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Adam Harrison Hirsh
College of William & Mary - Arts & Sciences

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Visual Attention and Distraction: Contribution of Orexins

Adam Harrison Hirsh
Medford, New Jersey

Bachelor of Arts, Muhlenberg College, 2009

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Department of Psychology

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Adam Harrison Hirsh

Approved by the Committee, July 2011

Committee Chair
Associate Professor Joshua Burk, Psychology
The College of William and Mary

Professor Pamela Hunt, Psychology
The College of William and Mary

Assistant Professor Paul Kieffaber, Psychology
The College of William and Mary
Research approved by

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Acute exposure to distracters are well-known to disrupt attentional performance (McGaughy & Sarter 1995). In the present experiments, the effects of long-term exposure to distracters on performance during a sustained attention task and then on acquisition of a new place discrimination task were examined. Results indicated that while attentional performance initially suffered after distracter exposure, animals that were chronically exposed to the distracter tended to learn the new visual discrimination task more quickly and to retain the sustained attention task performance more effectively than animals that had not been exposed to visual distraction. However, the strength and consistency of these effects varied across rat strains. Our third experiment examined a possible neural basis for the most consistent effect from Experiments 1 and 2, attentional impairments following acute distracter exposure. Previous research by Boschen et al. (2009) has implicated orexin A as a possible mediator of cholinergic activation during sustained attention performance; our third experiment evaluated this mediation. Animals were administered different doses of orexin A prior to training in a sustained attention task for four session. Each training session was comprised of performance during a non-distracter section, then a distracter section, followed by a second non-distracter testing section. Results indicated that at the highest dose of orexin A, attentional performance was enhanced, specifically on trials that required that animal to recognize the lack of a signal presentation. These results extend the available literature by suggesting that orexin A can mediate attentional performance during distracter and non-distracter conditions.
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Visual Attention and Distraction: Contribution of Orexins

The detection of salient or instrumental stimuli and the selection of cue-evoked responses are mediated by a fronto-parietal network that is modulated by cholinergic inputs originating from the basal forebrain (Sarter, Hasselmo, Bruno, & Givens, 2005). This neural network may be responsible for sustained attention. It is possible to evaluate attentional processing through behavioral measures. Specifically, changes in responding behavior can be measured after the manipulation of various stimulus parameters. The neural mechanisms thought to underlie attention will first be discussed in detail, followed by an overview of the procedures for manipulating attentional demands.

Neural Basis of Attention

A two-choice visual discrimination task has been used to evaluate which neural mechanisms may be involved during a sustained attention task performance. Bushnell, Oshiro, and Padnos (1997) administered several drugs prior to a sustained attention task that either reduced (scopolomine, mecamylamine, and clonidine) or elevated (pilocarpine, nicotine, and idazoxan) cholinergic and adrenergic tone. Decreasing cholinergic and adrenergic activity resulted in impairment of overall signal detection as well as an increase in ‘false alarms.’ A false alarm was defined as selecting the incorrect lever after a non-signal trial. Cholinergic and adrenergic agonists, however, resulted in signal detection impairment without any effect on false alarm rates (Bushnell et al. 1997). By contrast, the GABA-benzodiazepine receptor complex agonist, chlordiazepoxide, was found to affect task performance by altering visual
thresholds rather than attentional processing (Bushnell et al. 1997). The results of these studies suggest that multiple neurotransmitter systems are involved in attentional processing.

Research has also tended to focus on a possible neural basis for sustained attentional processing during acute distraction (Himmelheber, Sarter, & Bruno, 2001). Himmelheber et al. (2001) reported that performance on a sustained attention task was associated with significant increases in ACh efflux. However, the increase in ACh efflux did not occur during initial distraction but instead during the second distraction training block, while performance on the task was recovering. This indicates that ACh plays an important role in the recovery of performance following the introduction of a distracter. It was also found that widespread depletions of cortical cholinergic inputs (produced through lesioning) had no effect on performance on a low-demand attention task. The authors concluded that the importance of cortical cholinergic inputs during task performance may be dependent on how explicitly demanding the task is on attention. The noradrenergic system is also thought to be important for attention and behavioral flexibility. Aston-Jones, Rajkowski, and Cohen (1999) have hypothesized that the locus coeruleus-norepinephrine system (LC-NS) plays a central role in the regulation of attention between focused states and “scanning” or labile attentiveness. The authors propose that the locus coeruleus (LC) acts as a modulator for attentional processing systems, eliciting responses only if the LC discharges to a sufficient but not overwhelming degree (Rajkowski & Cohen 1999). Electrophysiological evidence has also been found linking the locus
coeruleus to alertness and selective attending (Foote, Berridge, Adams, & Pineda 1991). Specifically, results of electroencephalographic (EEG) measures during a visual discrimination attention task suggest that LC activation results in forebrain activity changing from patterns that are characteristic of a non-alert state to those characteristic of an alert state (Foot et al. 1991). Additionally, event-related potential (ERPs) results suggest that the LC may modulate forebrain components of orienting attention that are indexed by specific ERP components (Foot et al. 1991).

In addition to research attempting to reveal which neurotransmitter systems are involved in attention, research has aimed to localize different aspects of attention to specific brain regions. One paradigm that has been employed involves testing attentional orienting. Attentional orienting has been defined as the allocation of attentional resources and have categorized the orientations as either spatial, temporal, or both (Coull & Nobre 1998). PET scans have measured activation of the inferior parietal lobule, the occipital-temporal sulcus, and the cerebellum during tasks requiring spatial orienting. Tasks requiring temporal orienting have elicited activation of the intraparietal sulcus, lateral inferior premotor, as well as the cerebellum. Finally, tasks requiring both temporal and spatial attentional orienting have produced activation of the temporal-parietal junction, and the intraparietal sulcus (Coull & Nobre 1998). From a neural perspective, it is clear that attention cannot be attributed to a single brain region or neurotransmitter system.

Taxing the Attentional System
In a task where an animal is forced to discriminate between signal presentations (panel illuminations) from non-signal trials, various manipulations exist for taxing the attentional system. The task itself contains signal and non-signal trials in order to prevent the animal from being able to predict that a signal will appear each trial. Past research on such tasks has focused specifically on varying the duration of signal presentations as well as varying the time between signal presentations, the intertrial interval (Burk, Lowder, & Altemose 2008). Research by Bushnell (1999) and McGaughy and Sarter (1995) has shown that decreasing the ITI during a visual-cued discrimination task disrupts attentional performance. Additionally, accuracy decreases in this attention task on trials when shorter duration signals are presented (Burk et al. 2008; McGaughy, Kaiser, & Sarter 1996). A task that did not involve variable signal durations would require less sustained attention because the task would become predictable and thus require less of the attentional system.

The 5-choice serial reaction time task requires animals to monitor the appearance of a brief stimulus (light) projected into one of five holes. Correct responses (provided via a nose poke into the appropriate hole) are rewarded while incorrect choices typically receive a brief punishment (Robbins 2002). Task manipulations for the 5-choice serial reaction time task are similar to a two stimulus paradigm and include stimulus duration, stimulus brightness, stimulus frequency, variable intertrial interval, and auditory and visual distracters (Robbins 2002). The task heavily taxes the attentional system because animals are not able to predict any aspect of signal presentation but must remain attentive in order to
receive reward and avoid punishment. Overall, the data suggest that there are key parameters that can impact attention demands in different tasks.

Past research has primarily focused on sustained attention as well as the effects of acute distraction on attentional processing. One commonly employed procedure for distracting rats in this task is to flash the houselight. Brief presentation of this visual distracter disrupts performance in attention-demanding tasks in rats (Newman & McGaughy, 2008). There is potential for generalizing distracting effects to a non-rat model of attention. This can be seen by the fact that similar results have been observed in humans with distracting visual stimuli impairing behavioral performance on a sustained attention task (Demeter, Hernandez-Garcia, Sarter, & Lustig 2011). Presumably, performance suffers due to the attentional effort required to ignore the irrelevant distracter stimulus while maintaining attention to the target stimulus. Sarter, Gehrig, and Kozak (2006) define attentional effort as a cognitive incentive, that is, there must be sufficient motivation to overcome a detrimental mechanism, such as a distracter. From that point of view, a distracting stimulus would result in a continual decrease in performance if there is a lack of motivated activation of top-down mechanism to counter performance decline (Sarter et al. 2006).

Current Experiment

The goal of the present experiment was to characterize the effects of long-term distracter exposure on performance of an attention-demanding task as well as on acquisition of a new visual discrimination. We were led to formulate two converse hypotheses based on past research focusing on acute distraction.
Specifically, it has been shown that exposure to acute distraction results in significant decrements in performance (Newman & McGaughy, 2008). We expected, based on previous experiments, that the rats’ performance would not be affected with continued distracter exposure. However, our key research question was whether the distracter would continue to place relatively high cognitive demands on the rats that would affect new learning. If so, new learning may be disrupted by continued distracter exposure. Alternatively, the restoration of attentional performance following chronic distracter exposure may promote the use of new strategies which may be adaptive to learning. If so, distracter-exposed rats would be expected to demonstrate improved learning. The potential improved learning could then be interpreted as a cognitive flexibility, an enhancement in the systems responsible for attending to visual cues and filtering extraneous stimuli.

Method—Experiment 1

Subjects

A total of 15 male Long-Evans rats weighing between 151g-175g at the beginning of the experiment were used (Charles River Laboratories, Inc., Wilmington, MA). The rats were individually housed in hanging wire racks, in a temperature and humidity controlled room with a 14:10-h light/dark cycle. All behavioral testing took place between the hours of 0900 and 1100, 5 days per week. Animals were water restricted throughout behavioral testing, only receiving water during the task and for 30 minutes after training. Rats were allowed a minimum of one hour of water on days when no behavioral testing
occurred. Food was available *ad libitum* for the duration of experiment. All experimental protocols were approved by the Institutional Animal Care and Use Committee at the College of William and Mary. All animals were treated according to the Guidelines for the Care and Use of Laboratory Animals as set forth by the National Institutes of Health (National Research Council 1996).

Apparatus

The rats were trained in one of 12 chambers. One side of the chamber contained two retractable levers, a water port with a water delivery dipper (0.01 ml) located between the two levers, and three panel lights. One panel light was positioned above each retractable lever and one above the water port. A house light was located on the other side of the chamber; it was constantly illuminated during the initial training and eventually served as the visual distracter during later stages. Behavioral testing programs were controlled by a personal computer using the Med-PC version IV software.

Initial Behavioral Training

During the first day of training, levers were extended into the boxes at all times. The rats were rewarded with water after each lever press. In order to reduce the possibility of a specific-side bias, five consecutive lever presses on the same side resulted in the discontinuation of reward until the other lever was pressed. Rats were required to meet a criterion of 120 reinforcers per session for three sessions in order to move onto the next stage of training. During the next stage of training, rats had to discriminate a signal from a non-signal. Only the central panel light was used during this stage of training. A signal was presented
as a 1 s illumination of the central panel light while no illumination of the central panel light occurred on nonsignal trials. The levers were extended into the chamber after a signal or no signal. Half of the rats were rewarded with water after pressing the right lever after a signal presentation; this was recorded as a hit. If the animals pressed the left lever after a signal trial, it was recorded as a miss. After a non-signal trial, animals were rewarded with water if they pressed the left lever. This was recorded as a correct rejection. Pressing the right-side lever after a non-signal trial was recorded as a false alarm. These rules were reversed for half of the animals. Therefore, a hit for these animals was recorded after a left lever press followed a signal presentation. A correct rejection was recorded after a right lever press followed a non-signal. Incorrect choices were followed by a correction trial that was identical to the previous trial. Three consecutive incorrect choices resulted in a forced signal trial in which only the correct lever was extended into the chamber for 90 s. If the consecutive errors occurred during a signal trial, the central panel light remained illuminated during the forced signal trial. An omission was recorded for all trials if no response was made within 3 s after the levers were extended into the chamber. The intertrial interval (ITI) for this stage of training was 12 s. Criterion for the next stage of training was 70% accuracy on hits and 70% on correct rejections for three consecutive training sessions.

During the next stage of training, three signal durations were utilized. The presentation of these signals was randomly varied. The signal durations were either 500ms, 100ms, or 25ms. The ITI was changed to 9 ±3 seconds. The
changes to the signal durations and to the ITI were intended to increase attentional demand (Parasuraman et al. 1987; Koelega et al. 1990). Each training session was comprised of 162 total trials (81 signal, 81 non-signal). Of the 81 signal trials, each signal duration was presented for 27 trials. The trials were presented in blocks of 18 (9 nonsignal and 9 signal, 3 of each signal duration) and each trial type was chosen randomly without replacement. No correction trials or forced signal trials were used. All animals trained on this task until the criterion of 70% accuracy on the longest signal duration and 70% accuracy on correct rejections was achieved.

Distracter Training

After all rats achieved criterion, the animals were randomly placed into one of two groups. The first group continued to train on the standard version of the task. Training of these rats was not altered in any way. The second group of rats also continued to train on the standard task with the addition of a visual distracter. The house light which had previously remained illuminated now flashed (1s on/1s off) for the duration of the training of the second group of animals. The rules of the task did not change at all. Rats continued to train on this task for a total of 15 training sessions.

New Discrimination Training

During the final stages of training, rats were introduced to a new discrimination task. In addition to the original standard task, rats were now presented with a 500ms illumination of the left and right panel lights. A left-lever press was rewarded following illumination of the left panel light and a right-lever
press was rewarded following illumination of the right panel light. Rats were introduced to the visual discrimination trials interspersed with the standard attention trials within each training session. Specifically, the number of total trials within each block was increased from 18 to 20. One of the two additional trials was with the left light illuminated and the other additional trial was with the right light illuminated. The total number of trials per training session was increased from 162 to 180 (9 blocks of 20 trials). Thus, 10% of the total trials were the new visual discrimination task and 90% were standard sustained attention task trials. After training at the 10% level for nine sessions, the total number of visual discrimination trials was increased from two to eight per block of 20 trials (4 left and 4 right). The remaining 12 trials in each block of 20 trials were sustained attention task trials (6 non-signal trials and 6 signal trials, 2 trials at each signal duration). The spatial discrimination trials were thus increased from 10% of all trials to 40% of all trials. Animals trained in this condition until the number of spatial discrimination trials was increased to 14 per block of 20 trials (7 left-light illuminations and 7 right-light illuminations). The remaining 6 trials of each 20 trial training block were standard sustained attention task trials (3 non-signal trials and 3 signal trials, one at each signal duration). New visual discrimination trials accounted for 70% of all trials during this final training condition. Animals trained at the 70% visual discrimination level for a total of nine sessions.

Behavioral Measure and Statistical Analyses

The number of hits (H), misses (M), correct rejections (CR), false alarms (FA), omissions, and correct place discrimination trials were recorded for each
testing session. The relative number of hits at each signal duration, as well as for the overall session, and for the training block, was calculated as \[ \frac{H}{H+M} \], and the relative number of correct rejections per block and for the overall session was calculated as \[ \frac{CR}{CR+FA} \]. Relative hits could range from 0 (the correct rejection/miss lever was pressed every time a signal was presented) to 1 (the hit/false alarm lever was pressed following every signal). Relative correct rejections have a similar range, with the hit/false alarm lever being pressed following no signal presentation for values of 0. Omissions were analyzed separately from measures of response accuracy. Blocks of three training sessions were used as the unit of analysis once the new visual discrimination trials were introduced.

The relative number of hits was analyzed using a mixed-design analysis of variance (ANOVA) with the factors of signal duration, session, and distracter condition. The relative number of hits was analyzed using an analysis of variance (ANOVA) with factors of new signal accuracy and distracter condition. The relative number of correct rejections and omissions were analyzed using ANOVA with the factors of block and distracter condition. Data analyses were conducted with SPSS 17.0 for Windows (SPSS, Chicago, IL, USA). A level of \( \alpha=0.05 \) was used to determine statistical significance.

Results—Experiment 1

Data analyses for this study were divided into three main parts: the initial effects of the distracter, performance on the standard task after the introduction of the distracter, and performance on the new visual discrimination task. We
computed analyses of variance (ANOVA) in order to assess the possible effects that distraction had on attention and learning.

**Initial Distracter Effects**

A condition (distracter-exposed vs. non-exposed) x signal length (500ms, 100ms, 25ms) ANOVA was conducted to determine whether or not the introduction of a visual distracter affected relative hits in the standard attention task. The ANOVA yielded a marginally significant main effect of condition $F(1,13) = 4.400$, $p = .056$ and a marginally significant condition x signal length interaction, $F(2,26) = 3.04$, $p = .073$. At the 500ms signal duration, distracter animals performed significantly worse than standard task animals, $t(13)=3.56$, $p=.004$. A similar result was also found on trials when the 100ms signal was presented, $t(13)=3.086$, $p=.009$. Animals did not differ significantly for the 25ms signal duration or for correct rejections, $p>.05$. For the final three testing sessions with the distracter, the animals did not differ significantly on any measure of accuracy. The detrimental effects of initial exposure to the distracter did not.

**Standard Task Accuracy**

In order to evaluate performance, we next examined accuracy on the remaining sustained attention task trials after the introduction of the new visual discrimination task using ANOVA. Accuracy was examined during all three exposure levels of the place discrimination task, beginning at 10%.

A condition x signal duration ANOVA revealed that animals in the distracter condition did not differ significantly from animals in the standard
condition on any measure of accuracy at the 10% or 40% place discrimination task exposure level (p > .05) as can be seen in Figure 2. There was also no difference between distracter-exposed and -unexposed animals during the 70% place discrimination condition. However, visual examination of the data suggested that distracter-exposed animals were performing more accurately than distracter-unexposed rats on trials when the 500-ms signal was presented. This observation was supported by a significant main effect of distracter condition when only the data from the 500-ms trials were included in the analysis, F(1,13) = 9.244, p = .009, an effect that interacted with block of sessions, F(1,13) = 4.430, p = .022. A t-test revealed that during training block 7, distracter animal’s performance on the standard task was significantly better than animals in the standard task condition t(13) = -3.607, p = .003, (See Figure 3). A t-test also revealed that during training block 8, distracter animals performed significantly better than animals in the standard condition t(13) = -2.44, p = .03. By training block 9, animals in the standard condition were no different than animals in the distracter condition in terms of standard task accuracy.

New Discrimination Task Accuracy

Our final measure of performance examined accuracy on the place discrimination task during all exposure levels. In order to assess this for all three new discrimination exposure levels, we used ANOVA.

An ANOVA revealed that standard and distracter animals did not differ significantly in their performance on the visual place discrimination task at the 10% exposure level, F < 1 (see Figure 3). An ANOVA revealed that at the 40%
exposure level, there was a significant main effect of condition such that distracter animals performed significantly more accurate compared to standard task animals in the place discrimination task \( F(1,13) = 8.81, p = .011 \). When 70\% of the trials required place discrimination, the main effect of condition approached significance \( F(1,13) = 3.94, p = .069 \). The source of this trend was primarily due to higher accuracy of distracter-exposed animals during the first block of training \( (t(13) = -2.26, p = .042) \), see Figure 3.

Discussion – Experiment 1

The present experiment aimed to investigate the effects of prolonged exposure to distraction on attentional functioning and new visual task acquisition. In references to our hypotheses, one of two outcomes was expected. Distracting stimuli would continue to place a high attentional demand on the animals and would in turn affect new learning, or, the restoration of attentional performance following prolonged exposure to a distracter would enable animals to use new strategies and thus demonstrate improved learning as compared to non-distracted controls. The results of this experiment were in support of the latter hypothesis; animals exposed distraction exhibited a significant enhancement in learning the new visual discrimination task.

As was expected, animals displayed an initial decrease in signal detection after the introduction of the visual distracter. This finding is in-line with previous research findings that as attentional demands are increased, performance tends to suffer (McGaughy & Sarter, 1995). Our finding confirms that our visual distracter was sufficiently taxing that it initially resulted in attentional deficits.
These deficits were significant, however, all animals were statistically the same on all measures of task accuracy by the time the place discrimination task was introduced.

The introduction of the place discrimination task forced animals to learn new task rules while simultaneously retaining the rules of the standard attention task. Performance on the standard task decreased for all animals after the introduction of the place discrimination and continued to suffer as the new task increased from 10% to 40% of all session trials. All animals began to recover on new task performance by the time the new task was increased to 70% of all trials, however, distracter animals’ performance showed significant increases an entire 3-day block before standard task animals. Additionally, animals exposed to the distracter performed significantly better than standard task animals on the standard task for the first two of the final three training blocks.

In addition to performance on the standard task, assessment of animal’s accuracy on the place discrimination task revealed that distracter animals outperformed standard task animals at several stages of training. When the place discrimination task was initially introduced at 10% exposure, control and distracter animals both performed equally poorly on the task indicating that neither group had sufficiently learned the rules of the task. When place discrimination exposure was increased to 40%, both groups of animals displayed increases in accuracy, however, distracter animals outperformed standard task animals during all three training blocks. This trend continued for the first 3-day block of the 70% place discrimination exposure. For the final two training blocks
of the experiment, both groups of animals displayed a high level of accuracy in the new task, indicating that the rules had been learned and successfully incorporated into training. Collectively these findings suggest that distracter animals may have increased cognitive flexibility. Specifically, the ability to switch from one task to an entirely new one was not as difficult because animals had already been required to overcome the constant performance impairment of distraction. Another possibility is that distracter animals became better sensory filters. After being exposed to a distracter and learning to filter it out, filtering extraneous task rules may have been easier. This is compared to control animals who would only been exposed to the initial standard task prior to the introduction of the new task.

It is unknown exactly as to why distracted animals were more efficient learners than standard task animals, however, the answer may be related to neural activation. Past research has shown that sustained attention is associated with activation of Brodmann’s Area 9 (Cabeza & Nyberg, 2000) in humans as well as greater acetylcholine efflux in the frontoparietal cortex in rats (Himmelheber, Sarter, & Bruno, 2001). Research has also shown that sustained attention in humans and rats is a similar process (Bushnell, 1999). Also, attention-demanding tasks tend to elicit similar results in both humans and rats (Demeter, Sarter, Lustig, 2008). It is possible that increased activation of the attentional processing system as a result of repeated distraction enabled the rats to more readily activate the system when presented with additional attentional demands, the new task. The cholinergic system is potentially implicated in such a scenario. It has been
found that there is an increase in Ach efflux during recovery from visual distracter exposure (Himmelheber et al. 2000). In our experiment, the recovery from distraction would have taken place over the course of several training sessions; increased activation of the cholinergic system would then be associated with recovery from attentional impairments. Conversely, because standard task animals had not been required to place additional demands on attention, their processing was slower.

Foerde, Knowlton, and Poldrack (2006) offered an alternative explanation as to the beneficial effects of distraction. In their study, it was concluded that exposure to a distracter may have elicited a new type of knowledge in participants. Specifically, participants were required to perform a task while simultaneously attending to an entirely different task. It is possible that a bias was then formed for the processing of the task-relevant information. This proposed bias could then influence similar situations in the future. Such a bias would enable the flexible transition from task to task, assuming that the bias is relevant. In our study, exposure to the visual distracter may have elicited a bias towards standard-task relevant information, specifically the flashing of front-panel lights. Because the new task utilized the front-panel lights, distracter animals would have benefited from their pre-existing biases. If we had chosen to use a distracter paradigm entirely unlike our new task, i.e. odor or pain, we would still have expected animals to develop a learning bias, however, it would not have aided them in performing the new task.
The results of this experiment were intriguing in that they suggested a possible beneficial role of attentional impairments. Sensorimotor performance has been shown to vary based on rat strain (Biesiadecki, Brand, Koch, Metting, and Britton 1999) and thus we felt our results were not generalizable without successful replication using a different strain of rat. We selected the FBNF1 hybrid rat for replication because of past research supporting their strong attentional processing ability, especially as they age (Hebda-Bauer, Morrano, & Therrien 1999). Both Long-Evans and FBNF1 hybrid rats have been shown to perform well on tasks requiring sustained attention (Boschen et al. 2009; Burk et al. 2002).

Method—Experiment 2

Subjects

A total of 14 male FBNF1 Hybrid Rats weighing between 151g-175g at the beginning of the experiment were used (Charles River Laboratories, Inc., Wilmington, MA). The rats were individually housed with a 14:10-h light/dark cycle. All behavioral testing took place between the hours of 0900 and 1100, 5 days per week. Animals were water restricted for the duration of behavioral testing; only receiving water during the task and for 30 minutes after training. Rats were allowed a minimum of one hour of water on days when no behavioral testing occurred. Food was available ad libitum for the duration of experiment. All experimental protocols were approved by the Institutional Animal Care and Use Committee at the College of William and Mary. All animals were treated
according to the Guidelines for the Care and Use of Laboratory Animals as set forth by the National Institutes of Health (National Research Council 1996).

Apparatus and Behavioral Training

Animals were trained in the same apparatus used in Experiment 1. Behavioral training was identical to Experiment 1 with the exception that nine additional training sessions of 70% new task exposure were added.

Behavioral Measures and Statistical Analyses

Relative hits and correct rejects (CR) were calculated in the same manner as in Experiment 1. The relative number of hits was analyzed using a mixed-design analysis of variance (ANOVA) with the factors of signal duration, block, and distracter condition. The relative number of hits was analyzed using an analysis of variance (ANOVA) with factors of new signal accuracy and distracter condition. The relative number of correct rejections and omissions were analyzed using ANOVA with the factors of block and distracter condition. Data analyses were conducted with SPSS 17.0 for Windows (SPSS, Chicago, IL, USA). A level of α=0.05 was used to determine statistical significance.

Results – Experiment 2

Results for this experiment were analyzed in the same fashion as for the first experiment: initial distracter effects, standard task performance after the introduction of the new visual discrimination task, as well as new place discrimination task performance. We expected to replicate the results of our first experiment, thus supporting our second hypothesis that distracter-exposed animals
would outperform distracter-unexposed animals. Analyses of variance (ANOVA) were computed in order to assess the possible effects that distraction had on attention and learning.

*Initial Distracter Effects*

A condition (distracter-exposed vs. non-exposed) x signal duration (500ms, 100ms, 25ms) for hits did not yield any significant effects of condition (Figure 4). For correct rejections, there was a significant decrease in accuracy for distracter-exposed rats compared to those not exposed to the distracter, $t(12) = 4.081, p < .05$. There were no group differences after sufficient training with the distracter.

*Standard Task Accuracy*

ANOVA was used to assess possible differences in standard task performance after the introduction of the novel visual discrimination task. Animals did not differ significantly in their standard task accuracy at the 10%, 40%, and first three blocks of the 70% exposure levels as revealed by ANOVA (See Figure 5). Similarly to Experiment 1, during the final three blocks of testing sessions when 70% of the trials were place discrimination trials, there was a trend for distracter-exposed animals to exhibit higher levels of accuracy in the remaining sustained attention task trials compared to distracter-unexposed rats $F(1,12) = 3.212, p = .098$ (Figure 5).

*New Discrimination Task Accuracy*

ANOVA was once again conducted to assess differences in accuracy on the novel visual discrimination task at all exposure levels. Results of these
analyses found no significant differences between distracter and standard task animals at any of the exposure levels. Despite a lack of significance, results were all in the same direction as those of Experiment 1, with distracter animals and standard task animals performing similarly at lower exposure levels (See Figure 6) and distracter animals performing better as the percentage of place discrimination trials increased within the session (See Figure 6).

Discussion Experiment 2

The results of our second experiment offer supporting evidence for our hypothesis that animals exposed to a distracter and then required to learn a novel task would outperform animals trained only on a standard task. Thus, these results are also in-line with the results of our first experiment.

As predicted, animals in both experiments showed significant decreases in accuracy after the initial introduction of the distracter. This is in support of previous research findings that increased attentional demands disrupt performance (McGaughy & Sarter, 1995). Also similar to experiment 1, distracter animals from experiment 2 performed significantly better on the standard task during the final three blocks of new-task training. Unlike experiment 1, however, distracter animals did not perform significantly better than standard task animals on new-test accuracy. Despite the fact that results for this measure were non-significant, they were in the same direction as results for experiment 1. It is possible that the difference in significance between the two studies is due to strain differences between Long-Evans and FBNF1 hybrid rats. Research has shown that rat strain may have an effect on numerous things, attention included (Andrews, 1996). The
comparison of two different strain’s performance in one paradigm does not necessarily predict performance in any other behavioral paradigm (Andrews, 1996). It may be that one strain of rat simply underperformed in our specific training paradigm while another excelled. Additionally, there is further evidence that rat strain may have a significant effect on sensorimotor performance (Biesiadecki et al. 1999).

Although they are not entirely generalizable to a human model, the results of these two experiments suggest that a beneficial-distracter effect is a distinct possibility. Humans are bombarded daily with countless sensory distracters and not only must we filter them out but we must do so in a way that keeps us functioning normally. The human brain may filter out visual distracters beginning in the posterior parietal cortex (Friedman-Hill, Robertson, Desimone, & Underleider, 2003). Perhaps, as was postulated to have occurred in these two experiments, frequent activation of a visual distracter filtering system enables the brain to more readily filter new distracters. Prolonged exposure to a visual distracter had beneficial effects for both new task acquisition as well as standard task retention. Future research in this area should aim to replicate the beneficial distracter effects we found but should also aim to investigate a possible neural basis for the cognitive flexibility observed during the restoration of attentional performance.

While the results of these two experiments supported our second hypothesis, the lack of significance in experiment 2 prompted us to focus on the aspect of our results that were most consistent. In both experiments, the effects of
acute exposure to a distracter reached significance. Given this result, it seemed logical to next investigate a possible neural basis of the acute effects of a distracter. The effects of prolonged exposure to a distracter were less consistent for Experiments 1 and 2 and thus were not investigated in Experiment 3.

Experiment 3

Orexins are a pair of neuropeptides that can be classified as either orexin A or orexin B (also known as hypocretin 1 and 2). Orexin A is a 33 amino-acid peptide while Orexin B is a 28 amino-acid peptide; the cell bodies for orexinergic neurons are located in the lateral hypothalamus and contiguous perifornical area (Evans 1998, Sakurai et al., 1998). These orexinergic neurons project to numerous brain regions, including to the basal forebrain (Cutler et al. 1999; Peyron et al. 1998). Orexinergic synapses onto basal forebrain cholinergic neurons have been reported (Fadel, Pasumarthi, & Reznikov 2005). There are two receptors for orexins, the orexin-1 and orexin-2 receptors. The orexin-1 receptor is selective for orexin A whereas the orexin-2 receptor has a similar affinity for orexin A and orexin B (Sakurai et al., 1998). Recent study of the neuropeptide orexin A has suggested that it may play a key role in many important aspects of normal functioning, including feeding behavior, sleep and wakefulness, alcohol-seeking behaviour, as well as attentional processing (Sakurai et al. 1998; Lin et al. 1999; Ohno & Sakurai 2008; Selbach & Haas 2006; Lawrence, Cowen, Yang, Chen, & Oldfield 2006). Given what is known about orexinergic projections to the cholinergic system, it is surprising that attention remains the least studied of these areas.
It has been suggested that the fronto-parietal neural network responsible for some aspects of attention is mediated by cholinergic inputs originating in the basal forebrain (Sarter et al. 2005). Intrabasalis administration of orexin A has been found to dose dependently increase ACh within the prefrontal cortex as measured by in vivo microdialysis (Fadel, Pasumarthi, Reznikov 2005). Additionally, it has been suggested that orexin activation of the basal forebrain cholinergic system may be especially relevant when stimuli relate to homeostatic challenges (Fadel & Frederick-Duus 2008). This in turn means that orexinergic activation may play an important role in attention, especially in aspects of motivated behavior (Fadel et al. 2008).

The orexinergic system has also been investigated in terms of relevance to working memory. Akbari et al. (2006, 2007, 2008) found that administration of the orexin-1 receptor antagonist SB-334867 can disrupt aspects of working memory, specifically in the Morris water maze task. The orexin-1 receptor antagonist was found to impair acquisition, consolidation, and retrieval in the Morris water maze task but had no effect on the escape latency of a non-spatial visual discrimination task (Akbari et al. 2006, 2007). If a selective orexin-1 anatagonist can disrupt aspects of working memory, orexin A may be linked to normal memory functioning, specifically when the presented stimuli require spatial discrimination.

The present experiment was designed to investigate whether the administration of orexin A could have beneficial effects for attentional processing, including when a visual distracter was presented. Disruption of orexinergic
transmission has been shown to disrupt attentional performance. Boschen et al. (2009) found that administration of the orexin-1 receptor antagonist SB-334867 prior to training on a sustained visual discrimination task impairs attentional processing. Specifically, systemic administration of SB-334867 decreased signal detection at the longest signal duration in the standard two-choice attention task while intrabasalis administration decreased overall accuracy on trials with longer signal durations (Boschen et al. 2009). Given the negative effects observed after the administration of an orexin-1 antagonist, we expected administration of orexin A to have the reverse effects. We expected that the intraventricular infusion of orexin A would protect against impairments in accuracy that result from distraction. Intraventricular infusion was chosen as the appropriate means of administration because orexinergic projections are not localized to a specific brain region and brain-wide administration would have more clinical relevance compared with a specific-site administration. We utilized a visual distraction (houselight 1s on/1s off) but the training paradigm was structured differently as compared to Experiments 1 and 2. This was because the focus of Experiments 1 and 2 were the effects of prolonged exposure to distraction while Experiment 3 focused on acute exposure, which produced the most robust effects in Experiments 1 & 2. Within each session, trials were equally divided into a standard task block, followed by a distracter block, followed by another standard task block. The distracter trials require more attentional effort as compared to standard task trials and would thus benefit from the infusions of orexin A, to the extent orexins are involved in attentional effort.
Methods

Subjects

A total of 14 male FBNF1 Hybrid Rats weighing between 151g-175g at the beginning of the experiment were used (Charles River Laboratories, Inc., Wilmington, MA). FBNF1 rats were chosen because previous research that has demonstrated the neuroanatomical connections between orexins and basal forebrain cholinergic neurons employed this strain (Frederick-Duus, Guyton, Fadel, 2007). All behavioral testing took place between the hours of 0900 and 1100, 5-6 days per week. Animals were water restricted for the duration of behavioral testing, only receiving water during the task and for 30 minutes after training. Rats were allowed a minimum of one hour of water on days when no behavioral testing occurred. Food was available *ad libitum* for the duration of experiment. All experimental protocols were approved by the Institutional Animal Care and Use Committee at the College of William and Mary. All animals were treated according to the Guidelines for the Care and Use of Laboratory Animals as set forth by the National Institutes of Health (National Research Council 1996).

Apparatus

The apparatus used in this experiment were identical to those utilized in the first two experiments. However, unlike the first two experiments, only the center panel light was utilized in this experiment as compared to all three panel lights in Experiments 1 and 2.

Behavioral training prior to drug administration
Behavioral training prior to drug administration was identical to the initial training procedures discussed in experiments 1 and 2. Initially, both levers were extended into the chamber and rats were rewarded after pressing either lever. To counteract the possibility of a side-bias, five consecutive lever presses on one side resulted in the discontinuation of reward from that lever press until the other lever had been pressed. After rats reached a criterion of 120 reinforcers per session for three or more consecutive sessions, they moved on to the next phase of training. During this phase, animals were trained to distinguish a signal presentation from a non-signal trial. Levers were extended into the chamber after a 1s illumination of the central panel light or no illumination for non-signal trials. Animals were rewarded with water after pressing the left lever following a signal presentation (a hit) or the right lever following a non-signal (a correct rejection). A miss was recorded if a right lever press followed a signal presentation and a false alarm was recorded if a left lever press followed a non-signal. These rules were reversed for half of the animals. Three successive incorrect choices resulted in a forced choice trial in which only the correct lever was extended into the chamber for a duration of 90 s. If the consecutive errors occurred during a signal trial, the panel light remained illuminated during the forced signal trial. An omission was recorded for all trials if no response was made after 3 s. The intertrial interval (ITI) for this stage of training was 12 s. Criterion for the next stage of training was 70% accuracy on hits and 70% on correct rejections for three consecutive training sessions.
During the final stage of presurgical training, three different signal durations were utilized. The presentation of these signals was randomly varied. The central panel illuminations lasted 500ms, 100ms, or 25ms. The ITI was changed from 12 s to 9 ±3 seconds. The changes to the signal durations as well as to the ITI were intended to increase attentional demand on the animals (Parasuraman et al. 1987; Koelega et al. 1990). Animals received no correction or forced trials as in the previous stage. All animals trained on this task until the criterion of 70% accuracy on the 500ms signal duration and 70% accuracy on correct rejections was achieved.

Surgical procedures

After animals reached criterion in the aforementioned standard attention task, they received an intraventricular cannula implantation. The night before surgery, animals received 2.7mg/ml acetaminophen diluted in drinking water. Animals were sedated using intraperitoneal injections of 90.0 mg/kg ketamine and 9.0 mg/kg xylazine. After the surgical area was shaved with an electric razor, rats were placed in a stereotaxic device (Kopf Instruments, Tujunga, CA, USA) with the incisor bar set 3.3 mm below the interaural line. An incision was made along the midline from anterior to posterior (AP), exposing the skull. A hole were drilled over the target coordinates for guide cannula implantation (AP and medial–lateral (ML) from bregma, dorsal–ventral (DV) from dura; AP –0.8 mm, ML 1.6 mm, DV -2.5). The hemisphere that received the cannula implantation was counterbalanced for half of the animals. An eight millimeter guide cannula (22 gauge) was used with the internal cannula extending a full 1mm beyond the
end of the guide cannula. Three stainless steel screws were also inserted into the skull, spaced evenly around the guide cannula. The cannula was then secured to the skull and steel screws with dental cement. A dummy cannula was inserted in order to prevent clogging prior to training. After receiving surgery, rats received free food and water for the duration of a one-week recovery period. After this period, rats were once again water restricted and began training on the standard task until they reached criterion.

After reaching criterion post-surgery, rats were exposed to a new behavioral training procedure for two training sessions. Training procedures were identical to the standard task procedures, however, each session was divided into three blocks. The first and final blocks of each session were identical to the previously discussed training procedure, however, the middle training block differed. During the middle training block of these new sessions, animals were exposed to a visual distracter in the form of a flashing houselight. This distraction (1s on/ 1s off) matches the visual flashing houselight distraction utilized in Experiments 1 and 2 in both duration and intensity. Animals trained on this task for the remainder of the experiment.

Procedures for Orexin A infusions

All animals received two to three sham infusions prior to any actual drug administration. During these sham infusion sessions, a short internal cannula was inserted into the guide cannula but no drug was administered. Sham infusion sessions were used to acclimate rats to the infusion process. Each rat received four drug doses: vehicle solution, 10pM, 100pM, and 1000pM Orexin A infused
into the lateral ventricle in a randomized order. Orexin A was dissolved in sterile saline. The drug was infused through the internal cannula attached to a 1.0-μl Hamilton syringe via polyethylene tubing. A total volume of 0.5 μl was infused into each cannula at a rate of 1.0 μl/min. After the infusions were completed, the internal cannula remained in place for 60 seconds to allow drug diffusion. Rats were then immediately placed into the behavioral testing chambers and the task began 1 min after the rats were placed in the box. At least 2 days of behavioral training took place between each infusion to reestablish baseline task performance.

Histological procedures

Rats were anesthetized with 100.0 mg/kg ketamine and 10.0 mg/kg xylazine (ip). Rats were next transcardially perfused with 10% sucrose and then with 10% formalin at a pressure of 300 mmHg using a Perfusion One tool (myneurolab.com, St. Louis, MO, USA). The brains were then removed, and individually placed into formalin for not more than 48 h and then into a 30% sucrose solution in phosphate-buffered saline for a minimum of 3 days in order to cryoprotect the tissue. The tissue was then sectioned (50 μm) using a freezing microtome (Leica, Wetzlar, Germany). Brain sections were stained using cresyl violet. Sections were viewed using an Olympus BX-51 Research microscope to assess cannula placement.

Behavioral measures and statistical analyses

The number of hits (H), misses (M), correct rejections (CR), false alarms (FA), and omissions were recorded for each testing session following the
administration of the drug. As previously stated, each session was divided into 
three sections (standard-trials 1–54, distracter-trials 55–108, and standard-trials 
109–162) to assess the effect of the drug within each session. The relative number 
of hits per sections at each signal duration (25ms, 100ms, 500ms), as well as for 
the overall session, was calculated as \[ \frac{H}{H+M} \], and the relative number of CR 
per section and for the overall session was calculated as \[ \frac{CR}{CR+FA} \]. 
Relative hits can range from 0 (the correct rejection/miss lever was pressed every 
time a signal was presented) to 1 (the hit/false alarm lever was pressed following 
every signal). Relative correct rejections have a similar range, with the opposite 
lever being pressed following no signal presentation for values of 0 or 1. These 
are similar to the analyses described by Boschen et al. (2009).

The relative number of hits was analyzed using a mixed-design analysis of 
variance (ANOVA) with the factors of signal duration, dose, and trial section. 
The relative number of correct rejections and omissions were analyzed using 
ANOVA with the factors of dose and trial section. Data analyses were conducted 
with SPSS 17.0 for Windows (SPSS, Chicago, IL, USA). A level of \( \alpha = 0.05 \) was 
used to determine statistical significance

Results—Experiment 3

Two animals had to be dropped from data analysis due to incorrect 
cannula placement. The location of the guide cannula was determined to be 
appropriate for the remaining animals. We computed analyses of variance
(ANOVA) in order to assess the possible effects of orexin A administration on the accuracy of detecting signals and nonsignals.

For hits, a dose X trial section X signal duration ANOVA was conducted to assess the effects of orexin A dose on hit accuracy; it did not yield any effects of dose. Animals did not perform significantly differently in terms of hits at any signal duration during following the administration of any orexin A dose.

For correct rejections, a dose X trial section ANOVA yielded a significant main effect of dose, $F(3,33) = 3.556, p = .030$ that did not interact with trial section. T-tests were conducted between the vehicle and each of the orexin doses. At the lowest dose of orexin A, correct rejections were elevated as compared to vehicle, but remained nonsignificant $t(11) = 2.177, p = .052$. The middle dose of orexin A also elevated correct rejections to a non-significant level as compared to vehicle $t(11) = 1.976, p = .074$. The highest dose of orexin A elevated correct rejections to a significant level as compared to vehicle administration $t(11) = 2.964, p = .013$. The means and SEMs for the correct rejections at each dose can be seen in Figure 7.

Discussion

We hypothesized that the intraventricular administration of orexin A would result in higher accuracy during distracter training as compared to distracter training without an infusion of orexin A. Our expectation was that orexin A would only serve to partially negate negative effects of distraction.

We found that at the highest dose of orexin A (1000pM), animals responded significantly more accurately on correct rejections as compared to
vehicle administration. Animals displayed attentional enhancement following the administration of orexin A, but this enhancement was regardless of trial block. If orexin A had no enhancing effect, we would not have expected to see differences across dose. Orexin A enhanced attentional performance during distracter training and during standard task training. Previous research has found that intrabasalis administration of the orexin-1 antagonist SB-334867 decreased overall task performance while systemic administration of the antagonist decreased signal detection at a higher signal duration (Boschen et al. 2009). Our study was the first to examine the effects of orexin A administration in this task, rather than blocking the receptors. We believe that our enhancements were due to orexin A-mediated increased activation of the cholinergic system. Future studies could use microdialysis during attentional testing to measure cholinergic efflux following the administration of orexin A to test this mediation.

Animals in our experiment were able to better facilitate signal processing in the face of increased background noise. However, the cholinergic system is more than likely not the only neural system responsible for our results; orexins project to numerous brain regions and our drug administration was not localized. Attentional processing is hypothesized to involve a large number of brain regions, including the inferior parietal lobule, the occipital-temporal sulcus, and the cerebellum (Coull et al. 1998).

Collectively, the results of our final experiment suggest that there is a link between orexin A and attentional processing. Previous lines of research have investigated the relationships between orexins and the cholinergic system as well
as the relationships between attentional processing and the cholinergic system. Our experiment, however, represents a relatively new line of research investigating the effects of orexin A administration and possible attentional benefits.

The purpose of the experiment was to examine the effects of orexin A administration on attentional performance, however, it is possible that some methodological limitations affected our work. As stated previously, our drug administrations were not made directly into the basal forebrain, the brain region where orexergic projections from the hypothalamus connect to cholinergic inputs.

As this line of research is relatively new, future research in this area should aim to replicate these results. We observed no enhancements on other measures of task accuracy besides correct rejections, so investigating this phenomenon is crucial. How may orexin A have affected performance in such a way that enhancements occurred when the animals were attending to the lack of a visual stimuli? Our expectation was that we would see some enhancement in the accuracy of hits, but instead enhancements occurred only on correct rejections. The standard-distracter-standard paradigm may have biased the animals to attend more to the nonsignal trials because these were the trials that required the animals to filter the irrelevant signal (visual distracter). For nonsignal trials, interpreting the visual distracter as a signal would be an error. By contrast, on signal trials, the animal would be correct if it presses the hit lever regardless of whether or not it was responding to the distracter or central panel light. Thus, this paradigm may
have biased the animals to attend more to nonsignal trials. The present study utilized only three doses of orexin A as well as one vehicle dose. Because our effect was significant only at the highest dose, it would be beneficial for future research to investigate the effects of the drug using higher doses of the drug. It is possible that our observed effects would be visible at even higher doses than the 1000pM dose we administered. Studies in the future could aim to explicitly test the possible enhancing effects of orexin under standard conditions, without the effects of a distracter. This would test the possibility that orexin A has the potential to enhance attentional performance under conditions which are not as explicitly demanding as we once thought was necessary to see behavioral improvements.

Overall, the collective results of these three experiments suggest several key contributions to the literature. Importantly, the results speak to the power effects of distracters. Experiments 1 and 2 demonstrated that the implementation of a visual distracter can potentially enhance animals’ abilities to attend to a specific aspect of a sustained attention task. In experiment 3, visual distracters were initially introduced to disrupt attentional performance; the administration of orexin A provided non-selective attentional enhancement including during distracter sections. Had we decided to replicate Experiments 1 and 2 with the inclusion of orexin A infusions, it’s possible that the beneficial effects of distracters would no longer become significant. The drug infusion would enhance the animal’s abilities to filter out the distracter; however, the distracter would no longer be encouraging the use of new attentional strategies.
In addition to the positive and negative effects of distracters, the results of these experiments demonstrate how multifaceted the neural systems involved in attentional processing are. We utilized two separate, although similar, paradigms for taxing attentional processing. Both paradigms lead to results that were not entirely predictable. Despite our intentions, it was impossible to alter tasks so that the manipulations only affected one specific aspect of the attentional processing system.
Figure 1: Initial effects of exposure to the visual distracter on signal trial accuracy, divided by standard task and distracter Long-Evans rats. Distracter animals perform significantly less accurately than standard task animals after acute distracter exposure. Standard errors are represented in the figure by the error bars attached to each column.
Figure 2: Accuracy on the standard task after the introduction of the new task at all exposure levels divided by standard task and distracter Long-Evans rats. Distracter and standard task animals did not differ significantly during the 10% and 40% new-task exposure levels. Distracter animals performed significantly better than standard animals on the standard task during blocks 7 and 8 of the 70% new-task exposure level. Standard errors are represented in the figure by the error bars attached to each column.
Figure 3: Animals did not differ significantly from each other at the 10% place discrimination exposure level. At the 40% new-task exposure level, distracter animals performed significantly better than standard task animals. Animals performance did not differ at the 70% exposure level. Standard errors are represented in the figure by the error bars attached to each column.
Figure 4: Initial effects of exposure to the visual distracter on signal trial accuracy, divided by standard task and distracter FBNF1 hybrid rats. Distracter animals’ performance was no different than standard task animals’ performance after acute distracter exposure. Standard errors are represented in the figure by the error bars attached to each column.
Figure 7: Accuracy on the standard task after the introduction of the new task at all exposure levels divided by standard task and distracter Long-Evans rats. Standard and distracter animals did not differ significantly during the 10%, 40%, and first 70% exposure levels. However, distracter animals were performing significantly better than standard task animals by the twelfth and final training block. Standard errors are represented in the figure by the error bars attached to each column.
Figure 6: Animals did not differ significantly from each other at the 10% place discrimination exposure level. Additionally, animals did not differ in accuracy at the 40% new task exposure level or during the first three blocks of the 70% exposure level. Performance differences during the final three blocks of training at 70% new-task exposure remained insignificant, however, results were in the same direction as Experiment 1. Standard errors are represented in the figure by the error bars attached to each column.
Figure 12: Percentage of correct rejections divided by dose of orexin A. Animals showed elevations in correct rejections at all doses of orexin A with significant enhancement only at the 1000pM dose. Standard errors are represented in the figure by the error bars attached to each column.
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