TRANSLATIONAL RESEARCH ON SUSTAINED ATTENTION AND ATTENTIONAL CONTROL IN RATS, HEALTHY HUMANS AND PATIENTS WITH SCHIZOPHRENIA

by

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LIST OF ABBREVIATIONS

ACh	acetylcholine
AMPH	amphetamine
BA	Brodmann's area
ASL	arterial spin labeling
dSAT	distractor condition Sustained Attention Task
fMRI	functional magnetic resonance imaging
MFG	middle frontal gyrus
SAT	Sustained Attention Task
VSL	variable signal location

ABSTRACT

Attentional deficits are often studied in schizophrenia, yet treatments to alleviate these impairments remain undeveloped. In part, this gap between basic and clinical research stems from a lack of tasks validated for translational research. The current work develops the distractor condition sustained attention task (dSAT), an attentional control paradigm traditionally used in rats to investigate the cholinergic system's role in attention, for cross-species, translational research by adapting it for use in humans. In the basic sustained attention task (SAT), subjects report the presence or absence of a brief, centrally-presented signal of varying duration. In the distractor condition (dSAT), a visual distractor evokes top-down control mechanisms in order to stabilize performance. The current work demonstrates that rats and healthy, young human adults have qualitatively similar patterns of performance on the SAT and dSAT, including decreased attentional performance during distraction. Neuroimaging in young human adults shows that this decreased attentional performance is correlated with increased activation of right middle frontal gyrus (MFG). The sensitivity of right MFG to the attentional effort demands in the dSAT is of interest because this region is implicated as a site of disruption in patients with schizophrenia (Minzenberg et al., 2009). To investigate the dSAT's sensitivity to attentional deficits in schizophrenia, stable, medicated schizophrenic outpatients and healthy controls were tested on the dSAT. Healthy children were also tested to compare the patients to a group with similar overall accuracy levels. While

patients are only minimally impaired on the task in the absence of distraction, their attentional performance levels decline dramatically during distraction, exceeding the declines seen in healthy adult controls or children. Children also show time-on-task declines in SAT performance, suggesting that impairments on the SAT and dSAT may be dissociable in different populations. The ability to implement the dSAT in both rat psychopharmacological and neurochemical experiments and human neuroimaging research, as well as the dSAT's sensitivity to the cognitive deficits in schizophrenia, makes the dSAT a useful instrument for translational research on attention systems in animal models of cognitive disorders, healthy human subjects, and patients with neuropsychiatric disorders.

Chapter I

INTRODUCTION

Opening remarks

The ability to maintain attention over time and to detect relevant stimuli is critical to a variety of everyday life situations, such as listening to a speech or lecture or driving in inclement weather or heavy traffic. A distraction, such as your cell phone ringing while you're driving, requires you to increase your attentional effort in order to overcome the impairment in attention resulting from the distraction and to continue performing your task at hand, here driving. As these real-world examples suggest, sustained attention involves both "bottom-up" attention processes involved in detecting and processing relevant signals and "top-down" processes involved in determining which inputs are relevant, ignoring irrelevant inputs and maintaining the appropriate task set in the face of competing internal or external demands (Kastner & Ungerleider, 2000; Sarter et al., 2001; Sarter et al., 2006; Treisman & Gelade, 1980). Our ability to control our attention through the activation of top-down executive processes becomes especially critical when there is distraction present, helping us to avoid hitting the car in front of us when our phone rings.

Challenges to attention and attentional effort

Challenges to attention, including fatigue, sickness and distractors, interfere with our ability to sustain our attention. Such challenges require an increase in attentional effort (Sarter et al., 2006), or the activation of top-down attentional control systems, to maintain or improve performance under challenging conditions. Whether participants will maintain attentional performance under challenging circumstances seems to depend on whether subjects are motivated to perform well by either intrinsic or extrinsic sources (Tomporowski & Tinsley, 1996). When motivated subjects become aware of declines in performance, for example, through less frequent rewards or increased feedback about errors, they will increase their attentional effort in order to counteract these self-perceived performance declines. Increases in attentional effort are thought to engage the frontal and parietal regions that comprise the anterior attention system (Posner, 1994; Posner & Dehaene, 1994), helping to optimize goal-directed behavior and cognitive processes. This includes optimizing input processes, filtering noise and re-distributing processing resources, helping collectively to stabilize or recover attentional performance in the face of a challenge (see Sarter et al., 2006 for further discussion of attentional effort).

Manipulation of attentional effort demands with the sustained attention task (SAT) and the distractor condition sustained attention task (dSAT)

The current work investigates the effect of distraction on behavioral performance in a sustained attention task and on the brain regions activated by performance of the sustained attention task. Distraction is predicted to impair attentional performance, but increase activation of regions thought to be involved in attentional control. In order to

study the effects of distraction on sustained attention, the sustained attention task (SAT, McGaughy & Sarter, 1995) and the distractor condition sustained attention task (dSAT, Gill et al., 2000; Himmelheber et al., 2000; McGaughy et al., 1996) were used. Each trial of the SAT requires participants to monitor for the presence or absence of a brief, centrally-presented signal. Signals are presented on approximately half of the trials. Signal duration and the amount of time preceding the presentation of a signal (signal present) or nonsignal (signal absent) event also varies in order to impose a cognitive load and ensure that participants must maintain their attention throughout the task (c.f., Parasuraman & Davies, 1977; Parasuraman et al., 1978; Parasuraman & Mouloua, 1987). In the subsequent response period, participants report whether the signal did or did not occur and receive feedback on their accuracy. While stimulus detection is thought to be driven primarily by bottom-up attention processes (i.e., capture of attention by a sudden-onset signal), maintaining performance over time and dealing with the uncertainties imposed by the unpredictable occurrence, timing, and duration of the signal stimulus requires some top-down control (see discussion in Sarter & McGaughy, 1998). This task is relatively unique in that in addition to this basic paradigm, the demands on attentional control can be manipulated through the introduction of a visual distractor in the distractor condition sustained attention task (dSAT). The dSAT condition is identical to the SAT, except that participants now perform the task in the presence of a global distractor (flashing houselight for rats, flashing background on the computer screen for humans). The distractor is theorized to increase the attentional demands of the task, thereby requiring participants to increase their attentional effort in order to continue to perform the task.

Role of the cortical cholinergic input system in implementing attentional effort

The SAT and dSAT have been extensively used with rodent models to investigate the role of the cortical cholinergic input system in attention and attentional effort. Lesions of the cholinergic neurons in the basal forebrain result in robust and lasting impairments in attentional performance on the SAT (McGaughy et al., 1996). *In-vivo* microdialysis experiments demonstrate that right prefrontal acetylcholine (ACh) release increases during SAT performance (Himmelheber et al., 2000; Kozak et al., 2006, Kozak et al., 2007), above and beyond the increases seen in control tasks with matched motor and reward components but minimal demands on attention (Arnold et al., 2002; Dalley et al., 2001). Challenges to attention, such as pharmaceutical manipulations or distractions, further augment ACh release levels and neuronal activity in right prefrontal cortex (PFC; Kozak et al., 2006; Gill et al., 2000), an increase that is theorized to reflect increases in attentional effort (Sarter et al., 2006). Cholinergically-mediated projections to parietal cortex also appear to be particularly important for performance during the distractor (Broussard et al., 2009). Right PFC is thought to be a key component of the neural circuitry mediating interactions between top-down and bottom-up attention, based partly on bidirectional circuitry between PFC and basal forebrain as well as limbic regions which influence the basal forebrain (Brooks et al., 2007; Broussard et al., 2009; Gaykema et al., 1991; Sesack et al., 1989; Zmarowski et al., 2007).

Attentional impairments in schizophrenia

In addition to its usefulness in determining the role of the cholinergic system in attention in animal studies, the ability to manipulate attentional control demands within a single paradigm also makes the SAT and dSAT an attractive tool for attention research in humans, including investigations of the attentional deficits found in various neuropsychiatric disorders like schizophrenia. Impairments in attention and attentional control represent a core deficit in schizophrenia (Heinrichs & Zakzanis, 1998; Nuechterlein et al., 2004). Patients with schizophrenia have difficulties with controlled, effortful attentional processing (Cornblatt et al., 1989), difficulties that become even more apparent when the attentional systems are highly taxed such as in tasks with high loads, tasks with rapid processing of information requirements, and in tasks with distraction (e.g., Braff & Saccuzzo, 1985; Dawson & Nuechterlein, 1984; Dawson, 1990; Kietzman et al., 1985). These attentional impairments are found not only in periods of psychosis, but persist even in periods of remission (Asarnow & Maccrimmon, 1978; Nuechterlein et al., 1992; Wohlberg & Kornetsky, 1973). Deficits in attention have a significant relationship to functional outcome, including the ability to acquire basic life skills, social problem solving and social competence (Green et al., 2000), suggesting that improving attentional capabilities may benefit several aspects of patients' lives.

Translational research on the cognitive deficits of schizophrenia

Despite the importance of attentional control for everyday life situations and the body of evidence showing it is disrupted in schizophrenia, few treatments exist to effectively treat the cognitive symptoms of schizophrenia. In part, this lack of effective

treatments stems from a lack of translational research into the attentional control deficits of schizophrenia that could serve to bridge the animal model research where the neural underpinnings of attention are studied and drug-development studies are conducted, with human neuroimaging and behavioral work in both healthy participants and patients with schizophrenia. As part of its efforts to bridge this gap, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative has selected a set of cognitive tasks in different cognitive domains for further translational research development (Carter & Barch, 2007; Carter et al., 2008). The distractor condition sustained attention task (dSAT) used in the present work was selected for development under the domain of attentional control (Nuechterlein et al., 2009). This task was seen as particularly promising for treatment research due to the ability to implement this task in both rodent models and human neuroimaging experiments.

Overview of the present dissertation

The current work presents a series of experiments that lay the groundwork for translational research on the control of attention and attentional effort. Overall, these experiments demonstrate that distraction impairs sustained attention and activates brain regions thought to be involved in increasing our attentional effort. These studies make use of the sustained attention task (SAT) and the distractor condition SAT (dSAT), where attention is challenged via the presentation of a visual distractor. Chapter 2 adapts and validates the SAT and dSAT for use in humans by demonstrating that rats and humans show qualitatively similar patterns of attentional performance on the task conditions. While these results and the behavioral results in Chapter 3 show that the distractor

condition (dSAT) results in reduced attentional performance compared to performance without distraction, Chapter 3 also presents neuroimaging data that find that right prefrontal regions are especially sensitive to the top-down demands of the distractor and show greater activation in the dSAT condition than in the SAT condition. This increased activation is interpreted as reflecting increased attentional effort. Finally, in order to see whether the SAT and dSAT are sensitive to the attentional control impairments found in certain neuropsychiatric disorders, attentional performance on the SAT and dSAT was examined in stable, medicated outpatients with schizophrenia. While patients are able to perform the SAT without distraction fairly well, their attentional performance decreased significantly in the presence of the distractor. Moreover, the amount of decline seen in patients' performance outmatched the declines seen in healthy individuals during distraction, suggesting that the dSAT is sensitive to the attentional control deficits seen in schizophrenia. Future work could not only investigate how patients' neural activation compares to that of healthy individuals performing the task, but also whether pharmaceutical manipulations are able to successfully rescue patients' distractor performance.

Taken together, these results demonstrate that the SAT and dSAT have strong potential for translational research on the attentional deficits in schizophrenia and drug-development studies to develop treatments for these deficits. Furthermore, the close ties between the animal and human versions of this task allow for precise, hypothesis-driven investigations into the role of the cholinergic system in mediating sustained attention performance with and with out distraction, with direct application to healthy human and patient research.

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Chapter II

RATS AND HUMANS PAYING ATTENTION: CROSS-SPECIES TASK DEVELOPMENT FOR TRANSLATIONAL RESEARCH

Introduction

Animal models play a critical role in research designed to determine the neuronal bases of cognition and behavior. In particular, animal research provides a degree of experimental control and precision not usually feasible in studies using human subjects, as well as avenues for manipulating and monitoring specific neurotransmitter and receptor systems. Attempts to use evidence from animal-based research to inform the design and interpretation of human studies inherently assume that different species draw on similar cognitive processes to perform tasks that are similar in terms of face validity. However, this assumption has been rarely tested, limiting the potential benefits of direct cross-utilization of evidence. Perhaps as a result, treatment approaches for cognitive disorders that are based on animal research frequently fail to translate into clinical efficacy (e.g., Sarter, 2004; 2006).

This paper describes a set of studies designed to address this issue by characterizing human performance in a task (McGaughy & Sarter, 1995) that has been extensively used in rat research to determine the role of the cholinergic system in sustained attention and in responding to challenging situations that require the intentional,

top-down control of attention (for review see Sarter et al., 2005). Here, I compare rat and human performance patterns on the sustained attention task (SAT) under standard conditions and under distraction (dSAT). My main focus is on the distraction condition, which in rats has been biologically linked to increased acetylcholine efflux and theoretically linked to an increased demand for the top-down control of attention (Sarter, et al., 2006). My central question was whether the distraction manipulation leads to qualitatively similar performance changes across the two species, a finding which would support the idea that it taxes similar cognitive processes.

The basic rat paradigm is a signal-detection paradigm, which in most studies uses a short, centrally-presented light cue as the signal. Signal and non-signal events are presented in a randomized order and with equal probability. The subject's task on each trial is to indicate whether or not a signal appeared by pressing the correct lever (one for hits, another for correct rejections) during the response period, which is indicated by a separate event (extension of the lever for rat studies; a distinct auditory tone for the human experiments reported here). The task includes several features (competing response rules, variable signal duration, and variable inter-trial interval (ITI)) that impose a cognitive load, ensuring that even the basic version of the task cannot be successfully completed on the basis of side biases or simple response timing and instead requires directed attention to the presence or absence of the stimulus on each trial (c.f., Parasuraman & Davies, 1977; Parasuraman et al., 1978; Parasuraman & Mouloua, 1987). Distraction (in the form of a flashing houselight) can be introduced to challenge performance and increase the demands for top-down control (Gill et al., 2000; Himmelheber, et al., 2000; Sarter et al., 2006).

The initial studies using this task in animals (Bushnell, 1999; McGaughy & Sarter, 1995; see Mohler et al., 2001, for a mouse version) characterized the effects of variables that form the basis of Parasuraman's taxonomy of attention (Parasuraman & Davies, 1977; Parasuraman & Mouloua, 1987). These included the effects of signal intensity, signal duration, event rate, and distractors (see also Bushnell, 1999; Echevarria et al., 2005; Newman & McGaughy, 2008). In the subsequent decade, neurobiological research using this task with rats has played an important part in establishing the role that cholinergic inputs to prefrontal regions play in signal detection and attentional shifts, particularly under challenging conditions (for review, see Sarter et al., 2005; Sarter et al., 2006). For example, it has recently been shown that transient increases in cholinergic activity in the prefrontal cortex mediate the shift from internally-directed processing modes to input processing and signal detection (Howe et al., 2007).

Lesion and neuroimaging research with human and non-human primates generally concurs with rodent-based research in the view that fronto-parietal networks mediate elementary aspects of attention (e.g., Braver et al., 2003; Hopfinger et al., 2000; Pessoa et al., 2003; Sylvester et al., 2003). However, these studies lack the precise information that can be provided by rodent-based studies about the specific role of the cholinergic system (or other neurotransmitter systems) in that network. Recent studies that combine pharmacologic manipulations with functional neuroimaging approaches are an important step toward understanding this role (e.g., Bentley et al., 2004; Thiel et al., 2002). Even in these pharmacologic-fMRI studies, the drug manipulations affect neurotransmitter function at a very gross level both temporally and anatomically when compared to the usually more event- and region-specific action observed using contemporary

electrochemical recording techniques in animals (Parikh et al., 2007). Further, most lesion- and neuroimaging-based attempts to understand the organization of attention and other cognitive functions focus on the *where* issues of what brain regions are involved, with limited consideration of the *how* issues related to transmitter function (e.g., Wager et al., 2004). A better integration of information across species (rodent, nonhuman primate, human) and levels of analysis (molecular, systems) would improve hypothesis generation, theory development, and practical application.

Although examples of such integration are rare, there is some precedent for this type of approach. In particular, the CANTAB (Cambridge Neuropsychological Test Automated Battery; Morris et al., 1987) is used to assess a range of cognitive functions in humans and nonhuman primates. It has been very effective in establishing the role of specific transmitter and receptor systems in normal function and in diseases such as Alzheimer's, schizophrenia, and Parkinson's disease (see reviews by Fray & Robbins, 1996; Levaux et al., 2007). Bushnell and colleagues (Bushnell et al., 2003) examined rat and human performance in a simple sustained attention task similar to the task used here. They found similar performance across the two species, although there was some suggestion that human males were differently affected by trial rate (intertrial interval length) than were the other groups.

The present experiments examine rat and human performance in the McGaughy and Sarter (1995) sustained attention task under standard and distracting conditions. For each trial, the participants' task was to detect the presence or absence of a brief, sudden-onset visual signal (rather than the change in luminance to a constant signal used by

Bushnell et al., 2003; c.f., Parasuraman & Davies, 1977; Theeuwes, 1991). Changes in stimulus duration were used to manipulate stimulus strength.

As described previously, I was especially interested in the effects of the distractor manipulation, which in rat studies has been used to tax *top-down attention*, the voluntary cognitive control functions used to modulate behavior in the face of challenge or changing reward contingencies (Posner & Snyder, 1975; Schiffrin & Schneider, 1977; see Gill et al., 2000; Himmelheber et al., 2000; McGaughy et al., 1996, for previous rat studies using this manipulation). For both species, I compared patterns of performance under normal conditions and after the introduction of a challenging distractor in the form of flashing background illumination. Maintaining performance in the face of attentional challenges is particularly dependent on increases in prefrontal cholinergic activity (Gill et al., 2000; Kozak et al., 2006). For the human experiments, I also examined how performance changed in response to changes in reward contingencies, a manipulation that likewise requires top-down, voluntarily controlled processes rather than lower-level perceptual or stimulus-driven (bottom-up) regulation of attentional systems (Sarter et al., 2006). Taken together, my results show that rats and humans show similar – though not identical – performance on the standard sustained attention task and similar responses to distraction, supporting the use of this task in translational research.[1]

[1] It is important to note that the central question in cross-species task validation is *qualitative*, not quantitative, similarity in responses to manipulations of construct-related variables. Although quantitative similarity has an intuitive, superficial appeal in terms of face validity, it would in fact be quite surprising if humans, who presumably have greater top-down control abilities, were not more robust than rats when dealing with challenges to such control. The criterion of qualitative rather than quantitative cross-species similarity has been used successfully both in the development of nonhuman primate versions of the CANTAB (e.g., Dias et al., 1996; Roberts et al., 1988; Weed et al., 1999) and a recent translation of human memory tests of familiarity and recollection to rodents (Fortin et al., 2004; Sauvage et al., 2008). See also Olincy and Stevens (2007) for a short review of the use of the prepulse inhibition task in humans and mice.

Experiment 1: Effects of Distraction on Sustained Attention in Rats and Humans

Method

General procedures

My main question was whether the demand to sustain attention over time and in the face of distraction resulted in similar patterns of performance for rats and humans. Both species performed a version of a sustained-attention signal-detection task (Figure 2.1; McGaughy & Sarter, 1995) under standard and distracting conditions. For each trial, participants indicated the presence or absence of a small, variable-duration stimulus presented under either standard (constant lighting) or distracting (flashing houselight for rats, flashing computer screen for humans) conditions, with rewards for correct performance.

The long trial blocks, varied signal durations, and varied inter-trial intervals (ITI) employed in this task require participants to sustain high levels of attention in order to maintain successful performance (Bushnell et al., 2003; McGaughy & Sarter, 1995; Parasuraman & Mouloua, 1987). Distraction further challenges attention and performance (Gill et al., 2000; Sarter et al., 2006). My primary prediction was that distraction would reduce accuracy as a function of signal duration and block of trials for both species. I also explored whether other factors that might influence attentional challenge, such as event rate and the length of distractor presentation influenced standard task performance and interacted with distraction effects.

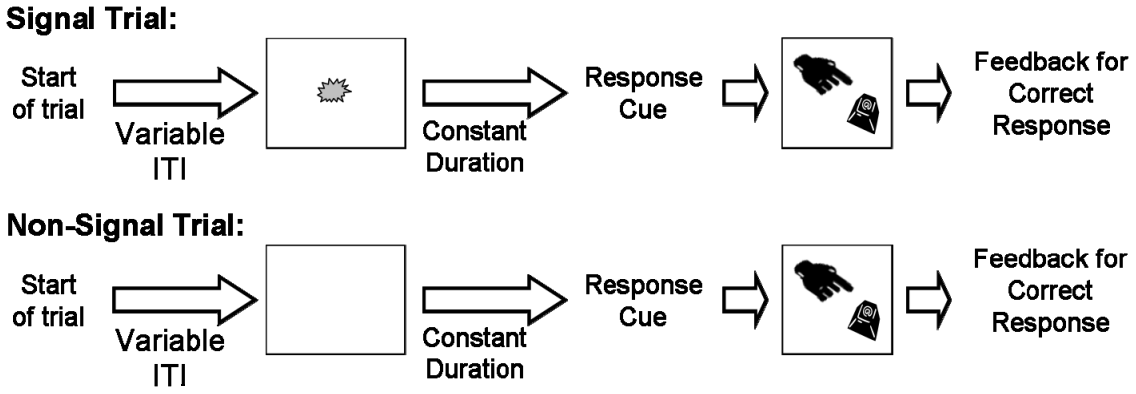

Figure 2.1. Schematic of sustained attention task used for rats and humans. Each trial began with a variable delay separating it from the previous trial (intertrial interval, ITI), after which a brief light stimulus either appeared (signal event) or did not appear (nonsignal event) in the center of the display. Signal and non-signal events were pseudo-randomized with 50% trials of each type. After a short, constant delay, participants were then cued to indicate whether a signal had or had not occurred on that trial. Correct responses (both hits and correct rejections) were rewarded (water reward for rats, feedback tone signaling a monetary reward for humans); incorrect responses and omissions did not receive any feedback.

Experiment 1A: Sustained Attention in Rats

This experiment used the rat sustained-attention task described and validated by McGaughy and Sarter (1995) and used extensively to test acetylcholine's role in supporting sustained attention and performance in the face of attentional challenges (e.g., Kozak et al., 2006; McGaughy & Sarter, 1998). This experiment most closely follows the version used by Gill et al. (2000), Himmelheber et al. (2000), and McGaughy et al. (1996) in using the presence or absence of a flashing-houselight distractor as the major manipulation of challenge. An additional feature of this experiment is that I varied the number of blocks during which the distractor was presented to ask how distractor-related impairments might change over time: Does performance recover as the animal adapts,

perhaps by increasing top-down control, further decline as a result of fatigue, or remain relatively stable?

Animals and animal housing.

The subjects were 11 male Wistar rats (Harlan Sprague-Dawley, Indianapolis, IN) weighing 300-350 g at beginning of behavioral training. Animals were individually housed in a temperature- (23 °C) and humidity-controlled (45%) environment on a 12 h light/dark cycle (lights on at 7:00 a.m.). Animals were extensively handled prior to the beginning of training so that handling during experimental procedures would not lead to increased arousal. Food was available *ad libitum* (Rodent Chow, Harlan Teklad, Madison, WI). Water was provided as a reward for successful task performance (described below). Access to water was otherwise restricted to an 8-min period following daily operant training. Animal care and experimentation were performed in accordance with protocols approved by the University of Michigan's University Committee on Use and Care of Animals (UCUCA).

Apparatus.

Behavioral training and testing was conducted in operant chambers (Med-Associates, St Albans, VT, see Appendix I, Figure 1.1 for a schematic of the chambers), located inside larger sound-attenuating chambers. Each operant chamber was equipped with an intelligence panel consisting of three panel lights (2.8 W), two retractable levers, and a water dispenser (40-45 µL of water per delivery). A houselight (2.8 W) was located on the rear wall. Signal presentation, lever operation, reinforcement delivery, and data collection were controlled by a Pentium PC and Med-PC for Windows software (V 4.1.3; Med-Associates).

Behavioral training procedures.

The task, training method, and performance measures have been previously validated with respect to sustained attention (McGaughy & Sarter, 1995), and are briefly outlined.

The first step was to familiarize animals with the equipment and methods for obtaining reward. Animals were initially shaped to lever-press in accordance with a modified fixed-ratio schedule (each lever press was rewarded) for water reinforcement. Following at least three consecutive runs of 100 reinforced lever presses, animals began the first stage of training on the sustained attention task *per se*. During this stage, the houselight was turned off to increase the salience of the signal, which consisted of a 1 s illumination of the central panel light. Animals were trained to discriminate between the presence (signal event) and absence (nonsignal event) of this stimulus on each trial. Two seconds after the occurrence of each signal or nonsignal event, both levers were extended into the operant chamber. Responses were reinforced when one lever was pressed on signal trials (hits) and the other lever pressed on nonsignal trials (correct rejections). Incorrect lever presses (miss or false alarm errors) were not reinforced. If no response occurred within 4 s, the levers were retracted and an omission was recorded. The intertrial interval (ITI) was 12 ± 3 s. Intertrial interval, trial type (signal or non-signal), and signal duration were presented in a pseudorandom order with an equal distribution across trials (81 trials total). Left-right assignments were counterbalanced across animals. At this stage of training, incorrect responses resulted in up to three correction trials, in which the trial was repeated if the animal did not give a correct response. Continued incorrect responses resulted in a forced-choice trial, where only the correct lever was

extended for 90 s or until a response was made. Correction and forced-choice trials aid in acquisition of response rules and help prevent development of a side bias (McGaughy et al., 1996).

Testing continued under these conditions until performance was stable, defined as at least three consecutive days in which performance reached a criterion of ≥ 60% correct responses to both signal and nonsignal events and < 20% omissions. The next stage introduced multiple signal durations (25, 50, 500 ms), shortened the ITI to 9 ± 3 s, and discontinued the correction and forced-choice trials. Following at least three days of criterion performance under these conditions, the houselights were illuminated throughout the task. This important modification requires the animals to constrain their behavior and presumably to maintain persistent orientation towards the intelligence panel.

After animals' performance stabilized at criterion for at least three consecutive days with the houselight illuminated, the next stage set the task length to 40 minutes, the duration to be used during data collection. Task runs were divided into five 8-min blocks. Animals were trained on the sustained attention task under standard conditions (houselight constantly illuminated) until reaching criterion performance levels for three consecutive runs. Animals were then trained under the distractor condition to familiarize them with the flashing (on/off at 0.5 Hz) houselight. Animals were first exposed to the distractor condition present in blocks 2 and 3 out of the 5 task blocks ("short" distractor condition). The distractor condition ran continuously throughout the blocks it was presented in. Animals next returned to testing under standard conditions until performance was at criterion for two consecutive days. They were then exposed to the

distractor condition presented continuously through blocks 2-5 ("long" distractor condition). This "long" distractor condition differs only from the "short" distractor condition in the number of blocks distraction is present. Exposure to the distractor condition was again followed by standard testing for two days or until performance reached criterion.

Testing procedures.

Upon completion of all training stages animals were tested on the full version of the sustained attention task (five consecutive 8-minute task blocks) under standard conditions, with the short distractor, and with the long distractor. Only one condition was tested each day. Order of the distractor conditions (short, long) was counterbalanced across subjects. In between the distractor conditions, rats performed the task under standard conditions for two days or until performance was at criterion for two consecutive days. Data used for performance in the task were measured by averaging performance on the day prior to each of the two distractor conditions.

Experiment 1B: Sustained Attention in Humans

College students were tested in a conceptual replication of the rat experiment described above. The procedures used with humans differ from those used with rats in that they do not require extensive pre-training and are completed within a single session (see similar procedures by Bushnell et al., 2003; Mar et al., 1996). However, they preserve the critical features of standard and distractor-condition testing, varying signal durations and ITIs, and reward for correct performance.

Participants.

Sixteen participants (12 females, mean age = 19.7 years) were recruited through the introductory psychology subject pool and paid subject pools at the University of Michigan. All participants were right-handed as determined by the Edinburgh Handedness Scale (Oldfield, 1971), scored at least a nine on the Extended Range Vocabulary Test (ERVT; Version 3, Educational Testing Service, 1976; mean score = 16.9), had normal or corrected-to-normal vision, and had no conditions affecting attention or memory. The vocabulary test was used to screen out participants who might have had difficulty understanding the instructions or who were unmotivated or uncooperative. Participants were financially compensated or received course credit for their participation. They also received a small financial reward for performance on correct trials, analogous to the water reward used for rats. Participant recruitment and experimental procedures were in accordance with protocols approved by the University of Michigan's Behavioral Sciences Institutional Review Board.

Apparatus and procedures.

A Dell PC with E-Prime software (Psychology Software Tools) was used for stimulus presentation and data acquisition. The standard "silver" color in E-prime was used as the static background for the standard condition, and the screen alternated between silver and black at 10 Hz for the distractor condition. The signal consisted of a small (3.5 mm^2) gray square in the center of the screen. Headphones were used to present auditory cues and feedback; participants' responses were collected using the standard keyboard.

Participants were familiarized with task instructions and trained on the sustained attention task under standard conditions for 30 s and under distractor conditions for 30 s. Participants repeated practice until they reached ≥ 60% accuracy on the standard condition practice.

Testing procedures.

Participants completed four 10-minute runs of the sustained attention task. Task parameters were chosen on the basis of limited previous human work on this task (Mar et al., 1996) and pilot testing. Each experimental run consisted of 5 blocks of 2 minutes each. The four runs were a slow event-rate run (ITI = 6 ± 3 s) with all blocks in standard conditions, a fast event-rate (ITI = 2 ± 1 s) run with all blocks in standard condition, a fast event-rate run with block 2 in the distractor condition ("short" distractor), and a fast event-rate run with blocks 2 and 3 in the distractor condition ("long" distractor). The distractor stimulus ran continuously throughout the blocks it was presented. As for rats, the "short" and "long" distractor condition differ only in the number of blocks distraction is present. Run order was counterbalanced across participants.

The structure of individual trials was similar to that used for the rat experiment. Participants were required to detect a signal (small gray square) of varying durations (17, 50, or 100 ms) and to discriminate between signal and nonsignal events. One hundred milliseconds after the occurrence of a signal or nonsignal event, the response period was cued by a 75 ms low-frequency buzzer. Parallel to the rat experiment, responses were reinforced for pressing one key for signal trials and the other key for nonsignal trials (z key for left-hand responses; / key for right-hand responses, left-right assignments to signal or nonsignal trials counterbalanced across participants). Participants received one

cent for every percentage point of overall accuracy for each run ($1 maximum per run). A 75 ms high-frequency feedback tone followed correct responses, indicating to the participant that this trial would contribute to the performance-dependent financial reward. No feedback was given following incorrect trials or omissions (failures to respond within 1 s after the response buzzer). Within each run, ITI, trial type (signal or nonsignal), and signal duration were varied in a pseudorandom order with an equal distribution across trials.

Data analysis

Responses were recorded as hits, misses, correct rejections, false alarms, and omissions. The primary dependent measure used for subsequent analysis was the SAT score, which reflects performance across both signal and nonsignal trials. SAT score is used rather than the sensitivity index (SI; Frey & Colliver, 1973) because unlike SI, it is not confounded by errors of omission. It is calculated for each signal duration using the formula SAT score = (hits – false alarms) / [2(hits + false alarms) – (hits + false alarms)^2]. SAT score varies from +1.0 to -1.0, with +1 indicating that all recorded responses were hits or correct rejections and -1 indicating all recorded responses were misses or false alarms (see Tables for detailed hit and false alarm data).

The design of this experiment potentially allows the analysis of a relatively large number of effects and interactions. To reduce the number of Type I errors, my analyses were limited to my central questions about the effects of distraction and signal duration. For example, ITI was varied within each run so that trials appeared unpredictably, thus increasing the demands on attention, but ITI level was not a variable of primary

theoretical interest and is not included as an independent variable. In addition, for the human experiments, I varied the ITI between the two standard runs (2 ± 1 s vs. 6 ± 3 s) to examine whether this manipulation had any effect on this condition (Bushnell et al., 2003; Parasuraman & Mouloua, 1987). However, this comparison did not result in reliable effects or interactions. Thus, for humans, repeated-measures ANOVAs were conducted on the standard and distractor conditions that used the 2 ± 1 s ITI. The independent variables were Run (standard, short-distractor, and long-distractor conditions), Block, and Signal Duration. For each experiment, I first report the results of the 3-way interaction tests, followed by simpler tests targeted at my questions about distraction and signal duration. Separate repeated-measures ANOVAs were conducted on omissions.

I also conducted signal detection analyses (Swets et al., 1961) to better assess the effects of my variables on perceptual sensitivity (*d'*) and bias (B''_D), with the latter presumably more influenced by top-down, voluntary control processes. *d'* sensitivity measures were calculated from z scores of the proportions of hits and of false alarms, P_H and P_{FA} for each stimulus duration using the formula: $d' = z(P_H) - z(P_{FA})$ (Green & Swets, 1966). Data from short- and long-distractor runs were combined within no-distractor and distractor blocks to calculate P_H and P_{FA} for each subject. For *d'* measures, the effective limit (with $P_H = 0.99$ and $P_{FA} = 0.01$) is 4.65 and *d'* is zero when $P_H = P_{FA}$. B''_D measures of bias were calculated using the formula $B''_D = [(1- P_H)(1- P_{FA}) - P_H P_{FA}] / [(1- P_H)(1- P_{FA}) + P_H P_{FA}]$ (Donaldson, 1992). B''_D scales from -1 to +1, with negative numbers indicating a liberal bias, positive numbers indicating a conservative bias, and zero indicating no bias. Both measures were analyzed using repeated-measures ANOVAs

with the independent variables Distraction (no-distraction, distraction) and Signal Duration, followed by simpler tests to investigate distraction effects within each signal duration.

For all analyses, the Huyhn-Feldt sphericity correction was applied as needed. Corrected *F* and *p* values are reported, but degrees of freedom are rounded to integer values for easier reading. For repeated measures ANOVAs, effect sizes were computed using generalized eta squared (η^2_G, Olejnik & Algina, 2003). Bakeman (2005) suggested for η^2_G sizes 0.02 be classified as small, 0.13 as medium, and 0.26 as large, similar to η^2 guidelines (Cohen, 1988). For *t* tests, effect sizes were reported using Cohen's *d*, with corrections for repeated measures (Cohen, 1988).

Experiment 1: Results and Discussion

My main question was how overall performance, as indicated by SAT score, varied across conditions for rats and for humans (Figure 2.2). As described above, analyses were restricted to the standard, short-distractor, and long-distractor runs with the same ITI parameters. The 3-way Run X Block X Duration interaction was not statistically significant for the rat experiment, $F(16, 160) = 1.00$, $p = 0.45$, $\eta^2_G = 0.03$, but was significant within the human experiment $F(16, 240) = 4.47$ $p < 0.0001$, $\eta^2_G = 0.06$. As I elaborate on below, the major differences between the species were that rats showed lower performance overall, with distractor-related declines at all durations and difficulty recovering performance after distraction, whereas humans showed very high performance

overall and only had statistically significant effects of the distractor at the shortest signal duration.

Omissions were generally low in both species (for rats, 2.47 ± 1.07% of trials per run; for humans, 1.61 ± 0.55% of trials per run) and did not differ significantly across experimental conditions, $F < 1.00$ for both species.

Performance without Distraction is Signal Duration-Dependent

Performance (SAT score) on the standard task was duration-dependent for both rats ($F(2,20) = 54.35$, $p < 0.0001$, $\eta^2_G = 0.45$) and humans ($F(2,30) = 4.45$, $p = 0.03$, $\eta^2_G = 0.04$), with better performance at longer durations (Figure 2.2, see Tables 2.1 and 2.2 for hit and false alarm data that go into the calculation of SAT score). Mere time on task did not influence performance for either species, as indicated by the lack of a Block main effect or significant Block X Duration interaction for either rats or humans, all $F \leq 1.00$.

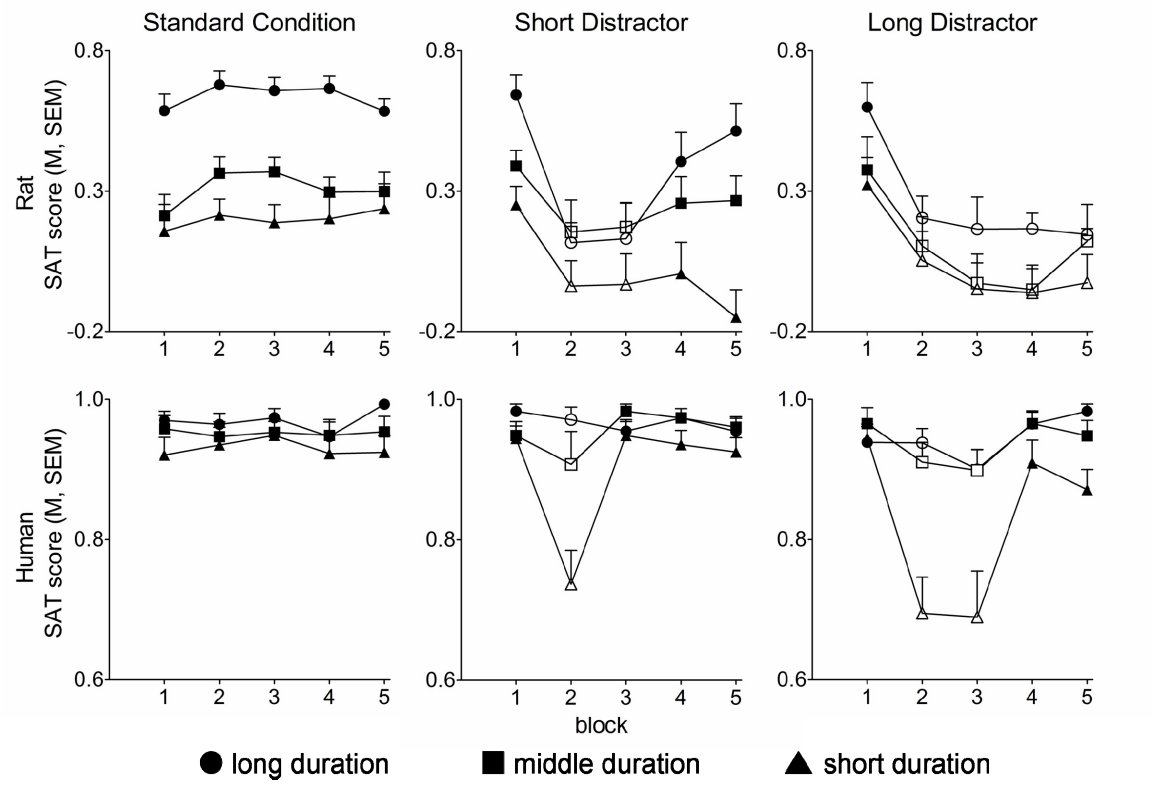

Figure 2.2. Both species are influenced by stimulus duration and distraction. Each graph shows the mean SAT score (see text for calculation) across blocks and distraction conditions for the three different run types. Rat data are in the top panels, human data in the bottom panels. The leftmost panel shows data from the no-distractor run, the middle panel shows data from the run with only a short period of distraction (2 blocks for rats, 1 block for humans), the right panel shows data from the run with a longer period of distraction (4 blocks for rats, 2 blocks for humans). Solid symbols indicate a block with no distraction; hollow symbols indicate a block with distraction. Symbol shape indicates whether the signal was presented for a short, middle, or long duration (25, 50, or 500 ms for rats; 17, 50, or 100 ms for humans). Both species show substantial effects of signal duration even in the standard, no-distraction condition (leftmost panels and solid symbols in all panels). Neither species showed performance declines as a function of mere time on task. Rats showed substantial performance declines in the face of distraction at all durations, whereas for humans the effects of distraction were most pronounced at the shortest signal duration. (See text for statistical details.)

Table 2.1. E1A: Hit and false alarm proportions for sustained attention task in rats. Data are means (standard error around the mean). Distraction is present in blocks 2 and 3 of the short-distractor condition and in blocks 2-5 of the long-distractor condition, indicated with italics.

Block	Hits to 500 ms signal	Hits to 50 ms signal	Hits to 25 ms signal	False alarms
SAT				
1	0.78 (0.05)	0.42 (0.06)	0.37 (0.06)	0.22 (0.03)
2	0.83 (0.05)	0.52 (0.05)	0.35 (0.04)	0.17 (0.01)
3	0.82 (0.05)	0.52 (0.07)	0.35 (0.06)	0.20 (0.03)
4	0.82 (0.04)	0.44 (0.06)	0.35 (0.04)	0.19 (0.03)
5	0.75 (0.05)	0.48 (0.05)	0.43 (0.05)	0.20 (0.03)
Short dSAT				
1	0.79 (0.07)	0.51 (0.06)	0.38 (0.05)	0.17 (0.03)
2	*0.55 (0.06)*	*0.57 (0.09)*	*0.45 (0.07)*	*0.47 (0.06)*
3	*0.45 (0.09)*	*0.41 (0.07)*	*0.25 (0.05)*	*0.28 (0.05)*
4	0.49 (0.07)	0.32 (0.06)	0.19 (0.05)	0.11 (0.01)
5	0.69 (0.06)	0.42 (0.06)	0.14 (0.05)	0.20 (0.07)
Long dSAT				
1	0.78 (0.06)	0.54 (0.1)	0.46 (0.09)	0.19 (0.04)
2	*0.62 (0.07)*	*0.56 (0.09)*	*0.49 (0.08)*	*0.46 (0.07)*
3	*0.44 (0.11)*	*0.31 (0.09)*	*0.26 (0.07)*	*0.28 (0.06)*
4	*0.45 (0.07)*	*0.26 (0.05)*	*0.28 (0.07)*	*0.29 (0.04)*
5	*0.42 (0.09)*	*0.35 (0.05)*	*0.27 (0.06)*	*0.25 (0.04)*

Table 2.2. E1B: Hit and false alarm proportions for sustained attention task in humans. Data are means (standard error around the mean). Distraction is present in block 2 of the short-distractor condition and in blocks 2-3 of the long-distractor condition, indicated with italics.

Block	Hits to 500 ms signal	Hits to 50 ms signal	Hits to 25 ms signal	False alarms
Standard Condition				
1	0.98 (0.01)	0.97 (0.02)	0.92 (0.03)	0.01 (0.01)
2	0.93 (0.02)	0.96 (0.02)	0.93 (0.04)	0.01 (0.01)
3	0.98 (0.01)	0.96 (0.02)	0.95 (0.03)	0.01 (0.01)
4	0.96 (0.02)	0.97 (0.02)	0.94 (0.03)	0.02 (0.01)
5	1.00 (0.00)	0.96 (0.02)	0.92 (0.03)	0.01 (0.01)
Short Distractor Condition				
1	0.99 (0.01)	0.95 (0.03)	0.95 (0.02)	0.01 (0.01)
2	*1.00 (0.00)*	*0.94 (0.03)*	*0.70 (0.06)*	*0.04 (0.02)*
3	0.96 (0.02)	0.99 (0.01)	0.95 (0.03)	0.01 (0.01)
4	0.98 (0.01)	0.98 (0.01)	0.94 (0.02)	0.01 (0.01)
5	0.96 (0.02)	0.97 (0.02)	0.92 (0.03)	0.01 (0.01)
Long Distractor Condition				
1	0.94 (0.03)	0.97 (0.02)	0.95 (0.02)	0.01 (0.01)
2	*0.99 (0.01)*	*0.96 (0.02)*	*0.69 (0.06)*	*0.06 (0.03)*
3	*0.93 (0.03)*	*0.93 (0.03)*	*0.68 (0.07)*	*0.03 (0.01)*
4	0.98 (0.01)	0.98 (0.04)	0.91 (0.04)	0.02 (0.01)
5	0.99 (0.01)	0.95 (0.03)	0.85 (0.03)	0.01 (0.01)

Distraction Impairs Task Performance

The Run X Block interaction comparing performance (SAT score) across blocks for the standard, short-distractor, and long-distractor runs was significant (both $p < 0.001$) for both rats and humans, indicating that the distractor impaired performance for both species (Figure 2.2). The Block x Duration interaction was not significant for rats,

$F(8,80) = 1.31$, $p = 0.25$, $\eta^2_G = 0.01$, but was for humans, $F(8,120) = 7.76$, $p < 0.0001$, $\eta^2_G = 0.05$. Subsequent analyses looked within each distractor run to compare the results for those blocks during which the distractor was present versus those during which it was not.

In simple analyses comparing all no-distractor blocks with all distractor blocks, distraction reduced performance for both rats and humans in both the short- and long-distractor runs: Rat short-distractor run, $t(10) = 3.79$, $p < 0.01$, Cohen's $d = 1.20$, long-distractor run, $t(10) = 4.02$, $p < 0.01$, Cohen's $d = 1.73$; human short-distractor run, $t(15) = 2.83$, $p = 0.01$, Cohen's $d = 0.88$, long-distractor run, $t(15) = 4.13$, $p < 0.005$, Cohen's $d = 1.16$. Inspection of Figure 2.2 suggests that the main differences between the species were that rats had low performance overall, with floor effects in some distraction cells (SAT score ~= 0), and also had difficulty recovering performance after distraction. When the rats' distractor blocks were compared only to the first no-distractor block in each run, they showed marginal Block x Duration effects for the short-distractor run, $p = 0.06$ and $\eta^2_G = 0.08$, paralleling the results found for humans. However, SAT score was not significantly different from zero (chance performance) in all distraction cells for the short distractor, and in all cells for the long distractor except for SAT score 500 in blocks 2 and 4 and SAT score 50 in block 5 (all $p < 0.05$ and Cohen's $d > 0.78$). For the short-distractor run, the first no-distractor block following distraction (block 4) was significantly lower than the first block in the run ($p = 0.04$, Cohen's $d = 1.04$) and not different from the distractor blocks (all $p > 0.10$, Cohen's $d < 0.69$). For all but the shortest duration, performance began to recover by the second postdistractor block and was intermediate. Similar floor effects at shorter signal durations following an attentional

challenge were previously reported on this task in rats (e.g., Kozak et al., 2006; McGaughy et al., 1996), suggesting the 500 ms duration may be the most useful to examine when considering manipulations that decrease hit accuracy.

Humans showed higher performance overall; smaller distraction effects that were only statistically significant at the shortest duration and had near-immediate, full recovery after exposure to the distractor. The Block X Duration interaction was significant for both distractor runs (both $p < 0.0001$). Analyses at each Duration level showed that for the 17 ms condition, SAT score was significantly lower for distractor blocks than no-distractor blocks in both distractor runs, both $p < 0.005$, $\eta^2_G = 0.36$ for the short-distractor condition, and $\eta^2_G = 0.30$ for the long-distractor condition. In contrast, the distraction effect was not statistically significant for the two longer durations, all $p > 0.07$, although performance was numerically worse in the distractor condition even for these durations. (For the short-distractor run, $\eta^2_G = 0.07$ for the 50 ms duration and $\eta^2_G = 0.03$ for the 100 ms duration. For the long-distractor run, $\eta^2_G = 0.08$ for the 50 ms duration and $\eta^2_G = 0.11$ for the 100 ms duration.) Humans did not show significant differences between pre-distractor and post-distractor blocks, all $p > 0.20$.

Distraction effects on perceptual sensitivity (*d'*) and response bias (B''_D)

Signal detection analyses were performed to better understand the performance of both species. In particular, I was interested in the degree to which performance drops in the distraction condition were related to a loss of perceptual sensitivity and in potential species difference in response criterion (cf., Bushnell et al., 2003).

For rats, the *d'* measure in the distraction condition at the shortest signal duration was near zero, consistent with the impression of floor performance in this condition given by the SAT score analyses (Figure 2.3). For the other two durations, performance in the distraction condition was low but significantly above zero (both $p < 0.005$). By contrast, humans' *d'* was significantly above zero for all conditions, including the shortest duration under distraction conditions, Figure 2.3, all $p < 0.0001$). Further, while *post hoc* analyses of humans' SAT score (above) found significant distraction effects within only the shortest duration, *post hoc* tests on their *d'* results showed significant effects of distraction within both the 17 ms and the 50 ms signal durations (both $p < 0.05$, $\eta^2_G > 0.08$). This suggests that, especially in the longer-duration conditions, humans may have been able to use top-down attentional control to partially counteract the perceptual difficulties imposed by distraction. For both species, all other effects for the *d'* measure were in the expected direction, with significant effects of Distraction, Duration, and their interaction, all $p < 0.01$.

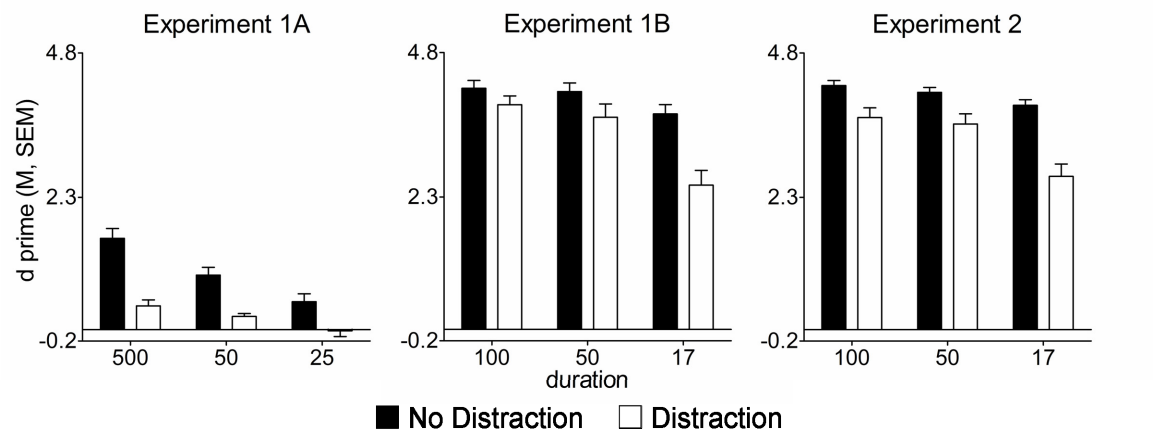

Figure 2.3. *d'* sensitivity measures for rats (Experiment 1A) and humans (Experiment 1B and 2). Bars represent the sensitivity measures from the no-distractor (black bars) and distractor (white bars) blocks combined across the short- and long-distractor runs. Error bars represent standard error around the mean. Both species show a reduction in sensitivity as a result of shortened signal duration and distraction, although these effects are more pronounced for rats than for humans. Supporting the conclusions drawn from the SAT score results, the rats show lower sensitivity overall and are at floor in the lowest signal duration. Changes in reward contingency for humans did not affect the *d'* sensitivity measures (compare E1B and 2).

I also calculated measures of response bias (B''_D) for both species. For rats, both misses and false alarms increased under distraction, $p < 0.001$ and $\eta^2_G > 0.15$, for the short- and long-distractor runs. However, for humans, misses were sensitive to distraction for each of the distractor runs, $p < 0.005$, $\eta^2_G > 0.11$, but false alarms were only marginally affected, $p < 0.05$, $\eta^2_G > 0.06$. This difference suggested rats and humans had different criterion shifts in response to the uncertainty introduced by distraction, a suggestion borne out by analysis of the B''_D measure (Figure 2.4).

The signal detection analyses revealed that rats had a more conservative response bias overall, but shifted towards a more liberal criterion when distraction introduced uncertainty. Of interest, duration and distraction had opposite effects: Shortened duration led to a more conservative response bias, $F(2,20) = 41.70$, $p < 0.0001$, $\eta^2_G = 0.01$, whereas distraction led to a more liberal response bias, $F(1,10) = 4.85$, $p = 0.05$, $\eta^2_G = 0.07$. Humans showed very little response bias at the two longer durations, consistent with their overall high performance in these conditions. In keeping with the effects of duration found in rats, humans also showed a shift towards a more conservative response criterion in the shortest duration. However, distraction in the short-duration condition had the opposite effect on humans than it did in rats, leading to a more conservative, rather than a more liberal, response bias (Figure 2.4).

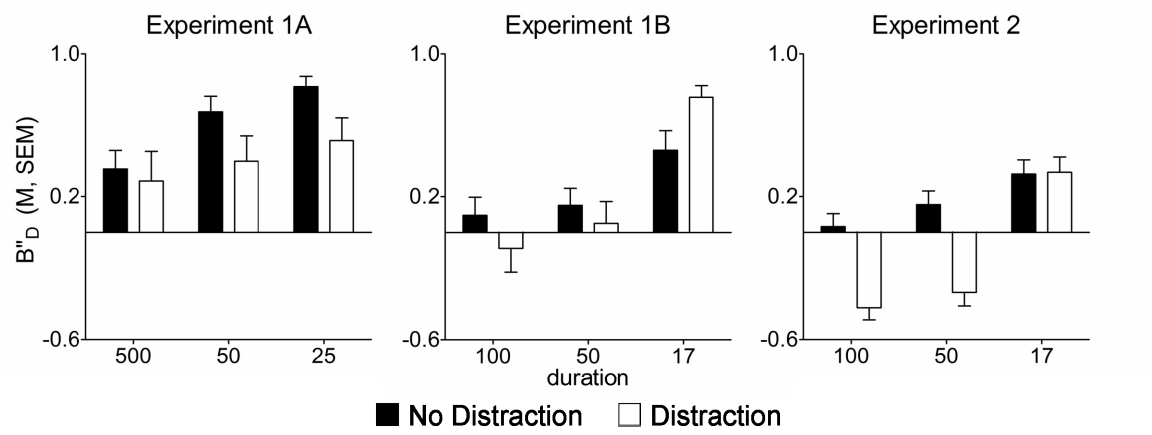

Figure 2.4. Bias measures for rats (Experiment 1A) and humans (Experiment 1B and 2). Bars represent the bias measures from the no-distractor (black bars) and distractor (white bars) blocks combined across the short- and long-distractor runs. Error bars represent standard error around the mean. Both species show an increasingly conservative bias in response to reduced signal duration. However, rats show a more conservative bias overall and a liberal shift in response to distraction. E1B: Humans show the opposite response to distraction in the shortest duration, adopting a very conservative response bias. E2: When misses are penalized, humans tend to adopt a liberal response criterion under distraction, so that the effects of distraction on their bias measures resemble the effects on rats (E1A).

In summary, my results showed fundamental similarities between rat and human performance both in the standard task and in the two species' response to distractor challenge, but I also found important differences that were likely due to humans' greater capacity for top-down control. The strongest similarities were seen in the standard, no-distractor condition: both species showed better performance for longer signal durations, and neither species' performance was influenced by mere time-on-task. Both species showed performance declines in the face of distraction, although these effects were more evident in rats than in humans with the sample sizes and stimulus parameters used here. In part because of the floor effects and slow recovery postdistraction on the two shorter durations in rats, across species the pattern of distraction effects are most similar when

comparing rats' performance at 500 ms duration to humans' performance at 17 ms. The signal detection analyses revealed that distraction similarly reduced perceptual sensitivity for both species. In contrast, rats and humans responded somewhat differently in their (presumably top-down) shifts in response criterion. Both species responded to shorter durations by becoming more conservative, but rats became more liberal in the face of distraction, whereas humans showed the opposite effect.

To better understand the effects of distraction on human performance and the influence of top-down control processes on their response to distraction, I conducted a second experiment using only human participants. This experiment used a larger sample size, to test whether the numerical effects of distraction seen at the longer durations (Figure 2.2, bottom panel) would be significant with greater power. It is more important to note I changed the reward contingencies to encourage a shift towards a more liberal response criterion. Specifically, an increased penalty was imposed for "miss" responses, with the expectation that this would increase the probability of false alarms and lead to a more liberal response bias under conditions of uncertainty.

Experiment 2: Top-down Manipulation of Sustained Attention Task Performance in Humans

Method

General Procedures

Procedures were identical to Experiment 1B except that the reward contingencies for performance-based payment were changed to penalize misses. Thirty-two participants (19 females, mean age = 18.7 years, mean Extended Range Vocabulary Test score = 18.7) were instructed that they would be monetarily penalized 5 cents for each percentage point of misses for every run. This penalty was subtracted from the 1 cent per percentage point correct payment the subjects earned on each run.

My primary prediction for this experiment was that, relative to Experiment 1B, participants would show fewer misses and more false alarms if performance on this task were sensitive to top-down manipulation. In line with this shift towards more false alarms, I also predicted participants in this experiment would have a more liberal response bias than participants in Experiment 1B. Finally, the large number of misses relative to false alarms during distraction in Experiment 1B raises a potential concern about the source of the errors (problems perceiving the stimuli versus top-down biases to respond negatively under conditions of uncertainty). Changes in the error distributions and in the response bias measures between Experiment 1B and 2 would support the role of top-down biases in generating the error data seen in Experiment 1B.

Data analysis

Analysis of data followed the procedures outlined for the animal experiment and the first human experiment. To examine the error data between this experiment (Experiment 2) and the prior human experiment (Experiment 1B), a 3-way ANOVA was conducted with Error Type (false alarms, misses) and Distraction (no distraction, distraction) as within-subject factors, and Experiment (E1B, E2) as a between-subject factor. As in the first experiment, analyses focused on the three runs (standard, short-distractor, long-distractor) with similar ITIs.

Experiment 2: Results and Discussion

For SAT score, the 3-way Run X Block X Duration interaction was significant, $F(16,496) = 3.92$, $p < 0.001$, $\eta^2_G = 0.02$. Errors of omissions were generally low (2.50 ± 0.53% of trials per run) and did not differ significantly across experimental conditions ($F(2,62) = 1.23$, $p = 0.30$, $\eta^2_G < 0.01$).

Replication of Experiment 1B effects: Duration and distraction influence performance

Performance (SAT score) in the standard, no-distractor condition replicated the effects found in Experiment 1B (Figure 2.5; see Table 3.3 for hits and false alarms). Performance was better for longer durations than for shorter ones, $F(2,62) = 13.70$, $p < 0.0001$, $\eta^2_G = 0.04$, and remained stable across the five task blocks.

Table 2.3. E2: Hit and false alarm proportions for the penalized misses experiment in humans. Data are means (standard error around the mean). Distraction is present in block 2 of the short-distractor condition and in blocks 2-3 of the long-distractor condition, indicated with italics.

Block	Hits to 500 ms signal	Hits to 50 ms signal	Hits to 25 ms signal	False alarms
Standard Condition				
1	1.00 (0.00)	0.98 (0.01)	0.93 (0.02)	0.03 (0.01)
2	1.00 (0.00)	0.99 (0.01)	0.96 (0.02)	0.01 (0.01)
3	0.98 (0.01)	0.97 (0.01)	0.93 (0.02)	0.02 (0.01)
4	0.98 (0.01)	0.97 (0.01)	0.95 (0.02)	0.01 (0.00)
5	0.98 (0.01)	0.97 (0.01)	0.96 (0.02)	0.02 (0.01)
Short Distractor Condition				
1	0.99 (0.01)	0.97 (0.01)	0.95 (0.02)	0.02 (0.01)
2	*0.98 (0.01)*	*0.97 (0.01)*	*0.84 (0.04)*	*0.06 (0.02)*
3	0.99 (0.01)	0.98 (0.01)	0.96 (0.01)	0.01 (0.01)
4	0.97 (0.02)	0.96 (0.02)	0.93 (0.02)	0.01 (0.01)
5	1.00 (0.01)	0.95 (0.02)	0.93 (0.02)	0.02 (0.01)
Long Distractor Condition				
1	0.98 (0.01)	0.99 (0.01)	0.94 (0.02)	0.02 (0.01)
2	*0.98 (0.01)*	*0.97 (0.01)*	*0.81 (0.04)*	*0.09 (0.03)*
3	*0.96 (0.01)*	*0.96 (0.02)*	*0.79 (0.04)*	*0.08 (0.02)*
4	0.98 (0.01)	0.97 (0.01)	0.97 (0.01)	0.02 (0.01)
5	0.97 (0.01)	0.97 (0.01)	0.96 (0.01)	0.01 (0.01)

Also replicating the previous experiment, distraction again impaired performance. Collapsing across durations, distractor blocks showed significantly lower SAT score values than no-distraction blocks for the short- and long-distractor runs, both $p < 0.05$ (Figure 2.5). The Duration X Block interaction was also statistically significant, $F(8,248) = 3.72$, $p < 0.01$, $\eta^2_G = 0.04$, for the short-distractor condition and $F(8,248) = 7.79$, $p < 0.0001$, $\eta^2_G = 0.04$, for the long-distractor condition, with larger distraction effects for the

shorter durations. However, the greater power of this experiment revealed significant distraction effects for all durations, not just the shortest one. For the long-distractor run, the distractor effect was statistically significant within every signal duration, all $p < 0.05$ and $\eta^2_G > 0.08$. For the short-distractor run, the distraction effect was statistically significant for the 17 ms and 100 ms durations, both $p < 0.05$, $\eta^2_G = 0.16$ for 17 ms duration and $\eta^2_G = 0.06$ for the 100 ms duration, and marginal for the 50 ms duration, $F(4,124) = 2.45$, $p = 0.06$, $\eta^2_G = 0.05$. These effect sizes are very similar to the ones found in E1B ($\eta^2_G = .03$ - $.11$), suggesting that my failure to detect statistically significant distraction effects at the longer durations in Experiment 1B were the result of insufficient power.

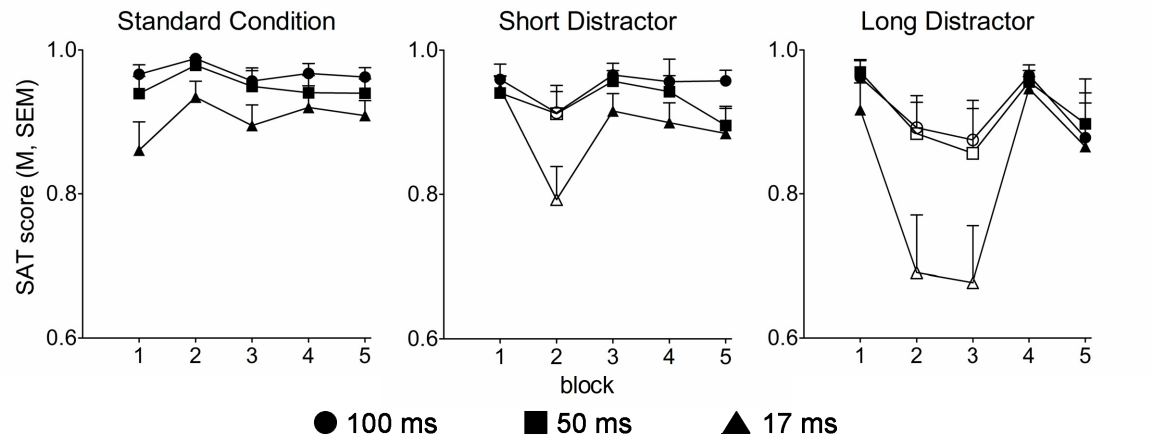

Figure 2.5. E2: Overall human attentional performance (SAT score) when misses are penalized is similar to performance under equal reward contingencies (compare to Figure 2.2). Data shown are from Experiment 2, in which misses were penalized more than false alarms. As in Figure 2.2, black symbols indicate the no-distractor condition whereas white signals indicate the presence of the distractor, and error bars represent standard error around the mean. These patterns generally replicate those seen in the first human experiment (Figure 2.2). The size of the distractor effects is generally similar across experiments (see text), but is significant for all durations in this experiment in part because of the increased sample size.

Similarly to the previous human experiment, analysis of *d'* sensitivity measures found a significant Distraction by Duration interaction, $F(2,62) = 13.44$, $p < 0.0001$, $\eta^2_G = 0.04$. The main effects of Distraction and Duration were likewise significant, (both $p < 0.0005$, $\eta^2_G \geq 0.12$), as in the previous experiment. In line with the distraction effects described for SAT score, sensitivity measures revealed distraction effects at all three signal durations. Within each duration, sensitivity measures were significantly lower during distraction than without distraction for each of the three signal durations (all $p < 0.05$, Figure 2.3).

Performance is sensitive to top-down manipulations

Besides the increased sample size, the major difference between the current experiment and E1B was the 5-cent penalty for misses. In Experiment 1B, most errors were misses, with very few false alarms. This could occur either because participants had primarily bottom-up difficulties in perceiving the signal stimulus, particularly under distracting conditions, or because of a top-down bias to respond negatively when distraction increased uncertainty. If the results were due to bias, a shift in the reward contingencies should lead to a shift in how people responded under uncertain conditions and a different distribution of error types.

The shift in reward contingencies indeed resulted in a shift in error distribution, consistent with manipulations of top-down control processes (Figure 2.6). A 3-way ANOVA comparing Experiment (1B, 2), Distraction (no-distraction, distraction), and Error Type (false alarms, misses) resulted in a significant 3-way interaction, $F(1,46) = 5.11$, $p = 0.03$, $\eta^2_G = 0.01$. It is important to note that the main effect of Experiment (E1B,

E2) was not significant, $p > 0.60$, indicating that the two experiments did not differ in the overall amount of errors, only in their distribution. Simpler analyses to probe the interaction revealed that there were no significant differences between the two experiments in the no-distractor condition, $F(1,46), = 0.32$, $p = 0.58$, $\eta^2_G < 0.01$. Instead, the effects of reward contingency were most evident in the distraction condition: In Experiment 1B, distraction primarily increased the number of misses, $F(1,15) = 12.01$, $p < 0.005$, $\eta^2_G = 0.15$, but the increase in false alarms was marginal, ($p = 0.06$, $\eta^2_G = 0.10$). By contrast, in E2, the proportion of misses and false alarms were almost equal under distraction, $F(1,31) = 0.32$, $p = 0.58$, $\eta^2_G = 0.002$.

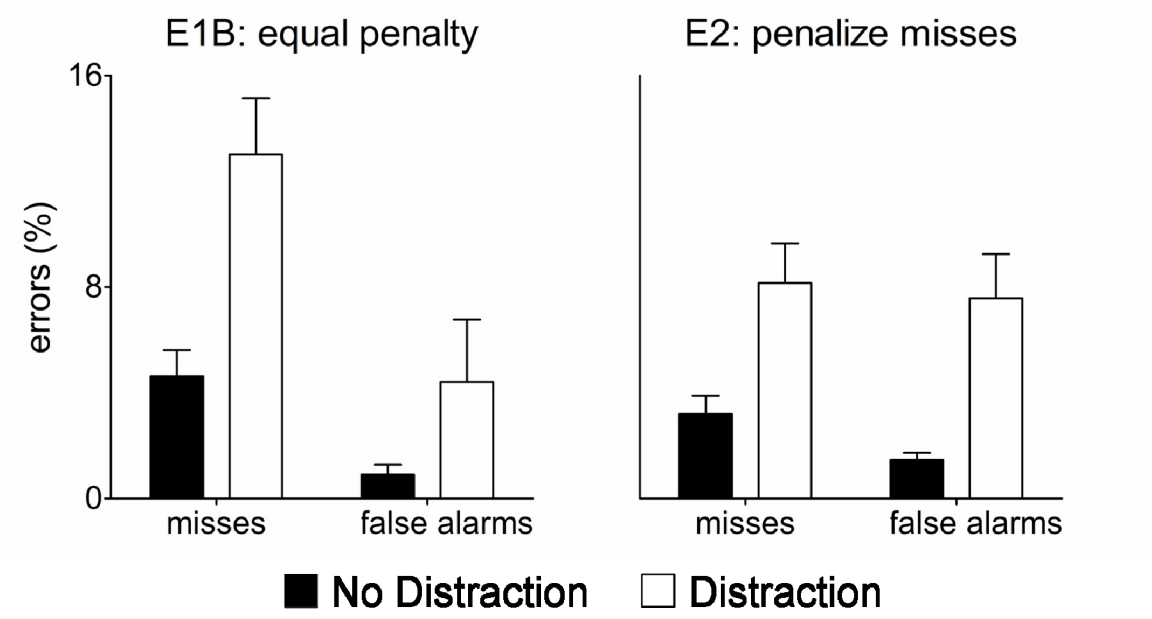

Figure 2.6. Changes in reward contingencies to penalize misses reduce misses and increase false alarms under distracting conditions. Bars represent the error data from E1B (equal penalties) and E2 (misses penalized), collapsed across short- and long-distractor runs. Error bars represent standard error around the mean.

The signal-detection analyses for this experiment also supported the idea that the types of errors seen in E1B (mostly misses) were attributable to top-down biases in how

to respond under conditions of uncertainty, rather than simply difficulty perceiving the signal stimulus during distraction. A 3-way ANOVA comparing Experiment (1B, 2), Distraction (no-distraction, distraction), and Duration (17 ms, 50 ms, 100 ms) found no effects of Experiment on *d'* sensitivity measures**.** In contrast, the Distraction X Experiment interaction was statistically significant for the B''_D bias measure, $F(1,46) = 8.90$, $p < 0.005$, $\eta^2_G = 0.03$. In particular, whereas in E1B distraction led to a more conservative response bias for humans within the shortest signal duration, in E2 it led to a more liberal response bias, an effect paralleling the results found for rats (E1A, see Figure 2.4).

Discussion

Although animal models play a critical role in developing treatments for various neuropsychological disorders, the degree to which an experimental task measures similar cognitive functions across species has been rarely determined. The present experiments address that issue, with a particular focus on manipulations thought to invoke voluntary or "top-down" modulation of attentional performance. These functions are of interest because they are thought to rely on frontal-parietal circuits, to be mediated by the function of the cholinergic system and, if disrupted, to contribute to the cognitive symptoms disruptions in a variety of neuropsychiatric disorders, including schizophrenia (e.g., Mar et al., 1996; Sarter et al., 2005).

My results generally support the view that tasks developed for animal research can be effectively redesigned for research in humans, while also revealing important

differences apparently related to humans' greater top-down control. Both species maintained performance over time in the standard condition, showed reduced performance at shorter durations compared to longer durations, and also showed reduced performance under distracting conditions. These patterns partially replicate the findings of Bushnell and colleagues (2003), in that they find generally similar performance in the task overall and in response to manipulations of signal strength (signal intensity in their study, signal duration in ours). However, I did not find support for gender[2] and species differences in the effects of trial rate, although this may have been due to my particular stimulus parameters and a failure to find strong effects of trial rate overall.

The signal detection analyses provided important insights as to potential species differences in top-down control versus bottom-up perceptual processes, particularly in response to the distraction manipulation.[3] Although humans had greater sensitivity overall, both species showed a reduction in sensitivity (*d'*) in response to reduced signal duration and in response to distraction. As would be expected, this measure of perceptual sensitivity was not affected by the manipulation of reward contingency. The bias or response-criterion measures showed quite different effects, revealing interesting distinctions in both species' reactions to different sources of uncertainty. Both rats and humans responded to reduced signal duration by becoming more conservative. However,

[2]Gender analyses were conducted in human experiment (E2) to investigate whether the gender differences found by Bushnell et al. (2003) were replicated here; no consistent effects of gender were found. Evaluation of the effects of gender is limited by the relatively low number of subjects (13 males in E2) and is not possible here in rats (all males used).

[3]Bushnell et al. (2003) informally suggested that their human participants might have a more conservative response bias than did rats. However, this suggestion was based on the species differences in false alarm rates; formal signal-detection analyses were not conducted. Inspection of their data shows that the two species did not significantly differ in terms of hits. A simpler way to summarize the results of the two experiments might be to say that regardless of hit rates, humans generally produce very low false alarm rates when different error types are equally penalized.

they responded quite differently to distraction: Rats adopted a more liberal response criterion under distracting conditions. In contrast, humans became more conservative when distraction was introduced, with a large drop in hits accompanied by only a small increase in false alarms. However, a change in reward contingencies that penalized misses led humans to show a performance pattern much more like that of the rats, with a generally more liberal response criterion under distraction conditions than under the standard conditions. Taken together, the *d'* and bias measures suggest that both species show similar bottom-up effects of changes in signal strength (duration) and distraction and that both respond to these effects by exercising top-down control processes – albeit in somewhat different directions. It is important to note that prior work suggests response bias and responsivity to positive or negative feedback may differ in clinical populations, such as Parkinson's (e.g., Frank et al., 2004), amnesia (e.g., Yonelinas et al., 1998) or in aging (e.g., Marschner et al., 2005; Samanez-Larken et al., 2006). Thus, in addition to basic variables like signal duration, the effects of manipulating reward contingencies may need to be separately reexamined in populations outside the normal young adult population used here.

This brings us to the larger point that the experiments reported here are the first steps in the development and validation of this task for cross-species and patient research. As described earlier, the usual criterion for such task validation is qualitative (not quantitative) similarity across species (cf., Sauvage et al., 2008; Weed et al., 1999). Inherent species differences in perception, motivation, and top-down control make it difficult to obtain quantitative matches without extreme manipulations. For example, Bushnell et al. (2003) used a three-times longer signal duration and 42-times larger

stimulus range for rats as compared to humans in order to roughly equate mean performance between rats and humans. In the present paper, for the rat task I used stimulus parameters common to previous studies using this task in rats (Himmelheber et al., 2000**;** Kozak et al., 2006, McGaughy & Sarter 1995); for the human studies, I used stimulus parameters based on a paper exploring a somewhat different version of this task in humans (Mar et al., 1996) and on my own pilot testing. These parameters were chosen to facilitate the comparison of the present results with the relevant literature. It is of some interest that overall performance and the effects of distraction (in terms of both the basic SAT score measure and the effects on *d'*) are similar for the rats in the 500 ms condition and humans in the 17 ms condition. However, rather than attempting to quantitatively match rat and human performance (which would likely rely on increasing stimulus durations for rats rather than further reducing them for humans, given the already low values for the former species), a more useful direction would be to establish the stimulus parameters and reward contingencies that would avoid floor and ceiling effects and allow the full examination of performance within each species.

The cross-species performance differences that exist are most likely due to differences in top-down control and task constraints. It is also possible that perceptual differences between the species influence performance, although previous work suggests that rats do not fare any better on an auditory version of the task (e.g., Turchi & Sarter, 1997). The most obvious differences related to task constraints and top-down control are that humans can be explicitly instructed, require less extensive training, and are seated in front of a computer screen with little else to do – it is unlikely that they will miss a signal because they happen to be engaged in grooming behavior. That said, rats have a very low

rate of omissions (which would indicate inattention to the task) and maintain this low rate even during distraction, suggesting that they remain highly motivated and engaged with the task. It is possible that even the standard task requires a reasonable degree of top-down control in rats, whereas in humans it may be largely driven by bottom-up processes. If so, the difficulty rats show in recovering performance after distraction could reflect these greater demands on top-down control resources. Another possibility, not exclusive with differences in the standard task, is that continued performance in the face of distraction is more exhausting of top-down control resources for the rats. The difference in postdistractor recovery is the most prominent qualitative difference between the species, and will require further exploration (e.g., if human performance in the standard condition is largely a function of bottom-up, stimulus-driven attention, performance in the distractor condition but not the standard condition should be affected by other demands on top-down control, such as cross-modal distraction or a verbal shadowing task.)

These questions of motivation, perception, and top-down control will also need to be considered when adapting the task for use with patient populations who may also differ from normal controls on these variables. For example, in patient research it may be useful to select a range of stimulus durations that allows good performance by both patients and controls in the standard version of the task and then test whether distraction differentially impacts the performance of these two groups. Other critical steps for task validation and development will be tests of psychometric properties (e.g., test-retest reliability, correlations with other measures of attention, and top-down control to further establish construct validity), and examination of the neural substrates of standard and

distractor-task performance in humans to see how well they correspond to the predictions made from the neurobiological examinations of this task in rats.

In summary, the goal of the present experiments was to examine the feasibility of translating the rat-based distractor-condition version of a sustained attention task into a version that can be used in humans. This was done by testing the hypothesis that both species would show qualitatively similar responses to the manipulation of variables related to the constructs of interest, in this case sustained attention and top-down control. The results are quite promising: Rats and humans show largely similar patterns of performance both in the standard task and in response to manipulations of distraction and other stimulus variables. In particular, both showed reduced accuracy, perceptual sensitivity and changes in top-down bias under conditions of shortened duration or increased distraction, although the direction of top-down responses to the distraction manipulation were somewhat different. Further testing will be needed to better understand the differences that remain between the species, to establish the psychometric properties of the test, and to determine the task parameters that will be most useful for different patient populations or drug research. The present chapter lays the groundwork for such experiments and for studies examining the neuronal mechanisms underlying genetic variation in attentional performance (e.g., Kim et al., 2006). Although cross-species translational work imposes considerable challenges, it also holds great promise for better understanding the specific neurotransmitter systems underlying attention-network activations seen in human neuroimaging studies and refining animal models of human cognition in both healthy and disordered groups.

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Chapter III

CHALLENGES TO ATTENTION: A CONTINUOUS ARTERIAL SPIN LABELING (ASL) STUDY OF THE EFFECTS OF DISTRACTION ON SUSTAINED ATTENTION

Introduction

The ability to sustain attention over long periods of time and detect relevant stimuli is critical for the factory worker monitoring an assembly line, the student sitting in lecture, and the driver negotiating rush-hour traffic. Adding distraction (e.g., your cell phone ringing while driving) increases the demands on top-down control in order to counteract declines in attentional performance. In keeping with these real life examples, sustained attention tasks usually involve both "bottom-up" attention processes associated with the detection and processing of relevant signals and "top-down" processes associated with determining which inputs are relevant, ignoring irrelevant inputs, and maintaining the appropriate task set over time in the face of competing internal or external demands (Kastner & Ungerleider, 2000; Sarter et al., 2001; Sarter et al., 2006; Treisman & Gelade, 1980). Challenges to attention such as distractors, fatigue, sickness, or pharmacological manipulations place further demands on top-down control. These demands engage neuronal processes designed to enhance the detection and processing of

targets, the filtering of distractors, and the modification of sensitivity and biases; in other words, the processes that collectively act to regain and stabilize motivated performance under challenging conditions (e.g., Sarter et al., 2006).

The behavioral and neural processes involved in sustaining attention and dealing with challenges to attention are of interest to researchers in several areas of basic and clinical science, but these fields often make limited contact with each other. Large discrepancies in methodology and in the specific experimental questions pursued by researchers in these fields often impede translation from one field to the next. For example, although it may be known that healthy young adult humans activate a region during an attention task, and that patients with a particular disorder have abnormal activations or atrophy of this same region, this information does little to improve drug development and treatment outcomes unless the neurotransmitter systems modulating that region are also carefully considered. Likewise, drug-development efforts based on molecular- and systems-level research in animal models without sufficient attention to construct and predictive validity in translation to humans often result in treatments with extremely limited effectiveness (Sarter, 2006; Sarter et al., 2010).

The present work helps to bridge the gap between basic and clinical research on sustained attention and challenges to attention by investigating in healthy humans the fMRI neural correlates of a task used extensively in rodents to determine the role of the cholinergic system in sustained attention and top-down control (Hasselmo & Sarter, 2010; McGaughy & Sarter, 1995). Validation studies demonstrate that rats and humans show qualitatively similar patterns of behavior on the task (Demeter et al., 2008, Chapter 2), making the task a useful tool for research integrating behavioral and cognitive

neuroscience methods and giving it strong translational potential for patient and drug-development studies (Nuechterlein et al., 2009). In addition, a relatively unique aspect of this task is that it includes both a basic sustained attention task (SAT) and a distractor condition (dSAT) designed to challenge attentional performance. As described below, the distractor condition allowed me to experimentally test the hypothesis that the right middle frontal gyrus (MFG) activation often seen in sustained attention studies reflects the engagement of processes that maintain attention and performance (e.g., Cabeza & Nyberg, 2000; Lawrence et al., 2003; Lim et al., 2010).

Each trial of the basic sustained attention task (SAT) requires participants to monitor for a brief, variable-duration signal (a small, centrally-presented visual stimulus). The signal occurs on only some trials (usually 50%) and the trial interval in which it may occur varies in duration, increasing uncertainty and requiring participants to maintain attention throughout the entire interval. In the subsequent response period, participants indicate whether the signal did (signal event) or did not (nonsignal event) occur. Stimulus detection *per se* is thought to be largely driven by bottom-up attention processes (i.e., capture of attention by a sudden-onset signal), although maintaining performance over time and in the face of the uncertainties caused by the unpredictable occurrence, timing, and duration of the stimulus requires some top-down control (see discussion in Sarter & McGaughy, 1998). Challenges to attentional performance are manipulated through the distractor (dSAT) condition, in which a rapidly-changing background (flashing houselight for rats, strobing background screen for humans) makes discrimination of

signal and nonsignal events more difficult and impairs performance.[1] Previous behavioral work in humans has also shown dSAT performance is sensitive to top-down manipulations, as shifts in the reward contingencies (penalty on misses) for the task result in a shift in the distribution of misses and false alarms (Demeter et al., 2008, Chapter 2).

In rats, SAT and dSAT performance is strongly associated with right prefrontal and parietal regions. SAT performance results in increased release of acetylcholine in right medial prefrontal cortex (Arnold et al., 2002; Kozak et al., 2006; 2007), an increase not seen in control tasks with matched sensory, motor, and reward components (Arnold et al., 2002; Dalley et al., 2001). Furthermore, cholinergic activity within these frontal regions and cholinergically-mediated projections to parietal cortex appear to be particularly important for performance during the distractor (Broussard et al., 2009; Gill et al., 2000). Challenges to attention, including the distractor manipulation used in the present study, typically result in reduced performance but performance-associated increases in right prefrontal acetylcholine release. These increases in acetylcholine release are thought to reflect increased attentional effort, or the recruitment of attentional systems in order to help maintain or improve performance under challenging circumstances, and the engagement of top-down control (Kozak et al., 2006; see also review by Sarter et al., 2006). Right prefrontal cortex is thus considered a critical part of the neural circuitry mediating interactions between top-down and bottom-up attention, based in part on bidirectional circuitry between prefrontal cortex and basal forebrain as well as limbic regions which influence the basal forebrain (Brooks et al., 2007; Broussard et al., 2009; Gaykema et al., 2992; Sesack et al., 1989; Zmarowski et al., 2007).

[1] The term "distractor" here is used in the general sense of irrelevant external inputs presumed to challenge the processing of targets and their discrimination from nontargets, not in the specific sense of nontarget lure items that often have strong perceptual similarities to target items, c.f., Gold et al., 2007.

In humans, EEG studies of sustained attention often show increases in widespread slow-wave theta activity over the course of a task, thought to represent increased drowsiness or drifts of attention (e.g., Paus et al., 1997), although frontal-midline theta increases are often associated with increases in attentional demand (Sauseng et al., 2007). fMRI studies of sustained attention are rather limited, in part because the long task blocks often required by sustained attention tasks are not well-suited to investigation with traditional BOLD fMRI. However, two recent investigations (Kim et al., 2006; Lim et al., 2010) circumvented this limitation by using arterial spin labeling (ASL) methods. Unlike BOLD methods, ASL imaging results in time-series data mostly free from autocorrelation noise and less susceptible to temporal drift, allowing for long task blocks and detection of the slow, low-frequency signal changes of interest in investigations of the tonic components of maintaining attention over time (e.g., Aguirre et al., 2002, Liu et al., 2005, Mumford et al. 2006). These studies found right-lateralized frontal activations associated with sustained attention performance, with Lim et al. (2010) also finding right parietal activations. Furthermore, Lim et al. found that those participants with high resting-state activity in right middle frontal gyrus pre-task and with the greatest reductions in resting-state activity post-task showed the greatest decline in performance (slowdowns in reaction time during a psychomotor vigilance task) over the course of the task period.

The right middle frontal gyrus (MFG, at or near BA 9) activation frequently seen in sustained attention tasks is at least grossly consistent with the right-lateralized pattern seen in rodent studies (c.f., Martinez & Sarter, 2004; see Brown & Bowman, 2002 for a discussion of homologies between rat and human frontal cortex). This activation is often interpreted as reflecting top-down control processes that sustain attention and

performance (e.g., Lim et al., 2010; see also Cabeza & Nyberg, 2000 and Lawrence et al., 2003), although control demand was not experimentally manipulated in these previous investigations. Instead, this relationship is typically inferred from group-level activation in a task designed to measure sustained attention, correlations with behavioral performance, or time-on-task effects on activation – but always at one level of difficulty or cognitive-control demand in the task itself. Time-on-task effects provide a quasi-experimental manipulation of demand, but their interpretation has been ambiguous. For example, decreases in right MFG activity as a function of time on task have been variously interpreted as reflecting increased automaticity and reduced demands on control processes, a decline in motivation over time, or a depletion of attentional resources (e.g., Coull et al., 1998, Lim et al., 2010; Paus et al., 1997).

The current block-design ASL fMRI study experimentally manipulates demands on cognitive control via the distractor manipulation. The SAT condition emphasizes bottom-up, stimulus-driven processes in a simple detection task, whereas the dSAT increases demands on top-down attention by introducing distraction. This procedure allows me to determine which aspects of the sustained attention network are modulated by distraction-related increases in the demand for attentional control. If right MFG is sensitive to attentional control demands, activation within this region should increase during the distractor condition relative to task performance without distraction. I also sought to examine the relationship between the hypothesized distraction-related increases in activation and behavioral performance during the distractor. If participants with the smallest declines in performance showed the largest increase in right MFG activity, it would suggest that the right MFG is important to the implementation of the specific

processes that help sustain attentional performance in the face of a challenge to attention. On the other hand, if as the rodent literature suggests, the participants with the largest increases in right MFG activation showed the biggest declines in performance, this would suggest that right MFG activation reflects a motivated increase in attentional effort, rather than capability to maintain performance.

Method

Participants

Participants consisted of 16 young adults (8 female, mean age = 22 years, range = 19 – 29 years). Data from an additional 4 participants were excluded due to excessive head motion (greater than 3 mm translation or 3 degrees rotation in any plane). All participants were right-handed as determined by the Edinburgh Handedness Scale (Oldfield, 1971), scored at least a nine on the Extended Range Vocabulary Test (ERVT, Version 3, Educational Testing Services (ETS), 1976; mean score = 23.3, range = 10.75 – 43), had corrected-to-normal visual acuity, and did not report conditions known to affect attention or memory. The vocabulary test was used to screen out participants who might have had difficulty understanding the instructions or who were unmotivated or uncooperative. Each participant practiced the experimental tasks both outside of the scanner and in the scanner prior to acquisition of the functional runs. Participants were financially compensated at a rate of $20/hour. Sessions lasted ~1.5 hours. Participants also received a small financial reward for performance on correct trials. Participant

recruitment and experimental procedures were in accordance with protocols approved by the University of Michigan's Institutional Review Board.

Experimental task

A PC with E-Prime software (Psychology Software Tools) was used for stimulus presentation and data acquisition. Visual stimuli were projected onto a screen at the back of the bore of the magnet. Participants viewed the screen using mirrored goggles. Auditory stimuli were delivered binaurally through MR-compatible headphones. Headphone volume was adjusted for each participant so that they could hear the auditory stimuli over the background noise of the scanner. Responses were made using the right and left index fingers and recorded with an MR-compatible response box.

Participants were tested on the sustained attention task (SAT) and the distractor-condition sustained attention task (dSAT; Figure 3.1). For the SAT, the standard "silver" color in E-prime was used as the background color. On each trial participants monitored for the presence or absence of a signal (3.5 mm^2 gray square in the center of the screen) of varying durations (17, 29, or 50 ms). The time before the signal occurred (signal event) or did not occur (nonsignal event) varied unpredictably (1,000, 2,000 or 3,000 ms) to prevent anticipatory responses and to encourage participants to sustain attention and monitoring throughout. One hundred milliseconds after the occurrence of a signal or nonsignal event, the response period was cued by a 75 ms low-frequency buzzer. Participants had 1000 ms to make a response before the onset of the next trial. Participants responded with one index finger for signal trials and with their other index finger for nonsignal trials (left-right assignments to signal or nonsignal trials

counterbalanced across participants). Separate responses for signal and nonsignal events allowed true misses (failures to detect the signal) to be assessed separately from omission errors (failures to respond). A 75 ms high-frequency feedback tone followed correct responses. No feedback was given following incorrect trials or omissions (failure to respond within 1000 ms after the response cue). Signal and nonsignal trials were randomized and equally presented within each task block. Signal duration and the time before a signal or nonsignal event were also randomized within each block.

Participants received two cents for every percentage point of overall accuracy and were penalized 5 cents for the percentage of misses. The penalty on misses has previously been shown to encourage false alarms, particularly under conditions of increased uncertainty like the dSAT (see Demeter et al., 2008, Chapter 2). The dSAT condition is identical to the SAT, except that while participants are performing the task the background screen alternates between silver and black at 10 Hz. Signals were always presented on the silver background.

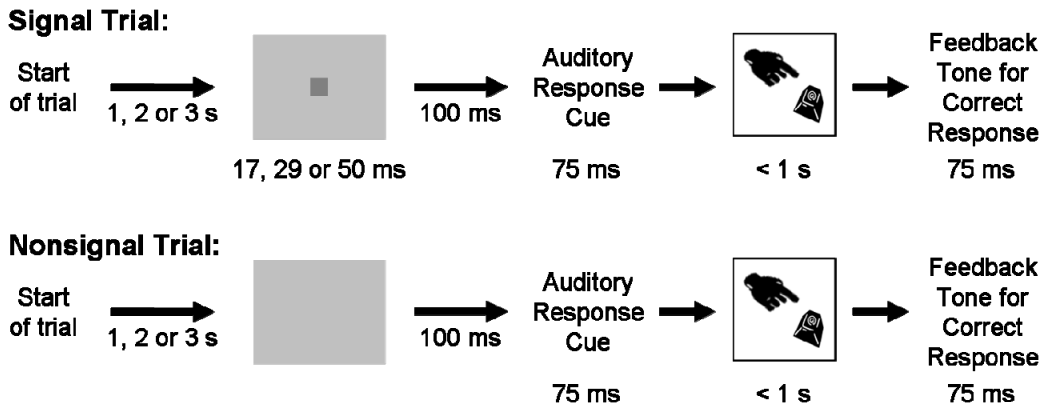

Figure 3.1. Sustained Attention Task (SAT). Participants completed 140 and 160 s blocks of the SAT and distractor condition SAT (dSAT). After 1, 2 or 3 s a short signal appeared (signal trials) or did not appear (nonsignal trials). Signal and nonsignal trials were pseudo-randomized and equally presented. After a short, constant delay, participants heard a low frequency buzzer (response cue). Participants then made a button-press response to indicate whether a signal had or had not occurred on that trial. Correct responses (both hits and correct rejections) generated a high frequency feedback tone signaling a monetary reward; incorrect responses and omissions did not receive any feedback. During dSAT blocks, participants performed the SAT in the presence of a visual distractor, the screen flashing silver to black at 10 Hz.

Block design

Participants completed four functional runs. Each run contained four 150 ± 10 s task blocks with 40 s of fixation between blocks. Two runs alternated between blocks of SAT and blocks of dSAT. The other two runs alternated between dSAT and blocks of distractor fixation (dFIX) designed as a visual control for the strobing screen in the dSAT. During the dFIX blocks, the screen alternated from silver to black at 10 Hz with a fixation cross in the center of the screen. There was no task to do during dFIX blocks. This block design allowed me to address my main questions concerning changes in activation between different conditions (dSAT, SAT, dFIX and fixation), but was not

designed to separate out neural activity for task parameters such as trial type (signal or nonsignal), signal duration, or the time before a signal or nonsignal event.

fMRI parameters

Continuous arterial spin labeling (CASL) was used to allow for long task blocks and detect the tonic components of maintaining attention over time (e.g., Aguirre et al., 2002, Liu et al., 2005, Mumford et al. 2006). ASL was chosen over BOLD methods because given the long periodicity of the dSAT paradigm, BOLD analyses would have been severely confounded by low frequency autoregressive noise (AR; Aguirre et al., 2002). Zarahn et al. (1997) characterized the noise properties of null BOLD FMRI data and observed an inverse frequency relationship with the power spectrum of the noise. This "1/f" pattern can also be characterized with an AR noise model. Most importantly, at very low frequencies the intrinsic noise becomes prohibitively high and severely reduces the sensitivity of BOLD data. The fundamental frequency of my blocked design task was approximately 0.005 Hz, well in the range of the sensitivity loss predicted by Zarahn et al. (1997).

While the long periodicity of the dSAT paradigm would result in BOLD analyses severely confounded by low frequency AR noise, ASL techniques are very well suited for this sort of situation. Indeed, Aguirre et al. (2002) predicted that ASL data become more sensitive than BOLD data at paradigm frequencies slower than 0.006 Hz, an observation subsequently corroborated by Wang et al. (2003). Previous work demonstrated (Liu et al., 2005, Mumford et al., 2006) ASL's alternating control – tag acquisition sequence modulates the perfusion effects (i.e., the baseline perfusion and the changes in perfusion

due to the paradigm) by a frequency corresponding to half of the sampling rate. This modulation means that in the frequency domain, those perfusion effects get shifted from the low end to the high end of the spectrum, and away from the AR noise. The perfusion effects are then no longer confounded with the low frequency noise present in the BOLD effect. One could perform pair-wise subtractions of the ASL time course (or a number of other subtraction schemes as well) and effectively remove the low frequency noise altogether, but a Generalized Least Squares analysis of the unsubtracted data yields the most efficient parameter estimates in most cases (Mumford et al., 2006).

While ASL techniques have several advantages over BOLD techniques, especially for long task blocks, their lower sensitivity has limited their use in studies of higher cognition (see discussion by Olson et al., 2006 and by Kim et al., 2006). To optimize my ability to detect activations for this first neuroimaging study of the dSAT paradigm, the arterial signal was preserved by not using post-labeling delays or flow crushers. Hence, the resulting images were flow-weighted images rather than quantitative perfusion images. Although the quantitative data provided by some other methods have advantages for some research questions (e.g., longitudinal studies, pharmacologic studies), those were not of central interest here. Instead, the methods were chosen to optimize detection and sensitivity to the differences in condition, and specifically to allow me to identify which brain regions were sensitive to the demands of performance during the distraction condition (dSAT) after controlling for base task performance (SAT) and visual stimulation (dFIX).

A 3 T Signa LX system (GE, Milwaukee, WI) whole-body scanner was used for imaging. CASL was carried out by a separate transmitter coil placed on the participant's

neck, as described in Zhang et al. (1995), to avoid magnetization transfer effects (Hernandez-Garcia et al., 2004; Talagala et al., 2004). The standard GE birdcage coil was used for imaging. The labeling coil was a custom figure-8 coil (described in Hernandez-Garcia et al., 2004; Hernandez-Garcia et al., 2005) powered by a separate signal generator (PTS 500, Programmed Test Resources Inc., Littleton, MD) and a RF amplifier (custom-built by Henry Radio Supply, Los Angeles, CA). The RF amplifier was gated by TTL pulses from the MRI scanner. Tagged-control image pairs were collected using a spin echo acquisition sequence (TR, 5 s; TE, 12 ms; FOV, 24 cm; 12 slices, 7 mm thick with 1 mm spacing between slices; in plane resolution, 3.75 x 3.75 mm, tagging time was 3.5 s). Slices were prescribed from top to bottom to maximize the signal from the labeled spins. Anatomical images were collected in-plane with the functional images using T1-weighted gradient-echo (GRE) sequence (TR, 250 ms, TE, 5.4 ms; flip angle, 90°; in-plane resolution 0.86 x 0.86 mm). Each participant completed four functional runs of 164 time points each. The first four time points of each run consisted of only fixation and were discarded.

Behavioral analysis

Task responses were recorded as hits, misses, correct rejections, false alarms and omissions. I restricted my analysis to my central questions about the effects of distraction and signal duration on task performance in order to reduce the number of Type I errors. The main dependent variable used for analysis was the SAT score (also known as vigilance index, or VI), a measure that reflects performance on both signal and nonsignal trials. SAT score is used instead of the sensitivity index (SI; Frey, 1973) because unlike

SI, the SAT score is not confounded by errors of omission. The SAT score is calculated for each signal duration using the proportion of hits and the proportion of false alarms via the formula SAT score = (hits – false alarms) / [2(hits + false alarms) – (hits + false alarms)^2]. SAT scores vary from -1 to +1, with -1 indicating all responses were misses or false alarms and +1 indicating all responses were hits or correct rejections.

For all behavioral and ROI analyses, the Huyhn-Feldt sphericity correction was applied as needed. Corrected *F* and *p* values are reported, but degrees of freedom are rounded to integers for ease of reading. For repeated measures ANOVAs, effect sizes were computed using generalized eta squared (η^2_G; Olejnik & Algina, 2003). Bakeman (2005) suggested for η^2_G sizes 0.02 be classified as small, 0.13 as medium, and 0.26 as large, similar to η^2 guidelines (Cohen, 1988). For *t* tests, effect sizes were reported using Cohen's *d*, with corrections for repeated measures (Cohen, 1988).

A repeated-measures ANOVA on all of the dSAT blocks showed no difference in performance among the four experimental runs ($F(3, 45) = 1.50$, $p = 0.23$, $\eta^2_G = 0.02$). Therefore, the dSAT blocks from only the two runs that contained both SAT and dSAT blocks were used for behavioral analysis, so that the time on each task was matched. A 2 x 3 repeated-measures ANOVA was conducted on SAT scores from these SAT and dSAT blocks with the factors of distraction (SAT, dSAT) and signal duration (17, 29 or 50 ms). Separate repeated-measures ANOVAs were conducted on omissions.

fMRI analyses

All analyses were carried out in FSL 4.0 (FMRIB's Software Library; Smith et al., 2004). Functional images were corrected for asynchronous slice acquisition (using

FSL's slicetimer) and for head movement using MCFLIRT (Motion Correction using FMRIB's Linear Image Registration Tool; Jenkinson et al., 2002). Unsubtracted time-series data were analyzed using a generalized least squares model (Mumford et al., 2006)[2]. Data were spatially smoothed with a three-dimensional Gaussian filter (10 mm kernel) and pre-whitened using FILM (FMRIB's Improved Linear Model) to improve estimation efficiency of the time-series data. A high pass filter of 380 s was applied.

Custom regressors were entered into FEAT 5.92 (FMRI Expert Analysis Tool; Beckmann et al., 2003; Woolrich et al., 2001) to construct a model (design matrix) of the observed time series. This model consisted of regressors characterizing effects of SAT, dSAT, dFIX and fixation blocks on the ASL signal. Although the data were collected using a spin echo acquisition sequence, the model also contained regressors to account for any residual BOLD effects in the ASL time series. The BOLD-related regressors modeled the onset through offset of the blocks convolved with a standard hemodynamic response function and the perfusion-related effects modeled out the tag and control image pairs (implicitly modeling a pair-wise subtraction, see Mumford et al., 2006). Contrasts were performed for the following: SAT – fixation, dSAT – fixation, dSAT – dFIX and dSAT – SAT. Registration was carried out via FLIRT (FMRIB's Linear Image Registration Tool; Jenkinson et al., 2002; Jenkinson & Smith, 2001); each functional run was registered to an MNI (Montreal Neurological Institute) T2-weighted template with dimensions 2 mm x 2 mm x 2 mm. The contrasts on the parameter estimates were

[2]Since respiratory and cardiac waveforms were not available, data were re-analyzed with a retrospective method for correcting physiological noise based on an in-house version of COMPCOR (Behzadi et al., 2007). This method did not improve group-level z-scores or change the general patterns of the results, thus I decided to present the data without the *post-hoc* corrections to keep the data closer to their original form.

hierarchically fed up into a second-level fixed-effects analysis within subjects to combine the two pairs of conceptually-identical runs (1 pair of runs with dSAT and SAT blocks, 1 pair of runs with dSAT and dFIX blocks).

To examine how the current dataset corresponded with the sustained attention results seen in the ASL study by Kim et al. (2006), region of interest (ROI) analyses were conducted. Peaks from Kim et al. (2006) were converted from Talaraich to MNI space using GingerALE (www.brainmap.org). The contrasts of parameter estimates obtained from the GLM analysis were averaged within thresholded spheres with 8 mm radii, which were created based on coordinates within 12 mm of the Kim et al. (2006) peak coordinates using in-house software (ORTHO 2005, http://www.eecs.umich.edu/~hernan/Public/Programs/). The contrasts of interest corresponded to three main task conditions (SAT, dSAT, and dFIX). Estimates for fixation blocks were omitted from this analysis as there are fewer time points per block compared to the other conditions, and fixation did not factor into the main comparisons of interest for this analysis.

For the whole brain analyses, third-level mixed-effects analyses were performed to generate the mean group effects across subjects. Group level *t*-tests were conducted to ask which regions showed greater activation for SAT blocks than for fixation, for dSAT blocks than fixation, for dSAT blocks than dFIX blocks, and greater activation for the dSAT blocks than for the SAT and dFIX blocks (a "tripled" *t*-test, see FEAT version 5.92 User Guide). Significant clusters were determined using a *Z* statistic threshold of 3.0 to first define contiguous clusters and then a (corrected) cluster significance threshold of $p = 0.001$ (Worsley, 2001).

Finally, in order to assess the relationship between neural activity and behavioral performance on the SAT and dSAT, ROI analyses were performed based on peak coordinates from the whole brain analyses. Two ROIs were used: a region in right MFG (BA 9, centered on MNI coordinates (36, 10, 34)) and a region in right cuneus (BA 7, centered on MNI coordinates (10, -68, 32)). The contrasts of parameter estimates obtained from the GLM analysis were averaged within thresholded spheres with 8 mm radii using in-house software (ORTHO 2005, http://www.eecs.umich.edu/~hernan/Public/Programs/). The contrast values from these regions were correlated with participants' mean SAT scores on the dSAT blocks with distraction. For the right MFG region the contrast values were also correlated with the distractor effect, or the difference between each participant's mean SAT scores without distraction and their mean scores with distraction, in order to see how neural activity estimates related to the amount a participant was impaired by the distractor. For these analyses, behavioral data from the two runs that contained both SAT and dSAT blocks were used and Pearson's correlation coefficients are reported.

Results

Distractor-evoked impairments in attention.

The behavioral results obtained within the scanner in this experiment generally replicated the effects found in my previous non-fMRI studies (Demeter et al., 2008, Chapter 2). ANOVA analyses focusing on the SAT score measure of attentional performance showed that both distraction and signal duration influenced performance,

and that the impact of signal duration was more evident under distracting conditions. The hit and false alarm data from which the SAT score is derived are reported in Table 3.1. Omissions were generally low, occurred at a relatively consistent rate across blocks (3.27 % ± 0.51 per block) and did not significantly differ for the SAT and dSAT conditions ($p = 0.11$).

Figure 3.2 shows the mean SAT score and between-subject standard errors across conditions. Distraction significantly impaired performance across all durations, $F(1,15) = 59.62$, $p < 0.0001$, $\eta^2_G = 0.60$. Conversely, the duration effect was much stronger in the distractor condition than in the standard task, $F(2,30) = 10.87$, $p = 0.001$, $\eta^2_G = 0.04$. *Post-hoc* ANOVAs within the SAT and within the dSAT conditions found signal duration had little effect on performance in the SAT condition, $F(2,30) = 1.70$, $p = 0.20$, $\eta^2_G = 0.02$, although this should be interpreted with some caution given the near-ceiling performance across all durations in the SAT condition. In the distractor condition, however, duration had a small-to-medium effect on performance, $F(2,30) = 17.40$, $p < 0.0001$, $\eta^2_G = 0.09$, with lower levels of attentional performance seen for the shorter signal durations.

These results show that the behavioral patterns found in the scanner replicate the findings from my previous non-fMRI studies (Demeter et al., 2008, Chapter 2), and indicate that presentation of the distractor induces significant challenges to attentional performance (see Chapter 6, Appendix for *d'* sensitivity measure and response bias measures for this dataset). I next examined the neural correlates of task performance and the effect of distraction.

Table 3.1. Hit and false alarm proportions for dSAT and SAT blocks. Data are means (standard error around the mean). Distraction is present during the dSAT blocks.

Block	Hits to 50 ms signal	Hits to 29 ms signal	Hits to 17 ms signal	False alarms
SAT	0.96 (0.01)	0.97 (0.01)	0.94 (0.02)	0.03 (0.01)
dSAT	0.79 (0.04)	0.75 (0.04)	0.57 (0.03)	0.31 (0.05)

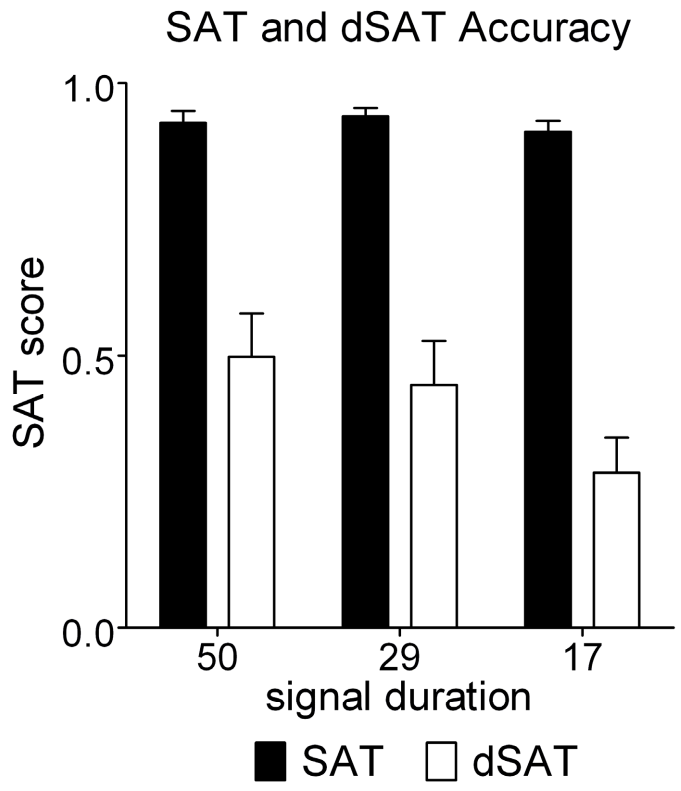

Figure 3.2. Distraction impairs task performance. The bars show the mean SAT score (see text for calculation) collapsed across SAT (black bars) and dSAT (white bars) task blocks. Error bars represent between-subjects standard error around the mean. Chance performance is a SAT score of zero. While duration did not lead to strong effects within the SAT, the presence of distraction decreased performance in a duration-dependent manner, with the biggest deficits evident on the shortest signal duration condition.

***A priori* region of interest analyses.**

My first set of fMRI analyses focused on regions of interest (ROIs) based on a previous ASL study of sustained attention (Kim et al., 2006). (Please see section 2.6 *fMRI Analyses* for details of ROI creation and estimation of contrast values.) Two right frontal regions (right middle frontal gyrus and right medial frontal gyrus) were examined to test the hypotheses that task performance in the presence of the distractor would increase activation in right frontal attention networks. (See Appendix II, Figure 1 for coordinates and overlap with voxel-wise activations.) An occipital region (right cuneus) was included to assess the perceptual effects of the flashing screen independent of task performance (i.e., in both the dSAT and dFIX conditions). The mean contrast values for each condition and between-subject standard errors are presented in Table 3.2.

Table 3.2. Contrast values on parameter estimates for ROI analyses. Numbers represent mean (standard error) of the raw data for the contrast values on parameter estimates for the ROI analyses presented in Figure 3.3.

Region	dSAT	SAT	dFIX
Right Middle Frontal Gyrus	80.26 (8.97)	74.73 (8.27)	71.60 (7.98)
Right Medial Frontal Gyrus	55.04 (6.67)	50.44 (5.12)	49.18 (5.65)
Right Cuneus	21.56 (5.08)	19.51 (4.35)	22.47 (5.06)

The Region by Block Type (SAT, dSAT, dFIX) interaction was significant ($F(4,60) = 3.33$, $p = 0.03$, $\eta^2_G = 0.01$), indicating that the pattern of activation associated with each block type differed as a function of brain region. As illustrated in Figure 3.3,

the two right frontal regions showed greater activation associated with task performance under distraction (dSAT) than with passive viewing of the distractor (dFIX), and more activation when performing the task under distraction (dSAT) than when performing under conditions without distraction (SAT). These patterns are consistent with the hypothesis of right prefrontal involvement in attentional performance and modulation with distraction. In contrast, the right cuneus region showed less activation during task performance during distraction than under passive viewing of the distractor, and the small difference between the dSAT and SAT conditions is most easily explained by the different visual characteristics of the two conditions.

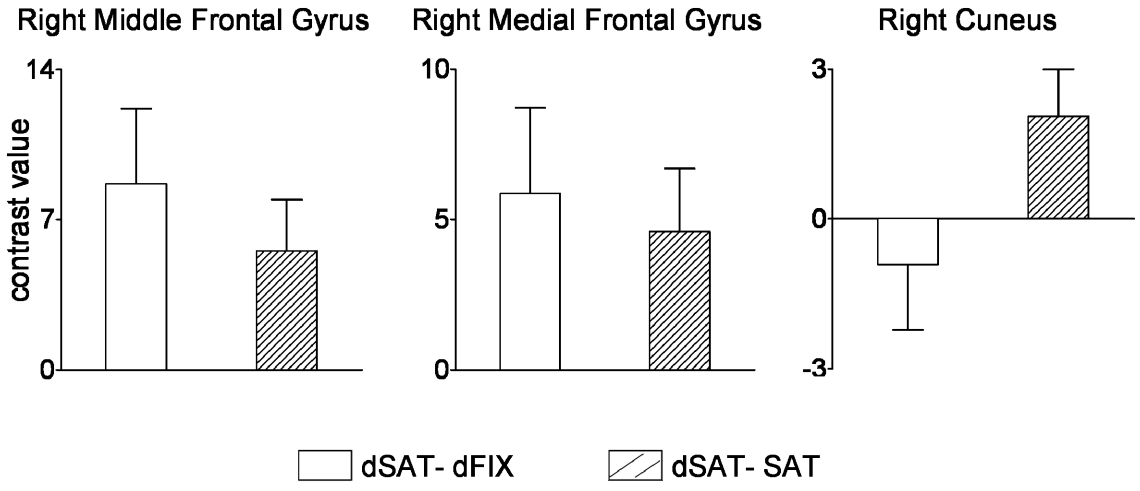

Figure 3.3. Region of interest analyses in frontal and occipital cortex. Bars depict mean and between-subjects standard error of difference scores for the contrast values on the parameter estimates for dSAT – dFIX and dSAT – SAT. In right MFG and right medial frontal gyrus, dSAT activity is greater than dFIX activity and than SAT activity. However, in right cuneus, dSAT activity is greater than SAT, but not greater than dFIX activity. This suggests that while activation in visual regions during dSAT blocks is largely driven by the flashing screen, the visual stimulation does not fully account for the activity during dSAT blocks in frontal regions.

Formal analyses generally confirmed these observations. All three regions showed greater activation for the dSAT than SAT conditions (paired *t*-tests, all $p < 0.05$, Cohen's $d > 0.54$). However, very different patterns were found for prefrontal cortex versus occipital cortex when considering the potential contributions of attentional task performance versus the passive visual stimulation provided by the distractor. For the right prefrontal regions, the dFIX condition (passive viewing of the flashing screen) had the lowest parameter estimates. Activation in this condition was significantly lower than in the dSAT condition (where the flashing screen was presented as a challenge to attention) for right MFG ($t(15) = 2.46$, $p = 0.03$, Cohen's $d = 0.62$); the same pattern was marginally significant for the right medial frontal region, ($t(15) = 2.05$, $p = 0.06$, Cohen's $d = 0.51$). In contrast, the right cuneus region showed no significant difference between the dFIX and dSAT conditions, p = 0.50, Cohen's $d = 0.17$. In short, activation in the right prefrontal cortex was a function of task performance and attentional demands, whereas activation in right cuneus was dominated by the visual stimulation provided by the flashing screen.

Exploratory voxel-wise analyses.

I next conducted exploratory voxel-wise analyses contrasting SAT and dSAT performance against a fixation baseline to reveal the regions associated with task performance in each of these two conditions. I also compared activations during dSAT performance against a distractor fixation (dFIX) condition that presented the flashing-screen distractor under passive viewing conditions, in order to control for visual-stimulation effects of the distractor that were unrelated to attentional performance.

Finally, a fourth analysis illustrates those voxels specifically associated with attentional performance under distraction in the dSAT condition over and above activation associated with the SAT and visual stimulation of the distractor (dFIX). Figure 3.4 illustrates changes in activation across these different contrasts, and peaks are listed in Table 3.3. In general, the activations associated with sustained attention performance in the current study show good correspondence with those earlier reported by Kim et al. (2006; see Appendix II, Figure 1 for overlap of ROIs used in section 3.2 with whole-brain results).

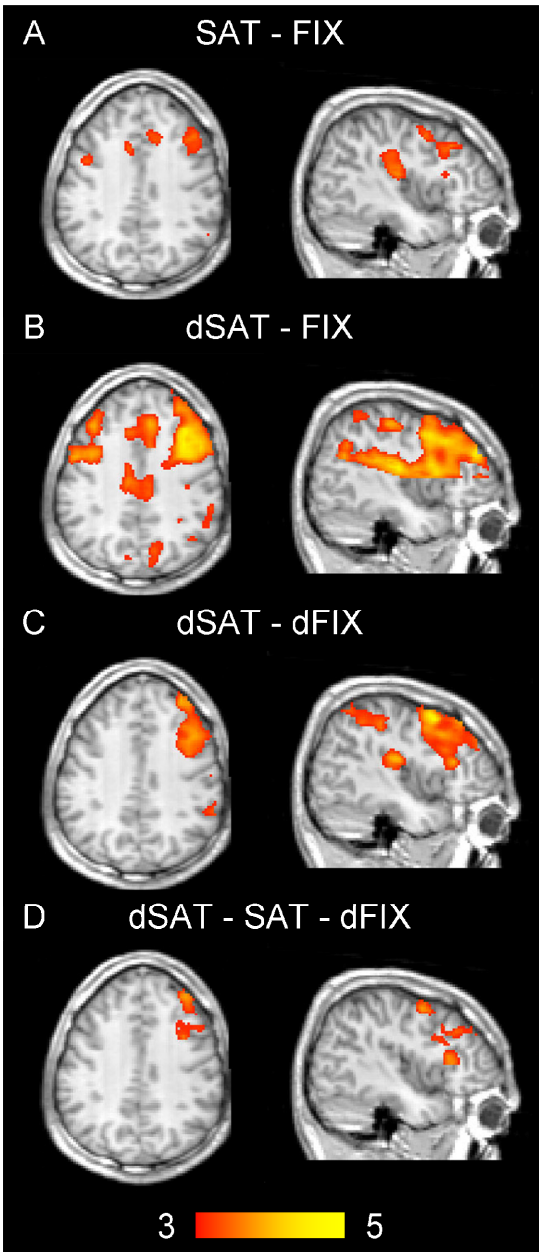

Figure 3.4. Activation in right frontal regions during SAT performance increases in the presence of distraction. SAT performance (A) elicited activation in right dorsolateral prefrontal cortex as well as bilateral motor, cingulate and insular cortex regions. The presence of distraction (dSAT blocks, B) activated regions in frontal and parietal cortex. These regions were strongly right lateralized after controlling for the visual distractor stimulus (C). Compared to the SAT blocks, dSAT performance resulted in increased activation in parts of right dorsolateral prefrontal cortex (BA 9, D). Color bar indicates Z scores ranging from 3 to 5. Anatomical image represents the average of each subject's normalized structural scan. Axial slices shown at z = 36, saggittal slices at x = 44, MNI coordinates.

Table 3.3. Clusters of significant activation by the SAT and dSAT tasks in whole-brain group analyses. The cluster sizes are in voxels. For local maxima within these clusters, the anatomical labels of the nearest gray matter are reported. R. = Right. L. = Left. BA = Brodmann area. MNI = Montreal Neurological Institute.

Contrast: Sustained Attention Task (SAT) versus fixation

Size (Voxels)	Anatomical Label	BA	MNI coordinates			Z score
			x	*y*	*z*	
3,453	L. Insula	--	-42	-22	20	5.11
	L. Postcentral Gyrus	43	-53	-10	16	4.69
	L. Putamen	--	-26	14	8	4.14
	L. Cingulate Gyrus	32	-10	16	38	3.82
	L. Precentral Gryus	6	-32	-6	54	3.70
2,835	R. Middle Frontal Gyrus	6	32	4	50	4.14
	R. Insula/ Transverse Temporal Gyrus	41	46	-20	14	4.11
	R. Insula	--	52	-18	20	4.08
	R. Inferior Parietal Lobule	40	56	-42	22	3.96
	R. Precentral Gyrus	6	30	0	52	3.73
	R. Middle Frontal Gyrus	9	44	22	34	3.64
	R. Medial Frontal Gyrus	8	8	26	48	3.30

Contrast: distractor condition Sustained Attention Task (dSAT) versus fixation

Size (Voxels)	Anatomical Label	BA	MNI coordinates			Z score
			x	*y*	*z*	
28,100	L. Insula	--	-34	22	6	5.49
	L. Middle Frontal Gyrus	10	-36	36	28	4.54
	L. Superior Temporal Gyrus/ Insula	41	-50	-32	16	4.40
	L. Precuneus	31	-4	-68	22	4.33
	L. Middle Frontal Gyrus	9	-36	30	34	4.29
	L. Inferior Frontal Gyrus	9	-40	6	34	4.11
	L. Cuneus	7	-12	-76	30	4.00
	L. Cingulate Gyrus	--	-2	-20	42	3.93
	R. Middle Frontal Gyrus	10	40	44	28	5.23
	R. Precuneus	31	10	-62	20	5.15
	R. Middle Frontal Gyrus	10	34	50	24	5.13
	R. Insula	--	42	-22	14	5.10
	R. Middle Frontal Gyrus	9	36	14	36	5.02
	R. Cuneus	7	10	-68	32	4.56
	R. Cingulate Gyrus	24	4	-20	42	4.50
	R. Cingulate Gyrus	32	8	30	32	4.32
	R. Postcentral Gyrus	40	46	-26	50	4.25

Contrast: distractor condition Sustained Attention Task (dSAT) versus distractor fixation (dFIX)

Size (Voxels)	Anatomical Label	BA	MNI coordinates			Z score
			x	*y*	*z*	
4,793	R. Middle Frontal Gyrus	6	44	8	50	5.21
	R. Insula	--	28	20	6	4.60
	R. Precentral Gyrus	6	34	-4	54	4.55
	R. Middle Frontal Gyrus	10	28	56	16	4.44
	R. Middle Frontal/ Inferior Frontal Gyrus	9	36	10	30	4.43
	R. Middle Frontal Gyrus	9	42	20	34	4.00
	R. Inferior Frontal Gyrus	46	49	21	22	3.64
2,757	R. Insula/ Superior Temporal Gyrus	42	62	-32	18	4.66
	R. Insula	--	46	-22	16	4.52
	R. Postcentral Gyrus	43	58	-16	20	4.26
	R. Supramarginal Gyrus	40	60	-46	32	3.82
	R. Intraparietal Sulcus/ Inferior Parietal Lobe	40	42	-34	42	3.43

Contrast: distractor condition Sustained Attention Task (dSAT) versus Sustained Attention Task (SAT) and distractor fixation (dFIX)

Size (Voxels)	Anatomical Label	BA	MNI coordinates			Z score
			x	*y*	*z*	
1,661	R. Middle Frontal Gyrus	9	38	42	32	4.69
	R. Insula/ Inferior Frontal Gyrus	45	42	22	10	4.27
	R. Middle Frontal Gyrus	9	36	10	34	4.12
	R. Middle Frontal Gyrus	9	36	28	28	4.08
	R. Precentral Gyrus	6	44	0	52	4.08

SAT performance activates bilateral frontal, temporal and insular regions.

These patterns are again consistent with the involvement of right middle prefrontal gyrus regions in sustained attention. Additional activations were in motor regions (BA 6; bilateral precentral gyri), bilateral insula, and primary auditory cortex (right transverse temporal gyrus in or near BA 41). This latter activation was most likely related to the auditory cues for the response window and accuracy feedback.

Performance under distraction activates frontal, parietal, occipital and insular regions.

As expected, the dSAT versus fixation contrast revealed a similar set of regions, but with greater extent and magnitude of activation (Figure 3.4B). Activation was seen bilaterally in middle frontal gyri (BA 9), frontal pole (BA 10), cingulate gyri (BAs 24 and 32), and in insula. Additional activations were seen in left superior temporal gyrus (BA 41)**,** right postcentral gyrus (BA 40), and bilateral cuneus (BA 7) and precuneus (BA 31). The activations in cuneus and precuneus, regions involved in visual processing, were most likely related to the visual distractor stimulus in the dSAT blocks. In general, activations tended to be stronger on the right side of the brain than on the left for this contrast.

Controlling for the perceptual aspects of the distractor reveals a right-lateralized fronto-parietal network for performance under distraction.

To control for the perceptual aspects of the dSAT condition, a contrast on the dSAT blocks versus the dFIX blocks was conducted. This contrast isolated the right frontal and parietal regions seen in the dSAT versus fixation contrast (Figure 3.4C). Shared regions of activation with the dSAT versus fixation and SAT versus fixation contrasts included right MFG and right insula. The dSAT versus dFIX contrast

additionally activated right inferior frontal gyrus (BA 46), right frontal pole (BA 10), and several parietal regions (supramarginal gyrus, BA 40; right inferior parietal including intraparietal sulcus). These regions may be involved in processing related to maintaining attention to the location in which the signal might occur and detecting its onset amidst distraction. While SAT performance was associated with bilateral prefrontal activations, after controlling for the flashing stimulus presented in the dSAT condition, prefrontal activation in the dSAT condition was strongly right-lateralized. Although speculative, one possible explanation for this pattern is that maintaining performance under the distractor challenge required a stronger biasing of brain activity to top-down attentional networks (Fan et al., 2005).

Dorsolateral prefrontal cortex is especially sensitive to the demands of performance under distraction.

To isolate the regions associated with performance under distraction while controlling for the visual stimulation of the distractor, a final contrast was conducted comparing the dSAT blocks to the SAT blocks and the dFIX blocks (Figure 3.4D). Voxels in the right MFG (BA 9) region previously seen in both tasks remained significantly activated in this contrast. This pattern is likewise consistent with the *a priori* ROI analysis and supports the hypothesis that this region is sensitive to performance demands and the challenge to performance introduced by the distractor. Of interest, this pattern appears to be restricted to right prefrontal cortex and does not extend significantly to parietal or other regions (Table 3.3), suggesting that right prefrontal cortex is especially sensitive to the challenge imposed by the distractor condition.

Brain-behavior analyses.

At the group level, distraction reduced behavioral performance and increased activation in right middle frontal gyrus (BA 9). To further test my hypothesis that activation in this region reflects sensitivity to the challenges imposed by the distractor condition, I examined the correlations between individuals' parameter estimates for the dSAT – SAT contrast within the right MFG (BA 9) ROI described in the methods section and their behavioral performance. To further test the interpretation that any correlations found reflected attentional effects and not simple visual stimulation, the correlation patterns for the right MFG region were compared with those for a visual region, right cuneus (BA 7).

Increased right dorsolateral prefrontal cortex activation during distraction is correlated with greater behavioral impairments.

Overall, those subjects with greater dSAT – SAT contrast values for the ROI in right MFG (BA 9) had lower performance during the distractor condition (Figure 3.5A). The contrast values for this ROI were negatively correlated with performance (SAT score) in the distraction blocks for both the 50 ms (r = -0.60, p = 0.01) and 29 ms (r = -0.61, p = 0.01) signal durations, with a similar trend for the 17 ms signal duration (r = -0.47, p = 0.07). In other words, those subjects with greater right MFG activation during the distractor condition had worse performance during the distractor.

Furthermore, distraction-related increases in activation (dSAT – SAT contrast values) in this region correlated not only with performance in the distractor, as described above, but more specifically, with the degree to which the participant's performance was impaired by the distractor relative to the standard task (i.e., the distractor effect, Figure

3.5B). The distractor effect was calculated as the mean SAT score for the blocks without distraction minus the mean score for the blocks with distraction. Higher right MFG contrast values coincided with greater behavioral distractor effects, with the positive correlation significant for all three signal durations (all $r > 0.51$, $p < 0.04$).

In contrast to the pattern seen in right MFG, behavioral performance, regardless of whether it was assessed only during the distractor period or as the difference in performance between the SAT and dSAT conditions, was not correlated with right cuneus activation for any of the three signal durations (all $r < -0.25$, $p > 0.35$, Figure 3.5C). In fact, dSAT – SAT contrast values for other regions including motor cortex, insula, temporal cortex regions and other frontal regions like superior frontal gyrus were also not correlated with behavioral performance. This suggests that the patterns seen in right MFG are specific to that region, rather than a more general effect. In addition, neither the right MFG nor the cuneus regions showed correlations with response-time measures, all $p < 0.10$. Overall, these correlational data are consistent with the notion that the increase in right MFG activity during the distractor stems from the increased demands on attention, and is not just an artifact of visual stimulation.

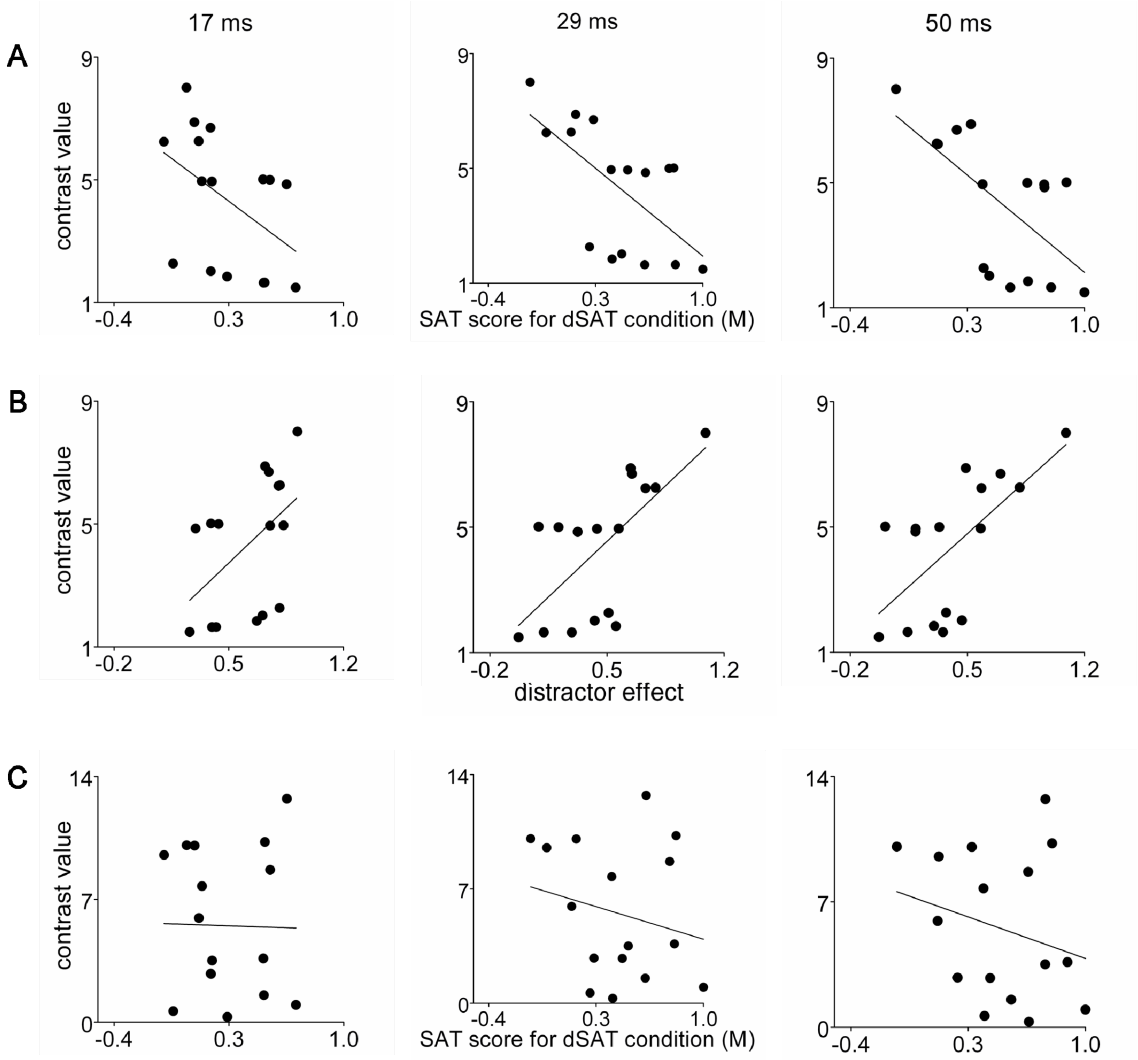

Figure 3.5. Right frontal activation during distraction correlates with behavioral performance decrements. (A) Right MFG (BA 9, ROI centered on MNI coordinates (36, 10, 34)) activity was negatively correlated with SAT scores during distraction. Scatterplots depict participants' contrast on the parameter estimate values for the dSAT – SAT contrast versus their mean SAT score for each signal duration during the task blocks with distraction. The contrast values were negatively correlated with the 50 and 29 ms SAT scores, with a trend for a negative correlation seen on the 17 ms SAT scores. (B) The contrast values for right MFG were also positively correlated with the distractor effect, or the difference for each participant between their mean SAT scores on blocks without distraction and their mean scores on blocks with distraction. (C) This pattern was not seen in visual regions, as no correlations were observed between contrast values in right cuneus (BA 7, ROI centered on MNI coordinates (10, -68, 32)). These data support the idea that the increased activity in right MFG during distraction is related to the increased attentional control demands of the dSAT condition.

Inspection of the evidence shown in Figure 3.5 raised the question of whether two groups were emerging in the data, a group with lower contrast values and a group with higher contrast values, and whether this might be affecting the correlation analyses. To explore whether the participants in the lower group simply had low perfusion in general, I extracted the whole brain mean contrast values for fixation for each participant. Most of the subjects in the lower group on the correlation graphs were indeed also in the bottom half of fixation contrast values. However, after controlling for the values during fixation using partial-correlation methods, the pattern of correlations described above still held: dSAT – SAT contrast values for right MFG were negatively correlated with SAT scores during distraction (all $r > -0.55$, $p < 0.04$) and positively correlated with the distractor effect (all $r > 0.56$, $p < 0.03$). No correlations were found again for right cuneus (all $p > 0.55$). Excluding the six participants that had the lowest dSAT – SAT contrast values in right MFG strengthened the correlations, increasing the negative correlations with SAT scores during distraction to all $r > -0.65$, $p < 0.04$ and the positive correlations with the distractor effect to all $r > 0.64$, $p < 0.05$. The correlations were still not significant for right cuneus. Given the regional specificity of the pattern of correlations seen and the results of these analyses, overall these data support the idea that distraction lowers behavioral performance and increases activation in right MFG.

Discussion

In the present study, I manipulated the demands on attentional load during a sustained attention task to identify which of the regions involved in sustained attention are specifically sensitive to demands for attentional control. Specifically, I hypothesized that right middle frontal gyrus (BA 9) would be particularly sensitive to the increased control demands of the distractor condition of my task. Furthermore, this study was aimed at establishing in healthy, young adult humans the neural correlates of a sustained attention task that has been extensively used in basic neuroscience research to investigate the precise contributions of defined neurotransmitter systems to attention- and performance-associated activity changes in frontal regions (e.g., McGaughy et al., 1996, Arnold et al., 2002; Kozak et al., 2006; 2007). Future work, including combined pharmacologic and neuroimaging studies, will determine the extent and boundaries of the correspondence between cognitive and behavioral neuroscience findings, with the long-term goal of understanding how specific neurotransmitter systems contribute to different aspects of the activation patterns seen with human neuroimaging methods.

Role of the right MFG in sustained attention and attentional control

The basic sustained attention task (SAT) activated right-lateralized frontal and parietal regions, corresponding to previous work (e.g., Kim et al., 2006; Lim et al., 2010; see also Cabeza & Nyberg, 2000). The distraction manipulation identified those regions specifically responsive to the increased demands for control imposed by the distractor. As predicted, right MFG showed this demand-sensitivity in both *a priori* ROI and

exploratory voxel-wise analyses. These results, along with the correlation analyses, help to constrain interpretations of right MFG's involvement in sustained attention tasks. At both the group mean and individual-differences levels of analysis, increases in right MFG activation were associated with reduced performance in response to the distractor.

Right MFG activity reflects increased attentional effort

One advantage of my paradigm is the ability to manipulate attentional control demands within the two conditions of my sustained attention task. Thus, while my correlation data remains indirect evidence on the role of the right MFG, the task design helps narrow down the possible interpretations. The distractor condition was designed to increase the demands associated with the task while minimizing the need for additional cognitive operations. Under these conditions, I found that those participants who had the greatest increases in right MFG activation during the distractor condition also had the largest drops in performance. No such correlations were found for reaction-time measures or between performance and activation in visual cortex. Furthermore, examination of the data revealed that trends in performance or activation change as a function of time on task were small and nonsignificant and omissions did not significantly vary with either time or condition, suggesting that the monetary incentive given to participants was sufficient to maintain performance throughout the session. Thus, distractor-related increases in right MFG activity and decreases in performance are not easily explained in terms of motivational differences, simple visual stimulation or general (noncognitive) arousal resulting from such stimulation, or time-on-task artifacts associated with longer response times. Instead, the most parsimonious explanation appears to be that activation

in this region reflects an increase in attentional effort (Sarter et al., 2006), or the activation of attentional systems in an effort to maintain or improve performance under challenging conditions.

Somewhat in contradiction to the correlation patterns seen here, Lawrence et al. (2003) found that subjects with greater right MFG activity had better performance during a rapid visual information processing task. However, interpretation of those results is complicated by difficulties in determining the degree to which the higher right MFG (and other regions) activation seen in good performers was driven by the maintenance of attention *per se* as opposed to the working memory demands of the information processing task, which required participants to monitor a rapid stream of digits for three consecutive odd or even values. Rather than a fixation baseline, the authors used a baseline task for comparison that could also be construed as a sustained attention task, but with lower working-memory demands (monitoring for one specific digit, "0", in the ongoing stream). Additionally, both the main task and the baseline task saw declines in accuracy or reaction time indicative of vigilance decrements, but these declines did not correlate with activation. Therefore, it is difficult to know the degree to which the higher right MFG activations seen in good performers in their study reflected better sustaining of attention *per se*, versus working memory processes involved in the storage, processing, and updating of memory representations of digits in the ongoing stimulus stream. Alternatively, the working memory demands of their task may have made a strong engagement of attentional effort essential for good performance.

Increases in attentional effort are thought to be under the control of the 'central executive' (Baddeley, 1986) and the anterior attention system (Posner, 1994; Posner &

Dehaene, 1994), including frontal and parietal regions. Attentional effort is thought to engage top-down attentional control processes that are employed in order to carry out goal-directed behaviors (Sarter et al., 2006). The right MFG results in this study support the idea that this region is particularly sensitive to the attentional control demands of a given task and is engaged to a greater extent under more demanding conditions. While further activation of the right MFG seen here does not seem to be sufficient to completely overcome the challenges to attention, its engagement and the engagement of downstream regions may help stabilize residual levels of performance and allow participants to stay on task.

Motivation from either extrinsic or intrinsic sources seems to be a key factor in whether or not participants will engage attentional control processes in order to continue performing under more difficult circumstances. For example, Tomporowski and Tinsley (1996) found that unpaid participants showed significantly greater vigilance decrements on a sustained attention task than paid participants performing the same task. In this sense, the feedback given on correctly-responded trials in the SAT and dSAT may be especially important, as a decline in feedback or reward for correct responses may help signal to the participants that they need to further engage attentional control processes. As discussed, the omissions data suggest that the current participants remained motivated throughout the scanning session. While the increases seen in right MFG were associated with the greatest drops in attentional performance, these participants may indeed have been increasing their attentional effort the most in order to continue to stay on task and perform to the best of their abilities under the difficult distraction condition.

Role of the cortical cholinergic input system in implementing attentional effort

The finding that decreased performance during the distractor condition was associated with increases in right frontal activation has a strong parallel to rodent research on the role of the cortical cholinergic system in sustained attention. Rats performing the rodent version of the dSAT had lower accuracy during the visual distractor condition than without distraction, but showed increases in right prefrontal activity (Gill et al., 2000). Similarly, rats given a pharmaceutical challenge showed impaired attentional performance, but a strong increase in right prefrontal acetylcholine release compared to task-performing control animals (Kozak et al., 2006). Other studies have shown that acetylcholine release is related to the number of completed trials (but not to the accuracy of those trials) and continued engagement in the task when demands on attention are increased (Passetti et al., 2000), further suggesting a motivated increase in effort that is not itself sufficient to maintain the quality of performance under challenge. However, manipulation of the frontal-parietal cholinergic system via drug or deafferentiation has dramatic effects on performance and interacts with the distractor (e.g., McGaughy et al., 1996; Parikh et al., 2007; Broussard et al., 2009; Howe et al., 2010), suggesting that while performance- and challenge-related increases in right prefrontal activity and acetylcholine release are not sufficient to keep performance levels up, they are central and necessary to the motivated recruitment of the thalamic and parietal downstream systems that do.

More specifically, tonic increases in prefrontal activity and acetylcholine release are often described as increasing readiness for input processing, influencing the sensitivity and gain functions of structures and processes involved in detecting signals

and activating the appropriate behavioral sets in response (e.g., Everitt & Robbins, 1997; Hasselmo, 1995; Hasselmo & McGaughy 2004; Parikh et al., 2007; Sarter & Bruno, 1997). Conceptually-related results have been reported in the EEG literature, where changes in tonic alpha power in posterior parietal and occipital regions, thought to reflect downstream effects of frontal-parietal control regions, modulate phasic responses to signal events (Dockree et al., 2007). It has also been suggested (Huang et al., 2008) that increases in tonic alpha during periods of poor performance may represent an increase in attentional effort, paralleling the interpretation of right MFG activation in the present study. Returning to the real-world example of driving performance described in the present chapter's introduction, Huang, Jung, & Makeig (2007) found that, subjects performing a driving-simulator task that required them to correct unpredictable experimenter-controlled vehicle drifts showed increases in tonic alpha (and in theta and beta) that were associated with periods of high error and challenged performance. Transient responses were also observed, with depressions in alpha before an error and transient rebounds in alpha when the deviation was detected and corrected.

Contribution of the cholinergic system to activity seen in fMRI and EEG studies

Currently, I can only speculate as to how changes in cholinergic neurotransmission may contribute to these patterns and more generally to demand-related increases in right frontal and parietal cortex activation seen in human fMRI and EEG studies. In the present study, I analyzed tonic, block-level activity, as this has more obvious relevance to the concept of sustained attention and to the tonic releases of acetylcholine measured in microdialysis studies. Likewise, the distractor was

implemented at the block level and served as a general challenge to sustained attention, again in keeping with the overall concept of challenges to maintaining effort and attention over long task periods rather than trial-level variations in the number or similarity of nontarget lures. The corresponding limitation of this level of analysis is that I cannot directly examine or rule out the potential contributions of trial-level or sub-trial (e.g., cue versus response) effects (e.g., Drummond et al. 2005). Future investigations may make use of event-related or mixed block-event designs (Chawla et al., 1999; Donaldson, 2004; Visscher et al., 2003) to disentangle these effects and their interactions.

However, the close ties between the rodent and human versions of this task provide principled guidance for those speculations, and make it a promising tool for future pharmacologic-fMRI studies aimed at understanding the neurotransmitter systems that underlie activation changes seen in human neuroimaging studies. For example, animal investigations using the SAT suggest that tonic increases in prefrontal acetylcholine modulate transient responses related to the detection of and response to individual signal trials (Parikh et al., 2007). Preliminary data suggest that the transient cholinergic responses associated with individual signal trials do not vary with signal duration, whereas the thalamic glutamatergic responses that precede cholinergic transients do (Howe et al., 2010). These patterns lead to specific hypotheses for future human neuroimaging studies, e.g., pharmacologic manipulations that increase tonic acetylcholine levels should affect both block- and event-related related activations in frontal and parietal cortex, whereas manipulations of the glutamatergic system would be expected to more specifically influence event-related (transient) activations.

The dSAT as a tool for translational research

The dSAT's potential for strong links between human neuroimaging studies and rodent systems-neuroscience studies also make it a useful task for clinical use and drug development (Nuechterlein et al., 2009). Notably, a recent meta-analysis (Minzenberg et al., 2009) identified right MFG in BA 9 as a major area of disruption in schizophrenia. My colleagues have recently developed an animal model of schizophrenia using the dSAT that implicates disruptions in the cholinergic modulation of frontal cortex in poor task performance and disruption by distraction (Sarter et al., 2009), further suggesting a link. This model, and the preceding research that led to its development, may help to explain, for example, why acetylcholinesterase inhibitors and α7 nicotonic acetylcholine receptor agonists have had only limited success in treating the cognitive symptoms of schizophrenia (Sarter et al., 2010). The strong connections between the human version of the SAT/dSAT and the analogous animal task allow the testing of precise biopsychological hypotheses on the control of attention and the neuronal mechanisms mediating attentional control deficits in schizophrenia, and potentially in other disorders.

Conclusions

In summary, the present experiment used ASL fMRI to reveal the neural regions activated during a sustained attention task with strong ties to the animal literature on sustained attention and top-down control. My results extend the work of previous studies of sustained attention in humans, demonstrating that specific aspects of the sustained-attention network, particularly right prefrontal cortex, are sensitive to performance challenges and demands for top-down control. Greater activation of right prefrontal

cortex during a distractor condition that challenged attention was associated with reduced performance, at both the group and individual levels. In combination with animal studies using this task, these patterns suggest that although these regions are an important part of the brain's response to demands for increased attentional effort, they are not sufficient for preserving performance in the face of such demands. Future studies will test the hypothesis that this demand-sensitivity is cholinergically mediated in humans, as it appears to be in rodents, and evaluate the potential utility of the task as a tool for assessment and drug development in disorders of attention such as schizophrenia.

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Chapter IV

ATTENTIONAL CONTROL DEFICITS IN SCHIZOPHRENIC PATIENTS PERFORMING A TRANSLATIONAL SUSTAINED ATTENTION TASK

Introduction

Attention represents one of the core cognitive deficits in schizophrenia (Heinrichs & Zakzanis, 1998; Nuechterlein et al., 2004). Problems with attention in patients with schizophrenia were recognized early on in the literature (e.g., McGhie & Chapman, 1961), and more recent work has demonstrated that patients with schizophrenia show deficits in controlled, effortful processing, or voluntary control of attention (Callaway & Naghdi, 1982; Cornblatt et al., 1989). These deficiencies become especially apparent under conditions with high processing loads, tasks requiring fast processing of information or performance of multiple tasks, or when distraction is present (see research and reviews by Braff & Saccuzzo, 1985; Dawson & Nuechterlein, 1984; Dawson, 1990; Kietzman et al., 1985). Attentional impairments in patients with schizophrenia persist across periods of psychosis and remission (Asarnow & Maccrimmon, 1978; Nuechterlein et al., 1992; Wohlberg & Kornetsky, 1973), and are found to a lesser degree in unaffected first degree relatives and children considered at high risk for developing schizophrenia (e.g., Siever, 1991). Attentional impairments also have a significant relationship to

functional outcome, such as the ability to acquire basic life skills, to engage in social problem solving and to exhibit social competence (Green et al., 2000).

Despite the large body of evidence demonstrating that attentional deficits exist in schizophrenia, few procognitive treatments exist. In part, this lack of treatment options stems from a lack of translational research connecting animal model work, where drug development studies often begin, with cognitive neuroscience research in healthy humans and clinical research in patient groups. The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative was formed to help develop measurement approaches from cognitive, social and affective neuroscience with the goal of promoting translational research on the cognitive deficits in schizophrenia (Carter & Barch, 2007). As part of this initiative, the distractor condition sustained attention task (dSAT) was selected for further development under the domain of control of attention (Nuechterlein et al., 2009).

Here I present data from stable, medicated outpatients with schizophrenia on the dSAT as a first step towards developing this paradigm for translational research. The goal of this study is to investigate whether the dSAT is sensitive to attentional deficits in schizophrenia, and to characterize patient performance on the task. To this end, I compared dSAT performance data from patients with performance data from age- and gender-matched controls. To address the fact that this paradigm is relatively easy for healthy adults, I also compared my patient data to data from healthy, age- and gender matched controls run on a more challenging version of the task and to data from healthy, school-age children. This allowed me to compare the patients' results to results from participants with similar overall task accuracy.

Each trial of the basic sustained attention task (SAT) and the distractor condition (dSAT) requires participants to monitor for the presence or absence of a small, variable-duration signal. Signal events and nonsignal events are equally presented in a randomized order. Participants then receive an auditory cue indicating that they should make a button-press response to indicate whether a signal did or did not occur on that trial. A second auditory tone is used to give participants feedback for correct responses. The time preceding signal or nonsignal events varies in duration, increasing uncertainty and requiring participants to maintain attention throughout the entire interval. While stimulus detection *per se* on this task is thought to be driven by bottom-up attention processes (i.e., capture of attention by a sudden-onset signal), the maintenance of performance over time and in the face of the uncertainties caused by the unpredictable occurrence, timing, and duration of the signal places some demands on top-down control (see discussion in Sarter & McGaughy, 1998). The dSAT condition then directly manipulates the demands on attentional control by challenging attentional performance through the presentation of a visual distractor, where the background screen rapidly alternates between gray and black while participants perform the task. The presence of this distractor makes discrimination of signal and nonsignal events more difficult and impairs performance.

The dSAT possesses several qualities that make it an attractive measure to use for translational research on the cognitive impairments in schizophrenia, including a substantial history of research into the neural basis of sustained attention performance in rats. Both the SAT (McGaughy & Sarter, 1995) and the dSAT (Gill et al., 2000; Himmelheber et al., 2000) were first developed in rats to study the role of the cortical cholinergic input system in mediating sustained attention, and with the distractor

condition, top-down control of attention. This line of work demonstrates that the basal forebrain cholinergic system is necessary for task performance (McGaughy et al., 1996) and that acetylcholine release in right prefrontal cortex increases during task performance (Kozak et al., 2006; Kozak et al., 2007) above and beyond the increase seen in rats performing control tasks with similar motor and reward components (Arnold et al., 2002, Dalley et al., 2001). Furthermore, right prefrontal activity is further augmented during attentional challenges (Gill et al., 2000; Himmelheber et al., 2000; Kozak et al., 2006), an increase that is theorized to reflect an increase in attentional effort in response to a challenge to attention (Sarter et al., 2006).

The dSAT is also easily implemented in human behavioral and neuroimaging studies. Previous work translating and validating the SAT and dSAT for use in healthy humans shows that rats and healthy, young adults have qualitatively similar patterns of performance (Demeter et al., 2008, Chapter 2). Both show signal duration-dependent performance, with better performance levels seen for longer signal durations. Both also show declines in attentional performance in the presence of distraction in the dSAT condition. Functional neuroimaging work in healthy, young adults finds that SAT and dSAT performance is mediated by frontal and parietal regions, and that right middle frontal gyrus in particular is sensitive to the increased attentional control demands imposed by the distractor (Demeter et al., 2010, Chapter 3). A recent meta-analysis of neuroimaging work in schizophrenia has found that this right middle frontal gyrus regions is also a site of disruption in patients (Minzenberg, 2009), further supporting the potential usefulness of the dSAT for translational research on the cognitive impairments seen in schizophrenia.

The present work takes the next step forward in developing the dSAT as a translational research paradigm by establishing and characterizing the attentional performance of stable, medicated outpatients with schizophrenia on the SAT and dSAT. Beyond demonstrating the feasibility of implementing this task in this patient population, the current work also shows the dSAT's sensitivity to the attentional deficits that accompany schizophrenia, testing the prediction that patients with schizophrenia will show greater impairment in attentional performance during distraction than will healthy controls.

Method

Participants

Four groups of participants took part in this experiment. The first two groups consisted of stable, medicated outpatients with schizophrenia or schizoaffective disorder and age- and gender-matched healthy controls (n=10 per group, mean age of each group = 49 years, patients with schizophrenia ranged from 21 to 58 years, controls 24 to 59 years). For patients, scores on the Brief Psychiatric Rating Scale (BPRS) ranged from 23 – 42, with a mean of 34.11 ± 1.89 (mild to moderately ill). In order to address possible ceiling effects within the control group, two additional groups were tested. The first was a second group of age- and gender-matched healthy controls (n=10, mean age = 50 years, range from 21 to 59 years). These participants were run on a more attentionally challenging version of the task (VSL condition, described below). The final group consisted of healthy children ages 8 to 11 years of age (n=15, mean age = 9 years). The

children were run using the same procedures as the patients and the first control group. We predicted that since children of this age have yet to fully develop their frontal cortex, they would have lower accuracy on the task conditions than the healthy adults. Participants were financially compensated for their time. Participant recruitment and experimental procedures were in accordance with protocols approved by the University of Michigan's Institutional Review Board.

Experimental task and procedures

Dell PCs with E-Prime software (Psychology Software Tools) were used for stimulus presentation and data acquisition. All participants were tested on both the sustained attention task (SAT, Figure 4.1) and the distractor condition sustained attention task (dSAT). The standard "silver" color in E-prime was used as the static background for the SAT. On each trial, participants monitored the screen for the presence or absence of a signal, a small (3.5 mm^2) gray square in the center of the screen. The signal varied in duration (17, 29 or 50 ms). The time before the signal occurred (signal event) or did not occur (nonsignal event) varied randomly (1000, 2000 or 3000 ms) to prevent anticipatory responses and to encourage participants to sustain attention and monitoring throughout. Signal and nonsignal events were randomized and equally presented. One hundred milliseconds after the signal or nonsignal event, a 75 ms low frequency buzzer cued the participants to respond. Participants then had up to 1500 ms to respond, using one index finger for signal trials and their other index finger for nonsignal trials (left-right assignments to signal or nonsignal trials counterbalanced across participants). Separate responses for signal and nonsignal events allowed true misses (failures to detect the

signal) to be assessed separately from omission errors (failures to respond). A 75 ms high-frequency feedback tone followed correct responses. No feedback was given following incorrect trials or omissions (failure to respond within 1500 ms after the response cue). The dSAT condition was identical to the SAT, except that in this condition, the screen alternated between silver and black at a rate of 10 Hz. Signals were always presented on the silver background.

In order to increase the difficulty of the task for the second group of control participants, these participants performed the variable signal location (VSL) condition of the SAT and dSAT. This condition was altered in two ways from the SAT and dSAT the other groups performed. First, the signal location was varied on signal trials, showing up in equal proportions in one of three locations. The possible locations were all centered on the screen, and were 25%, 50% or 75% of the way down from the top of the computer screen. As in the other groups, signal and nonsignal trials were equally presented in a random order. The second change consisted of the introduction of a fourth signal duration, 150 ms. These changes were designed to increase the uncertainty in the task and make even the basic SAT version slightly more challenging. To distinguish this group of adult controls from the first, the control participants who performed the variable signal location condition of the task are referred to as VSL controls.

Participants were familiarized with task instructions and trained on the SAT and dSAT for 30 s each. For the adult groups, a point system was introduced to reward correct trials, with participants gaining one point for each percent correct they received on each of the runs. Children earned one ticket for each percent correct they received on each of the runs and turned in their tickets for a small toy at the end of the experiment.

All participants completed two 12 minute runs of the SAT and two 8 minute runs of the dSAT. Run presentation alternated between SAT and dSAT runs, with half of the patients and controls starting on a SAT run and the other half starting on a dSAT run. Each run was subdivided into 2 minute blocks. For the dSAT runs, the distractor (screen flashing silver to black) was presented in blocks 2 and 3.

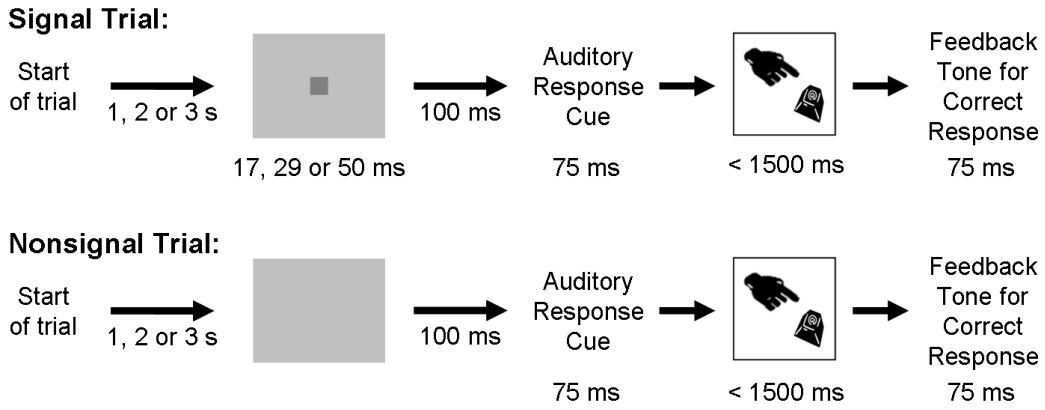

Figure 4.1. Sustained Attention Task (SAT). Each trial of the SAT consists of a variable interval (1000, 2000 or 3000 ms) followed by the presentation of a signal or nonsignal event. The signal is a 3.5 mm^2 gray square on a silver background and varied in duration (17, 29 or 50 ms). Signal and nonsignal events are randomized and equally presented over the course of each 2-minute task block. One hundred milliseconds after a signal appears or does not appear, participants hear a low frequency buzzer cuing them to respond. Participants respond on a keyboard using one index finger for signal trials and with their other index finger for nonsignal trial (left-right key assignment counterbalanced across participants). Participants have up to 1500 ms to respond before the initiation of the next trial. Correct responses are followed by a 75 ms high frequency feedback tone; incorrect responses or omissions do not result in feedback. For the healthy adult controls in the variable signal location (VSL) condition, the signal was presented in one of three locations on the screen and a fourth signal duration (150 ms) was used.

Data analysis

Responses were recorded as hits, misses, correct rejections, false alarms, and omissions. The primary dependent measure used for subsequent analysis was SAT score (formerly called vigilance index or VI), which reflects performance across both signal

and nonsignal trials. SAT score is used rather than the sensitivity index (SI; Frey & Colliver, 1973) because unlike SI, it is not confounded by errors of omission. SAT score is calculated for each signal duration using the formula SAT score = (hits – false alarms) / [2(hits + false alarms) – (hits + false alarms)^2]. It varies from +1.0 to -1.0, with +1 indicating that all recorded responses were hits or correct rejections and -1 indicating all recorded responses were misses or false alarms. For analyses including the VSL control group, the 150 ms duration was excluded and analyses focused on the 17, 29 and 50 ms durations tested in all groups.

My analyses focused on my main questions about the effects of distraction, signal duration, and time on task. While the SAT and dSAT runs were repeated twice within the course of the experiment in order to look at measures of reliability, there were no statistical differences between the two SAT runs or between the two dSAT runs. Analyses were therefore conducted on the average of the two SAT runs and the average of the two dSAT runs.

My main question centered on how distraction impacted attentional performance in each of the groups. For these analyses, data from the averaged dSAT run was used, with blocks 1 and 4 without distraction and blocks 2 and 3 with distraction combined in order to focus on the effects of distraction. Repeated-measures ANOVAs were conducted on SAT scores using the within-subjects variables of Distraction and Duration and the between-subjects variable of Group. The results of the repeated measures ANOVA including the patients and the first control group are reported first, followed by *t*-tests targeted at my questions about distraction and signal duration. I next report the results of the repeated measures ANOVA and *t*-tests comparing the patients and the VSL controls,

followed by the results from patients and the group of children. Separate repeated-measures ANOVAs were conducted on hits, false alarms and omissions; these results are organized the same as the SAT score results.

I also conducted signal detection analyses (Swets et al., 1961) to assess the effects of distraction and signal duration on perceptual sensitivity (*d'*) and bias (B''_D). *d'* sensitivity measures were calculated from the z scores of the proportions of hits and of false alarms, P_H and P_{FA}, for each stimulus duration using the formula: $d' = z(P_H) - z(P_{FA})$ (Green & Swets, 1966). For *d'* measures, the effective limit (with $P_H = 0.99$ and $P_{FA} = 0.01$) is 4.65 and *d'* is zero when $P_H = P_{FA}$. B''_D measures of bias were calculated using the formula $B''_D = [(1- P_H)(1- P_{FA}) - P_H P_{FA}] / [(1- P_H)(1- P_{FA}) + P_H P_{FA}]$ (Donaldson, 1992). B''_D scales from -1 to +1, with negative numbers indicating a liberal bias, positive numbers indicating a conservative bias, and zero indicating no bias ($P_{FA} = 1 - P_H$). For both measures, repeated-measures ANOVAs were conducted with Distraction and Duration as the within-subjects variables and Group as the between-subject variable, followed by simpler tests to investigate distraction effects within each signal duration and between the groups. The groups were compared in the same order as for the accuracy measures.

The longer SAT runs allowed me to investigate whether attentional performance changed as a function of time on task. Repeated measures ANOVAs were conducted on SAT scores using Block and Duration as within-subjects factors and Group as a between-subjects factor. The results of the repeated measures ANOVA including all four groups is reported first, followed by tests designed to investigate which groups, if any, showed declines in attentional performance over the course of the twelve minute run.

Finally, repetition of the two SAT runs and the two runs containing the dSAT condition allowed me to look at the internal reliability of the groups' data. For these analyses, Cronbach's alpha was calculated for the SAT condition using SAT score data from all blocks without distraction. For the dSAT condition, SAT scores from blocks 2 and 3 of the two dSAT runs (the blocks where distraction was present) were used. While the criteria for interpreting Cronbach's alpha varies in the literature, for these analyses I considered values greater than or equal to 0.8 to show good reliability.

For all analyses, the Huyhn-Feldt sphericity correction was applied as needed. Corrected F and p values are reported, but degrees of freedom are rounded to integer values for easier reading. For repeated measures ANOVAs, effect sizes were computed using generalized eta squared (η^2_G, Olejnik & Algina, 2003). Bakeman (2005) suggested for η^2_G sizes 0.02 as small, 0.13 as medium, and 0.26 as large, similar to η^2 guidelines (Cohen, 1988). For t-tests, effect sizes were reported using Cohen's d, with corrections for repeated measures (Cohen, 1988).

Results

Schizophrenic patients show greatest distractor-evoked impairments in attention.

I first compared the patients with schizophrenia to the age- and gender-matched controls. Overall, patients performed more poorly than controls, (SAT score, Figure 4.2, top panels; $F(1,18) = 7.59$, $p = 0.01$, $\eta^2_G = 0.24$). This was true for both the SAT condition and the dSAT condition ($F(1,18) = 5.20$, $p = 0.04$, $\eta^2_G = 0.20$ and $F(1,18) = 7.52$, $p = 0.01$, $\eta^2_G = 0.29$, respectively). However, the critical Group x Distraction

interaction indicated that patients showed a greater drop in attentional performance with the introduction of distraction compared to controls ($F(1,18) = 4.73$, $p = 0.04$, $\eta^2_G = 0.04$); this effect was not further modified by duration. Analyses of the Group x Distraction interaction within each signal duration confirmed this pattern, with patients significantly more affected by distraction at the 17 and 29 ms durations, both $p < 0.05$, $\eta^2_G > 0.05$), and marginally more vulnerable than controls at the 50 ms duration ($p = 0.07$, $\eta^2_G = 0.03$). Paired *t*-tests within each group showed that controls were numerically but not significantly affected by distraction at each duration, all $p > 0.13$, Cohen's $d > 0.15$. In contrast, patients were significantly affected by distraction at the 17 and 29 ms durations (both $p < 0.03$, Cohen's d both > 0.84) and marginally affected by distraction on the 50 ms signal duration ($p = 0.07$, Cohen's $d = 0.65$).

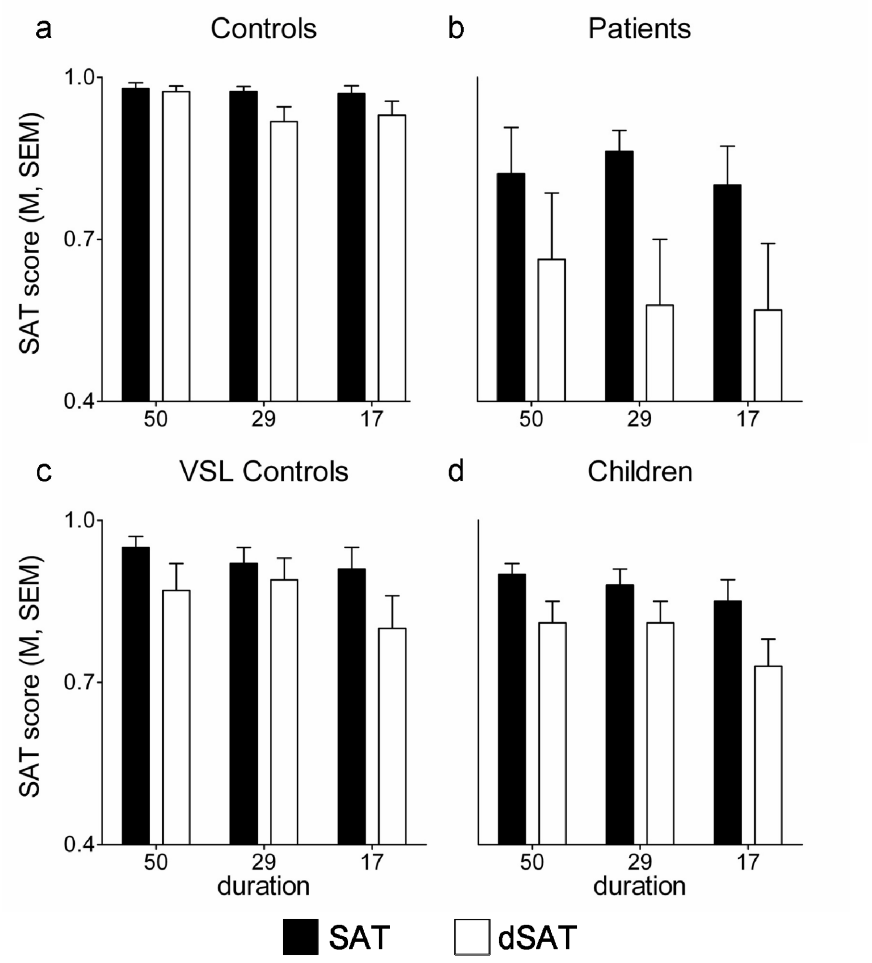

Figure 4.2. Effects of distraction on SAT scores for healthy adult controls, patients with schizophrenia, and school-age children. Data shown are from the averaged dSAT run, collapsed by whether distraction was absent (SAT condition, black bars) or present (dSAT condition, white bars). Bars represent the mean and standard error of the mean. **(a)** Healthy adult control participants show high levels of attentional performance, dropping only slightly and nonsignficantly when distraction is present. **(b)** In contrast, while schizophrenic patients performed relatively well without distraction, patients' SAT scores were disproportionally affected by the presence of distraction, declining further than the drop seen in healthy controls. This result held even when patients were compared to groups with more comparable performance levels without distraction. **(c)** Healthy adults run on a slightly harder version of the task (VSL condition, see Methods) showed SAT scores without distraction that were off of ceiling, but they still did not show as great of an impairment with distraction as the patients. **(d)** Healthy school-age children were even further off of ceiling in SAT scores without distraction. While these participants' SAT scores decreased significantly with distraction, children did not show as great of impairment with distraction as patients with schizophrenia. Collectively, these results indicate that patients with schizophrenia show deficits in attentional performance on this task that is amplified in the presence of distraction.

The results of these analyses were consistent with my hypothesis that patients would be more affected by distraction than age- and gender-matched controls. However, the controls performed near ceiling in the SAT condition and did not show significant effects of distraction. This raises the concern that the apparent Group x Distraction interaction was an artifact of ceiling performance by the control group.

To address this concern, I also compared the patients' performance to two groups of healthy individuals who did not have ceiling performance in the SAT condition (Figure 4.2, bottom panels). The first was a group of healthy, age- and gender-matched adults run on a more attentionally challenging version of the task (VSL controls, see Methods for details). The second was a group of healthy, school-age children run on the same version of the task as the original two groups (Figure 4.2, bottom panels). Both the VSL adult controls and the children's performance was off of ceiling in the SAT condition (VSL, 0.92 ± 0.03, one sample *t*-test against 1, $t(9) = 2.54$, $p = 0.03$, Cohen's $d = 0.80$; children, 0.88 ± 0.03, one sample *t*-test against 1, $t(14) = 3.95$, $p = 0.001$, Cohen's $d = 1.02$). In addition, the VSL controls had numerically but not statistically higher performance in the SAT condition than patients ($F(1,18) = 2.06$, $p = 0.17$, $\eta^2_G = 0.09$); differences between children and patients in the standard condition did not approach significance ($F(1,18) = 0.56$, $p = 0.46$, $\eta^2_G = 0.01$). I next asked whether patients with schizophrenia showed greater distraction effects than either of these groups.

Repeated measures ANOVAs on SAT scores between the VSL controls and the patients showed a significant Distraction x Duration x Group interaction ($F(2,36) = 3.60$, $p = 0.04$, $\eta^2_G = 0.01$). Repeated measures ANOVAs within each signal duration revealed that patients showed a significantly greater drop during distraction on the 29 ms duration

than did the VSL controls (Distraction x Group, $F(1,18) = 4.30$, $p = 0.05$, $\eta^2_G = 0.08$). This effect was not significant for the 17 and the 50 ms duration ($F(1,18) = 1.27$, $p = 0.28$, $\eta^2_G = 0.02$ and $F(1,18) = 0.73$, $p = 0.41$, $\eta^2_G = 0.01$, respectively). Looking within the VSL control group, these controls dropped numerically at each signal duration during distraction, particularly on the shortest signal duration. These declines during distraction were again not statistically significant (paired *t*-tests, all $p > 0.12$, $\eta^2_G < 0.55$).

Repeated measures ANOVAs between the children and the patients again revealed a Distraction x Duration x Group interaction ($F(2,46) = 3.83$, $p = 0.03$, $\eta^2_G = 0.01$). Repeated measures ANOVAs within each signal duration showed patients' performance declined significantly more during distraction than children's on the 29 ms condition (Distraction x Group, $F(1,23) = 5.57$, $p = 0.03$, $\eta^2_G = 0.07$). As with the VSL controls, this effect was not significant for the 17 and the 50 ms duration ($F(1,23) = 1.84$, $p = 0.19$, $\eta^2_G = 0.01$ and $F(1,23) = 1.02$, $p = 0.32$, $\eta^2_G = 0.01$, respectively). However, unlike what was seen in the adult control groups, paired *t*-tests revealed that children showed significant effects of distraction within all three signal durations, with the largest drop observed for the shortest signal duration (all $t(14) > 2.22$, $p < 0.04$, Cohen's $d > 0.57$).

Overall, the data suggest that patients show greater impairments with distraction than do healthy adults or children. While healthy individuals' performance also dropped during distraction, especially for the shortest signal duration, patients' showed large declines that extended to all signal durations. The greater impairment during distraction for the patients was especially pronounced at the middle signal duration condition, where

patients' decline in performance with distraction outmatched the decline seen in any of the other groups.

Patients' greater distractor effects stem from fewer hits during distraction.

I next examined the hit and false alarm data that go into the calculation of SAT score to see if the greater effect of distraction in schizophrenic patients stemmed from mostly errors on signal trials (misses), mostly errors on nonsignal trials (false alarms) or from errors on both trial types. In general, the hit and false alarm data followed the patterns seen for the SAT scores (see Table 4.1 for a breakdown of hits and false alarms by task block).

Table 4.1. Hit and false alarm proportions for SAT and dSAT. Data are means (standard error around the mean). Data from the two SAT and the two dSAT runs are collapsed. Distraction is present in blocks 2 and 3 of the dSAT condition, indicated with italics.

Adult controls

Block	Hits to 50 ms signal	Hits to 29 ms signal	Hits to 17 ms signal	False alarms
SAT				
1	0.99 (0.01)	0.98 (0.02)	0.98 (0.01)	0.00 (0.00)
2	0.98 (0.01)	0.99 (0.01)	0.98 (0.01)	0.02 (0.01)
3	0.99 (0.01)	0.97 (0.02)	0.99 (0.01)	0.01 (0.00)
4	0.96 (0.02)	0.96 (0.02)	0.99 (0.01)	0.01 (0.01)
5	0.96 (0.03)	0.95 (0.02)	0.93 (0.04)	0.00 (0.00)
6	0.97 (0.01)	0.94 (0.03)	0.93 (0.04)	0.01 (0.00)
dSAT				
1	0.99 (0.01)	0.97 (0.01)	0.97 (0.01)	0.01 (0.01)
2	*0.97 (0.02)*	*0.92 (0.04)*	*0.92 (0.03)*	*0.00 (0.00)*
3	*0.97 (0.01)*	*0.88 (0.05)*	*0.91 (0.04)*	*0.01 (0.00)*
4	0.96 (0.03)	0.97 (0.02)	0.96 (0.03)	0.00 (0.00)

Patients with schizophrenia

Block	Hits to 50 ms signal	Hits to 29 ms signal	Hits to 17 ms signal	False alarms
SAT				
1	0.94 (0.02)	0.86 (0.05)	0.94 (0.02)	0.12 (0.06)
2	0.92 (0.02)	0.91 (0.04)	0.90 (0.04)	0.10 (0.06)
3	0.91 (0.05)	0.90 (0.05)	0.91 (0.04)	0.13 (0.07)
4	0.89 (0.05)	0.82 (0.05)	0.92 (0.04)	0.12 (0.08)
5	0.88 (0.05)	0.85 (0.07)	0.90 (0.05)	0.06 (0.03)
6	0.99 (0.01)	0.95 (0.03)	0.95 (0.02)	0.10 (0.08)
dSAT				
1	0.90 (0.05)	0.93 (0.03)	0.83 (0.05)	0.08 (0.05)
2	*0.87 (0.05)*	*0.75 (0.08)*	*0.73 (0.06)*	*0.19 (0.08)*
3	*0.85 (0.05)*	*0.75 (0.06)*	*0.81 (0.06)*	*0.20 (0.09)*
4	0.92 (0.02)	0.92 (0.03)	0.92 (0.03)	0.12 (0.07)

VSL controls

Block	Hits to 150 ms signal	Hits to 50 ms signal	Hits to 29 ms signal	Hits to 17 ms signal	False alarms
SAT					
1	0.95 (0.05)	0.95 (0.03)	0.90 (0.04)	0.80 (0.06)	0.03 (0.01)
2	0.98 (0.01)	0.99 (0.01)	0.98 (0.02)	0.91 (0.04)	0.03 (0.02)
3	0.98 (0.02)	0.98 (0.02)	0.87 (0.06)	0.89 (0.04)	0.01 (0.01)
4	1.00 (0.00)	0.96 (0.02)	0.94 (0.03)	0.92 (0.03)	0.00 (0.00)
5	0.99 (0.01)	0.93 (0.05)	0.93 (0.03)	0.88 (0.05)	0.01 (0.01)
6	0.98 (0.02)	0.96 (0.02)	0.97 (0.02)	0.81 (0.04)	0.01 (0.01)
dSAT					
1	0.99 (0.01)	0.99 (0.01)	0.96 (0.03)	0.97 (0.02)	0.02 (0.01)
2	*0.98 (0.02)*	*0.96 (0.02)*	*0.92 (0.03)*	*0.89 (0.04)*	*0.08 (0.06)*
3	*0.95 (0.03)*	*0.88 (0.06)*	*0.92 (0.14)*	*0.76 (0.08)*	*0.06 (0.04)*
4	1.00 (0.00)	0.94 (0.03)	0.91 (0.05)	0.89 (0.06)	0.03 (0.01)

School-age, healthy children

Block	Hits to 50 ms signal	Hits to 29 ms signal	Hits to 17 ms signal	False alarms
SAT				
1	0.92 (0.03)	0.93 (0.03)	0.89 (0.03)	0.04 (0.01)
2	0.90 (0.03)	0.88 (0.03)	0.91 (0.03)	0.07 (0.01)
3	0.90 (0.03)	0.91 (0.03)	0.87 (0.02)	0.07 (0.01)
4	0.87 (0.03)	0.88 (0.04)	0.84 (0.04)	0.08 (0.02)
5	0.92 (0.02)	0.85 (0.04)	0.86 (0.03)	0.06 (0.01)
6	0.83 (0.04)	0.86 (0.03)	0.82 (0.04)	0.08 (0.02)
dSAT				
1	0.94 (0.02)	0.91 (0.03)	0.92 (0.03)	0.05 (0.02)
2	*0.92 (0.03)*	*0.89 (0.03)*	*0.74 (0.05)*	*0.08 (0.02)*
3	*0.86 (0.03)*	*0.88 (0.03)*	*0.82 (0.04)*	*0.10 (0.03)*
4	0.94 (0.02)	0.92 (0.02)	0.87 (0.04)	0.05 (0.01)

Repeated measures ANOVAs including the first adult control group and the patients revealed that patients had a significantly lower hit rate overall than controls ($F(1,18) = 10.09$, $p = 0.01$, $\eta^2_G = 0.20$). However, there were no significant interactions with group for these hit data (all $p > 0.22$, $\eta^2_G < 0.03$). There were also no Distraction x Group interactions looking within each signal duration (all $p > 0.23$, $\eta^2_G < 0.05$). For the control group, distraction decreased hits numerically but not significantly within each signal duration (paired *t*-tests all $p > 0.12$, Cohen's $d < 0.55$). For the patients with schizophrenia, distraction decreased hits significantly for the 29 ms duration ($t(9) = 2.52$, $p = 0.03$, Cohen's $d = 0.80$) and marginally for the 17 ms duration ($t(9) = 2.09$, $p = 0.07$, Cohen's $d = 0.66$). Hits did not significantly decrease with distraction for the 50 ms duration ($p = 0.20$, Cohen's $d = 0.44$).

Looking at the VSL controls and the patients, a repeated measures ANOVA on hits found that patients tended to have lower hits overall than the VSL controls, but these

groups were not significantly different ($p = 0.07$, $\eta^2_G = 0.08$). The Distraction x Duration x Group interaction was significant ($F(2,36) = 3.47$, $p = 0.04$, $\eta^2_G = 0.02$). To explore this interaction, I looked within each signal duration for Distraction x Group interactions. The Distraction x Group interaction trended towards significance for the 29 ms duration ($F(1,18) = 3.52$, $p = 0.08$, $\eta^2_G = 0.10$), but was not significant for the 17 or 50 ms durations ($p > 0.95$, $\eta^2_G < 0.01$). Looking at distraction effects within the VSL group alone, these participants' hits decreased numerically within each duration with distraction, but these decreases were not significant ($p > 0.18$, Cohen's $d < 0.47$).

Like with the VSL controls, a repeated measures ANOVA including patients and children found no difference in overall hits between the groups ($F(1,23) = 0.89$, $p = 0.36$, $\eta^2_G = 0.02$). The Distraction x Duration x Group interaction was again significant ($F(2,46) = 5.02$, $p = 0.01$, $\eta^2_G = 0.03$), and this time analyses within each signal duration revealed a significant Distraction x Group interaction for the 29 ms condition ($F(1,23) = 6.39$, $p = 0.02$, $\eta^2_G = 0.09$). The Distraction x Group interaction was not significant for the other 2 durations (both $p > 0.81$, $\eta^2_G < 0.01$). Children showed a significant decline in hits with distraction for the 17 and the 50 ms duration (both $p < 0.01$, Cohen's $d > 0.74$, for 29 ms duration, $t(14) = 1.77$, $p = 0.10$, Cohen's $d = 0.46$). Collectively, the hit analyses suggest that compared to groups with similar overall accuracy levels patients with schizophrenia have comparable numbers of misses during distraction for the shortest and longest signal durations, but a higher amount of misses to the middle signal duration.

Patients showed significantly more false alarms than seen in the first group of controls ($p = 0.04$, $\eta^2_G = 0.18$), but did not differ from either the VSL control group or the group of children (both $p > 0.17$, $\eta^2_G < 0.08$). Unlike what was seen with the hit data, for

false alarms there was no Distraction x Group interaction between the patients and the first group of controls ($F(1,18) = 2.82$, $p = 0.11$, $\eta^2_G = 0.03$), the patients and the VSL controls ($F(1,18) = 0.60$, $p = 0.45$, $\eta^2_G = 0.01$), or the patients and the children ($F(1,23) = 1.37$, $p = 0.25$, $\eta^2_G = 0.01$). Within the first control group, false alarms did not increase during distraction (paired *t*-test, $t(9) = 0.00$, $p = 1.00$, Cohen's $d = 0.00$). False alarms increased numerically but not significantly for the patients ($t(9) = 1.68$, $p = 0.13$, Cohen's $d = 0.53$), and this was also true for the VSL controls, $t(9) = 0.94$, $p = 0.37$, Cohen's $d = 0.30$. Unlike the other groups, the false alarm rate in children did significantly increase during distraction ($t(14) = 2.27$, $p = 0.04$, Cohen's $d = 0.59$). Taken together with the analyses on hits, these data collectively demonstrate that the increased impairments during distraction in SAT scores for the patients with schizophrenia stems mainly from a larger decrease in hits (increase in misses) on more signal durations than was seen in the other groups, rather than from a larger increase in false alarms.

All groups omitted fewer than 11% of trials on the SAT and on the dSAT. Patients omitted the most trials, omitting 7.90 ± 2.72% of trials on the SAT condition and 10.17 ± 3.11% of trials during the dSAT condition (increase with distraction not significant, $t(9) = 1.4$, $p = 0.19$, Cohen's $d = 0.45$). The Distraction x Group interaction was not significant between the patients and the first control group ($F(1,18) = 3.42$, $p = 0.08$, $\eta^2_G = 0.01$), but was significant between the patients and the VSL controls and the patients and the children (both $p < 0.02$, $\eta^2_G > 0.02$). However, this interaction stemmed from the fact that while patient's omissions did not differ significantly between the SAT and dSAT condition, the VSL controls and the children both had more omissions during the SAT condition than in the dSAT condition (both $p < 0.04$, Cohen's $d > 0.76$).

Importantly, errors of omission do not factor into the SAT score, hit and false alarm analyses, so these omissions results do not explain the augmented effects of distraction seen in patients. Rather, the relatively low omissions rate for each of the groups demonstrates that these participants were able to stay on task and, in the case of patients, supports the feasibility of using the SAT/dSAT in clinical settings.

Greater distractor effects seen in patients not due to a loss of perceptual sensitivity.

In addition to looking at accuracy measures of behavioral performance, I also analyzed the data using signal detection methods to calculate *d'* (Figure 4.3). *d'* values were the lowest for the patients with schizophrenia (patients significantly lower than both adult control groups, $p < 0.05$, $\eta^2_G > 0.15$), followed by the group of children (patients not significantly lower than children, $F(1,23) = 0.82$, $p = 0.37$, $\eta^2_G = 0.03$). Group did not interact with Distraction or Duration for the patients and the first control group (all interactions, $p > 0.21$, $\eta^2_G < 0.02$), for patients and the VSL controls ($p > 0.09$, $\eta^2_G < 0.01$), or for the patients and the children ($p > 0.07$, $\eta^2_G < 0.01$). Looking within the controls, distraction decreased perceptual sensitivity numerically but not significantly for all three durations (paired *t*-tests, all $p > 0.15$, Cohen's $d < 0.50$). In contrast, within the patient group, distraction significantly decreased *d'* for the 17 and the 29 durations (both $p < 0.05$, Cohen's $d > 0.72$). Distraction did not significantly decrease perceptual sensitivity for any of the 3 durations within the VSL control group (all $p > 0.14$, Cohen's $d < 0.51$), but did significantly decrease sensitivity for all three durations for the children (all $p < 0.02$, Cohen's $d > 0.71$). Overall these data suggest that the greater declines in hits

seen during distraction in patients compared to the other groups did not stem from a disproportionate loss of sensitivity during the distractor in the patient group.

A second question for this analysis was whether patients with schizophrenia were at floor for this measure of perceptual sensitivity when it came to their ability to detect the signal during distraction. One-sample *t*-tests confirmed that patients' *d'* values during distraction were significantly greater than zero (floor) for all signal durations (all $p < 0.002$, $\eta^2_G > 1.35$). Thus, the *d'* data indicate that despite being less able to detect the signal in general, patients' drop in sensitivity during distraction and on shorter signal durations was equivalent to the drop seen in the other groups and did not reach floor.

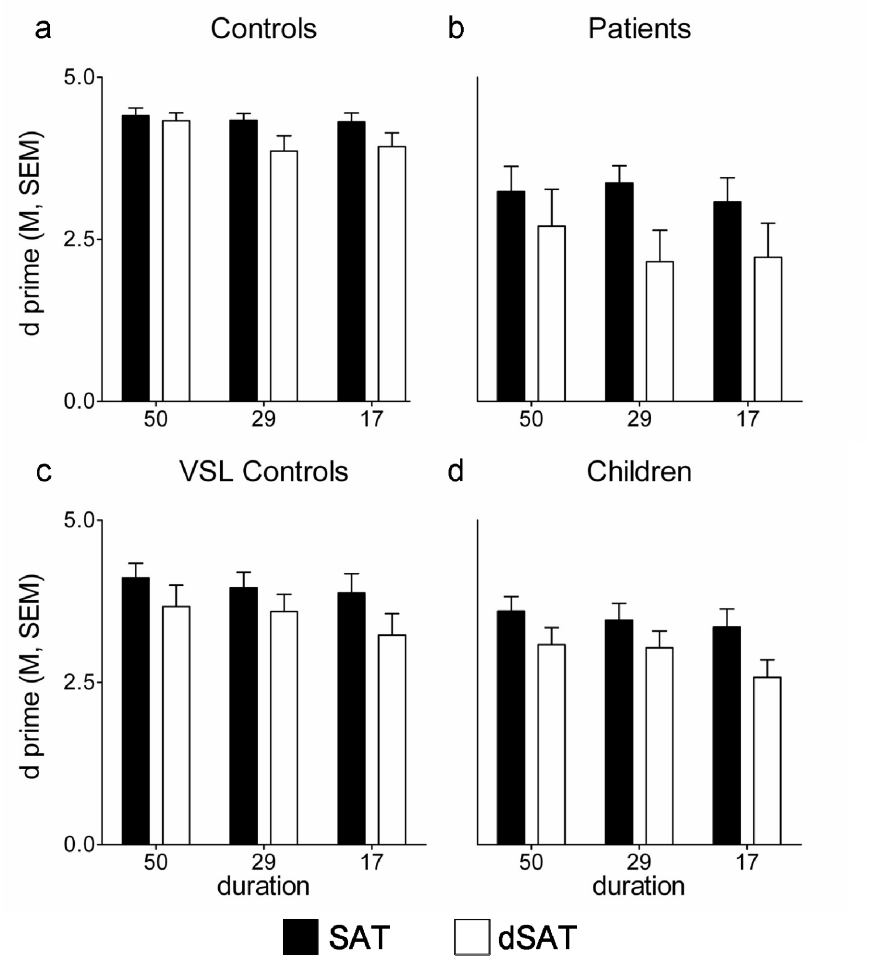

Figure 4.3. Distraction lowers *d'* sensitivity measures. Data shown are from the averaged dSAT run, collapsed by whether distraction was absent (SAT condition, black bars) or present (dSAT condition, white bars). Bars represent the mean and standard error of the mean. Perceptual sensitivity to the signal was lower during distraction and with shorter signal durations. Patients with schizophrenia **(b)** had lower *d'* measures than healthy adult controls **(a)**, VSL adult controls performing a more challenging task version **(c)** and school-age children **(d)**. However, the augmented distractor effects within the patient group did not stem the differences in perceptual sensitivity as there were no Distractor x Group interactions, or from a complete loss of perceptual sensitivity, as *d'* measures were well above floor (*d'* of zero) for all groups during all conditions.

Shorter signal durations result in more conservative response bias.

I next analyzed measures of response bias to see how signal duration and distraction influenced how liberal or conservative participants were in reporting that they saw a signal (Figure 4.4). Patients with schizophrenia did not differ on the whole from any of the other groups in their criterion for reporting signals (effect of Group for comparisons between patients and each of the other groups all $p > 0.49$, $\eta^2_G < 0.01$). There were also no interactions with Group and Distractor or Duration (all interactions $p > 0.21$, $\eta^2_G < 0.01$). For all participants, shortening the signal duration resulted in more conservative (B''_D closer to 1) response biases ($F(2,82) = 12.34$, $p < 0.0001$, $\eta^2_G = 0.04$). Distraction also tended to make participants more conservative in their response biases overall, but this was not significant ($F(1,41) = 3.21$, $p = 0.08$, $\eta^2_G = 0.02$). These data show that participants adapt a more conservative response bias, meaning they are less likely to report they saw a signal, as signal duration decreases, but do not significantly change their response bias during distraction. In addition, patients seem to use the same criterion for reporting signals as the other groups.

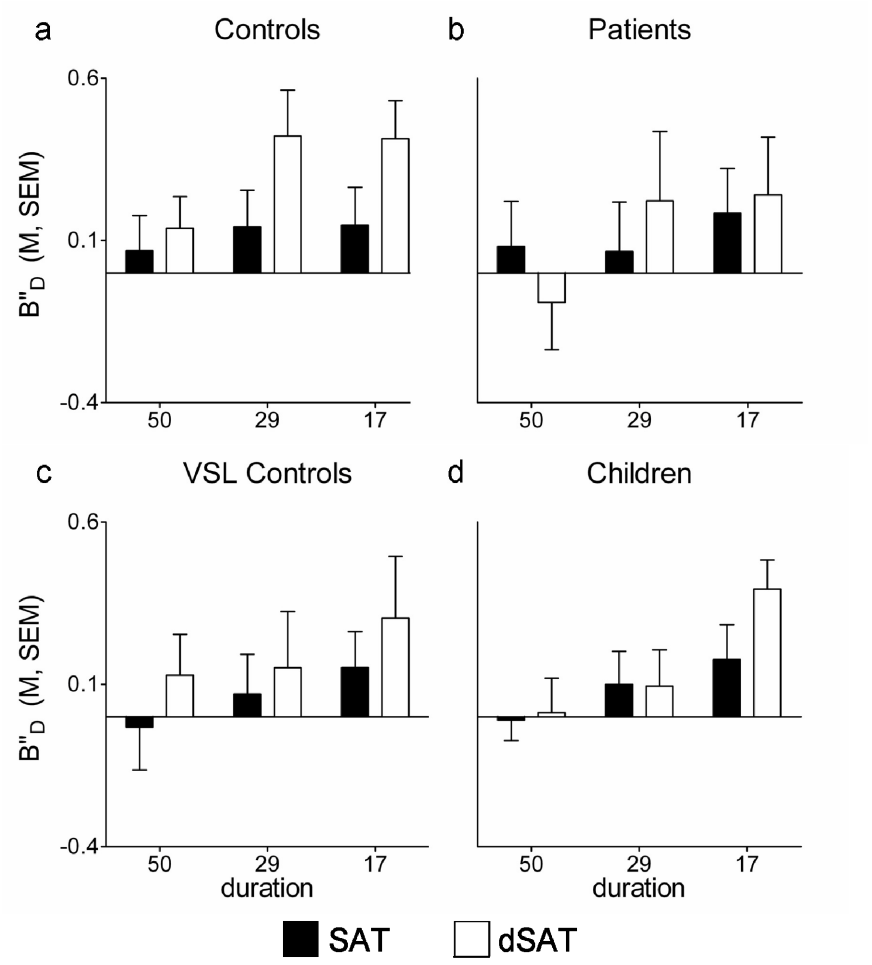

Figure 4.4. Response bias measures show participants become more conservative with shorter signal durations. Data shown are from the averaged dSAT run, collapsed by whether distraction was absent (SAT condition, black bars) or present (dSAT condition, white bars). Bars represent the mean and standard error of the mean. Healthy adult controls **(a)**, patients with schizophrenia **(b)**, VSL healthy adult controls run on a more difficult task version **(c)** and healthy school-age children **(d)** all show similar patterns in response bias (B''_D). All participants become more conservative in their criterion for reporting signals as signal duration decreased (B''_D values closer to 1.0). There were no differences between the groups in response bias.

Attentional performance declines over time in children, but remains steady in adults.

While the effects of distraction were the primary focus of this experiment, participants also completed two 12 minute SAT runs. SAT scores from the average of these runs were examined to see if any of the four groups' performance changed as a function of time-on-task (Figure 4.5). The repeated measures ANOVA including all four groups revealed a significant Block x Group interaction ($F(15,205) = 2.41$, $p = 0.01$, $\eta^2_G = 0.03$), in addition to the main effects of Duration and Group that would be expected given the SAT score results from the dSAT runs ($F(2,82) = 5.83$, $p = 0.004$, $\eta^2_G = 0.01$ and $F(3,41) = 2.98$, $p = 0.04$, $\eta^2_G = 0.13$, respectively). Patients with schizophrenia and children had the lowest SAT scores overall, and both were significantly lower than the first group of adult controls' SAT scores (both $p = 0.02$).

To determine the source of the block by group interaction, repeated measures ANOVAs were run within each of the four groups individually using the factors of Block and Duration. Only the school-age children showed a main effect of Block ($F(5,70) = 3.84$, $p = 0.02$, $\eta^2_G = 0.06$). For this group, performance was the highest in the first block (average SAT score of 0.89) and then steadily declined, reaching the lowest point during the final block (average SAT score of 0.77). This result is of interest because it suggests that different aspects of SAT performance tap different cognitive control functions, dissociating the control processes challenged by distraction (differentially affected in schizophrenics) from those challenged by the need to sustain performance over time (differentially affected in children). Although the brains of individuals with schizophrenia and healthy children differ structurally and functionally from those of healthy adults, they

also differ a great deal from each other. In particular, schizophrenia is most often associated with reduced volumes in prefrontal and medial temporal lobe regions, whereas children of the age tested here have not yet completed pruning or the prefrontal grey matter growth spurt that immediately precedes puberty (Giedd et al., 1999). An interesting avenue for future investigation will be the replication of the dissociation seen here and the investigation of whether each function can be linked to specific brain regions or networks.

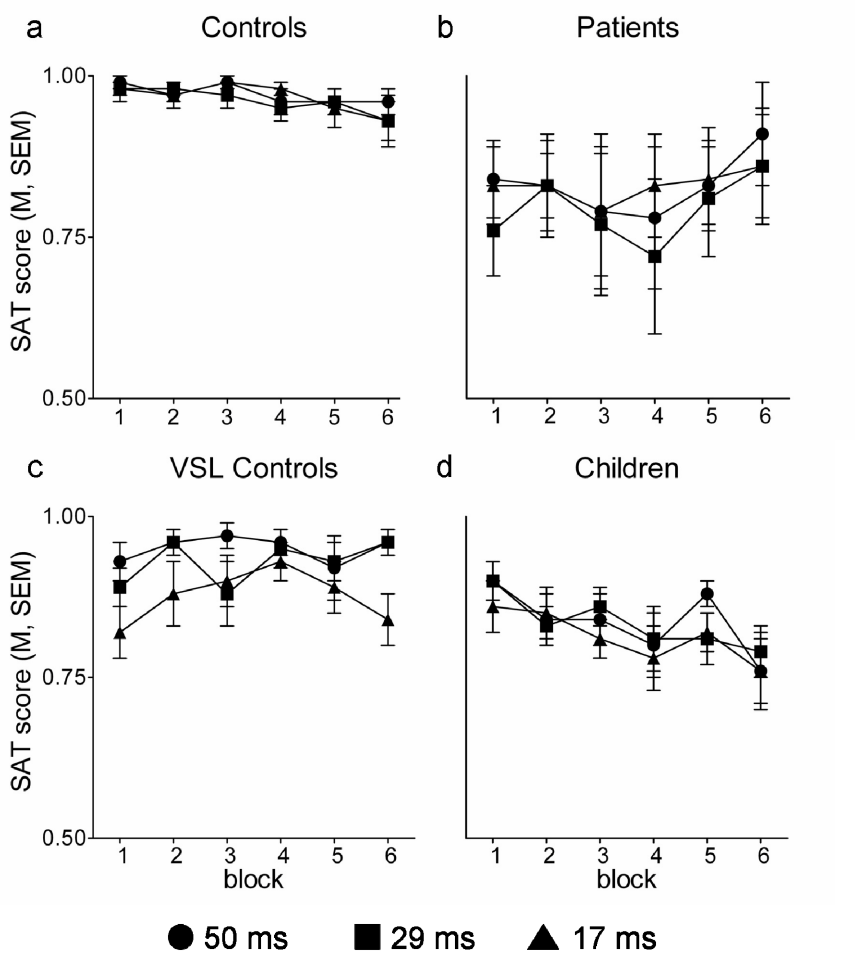

Figure 4.5. SAT scores decline over time in school-age children. Data are SAT scores (mean and standard error around the mean) for the 50 ms, 29 ms, and 17 ms durations from the average of the two SAT runs. Each run consisted of six 2 minute blocks. **(a)** Healthy adult controls and **(b)** patients with schizophrenia both showed relatively stable attentional performance levels over time. **(c)** Healthy adults performing a more challenging version (VSL condition) of the SAT had slightly lower scores than the adults in **(a)**, especially at the shortest duration, but performance did not vary significantly between blocks. In contrast, school-age children's **(d)** SAT scores declined over time, with their lowest levels of performance coming at the end of the run.

All groups show good internal reliability on repeated administration of SAT and dSAT.

Repetition of the runs allowed me to examine reliability for both the SAT and dSAT within the session for each group. Reliability questions, though often ignored in

experimental research, are important for the potential translation of the task to clinical settings. Ideally, performance should be internally consistent across the repeated runs, so that the task could be administered multiple times to the same patient without the confound of significant practice effects. For all groups, the Cronbach's alpha values exceeded the 0.80 value often used as a heuristic for "good" reliability for both the SAT and dSAT conditions (Table 4.2). While further studies will be needed to look at how stable performance in participants is across sessions and over weeks, months and years, these reliability analyses provide a first look at the task's internal consistency. Overall, these results support the feasibility of future studies using the SAT and dSAT in clinical settings with schizophrenic patients.

Table 4.2. Cronbach's alpha values for SAT and dSAT. Cronbach's alpha was calculated for the SAT condition using SAT scores from all blocks without distraction in each of the four runs. For the dSAT condition, scores from the blocks where distraction was present were used

Group	SAT	dSAT
Controls	0.92	0.84
Patients	0.99	0.95
VSL controls	0.92	0.84
Children	0.97	0.93

Discussion

Overall, the results of this experiment are in line with my prediction that patients with schizophrenia would have an enhanced susceptibility to distraction, showing a greater decline in attentional performance during distraction than would be seen in

healthy individuals. The current work also demonstrates the ease of implementing the dSAT in various populations of people, including school-age children and adult clinical populations. While future work is needed to delineate the underlying causes of the impairments seen here in patients, my results provide important evidence that the dSAT is sensitive to attentional control deficits in schizophrenia and will be a useful tool for translational research in this area.

While patients showed both fewer hits and more false alarms when distraction was absent than the other groups collected here, their performance levels were still quite good. This is in line with previous research that shows that patients with schizophrenia exhibit only mild attentional deficits on relatively easy tasks. However, when the demands on attention were increased by introducing the distractor, patients showed a robust impairment in attentional performance compared to the other control groups. In the control participants, the largest distractor effects were often observed at the shortest signal duration. In contrast, patients showed a more global impairment, with their attentional performance declining dramatically across the full range of signal durations. Inspection of the data revealed that while patients' misses and false alarms both increased with distraction, patients' disproportional impairments during the distractor stemmed mainly from having more misses on signal trials than did the control groups, particularly as compared to the variable signal location (VSL) adult controls and the group of children.

This impairment on signal trials during distraction cannot simply be attributed to an inability to perceive the signal stimulus during distraction or from a different bias in response criterion for reporting signals. The *d'* data demonstrate that despite having low

perceptual sensitivity compared to the other groups, patients are able to perceptually discriminate the signal stimulus from noise, and indeed are well off of floor (*d'* of 0) on this measure. Even more importantly, although patients had lower sensitivity overall, there were no interactions between group and distraction on the *d'* measure. Therefore, it seems unlikely that perceptual differences drove the group by distraction interactions seen for SAT scores and hits.

It is also unlikely that group differences in response bias (B''_D) had a significant influence on my results. All participants became more conservative in criterion for reporting a signal as signal duration was decreased. There was also a tendency for participants to become more conservative with distraction as well; however, this was not significant. Overall, patients' response bias scores were comparable to the other groups, indicating that the attentional performance differences seen during the distracter were not simply a result of a shift in response criterion (e.g., patients were not less likely to report seeing a signal than controls). These findings are in line with previous reports that patients with schizophrenia have impaired sensitivity, or a deficit in the ability to discriminate targets from nontargets (Nuechterlein, 1991; Seidman et al., 1998), but like healthy controls they generally become more conservative in their response bias as task difficulty increases (Seidman et al., 1998).

Overall, the data suggest that patients are unable to successfully engage top-down attentional control processes designed to optimize target detection in the face of the attentional challenge presented by the distractor. These results are conceptually consistent with previous findings from visual search procedures, particularly the guided search paradigm of Gold et al. (2007; see Nuechterlein et al., 2009, for an extensive discussion

of the guided search paradigm and dSAT and their potential as translational tools in schizophrenia research). In the guided search paradigm, the demands on bottom-up and top-down attention are manipulated by having participants search for a target with either highly salient features (target search guided by bottom-up mechanisms) or for a target in an array of very similar nontargets (requires engagement of top-down mechanisms to make search efficient). Patients with schizophrenia do not show impairments compared to controls when bottom-up attentional processes can be relied upon to find the target, but they do show strong impairments when top-down attentional processes are required (Gold et al., 2007). While my results in the absence and presence of distraction mirror these findings, the nature of the distractor (a global, continuous visual stimulus) is very different from the type used in Guided Search tasks. The present results show that schizophrenia-related deficits in top-down control impair not only the ability to discriminate a target from visually-similar distracters, but also the ability to detect a target in the face of a whole-field homogenous distractor.

A previous investigation by Mar et al. (1996) with schizophrenic inpatients incorporated some aspects of the SAT as used here, but without the distractor condition or any other manipulation of top-down control demand. They found that patients' and controls' performance levels were affected by signal duration, with worse performancefor shorter signal durations as seen in the current dataset. However, they also found that patients had slightly higher rates of hits compared to age-matched controls. This finding was taken to support a "hyperactivity" hypothesis of attention in schizophrenia. In addition to the use of an inpatient population and the lack of a distractor condition, the Mar et al. study also differed in several other ways from the methods used here. The

signals were relatively high-contrast (white dots on a black background), and varied in location. In addition, trial length was much longer (5.3 – 10.7 seconds) than in the current design. The lower contrast between my dark gray signal and light gray background and the faster pace of trials in the current experiment may have decreased the discriminability of the signal and increased the processing load required on the SAT, exposing the mild deficits seen in patients with schizophrenia when distraction was absent.

Previous work using a model of the cognitive impairments in schizophrenia in rats has demonstrated that these animals also show an enhanced vulnerability to distractors and abnormalities in their fronto-mesolimbic-basal forebrain circuitry (Sarter et al., 2009). In this model, rats receive either an escalating-dosage regimen of amphetamine (AMPH-pretreated) or saline over the course of several weeks. This work demonstrates AMPH-pretreated animals perform the SAT at comparable levels to saline-pretreated animals, but show dramatic impairments in attentional performance in the presence of distraction. These results are thus reminiscent of the distractor-sensitivity shown by patients in the current study.

Compared to saline-treated animals, AMPH-pretreated animals also show significantly higher levels of performance-associated cortical acetylcholine release in right prefrontal cortex during the SAT. This suggests that AMPH-pretreated animals need to engage higher levels of top-down control in order to perform even the basic SAT. While measures of brain activity were not collected from patients in the current study, the available animal model data as well as the neuroimaging results from Chapter 3 suggest a couple of scenarios for how patients' activation would compare to controls in an fMRI study with the SAT and dSAT. Both the animal model data and my results in Chapter 3

point to right frontal regions as a key site for SAT and dSAT performance. In line with the higher levels of prefrontal acetylcholine release seen in AMPH-pretreated animals performing the SAT and with the linear relationship between behavioral impairment and right frontal activation found in the fMRI study, one prediction would be that patients would show a greater degree of right frontal activation than controls even without the presence of distraction. This activation may then be further augmented by the distractor. A second plausible scenario would predict that compared to control participants, patients will show greater activation of frontal regions at relatively low levels of top-down control demand, and be unable to further increase activation in response to increased demands imposed by the distractor (see Reuter-Lorenz & Cappell, 2008 for a similar hypothesis in aging research).

Along with determining how the neural correlates of SAT and dSAT performance differ in stably-medicated outpatients like those tested here, future work will also have to see how attentional performance compares in unmedicated or first-episode patients. In addition, much work needs to be done to determine the test-retest reliability of the dSAT, an important consideration for moving this task into the clinic. Nonetheless, the current findings represent a key step in developing the dSAT for translational research by demonstrating that the dSAT is sensitive to the attentional control impairments seen in schizophrenia.

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Chapter V

CONCLUSION

Summary of findings

The current work set out to establish the usefulness of using the distractor condition sustained attention task (dSAT) for translational research on sustained attention and attentional control by adapting the original rat task for use in humans, investigating the neural correlates of task behavior using fMRI, and establishing the behavioral effects of distraction in healthy adults, school-age children, and outpatients with schizophrenia. Each of these represents important first steps for developing a line of translational research on the attentional control deficits seen in schizophrenia.

Chapter 2 described the adaptation and validation of the dSAT for use in healthy humans. Overall, comparison of rat and human behavioral data indicated that rats and humans show qualitatively similar patterns of performance. Both species showed declines in attentional performance as signal duration decreases and in the presence of distraction. Important differences existed between the species as well, which may be attributable to the higher levels of top-down control inherent in humans. Rats generally had lower levels of attention performance than humans, particularly at the shorter signal durations. The two species also showed different shifts in their response biases in response to distraction, with rats becoming more liberal in their response biases and showing both more misses and false alarms during distraction and humans becoming more conservative and

showing mostly more misses in the distractor condition. The second experiment in this chapter demonstrated that changing the reward contingencies (penalizing misses monetarily, a top-down manipulation) results in a shift in the distribution of errors in humans, increasing false alarms and making them more liberal during distraction. This penalizing misses contingency was also used in the fMRI experiment in Chapter 3, where participants showed a large increase in both misses and false alarms during distraction. Chapter 4 did not manipulate the reward contingencies (hits and correct rejections equally rewarded for all groups). Thus, as seen in the participants in the first experiment of Chapter 2, participants became more conservative with shorter signal durations and slightly more conservative with distraction. Patients with schizophrenia showed the same patterns in their response biases as the other control groups.

While behaviorally all participants in the experiments in Chapters 2 and 3 showed reduced attentional performance during distraction, Chapter 3 demonstrates that activity in right frontal regions actually increased in the presence of distraction. Correlational analyses between participants' drop in accuracy and the amount of brain activation during distraction demonstrated that participants with the greatest impairments on the dSAT showed the highest activation of right frontal regions. In light of these findings, the increased activation of right frontal regions during distraction is interpreted as reflecting increases in attentional effort, or the activation of attentional systems in an effort to maintain or improve performance under challenging conditions (Sarter et al., 2006). Thought to be under the control of the 'central executive' (Baddeley, 1986) and the anterior attention system (Posner, 1994; Posner & Dehaene, 1994), attentional effort is theorized to engage top-down attentional control processes in order to carry out goal-

directed behaviors (Sarter et al., 2006). While the activation of the right MFG seen in Chapter 3 did not seem to be sufficient to completely overcome the challenges to attention, its engagement and the engagement of downstream regions may have helped stabilize residual levels of performance and allowed participants to stay on task.

While the results of Chapters 2 and 3 showed that even healthy individuals' attention is impaired during distraction, Chapter 4 tested the hypothesis that patients with schizophrenia would be even more susceptible to distraction. This was indeed the case. While patients showed lower levels of attentional performance overall than control participants, their attentional impairments became especially apparent during the distractor condition. This is in line with previous research demonstrating that patients with schizophrenia have specific impairments of the top-down control of attention (see Braff & Saccuzzo, 1985; Heinrichs & Zakzanis, 1998; and Nuechterlein et al., 2009 for reviews). Chapter 4 also included data from children. This group was included with the idea that given that children in this age range (8-11 years) have yet to fully develop their frontal cortex and top-down executive control processes, they would likely be off of ceiling on the SAT and be a good comparison group for the patients. Children did have lower attentional performance levels than the adult controls. Children also showed consistent declines in performance during distraction across all signal durations, but these declines were not as dramatic as those seen in patients. However, children were more strongly affected by time on task compared to patients and adult controls, declining over the course of the twelve minute SAT runs. This suggests that different populations may show different types of impairments on the SAT and dSAT, rather than all populations other than healthy adults simply showing greater effects of distraction. While Chapter 4

focused primarily on the effects seen in patients with schizophrenia, the results in children are also interesting in their own right and the SAT and dSAT would also likely be useful for investigating how children with impaired attention such as in attention deficit disorder compare to healthy children.

Evaluation of the dSAT as a translational research tool

The results of the current experiments demonstrate the feasibility and utility of using the dSAT to study attentional control in animal models and in healthy and clinical human populations. A version of the SAT and dSAT has recently been developed for mice, allowing the addition of genetic manipulations to the already rich repertoire of neurochemical, pharmaceutical, and neuroimaging techniques available to use in combination with this task (see Demeter et al., 2010; Kozak et al., 2007 and Parikh et al., 2007 for representative examples). The ability to employ a single, cross-validated task in so many settings is an obvious strength of the dSAT as a translational research tool. The ability to manipulate the demands on attention directly in a single paradigm through the presence (dSAT) or absence (SAT) of distraction is also a strength of this task. Finally, as Chapter 4 demonstrates, the dSAT is a measure sensitive to the attentional control deficits seen in schizophrenia, making it a promising tool for future investigations of the nature and neural underpinnings of this deficit.

While the close nature of the rat and human versions of the SAT and dSAT makes it easy to link and interpret evidence from both species collectively, the dependence on keeping the rat and human tasks as parallel as possible also provides some limitations. One such limitation of the current task parameters is the floor effects seen in rats

(especially on the shorter durations during distraction) and the ceiling effects seen in healthy humans (especially in the absence of distraction). Altering the signal durations and other task parameters is a way to overcome those limitations, as seen in the variable signal location (VSL) adult control group (Chapter 4). The data also suggest that there is room to use a slightly harder version of the task in patients with schizophrenia without running into floor effects. The current experiments can help guide how parameters are optimized in future experiments, and establish a strong foundation for what patterns of behavior to expect in different species (rats, humans), in humans of different ages (children, young adults, middle aged adults) and in different environments (in the lab, in the MRI scanner) and in healthy and clinical populations.

Limitations of present work and considerations for future investigations

Much work remains to fully understand how the brain responds to attentional challenges like distraction and how this response may be altered in schizophrenia. Evidence from animals demonstrates the cortical cholinergic input system supports sustained attention and is important for mediating increases in attentional effort in response to challenges to attention (Arnold et al., 2002; Himmelheber et al., 2000; Kozak et al., 2006; McGaughy et al., 1996). In order to fully relate the evidence from animals to the perfusion data seen in the neuroimaging experiment in Chapter 4, a greater understanding of what component of the blood flow data is driven by cholinergic neurons is needed. Another limitation of the current work is the difficulty in disentangling the perceptual deficits in patients from the top-down attention deficits. Future neuroimaging studies can investigate the neural correlates of the SAT and dSAT in patients with

schizophrenia and control for the visual stimulation of the distractor to start to address this issue. Future behavioral work in patients could also employ other ways of manipulating top-down attention, including using cross-modal distractions.

Substantial work is also still needed to characterize the SAT and dSAT in patients with schizophrenia. In order to make the dSAT a useful clinical diagnostic and evaluation tool, more work needs to be done to determine the test-retest reliability of the paradigm. The data in Chapter 4 demonstrated the sensitivity of the dSAT to attentional control deficits in remitted, medicated outpatients. While impairments seen during remission are often considered to be 'core' symptoms of the disorder rather than acute symptoms brought on by psychosis, previous work on tasks like the Continuous Performance Task have shown the utility of studying the same paradigm in actively psychotic patients, remitted patients, and in children at risk for schizophrenia or in first degree relatives of patients with schizophrenia (e.g., Asarnow & Maccrimmon, 1978). Furthermore, future investigations of how cholinergic manipulations affect behavior and neural activation during the SAT and dSAT would provide key insights into the function and possible dysregulation of the cortical cholinergic input system in schizophrenia.

Conclusions

Despite the remaining questions, the present work lays the foundation for cross-species translational research on the role of the cholinergic system in mediating top-down attention in healthy individuals. The current body of evidence also suggests the dSAT will be a useful measure for evaluating cognitive impairments in patients and for assessing whether new pharmacological treatments are capable of rescuing attention in

schizophrenia. The close ties between the animal and human analogues of the SAT and dSAT add hope that any putative pro-cognitive enhancers developed in animal models will also translate into clinically efficacious treatments in patients.

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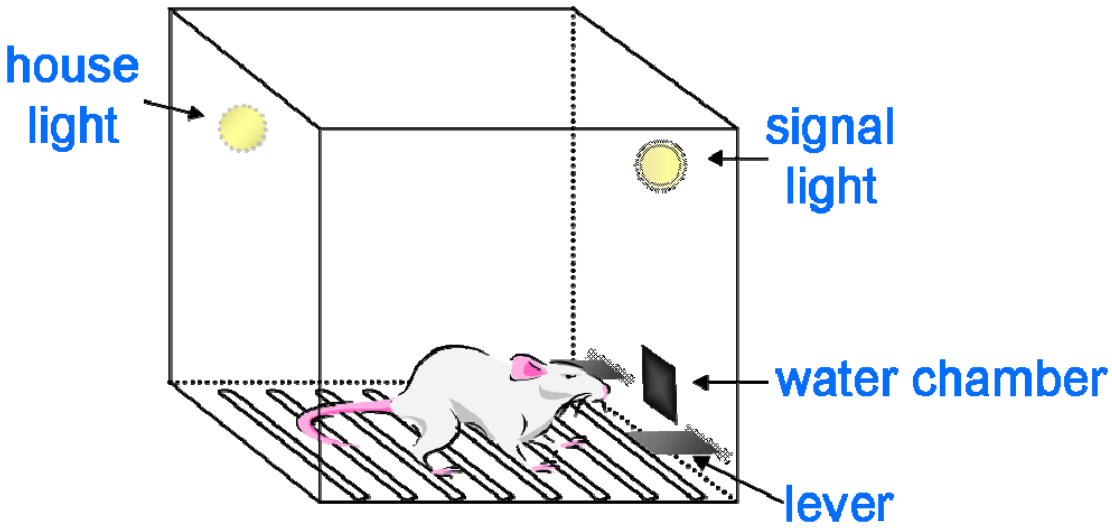
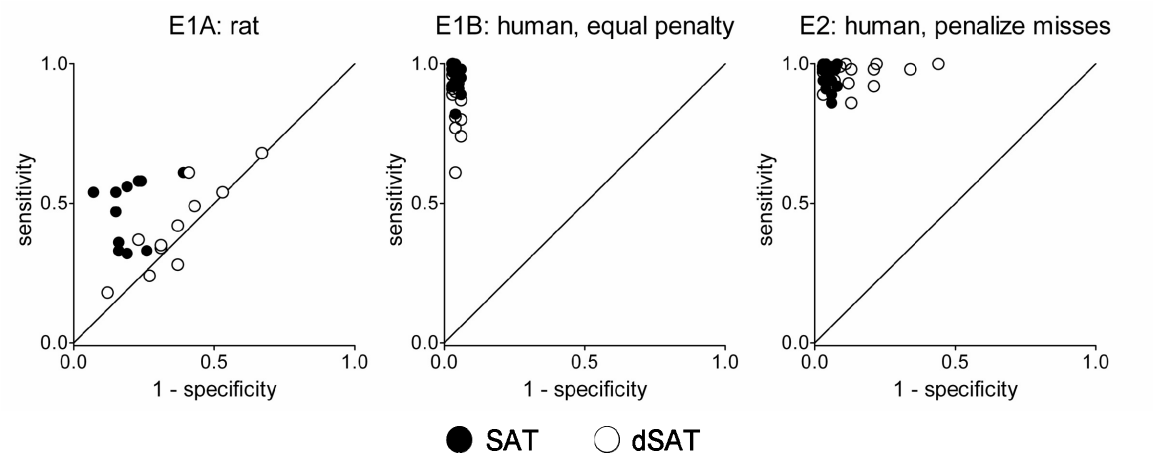
Appendix I

Supplementary Materials for Chapter II



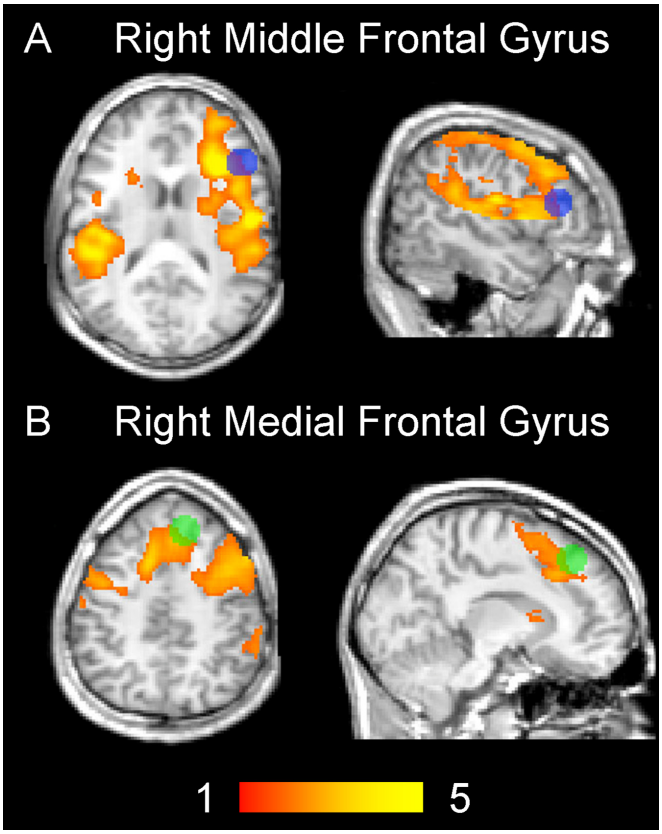
Appendix I Figure 1. Schematic of rat operant box chambers. Diagram illustrates the relevant components of the chambers where rats were trained and tested on the SAT. The task consisted of signal and nonsignal trials. After a variable intertrial interval, the signal light was either illuminated for 500, 50 or 25 ms (signal event) or not (nonsignal event). Two seconds later, the levers were extended into the chambers and remained extended until either the rat responded or 4 s had elapsed. Correct responses generated a water reward. During the SAT, the house light stayed illuminated the entire session. For the distractor condition, the house light flashed on and of at a rate of 0.5 Hz.



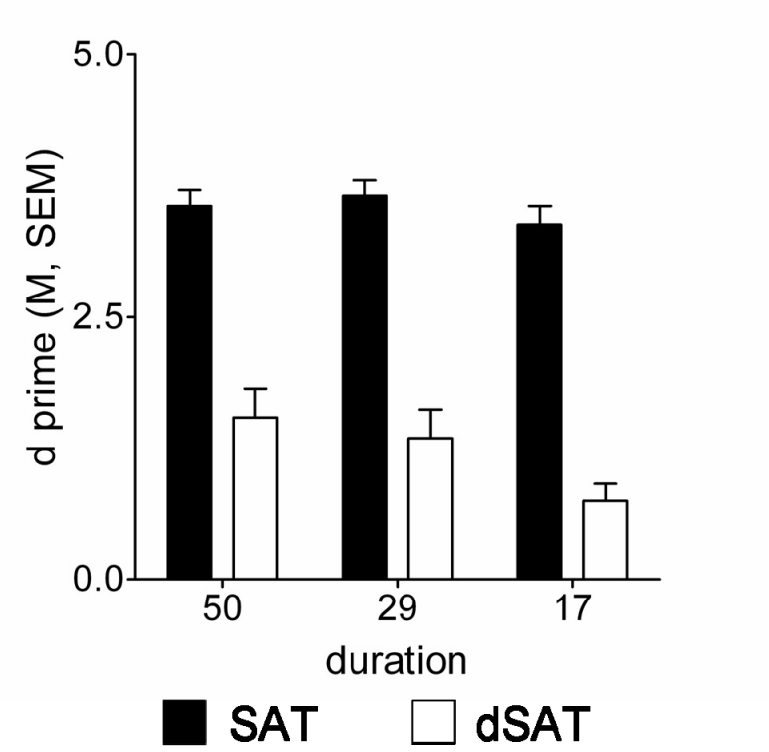
Appendix I Figure 2. Receiver operating characteristic plots for rats (Experiment 1A) and humans (Experiments 1B and 2). Data plotted are the mean proportion of hits (sensitivity, collapsed across signal durations) on the y-axis against the mean proportion of false alarms (1 – specificity) on the x-axis for each participant. Data from the no-distraction condition (SAT) are in the black circles and data from the distraction condition (dSAT) are in the white circles. The diagonal line represents the line of no-discrimination, or chance performance. Participants with the best classification of signal and nonsignal events (high proportions of hits, low proportions of false alarms) are the closest to the upper left corner, farthest from the line of no-discrimination. Overall, humans had higher sensitivity (more hits) and higher specificity (fewer false alarms) than rats. For rats, performance during the distraction condition resulted in poorer classification of signal and nonsignal events (lower hits and higher false alarms, closer to the line of no-discrimination), with several participants falling close to or on the line of no-discrimination.

Appendix II

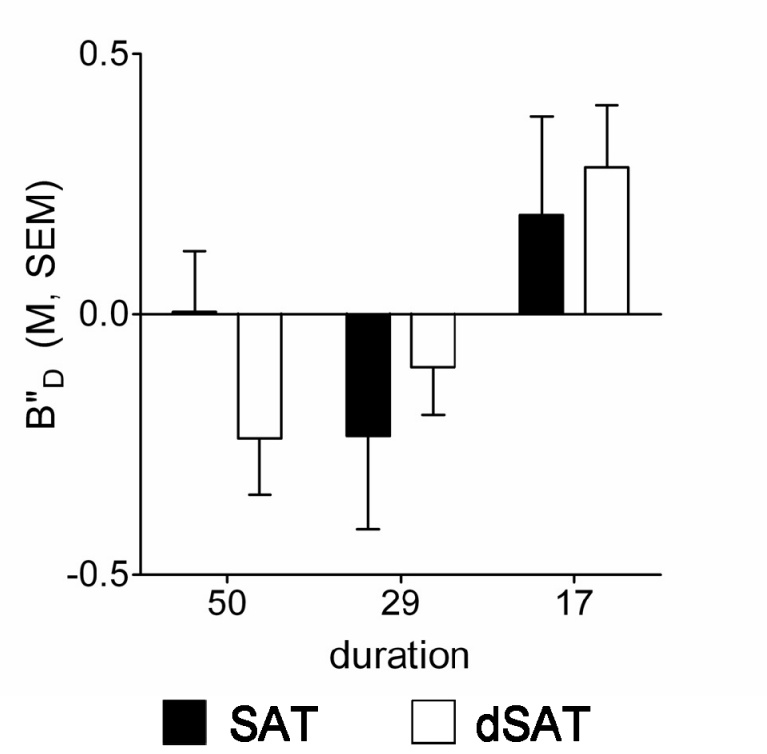
Supplementary Materials for Chapter III



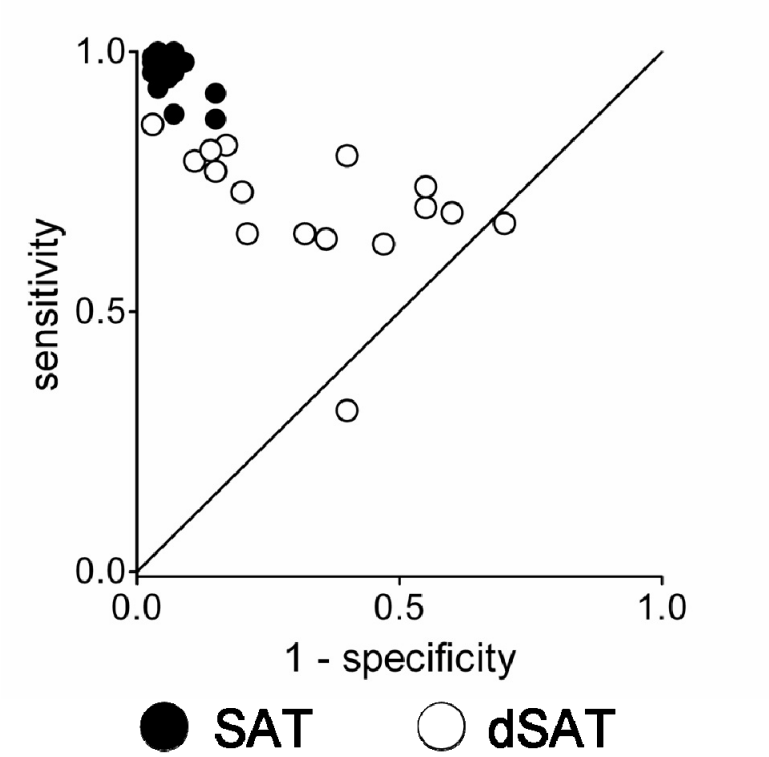
Appendix II Figure 1. Whole brain results correspond with frontal activations found by Kim et al. (2006). To illustrate correspondence, spheres (8 mm radii) centered on the peak coordinates of the frontal activations for the sustained attention task results described in Kim et al. (2006) are overlaid on top of a group level contrast showing regions with greater activation for SAT and dSAT blocks than for dFIX and fixation blocks. Color bar indicates Z scores ranging from 1 to 5. Axial and saggital slices shown at sphere centers: right middle frontal gyrus (A, blue sphere) (49, 26, 16), right medial frontal gyrus (B, green sphere) (11, 35, 47), MNI coordinates.



Appendix II Figure 2. *d'* sensitivity measures for SAT and dSAT data. Similar to the patterns of results seen in humans in Chapter 2, distraction interacted with duration, producing the lowest d' values during the 17 ms duration of the dSAT block ($F(2,30) = 4.41$, $p = 0.02$, $\eta^2_G = 0.02$). All *d'* values were significantly different than zero, indicating that even for the shortest signal durations during distraction perceptual sensitivity was not at floor (one-sample *t*-tests all $p < 0.01$, Cohen's $d > 1.11$).



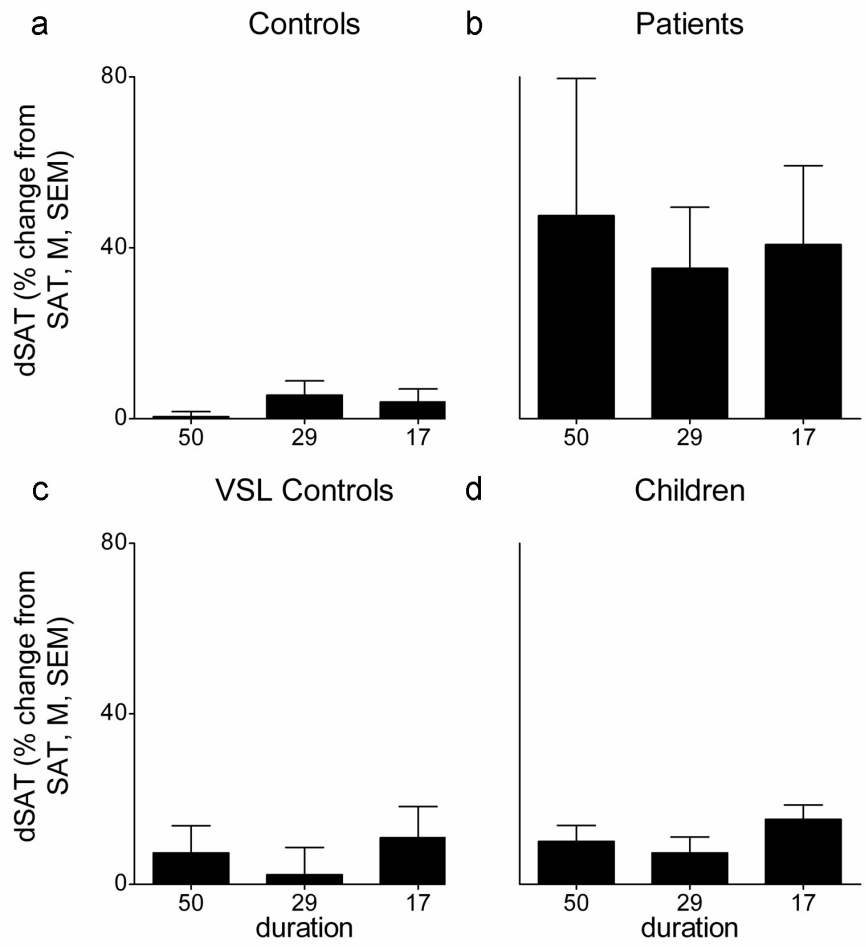
Appendix II Figure 3. Response bias measures for SAT and dSAT data. Calculation of the B''_D measure of response bias showed that participants became more conservative as signal duration decreased ($F(2,30) = 13.80$, $p < 0.01$, $\eta^2_G = 0.10$).



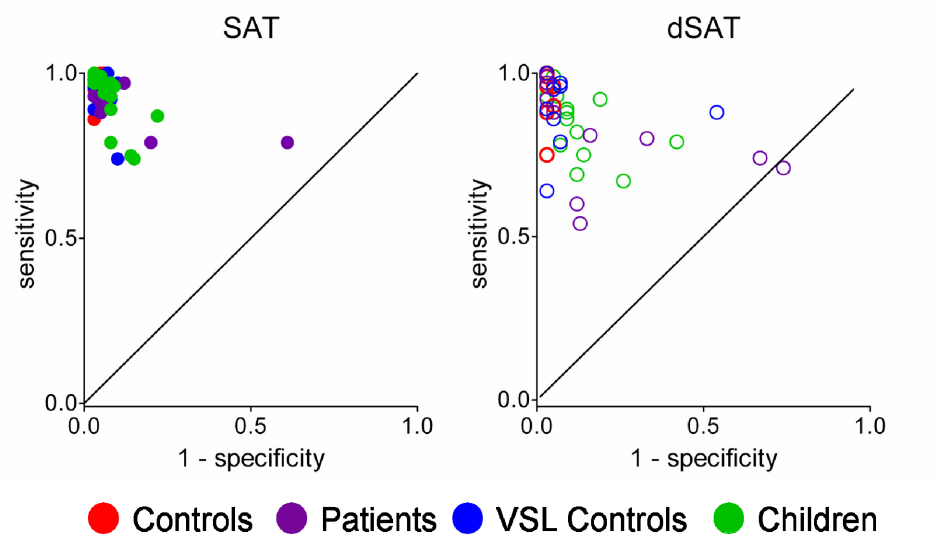
Appendix II Figure 4. Receiver operating characteristic plots for SAT and dSAT. Data plotted are the mean proportion of hits (sensitivity, collapsed across signal durations) on the y-axis against the mean proportion of false alarms (1 – specificity) on the x-axis for each participant. Data from the no-distraction condition (SAT) are in the black circles and data from the distraction condition (dSAT) are in the white circles. The diagonal line represents the line of no-discrimination, or chance performance. Participants with the best classification of signal and nonsignal events (high proportions of hits, low proportions of false alarms) are the closest to the upper left corner, farthest from the line of no-discrimination. Overall, participants had higher sensitivity (more hits) and higher specificity (fewer false alarms) without distraction than with distraction. Performance during the distraction condition resulted in poorer classification (lower hits and higher false alarms, closer to the line of no-discrimination), with several participants falling close to or on the line of no-discrimination.

Appendix III

Supplementary Materials for Chapter IV



Appendix III Figure 1. dSAT percent change from SAT. Data are the absolute value of the percent change in SAT score from the blocks with distraction from the blocks without distraction. A Duration x Group ANOVA including all four groups found a main effect of group ($F(3,41) = 2.72$, $p = 0.05$, $\eta^2_G = 0.14$). Pairwise comparisons between the groups revealed that patients had a greater percent change from the no-distractor blocks to the distractor blocks than each of the other groups (all $p < 0.03$).



Appendix III Figure 2. Receiver operating characteristic plots for controls, patients, VSL controls and children. Data plotted are the mean proportion of hits (sensitivity, collapsed across signal durations) on the y-axis against the mean proportion of false alarms (1 – specificity) on the x-axis for each participant. Data from the SAT condition are in the plot on the left with the filled circles and data from the distraction condition (dSAT) are in the plot on the right with the open circles. The diagonal line represents the line of no-discrimination, or chance performance. Participants with the best classification of signal and nonsignal events (high proportions of hits, low proportions of false alarms) are the closest to the upper left corner, farthest from the line of no-discrimination. Overall, participants had higher sensitivity (more hits) and higher specificity (fewer false alarms) without distraction than with distraction. Performance during the distraction condition resulted in generally poorer classification (lower hits and higher false alarms, closer to the line of no-discrimination), particularly for the patients with schizophrenia and the children. A few of the patients with schizophrenia fell close to or on the line of no-discrimination.