significant effect of signal salience condition on premature initiations, $F(4,72) = 9.762$, $p < .0005$. Mauchly's test indicated that the assumption of sphericity was met, χ^2

= 13.078, p = .161. Pairwise comparisons were run between conditions at a Bonferroni adjusted alpha level.

Post hoc analysis indicated that there were statistically significant mean differences between conditions one and two (p =.001); conditions one and three (p >.0005); conditions one and four (p =.002); and conditions one and five (p =.001) (Figure 5).

Premature Responses

There was a significant effect of signal salience condition on premature response, F(4,72) =46.995, p <.0005. Mauchly's test indicated that the assumption of sphericity was met, χ^2 = 11.219, p = .263. Pairwise comparisons were run between conditions at a Bonferroni adjusted alpha level.

Post hoc analysis indicated that there were statistically significant mean differences between conditions one and two (p <.0005); conditions one and three (p <.0005); conditions one and four (p <.0005); conditions one and five (p <.0005); conditions two and three (p =.003); conditions two and four (p <.0005); conditions two and five (p <.0005); and conditions three and five (p =.021) (Figure 6).

Completed Trials

There were no significant effects of signal salience condition on the total number of completed trials, F(4,72)= 1.827, p =.133 (Figure 7).

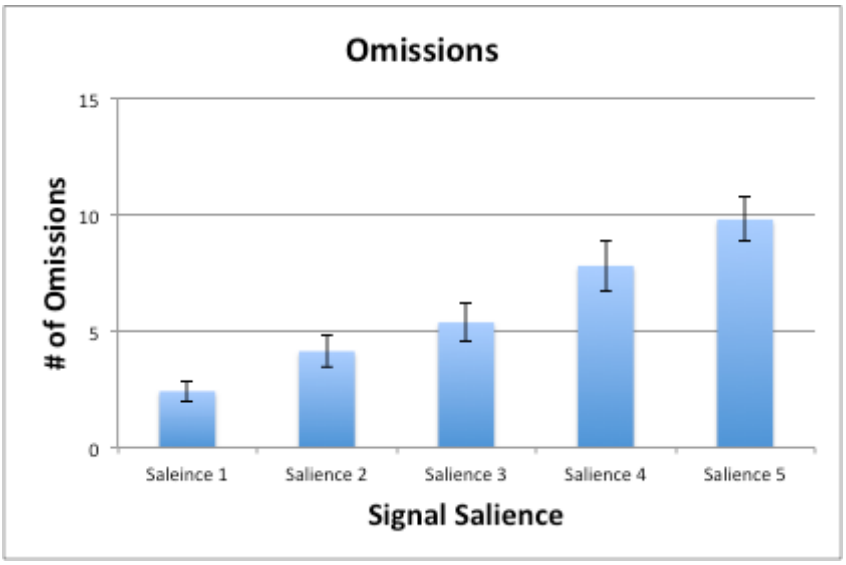


Figure 4: Effects of signal salience on omissions. Repeated-measures ANOVA. Main effect of signal salience: $F(4,72) = 32.423$, $P < 0.0005$. Post hoc comparisons (Bonferroni correction of $P < 0.005$). 1 vs 3, 1vs 4, 1 vs 5; 2 vs 4, 2 vs 5; 3 vs 5; 4 vs 5

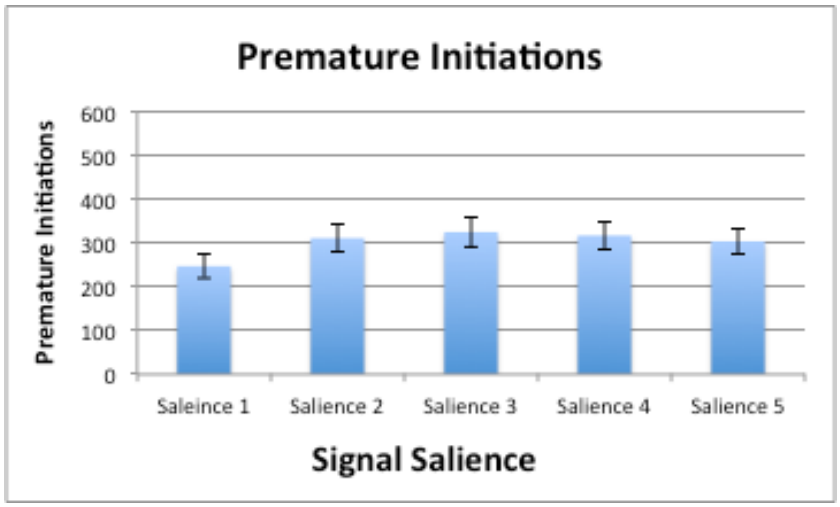


Figure 5: Effects of signal salience on premature initiations. Repeated-measures ANOVA. Main effect of signal salience: $F(4,72) = 9.762$, $P < 0.0005$. Post hoc comparisons (Bonferroni correction of $P < 0.005$). 1 vs 2, 1 vs 3, 1 vs 4, 1 vs 5

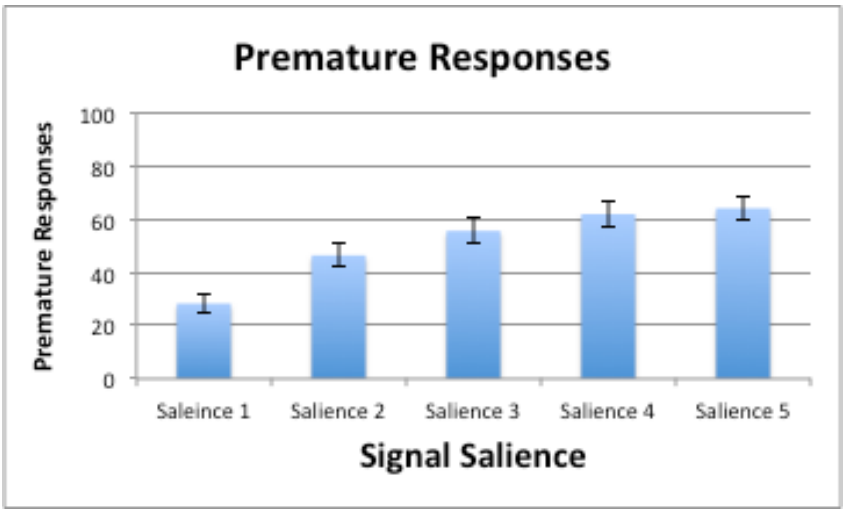


Figure 6: Effects of signal salience on premature responses. Repeated-measures ANOVA. Main effect of signal salience: $F(4,72) = 46.995$, $P < 0.0005$. Post hoc comparisons (Bonferroni correction of $P < 0.005$). 1 vs 2, 1 vs 3, 1 vs 4, 1 vs 5; 2 vs 3, 2 vs 4, 2 vs 5; 3 vs 5

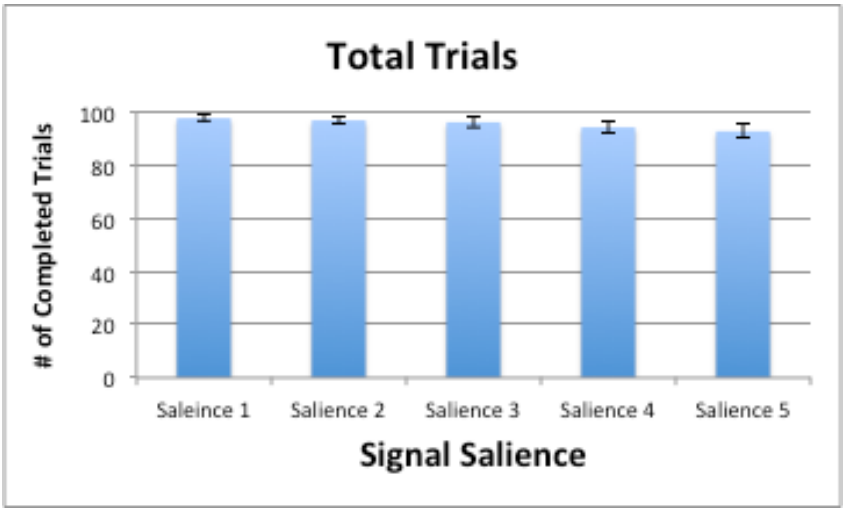


Figure 7: Effects of signal salience on the total number of completed trials. Repeated-measures ANOVA. No effects of signal salience: $F(4,72) = 1.827$, $P = 0.133$

Experiment Two

A three-way, mixed factors, repeated measures ANOVA was run in order to better understand the effects of scopolamine hydrobromide (scop HBr), signal salience, and intra-individual variability on reaction-time latency. For analysis, reaction-time latency was separated into initiation time latency (IT) and movement time latency (MT), and two components, mode and DevMode, were analyzed for each.

IT Mode

There was a significant effect of signal salience condition on IT mode, $F(2,34)= 8.026$, $p =.001$. Mauchly's test indicated that the assumption of sphericity was met, $\chi^2 = 4.618$, $p = .099$. Pairwise comparisons were run between signal salience conditions at a Bonferroni adjusted alpha level.

Post hoc analysis indicated that there were statistically significant mean differences between salience conditions one and two ($p =.006$); conditions one and three ($p = .002$), but not between conditions two and three ($p = 1.0$).

There was no significant effect of scop HBr condition on IT mode, $F(2, 34) = 1.136$, $p =.333$. There was no significant effect of baseline performance on IT mode, $F(1,17)= .974$, $p =.337$. There was no significant interaction effect between scop HBr and signal salience, $F(4, 68) = .728$, $p =.57$; no significant interaction effect between signal salience and baseline performance, $F(2,34)= 1.039$, $p =.69$; and no significant interaction effect between scop HBr and baseline performance, $F(2,34)= .598$, $p =.365$. There was no significant three-way interaction effect between scop HBr, signal salience, and baseline performance, $F(4,68)= .309$, $p =.871$ (Figure 8).

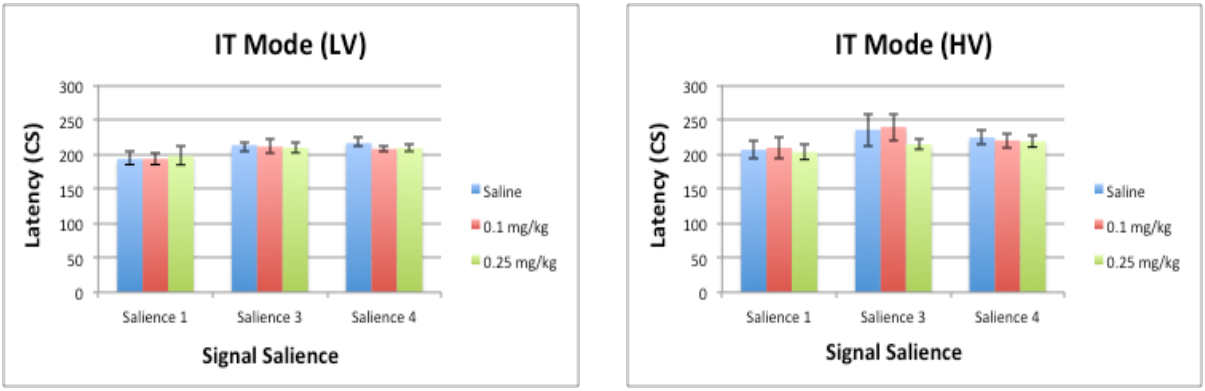


Figure 8: Effects of signal salience and scopolamine on IT Mode. Three-way, mixed factors, repeated measures ANOVA. Main effect of signal salience: F(2,34) = 8.026, *P*= 0.001. Post hoc comparisons (Bonferroni correction of *P*= 0.0167):1 vs 2, 1 vs 3. No effects of scop HBr: F(2, 34) = 1.136, *P*= 0.133. No effect of baseline performance: F(1,17) = .974, *P*= 0.337

IT DevMode

There was a significant main effect of signal salience condition on IT DevMode, F(1.459,24.795)= 20.879, p < .0005. Spherecity could not be assumed, χ^2 = 7.425, p = .024, so a Greenhouse-Geisser correction was applied. Pairwise comparisons were run between signal salience conditions at a Bonferroni adjusted alpha level.

Post hoc analysis indicated that there were statistically significant mean differences between conditions one and two (p < .0005); conditions one and three (p < .0005), but not conditions two and three (p = .173).

There was no significant effect of scop HBr condition on IT DevMode, F(2, 34) = .830, p =.445. There was no significant effect of baseline performance on IT DevMode, F(1,17)= 2.215, p =.155. There was no significant interaction effect between scop HBr and signal salience, F(4, 68) = .943, p =.445; no significant interaction effect between signal salience and baseline performance, F(2,34)= .124, p =.884; and no significant interaction effect between scop HBr and baseline performance, F(2,34)= 2.239, p =.122 (Figure 9).

There was a significant three-way interaction effect between scop HBr, signal salience, and baseline performance, $F(4,68)= 2.747$, $p =.035$; a large effect size (partial $\eta^2 = .139$); and a statistically significant linear contrast, $F(1,17) = 11.579$, $p =.003$.

In order to determine if a within-subjects factor was driving the three-way interaction, separate repeated measures ANOVAs were run for each between-subjects group (high and low variability in baseline performance) at a Bonferroni adjusted alpha level. The assumption of sphericity was met for both as assessed by Mauchly's test ($p > .05$).

Post hoc analysis indicated that there was no significant two-way interaction of scop HBr and signal salience for either high-variability baseline performance, $F(4, 36) = 1.513$, $p = .219$, or low variability baseline performance, $F(4, 32) = 2.096$, $p = .104$.

For a between-subjects effect determination, three post-hoc comparisons were made between the high and low variability groups for each signal salience condition under the highest dose of scop HBr (0.25 mg/kg). Using a Bonferroni adjusted alpha level, a significant difference between baseline performance groups was observed in salience condition three, $F(1, 17) = 6.354$, $p = .022$, and condition four, $F(1, 17) = 5.406$, $p = .033$), under 0.25 mg/kg scop HBr. No difference was observed in salience condition one, $F(1, 17) = .002$, $p = .961$ (Figure 10).

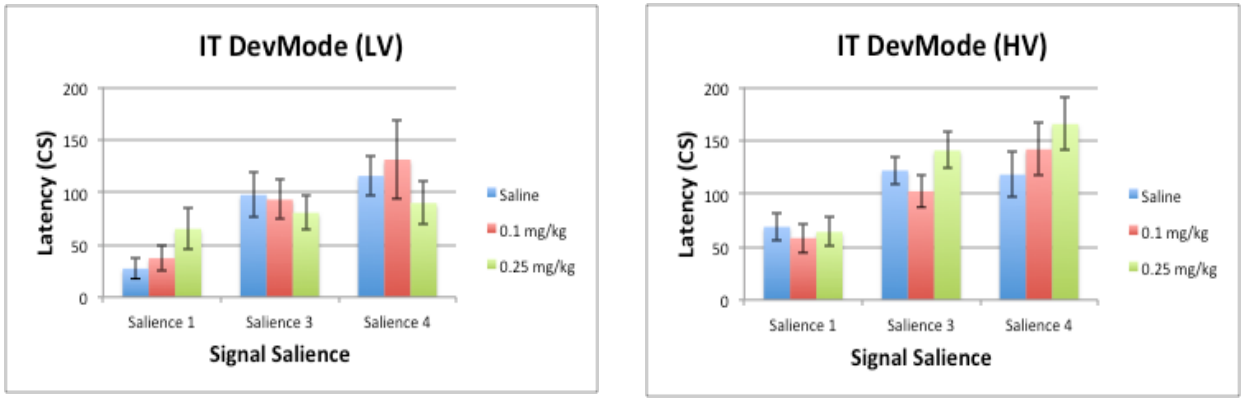


Figure 9: Effects of signal salience and scopolamine on IT DevMode Three-way, mixed factors, repeated measures ANOVA. Main effect of signal salience: F(1.459,24.795) = 20.879, *P*< 0.0005. Post hoc comparisons (Bonferroni correction of *P*= 0.0167): 1 vs 2, 1 vs 3. No effects of scop HBr: F(2, 34) = .830, P= .445. No effect of baseline performance: F(1,17)= 2.215, P= .155.

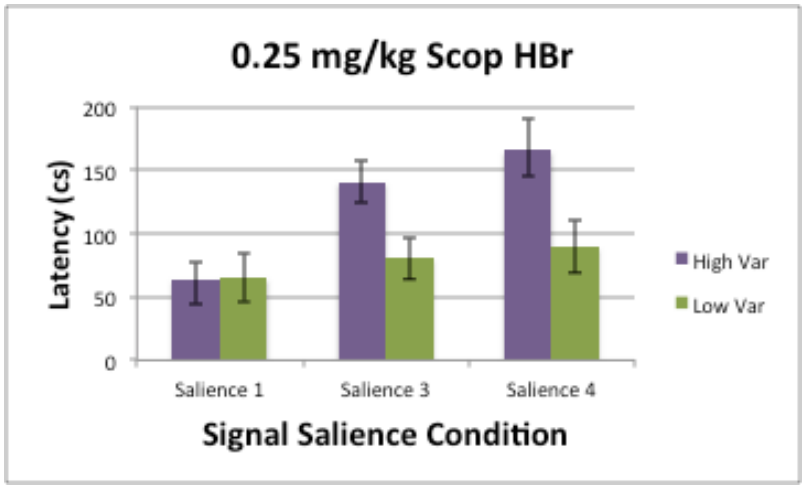


Figure 10: Three-way interaction. Significant three-way interaction effect of signal salience, scop HBr, and baseline performance: F(4,68) = 2.747, *P*= 0.035. Post hoc signal salience comparisons of LV vs HV at 0.25 mg/kg scop HBr (Bonferroni correction of *P*= 0.0167): condition 3, condition 4

MT Mode

There was no significant effect of scop HBr condition on MT mode, F(2,34)= 1.263, p =.296; no significant effect of signal salience condition on MT mode, F(2,34)= 2.408, p =.105; and no significant effect of baseline performance on MT mode, F(1,17)= .135, p =.718. There was no significant interaction effect between scop HBr and signal salience, F(4, 68) = .882, p =.479; no significant interaction effect between scop HBr and baseline performance, F(2,34)= .598, p =.555; and no significant interaction effect between signal salience and baseline performance, F(2,34)= .299, p =.744. There was no significant three-way interaction between scop HBr, signal salience, and baseline performance, F(4,68)= 2.332, p =.064 (Figure 11).

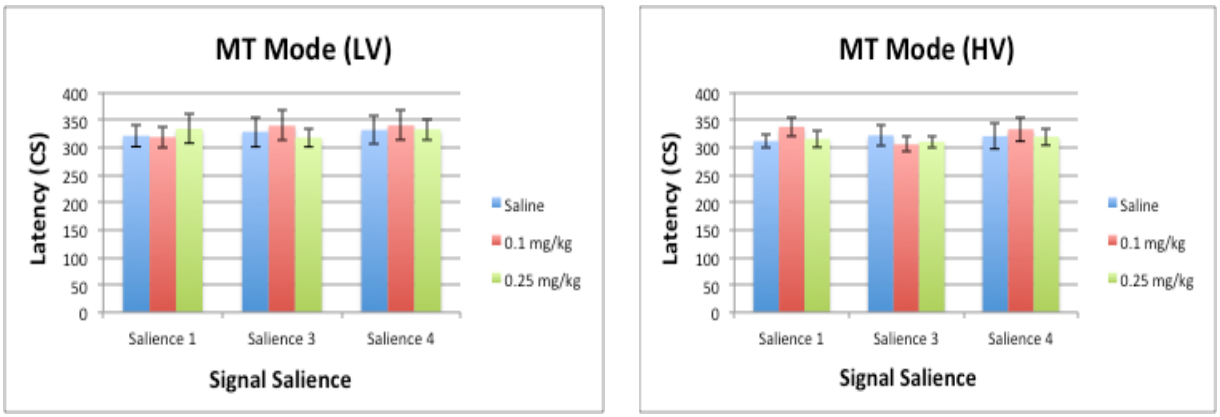


Figure 11: Effects of signal salience and scopolamine on MT Mode. Three-way, mixed factors, repeated measures ANOVA. No effects of signal salience: F(2,34) = 2.408, *P*= 0.105. No effects of scop HBr: F(2,34) = 1.263, *P*= 0.296. No effect of baseline performance: F(1,17) = .135, *P*= 0.718

Omissions

There was a significant effect of signal salience condition on the number of omissions, $F(2,34)=8.438$, $p =.001$. Mauchly's test indicated that the assumption of sphericity was met, $\chi^2 = 1.622$, $p = .444$. Pairwise comparisons were run between signal salience conditions at a Bonferroni adjusted alpha level, and post hoc analysis indicated that there was a statistically significant mean difference between salience conditions one and three ($p =.002$).

There was a significant main effect of scop HBr condition on the number of omissions, $F(2,34)= 3.895$, $p =.030$. Mauchly's test indicated that the assumption of sphericity was met for scop HBr, $\chi^2(2) = .057$, $p = .972$. Pairwise comparisons were run between scop HBr conditions at an adjusted Bonferroni alpha level, and post hoc analysis indicated that there was a significant increase in the number of omissions at the 0.25 mg/kg dose compared to saline.

There was no significant effect of baseline performance on the number of omissions, $F(1,17)= 2.043$, $p =.171$. There was no significant interaction effect between scop HBr and signal salience, $F(4,68)= .167$, $p =.955$, no significant interaction effect between scop HBr and baseline performance, $F(2,34)= .103$, $p =.903$; and no significant interaction effect between signal salience and baseline performance, $F(2,34)= 1.466$, $p =.245$. There was no significant three-way interaction between scop HBr, signal salience, and baseline performance, $F(4,68)= 1.115$, $p =.357$ (Figure 12).

Premature Initiations

There was no significant effect of scop HBr condition on premature initiations, $F(2, 34) = .112$, $p =.894$. There was a significant effect of signal salience condition on premature initiations, $F(2,34)=3.556$, $p =.040$. Mauchly's test indicated that the assumption of sphericity was met, $\chi^2 =$

4.611, p = .100. Pairwise comparisons were run between signal salience conditions at a Bonferroni adjusted alpha level.

Post hoc analysis indicated that there was a statistically significant mean difference between conditions one and three (p =.005), but not between conditions one and two (p = .515) or between conditions two and three (p = 1.0).

There was a significant effect of baseline performance on premature initiations, F(1,17)= 106.464, p =.002 (Figure 14). There was no significant interaction effect between scop HBr and signal salience on premature initiations, F(4,68)= 1.306., p =.277; no significant interaction effect between scop HBr and baseline performance, F(2,34)= .002, p =.998; and no significant interaction between signal salience and baseline performance, F(2,34)= 1.206, p =.312. There was no significant three-way interaction between scop HBr, signal salience, and baseline performance, F(4,68)= .332, p =.856 (Figure 13).

Premature Responses

There was a significant effect of signal salience condition on premature responses, F(2,34)=32.099, p <.0005. Mauchly's test indicated that the assumption of sphericity was met, χ^2 = 5.246, p = .073. Pairwise comparisons were run between signal salience conditions at a Bonferroni adjusted alpha level.

Post hoc analysis indicated that there were statistically significant mean differences between conditions one and two (p <.0005); and between conditions one and three (p <.0005); but not between conditions two and three (p =.041). There was no significant effect of scop HBr condition on premature responses, F(2, 34) = .087, p =.917.

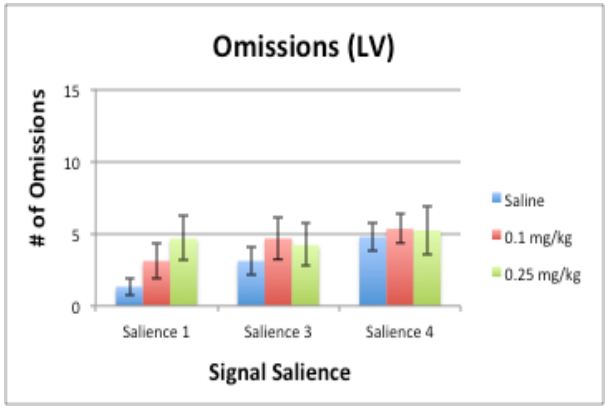
There was a significant effect of baseline performance on premature responses, F(1, 17) = 5.164, p =.036. There was no significant interaction effect between scop HBr and signal salience

on premature responses, F(4,68)= .689, p =.602; no significant interaction effect between scop HBr and baseline performance, F(2,34)= .999, p =.379; and no significant interaction effect between signal salience and baseline performance, F(2,34)= .425, p =.657. There was no significant three-way interaction effect between scop HBr, signal salience, and baseline performance, F(4,68)= 2.345, p =.063 (Figure 14).

Completed Trials

There were no significant effect of scop HBr condition on the number of completed trials, F(2,34)= 2.366, p =.109, and no significant effect of signal salience condition, F(2,34)= 9.57, p =.394.

There was a significant effect of baseline performance on the number of completed trials, F(1,17)= 5.612, p =.030 (Figure 16). There was no significant interaction effect between scop HBr and signal salience, F(4, 68) = .365, p =.833; no significant interaction effect between scop HBr and baseline performance, F(2,34)= 2.069, p =.142; and no significant interaction effect between signal salience and baseline performance, F(2,34)= .976, p =.387. There was no significant three-way interaction effect between scop HBr, signal salience, and baseline performance, F(4,68)= .328, p =.858 (Figure 15).



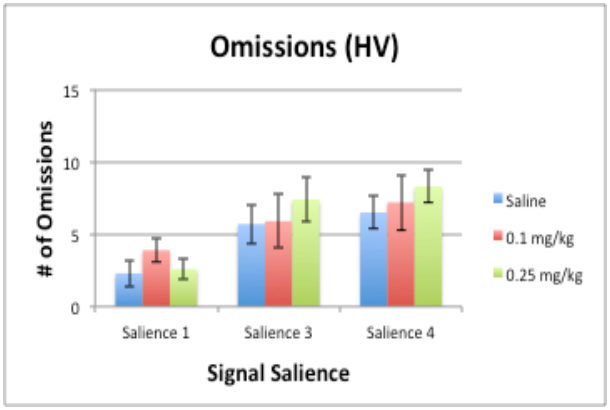
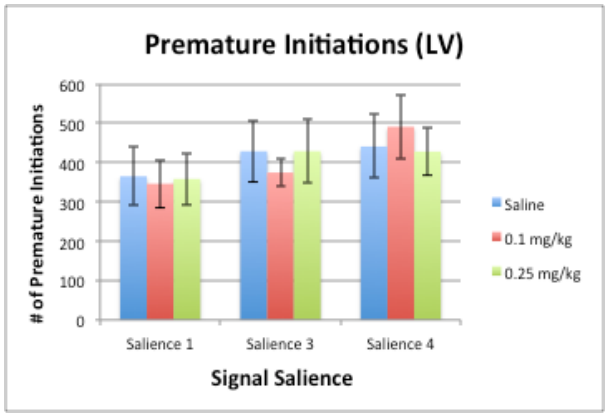


Figure 12: Effects of signal salience and scopolamine on omissions. Three-way, mixed factors, repeated measures ANOVA. Main effect of signal salience: $F(2,34) = 8.438$, $P = 0.001$. Post hoc comparisons (Bonferroni correction of $P = 0.0167$): 1 vs 3. Main effect of scop HBr; $F(2,34) = 3.895$, $P = 0.030$. Post hoc comparisons (Bonferroni correction of $P = 0.0167$): saline vs 0.25 mg/kg. No effect of baseline performance: $F(1,17) = 2.043$, $P = .171$. No significant interactions



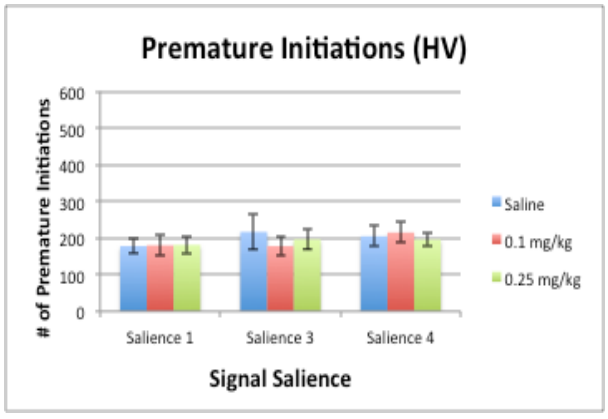
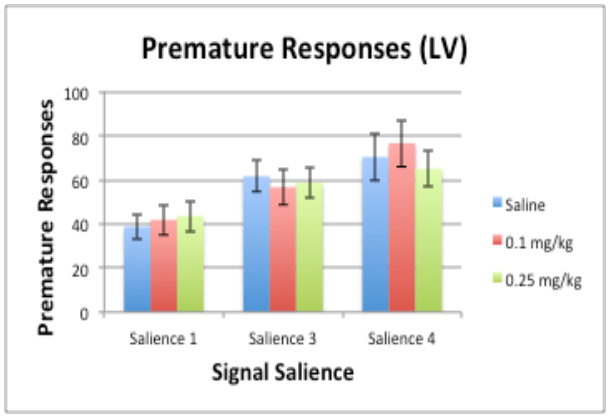


Figure 13: The effects of signal salience and scopolamine on premature initiations. Three-way, mixed factors, repeated measures ANOVA. Main effect of saliency: $F(2,34) = 8.026$, $P = 0.001$. Post hoc comparisons (Bonferroni correction of $P = 0.0167$): 1 vs 2, 1 vs 3. No effects of scop HBr; $F(2, 34) = 1.136$, $P = 0.133$. Main effect of baseline performance: $F(1,17) = 106.464$, $P = 0.002$. No significant interactions



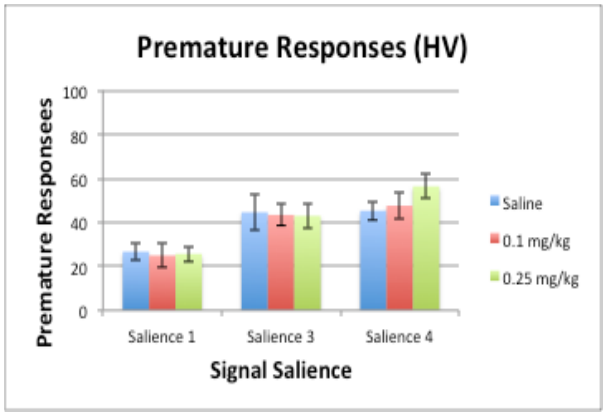
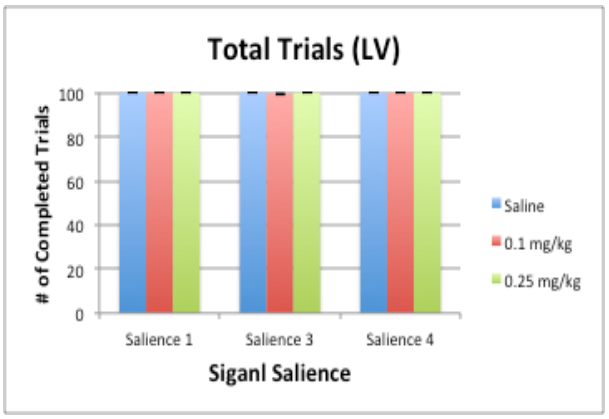


Figure 14: The effects of signal salience and scopolamine on premature responseThree-way, mixed factors, repeated measures ANOVA. Main effect of saliency: F(2,34) =32.099, *P*< 0.0005. Post hoc comparisons (Bonferroni correction of *P*= .0167): 1 vs 2, 1 vs 3. No effects of scop HBr; F(2, 34) = .087, *P*= .917. Main effect of baseline performance: F(1, 17) = 5.164, *P*= 0.036. No significant interactions



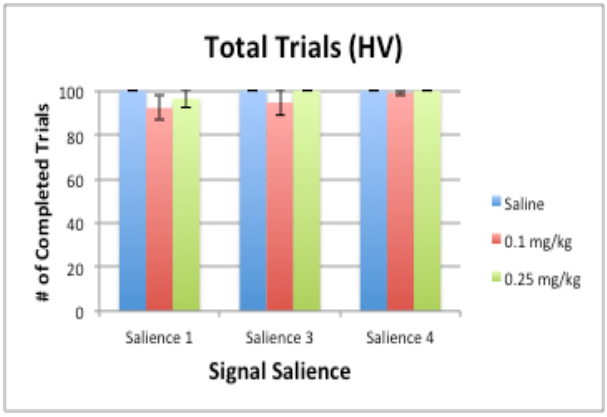


Figure 15: The effects of signal salience and scopolamine on the total number of completed trials. Three-way, mixed factors, repeated measures ANOVA. No effects of signal salience: F(2,34) = 9.57, *P*=.394. No effects of scop HBr: F(2,34)= 2.366, *P*=.109. Main effect of baseline performance: F(1,17) = 5.612, *P*= 0.030. No significant interactions

V. DISCUSSION

In the present experiments, signal salience and Acetylcholine were manipulated in a rodent model of attention in order to determine their effects on attention and lapses in attention. When salience decreases, *exogenous* attention is stressed as signal characteristics diminish, which is indicated on the current experiments by a decreased IT mode. Additionally, *endogenous* attention is stressed because more effort is needed in order to maintain vigilance when a signal is less salient. This effort is mediated by *endogenous* mechanisms. When *endogenous* attention is stressed to the point of interruption, a lapse in attention occurs. This effort is also mediated by individual factors, such as attentional capacity, resource competition, and resource allocation.

ACh facilitates *exogenous* attentional processing by enhancing characteristics, such as location, intensity, and/or duration, of a behaviorally relevant signal. This in turn facilitates *endogenous* attentional processing by decreasing the effort needed in order to maintain vigilance. ACh streamlines attention by acting as a gating mechanism, comparing signal parameters to what is already known. When the parameters of the signal meet expectations, information is quickly passed along to cortical areas mitigating the motor response. When expectations are not met, ACh aids in quickly updating and integrating new information.

In order to get a comprehensive picture of the effects of attentional stress on attention and lapses in attention in the rodent model, comparisons need to be made across models, across attentional tasks and measures, and when addressing reaction time specifically, across methods of analysis. In the currently used two-choice reaction time task and mode/devmode analysis,

reaction time is broken down into initiation time (IT) and movement time (MT). IT is the measure of interest for the proposed experiments, and it is broken down into mode and devmode.

For the current studies using the 2-CSRTT, attention is represented by IT mode and indicates sensory motor processing speed when the subject is attending to the task. For comparison, an increase in P (fa), or an incorrect response on a non-signal trial, and/or an increase in omissions indicates an attentional effect on signal detection tasks, while an attentional effect is inferred when a decrease in performance accuracy is observed on the 5-CSRTT.

Initiation-time devmode represents lapses in attention when measured using a 2-CSRTT task (Sabol et al., 2003; Hausknecht et al., 2005; Spencer et al., 2009; Richards et al., 2011). On the 5-CSRTT, lapses in attention can be inferred by an increase in omissions in the absence of a change in performance accuracy. On signal detection tasks, lapses cannot be inferred separate from attention due to the overlap of behavioral measures and were therefore not included when analyzing lapses in attention.

Signal Salience

Attention

Attention and attentional performance are functions of signal strength. Attentional performance is inversely related to attentional effort, with performance deteriorating as the required amount of effort increases. Detection of a signal when presented in a dark chamber requires the least amount of attentional effort, and the greatest increase in effort required is between salience condition 1 (most salient; dark chamber) and condition 2. Therefore, the biggest disruption in attention and attentional performance would be observed between those conditions. Therefore, we hypothesized that IT modes would increase as signal salience decreased and the effects would be most pronounced between the two most salient conditions.

Experiment one included five salience conditions, with condition 1 being the most salient and condition 5 being the least. With the signal intensity held steady at 100% max brightness, the chamber light was off for condition 1 (most salient). The chamber light was illuminated and held at 25% max brightness for condition 2, 50% for condition 3, 75% for condition 4, and 100% for condition 5 (least salient). As determined by modal IT outcomes from experiment one, three salience conditions were repeated for experiment two (1, 3, & 4).

Findings. For experiment one, IT modes were increased under salience conditions 2, 3, 4, and 5 compared to condition 1 (most salient). IT modes were also increased under conditions 3, 4, and 5 compared to condition 2. For experiment two, IT modes were increased under conditions 3 and 4 compared to condition 1, but no differences were observed between conditions 3 and 4. Results were consistent between experiments and both demonstrated that decreasing signal salience increased IT mode, which was consistent with our hypotheses.

Comparison to Prior Evidence. Results from the current study are consistent with existing 2-CSRTT evidence where, when the signal light was illuminated and held at 100% max intensity, an increase in IT modes was observed when the chamber light was illuminated and held at 100% max intensity compared to when it was turned off (Sabol et al., 2003; Hausknecht et al., 2005; Damico, 2004). Testing conditions in these studies were comparable to the least and most salient conditions from experiment one of the current study, or conditions 1 and 5 respectively.

Results from the current study are consistent with evidence reported from studies using a 5-CSRTT, wherein an attentional disruption was indicated by a decrease in performance accuracy (Risbrough et al., 2002; Shannon & Eberle, 2006). Risbrough reported decreases in performance accuracy following incremental reductions in signal intensity over four testing

conditions and signal duration over four testing conditions. Shannon reported a decrease in accuracy when the duration of the signal was reduced from 2.0s to 0.2s.

Finally, results from the current study are consistent with evidence from work carried out using a signal detection task, wherein an attentional effect was indicated by a decrease in P(hit) and an increase in omissions (McQuail & Burk, 2006). McQuail and Burk reported this effect pattern at signal durations of 25ms compared to 100 and 500ms.

Analysis of differences. Findings from the current study are consistent with the existing evidence regarding the attentional effects of decreased signal salience, and collectively, evidence is uniformly consistent across tasks.

Theory. Attention is theorized to be a function of signal salience, and when the intensity of behaviorally relevant signals decrease, the time and effort needed to accurately detect that signal increases (Posner, 1980; Carli et al., 1983; Parasuraman et al., 1987; Robbins, 2002). Signal parameters such as intensity and duration are environmental or external, and signal processes such as detection and discrimination drive attention from the bottom-up (Parasuraman, 1979; Parasuraman et al., 1987; Robbins, 2002; Warm et al., 2008). Therefore, decreasing the relative intensity of a signal places stress on exogenous attention, resulting in a predictable increase in sensorimotor processing time or disruption in attention (Risbrough et al., 2002; Sabol et al., 2003; Hausknecht et al., 2005; Shannon & Eberle, 2006).

Results Compared to Theory. Findings from the current study are consistent with the theory that attention is a function of signal strength. This is indicated in the current experiments by predictable increases in IT modes that coincide with reduction in the relative intensity of signal. As previously mentioned, IT mode on the 2-CSRTT indicates sensorimotor processing time when ready to attend or attention.

Lapses in Attention

We hypothesized that decreasing the salience of the signal would increase IT devmodes, and we predicted effects would be observed between all conditions. Again, experiment one included five conditions, with condition 1 being the most salient and condition 5 being the least. Testing conditions for experiment two were determined by results from experiment one, and three salience conditions were repeated (1, 3, & 4).

Findings. For experiment one, increased IT devmodes were observed between all successive salience conditions. For experiment two, increased IT devmodes were observed under conditions 3 and 4 compared to condition 1 (most salient) but not between conditions 3 and 4. While results from experiment one fully supported our hypothesis, results from experiment two only partially supported our hypothesis due to lost effect between conditions 3 and 4.

Comparison to Prior Evidence. Results from both experiments are consistent with findings from previous work carried out using the 2-CSRTT (Sabol et al., 2003; Hausknecht et al., 2005; Damico, 2004). On the 2-CSRTT, lapses in attention are represented by IT devmode, and in all three studies, an increase in IT devmodes was reported between the most and least salient conditions. These conditions are comparable to conditions 1 and 5, respectively, from experiment one of the current study.

Our results are consistent with previous findings from work carried out using a 5-CSRTT. Presenting a signal at intensity levels of 100%, 14%, 8%, and 3% maximum brightness, an increase in omissions was reported under the three less salient conditions (14%, 8%, and 3%) compared to the most salient (100%), while no effect of signal intensity on accuracy was observed (Jones & Higgins, 1995). This effect is consistent with both experiments in the current study, in that performance was impaired in the less salient conditions compared to the most

salient condition. Results from the current study are inconsistent, however, with the aforementioned Risbrough study, which reported no effects of reduced signal intensity (100%, 33%, 10%, and 0%) or duration (0.5, 0.25, 0.15, and 0.05s) on omissions (Risbrough et al., 2002).

Analysis of Differences. While the collective evidence indicates that reductions in signal salience will increase lapses in attention, one study stands alone in reporting no effect over a range of intensities and durations (Risbrough et al., 2002). In reviewing this study, the authors do not include a measure of brightness for the signal (e.g., lux or footcandles). Without this value, it is impossible to know how the absolute intensity of the signal in the Risbrough study compares to others, including the current study.

Interestingly, our findings were not consistent between experiments one and two, and despite using the same salience conditions, the mean difference of IT devmodes previously observed between conditions 3 and 4 was lost. This change was most likely due to an exposure or practice effect, as the same rats were used in both experiments.

Theory. Due to the interdependent nature of exogenous and endogenous attention, reduced signal salience also stresses attention from the top-down (Parasuraman, 1979; Parasuraman et al., 1987; Robbins, 2002; Warm et al., 2008). Therefore, in addition to stressing *exogenous* attention as described above, reducing the relative intensity of the signal stresses *endogenous* attention. As salience decreases and a signal becomes more difficult to detect, the allocation rate of attentional effort must increase in order to maintain focus. This focus, or vigilance, is modulated via *endogenous* attention, and a failure in vigilance will result in a lapse in attention (Posner, 1980; McGaughy & Sarter, 1995; Dalley et al., 2004).

Results Compared to Theory. Findings from both of the current experiments are consistent with the existing theory regarding the effects of reduced signal salience on lapses in attention. Decreasing the salience of a signal increased IT devmodes, or lapses in attention.

Summary

Attention is theorized to be a function of signal strength, and reducing the salience of a signal placed stress on exogenous attention via signal processing. This stress disrupted attention, as indicated by an overall slowing of modal initiation times. Reducing the salience of the signal also placed stress on endogenous attention. As the signal became more difficult to detect, so did the ability to maintain vigilance and sustain attention. This resulted in an increase in lapses in attention, as indicated by increased initiation time devmodes.

Scopolamine HBr

Attention

We hypothesized that an increase in IT modes would be observed following peripheral injections of scop HBr at the 0.25 mg/kg dose compared to 0.1 mg/kg and saline treated animals. We predicted no effects would be observed at the 0.1 mg/kg dose point compared to saline.

Findings. Our hypotheses were partially supported by the results of experiment two. In support of our predictions, no effects of scop HBr were observed on IT modes in the saline condition compared to 0.1mg/kg. Contrary to our predictions, no effects of scop HBr were observed on IT modes at the 0.25 mg/kg dose point compared to saline and 0.1mg/kg scop HBr.

Comparison to Prior Evidence. A dose of less than 0.1 mg/kg scop HBr is considered *low dose*. The lowest dose currently reported within the rodent attentional literature is 0.003 mg/kg, and following injection, no change in performance accuracy on a 5-CSRTT was observed (Shannon & Eberle, 2006). This same study, as well as two others, examined the attentional

effects of 0.01 mg/kg scop HBr on a 5-CSRTT, and again no changes in accuracy were reported (Jones et al., 1995; Mirza & Stolerman, 2000, Shannon & Eberle, 2006). At 0.03 mg/kg, these same three studies again reported no attentional effects, as did Jakala (1992). The 0.03 mg/kg dose point marks the first report from a study using a signal detection task, and attentional effects were not observed at that dose following I.P. injections of scop HBr, as indicated by no change in P(fa) or omissions (Bushnell et al., 1997). Again using a signal detection task, two studies reported no change in P(fa) or omissions following a dose of 0.05 mg/kg (McQuail & Burk, 2006; Bushnell et al., 1997). Lastly, in two separate studies, Jones reported no change in performance accuracy on a 5-CSRTT at a dose point of 0.075 mg/kg (Jones et al., 1995: Jones & Higgins, 1995).

A dose point between 0.1 and 0.2 mg/kg is considered *mid dose*. Results from experiment two are consistent with findings from a previous study using the 2-CSRTT, wherein no effect was observed on IT modes at 0.1 mg/kg compared to saline (Damico). The current results are also consistent with some prior evidence reported across attentional models. Using a 5-CSRTT, both Jakala (1992) and Hodges (2009) reported no change in performance accuracy following peripheral injections of 0.1 mg/kg scop HBr. Using a signal detection task, McQuail (2006) reported no change in P(fa) or omissions at 0.1 mg/kg (I.P.). Lastly, no change in performance accuracy on a 5-CSRTT was observed following 0.15 mg/kg (I.P.) (Jakala et al., 1992).

The current results are inconsistent with other studies that have reported an attentional effect at the 0.1 mg/kg dose point. Using a signal detection task, Bushnell (1997) reported increases in P(fa) and omissions at a 0.1 mg/kg dose of scop HBr, and three studies reported a decrease in accuracy on a 5-CSRTT following peripheral injections of the same dose (Jones & Higgins, 1995; Mirza & Stolerman, 2000; Shannon & Eberle, 2006).

A dose point between 0.21 and 0.3 mg/kg is considered a *high dose*. The current findings are consistent with evidence from studies that reported no change in performance accuracy on a 5-CSRTT at 0.2 mg/kg (Jakala et al., 1992; Hodges et al., 2009). At 0.3 mg/kg, the current findings are consistent with Hodges, who again reported no attentional effect, and with McQuail (2006), who, using a signal detection task, reported no change in P(fa) or omissions following peripheral injections. Our findings are not consistent, however, with Shannon (2006), who reported a decrease in performance accuracy on a 5-CSRTT at 0.3 mg/kg scop HBr.

Several studies have examined the attentional effects of scop HBr at *especially high doses*, which includes any dose point higher than 0.31 mg/kg. At 0.4 mg/kg, Hodges reported no attentional effect, and McQuail reported no attentional effect at 0.5 mg/kg. However, McQuail did report an increase in omissions without a change in P (fa) was reported at 1.0 mg/kg.

Analysis of Differences. Collectively, findings regarding the attentional effects of scop HBr are inconsistent within the rodent literature. Therefore, results from the current study are only partially consistent with the existing evidence. Unlike signal salience and attention, where only one study reported differing results, studies reporting an attentional effects of systemic scopolamine are evenly split for both the 5-CSRTT and signal detection tasks.

Attentional demands are lowest for signal detection tasks, as they were designed to primarily assess perception and signal processing. Between the forced choice tasks, the parameters of the 5-CSRTT place more stress on attention due to the increased number of target locations. Taking these parameters into consideration, increased attentional demand could account for the inconsistency in findings between tasks; however, the same cannot be said for the differential in findings within each task. For example, whereas three 5-CSRTT studies reported a decrease in accuracy at a dose of 0.2 mg/kg, one reported no attentional effects at 0.1 mg/kg.

Each model employs different behavioral measures. It is possible that the inconsistency in findings is due to a difference in the drug sensitivity of model specific parameters and behavioral measures. As previously stated, attention is driven from both the bottom-up (exogenous) and from the top-down (endogenous). If the attentional effects observed following transient ACh blockade can be primarily attributed to an exogenous disruption, then the model most sensitive detecting that disruption would be the signal detection task.

These factors might help to explain the differences in findings observed between tasks, but they cannot explain the differences observed within tasks. All things considered, there is no clear indication as to why findings regarding the role of ACh in attention are inconsistent and/or why that inconsistency exists at such a high dose differential. Therefore, more work would be needed in order to determine how ACh influences attention across tasks.

Theory. It is theorized that ACh facilitates attention by enhancing characteristics of behaviorally relevant stimuli, which aids in *exogenous* attentional processes, such as signal detection and discrimination. This enhancement facilitates sensory processing across the cortical mantle by causing the influence of exogenous attention to increase along the hierarchy of sensory areas (Arnold et al., 2002; Dalley et al., 2004).

Results Compared to Theory. Not only are the current findings inconsistent with the current theory of a cholinergic role in attention, almost half of the findings on the 5-CSRTT and signal detection task are inconsistent as well. While the difference in behavioral measures between tasks may account for the difference in effect(s) observed on the 2-CSRTT compared to the 5-CSRTT and signal detection tasks, it does not account for the differential effects observed within the latter two models and suggests more work is needed to clarify an ACh role in attention.

Lapses in Attention

We hypothesized that an increase in IT devmodes would be observed following peripheral injections of scop HBr at 0.25 mg/kg compared to 0.1 mg/kg and saline treated animals. We also predicted that no effects on IT devmodes would be observed at the 0.1 mg/kg dose point compared to saline.

Findings. No effects of scop HBr were observed on IT devmodes between any dose conditions. While this finding supports our hypothesis that no effect would be observed between 0.1 mg/kg scop HBr and saline, it does not coincide with our prediction of an effect at 0.25 mg/kg scop HBr compared to 0.1 mg/kg and saline.

Comparison to Prior Evidence. The current findings are partially consistent with the existing collective evidence. Regarding the effects of *low dose* scop HBr (less than 0.1 mg/kg) on lapses in attention on the 5-CSRTT, results are mixed. Consistent with the current findings, three 5-CSRTT studies reported no effects on attentional performance at doses ranging from 0.003 mg/kg to 0.03 mg/kg (Jones et al., 1995; Jones & Higgins, 1995; Shannon & Eberle, 2006). Inconsistent with the current findings, one 5-CSRTT study reported an increase in omissions but no effects on accuracy at 0.01 mg/kg and 0.03 mg/kg, while another reported the same effect at a dose of 0.05 mg/kg (Jakala et al., 1992; Mirza & Stolerman, 2000). Lastly, Jones reported increased omissions but no change in accuracy at a dose of 0.075 mg/kg in two separate studies (Jones et al., 1995; Jones & Higgins, 1995). There are currently no reports in the rodent attentional literature from studies examining the effects of low dose scop HBr using the 2-CSRTT.

At the mid-dose range, results from the current study are consistent with those from an unpublished 2-CSRTT study in which no effects on IT devmodes were observed between 0.1 mg/kg and saline conditions (Domico, 2004). However, the current findings are inconsistent with results in the mid-dose range on the 5-CSRTT, with all previously reviewed studies reporting an increase in lapses in attention (Jakala et al., 1992; Hodges et al., 2009). Jakala reported an increase in omissions with no change in accuracy at doses of 0.1, 0.15, and 0.2 mg/kg. Hodges reported the same at 0.1 and 0.2 mg/kg, and Shannon reported the effect at 0.1 mg/kg. Additionally, an increase in omissions with no change in accuracy was observed following high and extreme doses, or 0.3 and 0.4 mg/kg (Shannon & Eberle, 2006; Hodges et al., 2009).

Analysis of Differences. Evidence in the rat model regarding the effects of transiently blocked ACh transmission on lapses in attention is categorically divided by task. Whereas both 2-CSRTT studies, including the current one, consistently observed no effects of scop HBr on lapses in attention at the mid and high dose ranges, all 5-CSRTT reported an increase at the same dose ranges (Jakala et al., 1992; Domico, 2004; Shannon & Eberle, 2006; Hodges et al., 2009). No attentional effects were reported on the 5-CSRTT in the low dose range (Jones et al., 1995; Jones & Higgins, 1995; Shannon & Eberle, 2006). However, when the dosage of scop HBr was increased from 0.03 to 0.1 mg/kg in one of the studies, an increase in omissions with no change in accuracy was observed (Shannon & Eberle, 2006).

Collectively, these findings would suggest that the observed evidential inconsistency might be due to a difference in the drug sensitivity of each specific task and behavioral measures. This is supported by the consistent lack of an effect of *low* dose scop HBr (less than 0.1 mg/kg) on the 5-CSRTT followed by consistent effects observed at the *mid* dose (0.1-0.2 mg/kg). Furthermore, in the Shannon study, an increase in omissions was observed when the dose of scop

HBr was increased. Given this pattern, a higher dose of scop HBr may be necessary in order to elicit an increase in attentional lapse on the 2-CSRTT.

Parameters vary between tasks. For example, whereas orienting is always covert on the 2-CSRTT, it can be either covert or overt on the 5-CSRTT depending on the position of the rat at the time of signal onset. It is theorized that with covert orienting, attention has been allocated and the rat is in a readied state. When orienting is overt, however, the rat may or may not be in a readied state at the onset of the signal. It is therefore possible the ACh plays a larger role in the initial allocation of attention on the 5-CSRTT.

While the 2-CSRTT and 5-CSRTT are both forced choice, the response demands differ between models. On the 2-CSRTT, there are two possible signal locations, and a response answers the question of whether the signal was presented to the right or to the left. On the 5-CSRTT, there are five possible locations, and a response answers the question of where a signal was presented in an array of five locations. The decreased number of target locations makes this the 2-CSRTT less stressful to attention. The difference in attentional demands may be sufficient to mediate the effects of reduced ACh transmission, thus requiring a higher dose of scop HBr to elicit the same increase in lapses in attention on the 2-CSRTT.

Theory. Transiently blocking cortical ACh transmission stresses both exogenous and endogenous attention. It is theorized that ACh facilitates signal processing (*exogenous*) by comparing incoming information to what is already known about the environment. Known information is passed through and novel information is integrated, which helps to streamline the neural representation of a visual world that is continuously affected by the behavioral relevance of a signal. In doing so, ACh facilitates *endogenous* attentional processes, such as selection and sustained attention, by reducing the amount of effort needed to direct and maintain attention.

This results in fewer moments of inattention, or lapses in attention (Dalley et al., 2004; Sarter et al., 2005).

Results Compared to Theory. IT devmodes, which have been theorized to indicate lapses in attention, remained unchanged under all drug conditions in experiment two of the current study. This finding is not consistent with the current theory of attentional lapse and ACh. As previously suggested, this incongruence might be due to the nature of the task parameters, behavioral measurs, and/or attentional demands of the 2-CSRTT in evaluating a cholinergic role in preventing lases of attention. Considering the additive theory of attentional stress and the possibility that this stress may be experienced differently, depending on baseline characteristics of the test subjects themselves, either increasing the dose of scop HBr or altering other characteristics of the task as a means of increasing attentional demands (*e.g. decrease stimulus duration*) would be necessary to elicit effects on the 2-CSRTT similar to those observed on the 5-CSRTT.

Three-Way Interaction

Although not predicted, a three-way interaction between signal salience, scop HBr, and baseline performance was observed. Because a main effect of salience and scop HBr was predicted for all animals, the experimental hypotheses for the current study did not make predictions as to the effects of baseline performance.

Experiment two was run using two within-groups factors, signal salience and scop HBr, and one between-group factor, baseline performance. As described above, testing took place under three signal salience conditions, and the brightness level of the chamber light was varied while the level of the signal remained constant. For condition one, the chamber light was not illuminated. For condition three, the chamber light was illuminated and held constant at 50%

intensity compared to the signal, and for condition four, the chamber light was held constant at 75% intensity compared to the signal. All rats were tested under all salience conditions. The three drug conditions were saline, 0.1 mg/kg scop HBr, and 0.25 mg/kg scop HBr (IP), with all rats tested under all doses.

Baseline Performance. For the between-groups factor, rats were assigned to either a "high variability" group (HV) or "low variability" (LV) group based on a median split of baseline performance (*IT devmodes*), with group assignment being determined by collapsing devmodes across the final week of training. The signal light held was at maximum brightness and the chamber light was kept off throughout this week, thus minimizing attentional stress to allow for the most accurate representation of sensorimotor processing when attending and inherent susceptibility to lapses in attention.

Evidence in both the rodent and human/clinical attentional literature supports the use of baseline performance as an independent variable. One rodent study using a 5-CSRTT reported using a median split based on accuracy in order assess the attentional effects of atomoxetine, a non-stimulant medication prescribed for the treatment of ADHD. Following drug treatment, a selective improvement was observed in the poor performance group (Robinson, 2012). In the clinical literature, Acheson (2008) and colleagues reported no effects of d-amphetamine, the most commonly prescribed stimulant medication for the treatment ADHD, on IT devmode for LV responders, while HV responders showed a significant decrease in reaction-time variability (Acheson & de Wit, 2008).

Findings. The current findings are that, compared to LV baseline performers, the behavior of HV baseline performers was disrupted at the 0.25 mg/kg dose point under less salient

conditions (3 & 4), while no difference was observed between responders under the most salient condition (1) at the same dose.

Comparison to Prior Evidence. Evidence from the 5-CSRTT supports an interaction between scop HBr and signal salience on lapses in attention, as indicated by increased omissions with no change in accuracy. In a 1995 study, rats received scop HBr at dose points of saline, 0.03, 0.075, and 0.1 mg/kg and were tested under conditions of varied signal intensities (16, 45, 82, or 575 lux) (575 lux most salient) (Jones & Higgins, 1995). An increase in omissions was reported at all drug doses compared to saline, indicating an effect on lapses in attention, and at the 0.075 and 0.1 mg/kg dose points, this disruption was observed under all salience conditions. However, at the lowest dose (0.03 mg/kg), this disruption was only observed under the less salient conditions.

Analysis of differences. Although we did not find a two-way interaction between signal salience and scop HBr dose, the outcome of Jones is consistent with our three-way interaction in that both studies demonstrate the additive effects of attentional stress on lapses in attention. For the current experiment, HV responders differed from LV responders at the highest scop HBr dose (0.25 mg/kg) under the least salient condition (condition 4). The drug condition elicited the strongest ACh blockade, and the salience condition placed the most stress on attentional processing. Working together, they enhanced attentional stress for the low performing animals (HV responders) and disrupted performance. In the Jones study, the interaction was represented at the lowest dose (0.03 mg/kg) under the least salient condition. When the salience of the signal was increased, the low dose effect was no longer observed; suggesting that the higher signal intensity reduced attentional stress, which was sufficient to mitigate the diminished ACh function. At the higher doses (0.075, and 0.1 mg/kg), disruption in performance was observed

independent of signal salience and occurred under all intensity conditions. This indicates that increased salience was no longer sufficient to mitigate the greater loss in ACh function of the higher doses.

One marked difference between the current findings and those reported by Jones & Higgins is the effective dose. In Jones et al., the doses that effectuated lapses in attention, independent of salience, were 0.075 and 0.1 mg/kg. These doses were both less than the dose in the current study, which was still low enough to be counteracted by high salience and not cause lapses. As discussed above for attention, this difference in dose responsiveness may be due to the parameters and behavioral measures of the two tasks.

Another difference is that Jones did not separate high and low performers. If their data would have paralleled ours with a baseline difference between the two subgroups, it is possible that the low performers would have shown higher sensitivity to low salience at even lower doses.

Theory. Attentional stress is additive with the effects being collective. As discussed above, decreasing the saliency of a signal stresses both exogenous and endogenous attention. A less noticeable signal is more difficult to detect and/or discriminate (*exogenous*) so effort must be allocated at a higher rate in order to maintain focus and remain vigilant. Evidence indicates that this effort is modulated via *endogenous* attention (Parasuraman, 1979; Posner, 1980; McGaughy & Sarter, 1995; Robbins, 2002; Dalley et al., 2004; Warm et al., 2008). Reducing the amount of available ACh also stresses *endogenous* attention. It is theorized that ACh serves to streamline the neural-visual representation of a behavioral relevant signal by coding signal parameters such as intensity and/or duration *(exogenous).* This in turn facilitates *endogenous* attentional processes, such as selection and sustained attention, by reducing the amount of effort needed to direct and maintain attention (Dalley et al., 2004; Sarter et al., 2005).

It has been theorized that inherently high reaction-time variability is indicative of an increased susceptibility to attentional disruptions (Castellanos et al., 2005; 2006; Acheson & de Wit, 2008; O'Connell et al., 2009; Epstein et al., 2011; Antonini et al., 2013). Unlike decreased signal salience and reduced ACh transmission, poor baseline performance does not add to the collective attentional stress. Instead, it should lower the threshold wherein that stress will have an effect on attentional performance (Castellanos et al., 2005).

Results Compared to Theory. Our findings support the current theory. An increase in lapses in attention resulted from the collective effects of ACh blockade and decreased signal salience, and the effect was only observed in responders with inherently high baseline reaction-time variability. As was previously stated regarding to the two-factor analysis, the lack of an observed effect at the highest dose scop Hbr (0.25 mg/kg) indicates that attention was not sufficiently stressed and a higher dose would be needed under these task conditions. In the case of the three-way interaction, no additional stress was added to the attentional load. Instead, the effects of the existing attentional stress brought about by decreased signal salience and 0.25 mg/kg scop HBr was now seen in responders that are theorized to be more susceptible to lapses in attention.

Summary of Three-Way Interaction

Attentional demands differ between the reviewed rodent tasks of attention. The 2-CSRTT and 5-CSRTT are both forced choice tasks designed specifically to assess attention in rodents, with the 5-CSRTT being the task most commonly reported in the literature. Between these two tasks, the parameters of the 5-CSRTT places more stress on attention due to the increased number of target locations. The decreased number of target locations makes this the 2-CSRTT less stressful to attention. It is possible that the difference in attentional demands is significant to

mediate the effects of reduced ACh transmission, thus requiring a higher dose of scop HBr to elicit the same main effect on lapses in attention that was observed using the 5-CSRTT.

It was not until baseline performance was introduced as an independent variable that the effect of reduced signal salience and ACH blockade on lapses in attention was observed. In the current studies, under the less salient conditions (3 & 4) and at the highest scop HBr dose (0.25 mg/kg), an increase in lapses in attention was observed in *high* variability responders compared *low* variability responders. This increase was not due to additional increases in attentional stress; rather, it can be attributed to increased susceptibility to the existing attentional stress.

Reaction-Time Variability: human

The focus to the current study was attention and lapses in attention (inattention), and as will be developed below, reaction-time variability is the behavioral measure that has shown the highest correlation to inattention (Epstein et al., 2010). Reaction time is defined as "a time interval with boundaries marked off by an initiating stimulus event and a terminating motor response" (Antonini et al., 2013). It represents a convolution of attention, both exogenous and endogenous; related phenomena such as lapses in attention; as well as motor processing and response execution (Antonini et al., 2013).

Analysis

Reaction-time distributions present with a pronounced rightward skew. Rising rapidly and trailing off slowly, this skew is attributed to the disproportionate number and durations of slow responses compared to fast (Luce, 1986; Douglas, 1999). Due to the prevalence of this presentation, it has been theorized that the peak and the variability represent separate phenomena, and some studies have implemented methods of analysis that dissociate and analyze

the peak and skew separately. For the current studies, the peak is theorized to represent attention and the skew is theorized to represent lapses in attention.

Ex-Gaussian. The exponential (ex)-Gaussian method analyzes reaction-time distributions using three parameters: mu (μ), sigma (σ), and tau (τ), or the mean of the normal component, standard deviation of the normal component, and mean of the exponential component, respectively (Heathcote et al., 1991). In the ex-Gaussian model, it is proposed that tau represents lapses in attention, and the measure of attention (mu) and the measure of lapses (tau) can be reliably dissociated and analyzed separately (Leth-Steenson et al., 2000).

Mode/Devmode. Although the ex-Gaussian method separates the peak and the skew for reaction-time latency, the peak is still quantified using a variation of the mean and is therefore still influenced by outliers (Richards et al., 2011). The mode/devmode method of reaction-time analysis provides a similar dissociation of attention and lapses in attention but eliminates any effect of the skew on the peak (Richards et al., 2011). The mode represents the most frequently occurring reaction time when an attentive state is being maintained, while the deviation from mode represents the skew of the distribution and is theorized to represent lapses in attention (Spencer et al., 2009, Richards et al., 2011).

Clinical Assessment

Continuous performance tests of attention (CPTs) are repetitive, operant-based tasks in which human participants must sustain visual-spatial attention in order to continuously respond to behaviorally relevant signals (Conners, 2000). Because orienting on the CPT is covert, it provides a measurement of reaction-time latency in which the distribution peak and skew can be dissociated (Douglas, 1999; Leth-Steenson et al., 2000). Parameters of the CPT can be also

varied in order to increase attentional stress (e.g., signal salience, signal duration, inter-trial interval).

Measures/Correlates. CPTs provide quantitative scores for a number of performance measures, including reaction time, accuracy, omitted trials, and premature responses (Conners, 2000; Epstein et al., 2003; 2010). When correlated with the three major subtypes of attention deficit-hyperactivity disorder (inattention, hyperactivity, impulsivity), reaction-time variability showed a high correlation with behaviors indicative of inattention, while accuracy and omissions showed a low to moderate correlation. Premature responses were highly correlated with impulsivity and hyperactivity and showed a low correlation with inattention (Connors, 2000; Epstein et al., 2010).

IIV/ADHD

The variability of an individual's reaction-time latencies over a number of repeated trials is known as intra-individual variability, and this variability differs greatly between individuals within a given population. Intra-individual variability has become a focal point within the human/clinical research, as evidence has shown high intra-individual variability to the leading indicator of an ADHD diagnosis and the only quantitative diagnostic indicator. Evidence has shown that individuals with an inherently high intra-individual variability do not processes sensory information at a slower rate, but rather they experience lapses in attention more frequently and at longer durations (Douglas, 1999; Conners, 2000; Spencer et al., 2009; Epstein et al., 2003; 2010; Antonini et al., 2013). When comparing reaction-time distributions, ADHD and non-ADHD responders show no differences in the peak; however, ADHD responders present with a larger skew (Douglas, 1999).

Baseline Performance

In clinical practice, having an inherently high intra-individual variability is the foremost behavioral indicator of an ADHD diagnosis, and it has been theorized that high baseline intra-individual variability might represent a ubiquitous and etiologically important characteristic of ADHD (Castellanos et al., 2005; 2006). Studies have therefore begun to use baseline intra-individual variability as a stand-alone factor (Johnson et al., 2008; Acheson & de Wit, 2008). Findings from these studies indicate that improved performance following drug treatment is be attributed specifically to a decrease in lapses in attention in responders with a high baseline intra-individual variability (Acheson & de Wit, 2008).

Summary

Lapses in attention are defined as infrequent failures in endogenous attention and represent inefficiency in the executive deployment of attention. This in turn causes momentary failures in the attending to task relevant features, resulting in actions that are intended but not executed (Buzy et al., 2009).

Individuals with an ADHD diagnosis have difficulty in the initial deployment of attention; however, once attention has been engaged, they show no difference in attentional processing. Intra-individual variability is an individual's reaction-time variability over repeated trials, and a high baseline intra-individual is currently the leading indicator of an ADHD diagnosis. It is also the only quantitative indicator.

Initiation-Time Variability: animal/human parallels

The importance of reaction-time variability as a measurement of lapses in attention in rodents lies in its contribution to gaining insight into clinical disorders of attention, such as

ADHD. In order to reliably infer findings across species, valid parallels must be confirmed between models, independent measures, dependent measures, and construct of interest.

Models

The rodent 2-CSRTT most closely parallels human attentional tasks and clinical diagnostic tools in design and demands. The parameters of the rodent 2-CSRTT are such that the attentional component of reaction time (*initiation time*) can be measured separately from the motor component (*movement time*) on the 2-CSRTT. The motor component of reaction time is then represented by *movement time*, while attention and lapses in attention are represented by *initiation time*. This serves to tease apart the convolution of phenomena within reaction time; controls for possible motor confounds; and provides a measure (*initiation time*) that closely resembles the reaction-time measure used in human/clinical assessments of attention.

As stated above, signal presentation for the rodent 2-CSRTT is always within the visual field, and orienting is always covert, requiring no head or eye movements. By maintaining a fixed head position, it is theorized that the rat is in a readied state and attentional allocation has begun. A fixed position start for every trial also ensures that initiation time can be accurately quantified and the distribution skew reliably measured.

Measuring Lapses in Attention

The parameters of the rodent 2-CSRTT most closely parallel those on human attentional tasks/clinical diagnostic tools, and the utility of having a rodent reaction-time test of attention with a data analysis approach that parallels the ex-gaussian analysis allows for more direct comparisons with human experiments using reaction-time variability. The mode/devmode method of analysis provides this approach (Sabol et al., 2003; Hauskenecht et al., 2005; Spencer et al., 2009). Having been used in animal and human research, the 2-CSRTT coupled with the

mode/devmode method of analysis yields a behavioral measure in rodents, initiation time variability, akin to human intra-individual variability.

Baseline Performance

The *high* and *low variability* split most closely parallels clinical studies comparing reaction-time variability between ADHD and non-ADHD individuals. Several studies within the rodent literature have used baseline performance as an independent factor in order to study the differential effect(s) of drug treatment (Robinson, 2012; Turner & Burne, 2016; Turner et al., 2016). Although these studies used a median split based on baseline accuracy rather than intra-individual variability, all reported improved attention in the low performing group compared to the high performing.

Summary

There are no human data with regards to scop HBr and lapses in attention; however, Spencer and colleagues reported decreases in IT devmodes following the administration of methylphenidate, a dopamine and norepinephrine reuptake inhibitor, at both low and high doses compared to baseline (non-medicated) performance (Spencer et al., 2009). Another study found similar reductions in reaction-time variability following the administration of methylphenidate and atomoxetine, a selective norepinephrine transporter inhibitor, in ADHD diagnosed children. In the rat model, Redding (2019) reported decreased IT devmodes following the administration of atomoxetine and guanfacine, a selective α2A-adrenergic receptor agonist. Collectively, these findings support the use of analyses employed in the current study.

Behavioral Measures (Other)

MT Mode

Movement time is defined as the time occurring between the removal of the nose from the center port and insertion of the nose into the response port. No effect of either signal salience or scop HBr was observed on MT mode. The cholinergic system is diffuse with pathways outside of the central nervous system, and measuring movement time allows for the differentiation of central and peripheral effects following systemic scop HBr administration. The observation of no change in movement time in the current experiments indicates that there were no peripheral effects or unwanted motor confounds, and the observed behavioral disruptions were attentional in nature.

Omissions

Omissions are defined as an initiation time equal to or greater than 2s. For experiment one, an effect of signal salience was observed on omissions as indicated by an increase under all conditions as the signal became less salient. For experiment two, an increase was observed between condition 1 and condition 4 (least salient). The disruption previously observed between conditions 1 and 3 and conditions 3 and 4 was lost on experiment two. This loss may be attributed to either an exposure or practice effect, as the same loss was observed for signal salience and IT devmodes. Omissions differ for the 2-CSRTT and 5-CSRTT. When an omission occurs on the 5-CSRTT, the experimenter terminates the trial and the chamber goes dark for a period of time, indicating the onset of a new trial. However, for the 2-CSRTT, an omission is essentially an extended lapse in attention. The trial continues until a response is made, but because the response occurred after the 2s time limit, it is tallied as an omission.

There was also an increase in omissions following scop HBr at the highest dose 0.25 mg/kg compared to saline under all salience conditions for all animals. While this may also indicate an effect of scop HBr on lapses in attention, further investigation would be necessary in order to conclude the exact nature of this effect.

Errors of Commission

Premature initiations occur when the nose was removed from the center port prior to the onset of the stimulus light but a response is not completed. For experiment one, an effect of signal salience was observed on premature initiations as indicated by an increase on all conditions compared to condition 1 (most salient). For experiment two, an increase was observed between condition 1 and condition 4 (least salient). However, the disruption previously observed between condition 1 and condition 3 was lost on experiment two. Additionally, a main effect of baseline performance was observed with LV responders showing a higher number of premature initiations compared to HV responders.

These findings are not consistent with those previously reported examining the effects of decreased signal salience on the 2-CSRTT as Sabol and colleagues reported no difference in premature initiations between salient and non-salient conditions. The inconsistency between findings may be due to the number of salience conditions used in the current experiments compared to the number of conditions in the previous study. Whereas Sabol employed a 2x2 experimental design, we employed a 3x5 and 3x3 for experiments one and two respectively. T

Premature responses occur when the nose was removed from the center point prior to the onset of the stimulus light and the head was inserted into a response port. For both experiments, there was a main effect of signal salience and an increase in premature responses was observed between all conditions except condition 3 and 4.

As was the case with premature initiations, there was an effect of baseline performance and LV responders had more premature responses compared to HV responders specific to the interaction under the less salient conditions. For experiment one this included conditions 3 and 4, and conditions 3, 4, and 5 for experiment two.

These results are consistent with previous findings from studies examining the effects of decreased signal salience using a 2-CSRTT (Sabol et al., 2003; Hausknecht et al., 2005). Both studies reported a main effect of signal salience on premature responses with an increase reported under the non-salient condition compared to the salient condition.

Our results indicate that decreasing signal salience leads to an increase in errors of commission. The increase in premature initiations/responses in the low variability rats compared to the high variability rats suggests that errors of commission are less likely to occur in animals that are more likely to be inattentive. As was mentioned earlier, errors of commission have been highly correlated with impulsivity but only show a low correlation with inattention (Conners, 2000; Epstein et al., 2003). The median splits used for the current experiments were based on baseline IT devmode, a measure that has shown only a moderate correlation with impulsivity. Inattention was the focus of this project, so a median split using IT devmode may not be appropriate when assessing impulsivity. Therefore, our findings suggest further investigation is needed to in order to understand the relationship between errors of commission, impulsivity, and inattention using the 2-CSRTT model of attention.

Completed Trials

For both experiments a main effect of baseline performance was observed, with LV responders completing more trials than HV responders. However, this difference was due to a 99.951% completion rate for LV responders compared to a 98% completion rate for HV

responders. The less than 2% percent difference, while significant, does not translate into a "real world" disruption, as a 98% completion rate would otherwise indicate successful attending.

Conclusions

This research aimed to determine the role of acetylcholine in attention and lapses in attention in rats using the 2-CSRTT and mode/devmode method of analysis. Testing took place under varied levels of signal salience, and performance was compared for all rats between conditions and for low baseline variability versus high variability performers within conditions.

Based on quantitative analysis of initiation time latency, it can be concluded that ACh plays a role in the facilitation of attention, and the extent of facilitation is contingent on attentional stress and individual processing capacity. The results indicate that reducing the salience of a signal stresses attention, and this stress, in conjunction with a transient blockade in ACh transmission, increases lapses in attention for rats with inherently high initiation time variability.

In current series of experiments, we have attempted to accurately measure attention, attentional lapses, and control for confounds (e.g., motivation, decision-making time, and motor elements). Attention and lapses in attention were dissociated and analyzed separately. Water restriction controlled for motivation. Having only two-choices minimized decision making, and splitting reaction time into *movement time* and *initiation time* controlled for any possible gross motor confound(s). Signal presentation within the visual field ensured covert orienting and controlled for any possible fine motor confound(s) that could possibly affect eye/and or head movements.

By employing the 2-CSRTT and mode/devmode method of analysis, a determination as to the role of ACh in attention and lapses in attention was possible in a manner analogous to drug

studies carried out in a human population. Additionally, it provided validation to the use of baseline performance variability as an indicator of a susceptibility to lapses in attention in rats similar to humans. The current findings, therefore, uniquely contribute to the collective knowledge of attention by bridging the gap between rodent and human/clinical evidence and providing insight into how ACh depletions affect attention for both "normal" responders and responders possessing behavioral markers indicative of ADHD.

Evidence indicates that decreased signal salience disrupts attention and increases the frequency and duration of lapses in attention, and this effect is more pronounced when the responder presents with poor baseline attentional performance or a higher IT devmode (Sabol et al., 2003; Hauskencht et al., 2005; Turner et al., 2016). Evidence also indicates that this susceptibility can be overcome using drug treatment therapy, and improvements can be made selectively on lapses in attention in both humans and rat responders with poor baseline performance (Acheson & de Wit, 2008; Spencer et. al, 2009; Turner et al.; 2016). The current findings show that attentional performance can also be disrupted for these responders with a transient ACh blockade, as indicated by increased IT devmodes.

Lapses in attention are a defining characteristic for the inattention subtype of ADHD (Tamm et al., 2012). The leading quantitative indicator of an ADHD diagnosis is increased reaction-time variability, which is theorized to represent lapses in attention and has been highly correlated with behaviors indicative of inattention (Epstein et al., 2003; 2010; Antonini et al., 2013). The most often cited rodent task of attention, the 5-CSRTT, reports performance accuracy and omissions as indices of attention and lapses in attention (Robbins et al., 1998; Bushnell, 1998; Robbins, 2002; . Because these measures have been only moderately correlated with inattention, they may not provide an accurate analog to the measures reported in the

human/clinical literature to be indicative of ADHD. The 2-CSRTT is an alternative rodent model that provides a measure of *initiation* time, which most closely resembles the reaction-time measurement reported in the human/clinical literature. Using the same mode/devmode method of analysis employed in human testing, initiation time can be separated into a central component representing sensorimotor processing time when ready to attend (attention) and a variability component representing lapses in attention (Richards et al., 2011).

One limitation of the current study was the use of systemic injections rather than central infusions of scop HBr or lesions to central cholinergic structures. The current findings provide insight into the attentional function(s) of the central cholinergic system as a whole, since any confounding peripheral effects of scop HBr were ruled out through the analysis of movement time. Building on the current findings, future work would include examination into the role of localized structures within the basal forebrain cholinergic system (e.g., nucleus basalis, nucleus accumbens, and medial septal nucleus) and their widespread projections to muscarinic receptors within the neocortex and other brain structures.

Another limitation was the use of the same rats for both experiments. As mentioned in the results, effects observed in the first experiment were lost in the second. Using novel rats for each experiment would have controlled for possible exposure or practice effects.

While a median split according to baseline performance has been used in rodents as a means to further investigate a given construct of study, no published studies to date used baseline response or initiation time variability (Acheson & deWit, 2008). Given the current findings and the potential insight they can provide into ADHD related inattention, further investigation into the relationship between high intra-individual variability in rodents and humans would be recommended.

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