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Effects of intralaminar thalamic nuclei, prefrontal cortical, and hippocampal lesions on a seven-choice serial reaction time task

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EFFECTS OF INTRALAMINAR THALAMIC NUCLEI, PREFRONTAL CORTICAL, AND HIPPOCAMPAL LESIONS ON A SEVEN CHOICE SERIAL REACTION TIME TASK

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I dedicate this work to my parents, Tom and Anna Burk. I am grateful for such wonderful role models in my life. This would not be possible without their unending love and support.

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ABSTRACT

EFFECTS OF INTRALAMINAR THALAMIC NUCLEI, PREFRONTAL CORTICAL, AND HIPPOCAMPAL LESIONS ON A SEVEN CHOICE SERIAL REACTION TIME TASK

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Slow response speed has been associated with several neuropsychological disorders including Korsakoff's disease. The ability to respond to brief stimuli can be tested to assess whether slow response speed is due to slow stimulus processing. A seven choice serial reaction time task was developed to test the ability to respond to brief stimuli. Distractibility and stimulus discriminability were manipulated to challenge performance and cues were presented to enhance performance. In Experiment 1, six unlesioned rats were tested on this task. As expected, significant deficits were found when (1) stimulus duration was decreased, (2) a bright distractor light was briefly presented, (3) a bright overhead light was illuminated throughout the trial, and (4) when side cues were not given. Reaction time remained fairly consistent across all conditions although there was a significant increase when the bright overhead light was presented in the discrimination condition. These results are consistent with a previously used five choice serial reaction time task, and provide evidence that the current task may be useful for testing the ability to respond to brief stimuli.

In Experiment 2, presurgically trained rats were given lesions of the intralaminar nuclei (ILn), prefrontal cortex (PFC), or hippocampus (HP) or sham-control surgery, and then tested on the seven choice serial reaction time task. Generally, the results across all

behavioral conditions showed a significant decrease in accuracy for the PFC group at brief stimulus durations compared to all other groups. It does not appear these results are due to disruption of motivation, debilitation following surgery, or an inability to perform the requirements of the task as all groups performed well when stimuli were presented for a long duration. Both PFC and ILn groups showed significantly slower reaction time across all behavioral conditions. The HP group was not significantly different from controls. The accuracy deficit for the PFC group is thought to reflect the disruption of scanning and/or speed of processing sensory information. The slow reaction time for PFC and ILn groups may indicate motor dysfunction due to disruption of cortico-basal ganglia-thalamo-cortical connections that are innervated in striatum by the ILn.

INTRODUCTION

Neuropsychology of Response Speed

Several neurological disorders have been associated with slow response speed. Slow response speed is generally thought to reflect slow preparation and execution of motor movements and/or slow processing of stimulus information. In practice, it is difficult to selectively measure speed of stimulus processing or of motor functioning. Whether to attribute changes in response speed to deficits in stimulus processing, motor function, or both is not always clear. One approach to studying these deficits is to manipulate the stimulus processing demands while keeping the motor requirements consistent.

Response speed deficits can indicate slow motor preparation and execution, a condition known as bradykinesia. Bradykinesia is one of the most prominent symptoms in Parkinson's disease, a disorder thought to be caused by degeneration of the nigrostriatal pathway resulting in depletion of dopamine. Parkinson's disease is characterized by rigidity, resting tremor, difficulty maintaining posture, and bradykinesia (Stacy & Jankovic, 1992). Simple reaction time tasks have been used to measure slow movement in Parkinson's disease. Patients with Parkinson's disease have repeatedly been shown to respond slower during simple reaction time tasks (Lakke, 1990). This suggests that Parkinson's patients respond slowly even when the cognitive demands of a task are minimized.

Slow response speed can also result from slow stimulus processing. The psychological impact of slow stimulus processing can be illustrated by studying pathological conditions, such as schizophrenia, that have been associated with slow stimulus processing. Patients with schizophrenia require a longer presentation time to detect a briefly presented stimulus (Saccuzzo & Braff, 1981; Sacuzzo, Hirt, & Spencer, 1974). If stimulus processing was slow, it would be expected that detection would require a longer stimulus duration. These studies provide evidence that speed of early visual processing is disrupted in schizophrenia. Further evidence for early visual processing deficits in schizophrenia has been found using visual backward masking. In this paradigm, a letter or digit, the test stimulus, is briefly presented on a screen. This presentation is followed by a homogeneous visual stimulus (e.g., bright light or checkerboard pattern) known as the masking stimulus. Immediate presentation of the masking stimulus disrupts the ability to identify the test stimulus (i.e., the homogeneous visual stimulus can serve to 'mask' the test stimulus). The important variable is the time between the presentation of the test stimulus and the masking stimulus, known as the critical interstimulus interval. Shorter critical interstimulus intervals decrease the ability to identify the letter or the digit. One theory is that the mask interrupts processing of the test stimulus (Kahneman, 1968). With a short critical interstimulus interval, there is less time to process the test stimulus and performance declines. One of the most robust findings in patients with schizophrenia is that they require a longer critical interstimulus interval to overcome the masking effects of the homogeneous stimulus (Braff & Sacuzzo, 1981; Lieh-Mak & Lee, 1997; Saccuzzo & Braff, 1981; Sacuzzo, et al, 1974). These results suggest that patients with schizophrenia require a longer time to process visual stimuli (before the mask is presented) and thus are slow to process visual information.

It is impressive that the slow stimulus processing deficits have been achieved with different patient populations given the diverse nature of the symptoms in schizophrenia. Some researchers have speculated that the disruption of the speed of early visual processing may be critical in producing the host of psychopathological symptoms associated with schizophrenia (Braff & Sacuzzo, 1981; Saccuzzo & Braff, 1981; Sacuzzo, et al, 1974). These authors have provided mechanisms by which speed of stimulus processing may produce the symptoms in schizophrenia. They argue that one of the critical factors that produces the symptoms in schizophrenia is a distorted view of the environment. Events occurring rapidly may go undetected due to slow processing and lead to a misrepresentation of one's surroundings. Furthermore, if information is slowly processed, it may be that stimuli cannot be fully analyzed before additional stimuli from the environment are received. This deficit may disrupt the ability to form a clear and consistent perception of the environment (Braff & Sacuzzo, 1981; Sacuzzo, et al, 1974). It appears to be possible that slow stimulus processing is a critical factor leading to the symptoms of schizophrenia. Further research studying prepulse inhibition in patients with schizophrenia has provided evidence for impaired sensorimotor gating. Prepulse inhibition is a reduction in the startle response when a prepulse stimulus is presented. Patients with schizophrenia fail to show a reduction in the startle response following a prepulse stimulus (Swerdlow, Braff, Taaid, Geyer, 1994). The animal literature has provided evidence consistent with the human findings as the deficits in prepulse inhibition have also been observed when the dopamine agonist apomorphine was administered and when dopamine was infused into the nucleus accumbens (Swerdlow, et al, 1994). Both of these effects were reversed by antipsychotics (Swerdlow, et al, 1994). The impairments with prepulse inhibition have been attributed to a disruption of sensorimotor gating. Thus, in addition to slow stimulus processing, it has been hypothesized that impaired sensorimotor gating may contribute to the symptoms in schizophrenia.

The speed of stimulus processing can have implications for other psychological processes. For instance, learning and memory may be affected by slow stimulus processing. Information processing models have been used to describe how slow stimulus processing can affect learning and memory (Yates, 1966). These models of learning and memory speculate that environmental stimuli are briefly held (< 1 sec.) in 'iconic storage' (for a discussion regarding the time course of iconic decay, see Loftus, Duncan, & Gehrig, 1992). Selective attention mechanisms then focus on important stimuli which can be held for a longer time in working memory. This information must then be transferred to long-term memory to be remembered at a later time (Neisser, 1967). Slow stimulus processing limits the amount of information from the iconic store that can reach working memory and thus may ultimately disrupt the ability to store information in long-term memory. Slow stimulus processing may also affect the integrity of the information that enters working memory. Slowly processed information that does enter working memory may only be partially analyzed and thus lead to a degraded representation of the information (Yates, 1966). These implications highlight the need to explore the relationship between mnemonic disorders and speed of stimulus processing.

Slow stimulus processing has also been associated with Korsakoff's disease, a disorder resulting in severe memory impairment (see below). One of the goals of the current experiments is to test whether damage to some of the areas thought to be critical in Korsakoff's disease produces signs of slow stimulus processing. One approach to studying speed of stimulus processing is to test the ability to respond accurately to brief stimuli. Utilization of brief stimuli requires optimal scanning and perception. By comparing responding at several brief stimulus durations it is possible to test the limits of the speed of stimulus processing. In addition, response speed to brief stimuli can be measured when subjects are challenged by decreasing the discriminability of the stimulus or presenting a distractor. Manipulations of discriminability or distractibility place greater challenges on the speed of stimulus processing. Finally, the ability to use cues to enhance speed of stimulus processing can be tested. These conditions provide a careful assessment of the ability to respond to brief stimuli that is critical for distinguishing the effects of lesions.

A task using several behavioral manipulations to test speed of stimulus processing must be carefully controlled to rule out alternative explanations for the results. In order to attribute any observed deficits to stimulus processing, it is important that the contingencies remain consistent across all behavioral manipulations. Otherwise, an impairment in response speed may simply reflect differences in the difficulty of the tasks. It is also critical to keep any motor requirements consistent across the conditions. With consistent motor demands, changes in the dependent variables, reaction time and accuracy, can be attributed to manipulations of stimulus processing.

Neuropathology of the Wernicke-Korsakoff syndrome

The Wernicke-Korsakoff syndrome can be divided into the initial and more acute Wernicke stage and the chronic Korsakoff stage (commonly labeled Korsakoff's disease, Korsakoff's psychosis, or Korsakoff's syndrome). The Wernicke stage consists of a number of prominent symptoms including ataxia, nystagmus, polyneuropathy, confusion, and confabulation. With immediate thiamine treatment most of the symptoms from this phase recede within weeks and the manifestation of amnesia associated with the chronic Korsakoff phase remains as the principle characteristic. It may be that memory deficits are present during the Wernicke phase but the severe confusional state renders any memory assessment questionable (Victor, Adams & Collins, 1989). There is considerable debate about the neural structures that produce the symptoms in Korsakoff's disease. Regions that have previously been implicated include several diencephalic nuclei, prefrontal cortex (PFC) and pathways associated with the medial temporal lobe.

Diencephalon. Cases of mechanical brain damage, tumor, or Korsakoff's disease provide evidence that damage to medial thalamus can produce signs of amnesia. Case N.A., a patient who presented with a brain wound from a miniature fencing foil, displayed severe verbal memory impairments and mild deficits for remembering nonverbal information (Teuber, Milner, & Vaughan, 1968). Magnetic resonance imaging revealed unilateral pathology to several structures in medial thalamus including the mediodorsal nuclei, intralaminar nuclei (ILn), and internal medullary lamina in the left hemisphere (Squire, Amarel, Zola-Morgan, Kritchevsky, & Press, 1989). Squire et al (1989) also reported being unable to visualize the mammillary nuclei bilaterally suggesting that damage to this area might be important for N. A.'s deficits in remembering. Case N. A. provides evidence that lesions of medial thalamus can affect remembering, although it is difficult to attribute N.A.'s memory deficits to any particular region. Amnesia has also been reported following a tumor in medial thalamus that spared the mammillary bodies

(McEntee, Biber, Perl, & Benson, 1976). This case study does not rule out the possibility that damage to the mammillary bodies can result in memory loss. It does suggest however, that lesions involving medial thalamus can produce amnesia without concomitant damage to the mammillary bodies.

In their monograph, Victor and colleagues (1989) performed histological analyses of the brain tissue from 82 Korsakoff patients. They found that the two most commonly damaged structures were the medial mammillary bodies (affected in 47 out of 47 cases studied) and the thalamic mediodorsal nuclei (affected in 38 out of 43 cases studied). Furthermore, they reported that the five patients in which the mediodorsal nuclei were spared did not demonstrate long-term memory deficits after recession of their initial confusional state. The medial mammillary bodies were affected in all five of these cases. Based on these results, the authors concluded that damage to the mediodorsal nuclei, not the mammillary bodies, was critical for the mnemonic deficits of Korsakoff's disease (Victor et al, 1989).

The critical role of the mediodorsal nuclei has by no means been universally accepted. In a study of 70 Korsakoff patients, damage to periventricular hypothalamic and thalamic areas was found in all cases (Malamud & Skillicorn, 1956). However, the mediodorsal nuclei was only affected in 52% of the cases. The pathology in many cases apparently involved tissue near the third ventricle but did not extend laterally into the mediodorsal nuclei. Such a description is consistent with a careful psychological and histological examination of two Korsakoff patients (Mair, Warrington, Weiskrantz, 1979). The longitudinal psychological profile revealed that these two patients suffered chronic, severe amnesia and that one patient showed signs of dementia prior to death. Their histological results revealed damage to the mammillary bodies and a thin band of gliosis involving the paratenial nuclei, a region located medial to the mediodorsal nuclei and adjacent to the subependymal groups. Taken together, these results implicate the nonspecific nuclei along the midline rather than the mediodorsal nuclei as the region in medial thalamus that may be critically affected in Korsakoff's disease.

There have been additional cases of thalamic infarct that implicate the nonspecific thalamic nuclei, specifically the internal medullary lamina, in amnesia. Some of the initial evidence came from several thalamic infarct cases involving the polar and paramedian arteries (von Cramon, Hebel & Schuri, 1985). They reported that patients with damage involving the internal medullary lamina and mammillothalamic tract were amnestic. The authors also reported two patients with substantial pathology affecting the mediodorsal nuclei that did not show amnestic symptoms. The results from these patients suggest that damage circumscribed to the mediodorsal nuclei does not produce severe amnesia. Another case has been reported in which the patient showed deficits in verbal memory tests following thalamic infarction (Calabrese, Haupts, Markowitsch, & Gehlen, 1993). Magnetic resonance imaging revealed a relatively discrete lesion affecting the internal medullary lamina and posterior portions of the mediodorsal nuclei. The mammillothalamic tract was unaffected in this patient. Although not conclusive, these infarct cases provide evidence that damage involving the internal medullary lamina may be critically involved in thalamic amnesia.

The internal medullary lamina are a band of myelinated fibers that connect different thalamic nuclei. Rostrally, the internal medullary lamina enclose the nonspecific intralaminar thalamic nuclei (ILn). The ILn were affected in the cases of internal medullary lamina infarcts (von Cramon et al, 1985; Calabrese, et al, 1993). The ILn have not received a great deal of emphasis from studies with human Korsakoff patients, but there is some evidence from a human infarct case that these nuclei may play a role in amnesia. A 44-year old woman with a left thalamic infarct, mainly affecting the centromedian and parafascicular nuclei, showed deficits in the Peterson-Peterson task (Mennemeier, Fennell, Valenstein & Heilman, 1992). The patient was impaired at longer retention intervals in the Peterson-Peterson paradigm with distractors but was able to retain verbal and non-verbal information for up to 48 hours as well as controls in tasks without distractors. The researchers concluded that ". . . the intralaminar nuclei are not memory structures per se. Rather they appear part of a functional system important in regulating attention for simultaneous activities, possibly through maintaining cortical tone. Lesions in this area may give rise to memory disturbances through changing levels of distractability (p. 1057-8)." Although the deficits in this case study are less severe than in Korsakoff's disease or other reports of thalamic infarcts, it is not obvious whether these differences are due to the limited extent of the infarct in this patient or the unilateral nature of the damage. It appears from thalamic infarct cases that there is some evidence to suspect that damage to the ILn may be important in producing amnesia associated with pathology in medial thalamus.

Prefrontal Cortex. There has been some focus on the importance of the prefrontal cortex (PFC) in causing some symptoms in Korsakoff's disease. There is anatomical evidence indicating that PFC damage may be responsible for some of the cognitive deficits in Korsakoff's syndrome. First, PFC receives substantial projections from the mediodorsal nuclei, a brain area consistently observed to be damaged in Korsakoff patients (Goldman-

Rakic & Porrino, 1985; Groenewegen, 1988). The normal function of the PFC could be disrupted by the loss of input from mediodorsal nuclei or through damage resulting from transneuronal degeneration. Second, analyses of fluid volumes suggest damage to PFC in Korsakoff's disease. Quantitative analyses of computer tomography scans from seven Korsakoff patients revealed high fluid volumes in frontal sulcal and peri-Sylvian areas and lower estimated density in thalamus (Shimamura, Jernigan & Squire, 1988). The high fluid volumes in cortical areas suggest that the size of the nearby tissue is smaller and may be damaged in some respect. The involvement of PFC based on changes in fluid levels should be treated with some caution because histological analyses often fail to find cortical pathology in Korsakoff patients. Victor et al (1989) reported that the cerebral cortex displayed clear pathology in 29 out of 51 Korsakoff patients (56.9%). Malamud and Skillicorn (1956) only reported cortical pathology in 15 out of 70 patients with the damage in nine being classified as "Alzheimer glial change" and in six as "central neuritis." Taken together, these studies indicate that the involvement of direct PFC damage in Korsakoff's disease is controversial. Third, PFC seems to be particularly susceptible to damage following chronic alcohol use (Fadda & Rossetti, 1998). It is possible that neuronal damage from long term use of alcohol commonly associated with Korsakoff's disease may contribute to the reported cognitive impairments.

There is behavioral evidence that is consistent with the anatomical research suggesting that PFC damage may be involved in Korsakoff's disease. Computer tomography measures showing increased fluid volumes in frontal sulcal and peri-Sylvian areas and lower estimated density in thalamus correlated with behavioral tests of cognition and memory (Shimamura, et al, 1988). The investigators concluded that damage to both the PFC and diencephalon may be responsible for the cognitive deficits in Korsakoff's disease. Further behavioral evidence comes from observations that some of the deficits associated with Korsakoff's disease are similar to those observed in frontal lobe damaged patients. It has been argued that PFC patients (Fuster, 1989) and Korsakoff patients (Squire, 1982) are impaired in making judgments of temporal order. Squire (1982) read Korsakoff patients two lists of sentences and later asked whether a particular sentence was in the first or second list. Korsakoff patients were poorer than other amnesics at reporting the correct list. Both PFC damaged (Milner, 1964) and Korsakoff patients (Janowsky, Shimamura, Kritchevsky, & Squire, 1989) achieve fewer categories than controls in the Wisconsin Card Sorting task. Although there are alternative explanations, the deficits in the Wisconsin Card Sorting task are generally thought to reflect an increased tendency to perseverate (Milner, 1964). The similarities between the deficits in judgments of temporal order and the Wisconsin Card Sorting task found with PFC damage and Korsakoff's disease suggest that PFC damage may be involved in some of the deficits associated with Korsakoff's disease.

It is clear that PFC damage cannot entirely explain the all of the symptoms in Korsakoff's disease. Importantly, PFC damaged patients are not amnesic. In his book, Fuster (1989) described the spared mnemonic capacities of PFC damaged patients. "Clearly, the frontal patient is capable of acquiring, retaining, and retrieving new information. He or she is also capable of retrieving old information." (p. 136, Fuster, 1989). These observations have been confirmed by performance of these patients on standard psychological tests. On the revised version of the Wechsler Memory Scale and the Memory Subscale of the Dementia Rating Scale, frontal patients exhibited near normal performance while Korsakoff and non-Korsakoff amnesics were significantly impaired (Shimamura, Janowsky, & Squire, 1991). These results provide evidence that PFC damage does not produce a pattern of performance on standardized memory tests that would be consistent with amnesia.

Another behavioral distinction between Korsakoff patients and frontal lobe patients is observed when studying release from proactive interference. In the release from proactive interference paradigm, subjects are given several lists of words and after each list are asked to recall as many words as possible from the previous list. For the first few lists, all of the words are chosen from the same category which results in a decreased ability to remember as more lists with similar items are presented. After several such lists, a group of words from a different category is presented. With controls, the typical result is an improvement in remembering words from the new list that is thought to be due to a 'release' from intrusion of prior items. In several studies, Korsakoff patients do not show the typical release from proactive interference (Cermak, Butters & Moreines, 1974; Janowsky, et al, 1989; Winocur, Kinsbourne & Moscovitch, 1981). Frontal lobe damaged patients show normal release from proactive interference (Janowsky, et al, 1989). These findings suggest that the inability to show normal release from proactive interference in Korsakoff's disease is not due to PFC damage.

Taken together, there is evidence for some similar behavioral deficits (impairment in judgments of temporal order and the Wisconsin Card Sorting task) following damage to PFC and Korsakoff's disease. However, there are some deficits apparent in Korsakoff's disease (amnesia and failure to release from proactive interference) that are not present in frontal lobe patients. Understanding the contribution of PFC damage to Korsakoff's disease will allow a clearer assessment of the deficits due to diencephalic damage and those due to involvement of structures outside of the diencephalon.

Hippocampus. It has been argued that damage involving the hippocampus (HP) and related pathways is critical in producing the memory deficits associated with diencephalic amnesia (Graff-Radford, Tranel, van Hoesen, & Brandt, 1990). There is little evidence that direct pathology affects the HP in Korsakoff's disease. Victor et al (1989) found that only 8 of 22 cases of Korsakoff's disease showed HP involvement. In a study of 70 patients, the HP was only affected in 10 patients and the authors noted that in several of these cases the patients also presented with senile brain disease (Malamud & Skillicorn, 1956). Another group of researchers confirmed these results upon histological analysis but performed morphometric analyses that revealed decreased nucleolar volume of the pyramidal cells in the CA 1 field of HP in two Korsakoff patients (Mayes, Meudell, Mann, Pickering, 1988). Korsakoff's disease may result in some neuronal distortion of HP. Any functional consequences of the distortion of CA 1 pyramidal cells have not been determined.

Researchers have attempted to implicate the HP in diencephalic amnesia by arguing that damage to HP-related pathways or nuclei is critical in producing the observed amnestic symptoms (Graff-Radford, et al, 1990). The HP sends substantial projections to the mammillary bodies via the fornix (Bayer, 1985). The combined findings from Victor et al (1989) and Malamud & Skillicorn (1956) indicated that 114 out of 117 patients examined showed signs of gliosis in the mammillary bodies. These results suggest that pathology affecting the mammillary bodies may be crucial in producing amnesia. However, other reports have described patients with mammillary body pathology that does not result in chronic amnesia (see five cases from Victor, et al, 1989 described above). These reports along with the lesion research using animals (see below) draw into question the importance of mammillary body pathology in Korsakoff's disease. Taken together, there is little convincing evidence that damage to HP and HP-related pathways can account for the deficits in Korsakoff's disease.

Animal Research: Effects of Lesions on Tests of Remembering

Diencephalon. A number of candidate regions are affected in Korsakoff's disease. In particular, lesions of the mammillary bodies and the medial thalamus have been commonly studied with respect to learning and memory. Lesion studies enable a comparison of the effects of relatively discrete damage of brain areas thought to be important in Korsakoff's disease. Following lesions, animals can be tested on tasks thought to be sensitive to amnesia, such as delayed matching-to-sample (DMS) or delayed nonmatching-to-sample (DNMS). These delay tasks require that a sample (e.g., a particular location, lever, or object) be remembered during a retention interval on each trial in order to make an appropriate choice (usually between the sample and another alternative).

The importance of damage to the mammillary bodies in amnesia has been disputed by several researchers and has not been borne out by animal studies. A recent review suggested that complete damage of the mammillary region can disrupt the ability to remember locations in challenging tasks (Sziklas & Petrides, 1998). However, this is a selective deficit that is unlikely to account for the amnesia observed in Korsakoff's disease. Radiofrequency mammillary body lesions failed to produce significant deficits in DMS or DNMS trained with position cues (Harper, McLean, & Dalrymple-Alford, 1994; Mair &

Lacourse, 1992). Neurotoxic mammillary body lesions in rats receiving presurgical training on a DNMS task failed to reveal any significant deficits (Aggleton, Keith & Sahgal, 1991). In this study Aggleton, et al (1991) did report deficits on the DNMS task following fornix and anterior thalamic lesions suggesting that the task they used was sensitive to lesions of HP-related pathways. There are several explanations for the limited effects of mammillary body lesions. It is possible that fornical projections directly to the anterior thalamus are sufficient to mediate HP-related functions involving the diencephalon. Furthermore, the cortical projections from the HP through the entorhinal cortex are totally unaffected by mammillary body lesions (Bayer, 1985). Given the alternative pathways, it is not surprising that mammillary body lesions have minimal effects on tests of learning and memory, even on measures sensitive to HP function. Taken together, these studies indicate that damage to the mammillary bodies is likely to have a minor role in amnesia.

As described above, there is evidence from Korsakoff's disease (Victor, et al, 1989), thalamic infarct (Mair, et al, 1979, von Cramon, et al, 1985), tumor (McEntee, et al, 1976), and trauma (Squire et al, 1989) implicating lesions of medial thalamus in amnesia. The effects of mediodorsal nuclei lesions have been extensively studied in both nonhuman primates and rodents to assess whether damage to this region can account for the amnestic symptoms associated with pathology in medial thalamus. The primate research seems to provide some mixed results regarding the importance of the mediodorsal nuclei in remembering. Early studies tended to find minimal or no effects on tests of remembering following mediodorsal nuclei lesions (e.g., Chow, 1954). However, a more recent study with lesions primarily restricted to the posterior mediodorsal nuclei in cynomolgous monkeys found deficits in a trial unique DNMS task but normal performance on two pattern discrimination procedures (Zola-Morgan & Squire, 1985). The results from Zola-Morgan and Squire (1985) suggest that limited mediodorsal nuclei lesions can affect a task thought to be sensitive to amnesia. Findings from other lesion studies dispute whether circumscribed mediodorsal nuclei lesions disrupt tasks that require information to be updated on a trial-by-trial basis. This point is illustrated in a study by Isseroff, Rosvold, Galkin, & Goldman-Rakic (1982) in which they clearly showed that minimal or moderate damage to posterior mediodorsal nuclei in monkeys produced no significant deficits on delayed alternation or delayed response tasks. Extensive lesions, (73.8 ± 9.7 % of the nucleus damaged) on the other hand, produced significant delayed alternation and delayed response deficits. If more substantial mediodorsal nuclei lesions are necessary for producing behavioral deficits, it seems reasonable to conclude that these larger lesions are less likely to remain circumscribed within the mediodorsal nuclei and more likely to involve surrounding structures such as the midline nuclei and the ILn. It may be that previous studies that have found amnesic-like impairments following extensive mediodorsal nuclei lesions have involved damage to adjacent structures.

The rodent literature regarding the effects of mediodorsal nuclei lesions is decidedly mixed. Even using the same behavioral task (8 arm standard procedure in the radial arm maze) some studies have found deficits following mediodorsal nuclei lesions (Stokes & Best, 1988) while others have not (Kolb, Pittman, Sutherland & Whishaw, 1982). Given the lack of deficits in automated DNMS (Neave, Sahgal & Aggleton, 1993), DMS with position cues (Burk & Mair, 1998), and olfactory continuous DNMS (Zhang, Burk, Glode, & Mair, 1998) it would seem to be difficult to conclude that lesions circumscribed to the mediodorsal nuclei produce substantial mnemonic impairments. Taking the literature as a whole, there is not convincing evidence that damage circumscribed to mediodorsal nuclei produces amnesia (Markowitsch, 1982).

Damage involving the lateral internal medullary lamina provides an alternative explanation for the amnestic effects associated with medial thalamic lesions. Rodent research has provided evidence consistent with the position that lesions of the lateral internal medullary lamina have detrimental effects on tests of remembering. In a rat model of Korsakoff's disease, it was shown that DNMS deficits were substantial when there was damage involving the internal medullary lamina while animals with sparing of this area (with sufficient postsurgical retraining) performed comparable to controls (Knoth & Mair, 1991). The importance of the internal medullary lamina was confirmed when radiofrequency lesions aimed at the lateral internal medullary produced deficits on DNMS with position cues (Mair & Lacourse, 1992). To assess the generality of the deficit on remembering, lateral internal medullary lesions have been tested on several other measures of working memory. It has been shown that radiofrequency lesions of the lateral internal medullary lamina produce deficits in olfactory continuous DNMS (Koger & Mair, 1994) and a radial arm maze task with imposed delays (Harrison & Mair, 1996). The effects of lateral internal medullary lamina lesions are not confined to tests of remembering as deficits have been reported in auditory discrimination (Stevens & Mair, 1998). Taken together, these results confirm that lesions of the lateral internal medullary lamina can affect a number of measures of remembering. In addition, there is some evidence that the deficits associated with lateral internal medullary lamina lesions extend beyond mnemonic processes.

The lateral internal medullary lamina lesion damaged two major regions: the mediodorsal nuclei and the ILn. It has been suggested that the ILn may be the critically damaged region in L-IML lesions (Mair, 1994). A comparison of excitotoxic lesions of the ILn and mediodorsal nuclei indicated that ILn lesions decreased accuracy and speed of responding in DMS with position cues while lesions of the mediodorsal nuclei had no significant effect (Burk & Mair, 1998). The ILn lesioned animals consumed water at a comparable rate as controls and performed a FR 1 schedule at a similar rate to controls. These spared abilities suggest that the DMS deficits associated with ILn lesions were not due to disruption of motivation or of simple motor abilities. The effects of ILn lesions have been assessed on several other measures of remembering to test the generality of the ILn deficit on remembering and to study whether ILn lesions produce comparable deficits as those previously observed with lesions of the lateral internal medullary lamina. Lesions of the ILn produce deficits in an olfactory continuous DNMS task while sparing olfactory discrimination (Zhang et al, 1998), in a series of DNMS tasks trained in the radial arm maze, and in learning to swim to the location of a submerged platform (Mair, Burk, & Porter, 1998). Thus, the ILn lesion seems to produce impairments on a number of tasks thought to be sensitive to amnesia.

Even with localized injections of excitotoxic substances, it is difficult (in fact, it may be impossible) to produce complete ILn lesions without causing some damage to adjacent nuclei. Two approaches have been taken to test the importance of the ILn in remembering and address the issue of damage to nearby areas. First, smaller volumes of excitotoxin have been injected to limit the spread to other nuclei. Even with smaller volumes, ILn lesions continue to disrupt accuracy in DMS with position cues (Burk &

Mair, 1999a) and in olfactory DNMS (Burk, Ley, Koch, Toupin, Coy, & Mair, 1998). Second, lesions of specific regions within the striatum, an area receiving substantial projections from the ILn (Berendse & Groenewegen, 1990), have been tested on DMS with position cues. Lesions of the ventral striatum affecting the olfactory tubercle and ventral pallidum produced a significant decrease in accuracy and slower responding in DMS with position cues compared with all other treatment groups. Lesions of medial striatum and nucleus accumbens produced an intermediate deficit. Medial striatal and nucleus accumbens groups were significantly less accurate than controls but more accurate than animals receiving lesions of the olfactory tubercle. Reaction time was not significantly affected by lesions of medial striatum or nucleus accumbens. Lesions of the lateral striatum had no significant effect on this task (Burk & Mair, 1999b). This study suggests that specific lesions of the striatum can disrupt a task previously shown to be sensitive to ILn lesions. In particular, lesions of ventral striatum produced both the decreased accuracy and slower responding previously observed following ILn lesions. Taken together, these studies provide support for the position that ILn lesions can affect remembering.

Prefrontal Cortex. Lesions of PFC do affect selective tests of remembering. Many versions of delay tasks have been shown to be sensitive to the effects of PFC lesions. It has been known for over 60 years that PFC damage in monkeys produces deficits in delayed response and in delayed alternation tasks (Oscar-Berman, McNamara, Freedman, 1991). The delayed response task generally involves an apparatus with two choice locations that can be removed from the animal's view by lowering a screen. A trial begins with baiting one of the wells in view of the monkey followed by covering both wells with identical stimuli. The screen is lowered for a delay and is raised for the choice phase of a trial. The animal can retrieve the food by removing the stimulus over the previously baited well. The monkey is required to remember the spatial location of the well baited prior to the delay to respond accurately. In delayed alternation, either the left or right well is baited and after the delay the rewarded response is to the opposite well. For example, if the left well is baited prior to the delay (during which the screen is lowered and then raised) the animal must respond to the right port to receive reinforcement.

It is possible that the deficits on delay tasks following PFC lesions are due to neuronal dysfunction in connected cortical and/or subcortical sites. To address this possibility animals can be given a "temporary" lesion that can be reversed. Such techniques are often less likely to produce degeneration in brain areas connected with the lesion site. Furthermore, the effects of any degeneration can be tested when animals perform during sessions without the lesion technique. Fuster and colleagues have shown that reversible lesions produced by cooling the prefrontal cortex result in deficits on delay tasks when compared with sessions without this treatment (Bauer & Fuster, 1976; Fuster & Alexander, 1970). The effects of PFC damage on delay tasks do not appear to be due to degeneration of related brain areas.

One position is that the deficits on tests of remembering result (at least to some extent) from other cognitive deficits (Fuster, 1989). PFC damage has been associated with impairments in temporal organization of information, increased susceptibility to interference, a lack of inhibition, increased distractibility, and a tendency to perseverate (Fuster, 1989). Malmo (1942) found that delayed response performance was near normal for PFC lesioned monkeys if lights were turned off during the retention interval but accuracy decreased dramatically when a light was introduced for five seconds during the retention interval. The light presented during the retention interval was interpreted as a distracting stimulus that produced decreased accuracy. The deficit on the memory task was only apparent in the presence of a distracting stimulus.

More recent work has supported the idea that specific mnemonic deficits occur following PFC damage. Funahashi, Bruce, & Goldman-Rakic (1993) tested monkeys on a memory-guided eye movement task in which an object was presented on a screen to monkeys. After a retention interval (with the object removed from the screen), the monkeys were reinforced for moving their eyes to the location of an object presented prior to a delay. They found a delay dependent deficit in the contralesional hemisphere following unilateral lesions of the dorsolateral prefrontal cortex. A delay dependent deficit indicates that the PFC lesioned animals performed comparable to controls when the retention interval was brief but a deficit was present during trials with long retention intervals. The deficit extended to both hemispheres when lesions were bilateral. These results can be taken of evidence not only for a mnemonic deficit, but also that these memory-guided eye movements are lateralized.

PFC lesions in rats also produce impairments on many delay tasks. Specifically, DMS (Mair et al, 1998) and DNMS (Burk, Porter, & Mair, 1999) trained with position cues, spatial DMS trained in a six arm plus maze (Kesner, Hunt, Williams, & Long, 1996), spatial DNMS and DMS with two arms (Granon, Vidal, Thinus-Blanc, Changeux, & Poucet, 1994), and spatial DNMS trained in a radial arm maze using the same two arms as choice arms are sensitive to the effects of PFC lesions (Porter & Mair, 1997). In general, there is good correspondence between studies using monkeys and rats concerning the effects of PFC lesions on delay tasks. These similar findings with monkeys and rats lend credibility to the use of rodents to study the effects of PFC lesions.

Some studies have not found deficits on delay tasks following PFC lesions. Porter & Mair (1997) failed to find DNMS deficits following PFC lesions when all eight arms could be used as choice alternatives. The use of the same two arms as choice alternatives may have increased proactive interference. This task may have differentially affected rats with PFC lesions that have been associated with increased susceptibility to proactive interference (Fuster, 1989). Some "object" versions of DMS and DNMS have failed to find deficits following PFC lesions (Kesner, et al, 1996; Shaw & Aggleton, 1993). Furthermore, lesions of PFC do not impair olfactory continuous DNMS (Koger & Mair, 1994). These negative results suggest there is some specificity in the memory deficits associated with PFC lesions. The exact nature of the remembering deficits associated with PFC damage remains unclear. The specificity of the deficits does correspond with observations in human frontal lobe patients in suggesting that PFC damage does not produce global amnesia.

Hippocampus. Several studies have assessed the effects of large lesions that involve both HP and surrounding areas on object DNMS in monkeys (for reviews, see Squire, 1992 and Squire & Zola-Morgan, 1991). It was found that lesions involving the HP and the amygdala in monkeys produced deficits in visual and tactual DNMS with objects but spared the ability to learn a pattern discrimination (Mishkin, 1978; Murray & Mishkin, 1984). The spared performance is important because it demonstrates that the lesioned monkeys were not debilitated but rather showed a deficit on tasks that required updating information on a trial-by-trial basis. Lesions involving the HP and other surrounding structures (subiculum, entorhinal cortex, and parahippocampal cortex) in monkeys also disrupt object DNMS (Zola-Morgan, Squire, & Amarel, 1989). These results suggest that pathology affecting HP and adjacent structures produces deficits on tests of remembering.

The effects of circumscribed HP lesions are more debatable. Some studies have shown that selective HP lesions spare object DNMS in rats (Aggleton, Blindt, & Rawlins, 1989) and in monkeys (Mishkin, 1978). However, with no training prior to testing, HP lesioned monkeys have been shown to be impaired on object DNMS. Specifically, these animals required more trials to reach criterion at the shortest retention interval and when delays were then introduced, performed significantly worse than controls at longer retention intervals (Zola-Morgan & Squire, 1986). Under specific training conditions, circumscribed HP lesions produce impairments in object DNMS.

Animal models of ischemic damage have been used to test the effects of selective HP damage. Forebrain ischemic episodes initiated by carotid artery ligatures for 10-30 minutes produced significant pyramidal cell loss in the CA 1 subfield within HP and in the hilus of the dentate gyrus (Volpe, Hasker, Towle, & Dunlap, 1992; Wood, Mumby, Pinel, & Phillips, 1993). This procedure produces deficits in tactile discrimination learning, delayed spatial discrimination, and object DNMS (Volpe et al, 1992; Wood et al, 1993). Furthermore, it has been found that the cell loss in the CA 1 field correlates with performance in delayed spatial discrimination (Volpe et al, 1992) and object DNMS (Wood et al, 1993). It is difficult to reconcile the deficits found with selective HP damage following ischemic episodes with other studies that have failed to find deficits following complete HP lesions (Aggleton, et al, 1989; Mishkin, 1978). It is possible that undetected pathology lying outside of HP plays a role in producing the deficits associated with ischemia treatment.

The nature of the mnemonic impairment following HP lesions remains under dispute. Damage involving HP has been theorized to disrupt working memory (Olton, Becker, & Handelmann, 1979), configural associations (Sutherland & Rudy, 1989), encoding relationships between stimuli (Eichenbaum, Fagan, Mathews, & Cohen, 1988), or contextual retrieval of information (Hirsh, 1974). Another possibility is that HP damage disrupts the ability to use spatial information (Jarrard, 1993, 1995). Some of the initial research suggesting a role for HP in processing spatial information came from recordings of neural activity from HP cells while a rat was on a testing platform (O'Keefe & Dostrovsky, 1971). They found HP cells that preferentially responded when the rat was in a specific location while facing a particular direction on the platform. It was concluded that cells with these properties could be important for developing a spatial map of the environment.

Lesion studies have provided evidence that HP damage disproportionately affects tasks involving spatial information. Jarrard (1993) described the effects of HP lesions on a cue and a place task. Both tasks were trained in a radial arm maze with four arms (out of eight) being baited. In the cue condition, rats were reinforced each session for entering arms with the same inserts (e.g., sandpaper, cloth). In the place condition, rats were reinforced for entering the same arms each session. In the place condition, the rats had to remember the spatial location of the reinforced arms. It was found HP lesions did not affect performance on the cue task while a significant impairment was found in the place task (Jarrard, 1993). HP lesions impaired performance when the rats were required to remember the spatial location of the arms. These results have been interpreted as providing evidence that HP is critically involved in processing spatial information.

In our own work studying the effects of complete radiofrequency lesions of HP, we have found delay dependent deficits in DNMS trained in a radial arm maze (Mair, et al, 1998). That is, the HP lesion group was not significantly different from controls at brief retention intervals but a significant deficit was present at longer retention intervals. We have tested the effects of HP lesions in an olfactory continuous DNMS task with only one response location and thus no requirement involving spatial information. HP lesioned rats performed comparable to controls in the olfactory continuous DNMS task and actually performed significantly better than controls when learning a simple olfactory discrimination (Mair, et al, 1998). We have also studied the effects of HP lesions on DMS and DNMS with position cues trained in an operant lever box. HP lesions decreased DNMS accuracy but did not significantly affect DMS performance. Response speed was not affected in either study (Mair, et al, 1998; Porter, et al, 1999). These experiments indicate that HP lesions do not produce robust deficits on a number of tests of remembering. Rather, our results suggest that tasks that primarily require responding based upon spatial information are sensitive to the effects of HP lesions. However, even in radial arm maze DNMS tasks, performance is spared at the shortest retention interval. Thus, HP lesions do not appear to affect the ability to use spatial information over a relatively short retention interval. The different results found with DMS and DNMS using position cues with HP lesions were surprising. It seems unlikely that the different results were due to processing spatial information as both experiments were conducted in operant lever boxes. It is possible that the DNMS task required unique functions (which have yet to be clearly identified) that cannot be mediated by structures outside of HP.

The hypothesis that HP damage selectively or even disproportionately affects the ability to use spatial information has been challenged (Squire & Cave, 1991). Some results have simply disputed the roles of HP and entorhinal cortex in processing spatial information for different "memory systems" (Hunt, Kesner, & Evans, 1994). Others have made more substantial challenges by showing that HP lesions impair the ability to perform an object DMS task (Rawlins, Lyford, Seferiades, Deacon, & Cassaday, 1993). However, in the study by Rawlins et al (1993) the animals were not presurgically trained and were given aspiration lesions. Both of these factors have been shown to be critical in studying the effects of HP lesions in other tasks using nonspatial information (Jarrard, 1991, 1995).

Taken together, the evidence concerning the effects of HP lesions on tests of remembering yields a complex picture. HP lesions do not produce robust deficits on a number of tests of remembering. The exact nature of the effects of HP damage remains difficult to understand. Much of the research suggests that HP damage primarily affects the ability to utilize spatial information. Results with other tasks (e.g., DNMS with position cues) suggest that functions which have yet to be elucidated are also affected by HP lesions.

<u>Response Speed Deficits Following Brain Damage</u>

<u>Wernicke-Korsakoff syndrome.</u> Korsakoff patients have deficits that cannot be solely ascribed to impairments in mnemonic functioning. It is now clear from a number of studies that Korsakoff patients show slower response speed. This slow response speed

has been characterized by increased reaction time, decreased accuracy to briefly occurring events, and more time required to perceive or make judgments about stimuli.

Talland (1965) conducted a number of studies demonstrating slow response speed in Korsakoff patients. Using a tachistoscope, he presented several pen drawings of familiar objects on a single card for several stimulus durations. If response speed is slow, it would be expected that Korsakoff patients would recognize fewer figures than controls. Indeed, the findings showed that control subjects could identify more figures than Korsakoff patients at each stimulus duration. This result is consistent with the idea that Korsakoff patients slowly process stimuli. In another study, Talland (1965) tested the amount of time needed to identify nine words. He found that Korsakoff patients required 14.4 seconds while controls needed 7.1 seconds to recognize all of the words. If Korsakoff patients are slow responding, this result would be expected because it should take longer to identify environmental stimuli.

Talland (1965) tested Korsakoff patients on a simple reaction time task with either a visual (green light) or an auditory (bell) stimulus. On average, Korsakoff patients were about 50 milliseconds slower than controls, but the difference did not reach statistical significance. In choice reaction time tasks using visual or auditory stimuli, Korsakoff patients showed significantly higher reaction times than controls (Talland, 1965). These results indicate that slow responding in Korsakoff's disease can be observed (at least in choice reaction time tasks) even with relatively simple stimuli. It is unlikely that the more substantial slowing in the choice reaction time task was entirely due to motoric dysfunction as the subjects made identical responses in the simple and choice reaction time tasks. It is more likely that the choice reaction time task placed additional demands on the ability to respond to stimuli that exacerbated the reaction time difference between Korsakoff patients and controls. These additional demands may have placed a greater premium on speed of stimulus processing causing any difference in processing speed between Korsakoff patients and controls to become apparent.

Further research has continued to support the position that Korsakoff patients require more time to process visual information. Oscar-Berman, Goodglass, & Cherlow (1973) conducted two experiments to study the nature of visual processing in Korsakoff's disease. They found that Korsakoff patients had a higher threshold for detecting a word or a pattern than alcoholic controls. That is, Korsakoff patients needed the stimulus presented longer to be able to make an appropriate identification. If a subject processes a stimulus slowly, it would be expected that a relatively long presentation time would be needed to identify the stimulus.

In the second experiment, Korsakoff patients were tested on a backward visual masking procedure to further test the nature of the visual processing deficit (Oscar-Berman, et al, 1973). They presented target stimuli (words or patterns) for 10 msec. longer than the threshold for each subject and presented a checkerboard pattern afterward to mask the stimulus. Using the method of ascending limits, the critical interstimulus interval (i.e., time between presentation of the target stimulus and the mask) that was necessary to avoid the masking effect was determined. The interstimulus interval is thought to reflect the amount of time needed to process the target stimulus before the mask is presented. The results showed that Korsakoff patients required a longer critical interstimulus interval than alcoholic controls suggesting that early visual processing is disrupted in Korsakoff patients (Oscar-Berman, et al, 1973). These findings suggest that

Korsakoff patients require a longer uninterrupted time to process the target stimulus. The longer time required to process the target stimulus is consistent with the idea that Korsakoff patients are slow processing information.

Patients with Korsakoff's disease have been tested on a task in which they are asked to judge the sequence of two tones (high-low or low-high). If there is a very short interval between a low and a high tone it is more difficult to judge the sequence. If Korsakoff patients are processing slower, it would be expected that they would need more time to process each auditory stimulus. Thus, Korsakoff patients should have more difficulty than controls when the interstimulus interval is short. Korsakoff patients were impaired judging the two tones with short interstimulus intervals (10-300 milliseconds) but were comparable to controls when there was a three second delay between the tones (Meudell, Mayes, MacDonald, Pickering & Fairbairn, 1991). These results parallel those from Oscar-Berman et al (1973) and together suggest that Korsakoff patients require more time to analyze visual and auditory stimuli.

Another test that has been used to assess speed of processing in Korsakoff patients is dichotic listening. Presumably, if Korsakoff patients process slower, they may be able to respond when information is presented to one ear. However, they may have difficulty when multiple stimuli are presented because they cannot process the increase in information. A couple of studies have found that Korsakoff patients are impaired in dichotic listening tasks when they must attend to multiple stimuli presented to both ears but are able to respond comparable to controls when they must attend to a single stimulus presented to either ear or when they must only attend to information in one ear (Glosser, Butters & Samuels, 1976; Parkinson, 1979). These experiments suggest that any response speed deficits do not disrupt the ability of Korsakoff patients to perform normally on some relatively simple tasks. However, deficits that may be due to slower stimulus processing are apparent with tasks that require quicker analysis of stimulus information.

The ability to respond to briefly presented stimuli can also affect performance by Korsakoff patients in tests of remembering. Oscar-Berman and colleagues have tested the effects of varying the sample duration in several delayed conditional discrimination tasks. The investigators found that Korsakoff patients perform worse when the sample duration was decreased in DMS (Oscar-Berman & Bonner, 1985), DNMS (Oscar-Berman & Bonner, 1989), and delayed response (Oscar-Berman, Hutner, & Bonner, 1992). With DMS and delayed response, they found that Korsakoff patients showed a more substantial decrease in accuracy than controls when the sample duration was decreased. Because the retention interval was held consistent, this deficit is likely not due to impairments in mnemonic functioning. The effects of sample duration likely reflect an impairment in the speed of stimulus processing, as the deficit became prominent when the sample stimulus was briefly presented. Together, these studies suggest (1) that speed of stimulus processing may be disrupted in Korsakoff's disease and (2) that the speed deficit can affect performance on tests of mnemonic functioning.

The limited research on response speed with animal models of Korsakoff's disease has provided some evidence consistent with the deficits observed in the human research. An animal model of Korsakoff's disease, pyrithiamine-induced thiamine deficiency, has been shown to disrupt performance of a five choice serial reaction time task (Langlais, Anderson, Germeys, 1997). Specifically, Langlais et al (1997) reported that accuracy decreased as the signal duration was decreased and when distractors were presented. This result suggests that the ability to respond to briefly presented visual stimuli is disrupted in animals models of Korsakoff's disease.

Changes in response speed in tests of remembering have been studied in animal models of Korsakoff's disease. Pyrithiamine-induced thiamine deficiency produces decreases in response accuracy and speed in DNMS with position cues (Knoth & Mair, 1991). The slower DNMS reaction times is consistent with an impairment in speed of responding to environmental stimuli. However, it is clear that many factors (e.g., motor functioning, motivation) could affect DNMS reaction time making it difficult to attribute the findings to any specific deficit.

These studies provide considerable evidence that Korsakoff patients respond slower to environmental stimuli. While there is a sizeable human literature on the speed of stimulus processing in Korsakoff's disease the animal literature is relatively undeveloped. The current study will assess the effects of lesions aimed at the ILn, PFC, and HP on a task that requires responding to brief visual stimuli with minimal mnemonic demands. This comparison will allow for a better understanding of the critically damaged neuroanatomical structures that produce the slow responding in Korsakoff's disease.

Intralaminar nuclei. On anatomical grounds, it seems reasonable to predict that the ILn are involved in psychological processes beyond memory (Purpura & Schiff, 1997). The ILn receive efferent projections from the brainstem reticular activating system, cerebellum, superior colliculus, and substantia nigra (Jones, 1985). These connections have been suggested to mediate changes in saccadic eye movements, arousal, and attention (Purpura & Schiff, 1997). The ILn also receive GABAergic projections from the reticular thalamic nucleus (Jones, 1985; Kolmac & Mitrofanis, 1997), a structure that has been hypothesized to influence attentional processes (Crick, 1984; Guillery, Feig & Lozsadi, 1998). Taken together, the ILn receive projections from a number of areas thought to be involved in several cognitive processes. It is possible that ILn lesions disrupt this input and impair cognitive functions that in turn disrupt performance on tests of remembering.

The primary afferents from the ILn project to striatum and diffusely to several cortical areas (primarily to layers I and VI), particularly in frontal cortex (Berendse & Groenewegen, 1991). The two major projection sites of the ILn, striatum and cortex, are connected via a series of topographical cortico-basal ganglia-thalamo-cortical pathways (Alexander, DeLong, & Strick, 1986). Specifically, cortical areas innervate distinct areas of the striatum that then project to discrete areas within thalamus. The thalamic areas project back to the same cortical area (that projected to striatum). The ILn are situated to modulate activity in cortex directly or through cortico-basal ganglia-thalamo-cortical connections via the projections to striatum (Berendse & Groenewegen, 1990, 1991). ILn damage may affect several aspects of cognitive and motor functioning by disrupting the normal activity of the connections between cortex and basal ganglia.

It has recently been demonstrated that there is increased regional cerebral blood flow to the reticular nuclei and the ILn in intact human subjects during attention-demanding reaction time tasks (Kinomura, Larsson, Gulyas & Roland, 1996). Kinomura et al (1996) found that compared with a resting condition, there was increased reticular nuclei and ILn activation during a visual (press a key with the thumb after a light becomes brighter) and a somatosensory (press a key following an indentation on the right index finger) reaction time task. There was not increased activation of these nuclei during a control procedure in which subjects were asked to press the key without any time pressure while looking at a light visual field. This study provides evidence that the ILn and reticular nuclei may be important for processing abrupt changes in stimuli in multiple sensory modalities. However, the exact role of these thalamic nuclei and how they may affect speed of stimulus processing in these tasks remains unclear.

Lesion studies with rats have provided some evidence that damage involving the ILn can affect response speed during tests of remembering. Slow responding has been reported in DMS with position cues following excitotoxic lesions of the ILn (Burk & Mair, 1998). These response speed deficits could be due to a number of factors including impairments of mnemonic functioning, motor functioning, or speed of processing. A careful analysis of the slow DMS response speed found that ILn lesioned rats tended to be slow throughout the trial although the slowing was particularly prominent at early stages of each trial (Burk & Mair, 1999a). ILn lesioned rats tended to be slowest when completing the sample requirement or making a lever press at the end of the retention interval. If the slowing was due to an inability to remember the sample stimulus, the increase in reaction time would be expected during the choice phase of a trial. The pattern of slowing is opposite of the expected results if the impairment in response speed was due to a deficit in remembering. Thus, the slow responding does not appear to reflect a specific deficit in the ability to remember the sample stimulus. The precise nature of the slow responding is unclear but could represent a deficit in speed of stimulus processing or of motor functioning.

The current studies were designed to address the limited interpretations from our previous work by studying the effects of ILn lesions on responding to briefly presented stimuli. There were manipulations of distraction and discrimination to challenge the ability to respond to briefly presented stimuli. In addition, the ability to take advantage of cues following ILn lesions was tested. The motor response on each trial (i.e., nose poke) was the same and relatively simple. This study allowed a comparison of the effects of ILn lesions on response speed with varying demands on stimulus processing while holding the motor requirement consistent. Based on the report by Langlais et al (1997) following pyrithiamine induced thiamine deficiency, it was expected that performance following ILn lesions would decrease as the signal duration was decreased and when distractors were presented.

Prefrontal Cortex. It has been recognized that damage involving the frontal lobes affects speed of perception (Luria, 1966). A number of other cognitive deficits have been associated with PFC damage including deficits in temporal organization of information and response selection, increased susceptibility to interference and distractibility, a lack of inhibition, and a tendency to perseverate (Fuster, 1989). The slowing of stimulus perception following PFC damage has not been thoroughly studied, presumably due to the number of cognitive deficits associated with lesions of this area of the brain. Furthermore, it is difficult to attribute any particular result to one of these explanations.

Regardless of the challenges, it is clearly important to develop an understanding of how PFC damage affects speed of processing. As discussed above, patients with schizophrenia have been shown to have impairments in speed of stimulus processing (Braff & Sacuzzo, 1981; Saccuzzo & Braff, 1981; Sacuzzo, et al, 1974). Schizophrenia has long been associated with PFC dysfunction (Gur, 1995). It is important to understand the relationship between PFC damage and slow stimulus processing as well as any implications for psychological disorders such as schizophrenia.

Much of the research concerning response speed and PFC damage in humans has involved reaction time paradigms. For instance, it was shown that patients with left or right frontal lobe damage were slower than controls and unilateral temporal lobe damaged patients in a choice reaction time task (Alivisatos & Milner, 1989). Furthermore, unilateral frontal lobe patients were less able to take advantage of cueing information. It is difficult to assess the nature of the reaction time deficit as it could be due to slow stimulus processing or impairments in motor function. The inability to take advantage of cueing information suggests a stimulus processing deficit as the response in the neutral and cue conditions are the same. This study provides evidence of deficits in stimulus processing based on an inability to use cueing information.

Reaction times for frontal lobe damaged patients have been compared when the same stimulus (light or tone) is presented throughout a session with when the subjects must respond to one of two stimuli (light and tone; Godefroy, Lhullier, & Rousseaux, 1996; Godefroy & Rousseaux, 1996). In the first condition, they found that frontal lobe patients were slower than controls when required to respond to only one stimulus throughout a session. The results from this condition do not lead to a clear conclusion regarding the nature of the deficit. The slow reaction times could reflect a deficit in speed of stimulus processing or motor responding. In the second condition, frontal lobe patients showed a disproportionate increase in reaction time compared to controls when required to respond when one of two stimuli was presented. The disproportionate increase in reaction time for the PFC group during the second condition would suggest a deficit in information processing as the motor requirement remained consistent.

The reaction time results do not yield a clear indication whether speed of stimulus processing or motor functioning is primarily affected by PFC damage. The anatomical connections implicate PFC in both stimulus processing and motor functioning. As described above, PFC sends projections to basal ganglia and receives input back from the basal ganglia via thalamic nuclei (Alexander, et al 1986). The basal ganglia have long been associated with motor function, primarily based on diseases affecting motor function (e.g., Parkinson's disease) that are associated with degeneration of pathways in the basal ganglia (Stern, 1990). It would not be surprising if PFC lesions disrupted the connections with the basal ganglia and thereby disrupted speed of motor function. The anatomical evidence also indicates that PFC should be involved in stimulus processing. PFC receives projections from visual, auditory, and somatosensory cortical areas in the rat (Kolb & Tees, 1990). The frontal eye fields within PFC have been associated with exploratory scanning (Mesulam, 1981), a process necessary for responding to brief stimuli. In the rat, the medial agranular cortex within PFC is thought to be the homologue of the frontal eye fields in primates (Neafsey, Bold, Haas, Hurley-Gius, Quirk, Sievert, & Terreberry, 1986). Furthermore, the medial agranular cortex has reciprocal connections with visual cortex and projects to the superior colliculus (Neafsey, et al, 1986). The medial agranular cortex appears to be in a critical position for processing visual information. A recent study using monkeys demonstrated that in a backward visual masking procedure, the highest rate of firing of frontal eye field neurons occurred on trials when the target stimulus was presented and an accurate response (gaze shift) was made. Furthermore, an increase in firing was also observed when a target was presented even if the target was undetected (Thompson & Schall, 1999). This study suggests that changes in neural activity can be observed beyond visual cortical areas in a behavioral task involving processing of brief stimuli. PFC appears to be in a position to integrate sensory information and may be important for processing sensory stimuli. Taken as a whole, the anatomical evidence suggests that both motor and stimulus processing may be affected by PFC damage.

Research using lesions in animals provides evidence that PFC damage affects the ability to respond to brief stimuli. Muir, Everitt, & Robbins (1996) tested the effects of several cortical lesions, including medial PFC, on a five choice serial reaction time task. They found that medial PFC lesions resulted in decreased accuracy and in slower responding on this task. When the stimulus duration was decreased for one session or white noise was introduced as a distractor, medial PFC lesioned rats showed a disproportionate increase in response latency compared to controls and a trend for a more substantial decrease in accuracy (Muir, et al, 1996). These findings suggest that PFC damage can disrupt the ability to respond to brief stimuli indicating an impairment in the speed of processing visual stimuli.

The response speed deficits associated with PFC lesions have also been reported in tests of remembering. PFC lesioned rats have slower median reaction times and decreased accuracy in DMS and DNMS procedures using position cues (Mair, et al, 1998; Porter, et al, 1999). Evidence from monkeys suggests that these deficits are not due to retrograde damage as similar decreases in accuracy and reaction time during delay tasks have been found following cooling of the PFC (Bauer & Fuster, 1976). Thus, slower responding is a prevalent feature of PFC damage that can be observed in several experimental conditions.

It is difficult to attribute the slow responding in these delay tasks to any particular deficit (e.g., stimulus processing, motor functioning). The current experiments will attempt to characterize the response speed deficits by comparing the effects of PFC lesions on responding to briefly presented stimuli while keeping the motor requirement consistent.

As mentioned in previous sections, PFC damage has been thought to be responsible for many of the deficits associated with Korsakoff's disease (Janowsky et al, 1989). The deficits associated with PFC do not entirely explain the mnemonic deficits in Korsakoff's disease (i.e., lack of amnesia following PFC damage). Decreased response speed has been associated with PFC damage and Korsakoff disease. It is unclear what role, if any, PFC damage has in producing the slow responding associated with Korsakoff's disease. Thus, it is important to compare the relative contributions of circumscribed lesions of the areas thought to be critically damaged (i.e., PFC and ILn) on a task that measures response speed. The current experiments assessed changes in response speed to briefly presented stimuli following PFC lesions. Given the reported response speed deficits with PFC damage, it was expected that PFC lesions would disrupt performance in this task. Based on the results in the five choice serial reaction task with medial PFC lesions in rats (Muir et al, 1996) it is expected that performance would decline as the duration of the visual stimulus decreases and when distractors were presented.

Hippocampus. There are several reasons to expect that HP damage does not affect the speed of stimulus processing. It has been shown that HP lesioned patients perform comparable to controls on tasks thought to assess short term memory. HP lesioned patients have shown normal performance in: digit span, judging the number of dots flashed on a computer screen, remembering the location of a dot for a brief duration, estimating whether two lines were at the same angle as lines that had previously been presented, and judging whether a pattern when mentally rotated matched another pattern on a computer screen (Cave & Squire, 1992). Normal performance on these tasks suggests that early stimulus processing is not affected by HP damage.

Research with animals has indicated that lesions of HP do not substantially affect response speed. In a sustained attention paradigm trained in an operant chamber, HP lesions have been shown to have no significant effect (Miner, Ostrander, & Sarter, 1997). Knife cuts of the perforant pathway in rats do not disrupt performance on a five choice serial reaction time procedure (Kirkby & Higgins, 1998). The perforant pathway provides substantial efferents to HP (Bayer, 1985). These studies suggest that speed of stimulus processing as measured by the ability to respond to brief stimuli is unaffected by damage affecting HP functions.

Reaction time is unaffected in tests of remembering that are sensitive to HP lesions. HP lesions decreased accuracy in DNMS with position cues, but there was not any significant effect on reaction time (Porter, et al, 1999a). Thus, unlike ILn and PFC lesions, HP lesions have not been shown to affect response speed in delayed conditional discrimination tasks. Research involving short-term memory, response speed to brief stimuli, or reaction time during delayed conditional discrimination tasks does not provide credible evidence that HP lesions produce slower response speed.

Previous studies of response speed were not designed to test whether HP damage affects the ability to process briefly presented visual information from a number of widely distributed spatial locations. The current task differs from previous procedures in that the rats will be forced to respond to any of seven locations requiring analysis of a 315° arc (see below for a description of the apparatus and behavioral procedures). Thus, the area and number of locations that must be attended to is greater than in previous studies with five choice serial reaction or sustained attention tasks. Given the impairments in responding to spatial information associated with HP lesions (Jarrard, 1993, 1995), it may be that the spatial distribution of the response ports in the current experiments will differentially affect the response speed of HP animals. One of the behavioral procedures (cueing conditions) will test the effects of HP lesions following manipulations of the number and the distribution of visual stimuli.

Behavioral Methods for Studying Response Speed in Animals

In assessing slow responding deficits, it is important to study the relationship between speed of stimulus processing and motor function. For over a century, psychologists have used reaction time tasks to measure changes in stimulus processing and motor functioning. Choice reaction time tasks provide an opportunity to manipulate several aspects of stimulus processing while keeping the motor requirements consistent. Such procedures provide an opportunity to characterize speed of processing by measuring changes in response speed to briefly presented stimuli. The ability to respond to brief stimuli can be tested and challenged by manipulating discriminability and distractibility. In addition, the ability to use cues to enhance performance can be tested. Thus, choice reaction time tasks are suitable for studying response speed deficits associated with neuropsychological disorders such as Korsakoff's disease. The two most commonly employed choice reaction time tasks with rodents are a vigilance and a five choice serial reaction time procedure (Blokland, 1998).

One of the most carefully developed behavioral procedures is a previously validated vigilance task (McGaughy & Sarter, 1995). Rats were trained in an operant chamber with retractable levers and a stimulus light in the front of the box. Reinforcement was given for responding to one lever when a light was presented and to a different lever when no light was presented. They found that performance decreased (1) as signal length decreased, (2) when distractors were presented, and (3) as the event-rate increased (McGaughy & Sarter, 1995). Adjustments in the parameters of this task appear to produce the expected changes in performance. However, the exact location of the rat is unknown when the stimulus is presented and thus there is some lack of control for the measure of reaction time. In addition, the nature of the task, a conditional discrimination, is reasonably complex. Given that the goals of the current studies are to measure response speed rather than vigilance per se, it is desirable to have a relatively simple response requirement. A simpler task would avoid any confound of the response speed measure based on differential slow responding of lesioned animals due to the complexity of a conditional discrimination.

A five choice serial reaction time task has been commonly used to assess the effects of pharmacological manipulations and lesions (for a review, see Muir, 1996). The chamber is an arc with 9 holes at the back of the box (with four holes occluded during the task), each equipped with a stimulus light and a pair of photocells to detect head entries. A food tray is located in the front of the box with a hinged panel connected to a microswitch that is used to monitor responding to the food tray and allow access to pellets (Robbins, Muir, Killcross, Pretsell, 1993). Rats are reinforced for responding to the hole where a stimulus light is briefly illuminated. Some of the manipulations of the task include varying the stimulus duration, the brightness of the stimuli, temporal unpredictability (varying the intertrial interval) and distractibility (white noise). Generally, it is expected that performance declines when stimulus duration or brightness of the stimuli decreases, temporal unpredictability increases or when a distractor is presented. The measures of performance include: percent correct, omissions (failure to respond within the limited hold), premature responses (hole entries during the intertrial interval), perseverative responses (hole entries following the initial response), and latency to respond to the visual stimulus and to the hinged panel (Robbins, et al, 1993). While the latency to respond to the visual stimulus is interpreted in terms of cognitive processing, the latency to the hinged panel has been argued to be a measure of motivation.

The five choice serial reaction time task allows for a measure of responding to briefly presented stimuli without a challenging response rule. However, there are several limitations with the design of the task. First, as has been previously acknowledged (Muir, 1996; Robbins, et al, 1993), the location of the rat is unknown when the visual stimulus is presented and thus the measure of reaction time is poorly controlled. To address this issue, Robbins and colleagues developed a reaction time task with different behavioral procedures (Muir, 1996; Robbins, et al, 1993). Because of the different behavioral procedures, it is not possible to study performances on the five choice reaction time and reaction time tasks in the same group of rats. Unfortunately, there are only two response locations in the 'revised' reaction time task. With the 'revised' reaction time task it is not possible to assess responding to brief visual stimuli at several response locations.

Second, the effects of cues have not been studied in the five choice serial reaction time task. There has been considerable interest in the use of cues to study overt and covert orienting following brain damage in humans and animals (Posner & Peterson, 1990; Posner & Raichle, 1994). There are not any tasks currently available to study covert orienting in restrained rats but behavioral procedures have been developed to study the effects of cueing in rats for overt orienting (Bushnell, 1995; Robbins, et al, 1993). These procedures generally involve responding to two locations and do not allow for testing the ability to use cues with several response locations. This is an important limitation because cues may be of particular importance (especially following lesions) to the ability to respond to brief visual stimuli at several response locations.

Third, the five choice serial reaction time task does not require the rat to scan a broad spatial array. The effects of certain lesions may be more salient when the animal must scan a wide spatial distribution. Specifically, HP lesions, associated with deficits in processing spatial information (Jarrard, 1993, 1995), may produce deficits in response speed when a broad spatial distribution must be scanned. While the five choice serial reaction time task has been beneficial for studying the effects of a number of manipulations, there are some aspects of the task that can be improved to yield a more complete picture following neurobiological treatments.

In the current experiments with a seven choice serial reaction task, an octagonal radial arm maze hub with one arm extending from it was used. A retractable lever was at the end of the arm and a pair of photocells were located just before the entrance to the hub. In the hub, there were seven ports, each equipped with a stimulus light, photocells to record head entries, and a well into which water reinforcement could be delivered. There were two lights that provided bright or dim illumination above the hub and a speaker above the entrance to the hub. In the standard task, each trial began with a press on the lever, which caused the lever to retract and all seven stimulus lights to be illuminated. After the rat broke the photocells in the arm, six of the stimulus lights were turned off and one remained on for a brief time period (randomly varied within session). Rats received water reinforcement for entering the port where the stimulus light briefly remained illuminated. If an incorrect port was entered or there was a failure to respond within the limited hold, no reinforcement was given and the lever was extended for the next trial. Measures of percent correct (which can be analyzed for each stimulus duration and/or at each port) and omissions were recorded. In addition, the latency to respond from the arm photocells to the port was recorded on each trial. By always measuring latency from the arm photocells, the location of the rat and the distance traveled to each respective port was consistent on each trial allowing for a reliable measure of reaction time.

Several manipulations of the standard task were tested. A brief light or tone was introduced after the arm photocells were broken to test the effects of distraction. The effects of changing the discriminability of the stimulus lights were tested by presenting dim or bright lights following the lever press for the entire duration of the trial. The design of the task also allowed for the stimulus lights to cue the animals as to the correct choice. Specifically, performance when the stimulus lights on only one side of the chamber were illuminated could be compared with trials in which no cueing information was given. Furthermore, the effects of number of response locations could be studied by comparing performance with either four lights (two on either side of the chamber so no cueing information is given) or seven lights illuminated. Thus, the design of the task allowed for a relatively straightforward transition to a condition where the effects of cueing could be studied.

Because of this novel behavioral procedure, it was important to first study the effects of these manipulations on unlesioned animals. It was necessary to assess whether some of the manipulations (e.g., stimulus duration, distraction, discrimination) have effects comparable to those expected based on previous work with the five choice serial reaction time task. In the first experiment, six unlesioned rats were tested on the seven choice serial reaction time task. In Experiment 2, the effects of ILn, PFC, and HP lesions were compared on this task.

EXPERIMENT 1

Method

Subjects. Subjects included six male Long-Evans rats that were approximately eight weeks old when the experiment began (Charles River Laboratories, Wilmington, MA). Animals were singly housed in a vivarium with a 12 hr light/dark cycle (lights on 7:00 a.m. - 7:00 p.m.). Rats received ad libitum access to food and water during behavioral training and for 30 minutes at the completion of testing each day. Rats were handled and treated in accordance with the guidelines of the Animal Care and Use Committee at UNH.

Apparatus. Behavioral testing occurred in an octagonal radial arm maze hub with one arm extending from the hub (Figure 1). The stainless steel hub had a diameter of 28 cm and a height of 33 cm. The clear polycarbonate arm was 54 cm in length with a height of 17 cm. A retractable lever (MED Associates, Georgia, VT) was located at the end of the arm and a pair of photocells (MED Associates) were located 50 mm from the entrance to the hub.

Seven rectangular sheets of stainless steel were inserted in the remaining locations in the octagonal hub. A port was attached to a hole in each sheet of stainless steel. The ports were made of PVC tubing with a tightly fitting PVC cap at the back of the port. Each port had a diameter of 6 cm, a length of 5 cm, and extended 0.5 cm into the chamber. Ports were equipped with a light (2.8 W; MED Associates), photocells were mounted to detect head entries, and a small hole at the bottom of all ports through which water could be delivered as reinforcement. Each port light was located in a 2.5 cm hole in the back of each port. Water was delivered by activating a solenoid valve (The Lee Company, Essex, CT). Each time a rat was reinforced two pulses of water lasting for 0.1 second each (a total of .08 ml) were given. There were two additional lights in the chamber: a dim (6.5 W) and a bright (40 W) light mounted above the hub. Both lights were 56 cm above the floor of the hub. The dim light was 13 cm in front of the entrance to the hub while the bright light was 20.5 cm in front of the entrance to the hub. The luminance of each light was measured using a Litemate Photometer Model 504 (Rollmorgen Corp., Burbank, CA) from a polycarbonate surface placed at the entrance to the hub to more thoroughly assess the brightness of each light. Background illumination (lights turned off in the room) was .05 footlamberts (fl). The port directly ahead after entrance to the hub (port 4 in Figure 2 which was 25 cm from the polycarbonate surface) was .66 fl. The bright overhead light was 6.45 fl and the dim overhead light was .71 fl. A programmable audio generator (MED Associates) was located directly above the entrance to the hub. The entire chamber was enclosed within a wooden, sound insulated box and connected through an interface to a 486 computer that controlled procedures and collected all data.

Behavioral Procedures. Initial training was intended to shape rats to nose poke at each of the ports. The lever was placed at the front of the arm blocking access to the arm for this stage of training. All seven lights were illuminated and reinforcement was given for responding (nose poke) to each of the lit ports following a lever press to initiate a trial. After a response to a port the light at that port was turned off and no further nose pokes to that port were rewarded in that trial. After a response was made to each port the lever was extended. A press on the lever caused the lever to retract and a new trial to begin with all port lights turning on and reinforcement available for entering each port. Each session lasted until 20 trials were completed or one hour elapsed. After completing 20 trials in a session, the rats were shaped to move to the end of the arm to press the lever. The lever was placed at the end of the arm requiring the rat to travel through the arm to initiate a trial. After a lever press, each light was illuminated and reinforcement was provided after a nose poke in each port. This procedure was continued until rats completed a criterion of 20 trials in a session.

During the next stage of training, a trial began with a lever press that caused the lever to retract and all seven port lights to be illuminated. After the rat broke the photocell located in the arm, six of the lights were turned off. The light in one port (S+) that was randomly selected on each trial remained illuminated until the rat responded to it. After a response to the lit port, the light was turned off, reinforcement was delivered, and the lever was extended requiring a lever press to initiate the next trial. These sessions continued until a criterion of 90 trials was completed within one hour.

The standard version of the task was then implemented. As before, a trial began with a lever press causing the lever to retract and all seven lights to become illuminated (Figure 2a). When the arm photocell was broken, six lights were turned off. The light in one port remained on for a duration (2 s, 1 s, 0.5 s or 0.25 ms; Figure 2b) that was randomly chosen by the computer on a trial by trial basis. The light that remained on (S+) was turned off after the randomly chosen interval timed out (Figure 2c). A rat received reinforcement for entering the port with the light that remained on after the arm photocell was broken (Figure 2d). If the initial response was to any other port, no reinforcement was delivered during the trial. After a correct response, error, or failure to respond within the limited hold (10 seconds), the lever was extended for the next trial. In terms of accuracy, both the correct port and the port where the initial response was made were recorded for each trial. Collecting these variables allowed for general and detailed analyses of accuracy including: (1) an overall measure of percent correct, (2) percent correct at each port, and (3) the distance between the location of an erroneous response and the correct port. It was expected that the accuracy of responding would decrease as the stimulus duration was decreased.

Reaction time was also measured on each trial. The reaction time measure consisted of the time from breaking the arm photocells until a nose poke was made. Only correct trials were included in the analyses of reaction time in order to have a measure of speed that is independent of accuracy. For all statistical analyses, the median reaction time for each rat was used during each condition. The reaction time was expected to remain relatively consistent across all behavioral manipulations as only correct responses were included in this analysis. The animals were tested for 14 sessions with each session lasting for one hour or until 100 trials were completed.

After this training was completed, the stimulus duration was then decreased (1.2 s, 0.6 s, 0.3, 0.15 s) for seven additional sessions to further test the ability of unlesioned rats to respond to briefly presented visual stimuli. After completing these conditions, manipulations of three dimensions of the task occurred: (1) cueing, (2) stimulus discrimination, and (3) distraction.

Cueing. This manipulation assessed the ability to utilize information regarding where the S+ would be presented. There were two cueing conditions. Following a lever press to initiate a trial, either three lights on one side of the chamber were illuminated (cued condition) or six lights, three on either side of the chamber (uncued condition) were illuminated. The light in the port directly in front of the rat (port 4) was never illuminated. In the cued condition, after the arm photocells were broken two lights turned off and one remained on for a brief duration. In the uncued condition, after the arm photocells were broken five lights were turned off and one remained on for a brief duration. Similar to previous conditions, reinforcement was given for responding to the port that remained illuminated after the arm photocell was broken. Both the cued and uncued conditions were randomly presented within each session. The stimulus durations were shorter (0.8 s, 0.4 s, 0.2 s, 0.1 s) because it is likely that the cues would only be beneficial when the S+ was presented for a very brief duration. Accuracy should be high on trials with long stimulus durations regardless of whether cues are presented. This prediction would be confirmed by a significant cue condition X stimulus duration interaction. The cueing condition was tested for six sessions with 96 trials per session or a one hour maximum session length.

Stimulus discrimination. The dim and bright overhead lights were illuminated to decrease the discriminability of the S+. The behavioral training was similar to the standard task except that the background illumination was either bright, dim, or not present. The background illumination was provided by either turning on the 40 W bulb (bright condition) or the 6.5 W bulb (dim condition). The background lights were illuminated immediately after the lever was pressed to initiate a trial and remained illuminated until the trial was completed. Both the stimulus duration (1.2 s, 0.6 s, 0.3 s, 0.15 s) and the discriminability condition were randomly chosen on a trial-by-trial basis. It was expected that brighter background illumination would increase the difficulty in discriminating which port light served as S+ and subsequently decrease percent correct. It was expected that the interaction between discriminability and stimulus duration would not be significant because either overhead light was on throughout the entire stimulus duration. The rats were tested for 96 trials with a one hour time limit for 8 sessions.

Distraction The distraction procedure was similar to previous conditions except that on some trials a distractor was briefly introduced after the arm photocells were broken. Each trial was begun with a lever press that caused all seven port lights to become illuminated. One of the port lights remained on (S+) after the arm photocells were broken. After the rat broke the arm photocells one of three manipulations occurred: (1) the overhead bright light was illuminated for 100 ms, (2) a 100 dB tone (rise/fall time of 10 milliseconds) at either a low, medium, or high frequency (2,000, 6,000, or 12,000 Hz) was presented for 100 ms, or (3) no distractor was presented. A short blink of the distractor light was chosen to minimize the confound between discriminability and distractibility. The different frequency tones were presented to minimize habituation to this distractor. As in previous conditions, reinforcement was given following a response to the port with the light remaining illuminated after the arm photocell was broken. Both the distractor condition and the stimulus duration (1.2, 0.6, 0.3, or 0.1 seconds) were randomly manipulated within each session.

With longer stimulus durations, there was considerable time when the S+ was available with no distraction. Trials at longer stimulus durations should be unaffected by the distractor. Thus, it was expected that presenting visual or auditory distractors would decrease accuracy particularly when the stimulus duration was short. Evidence for this effect would be a significant discriminability X stimulus duration interaction. The distraction sessions lasted for 96 trials or one hour and were conducted for 8 sessions. One of the rats became ill and did not complete all of the distraction sessions.

Results

On the standard task with longer stimulus durations (2 s to .2 s) all rats tended to perform less accurately as the stimulus duration was decreased (Figure 3). This result was confirmed by a significant one-way analysis of variance (ANOVA; $F(3,15) = 20.57$, $p < .001$)). Median reaction time, on the other hand, did not significantly vary across stimulus duration (Figure 4; $F(3,15) = 1.28$, $p > .30$). Percent correct varied in the expected fashion with decreases in stimulus duration but the reaction time measure was stable even when responding to brief stimuli. The number of omissions tended to increase as the stimulus duration decreased (Figure 5). While the one way ANOVA to test changes in omissions at different stimulus durations was significant without any correction procedures ($F(3,15) = 3.88$, $p = .031$), it failed to reach significance with either the Geisser-Greenhouse ($p = .097$) or Huynh-Feldt ($p = .090$) corrections.

The accuracy and reaction time to respond to each port was measured to assess any differential responding to the ports. For this analysis, the ports were numbered one through seven with port one being immediately on the left, port two being adjacent to port one and so on for the rest of the ports (Figure 6). There was a significant difference in accuracy responding to the ports ($F(6,30) = 6.50$, $p < .001$). It is clear that rats performed more accurately at the ports on the immediate left and right of the rat as it entered the hub (ports one and seven). The reaction time effect was also significant across the ports ($F(6,30) = 26.45$). Responses were quicker to the ports immediately to the left and right of the arm (Figure 7). This effect is likely due to ports one and seven being located closer to the animal after it emerges from the arm. Taken together, these results indicate that animals respond more accurately and quicker to the ports on the immediate left and right of the rat after it emerges from the arm.

It is apparent from studying accuracy at each port (Figure 6) that these nonlesioned rats appear to have a side bias. To calculate the bias measure, the number of incorrect responses made to each port was determined. The total number of errors at each port was multiplied by each port number (e.g., *10* errors to port 2: *10* X 2 = 20). Each of these products was summed together and then divided by the total number of errors. This calculation yields a value between 1 and 7 with 1 being bias to make errors to the left side of the chamber, 7 being a bias to make errors to the right side of the chamber and 4 being no bias.

Observation of the bias for each rat suggests that many subjects had a small degree of bias (Figure 8). To perform statistical analysis, four was subtracted from the bias measure. The absolute value of the difference was calculated because it was not of concern whether an animal had a left or a right bias, but whether any side bias was present. A one sample t test was conducted to test whether the bias was significantly different from zero. The analysis was statistically significant ($t(5) = 2.88$, one-tailed $p = .017$) indicating that unlesioned rats have a side bias in this task.

To study the pattern of errors in this task, the number of locations away an incorrect choice was made from the correct port was calculated. An assessment of the pattern of errors revealed that the majority of errors were one port away from the correct port (Figure 9). A one way ANOVA indicated this effect was statistically significant ($F(2,10) = 47.19$, $p < .001$). It appears that errors in this task are not random but rather are usually made to locations near the correct port.

Percent correct and reaction time were compared to test the effects of decreasing the stimulus duration to a range from 1.2 s to 0.15 s. Rats continued to be less accurate as the stimulus duration was decreased (Figure 10). This effect was confirmed by a statistically significant one way ANOVA ($F(3,15) = 59.02$, $p < .0001$). Reaction time did not significantly change across the different stimulus durations ($F(3,15) = .385$, $p = .77$). These results are consistent with those during sessions with longer stimulus durations. That is, accuracy decreased but reaction time remained unchanged when the stimulus duration was decreased.

Cueing. Cueing the location of the correct port appeared to produce a slight improvement in accuracy (Figure 11). A two way ANOVA with stimulus duration and cue as the factors was used to test this observation. The main effects for stimulus duration ($F(3,15) = 60.44$, $p =.0001$) and cueing ($F(1,15) = 8.94$, $p = .031$) were statistically significant but the interaction between the factors was not ($F(3,15) = .54$, $p = .66$). The animals tended to perform better as the stimulus duration was increased and when the correct port was cued. There was no change in median reaction time for any rat in the cued and uncued conditions. Cueing produced a modest effect on percent correct without any effect on reaction time.

Stimulus discrimination. As expected, the effects of presenting a bright light throughout each trial decreased accuracy (Figure 12). The dim light did not have a substantial effect on performance. These observations were tested by performing a two way ANOVA with stimulus duration (4 levels; 1.2 s, 0.6 s., 0.3 s, 0.15 s) and discriminability (3 levels; no light, dim light and bright light) as the two variables. Both the main effect for stimulus duration ($F(3,30) = 90.12$, $p = .0001$) and for discriminability ($F(2,30) = 34.76$, $p = .001$) were significant. The interaction between the two variables was not significant ($F(6,30) = .735$, $p = .63$). Planned comparisons ($\alpha = .05$ using the Bonferroni procedure to correct for multiple comparisons) were conducted to test which of the discriminability conditions differed from each other. These results revealed that there was not a significant difference between trials with no overhead light and the dim light ($F(1,30) = 1.702$, $p = .22$). Percent correct with the bright overhead light was significantly lower than trials without an overhead light ($F(1,30) = 60.6$, $p = .0001$) or trials with the dim light ($F(1,30) = 41.99$, $p = .0001$). The bright light condition resulted in a substantial decrease in accuracy while the dim light had a negligible effect.

A comparison of reaction time over the discrimination conditions indicated that rats were slower when the bright overhead light was present (Figure 13). To assess the effects of changing discriminability on reaction time, a one way ANOVA was conducted with discrimination condition as the factor. Stimulus duration was not included in this analysis as reaction time did not significantly vary across stimulus duration in any previous analysis. The ANOVA was statistically significant ($F(2,10) = 5.91$, $p = .02$). Planned comparisons were conducted to assess which discrimination conditions affected reaction time. Reaction time with the bright overhead light was significantly slower than with no overhead light ($F(1,10) = 11.80$, $p = .0064$). Median reaction time with the dim light did not significantly differ from the no light ($F(1,10) = 2.57$, $p = .14$) or the bright light ($F(1,10) = 3.36$, $p = .097$) conditions. The presentation of a bright overhead light produced a decrease in accuracy and an increase in reaction time. The dim overhead light did not have any significant effect on performance.

<u>Distraction.</u> Presenting a brief visual stimulus as a distractor appeared to produce a modest accuracy deficit (Figure 14). The tone had little effect. These observations were tested by a two way ANOVA with stimulus duration and distraction condition as the two factors. The main effect for stimulus duration was statistically significant indicating that accuracy decreased as the stimulus duration became shorter ($F(2,24) = 288.9$, $p = .0001$).

The main effect for distraction condition was statistically significant ($F(2,24) = 5.50$, $p = .03$). This effect continued to be significant when the Huynh-Feldt correction was applied ($p = .031$) but not when the more conservative Geisser-Greenhouse correction was used ($p = .051$). The interaction of these factors was not significant when either the Huynh-Feldt or Geisser-Greenhouse correction procedures were applied ($F(6, 24) = 2.61$, $p = .043$, Huynh-Feldt $p = .103$, Geisser-Greenhouse $p = .146$). Taken together, these results suggest that the distractors produced a modest decrease in accuracy.

Planned comparisons were conducted to compare the effects of each distraction condition. Both the comparison of no distractor with light ($F(1,24) = 8.068$, $p = .0218$) and tone with light ($F(1,24) = 8.439$, $p = .0197$) yielded p values less than .05 while the comparison of no distractor and tone did not ($F < 1$). However, when corrected by the Bonferroni procedure, none of these comparisons were statistically significant. The planned comparisons yielded a trend indicating that the light was primarily responsible for the moderate effects of distraction on accuracy.

A one way ANOVA was conducted to assess the effects of distraction on reaction time. The results indicated that none of the distractors significantly affected median reaction time ($F(2,8) = 2.67$, $p = .13$).

Discussion

Effects of stimulus duration. One of the most consistent effects in Experiment 1 was that shorter stimulus durations were associated with decreases in accuracy. This effect was observed: (1) with a range of longer (.2 s to 2 s) stimulus durations, (2) with a range of slightly briefer durations (.15 s to 1.2 s), (3) during the cueing condition with a briefer range (.1 s to .8 s) and (4) during both discrimination and distraction conditions.

The effects of stimulus duration on accuracy are in stark contrast to the effects on reaction time. Reaction time did not significantly vary across stimulus duration. Omissions tended to be low for unlesioned control animals and did not significantly vary across stimulus duration when the Geisser-Greenhouse or Huynh-Feldt correction procedures were applied.

This task produces effects of stimulus duration similar to those reported in previous studies with the five choice serial reaction time task (Muir, et al, 1996; Robbins et al, 1993). In an experiment with several lesion groups, Muir et al (1996) found that the groups performed better at .5 s than during one session at .25 s. The design in the current experiments provides two advantages over the method in Muir et al (1996). First, the stimulus duration is randomly varied within session which produces the same number of trials at each stimulus duration. It is difficult to interpret any deficits with the shorter stimulus duration in Muir et al (1996) because any effects could be due to the different amount of training at each stimulus duration. With further training at .25 s, it is possible that performance would improve to be comparable to a .5 s stimulus duration. Second, a much greater range of stimulus durations are assessed in the current study. This design allows for a more fine grained analysis of the ability to respond to brief stimuli. The inclusion of trials with relatively long stimulus durations is critical for interpreting the data. Normal performance at the long duration would make it unlikely that any deficits at briefer durations are due to debilitation of the animal (e.g., following a lesion), an impairment of motivation, or an inability to respond based on the contingencies in this task.

The lack of change in reaction time at different stimulus durations suggests that this measure does not assess the ability to respond to brief stimuli. This is not surprising as the measure only reflects speed on correct trials. The interpretation of this measure cannot be unimpeachably stated. It may be that the reaction time measure primarily reflects changes in motor speed which would not be expected to vary substantially among unlesioned rats. Reaction time was fairly consistent among all unlesioned rats (Figure 4). The relatively small variability in reaction time is encouraging as this measure should be particularly sensitive to any effects of lesions.

Effects of cueing. Providing information about the side to be reinforced resulted in a modest but significant increase in accuracy compared to trials without any information about the S+. Cueing did not affect reaction time. The ability to cue the animals illustrates one of the strengths of this task. One of the fundamental differences between this task and the five choice serial reaction time task is that in the current procedures all lights are illuminated and turn off (except for the S+) after the photocell break. In the five choice task, one of the lights is briefly illuminated. The design of the seven choice task enables the ability to manipulate the lights illuminated following a lever press to cue the location of the S+. Furthermore, the cueing is conducted without changing the response rule (i.e., respond to the port where the last light remained illuminated). This relatively straightforward adjustment in training procedures allows for an analysis of performance during the standard seven choice task along with manipulations of cueing in the same group of rats. With this design it is possible to gather much more information from the same group of rats. The significant results in Experiment 1 encourage the use of cueing in future studies.

There are a number of changes in the experimental design that may enhance the cueing effect. First, shorter stimulus durations could be studied. It seems likely that providing cues to orient the rat to one side would only provide an advantage when the stimulus duration was brief. During a long stimulus duration, unlesioned rats are likely to respond correctly during the trial regardless of whether any cueing information is available. Decreasing the stimulus duration may place a greater premium on the ability to utilize cues in order to respond accurately. Second, the changes in accuracy at the different ports need to be considered. The analysis at different ports indicated that responding was nearly always correct when the S+ was the port either immediately to left or right of the animal. Responding may very well be accurate to these ports at brief stimulus durations regardless of whether cues are presented. In the current experiment, one-third of the cueing trials (when ports 1 or 7 served as S+) may have been affected by this issue. A clearer manipulation of cueing may be achieved by avoiding the use of these ports.

Two other design changes could be used to enhance the ease with which the rats learn to utilize the cues. It may be more difficult to learn to use cues when manipulated within session because the cues are not consistently available. It may be easier to learn to use cues if they are available on every trial within a session. A between session design in which entire sessions with and without cues are counterbalanced may facilitate learning to use cues. It may also be beneficial to provide some minimal training prior to testing in this task to allow rats to become accustomed to the briefer stimulus durations and presence of cues. It may be that effects of cueing are obscured because responding is more random during the initial sessions while the animal becomes accustomed to the adjustments in the parameters of the task.

Effects of stimulus discrimination. The manipulation of the discriminability of the port lights by presenting bright or dim overhead lights had a clear effect on performance. In particular, accuracy decreased when the bright overhead light was illuminated throughout a trial compared with no light or dim light. The effect of the bright light did not interact with stimulus duration. This finding was expected as the bright light remained illuminated throughout the stimulus duration. The dim light did not have a significant effect on performance.

The results with the bright light are consistent with effects found when decreasing the brightness of stimulus lights in the five choice reaction time task (Robbins, et al, 1993). Not surprisingly, the conditions in both studies show that accuracy decreases as visual stimuli become more difficult to detect. The dim light did not affect accuracy of unlesioned animals. These manipulations will be useful for studying the effects of lesions. It will be possible to compare whether the bright light differentially decreases performance of lesioned rats. Furthermore, it will be possible to test whether lesioned animals are susceptible to the effects of the dim light. This condition provides a range that will allow for a careful assessment of the effects of varying discriminability on performance.

Reaction time increased when the bright light was presented. There was no change in the motor requirements to respond during this condition. The increase in reaction time with the bright light indicates that this measure does not simply reflect motor responding. The reaction time measure does not seem to be particularly sensitive to the effects of manipulations of stimulus processing when comparing the results across all conditions. Reaction time did not change with manipulations of stimulus duration, cueing, or distraction suggesting that this measure is not particularly sensitive to the effects of manipulations in speed of stimulus processing. The natural tendency of rats to be photophobic may be a critical factor in the slow responding during the bright overhead light condition. The rats may be a bit slower entering the chamber (which is bright throughout the trial) due to a biological disposition to avoid bright illumination. In the distraction condition, reaction time may not be substantially affected because the light is very brief so the chamber is only bright for a brief interval. The consistency of the reaction time measure across conditions suggests it may be primarily influenced by motor responding although it can be sensitive to some changes in the parameters of the task.

Effects of distraction. A brief illumination of the bright overhead light produced a modest deficit (Figure 14). Evidence for this interpretation comes from a significant main effect for distraction with the Huynh-Feldt correction procedure (but not with Geisser-Greenhouse). Planned comparisons yielded p values less than .05 when the light condition was compared with either the tone or no distractor, but these comparisons were not significant when the Bonferroni correction procedure was applied. The tone did not have any apparent effect on performance. None of the distraction conditions significantly affected median reaction time.

It was predicted that performance should be more substantially affected at short stimulus durations by distraction. However, using either the Huynh-Feldt or Geisser-Greenhouse correction procedures, the interaction was not statistically significant. At the longest stimulus duration, performance was 99.1%, 94.1%, and 97.7% with no distractor, light, and tone respectively. At the shortest stimulus duration, performance was 39.3%, 21.3%, and 39.1% with no distractor, light and tone respectively. The means suggest that there is a greater decline in accuracy as the stimulus duration decreases when the light was presented as a distractor. This trend is consistent with the predicted effects at short stimulus durations but the interaction is not statistically significant.

These results suggest that the current design provides a distractor that affects accuracy (bright light) and one that does not (tone). It will be possible to test whether lesions exacerbate the deficit when the bright light is present. Furthermore, the effects of the tone, a distractor that does not affect unlesioned rats, can be tested following lesions. These manipulations allow an assessment of different degrees of distraction following lesions.

Implications for using the seven choice reaction time task. The results generally support the use of this task to measure responding to brief stimuli. One of the most critical and consistent findings to support this contention is that accuracy decreased at shorter stimulus durations. Manipulations of discriminability and distractibility involving the bright overhead light also decreased accuracy. This study showed that unlesioned rats are able to take advantage of cueing information in this task. Thus, the results confirm many of the predictions and support the use of this task to study responding to brief stimuli.

There are some results that need to be considered before using this task in future studies. First, there was a significant side bias reported with unlesioned controls (Figure 8). It is not apparent why this bias occurred. It may be that rats preferentially turn to one side when exiting the arm but results to support this notion are not available. It is important to know the bias exists regardless of its nature for future studies. In lesion studies it will be important to compare whether the bias is exacerbated (or not present) in the treatment groups.

Another factor to consider for future studies is that responding is not consistent to all of the ports. The finding of a significantly lower reaction time to the ports immediately on the left and right after exiting the arm is not surprising as the distance traveled is shorter to these ports. It was surprising, however, that accuracy was near perfect at these ports. It might seem that accuracy should be lower at these ports because a larger area would need to be scanned before detecting stimuli in these ports. There are several reasons why accuracy was better at the extreme ports. First, rats have eyes further to the side than primates and thus may have better peripheral vision. Second, at most of the ports the rats commonly make errors either to the port on the immediate left or right of the S+. When one of the extreme ports is S+, rats only have one alternative location (rather than two) because the arm extends from the other location. Thus, the improved accuracy at the extreme ports may be an intrinsic property of the design of the apparatus. However, statistically significant effects were still found with manipulations of stimulus duration, stimulus discrimination, and distraction when responding to all ports was used in the analyses. The differential responding across ports is an aspect of this task that needs to be considered in future studies, but does not eliminate the potential usefulness of this task for studying responding to brief stimuli.

Most of the findings suggest this task is useful for measuring changes in responding to brief stimuli. Many of the results of manipulations (stimulus duration, discrimination, distraction) were consistent with those reported using a five choice serial reaction time task (Robbins, et al, 1993). This task offers a number of advantages compared to the five choice task. First, the reaction time measure is more reliable in the current task as the location of the rat is known when the S+ remains illuminated. This reaction time measure proved to be very consistent for unlesioned rats across a number of behavioral manipulations. The exception to this consistency was increase in reaction time when the bright overhead light was illuminated throughout a trial. Second, this task allows for a test of the ability to use cues. This has not been done with the five choice reaction time task. Third, rats must scan a greater spatial area in the current task. The current task requires the animals to scan a 315° arc across seven ports. The differential performance across ports does not obscure this dimension of the task because animals must still scan all ports (and thus the entire arc) in order to respond accurately.

EXPERIMENT 2

Experiment 2 was undertaken to test the effects of ILn, PFC and HP lesions on the seven choice reaction time task. In addition, manipulations of distractibility, stimulus discriminability, and cueing were conducted to test whether any of these conditions differentially affected any treatment groups.

There were three substantial changes to the behavioral procedures in Experiment 1. These changes were intended to maintain responding on the task following lesions. First, several sessions were included with a long stimulus duration immediately following surgery. These sessions were included based on results from two animals that received ILn lesions at the end of the first experiment (not reported). These animals performed at chance levels for a few sessions following surgery and then failed to continue responding. These rats were given a number of sessions with a long stimulus duration in order to reinstate the task. Following these sessions, responding increased and substantially improved and thus these training procedures (i.e., sessions with a long stimulus duration immediately after surgery) were implemented in Experiment 2.

Second, when shorter stimulus durations were introduced, a number of relatively long stimulus durations were still randomly intermixed within each session. It was expected that accuracy would be high on these trials and thus maintain responding on the task. Third, the response window (after the rat breaks the arm photocell) was decreased from 10 s to 3 s. Failure to respond within 3 s resulted in an omission and the initiation of the next trial. The reaction times in Experiment 1 suggested this response window should provide sufficient time to nose poke at the correct port. The shorter response window minimizes the time an animal must wait (on omission trials) before another trial begins. This change should minimize long periods during which the animal is not performing any response. These adjustments in the parameters of the task should assist in maintaining responding following lesions.

Method

Subjects. Subjects included 48 male Long Evans rats (Charles River Laboratories) that were 6-8 weeks old at the beginning of the experiment. The light/dark cycle (lights on 7:00 a.m. - 7:00 p.m.) and the water deprivation schedule were the same as in Experiment 1. All testing occurred during the light cycle. Rats were handled and treated in accordance with the guidelines of the Animal Care and Use Committee at UNH.

Treatment. Rats were trained in two squads to ensure testing would occur on a regular basis. Rats were presurgically trained on the seven choice reaction time task and then randomly assigned to treatment groups (ILn, PFC, HP lesion or sham-control surgery) using a block randomization procedure. Rats were ranked for presurgical performance and divided into blocks of four. One rat from each block was then randomly assigned to each treatment.

Rats were required to achieve two criteria during presurgical and postsurgical training in order to be used in all conditions. Presurgically, they had to maintain 85 % overall accuracy (averaged across all stimulus durations) and complete all trials for two consecutive sessions. Forty-two rats reached this criterion and were used for postsurgical behavioral studies.

When retrained with a long stimulus duration after surgery, rats were required to perform at 90 % while completing all trials for two consecutive sessions before additional behavioral manipulations (i.e., stimulus duration, distractibility, stimulus discrimination and cueing) were introduced. One PFC rat in the first squad and one ILn rat in the second squad failed to reach this criterion. The total number of subjects in each group that were tested on all behavioral conditions was: ILn n = 9, PFC n = 11, HP n = 10, and Control n = 10. There were additional PFC rats included in the second squad because one rat from this group in the first squad failed to retrain with a long stimulus duration after surgery.

Surgery. Rats were anaesthetized by an intramuscular injection of ketamine (85 mg / kg) and xylazine (8.5 mg / kg). Subjects were placed in a Kopf stereotaxic instrument (Tujunga, CA) with the incisor bar set 3.3 mm below the interaural line (IA). The skull was then opened with aseptic procedures.

For the ILn group, lesions were made by injecting N-methyl-D-aspartate (NMDA; 150 mM in phosphate buffer, pH = 7.4) through a 26-gauge cannula attached to a 10-μl syringe. The syringe was controlled by a Kopf Model 5000 microinjection unit. The cannula remained at each site for 1 minute following each injection.

The ILn group was given bilaterally symmetrical injections at six sites (0.1 μl / site) in each hemisphere. The sites were identical to those used in Burk & Mair (1998). Anterior-posterior (AP) and dorsal-ventral (DV) sites were relative to IA, while medial-lateral sites were relative to midline. The coordinates (in mm) were AP = 7.2, ML = ± 1.4, DV = 4.0; AP = 7.2, ML = ±0.6, DV = 4.0; AP = 6.2, ML = ±1.4, DV = 3.6; AP = 6.2, ML = ±0.6, DV = 3.0; AP = 5.2, ML = ±1.6, DV = 3.6; AP = 5.2, ML = ±0.6, DV = 3.0.

PFC and HP groups were given radiofrequency lesions. To make the lesions, current was passed from a Radionics (Burlington, MA) RFG-4 lesion generator to the tip of a Radionics TCZ electrode. The tip of the electrode was heated to 70^0C for 30 s at each site. The temperature was 5^0 cooler than in previous studies to avoid damage to the electrode. For PFC and HP lesions, the same coordinates were used as in Mair et al (1998). For the PFC lesion, the AP coordinates were relative to bregma, the ML coordinates were relative to midline (in mm), and the DV coordinates (in mm) were relative to the surface of cortex. Lesions were made at 5 AP locations (in mm), +4.7, +3.7, +2.7, +1.7, +0.7. At + 4.7, lesions were made at ML = ± 0.8, DV = - 1.0 and at ML = ± 2.0, DV = -1.0; at + 3.7, lesions were made at ML = ± 0.8, DV = -1.0 and -2.2 and at ML = ± 2.0, DV = -1.0; at + 2.7, lesions were made at ML = ± 0.8, DV = -1.0 and -2.2 and at ML = ± 2.0, DV = -1.0; at + 1.7, lesions were made at ML = ± 0.8, DV = -1.0 and -2.2; and at + 0.7, lesions were made at ML = ± 0.8, DV = -1.0 and -2.2.

For HP lesions, AP and DV coordinates (in mm) were relative to IA and ML coordinates (in mm) were relative to midline. There were a total of 14 sites in each hemisphere at 4 AP locations. At AP = + 6.9, lesions were made ML = ± 1.0 and ±2.2 at a DV = + 6.5. At AP = + 5.6, lesions were made at ML = ± 1.0, ± 2.2, and ± 3.4, all at DV = + 6.5. At AP = + 4.3, lesions were made at ML = ± 1.4, DV = + 6.5; ML = ± 2.6, DV = + 6.7; ML = ± 3.8, DV = + 6.4; and ML = ± 5.0, DV = + 2.6, 4.0, and 5.4. At AP = +3.0, lesions were made at ML = ± 4.8, DV = + 2.4, 4.2, and 6.0.

Apparatus. A second chamber was built to facilitate training the number of animals in this experiment. Training occurred in two chambers with similar dimensions as described in Experiment 1.

Presurgical Behavioral Training. Animals were initially shaped to nose poke in the ports and enter the arm to press the lever using the same behavioral procedures as in Experiment 1. During the next stage of training, all seven port lights were illuminated after a lever press to initiate each trial. After the arm photocells were broken, the light in one port (S+; randomly selected) remained illuminated while six of the lights were turned off. The light in one port remained illuminated until the rat responded to it. A response to the lit port caused delivery of reinforcement, the light was turned off, and the lever was extended for the next trial. These sessions continued until a criterion of 96 trials was completed within one hour.

The standard version of the task was then implemented. As before, all seven lights were illuminated after a lever press. When the arm photocells were broken, six lights were turned off. The light in one port remained on for a duration (2 s, 1.6 s, 1.2 s, 0.8 s, 0.4 s or 0.2 s) that was randomly chosen by the computer on a trial by trial basis. The S+ was turned off after the stimulus duration timed out. Reinforcement was given for entering the port with the light that remained on after the arm photocells were broken. No reinforcement was delivered if the initial response was to any other port or the animal failed to respond within the response window (3 seconds). After a correct response, error, or an omission (i.e., failure to respond within 3 seconds after breaking the arm photocells), the lever was extended for the next trial. Sessions continued until 96 trials were completed or were terminated if 45 minutes elapsed. Rats were trained until achieving 85% accuracy across all stimulus durations and completing all trials.

Postsurgical Behavioral Training. Rats were given 12-14 days to recover after surgery during which time ad libitum access was given to food and water. After recovery, water deprivation was reinstated. Rats were then trained on a procedure similar to that prior to surgery except the stimulus duration was 3 seconds for all trials (i.e., the length of the response window). This procedure was included to re-establish the task after surgery. The ability to perform this task suggests that the animal is not completely debilitated after surgery. Rats were trained for at least 8 sessions on this procedure. A criterion of 90% accuracy and completing all trials for two consecutive sessions was required before an animal was further tested. An animal was discontinued from behavioral testing if it failed to reach criterion within 20 sessions.

All rats who achieved criterion performance with the long stimulus duration were then tested on the same procedures as trained immediately prior to surgery. Rats were reinforced for responding to the port in which a light remained illuminated for a duration (2 s, 1.6 s, 1.2 s, 0.8 s, 0.4 s or 0.2 s) after the arm photocells were broken. The durations were longer in this study to provide lesioned animals with a reasonable number of trials that would be reinforced in order to maintain responding. Each session continued until 96 trials were completed or 45 minutes elapsed. Training on this procedure continued for nine sessions before manipulations of distraction, stimulus discrimination, and cueing were tested.

Distraction. Distraction was tested using procedures similar to those in Experiment 1. After the arm photocells were broken, (1) no distractor was presented, (2) the bright light was illuminated for 100 ms, or (3) one of three tones (2,000, 6,000, or 12,000 Hz) was presented for 100 ms. The stimulus durations (2 s to .2 s) and response window (3 s) were the same as in the standard task. The distraction condition and stimulus duration were manipulated within session on a trial-by-trial basis. Each session lasted until 96 trials were completed or 45 minutes elapsed. The distraction conditions were tested for eight sessions.

Stimulus discrimination. Stimulus discrimination was tested using procedures similar to those in Experiment 1. After a lever press to initiate a trial, no overhead light was illuminated, the dim overhead light was illuminated, or the bright overhead light was illuminated. Any overhead lights remained illuminated throughout the extent of the trial. The range of stimulus durations and the response window were the same as in the standard task. The stimulus durations and stimulus discrimination conditions were manipulated on a trial-by-trial basis. Each session continued until 96 trials were completed or 45 minutes elapsed. The stimulus discrimination conditions continued for eight sessions.

Cueing. The cueing procedure was changed substantially from Experiment 1 in order to facilitate learning and increase the likelihood the cues would be used. The rats initially received five training sessions. These training sessions were designed to slowly adjust the stimulus duration and to learn to use cues. The stimulus duration was slowly decreased across these training sessions from the range used in previous conditions (i.e., from 2 s to 0.2 s) to a range including briefer durations (1.2 s, 0.8 s, 0.4 s, 0.2 s, 0.1 s, 0.05 s). During these training sessions, one side was cued on each trial. After the lever press to initiate each trial, only two lights were illuminated: either ports two and three or ports five and six (see Figure 2 for port numbers). One of the two illuminated lights remained on after the photocell was broken. As in all other conditions, reinforcement was given for a nose poke to the port remaining lit after the arm photocells were broken.

There were three cueing conditions implemented after completion of the training sessions. First, either ports two or three or ports five or six (as during the training sessions above) were illuminated after the lever press. Second, ports two, three, five, and six were all illuminated after the lever press to compare the effects of not providing cues about the correct side. Third, all seven ports were illuminated following the lever press. This condition tested the effects of forcing the animals to scan all seven port locations. In this third condition, only trials in which ports two, three, five, or six served as S+ were included in the analyses to be able to make direct comparisons with the other two conditions.

These three cueing conditions were tested between sessions in a pseudorandom order with each condition being tested on three occasions. By presenting cues consistently throughout a session, rats may be better able to learn to utilize the information. Each rat went through the sessions in the following order (each condition is designated by the number of lights illuminated following the lever press): two lights, four lights, seven lights, four lights, seven lights, two lights, seven lights, two lights, four lights. The range of stimulus durations was the same during all cueing conditions (from 1.2 s to 0.05 s). Each session continued until 96 trials were completed or 45 minutes elapsed.

Histological Analyses. Rats were sacrificed at the completion of behavioral training. Under deep anesthesia (100 mg / kg ketamine, 10 mg / kg xylazine), subjects were transcardiacally infused with physiological saline followed by 5% (vol/vol) neutral buffered formalin and the brains were then removed. For ILn and HP lesions, tissue was subsequently immersed in a solution of 10% glycerin/ 4% neutral buffered formalin for 24 hours followed by 20% glycerin/ 4% neutral buffered formalin for at least three days. PFC lesions were embedded using albumen-gelatin (Nauta & Ebbesson, 1970). In this process, tissue was immersed in a solution of 10% glycerin/ 4% neutral buffered formalin for 24 hours followed by 20% glycerin/ 4% neutral buffered formalin for at least one week. Tissue was then rinsed with distilled water, dried, and placed in a container. The albumen-gelatin mold was poured in the container. After becoming sturdy, the mold was placed in concentrated formaldehyde and put in a refrigerator for two days. All tissue was sectioned frozen in the coronal plane at 30 μm. Every fifth section was mounted, stained with cresyl violet, and examined under a light microscope for histological verification of the extent of the lesion.

Results

Long stimulus duration. There were no differences in accuracy between groups immediately prior to surgery ($F < 1$). When tested with a three second stimulus duration one ILn and one PFC rat did not reach criterion and were not further tested. In addition, two ILn rats required 13 and 15 sessions to reach criterion and one PFC rat required 10 sessions to reach criterion. All other rats reached criterion by the eighth session. An assessment of accuracy over the last eight sessions for all rats revealed that all lesion groups tended to be less accurate than controls for several sessions before improving and responding comparable to controls (Figure 15). These observations were tested with a two-way ANOVA with treatment (four levels: Control, HP, ILn, and PFC groups) as a between subject factor and session (eight levels: last eight sessions for each rat) as a within subject factor. Both the main effect for treatment ($F(3,36) = 10.13$, $p = .0001$), and for session ($F(7, 252) = 34.03$, $p = .0001$) were statistically significant. Post hoc analyses with the Tukey-Kramer statistic ($\alpha = .05$) revealed that the ILn group was less accurate than the HP and the control groups and the PFC group was less accurate than the control group. The interaction between the two variables was also significant ($F(21, 252) = 4.11$, $p = .0001$). While the ILn and PFC groups tended to perform worse than controls during the first few sessions, all groups were able to learn to respond accurately with a long stimulus duration. This finding is critical because it suggests the lesions did not affect motivation for reinforcement or impair the ability to respond selectively to light stimuli.

Reaction time was also analyzed for the last eight sessions (Figure 16). A one-way ANOVA indicated that there were group differences in reaction time when responding with a long stimulus duration ($F(3,36) = 10.20$, $p = .0001$). Post hoc analyses (Tukey-Kramer, $\alpha = .05$) suggested that ILn and PFC lesion groups were slower than control and HP groups. There were no other significant group differences. Reaction time for both the ILn and PFC groups is slower during this task when compared with the other treatment groups.

<u>Briefer stimulus durations.</u> Testing with a range of shorter stimulus durations indicated that the accuracy of the PFC group was lower than all other treatment groups particularly at the briefest stimulus duration (Figure 17). A two-way ANOVA with treatment and stimulus duration (six levels) yielded significant main effects for treatment ($F(3,36) = 16.02$, $p = .0001$) and for stimulus duration ($F(5,180) = 229.5$, $p = .0001$) and a significant treatment X stimulus duration interaction ($F(15, 180) = 10.08$, $p = .0001$). Post hoc tests (Tukey-Kramer, $\alpha = .05$) indicated that the PFC group was impaired compared to all other treatment groups. To further study the nature of the significant interaction, one-way ANOVAs were conducted at the shortest and longest stimulus durations. The lesion effect was statistically significant at the shortest stimulus duration

($F(3,36) = 16.98$, $p = .0001$). Post hoc tests (Tukey-Kramer, $\alpha = .05$) indicated that the PFC group was significantly worse than all other groups and the ILn group was significantly less accurate than the HP group. At the longest stimulus duration, the PFC group was still significantly impaired compared to the HP and control groups ($F(3,36) = 4.99$, $p = .0054$). The significant interaction generally seems to reflect that the magnitude of the difference between the PFC and other groups decreases at longer stimulus durations but a significant difference (at least between the PFC and the HP and control groups) remains at longer stimulus durations.

Median reaction time did not substantially vary across stimulus duration for any treatment group (Figure 18). The PFC and ILn groups appeared to respond slower than the HP and control groups. The reaction time results were assessed with a two-way treatment by stimulus duration ANOVA. The main effect of treatment was statistically significant ($F(3,36) = 10.33$, $p = .0001$). Post hoc analyses (Tukey-Kramer, $\alpha = .05$) indicated that HP and control groups had decreased reaction time compared to ILn and PFC groups. The main effect for stimulus duration was not significant ($F(5,180) = 1.76$, $p = .12$). The treatment X stimulus duration interaction was statistically significant ($F(15,180) = 2.40$, $p = .0035$, Geisser-Greenhouse $p = .01$, Huynh-Feldt $p = .006$). The interaction does not represent any substantial changes in the group differences. One way ANOVAs at each stimulus duration confirmed that the treatment effects remained statistically significant at each stimulus duration (at .2 s, $F(3,36) = 7.33$; at .4 s, $F(3,36) = 8.29$; at .8 s, $F(3,36) = 9.73$; at 1.2 s, $F(3,36) = 10.64$; at 1.6 s, $F(3,36) = 10.53$; at 2.0 s, $F(3,36) = 13.22$, all $ps \leq .0006$)

Analyses of omissions and responding to each port were conducted to further understand the effects of the treatments on responding in this task. There were few omissions in this task, although they did tend to occur at the briefest stimulus durations (Figure 19). A two-way ANOVA was tested (treatment X stimulus duration) for average omissions during each session. The main effect for treatment was not significant ($F(3,36) = 1.37$, $p = .27$). The main effect for stimulus duration was significant ($F(5,180) = 8.73$, $p = .0001$) reflecting that more omissions occurred at briefer stimulus durations. The treatment X stimulus duration interaction was not significant when corrected with either the Geisser-Greenhouse or Huynh-Feldt procedures ($F(15,180) = 2.22$, $p = .0073$, Geisser-Greenhouse $p = .081$, Huynh-Feldt $p = .073$). These correction procedures are important as the data were highly variable, particularly for the ILn group at the briefer stimulus durations.

In Experiment 1, it was found that unlesioned animals were significantly more accurate responding to ports immediately to the left and right of the arm. Similar effects were found for all treatment groups in the present experiment (Figure 20). A two-way treatment X port ANOVA tested these observations. This analysis produced significant main effects for treatment ($F(3,36) = 18.12$, $p = .0001$) and for port ($F(6,216) = 24.2$, $p = .0001$) and for the interaction between these factors ($F(18, 216) = 3.76$, $p = .0001$). Post hoc analyses (Tukey-Kramer, $\alpha = .05$) showed that all treatment groups were more accurate than the PFC group. The interaction reflects that the PFC group is comparable to other groups when the S+ is at the extreme ports. The accuracy at ports one and seven was averaged and a one-way ANOVA was conducted to test whether there were any group differences at the extreme ports. The effect of lesion was not significant when only the accuracy from the extreme ports was analyzed ($F(3,36) = .95$, $p = .43$). Most of the errors for all groups (with a larger number of errors by the PFC group) are committed when another port (ports 2-6) was the S+. Furthermore, the HP group does not show the expected port effect as accuracy is fairly consistent (above 90%) to all ports.

Experiment 1 also showed that animals were faster responding on correct trials when one of the extreme ports was reinforced. This pattern was also found for all groups in the present experiment (Figure 21). A two-way treatment X port ANOVA yielded significant main effects for treatment ($F(3,36) = 9.30$, $p = .0001$) and for port ($F(6,216) = 76.2$, $p = .0001$). Post hoc analyses (Tukey-Kramer, $\alpha = .05$) indicated that both the PFC and the ILn groups were slower than the HP group and that the PFC group was slower than controls. The interaction between the two variables was not significant when the Geisser-Greenhouse or Huynh-Feldt correction procedures were applied ($F(18,216) = 1.96$, $p = .0129$; Geisser-Greenhouse $p = .0794$, Huynh-Feldt $p = .0681$).

Three analyses of errors were calculated to study whether the pattern of errors was different for any of the treatment groups. First, the errors were subdivided into the distance away from the correct port (e.g., one port away, two ports away, etc.). Figure 22 depicts this subdivision with the average number of errors during each session (top panel) and as a percentage of the total number of errors made (bottom panel). As expected, the PFC group committed more errors than all other treatment groups. However, the PFC group, like the other treatment groups, commits the largest percentage of errors one port away from the correct port. Using the percent of total errors data for each rat, a two-way treatment X distance (4 levels) ANOVA was conducted. Importantly, the treatment X distance interaction was not significant when corrected by the Geisser-

Greenhouse or Huynh-Feldt procedures ($F (9,108) = 2.14$, $p = .032$, Geisser-Greenhouse $p = .082$, Huynh-Feldt $p = .073$). This analysis suggests that the pattern of errors (i.e., most errors made one port away from the S+) did not substantially vary across the treatment groups.

Second, the number of perseverative errors were evaluated. A perseverative error was recorded when an incorrect response was made to the same port that was responded to on the previous trial. Thus, if an incorrect response was made to port 4 and a response had been made to port 4 on the previous trial a perseverative error would be recorded. For the analysis, the proportion of total errors that were perseverative errors (i.e., perseverative errors / total errors) was calculated for each rat. There were no significant differences in proportion of perseverative errors between any treatment groups ($F (3,36) = 1.82$, $p = .16$).

Third, the bias measure used in Experiment 1 was calculated to assess whether errors were made primarily to the left or the right side of the chamber. To calculate this bias measure, the number of errors made to each port was determined (e.g., the number of incorrect responses made to port 1; *not the number of errors made when port 1 was the S+*). These errors were multiplied by each port number, each of these products was summed together and then divided by the total number of errors. This analysis produces a number between 1 and 7 with 1 being bias to make errors to the left side of the chamber, 7 being a bias to make errors to the right side of the chamber, and 4 being no bias. The bias measure and percent correct are shown in scattergram for each animal (Figure 23). For statistical analysis, four was subtracted from the bias measure and the absolute value of the difference was calculated. This adjustment allowed a comparison of the extent of bias for each animal (because it was not of concern whether an animal had a left or a right bias, but whether any side bias was present). A one-way ANOVA of bias was not statistically significant ($F(3,36) = 2.31$, $p = .093$). Taken together, it appears that most errors are made one location away from the correct port. The proportion of perseverative errors or tendency to respond to one side do not substantially vary for the different treatment groups.

Distraction. The effects of tone and light distractors for each treatment group at each stimulus duration are presented in Figures 24 and 25. In general, the PFC group performed worse than other treatment groups, particularly at shorter stimulus durations. The light distractor decreased performance, particularly at the shorter stimulus durations, but this effect was consistent for each treatment group. The tone had little effect on performance.

A three-way ANOVA (treatment X stimulus duration X distraction) was used to statistically verify the effects of the manipulations. The main effects for treatment ($F(3, 36) = 10.44$, $p = .0001$), for stimulus duration ($F(5, 180) = 231.58$, $p = .0001$), and for distraction ($F(2, 72) = 86.35$, $p = .0001$) were all statistically significant. Post hoc tests of the main effect for treatment (Tukey-Kramer, $\alpha = .05$) indicated that the PFC group was less accurate than the HP and control groups and the ILn group was significantly less accurate than the HP group. When planned comparisons with the Bonferroni correction procedure were conducted, the ILn group was not significantly different from controls ($F(1,36) = 6.29$, $p = .017$; Bonferroni correction requires $p < .0167$). The ILn group seemed to perform worse in the distraction condition than in the previous condition without distractors (and no longer significantly more accurate than the PFC group). However, the

ILn group did not significantly differ from controls in the current distraction conditions. Similar to the previous condition without distractors, the PFC group performed poorly compared to the control and HP groups.

The deficit between the PFC and control groups was quantitatively greater at shorter stimulus durations. This was verified by a statistically significant treatment X stimulus duration interaction ($F(15,180) = 9.57$, $p = .0001$). The stimulus duration X distraction interaction was also significant ($F(10,360) = 15.07$, $p = .0001$). This interaction seems to reflect the decrease in accuracy with the distractor light was evident at briefer stimulus durations. The treatment X distraction interaction ($F(6,72) = .68$, $p = .66$) and the three way treatment X stimulus duration X distraction interaction ($F(30,360) = 1.46$, $p = .0588$, Geisser-Greenhouse $p = .12$, Huynh-Feldt $p = .096$) were not significant.

Reaction time was slower for ILn and PFC groups and also tended to be slower when the light was presented as a distractor (Figure 26). A two-way ANOVA (treatment X distraction) yielded significant main effects for treatment ($F(3,36) = 13.46$, $p = .0001$) and for distraction ($F(2,72) = 53.5$, $p = .0001$) but not for the interaction between these factors ($F(6,72) = .59$, $p = .73$). Post hoc analyses (Tukey-Kramer, $\alpha = .05$) indicated that the ILn and PFC groups were significantly slower than the HP and control groups.

The number of omissions during each session tended to be low for all groups (Figure 27). A two-way treatment X distraction ANOVA was conducted to test for any group differences during the distraction procedures. The main effects for lesion ($F(3,36) = 3.78$, $p = .0187$) and for distraction ($F(2,72) = 4.73$, $p = .0117$) were significant. However, post hoc analyses (Tukey-Kramer, $\alpha = .05$) indicated that none of the groups were significantly different from each other. None of the groups differed significantly from controls with planned comparisons with the Bonferroni correction although the p value for the comparison between the PFC group and control group was less than .05 ($F(1,36) = 5.09$, $p = .03$). The treatment X distraction interaction was not significant ($F(6,72) = .87$, $p = .52$).

Discrimination. The effects of dim and bright overhead illumination throughout each trial are depicted at all stimulus durations for all treatment groups in Figures 28 and 29. A three-way treatment X stimulus duration X discrimination ANOVA was used to test the effects of these manipulatons on accuracy. All main effects and interactions were statistically significant. The following values were obtained from this analysis: main effects; treatment ($F(3,36) = 11.78$, $p = .0001$), stimulus duration ($F(5,180) = 248.5$, $p = .0001$), discrimination ($F(2,72) = 199.1$, $p = .0001$), and for interactions; treatment X stimulus duration ($F(15,180) = 4.58$, $p = .0001$), treatment X discrimination ($F(6,72) = 3.29$, $p = .0064$), stimulus duration X discrimination ($F(10,360) = 2.88$, $p = .0018$), treatment X stimulus duration X discrimination ($F(30, 360) = 5.31$, $p = .0001$). Post hoc tests (Tukey-Kramer, $\alpha = .05$) indicated that the PFC group was significantly less accurate than all other treatment groups.

The bright light produced a decrease in accuracy for all treatment groups while the dim light had minimal effects. The decrease in performance with the bright light is clear at all stimulus durations. The bright light resulted in a slightly larger decrease in performance compared with no overhead light at short stimulus durations for the control, HP, and ILn groups. For the PFC group, however, the bright light produced a prominent decrease in performance at long stimulus durations. When compared with the no light condition, the decrease in performance is more substantial at longer stimulus durations for the PFC group. It is possible that the PFC group is showing a floor effect at the briefest stimulus duration. While the performance in Figure 29 for PFC rats is above chance with seven locations, when data from the two extreme ports were excluded the PFC group average decreased to 24.7%, a value closer to chance performance with five port locations. The near chance performance of the PFC group at the shortest stimulus duration (with the data from the extreme ports excluded) suggests that there may be a floor effect that accounts for the smaller difference between the bright and the no light conditions at the shortest stimulus duration. The bright light had a substantial effect on performance, particularly (1) for the PFC group, (2) at shorter stimulus durations for the control, HP, and ILn groups, and (3) for the PFC group at longer stimulus durations.

Reaction time was slower for PFC and ILn groups and in the bright light condition (Figure 30). These effects were tested with a two-way treatment X discrimination ANOVA. This analysis yielded significant main effects for treatment ($F(3,36) = 11.44$) and for discrimination ($F(2,72) = 75.2$, $p = .0001$) but not for the interaction between these variables ($F(6,72) = 2.17$, $p = .0558$ Geisser-Greenhouse $p = .0625$; Huynh-Feldt $p = .0558$). Post hoc analyses (Tukey-Kramer, $\alpha = .05$) indicated that the ILn and PFC groups were significantly slower than the HP and control groups. All groups showed an increase in reaction time during the bright condition. The trend for a significant interaction may reflect a less substantial increase in reaction time during the bright condition for the HP group.

The average omissions during each session were relatively low for all groups in the discrimination condition (Figure 27). A two-way treatment X discrimination ANOVA was used to statistically assess the effects of these manipulations. Significant main effects were found for treatment ($F(3,36) = 3.38$, $p = .0285$) and for discrimination ($F(2,72) = 14.40$, $p = .0001$). Post hoc tests (Tukey-Kramer, $\alpha = .05$) indicated that the PFC group committed more omissions than the HP group. Planned comparisons indicated that the PFC group was significantly different from controls ($F(1,36) = 6.73$, $p = .0136$) and the comparison between the ILn and control groups was less than .05 but failed to reach significance with the Bonferroni correction ($F(1,36) = 5.72$, $p = .0221$). The treatment X discrimination interaction was not statistically significant ($F(6,72) = 1.65$, $p = .15$).

Cueing. The effects of illuminating two lights on one side of the chamber (cue), four lights on either side of the chamber (no cue 4), or all seven lights (no cue 7) following a lever press are compared for each treatment group in Figures 31 and 32. It is important to note that while all lights did serve as S+ in the no cue7 condition, the analyses only included trials when ports 2, 3, 5, or 6 were S+. It appears that decreasing the number of illuminated port lights from seven to four provided some benefits for all treatment groups. Cueing with two lights on one side of the chamber provided a benefit over illuminating four port lights when the stimulus duration was relatively brief. In addition, the effects of treatment group (PFC performing the worst) and of stimulus duration that have been observed in previous conditions are also present in the cueing condition.

To test these observations, a three-way ANOVA (treatment X stimulus duration X cueing condition) was tested. The main effects for treatment ($F(3,36) = 14.54$, $p = .0001$), stimulus duration ($F(5,180) = 818.2$, $p = .0001$), and cueing condition ($F(2,72) = 133.6$, $p = .0001$) were statistically significant. The treatment X stimulus duration ($F(15,180) = 11.93$, $p = .0001$), treatment X cueing condition ($F(6,72) = 2.97$, $p = .012$), and stimulus duration X cueing condition ($F(10,360) = 31.28$, $p = .0001$) interactions were also statistically significant. The three-way treatment X stimulus duration X cueing condition interaction was not statistically significant ($F(30,360) = 1.47$, $p = .056$, Geisser-Greenhouse $p = .119$, Huynh-Feldt $p = .095$). Post hoc analyses (Tukey-Kramer, $\alpha = .05$) indicated that the PFC group was less accurate than control, HP, and ILn groups. Contrasts of the means for the cueing conditions were conducted to test for differences between the conditions. Both the cue ($F(1,36) = 221.9$, $p = .0001$) and the no cue4 ($F(1,36) = 176.3$, $p = .0001$) conditions were significantly different from the no cue7 condition but were not significantly different from each other ($F(1,36) = 2.62$, $p = .11$). The groups were more accurate when either two or four lights were illuminated following a lever press. The significant stimulus duration X cueing condition interaction reflects that the effect of cueing condition was present at shorter stimulus durations. The treatment X cueing condition interaction seems to reflect the disproportionate benefit of decreasing the number of port lights for the PFC group (compare performance during the no cue7 and no cue4 conditions for each treatment group in Figure 31 and 32).

It was predicted that providing cueing information should only be beneficial at brief stimulus durations. A two-way lesion X cueing condition ANOVA was conducted at the briefest stimulus duration to further test the nature of the significant interactions. This analysis yielded significant main effects of lesion ($F(3,36) = 5.16$, $p = .0045$) and cue ($F(2,72) = 119.8$, $p = .0001$). The interaction was significant with the Huynh-Feldt correction but not with the Geisser-Greenhouse correction ($F(6,72) = 2.30$, $p = .0435$, Geisser-Greenhouse $p = .0565$, Huynh-Feldt $p = .0481$). The interaction appears to reflect the lack of improvement by the PFC group when two port lights on one side of the chamber (cue condition) were illuminated following a lever press. Post hoc analyses (Tukey-Kramer, $\alpha = .05$) indicated that the PFC group was significantly less accurate at the briefest stimulus duration compared to the ILn and the control groups. Planned comparisons between the cueing conditions suggested that each condition was significantly different from the other conditions (cue vs no cue 4: $F(1,72) = 34.5$, $p = .0001$; cue vs no cue 7: $F(1,72) = 235.3$, $p = .0001$; no cue 4 vs no cue 7: $F(1,36) = 89.5$, $p = .0001$). Illuminating two port lights on one side of the chamber leads to improved performance (at least for control, HP, and ILn groups). Illuminating four ports resulted in better performance for all groups than illuminating all seven ports.

The PFC and the ILn groups were slower than the HP and the control groups in all cueing conditions (Figure 33). These effects were tested with a two-way ANOVA (treatment X cueing condition). The main effects for treatment ($F(3,36) = 10.1$, $p = .0001$) and cueing condition ($F(2,72) = 6.05$, $p = .0037$) were significant but the interaction between the factors was not ($F(6,72) = 1.95$, $p = .084$). Post hoc analyses (Tukey-Kramer, $\alpha = .05$) indicated that the ILn and PFC groups were slower than the HP and control groups.

The number of omissions per session (divided by three sessions as the cueing condition was manipulated between session) was highly variable and did not show a consistent difference between the treatment groups (Figure 27). A two-way treatment X cueing condition ANOVA yielded a significant effect of cueing condition ($F(2,72) = 18.6$, $p = .0001$), but not for treatment ($F(3,36) = 2.19$, $p = .11$) or the interaction between the two variables ($F(6,72) = 1.56$, $p = .17$). It appears that all treatment groups committed fewer omissions in the no cue7 condition. This finding is a bit surprising, especially considering performance was poorest in the no cue 7 condition. This effect may be due to an increased tendency to respond when some trials with the extreme ports are included because these trials are usually reinforced.

Histological Analyses. Lesions of the ILn bilaterally affected the intended target in all cases. Pathology was characterized by dense gliosis for all animals. Figure 34 depicts a typical ILn lesion. The figure shows anterior (panels A, B, E, F at 6.5 mm anterior to IA; compare with Plate 28 in Paxinos & Watson, 1986) and posterior (panels C, D, G, H at 5.5 mm anterior to IA; compare with Plate 32 in Paxinos & Watson, 1986) regions in each hemisphere for one rat. Each bottom panel shows the area near the arrow in the figure immediately above at a higher power. In the largest lesions, the AP extent was + 7.7 mm to +5.0 mm relative to IA. In all animals, the centrolateral and paracentral areas were substantially damaged. The damage to the centromedial nuclei was more variable. As has been the case in previous studies, there was damage to adjacent thalamic nuclei. The mediodorsal nucleus (MD in Figure 34) was consistently affected in all rats. Larger lesions tended to involve the anterior and the ventromedial thalamic nuclei. The one animal that did not reach criterion on initial retraining did not show unusual pathology.

PFC lesions bilaterally affected the target in all cases. Pathology was characterized by complete removal of tissue and by gliosis in some cases. Figure 35 depicts a typical PFC lesion. The panels represent anterior to posterior sections within the same rat at 4.0 mm anterior to bregma (A; compare with Plate 7 in Paxinos & Watson, 1986), 2.5 mm anterior to bregma (B; compare with Plate 9 in Paxinos & Watson, 1986), and 1.0 mm anterior to bregma (C; compare with Plate 14 in Paxinos & Watson, 1986). In all cases, damage was observed in Cg 1, Cg 3 and Fr 2 cortical areas as described by Paxinos &

Watson (1986). In larger lesions, Fr 1 and infralimbic cortex tended to be involved. The largest lesion extended from + 5.2 mm to + 0.6 mm relative to bregma. The one animal that did not reach criterion on initial retraining did not show unusual pathology.

The HP group showed signs of pathology in both dorsal and ventral areas in all animals. The damage usually appeared as gliosis or as removal of tissue. Figure 36 depicts a typical HP lesion. The figure presents anterior to posterior damage in the same rat. Panel A depicts pathology 5.5 mm anterior to IA (compare with Plate 32 in Paxinos & Watson, 1986). Panels B and C display pathology in each hemisphere 4.5 mm anterior to IA (compare with Plate 36 in Paxinos & Watson, 1986). Panels D and E depict the damage in each hemisphere 3.5 mm anterior to IA (compare with Plate 40 in Paxinos & Watson, 1986). With smaller lesions, there was some sparing of the dentate gyrus dorsally and/or some ventral tissue, but the CA subfields were consistently affected in each animal. Larger lesions did not extend substantially beyond the intended areas but rather resulted in more complete destruction of the target.

Discussion

Effects of ILn lesions. Lesions of the ILn did not produce substantial effects on the ability to accurately respond to brief visual stimuli. In most of the behavioral manipulations, the ILn group tended to be less accurate than the control group but under no conditions with brief visual stimuli was this difference statistically significant. The only sign of an accuracy impairment for the ILn group was a significant deficit compared to the HP group when the short stimulus durations were initially introduced and in the distraction condition with the bright overhead light. It is difficult to attribute these findings to a disruption in speed of stimulus processing or greater susceptibility to distraction as the ILn group was not significantly different from controls.

The lack of a substantial effect on accuracy with ILn lesions is consistent with previous studies that have found spared olfactory discrimination and serial reversal learning following ILn lesions (Burk & Mair, 1998; Zhang, et al, 1998). Taken together, these findings indicate that ILn lesions do not disrupt the ability to perceive and to respond differentially to stimuli (even when briefly presented) in different sensory modalities. These results also limit the likely explanations for the deficits previously found with ILn lesions in tests of remembering. ILn lesions have been shown to disrupt accuracy in DMS with position cues, olfactory continuous DNMS, and DNMS trained in a radial arm maze (Burk & Mair, 1998; Mair, et al, 1998; Zhang, et al, 1998). It does not appear that an impairment in the ability to perceive, process, and accurately respond to brief stimuli can account for the previous findings with ILn lesions on memory tests. Furthermore, it seems as though slow stimulus processing, at least as tested by the seven choice reaction time task, is unaffected by ILn lesions and cannot account for previous accuracy deficits in tests of remembering associated with ILn damage. The psychological effects of ILn lesions that result in widespread deficits on a number of tests of remembering remain unclear.

The ILn group did show a significant accuracy deficit when tested with a visual stimulus of relatively long duration immediately following surgery. This result suggests that the ILn lesion produced a deficit in performing the relatively simple task immediately following surgery. There are a number of explanations for this result including difficulty recovering from excitotoxic surgery or a disrupted ability to remember previously learned stimulus-response relationships. Regardless of the nature of the deficit, it is clear that with sufficient retraining the ILn group could perform the requirements of the task.

The ILn lesion was associated with slower median reaction time in this choice reaction time task. Reaction time was consistently slower for this group even during initial retraining when the target stimulus was presented for three seconds. This deficit was also present responding to brief stimuli, with distractors or changes in discriminability, or when cues were available. The ILn group was not differentially slower during the behavioral manipulations (e.g., at shorter stimulus durations or when the bright light was presented as a distractor or during stimulus discrimination) suggesting that the slow responding is not primarily due to changes in the difficulty of the task. Rather, it seems to be a prevalent feature across all conditions tested in this experiment. Given the relative insensitivity of the reaction time measure to changes in stimulus processing demands, it seems reasonable to conclude this measure does not primarily reflect the changes in the ability to respond to brief stimuli. The reaction time deficit may represent a slowing of motor responding that is prevalent across all conditions in this task.

It has been shown that ILn lesions do not disrupt the speed of lever pressing when a FR 1 requirement was used (Burk & Mair, 1998). This result suggests that ILn lesions do not produce gross deficits in speed of motor responding. In previous studies using DMS with position cues, ILn lesions produced a significant increase in median reaction time (Burk & Mair, 1998). Both the seven choice reaction time task and the DMS task require the ability to respond based on information in the environment. Taken together, these results suggest that ILn lesions may critically affect response speed when information from the environment must be used to prepare and execute a motor response.

The involvement of the ILn in utilizing information to prepare a response is consistent with the anatomical projections of the ILn (Berendse & Groenewegen, 1990). The ILn sends substantial projections to the striatum, an area that has been associated with bradykinesia, that is, slow movements in conditions such as Parkinson's disease (Stern, 1990). It has been speculated that bradykinesia associated with diseases of the basal ganglia is due to a loss of excitatory dopaminergic innervation in the direct pathway from the putamen to the internal segment of the globus pallidus and to the substantia nigra pars reticulata (Wichmann & DeLong, 1996). There is evidence in squirrel monkeys that the ILn provide glutamatergic projections to striatum (Sadikot, Parent, Smith, & Bolam, 1992). Furthermore, these ILn projections terminate preferentially on the direct pathway within striatum in squirrel monkeys (Sidibe & Smith, 1996). The slow responding associated with ILn lesions in this task may be due to a disruption of the direct pathway within the basal ganglia due to a loss of excitatory innervation from the ILn. Thus, slow responding associated with diseases of the basal ganglia and ILn lesions may be due to a common mechanism (i.e., loss of excitatory dopaminergic innervation of the internal segment of the globus pallidus and the substantia nigra pars reticulata). Slow responding in DMS with position cues has been reported following lesions of the ILn (Burk & Mair, 1998) and of the olfactory tubercle in ventral striatum (Burk & Mair, 1999). These studies provide some evidence that at least in DMS with position cues, lesions of the ILn and striatum both produce slow responding. It remains to be seen whether striatal lesions produce slow responding in this choice reaction time task.

Any interpretation of the effects of ILn lesions in this task must be made with caution as several adjacent nuclei were affected. The finding of damage extending outside the target region is consistent with previous use of this lesion technique. The damage to the anterior thalamic nuclei is likely unimportant because complete lesions of HP, the structure providing the primary efferents either directly or via the mammillary bodies to the anterior thalamic nuclei (Bayer, 1985), did not have any substantial effect on performance. The effects of damage to the mediodorsal nucleus need to be considered. Previous studies have failed to find deficits following mediodorsal nucleus lesions in DMS with position cues or olfactory DNMS (Burk & Mair, 1998; Zhang, et al, 1998). Given the deficits with PFC lesions in this task and the projections from the mediodorsal nucleus to PFC (Groenewegen, 1988), it would seem important to study the effects of mediodorsal nucleus lesions in this task. Lesions of the ventromedial nuclei produce accuracy and slow responding in DMS, albeit the deficits are less severe than those observed following ILn lesions (Burk & Mair, 1999a). Ventromedial nuclei lesions do not affect olfactory continuous DNMS (Burk, et al, 1998). Thus, the ventromedial lesion does not appear to produce a deficit as severe as observed with ILn lesions in tests of remembering. However, the qualitatively similar effects of ventromedial nuclei lesions to ILn lesions in DMS with position cues suggests that it will be important to study the effects of ventromedial nuclei lesions in the seven choice reaction time task.

Effects of PFC lesions. PFC lesions produced a significant decrease in accuracy when briefer stimulus durations were included. A number of findings suggest this deficit cannot be attributed to an inability to respond to the ports based on a light stimulus or to a disruption of motivation. First, PFC lesioned animals continued to be able to respond accurately at longer stimulus durations. This result suggests the PFC group could perform all the requirements of the task as long as there was a relatively long stimulus duration.

Second, lesions of PFC did initially disrupt the ability to respond during trials with a long stimulus duration trained immediately following surgery. However, with sufficient training all PFC rats were able to reach a criterion of 90% accuracy for two consecutive sessions. Thus, PFC lesioned animals could perform comparable to other groups if the S+ was presented for a sufficient duration. Accurate responding at longer stimulus durations suggests that PFC lesions did not disrupt motivation or the ability to differentially respond to the ports in this task. Third, omissions were consistently low in all conditions although there was a significant difference between the control group and the PFC group with planned comparisons in the discrimination condition (and the distraction condition except when the Bonferroni correction was applied). The low number of omissions and accuracy at long stimulus durations suggests that the PFC group was motivated to perform the task.

One important caveat must be introduced with respect to the deficits at brief stimulus durations following PFC lesions. The analysis at each port suggested that all groups performed accurately (> 95%) at the extreme ports (Figure 20). One interpretation for these results is that there is a ceiling effect and thus it is difficult to evaluate whether a difference exists between treatment groups in responding to the extreme ports. However, it is clear that the PFC group was able to respond accurately to brief stimuli when the correct port was adjacent to the arm. This finding suggests that the PFC group was able to accurately respond to brief visual stimuli when conditions were relatively easy. It is not exactly clear what makes the extreme ports "easier" but this consistently observed effect could be due to the fewer number of ports adjacent to the S+ (there is only one port adjacent to the extreme ports) and thus fewer ports at which errors are likely to be made. This finding does not imply that speed of stimulus processing is normal following PFC lesions. Rather, the slowing is only clear during the more difficult trials in which the correct port is not adjacent to the arm.

Analyses were carried out to assess whether the PFC lesion resulted in a side bias or a tendency to perseverate. The results indicated that the deficits associated with PFC damage cannot be attributed to either side bias or perseveration. Furthermore, there was evidence that even when committing errors, the PFC group was responding to the port light that briefly remained illuminated after the arm photocell was broken. The analysis of the distance of each error from the correct port suggested that the pattern of errors by the PFC group was comparable to other treatment groups. That is, most errors were made one port away from the correct port. The analysis of errors suggests that the PFC animals were responding to the appropriate stimulus but simply made more errors.

The PFC group was not differentially affected by briefly presenting either a tone or a bright overhead light after the arm photocells were broken. In previous research, medial PFC lesions produced a disproportionate increase in reaction time and a trend for a decrease in accuracy when white noise was presented as a distractor (Muir, et al, 1996). It may be that white noise serves as a more effective distractor in choice reaction time tasks with rats. The current study decreased the likelihood of habituation to the stimulus by presenting tones of different frequencies, but did not effectively distract any treatment groups. The use of white noise in future studies may be a more potent distractor and allow more direct comparisons with findings in the five choice reaction time task. When the bright light was used as a distractor, there were decreases in accuracy, but these effects did not serve to differentiate any treatment groups.

PFC lesions had some interesting effects on the ability to use cueing information.

PFC lesioned animals showed a more substantial increase when the number of potential ports that could be reinforced was decreased from seven to four. The PFC group was still significantly impaired compared to the control group even with the number of illuminated ports was decreased. It is clear that PFC animals can take advantage of some cues that minimize the stimulus processing demands of the task although they do not perform as well as controls. PFC lesions impaired the ability to take advantage of the cues when only two port lights were illuminated. With side cues (i.e., two lights illuminated on one side of the chamber) the PFC group performed comparable to having four lights illuminated. All other treatment groups showed an improved performance at the briefest stimulus duration with side cues. The lack of improvement by the PFC group when two ports were illuminated may be due to the random nature of the task. The two lights could either be on the left or right side of the chamber, but it was not possible for the rat to know which side would be cued. PFC lesions may impair the ability for a more "flexible" use of cueing information that can vary from trial to trial. Taken together, the cueing results suggests that PFC lesioned animals could take advantage of cues that were consistent throughout each session (i.e., same four lights illuminated compared with seven lights illuminated) but were unable to benefit when the cueing information varied on a trial-by-trial basis.

The accuracy of the PFC group appeared to be differentially affected by the stimulus discriminability manipulation. In particular, accuracy significantly declined for the PFC group during trials with long stimulus durations when the bright overhead light was illuminated throughout the trial. The other treatment groups showed a more moderate decrease in performance during bright trials with long stimulus durations. It is not surprising that the decrease in performance would extend to longer stimulus durations during the bright condition because the light is illuminated throughout the trial. It may be that PFC lesions result in a greater susceptibility to deficits when discriminability of the target stimulus is decreased. The lack of an effect with the dim overhead light indicates that only the more extreme change in the discriminability of the port light affected performance of the PFC group.

A deficit in stimulus discriminability is unlikely to explain the deficits associated with PFC damage at brief stimulus durations without overhead illumination. This result is consistent with previous research that found a trend for a decrease in accuracy at a briefer stimulus duration following medial PFC lesions in a five choice serial reaction time task (Muir, et al, 1996). A brief presentation of the visual stimulus requires quick perception and processing of the stimulus. One explanation for the deficits at brief stimulus durations that PFC lesions produce slower processing of stimulus information and the functional consequences can be measured when the animals must respond to brief stimuli. PFC receives input from a number of cortical areas that analyze sensory information (Kolb & Tees, 1990). Lesions of PFC may result in slower processing of stimulus information due to disruption of the connections with these other cortical areas. The PFC lesions destroyed medial agranular cortex, the rat homologue of the frontal eye fields (Neafsey, et al, 1986). The medial agranular cortex sends projections to the superior colliculus and has reciprocal connections with visual cortex and may be an important area for analyzing visual information (Neafsey, et al, 1986). It has been argued that damage to the frontal eye fields can affect visual scanning, a deficit that could disrupt the ability to respond to brief stimuli (Mesulam, 1981). It is unclear whether the deficits in the current study are due specifically to impaired scanning, slow perceptual processing, or both. The anatomical connections indicate that the PFC is a critical structure for the behaviors and the sensory processes necessary for locating and analyzing briefly presented sensory information.

PFC lesions produced an increase in reaction time across all versions of this task. The slow responding was present with long and short stimulus durations as well as during manipulations of distractibility, discriminability, and cueing. Previous studies have reported slow reaction time following PFC lesions in the five choice serial reaction time task and in delayed conditional discrimination tasks (Bauer & Fuster, 1976; Mair, et al, 1998; Muir, et al, 1996). The consistency of the slow reaction times across all behavioral manipulations suggest this deficit cannot be attributed to speed of stimulus processing. The anatomical connections support the contention that motor function may be affected by these lesions. There are a number of parallel cortico-basal ganglia-thalamo-cortical connections that have been described (Alexander, et al 1986). Lesions of PFC may produce striatal dysfunction by disrupting these connections and thereby result in motor deficits.

Taken together, the deficits following PFC lesions appear to affect several aspects of performance in the seven choice reaction time task. The decrease in accuracy at brief stimulus durations indicates that speed of stimulus processing is slow. The PFC group also appeared to have some deficits utilizing cueing information and when the discriminability of the target stimulus was decreased. The reaction time deficit across all behavioral manipulations may reflect a general motor deficit. Given the critical anatomical connections between PFC and sensory and motor areas, it is not surprising that several aspects of performance were disrupted.

Effects of HP lesions. Radiofrequency lesions of HP did not substantially affect accuracy or speed of responding to briefly presented visual stimuli. This group was not differentially affected by presentation of a distractor, decreasing the discriminability of the target stimulus, or using cues to respond to brief stimuli. In many of the conditions, the HP group tended to perform better than controls, but this difference did not reach statistical significance.

The lack of a behavioral deficit following HP lesions is not likely due to limited pathology. The HP lesion involved more sites than the ILn or PFC lesions. The lesion appeared to produce substantial damage to dorsal and ventral portions of HP upon histological examination. The degree of damage is comparable to previous studies in our laboratory with radiofrequency HP lesions. It has been shown that similar lesions disrupt the ability to learn to swim to a submerged platform when starting from different locations in a Morris Water Maze (Mair, et al, 1998). In addition, delay dependent deficits in radial arm maze DNMS have been reported with similar HP lesions (Mair et al, 1998). Thus, in previous studies it has been shown that these lesions produce deficits in spatial tasks thought to be sensitive to HP function.

The normal performance of the HP group is not surprising given the negative results in previous studies with HP lesions. Knife cuts of the perforant path, an important afferent to HP and related areas (Bayer, 1985), did not affect performance in the five choice serial reaction time task (Kirkby & Higgins, 1998). Furthermore, a vigilance task requiring responding to brief stimuli was unaffected by HP lesions (Miner, et al, 1997). The current study is consistent with previous findings and suggests that HP lesions do not affect the ability to respond to brief visual stimuli.

The current experiment failed to find any substantial effect of HP lesions on reaction time. Previous studies with HP lesions in DNMS with position cues found an accuracy deficit but not a significant effect on reaction time (Porter, et al, 1999). Even in tasks sensitive to HP function, reaction time appears to be unaffected. Taken together, these studies suggest that HP lesions do not produce clear motor impairments in two tasks (DMS with position cues and seven choice reaction time task) requiring an integration of sensory information and motor responding.

Implications for Response Speed Deficits in Neuropsychological Disorders.

Korsakoff's disease. Previous studies have provided evidence that Korsakoff patients are slow processing stimuli from the environment. Evidence for this proposition has come from several experimental paradigms including: presentation of brief stimuli, backward visual masking (Oscar-Berman, 1973), dichotic listening (Glosser, et al, 1976; Parkinson, 1979), and judging the sequence of two tones (Meudell, et al, 1991). In a five choice serial reaction time task, a rodent model of Korsakoff's disease resulted in decreased accuracy when the stimulus duration was briefer and when distractors were presented (Langlais, et al, 1997). None of these tasks has a demanding mnemonic requirement suggesting that the well established amnestic symptoms in Korsakoff's disease cannot account for these deficits.

Recent findings suggest that ILn lesions produce deficits comparable to those observed with an animal model of Korsakoff's disease on delayed conditional discrimination tasks using position cues, olfactory stimuli, or trained in a radial arm maze (Burk & Mair, 1998; Mair, et al, 1998; Zhang, et al, 1998). Lesions of PFC and HP do not produce the same pattern of impairments across all of these tasks (Koger & Mair, 1994; Mair, et al, 1998; Porter & Mair, 1997). One goal of the current studies was to test whether ILn lesions produced deficits in a behavioral procedure designed to assess speed of stimulus processing. It does not appear that the effects of ILn lesions can account for deficits in processing brief stimuli that have been shown with animal models of Korsakoff's disease and in human subjects. ILn lesions resulted in consistently slower reaction time that did not vary across any manipulations of the stimulus parameters in this task. Accuracy was not significantly different from controls in any behavioral condition with brief stimulus durations suggesting that ILn lesions did not affect the ability to accurately respond to brief stimuli. Rather, it seems more likely that the ILn lesions resulted in slow motor function that cannot account for previously reported slow stimulus processing. These findings also indicate that lesions of HP cannot account for stimulus processing deficits as these lesions did not substantially affect performance in this task.

PFC lesions produced a disproportionate decrease in accuracy when the stimulus duration was decreased. Briefly presented stimuli place a demand on speed of stimulus processing. The stimulus must be perceived and located quickly to respond correctly in this task. Thus, the PFC lesion appears to affect the ability to process briefly presented stimuli. This finding suggests that PFC damage may be important in producing the slow stimulus processing deficits associated with Korsakoff's disease. This interpretation is consistent with other reports suggesting that some deficits in Korsakoff's disease, including judgments of temporal order and the Wisconsin Card Sorting task, may be due to PFC damage (Janowsky, et al, 1989; Squire, 1982). However, further research is warranted to address some of the inconsistencies with this interpretation. One of the major problems with the involvement of PFC damage in deficits associated with

Korsakoff's disease is that PFC pathology is frequently not observed during postmortem examination (Malamud & Skillicorn, 1956; Victor, et al, 1989). It may be that a more careful comparison of speed of stimulus processing in Korsakoff patients with and without PFC damage will clarify the relationship between stimulus processing speed and PFC pathology in Korsakoff's disease. It is clear that further research is necessary to establish whether slow stimulus processing deficits in Korsakoff's disease result from PFC dysfunction.

Schizophrenia. Patients diagnosed with schizophrenia require a longer interstimulus interval in visual backward masking (Braff & Sacuzzo, 1981; Lieh-Mak & Lee, 1997; Saccuzo & Braff, 1981; Sacuzzo, et al, 1974). One interpretation of these findings is that they represent an impairment in early stimulus processing that may be critical in producing signs of schizophrenia. Specifically, slow information processing may disrupt the integrity of information in iconic storage and impair the ability to form a stable representation of the environment (Braff & Sacuzzo, 1981).

It would be beneficial to develop a task that could be used to test changes in speed of processing in animal models of schizophrenia. Some preliminary evidence has been developed using the five choice serial reaction time task. Administration of amphetamine has been used to model symptoms of schizophrenia in animals. It was found that amphetamine decreased accuracy in the five choice serial reaction time task following 6-hydroxydopamine lesions of the dorsal noradrenergic bundle (Cole & Robbins, 1987). Unfortunately, stimulus duration (0.5 s) was not varied in this experiment. This study provides preliminary evidence that administration of amphetamine can affect performance in a choice reaction time task although the nature of the deficit is not well established.

PFC dysfunction has long been associated with schizophrenia (Gur, 1995). It is intriguing that the PFC lesion in Experiment 2 produced a pattern of responding that is consistent with an impairment in speed of stimulus processing. The effects of PFC lesions provide preliminary evidence that the seven choice serial reaction time task may be useful for testing the ability to respond to brief stimuli in animal models of schizophrenia. This task may also provide an opportunity to test whether drug treatments can improve speed of stimulus processing following brain damage or in animal models of schizophrenia.

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APPENDIX

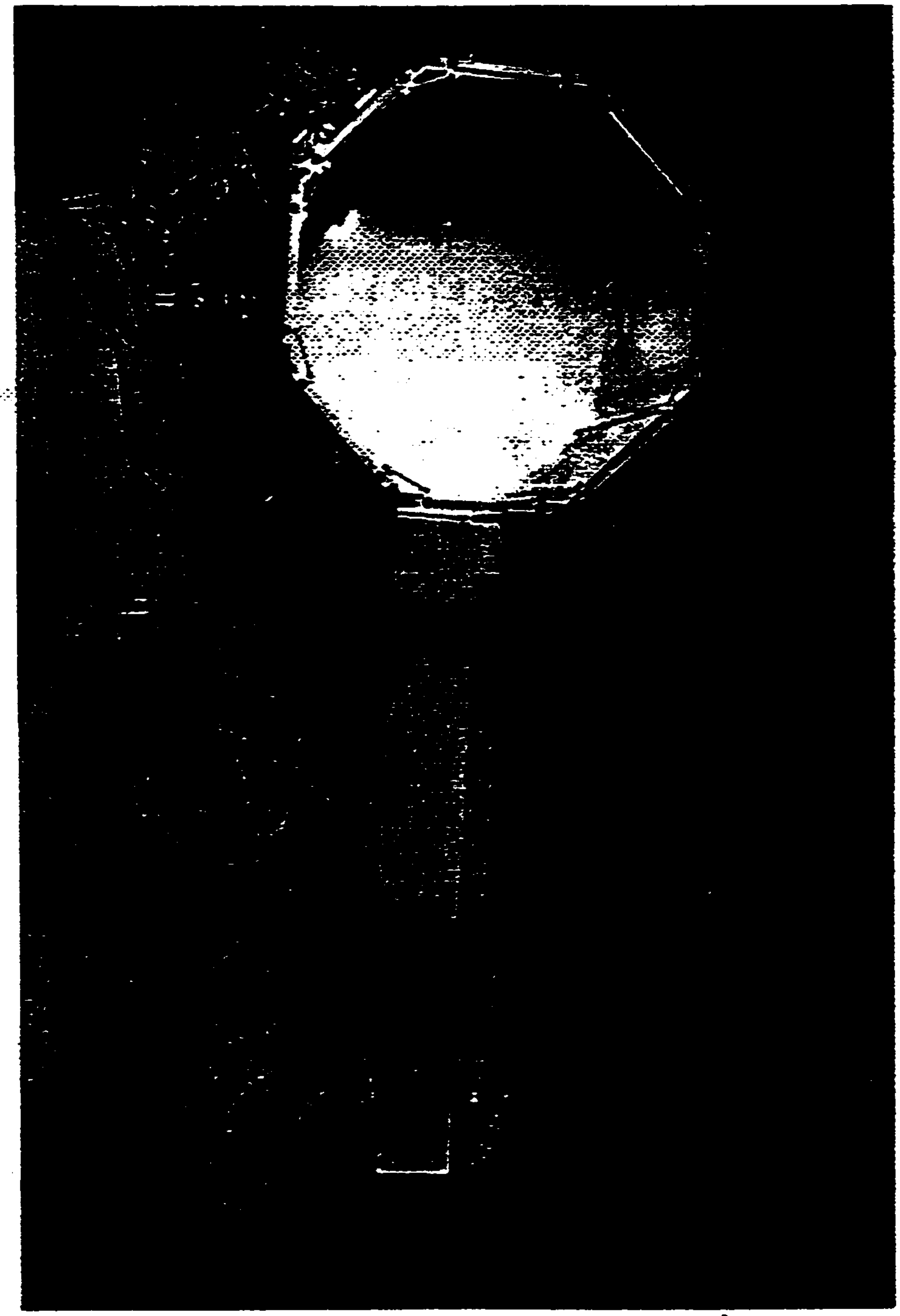

Figure 1. Overhead view of the training apparatus. See text for details regarding equipment and dimensions of the chamber.

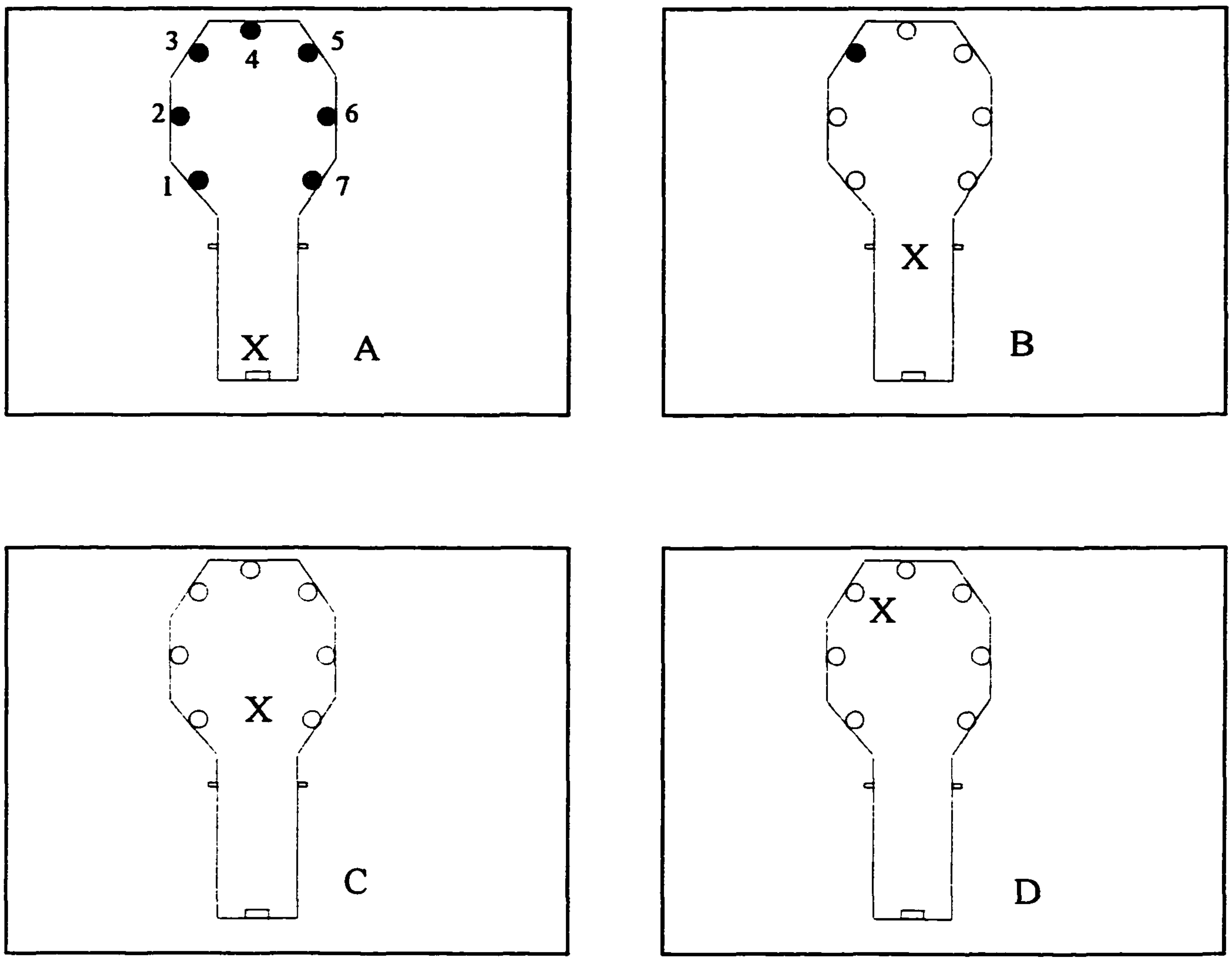

Figure 2. A schematic of the chamber labeling each port (A). Shaded circles represent illuminated lights and the 'X' designates the rat. Following a lever press, all port lights were illuminated (A). After breaking the arm photocells, six port lights were turned off and one remained illuminated (B). After a randomly determined stimulus duration, the last port light was turned off (C). Reinforcement was provided for responding to the port that remained illuminated after the arm photocells were broken (D).

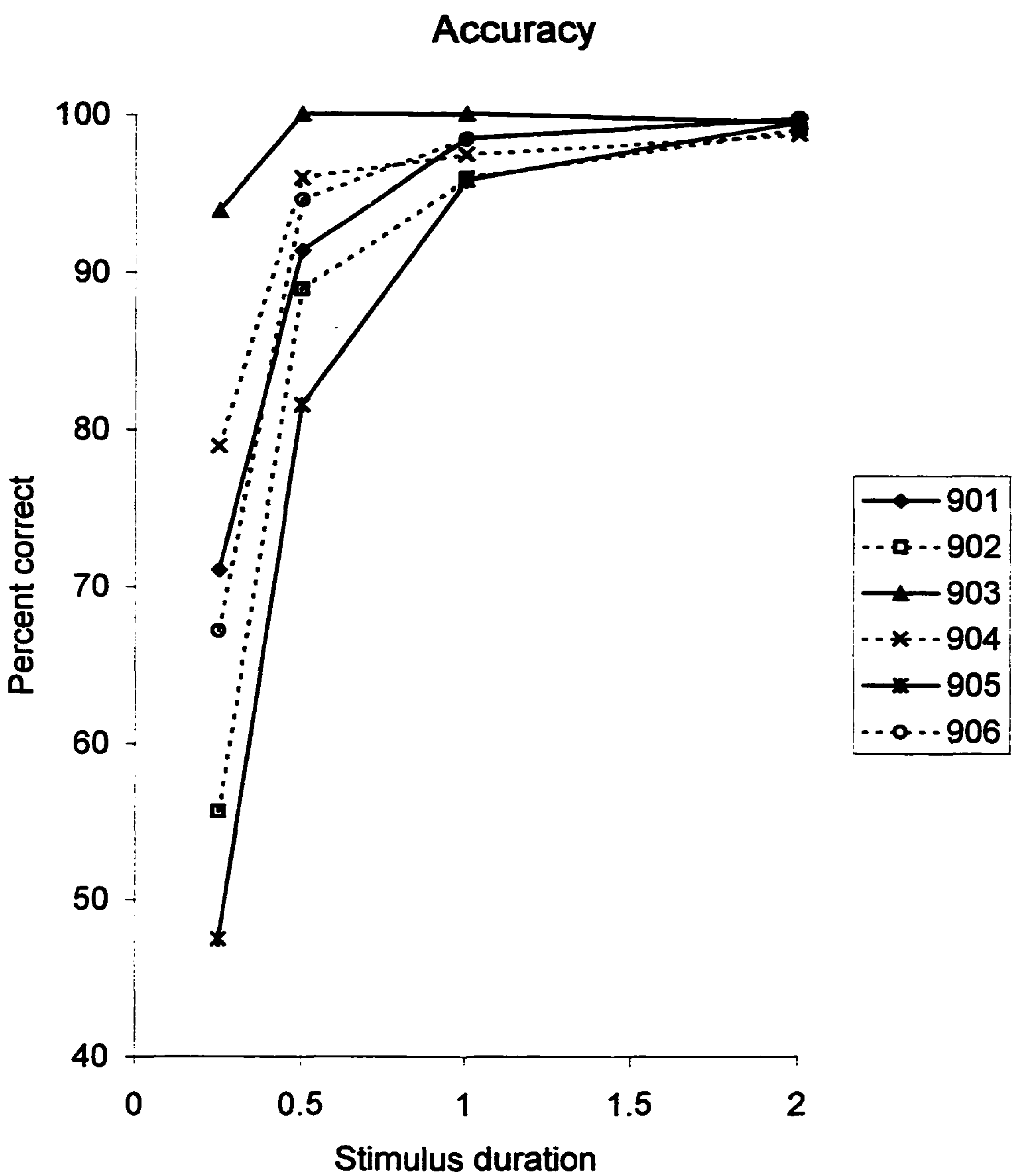

Figure 3. Percent correct for individual animals at each stimulus duration.

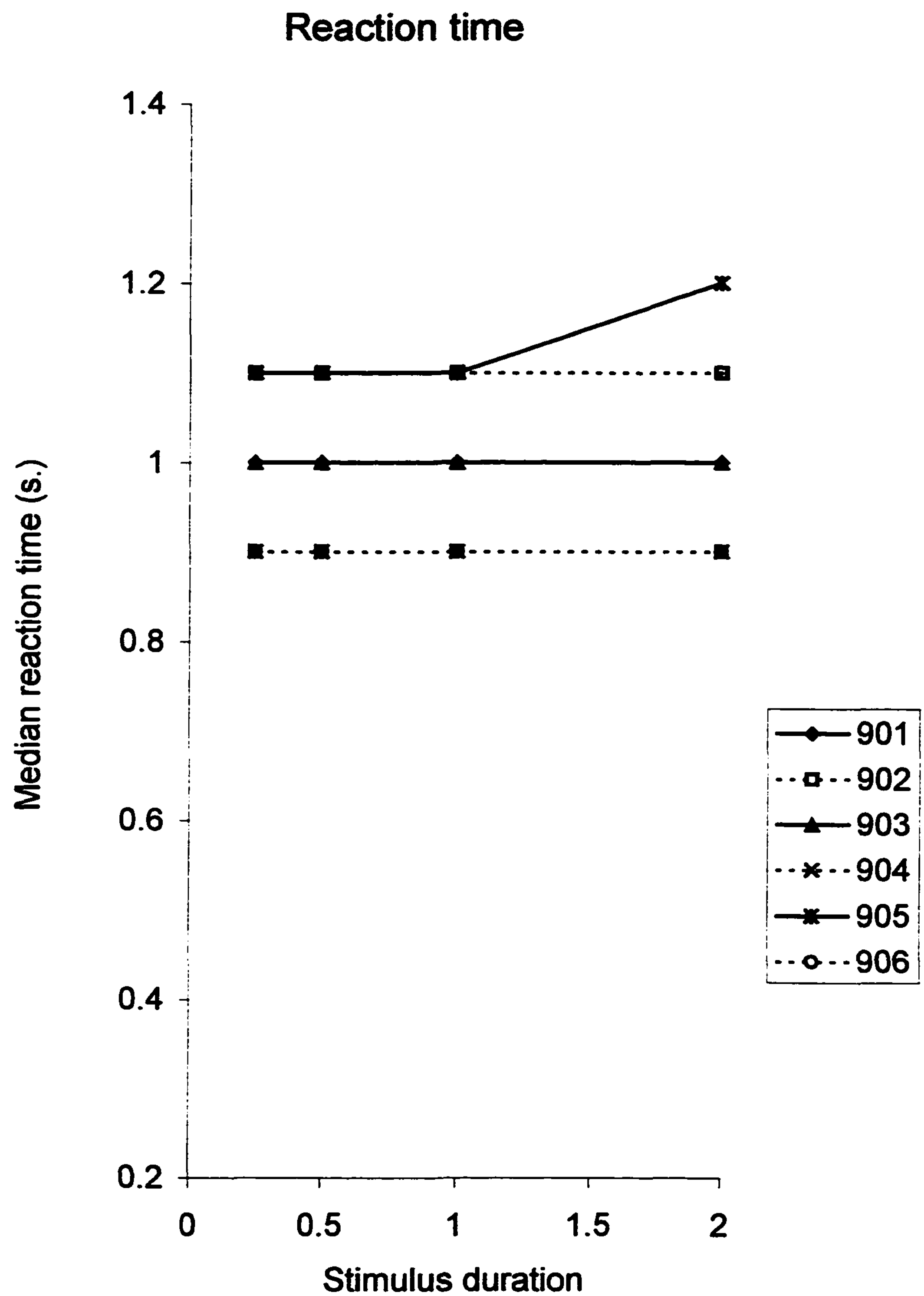

Figure 4. Median reaction times for individual animals at each stimulus duration.

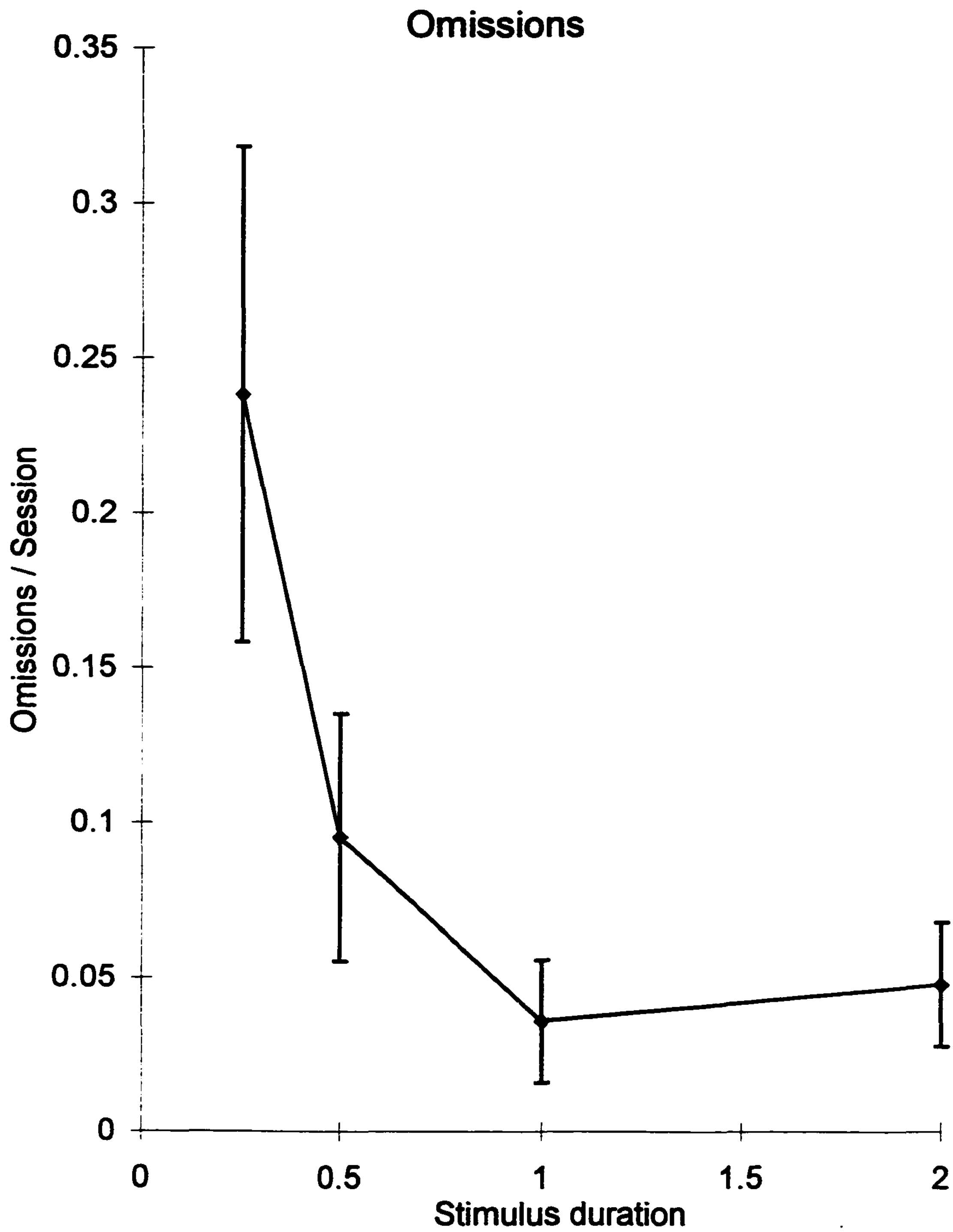

Figure 5. Average number of omissions during each session at each stimulus duration. Error bars represent standard error from the mean (SEM).

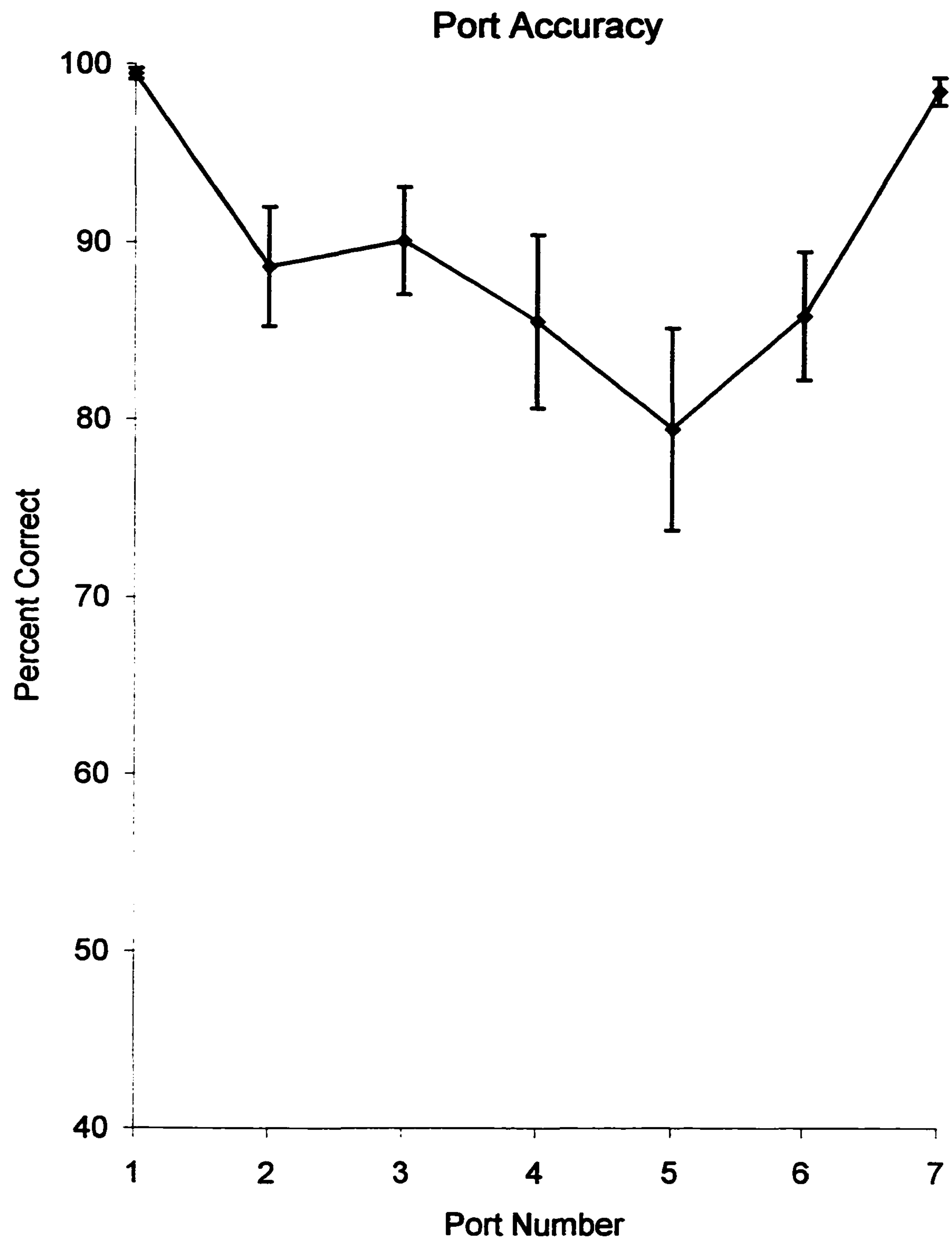

Figure 6. Mean percent correct at each port. Error bars represent SEM.

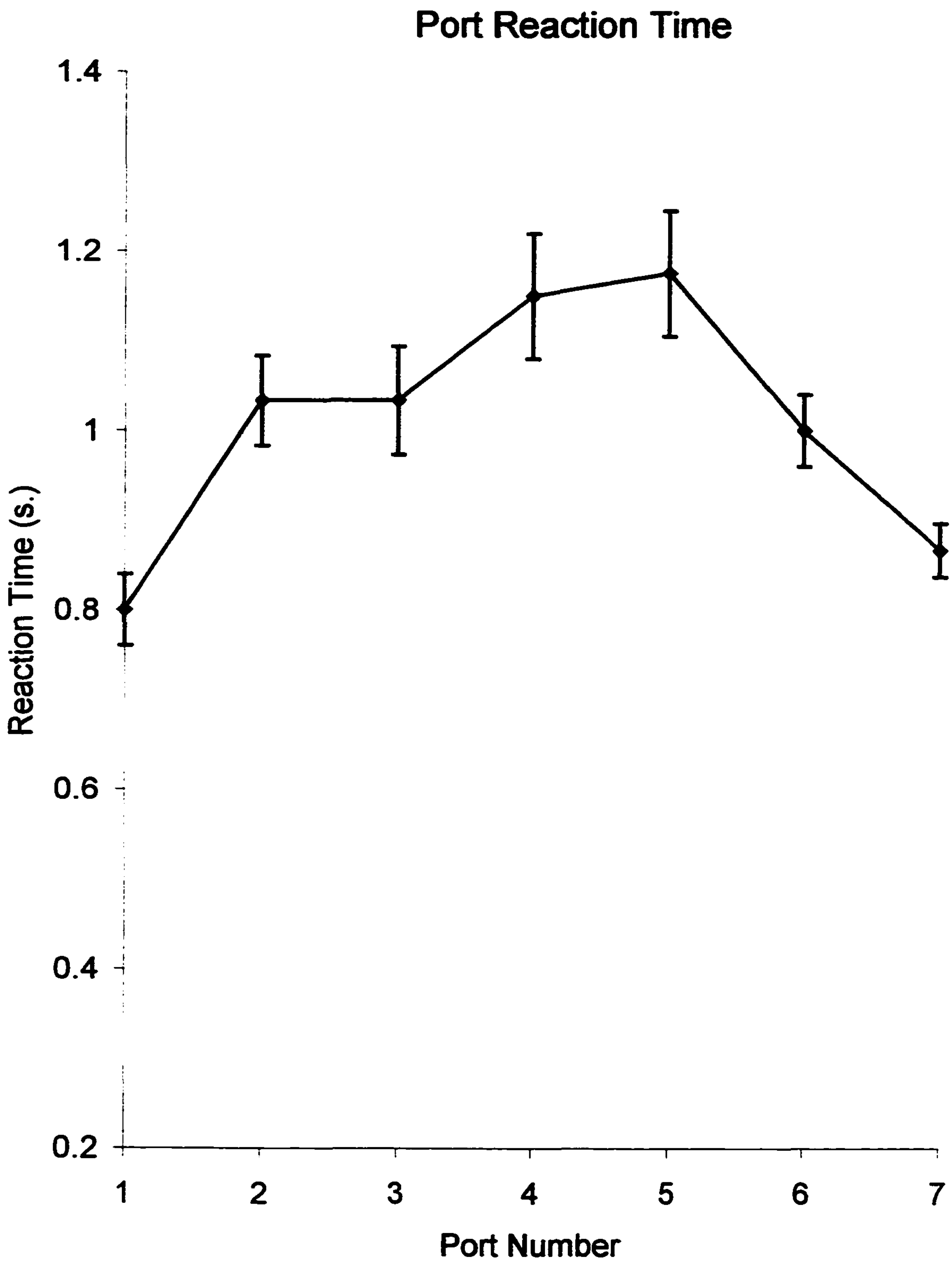

Figure 7. Mean of the median reaction time at each port. Error bars represent SEM.

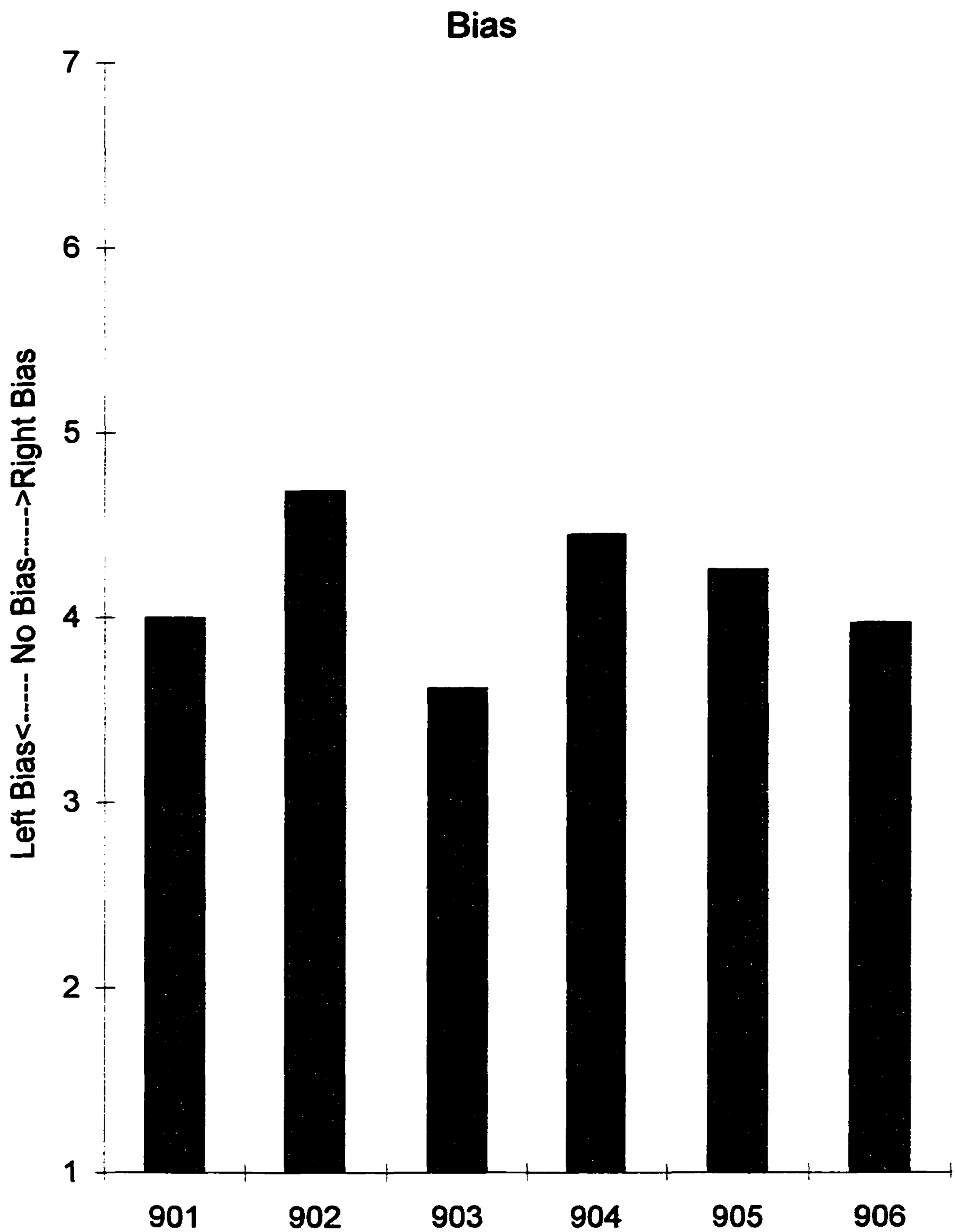

Figure 8. Side bias for individual rats.

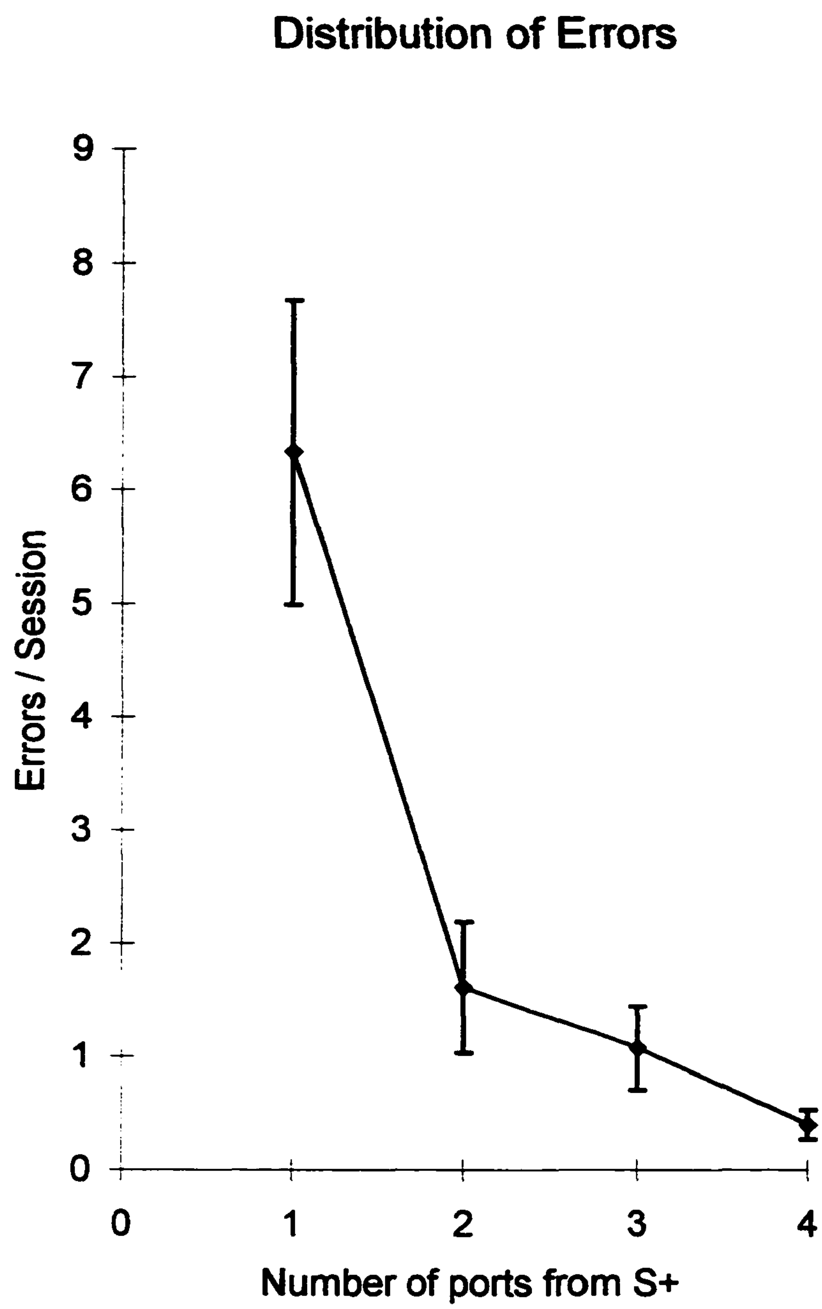

Figure 9. The abscissa represents the number of ports an error was made from the correct port. The ordinate is the average number of errors during each session. Error bars represent SEM.

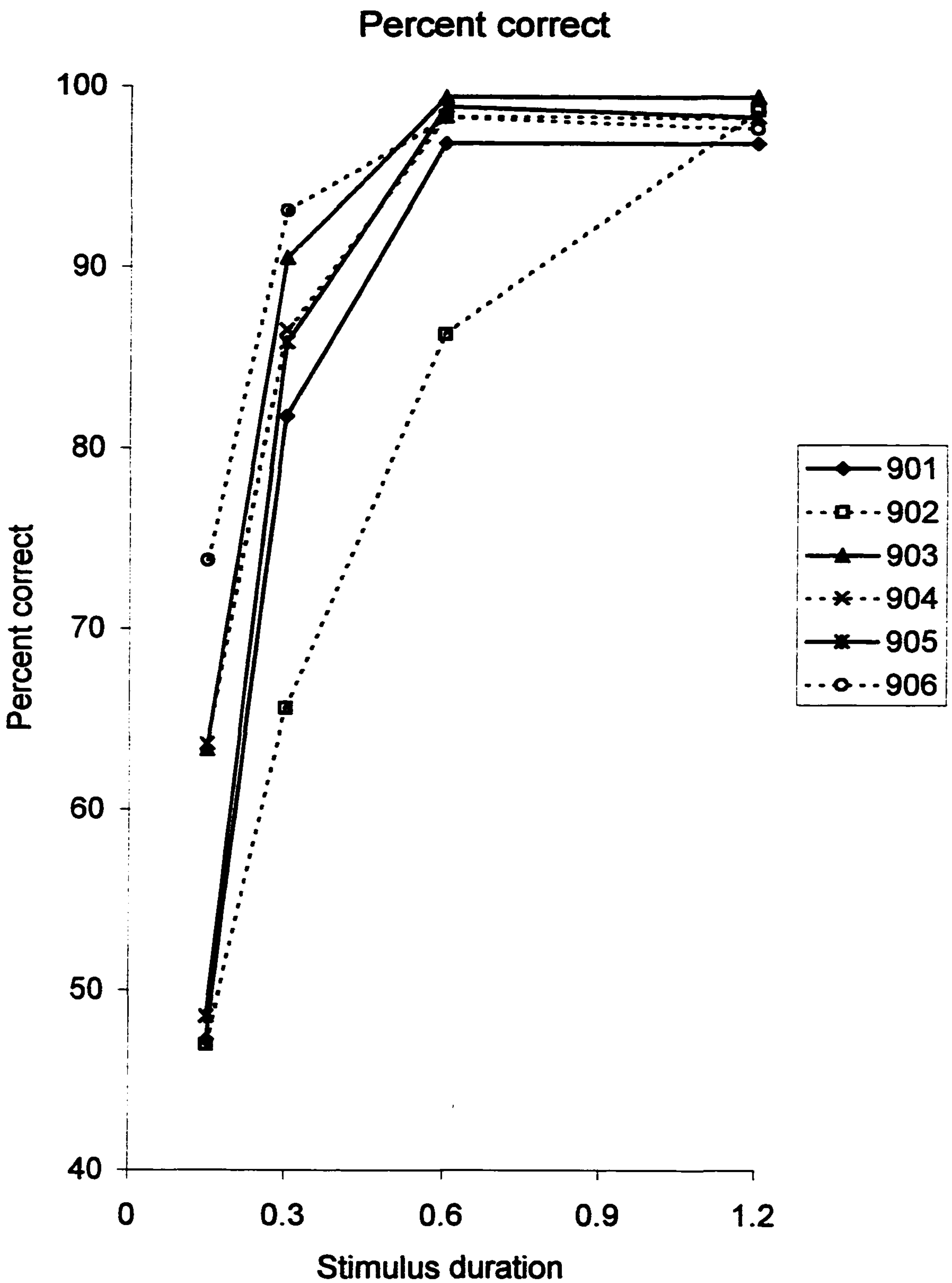

Figure 10. Percent correct for individual rats at each stimulus duration.

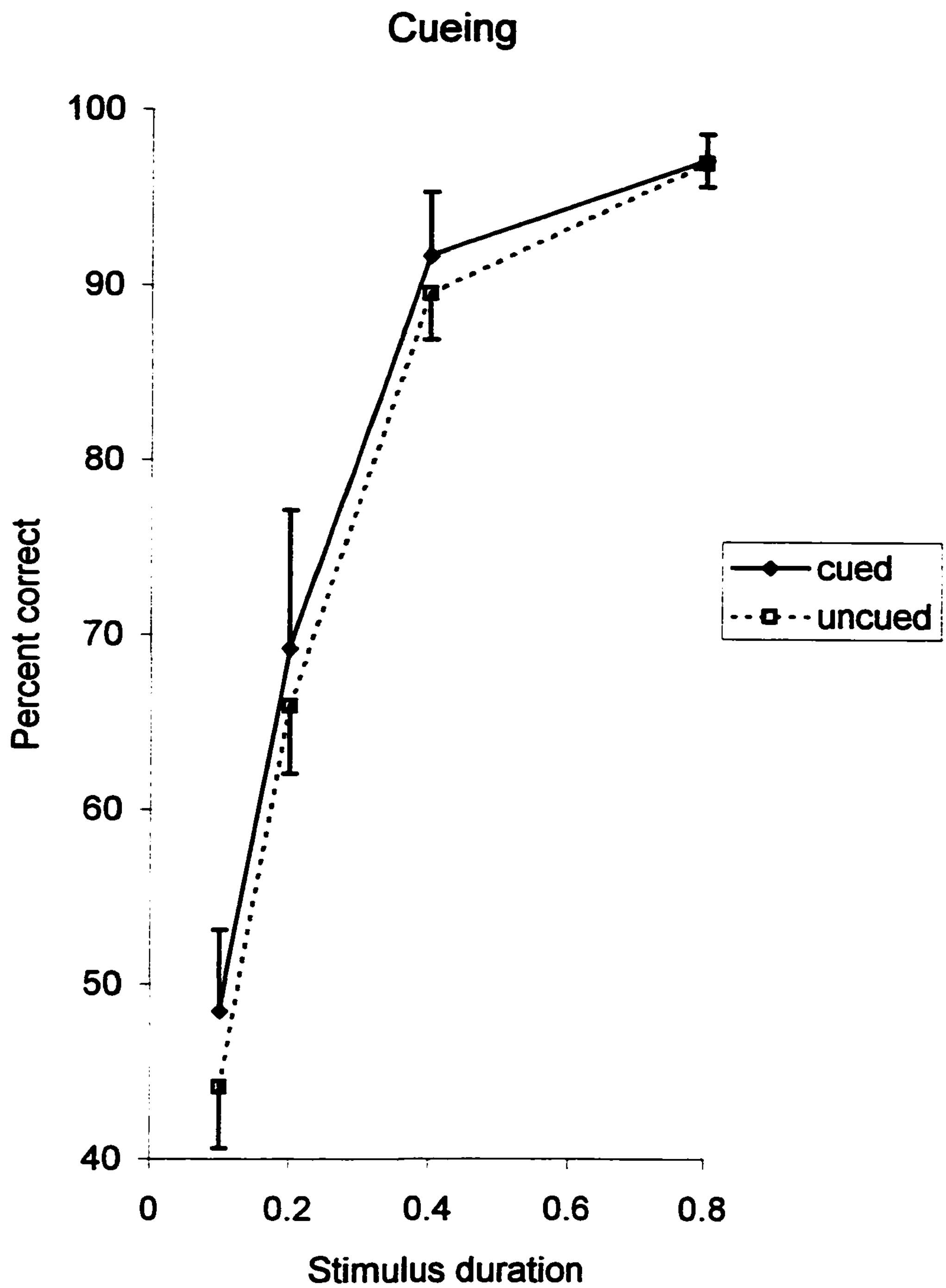

Figure 11. Mean percent correct in cueing conditions at each stimulus duration. Error bars represent SEM.

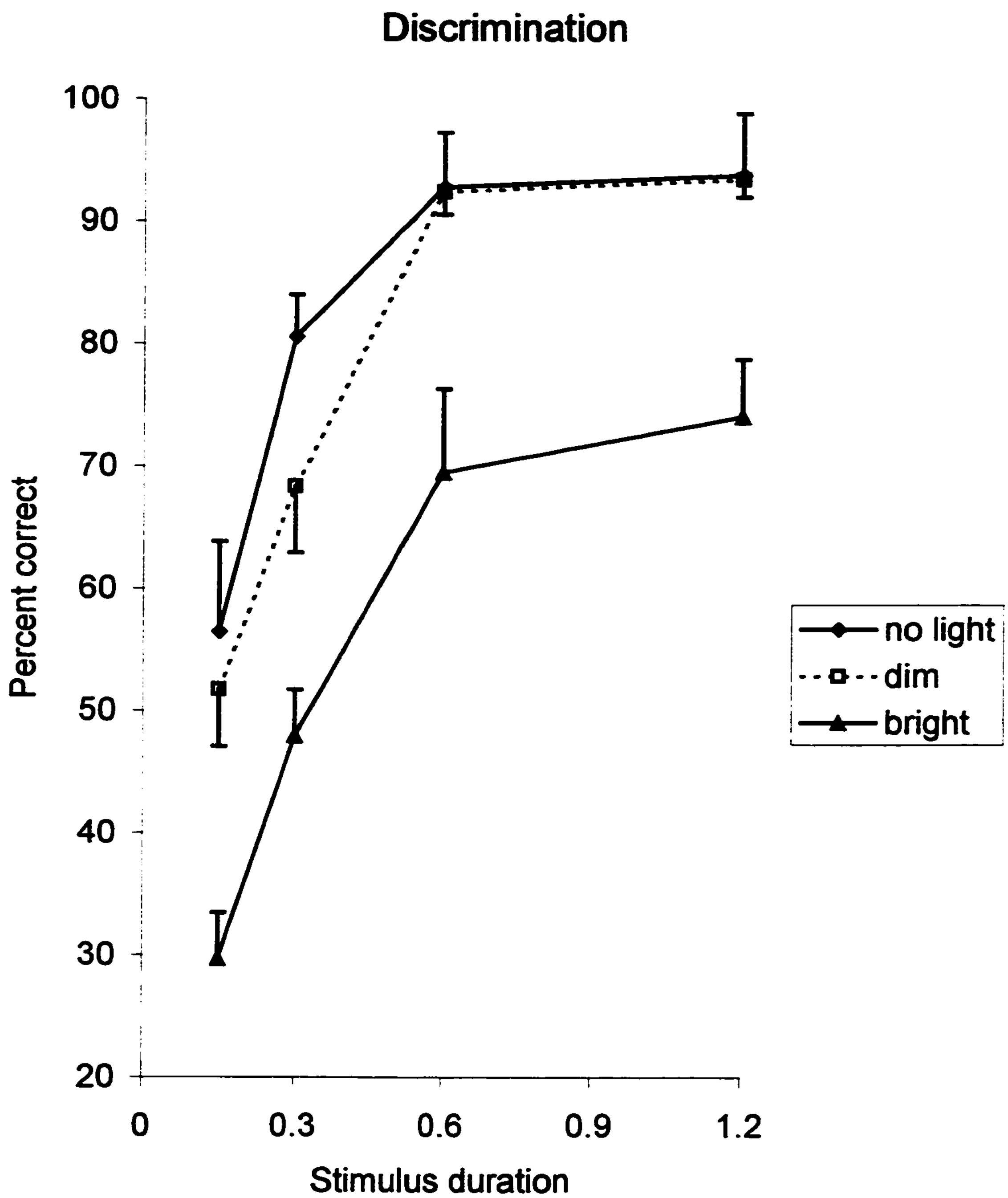

Figure 12. Mean percent correct in discrimination conditions at each stimulus duration. Error bars represent SEM.

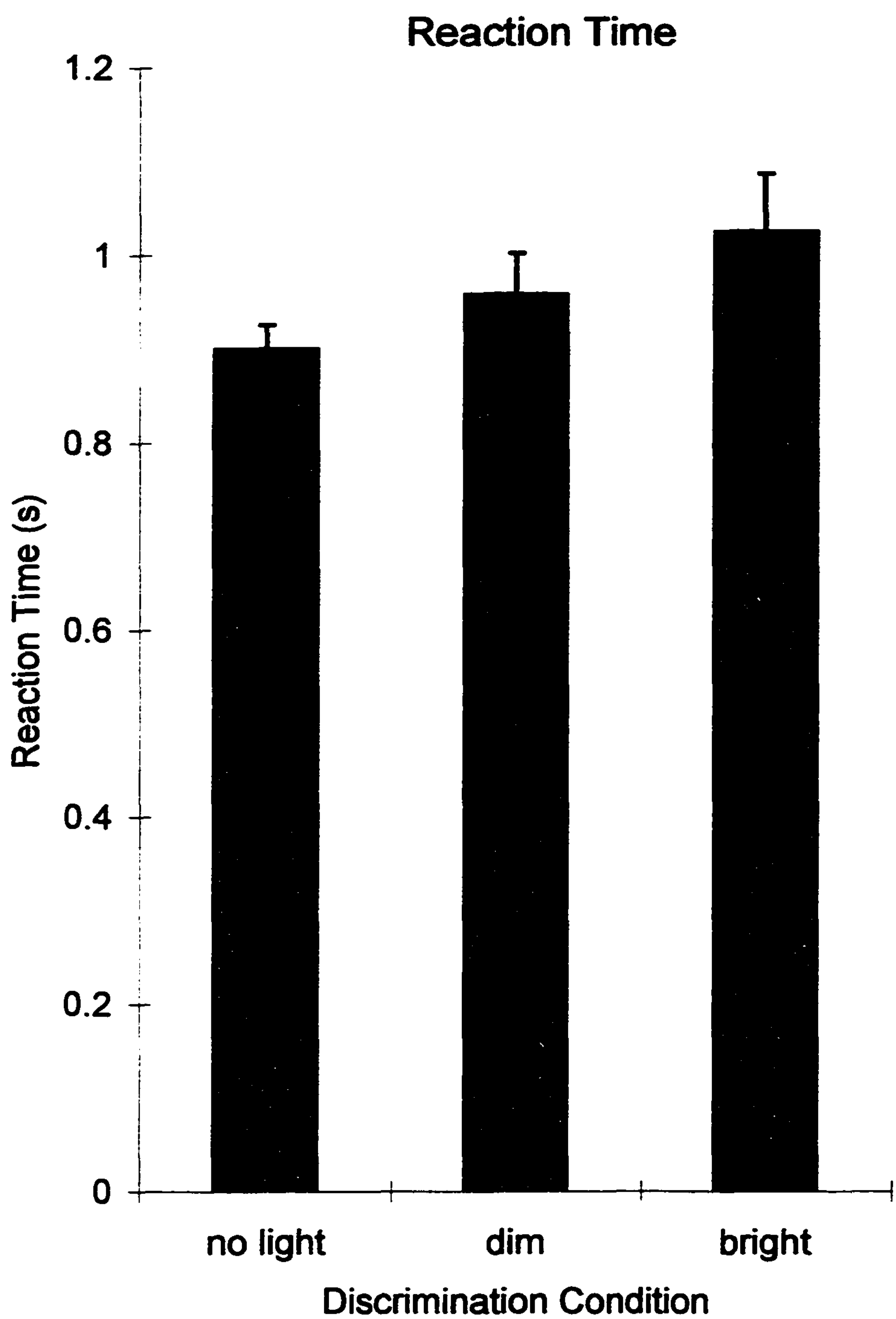

Figure 13. Mean of the median reaction time in each discrimination condition. Error bars represent SEM.

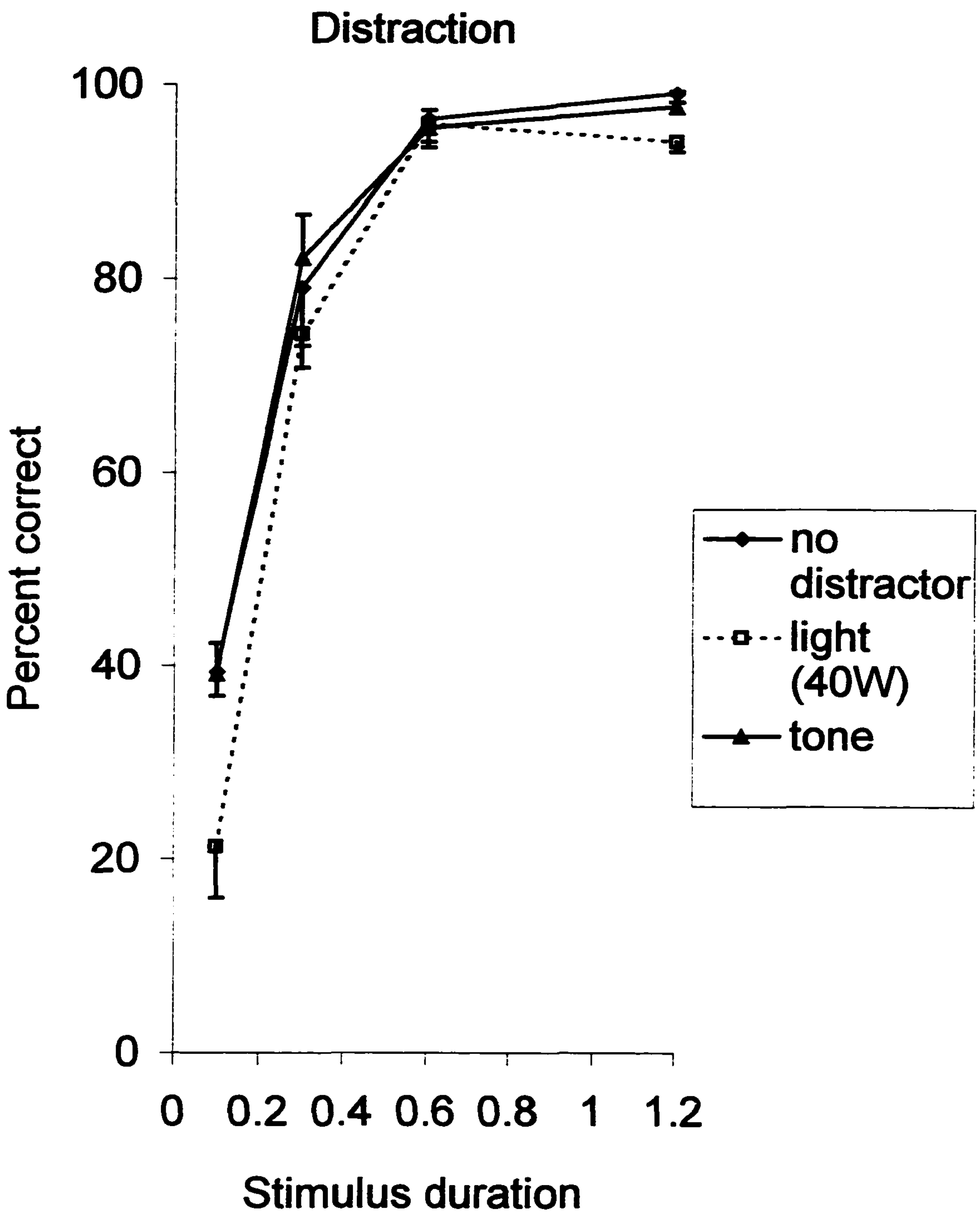

Figure 14. Mean percent correct in distraction conditions at each stimulus duration. Error bars represent SEM.

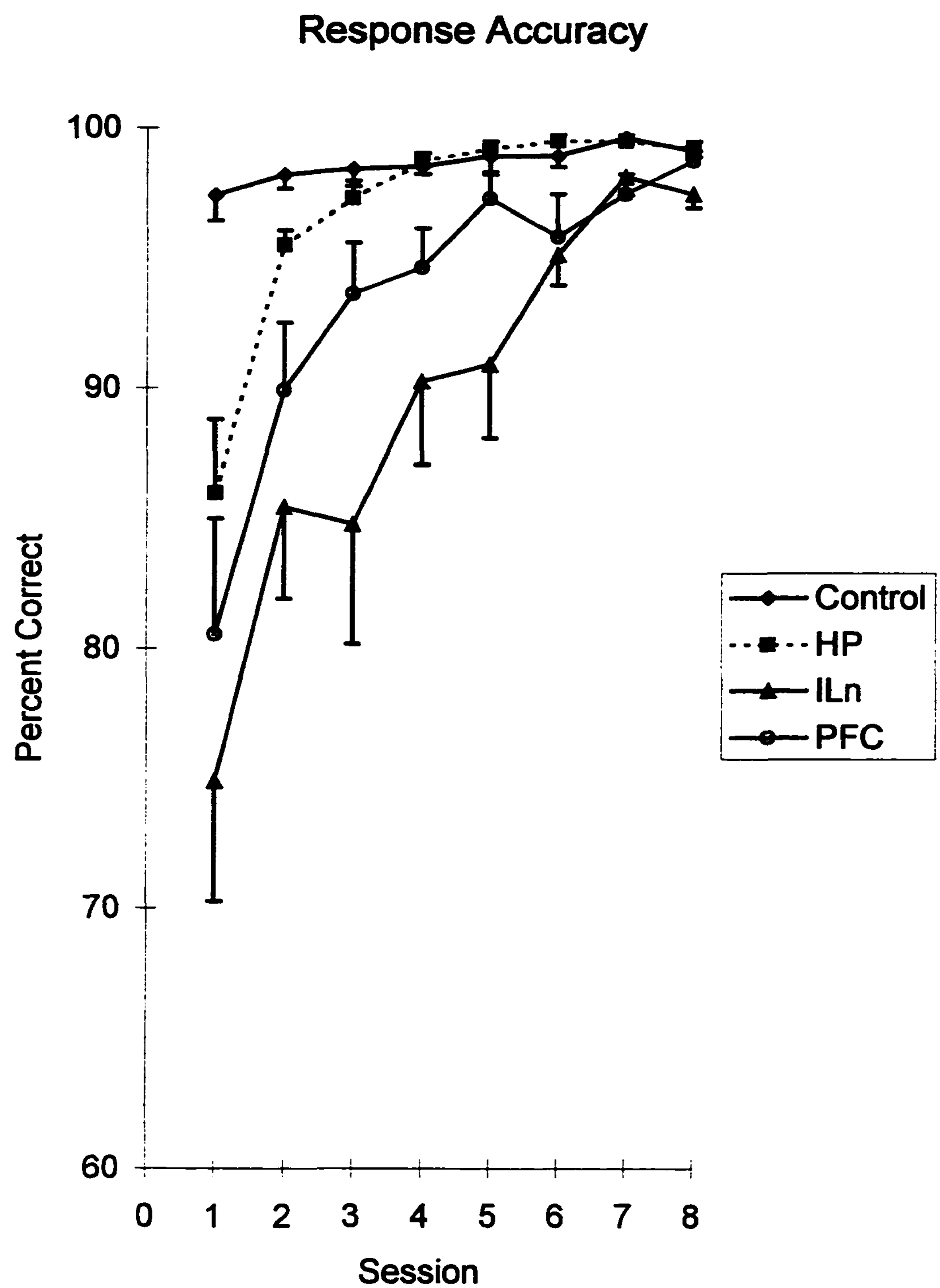

Figure 15. Mean percent correct for each treatment group during the last eight sessions with a long stimulus duration. Error bars represent SEM.

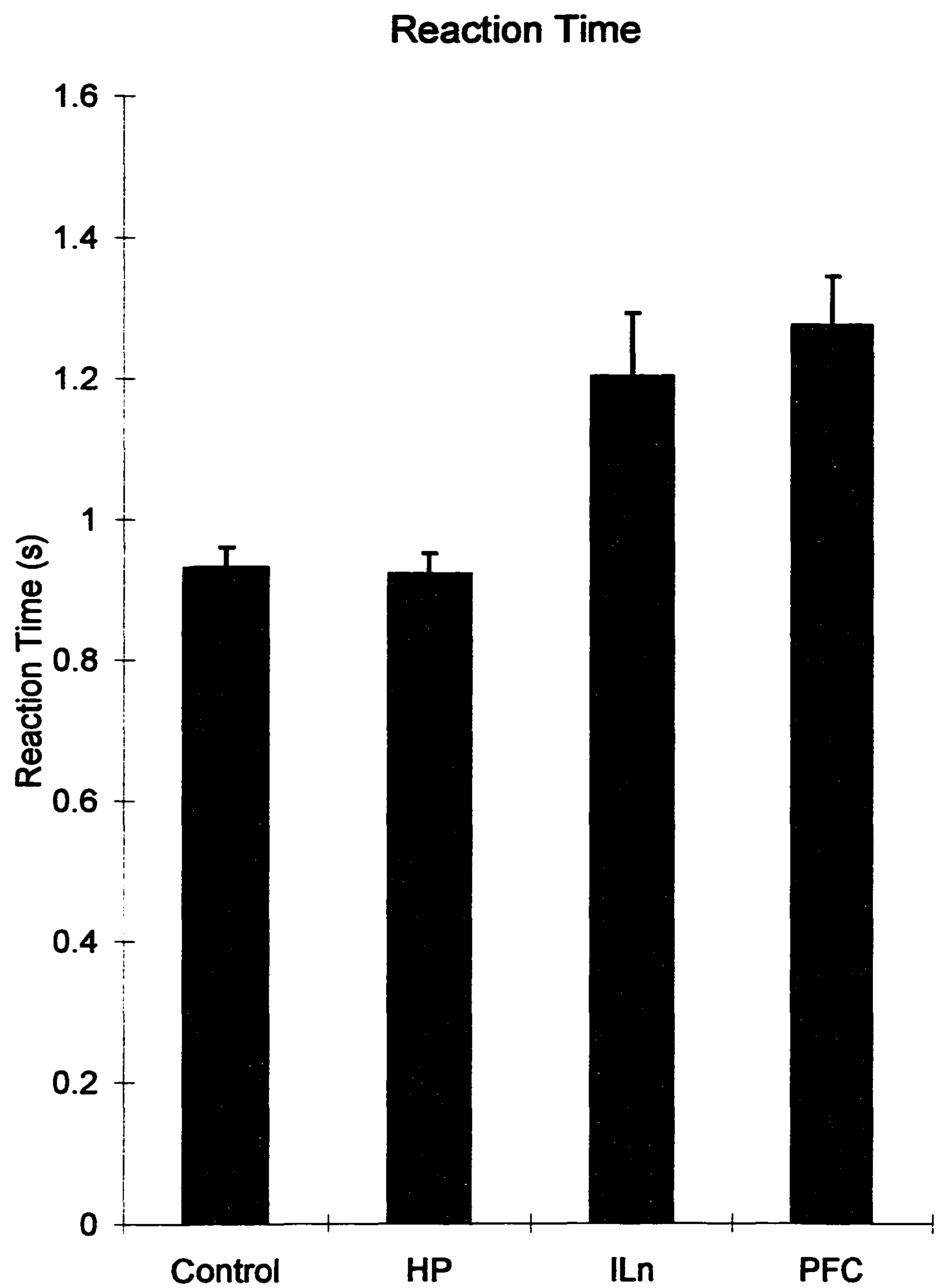

Figure 16. The ordinate represents the mean of the median reaction time. The abscissa designates each treatment group. Error bars represent SEM.

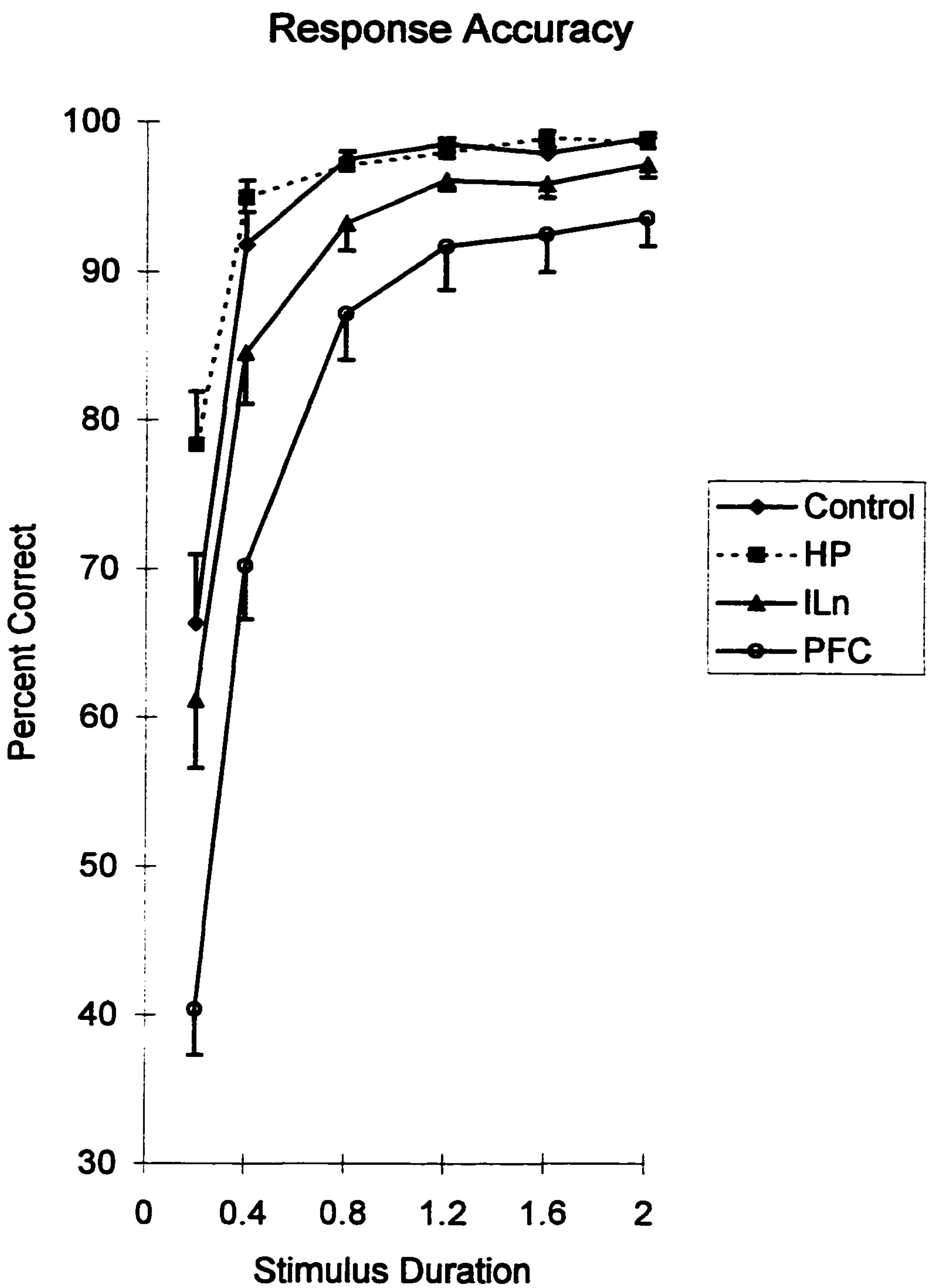

Figure 17. Mean percent correct for each treatment group at each stimulus duration. Error bars represent SEM.

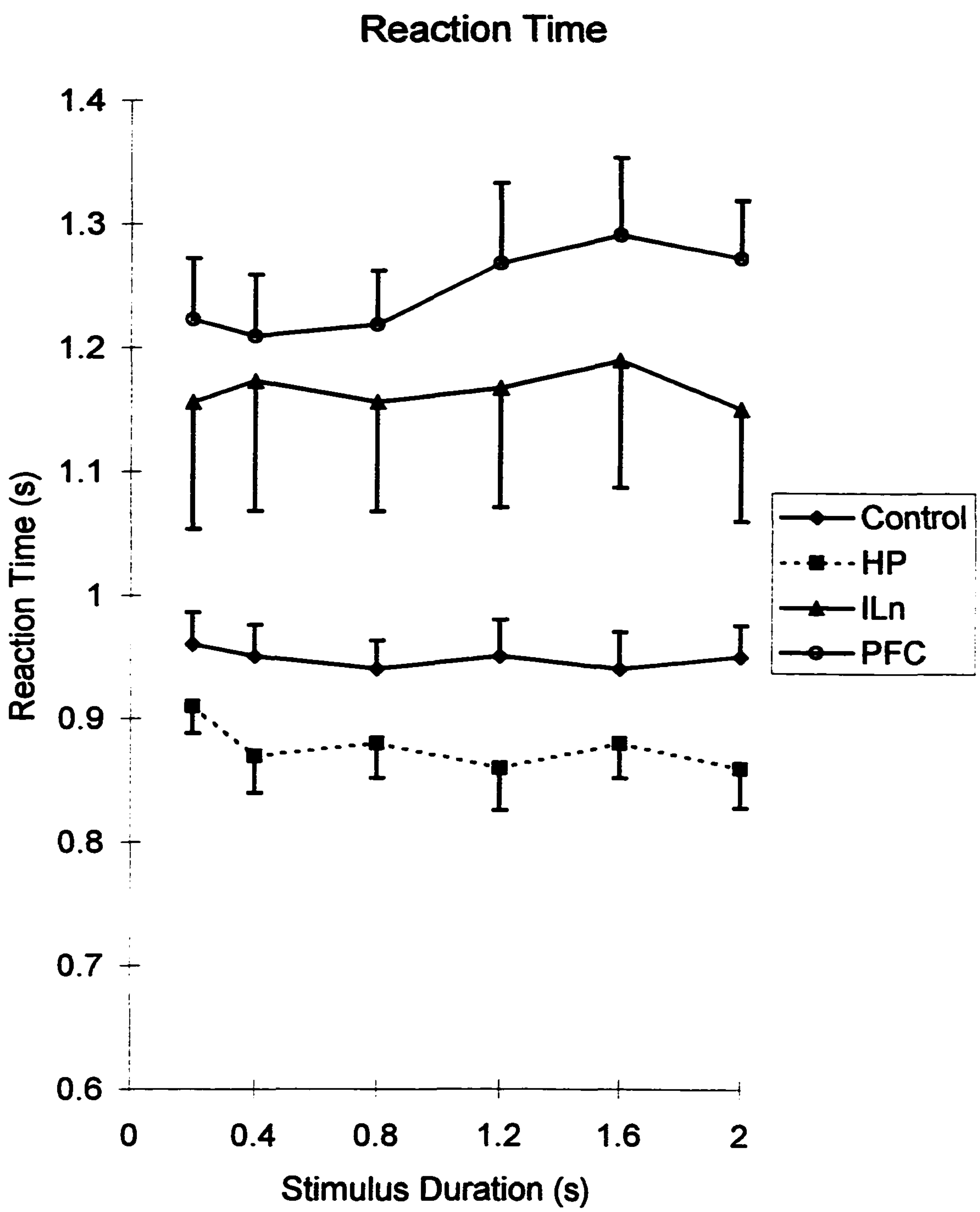

Figure 18. The ordinate represents the mean of the median reaction times. The abscissa designates the stimulus duration. Error bars represent SEM.

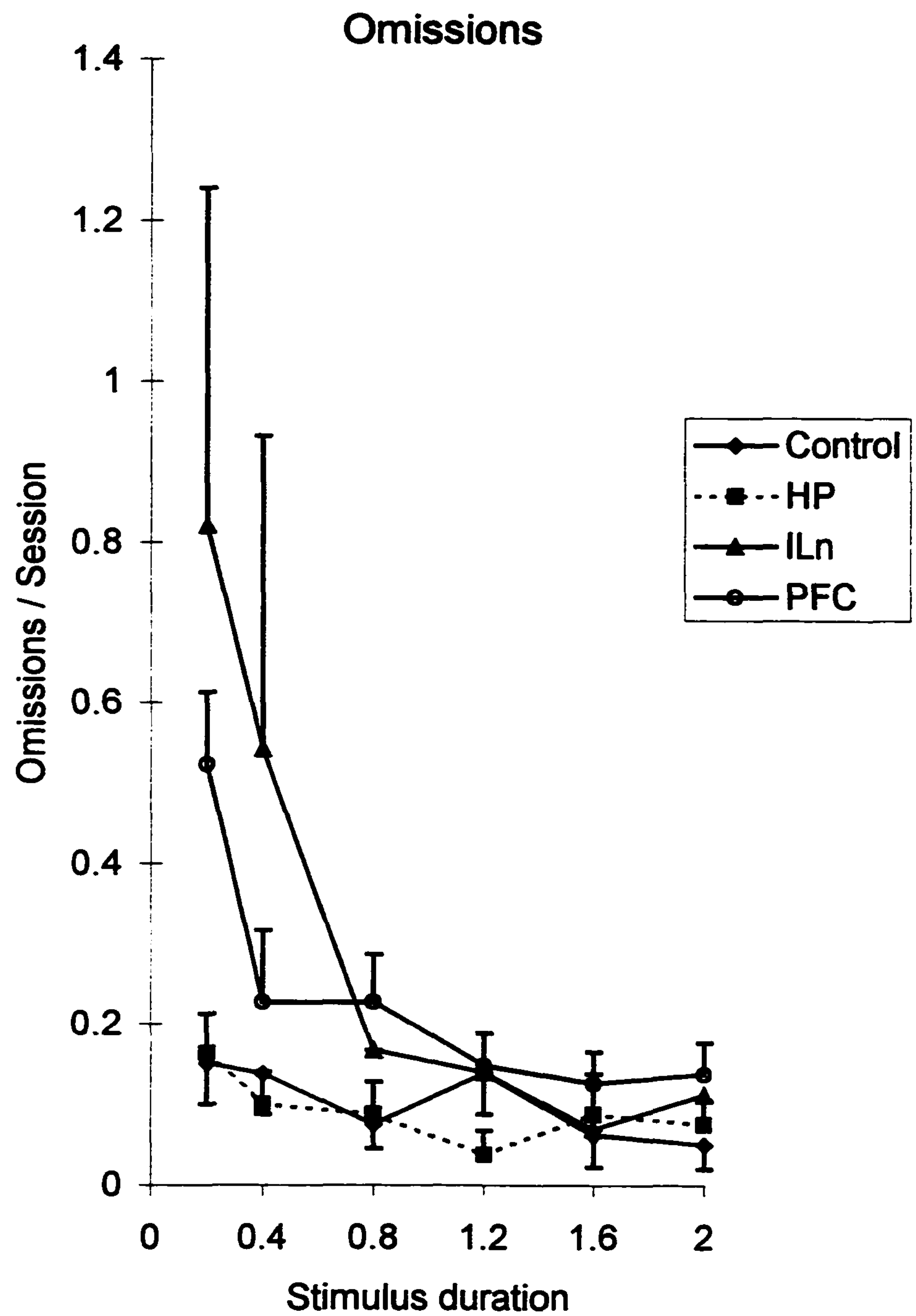

Figure 19. Mean omissions during each session for each treatment group at each stimulus duration. Error bars represent SEM.

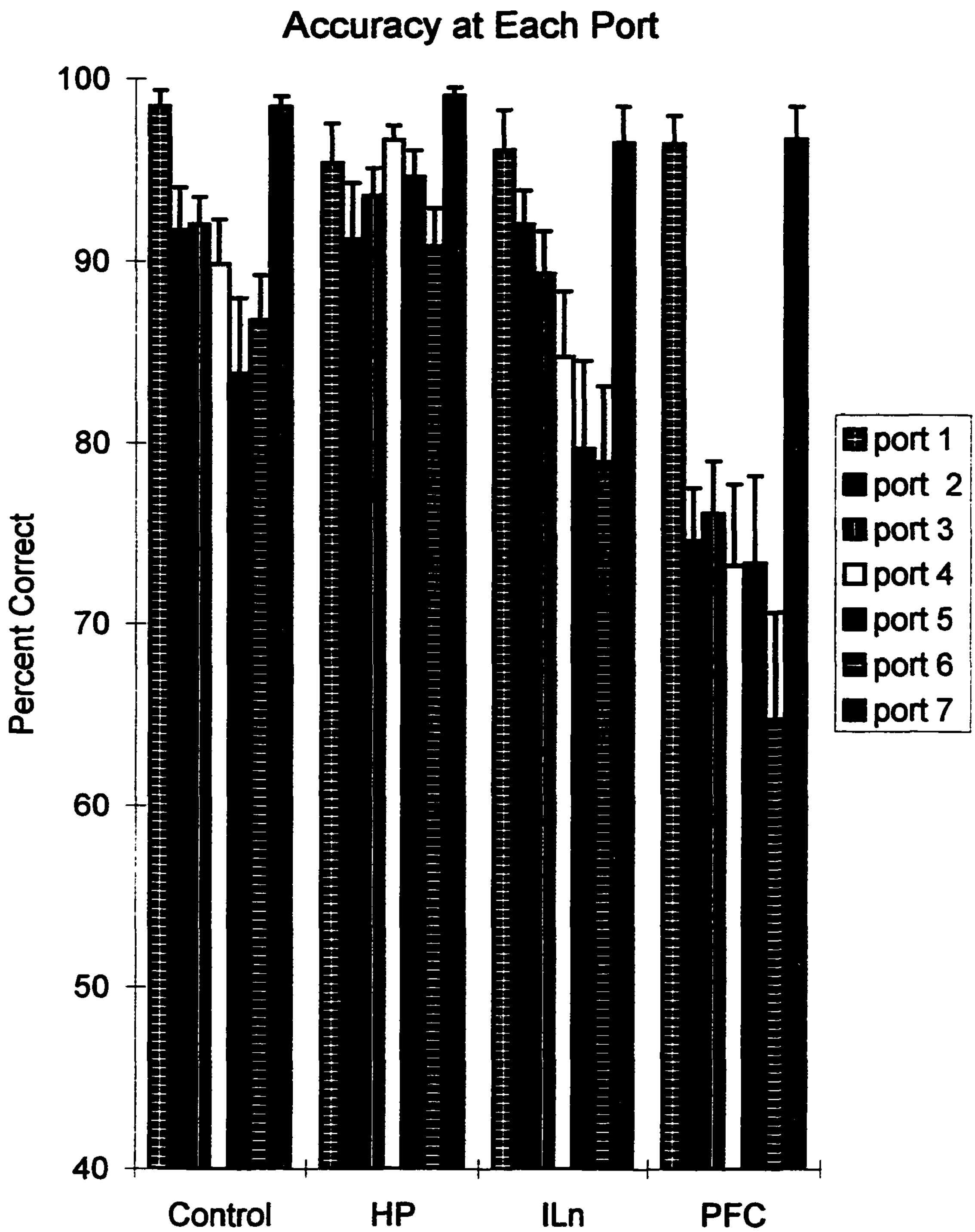

Figure 20. Mean percent correct at each port for each treatment group. Error bars represent SEM.

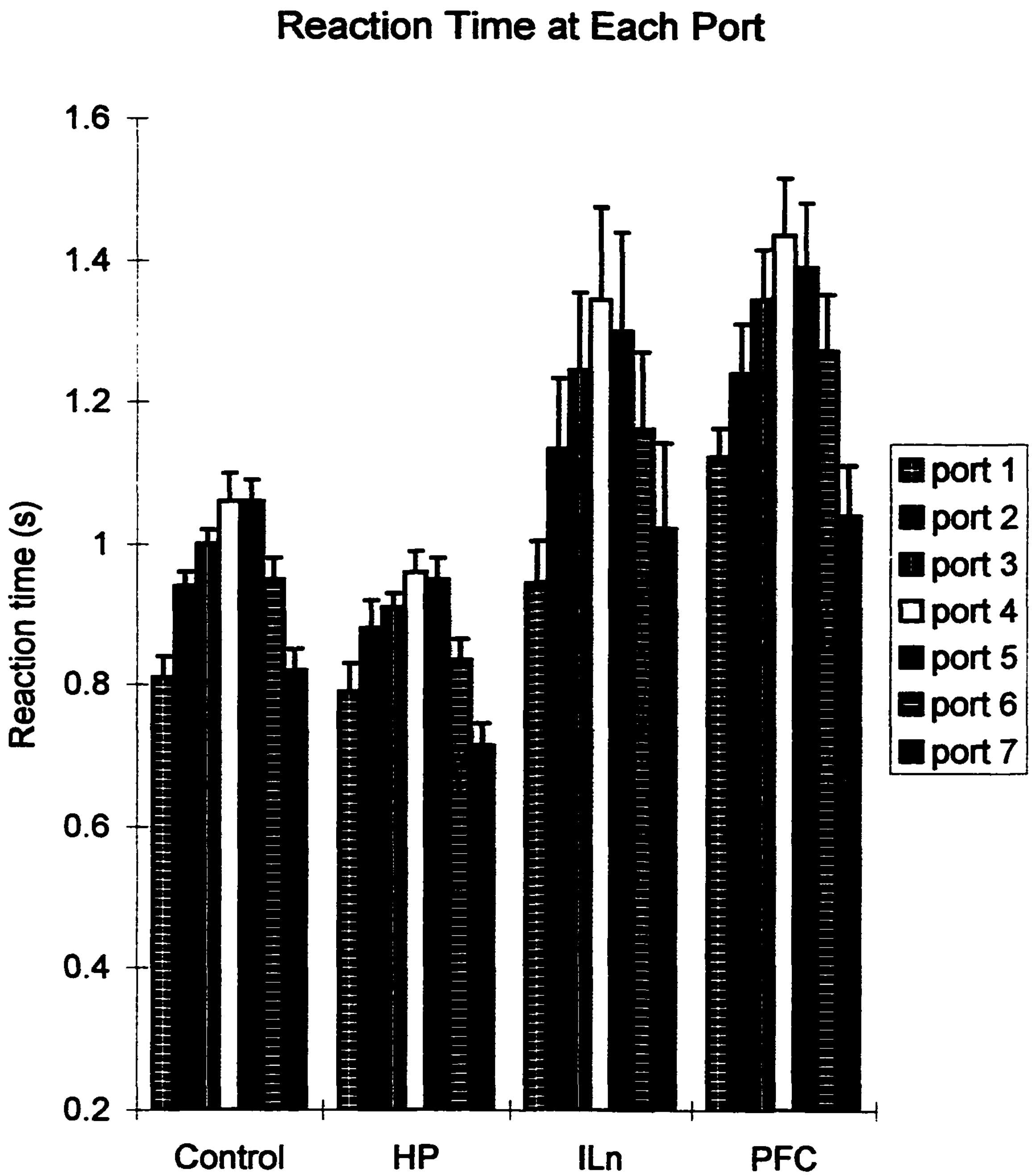

Figure 21. Mean of the median reaction times at each port. Error bars represent SEM.

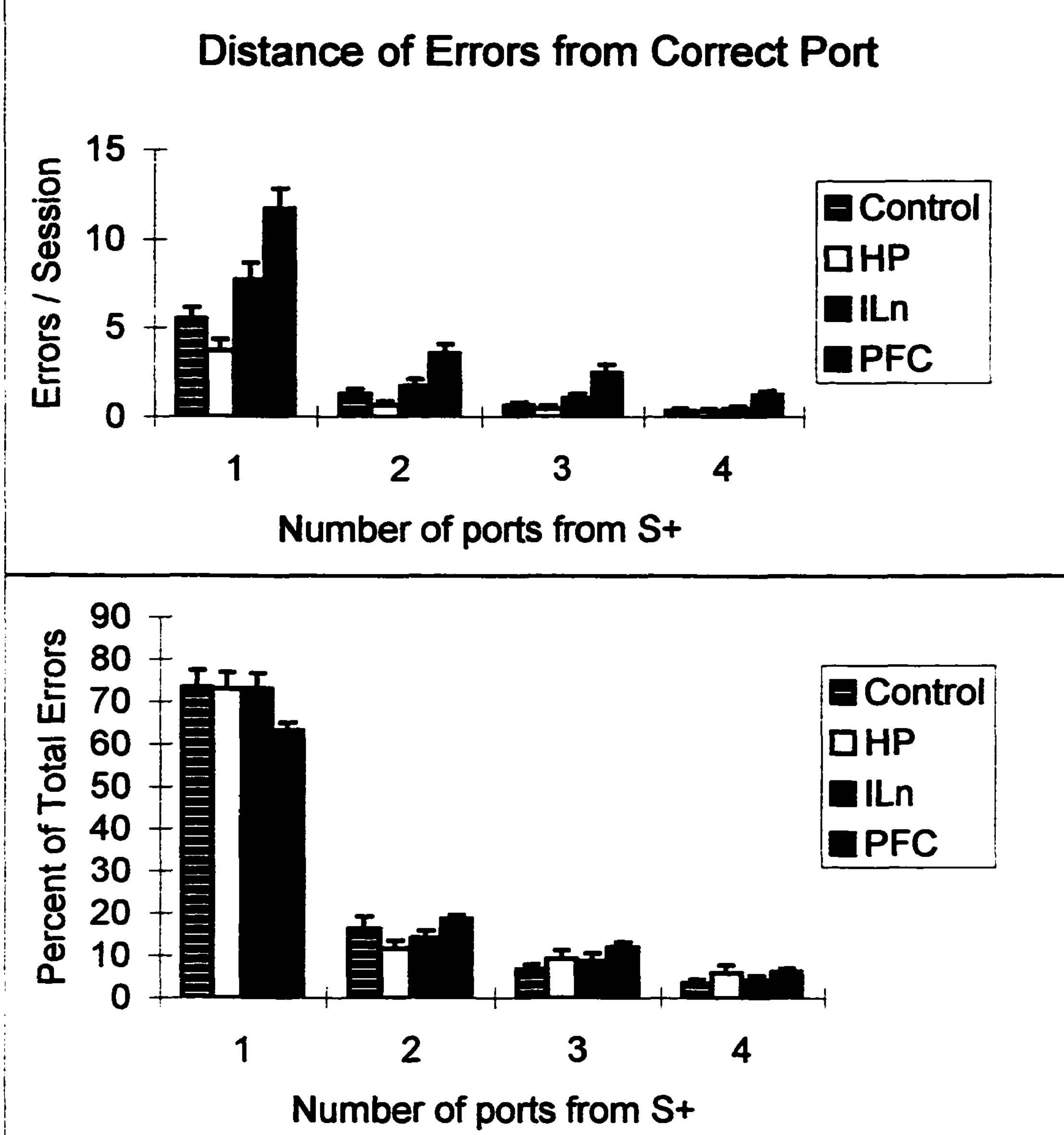

Figure 22. *Top panel:* The abscissa represents the number of ports away an error was made from the correct port. The ordinate represents the mean errors during each session. *Bottom panel:* The abscissa is the same as in the top panel. The ordinate designates the percentage of total errors. Error bars represent SEM.

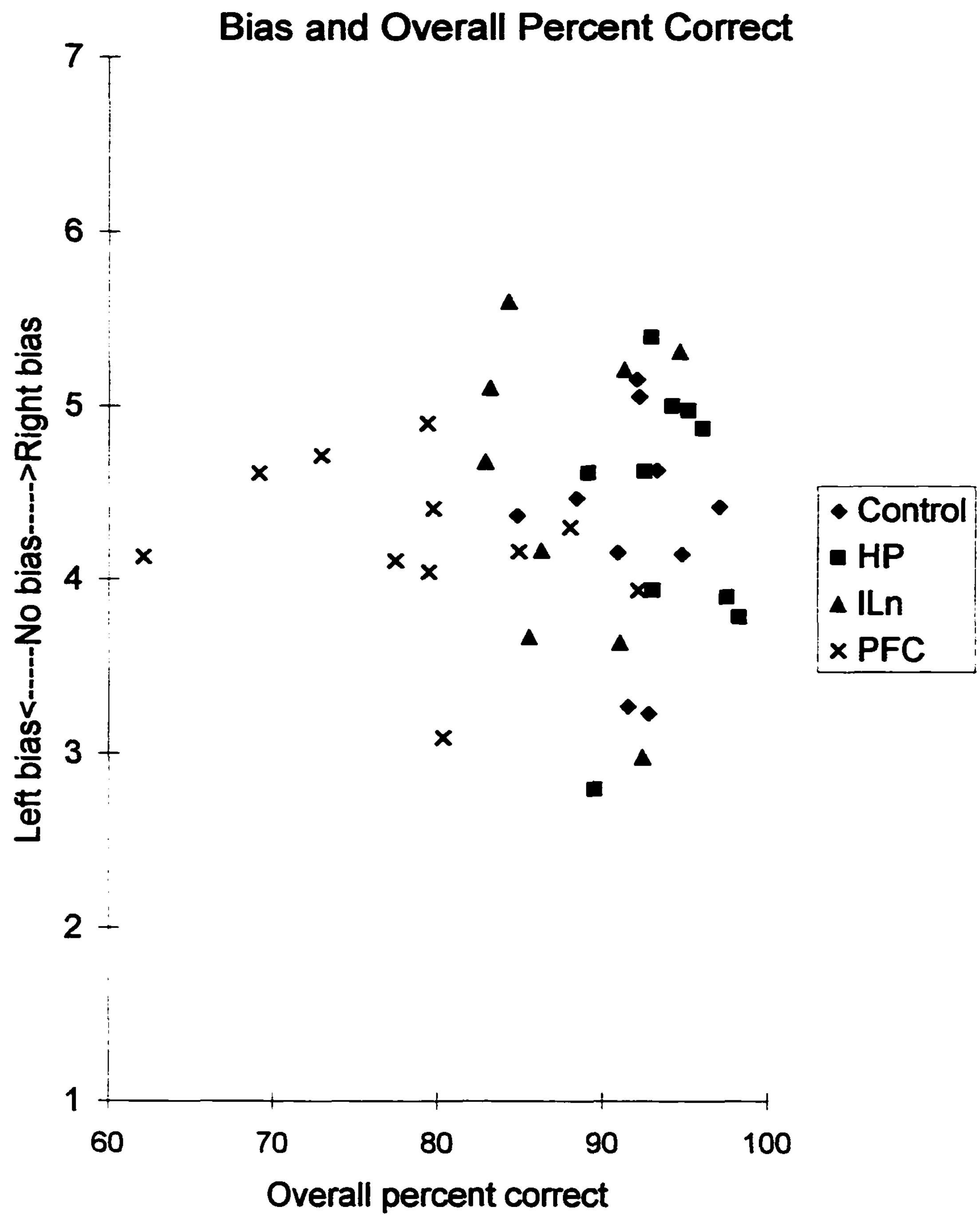

Figure 23. A scattergram comparing the bias and the overall percent correct (averaged across all stimulus durations) for each animal.

Distraction

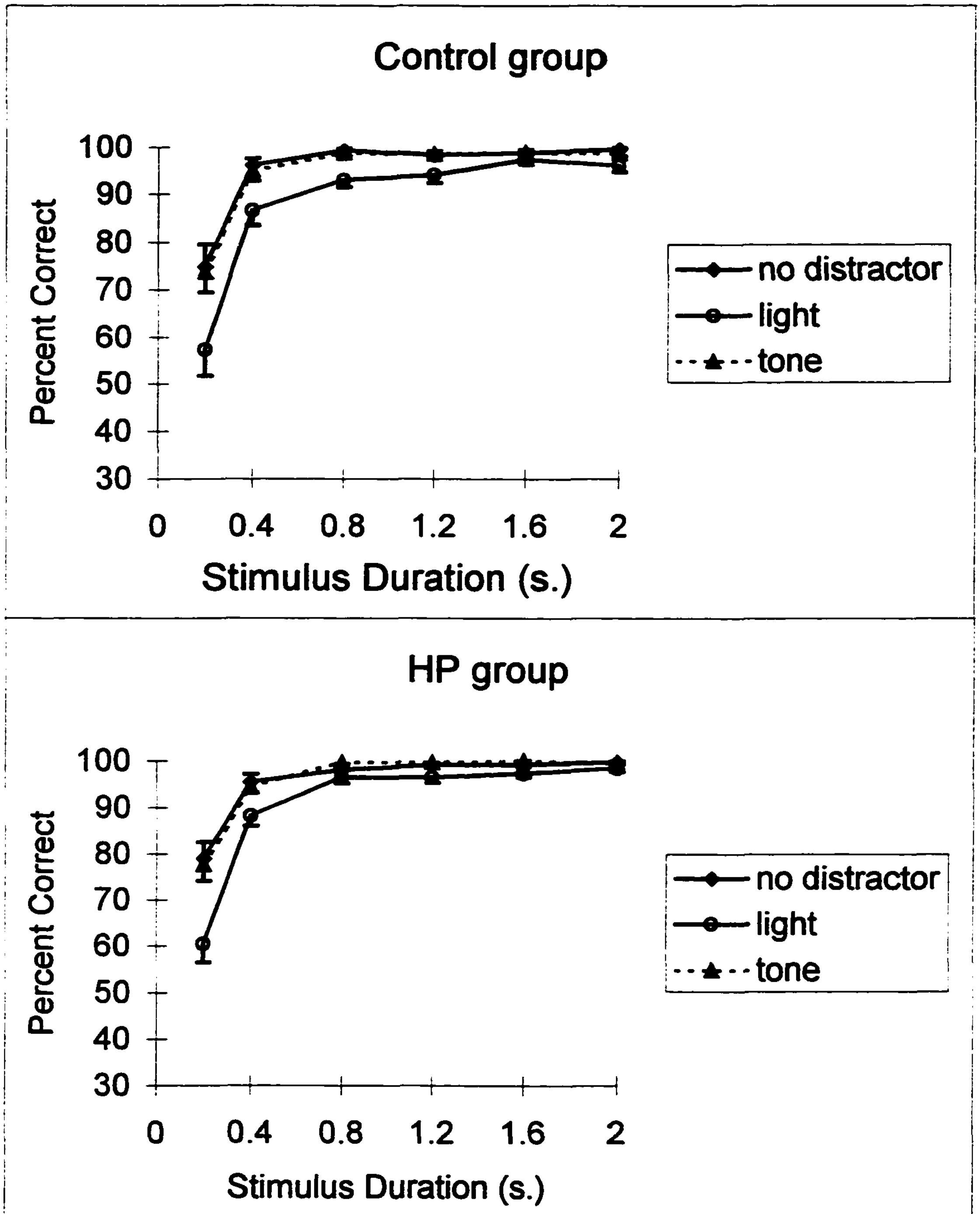

Figure 24. The ordinate represents the mean percent correct. The abscissa designates the stimulus duration on each distractor condition for the control group (top panel) and the HP group (bottom panel). Error bars represent SEM.

Distraction

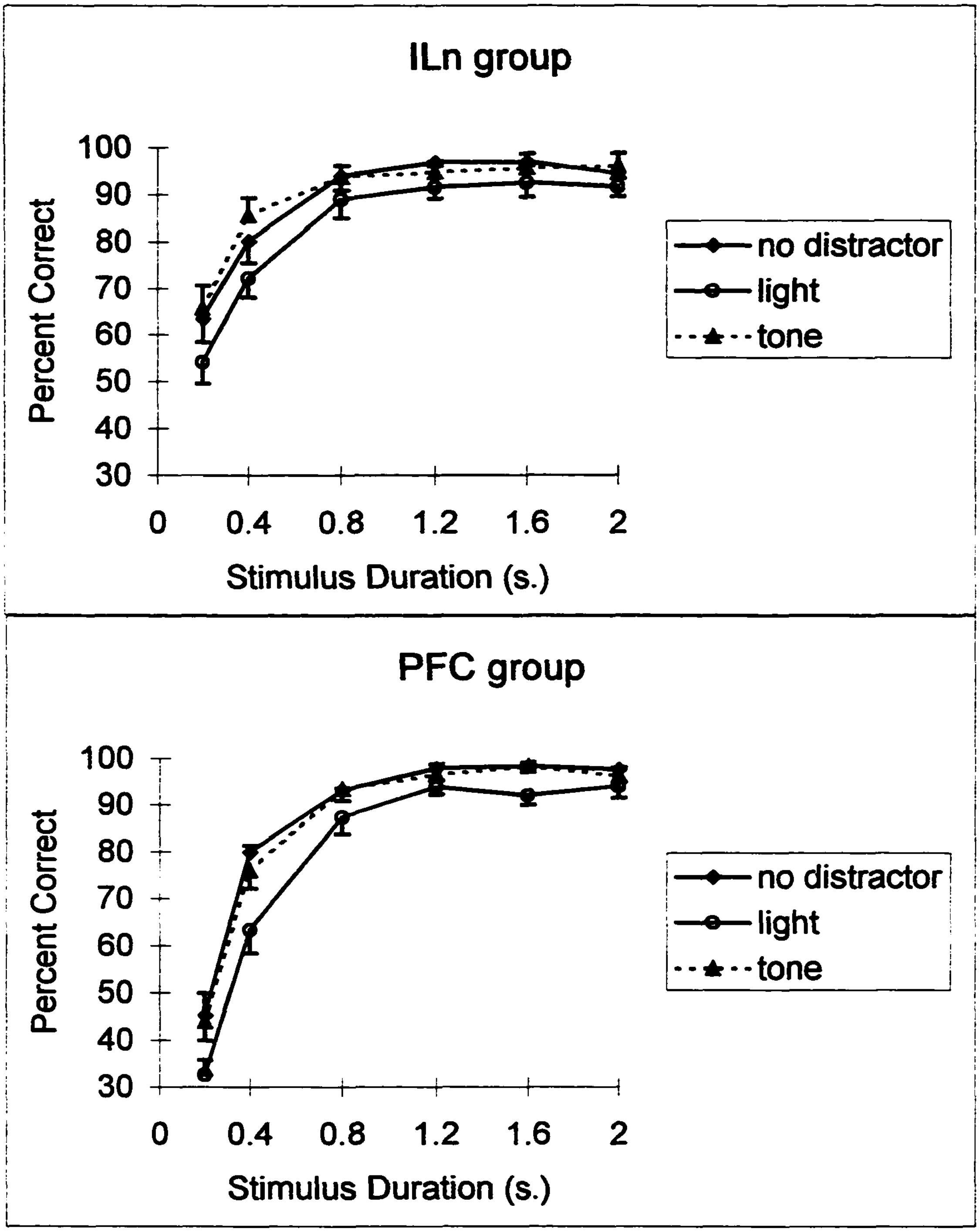

Figure 25. The ordinate represents the mean percent correct. The abscissa designates the stimulus duration on each distractor condition for the ILn group (top panel) and the PFC group (bottom panel). Error bars represent SEM.

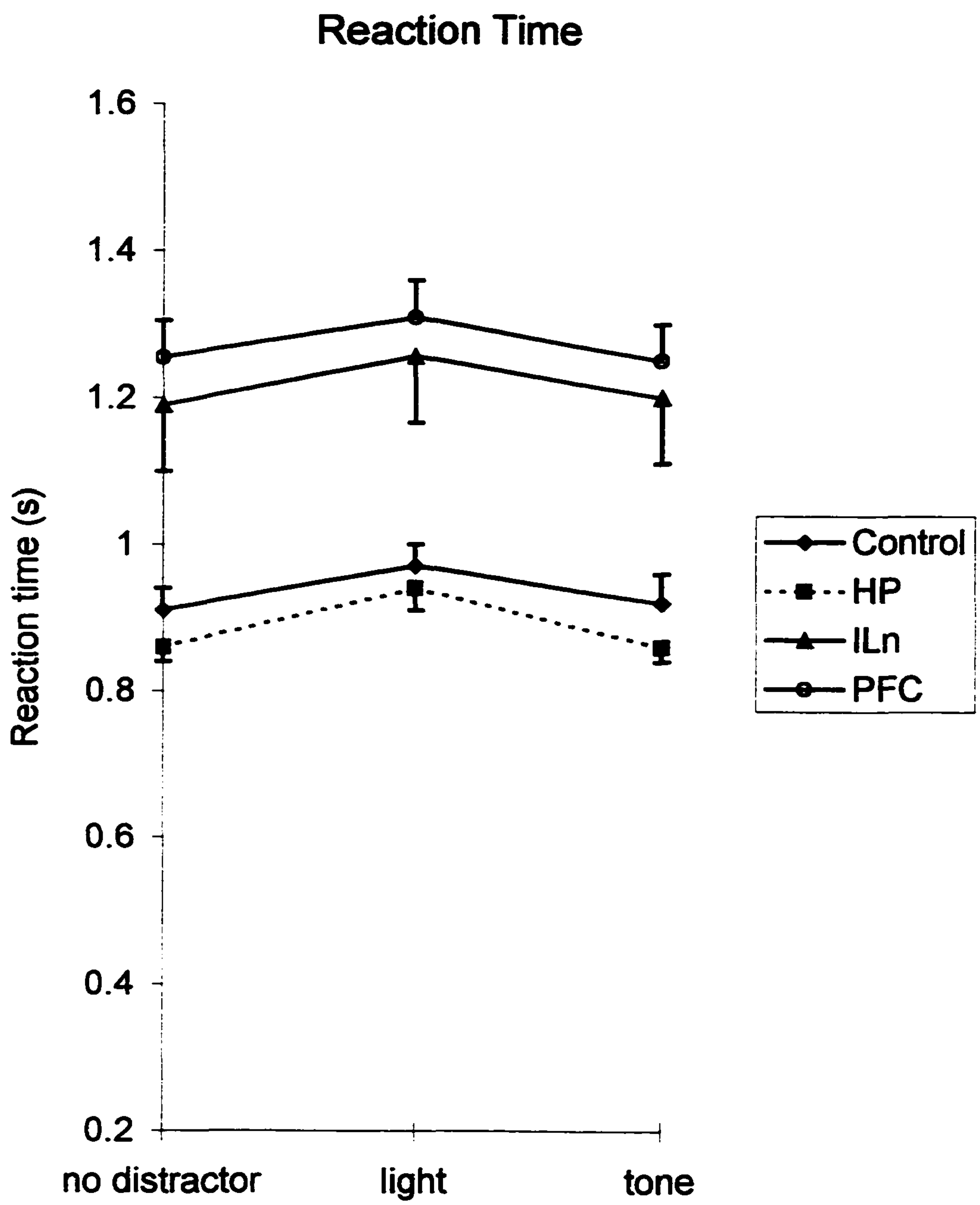

Figure 26. Mean of the median reaction times (ordinate) at each distractor condition (abscissa) for each treatment group. Error bars represent SEM.

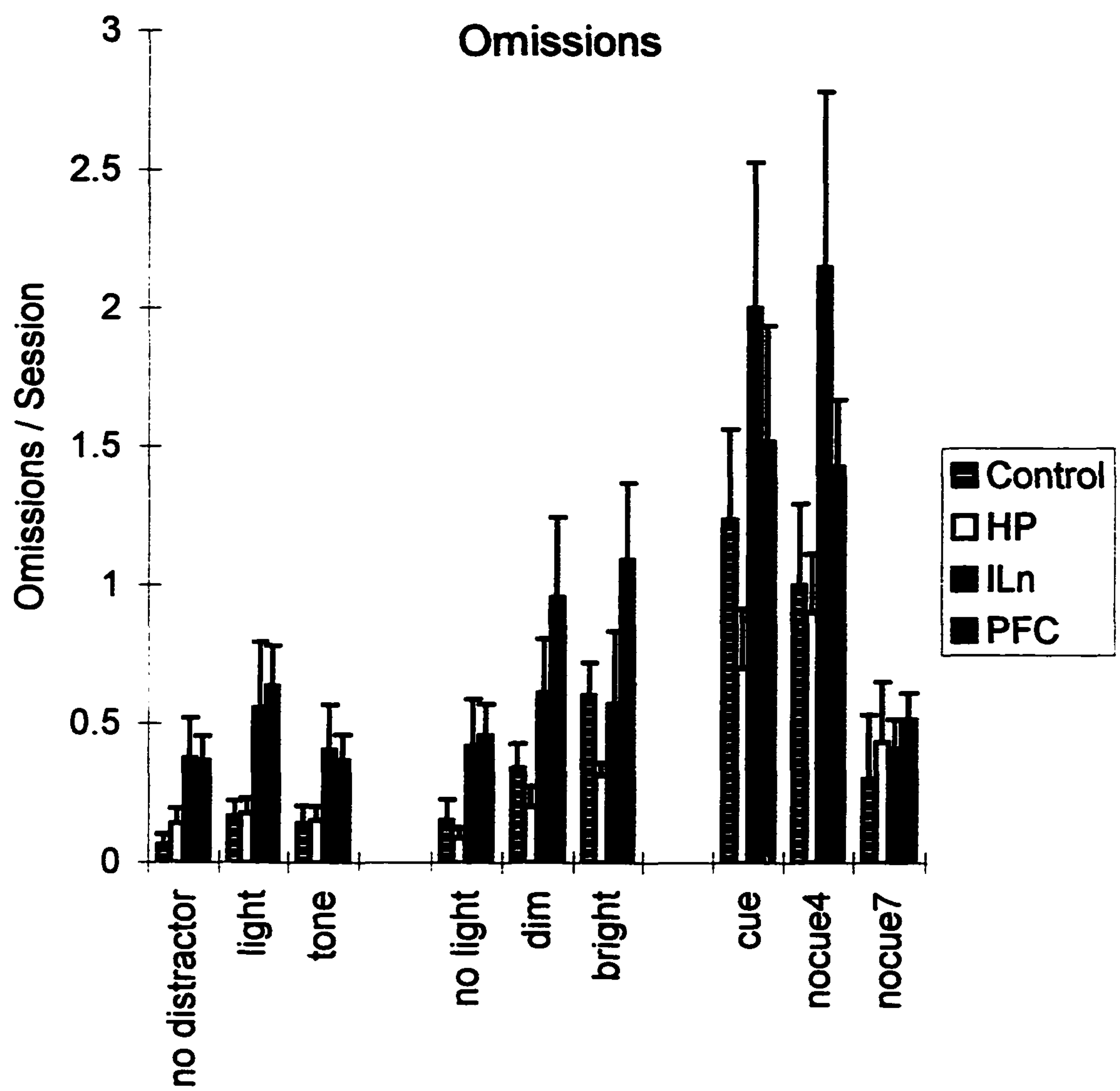

Figure 27. The abscissa designates the distractor, discrimination, and cueing conditions. The ordinate represents the mean omissions during each session (8 sessions for the distractor and discrimination sessions, 3 sessions for the cueing condition). Error bars represent SEM.

Discrimination

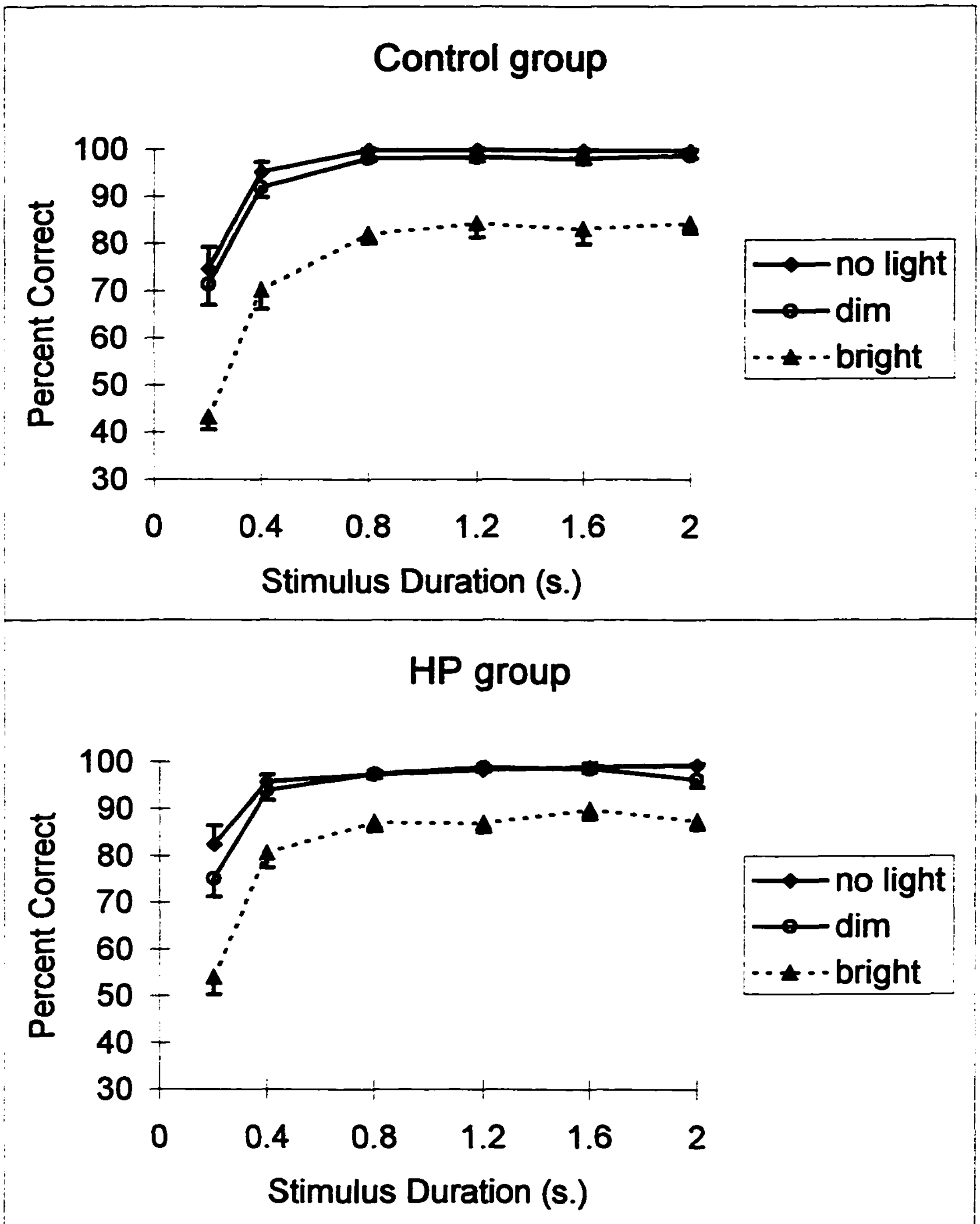

Figure 28. The ordinate represents the mean percent correct. The abscissa designates the stimulus duration on each discrimination condition for the control group (top panel) and the HP group (bottom panel). Error bars represent SEM.

Discrimination

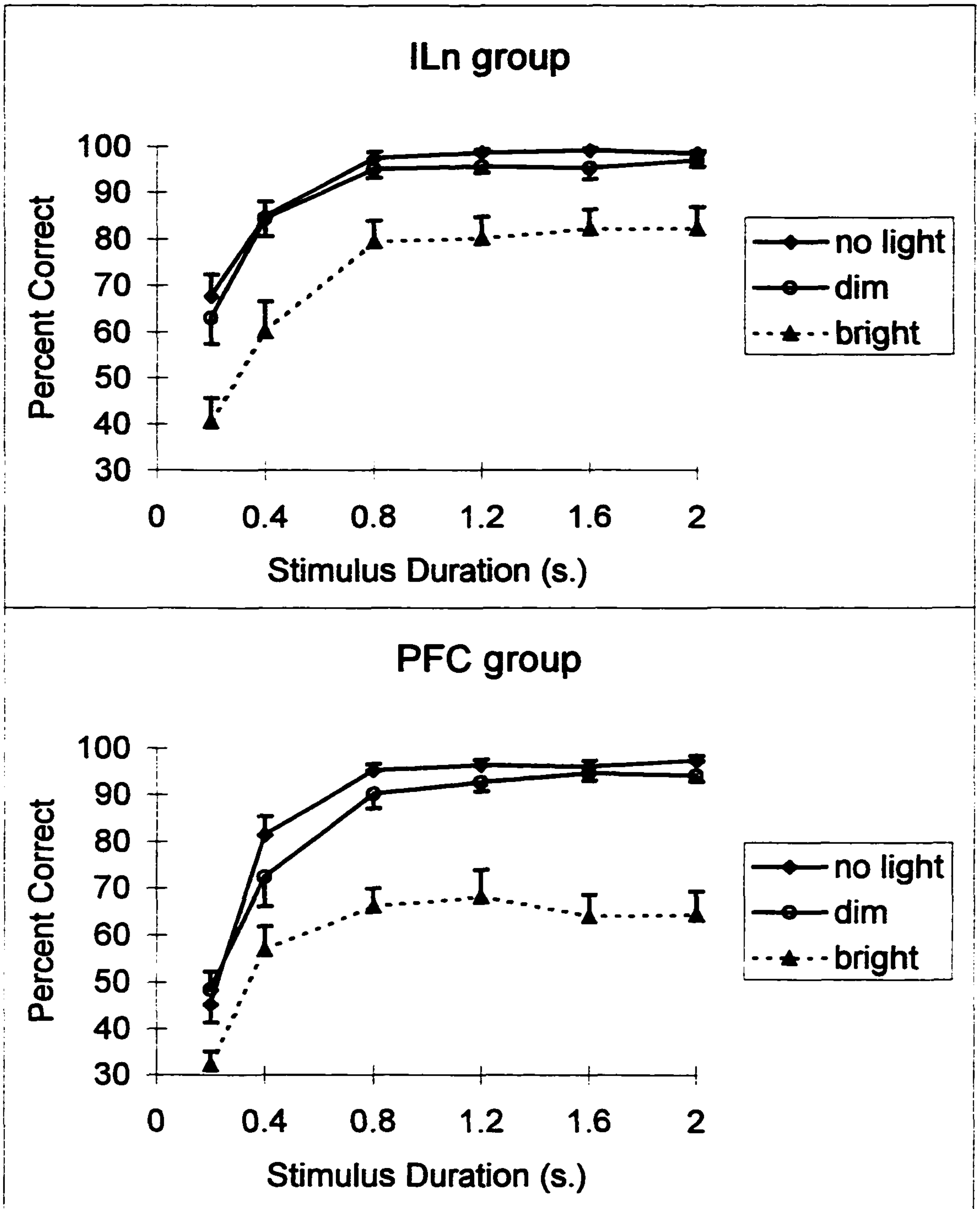

Figure 29. The ordinate represents the mean percent correct. The abscissa designates the stimulus duration on each discrimination condition for the ILn group (top panel) and the PFC group (bottom panel). Error bars represent SEM.

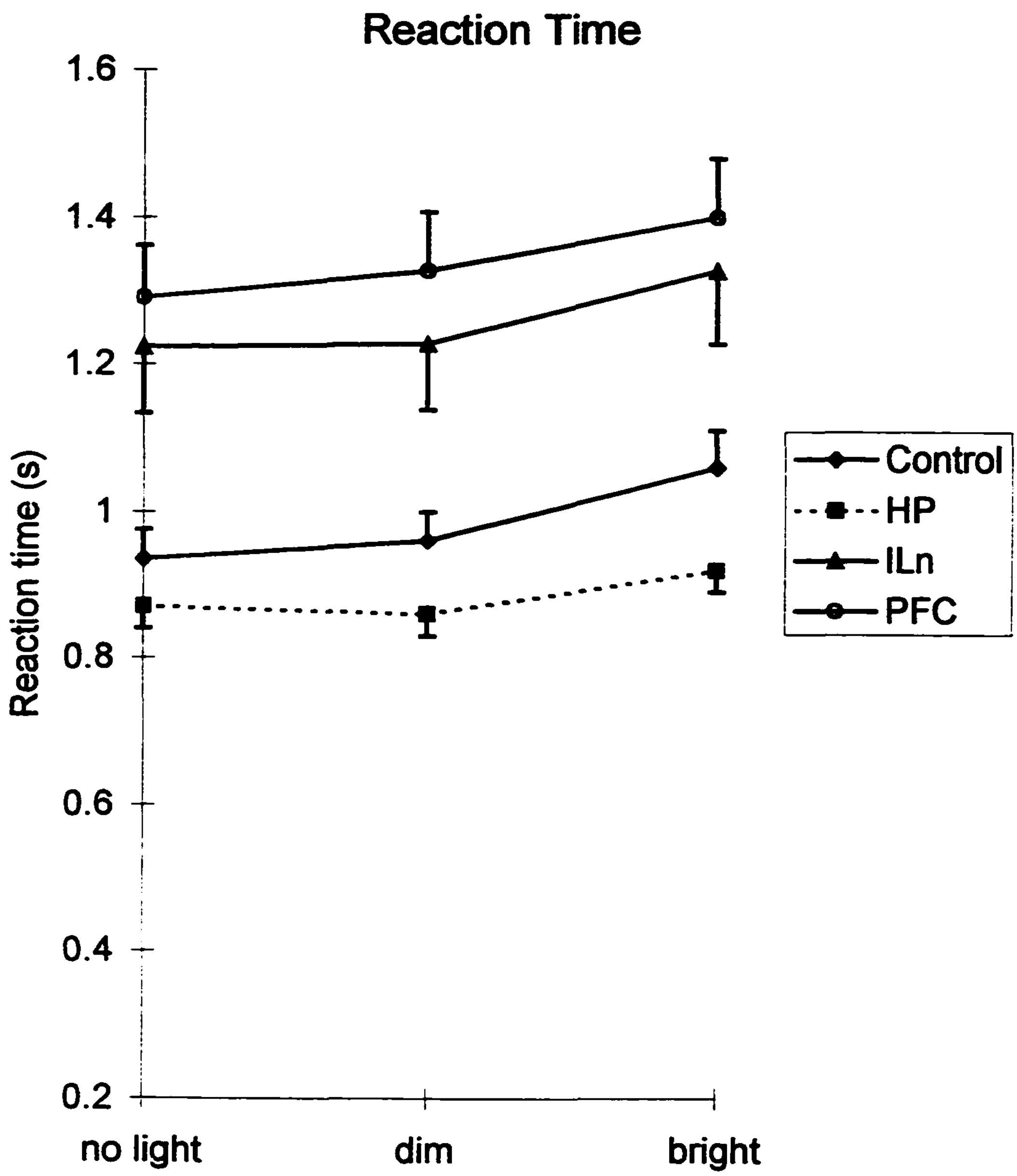

Figure 30. Mean of the median reaction times (ordinate) for each discrimination condition (abscissa) for each treatment group. Error bars represent SEM.

Cueing

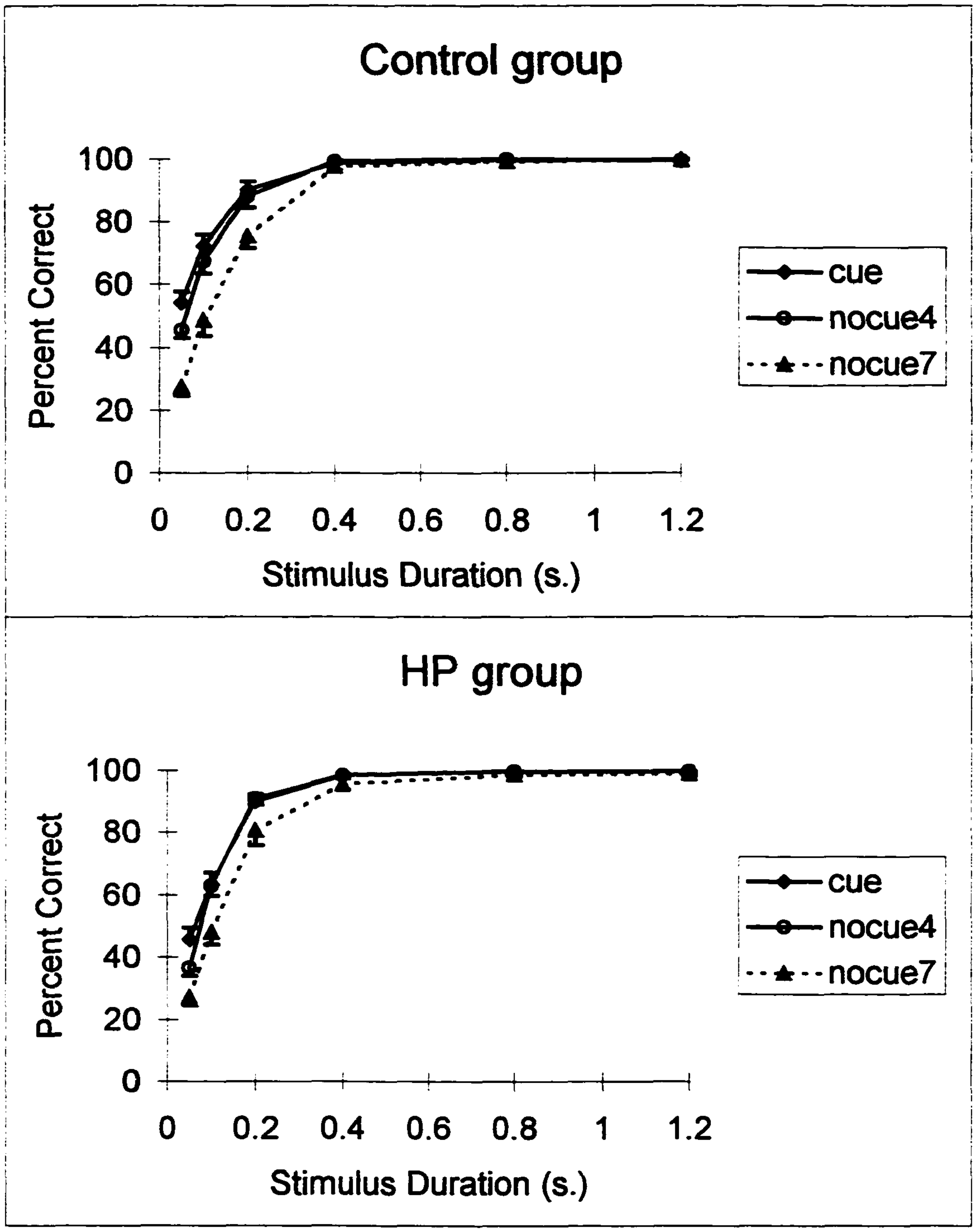

Figure 31. The ordinate represents the mean percent correct. The abscissa designates the stimulus duration on each cueing condition for the Control group (top panel) and the HP group (bottom panel). Error bars represent SEM.

Cueing

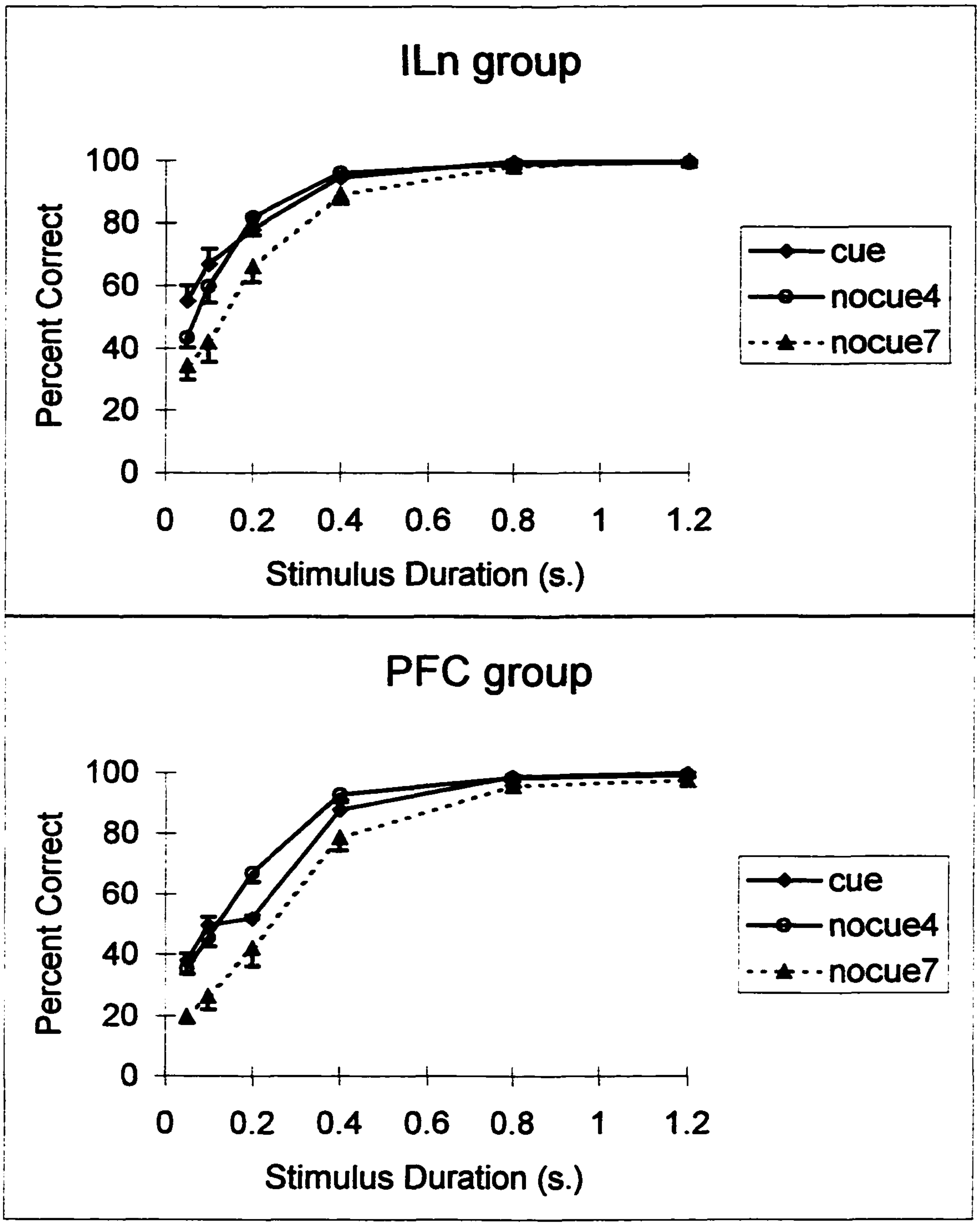

Figure 32. The ordinate represents the mean percent correct. The abscissa designates the stimulus duration on each cueing condition for the ILn group (top panel) and the PFC group (bottom panel). Error bars represent SEM.

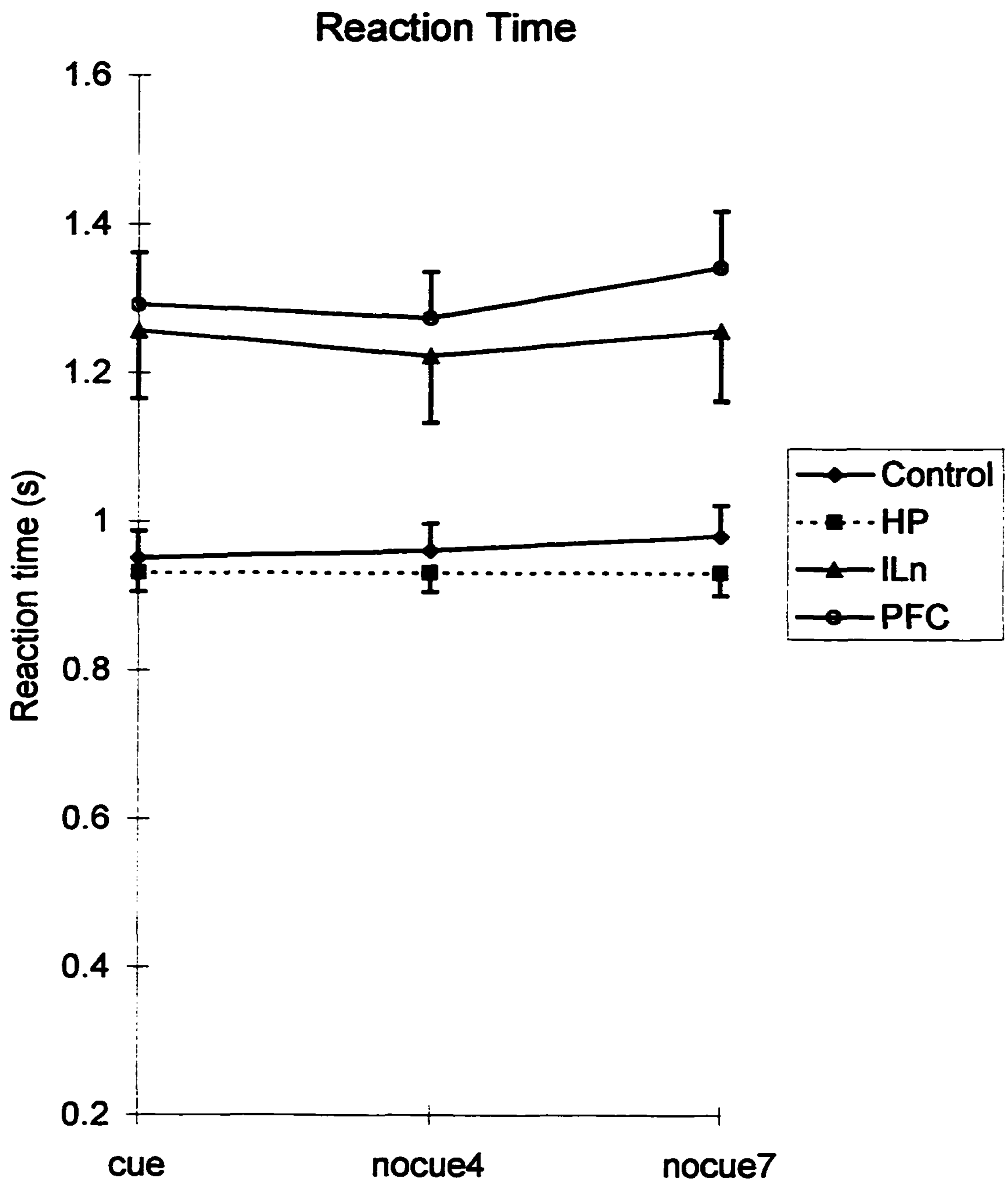

Figure 33. Mean of the median reaction times (ordinate) for each cueing condition (abscissa) for each treatment group. Error bars represent SEM.

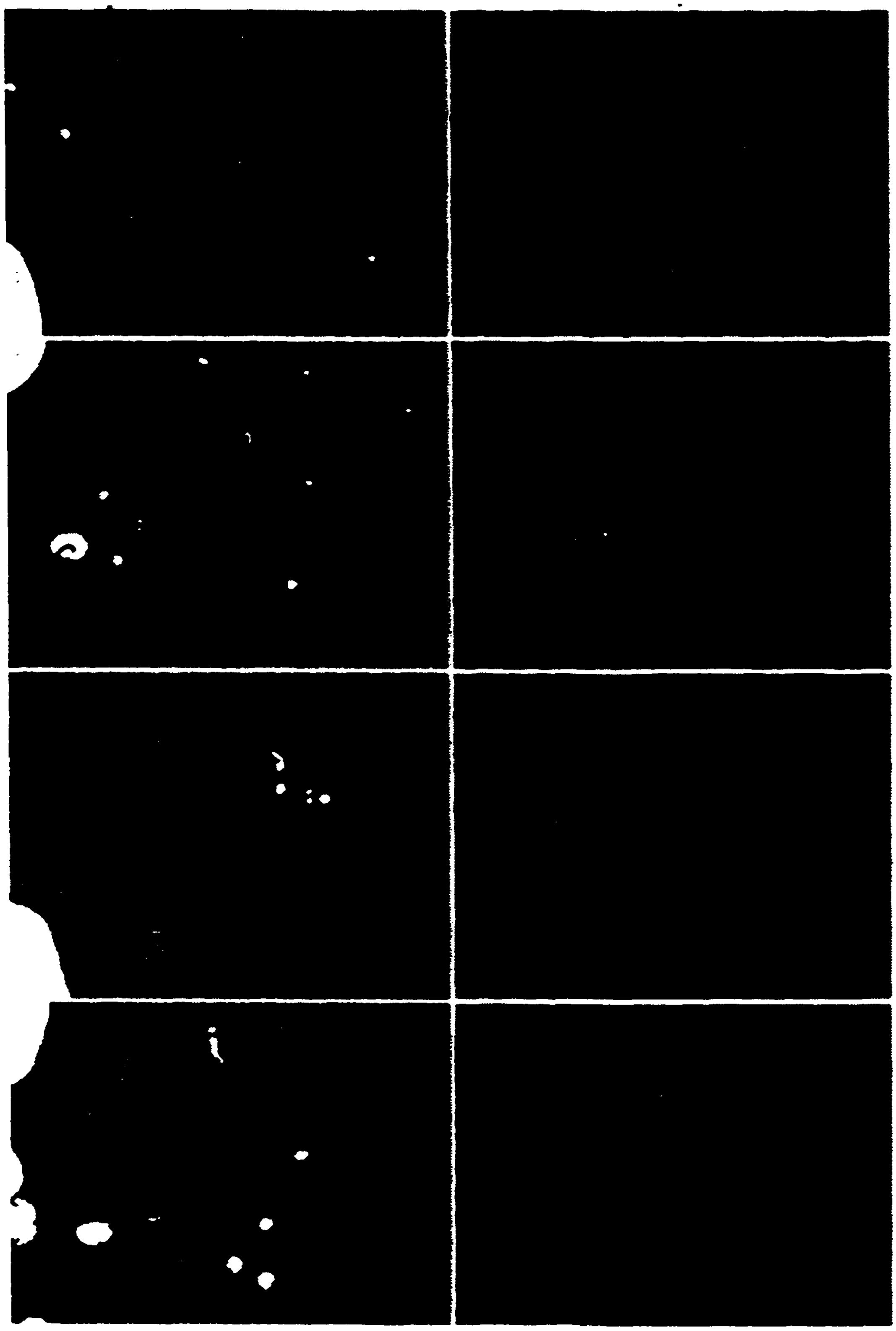

Figure 34. A typical ILn lesion. See text for details.

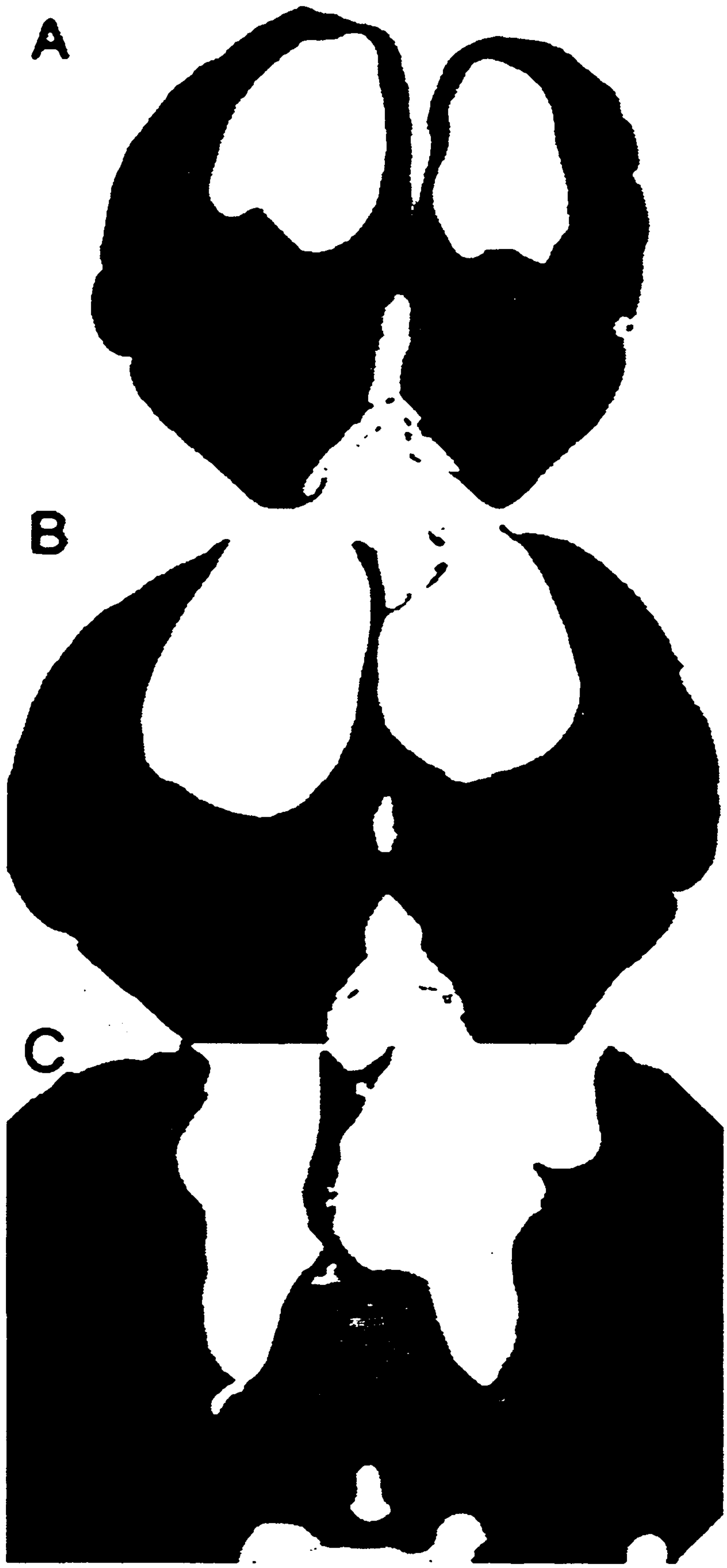

Figure 35. A typical PFC lesion. See text for details.

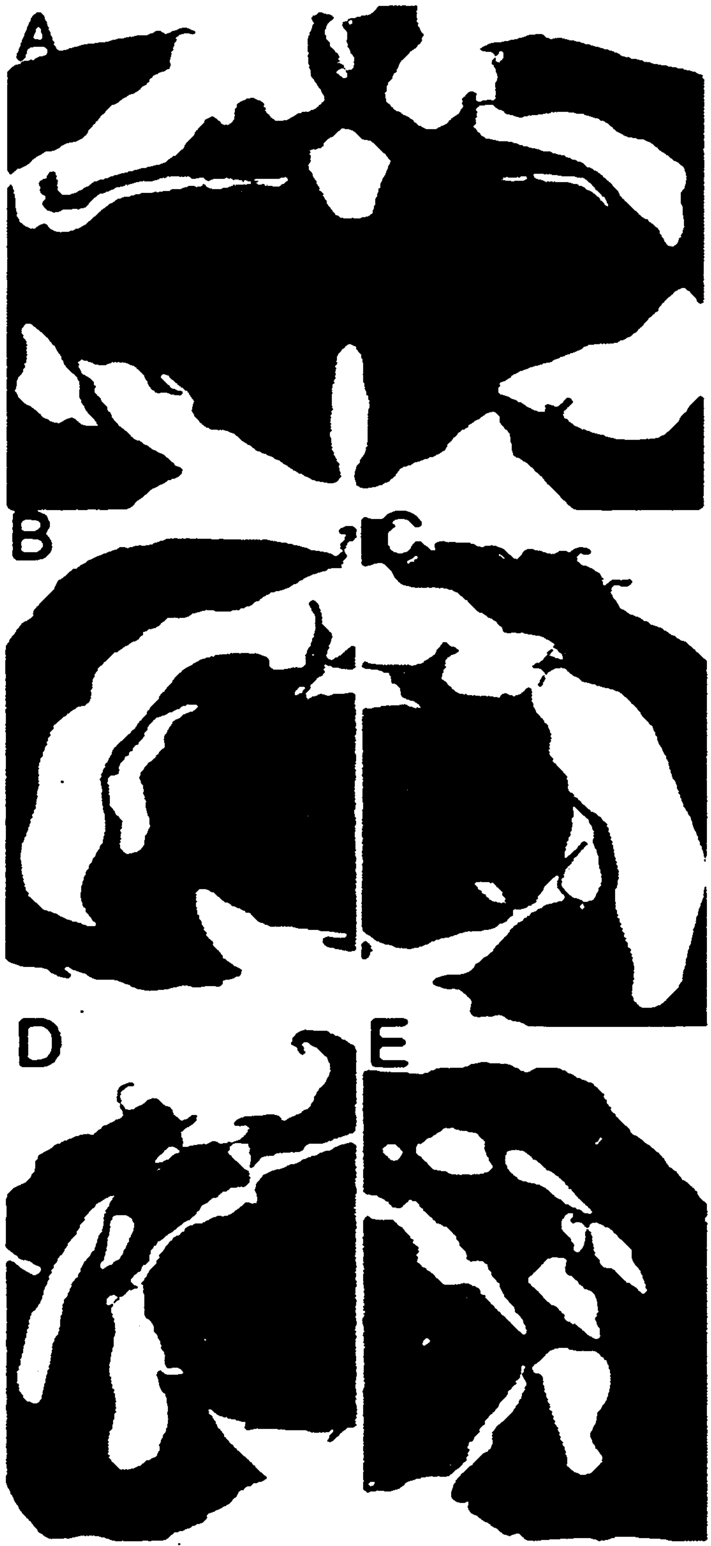

Figure 36. A typical HP lesion. See text for details.

IMAGE EVALUATION TEST TARGET (QA-3)

150mm

6"

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