SELECTIVE MEMORY IMPAIRMENTS PRODUCED BY TRANSIENT LIDOCAINE-INDUCED LESIONS OF THE NUCLEUS ACCUMBENS.

by

JEREMY KEITH SEAMANS


A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF ARTS

in

THE FACULTY OF GRADUATE STUDIES

(DEPARTMENT OF PSYCHOLOGY)

We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

AUGUST 1993

© JEREMY KEITH SEAMANS, 1993
In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

(Signature)

Department of Psychology
The University of British Columbia
Vancouver, Canada

Date 8/27/93
Abstract

Anatomical studies have identified major efferent pathways from the hippocampus to the nucleus accumbens (N.Acc.), but the functional significance of this interaction remains unclear. The delayed spatial win-shift radial arm maze task has been used as a selective behavioral measure of damage to the hippocampal system, whereas the cued win-stay version of this task is unaffected by hippocampal lesions, but is disrupted by lesions in the dorsal striatum. The present study utilized these two procedures, along with reversible lidocaine-induced lesions of the N.Acc., to determine whether the N.Acc. is part of the extra-hippocampal system that subserves efficient memory-based foraging behavior. These lesions impaired performance on the spatial win-shift but not the cued win-stay task. Pre-training lesions on the spatial win-shift task did not affect foraging for four pellets during either the training or test phases of the experiment. In contrast, lidocaine-induced lesions, given prior to the test-phase, significantly disrupted retrieval of four pellets on the 8-arm maze. Comparable deficits also were observed in animals trained to forage efficiently for four pellets on an 8-arm maze, without prior win-shift experience. State-dependent drug effects were ruled out by replicating the disruptive effects of lidocaine-infusions into the N.Acc. on spatial win-shift performance in animals receiving this treatment prior to both training and test phases. Collectively, these results indicate that the N.Acc. interacts with the hippocampus in guiding spatial win-shift behavior by allowing information about previously visited spatial locations to influence foraging in a complex radial arm maze environment.
Experiment 4: The Effects of Combined Pre-Training and Pre-Test Intra-N.Acc. Lidocaine Injections on Spatial Win-Shift Behavior: A Test for State Dependency........................................62

Methods.................................................................................................................62

Results......................................................................................................................63

Discussion...............................................................................................................73

The Effects of Intra-N.Acc. Lidocaine Infusions on Locomotor Behavior...........74

General Discussion.................................................................................................77

References...............................................................................................................87
Table 1. Mean latency to approach a food well for tasks on which the lidocaine group made numerous errors (left column) versus tasks which the lidocaine group made no more errors than controls (right column). The left column shows the mean approach latency for the lidocaine (top) and saline (bottom) groups during the test phase of the spatial win-shift task in Experiment 1 and Experiment 2b and the random foraging task (Experiment 3). The right column shows the mean approach latency for the lidocaine (top) and saline (bottom) groups during the training phase of Experiment 2a and the cued win-stay task of Experiment 1. * denotes significance at p<0.05. Standard errors are shown in brackets.
List of Figures

Figure 1.1 Mean number of visits to baited arms expressed as a percentage of the total number of all arm visits, the day prior to the injection (white) and the day of the injection (black) for the lidocaine and saline groups during the test phase of the spatial win-shift task in Experiment 1. ** denotes statistical significance at p<0.01. Standard errors are represented by vertical bars........................................21

Figure 1.2 Mean number of visits to lit arms expressed as a percentage of all arm visits, the day prior to the injection (white) and the day of the injection (black) for the lidocaine and saline groups during the cued-win-stay task of Experiment 1. Standard errors are represented by vertical bars.................................................23

Figure 1.3 Schematic representation of the infusion sites for all subjects included in Experiment 1. Black dots represent the location of the cannulae tips. Infusions spread approximately 0.5mm from the cannulae tips (see text). Illustrated brain sections are computer generated adaptations of plates found in Paxinos and Watson (1982). Histological abbreviations, N.Acc.=nucleus accumbens, cc=corpus callosum, ac=anterior commisure, CPu=caudate putamen......................................................25

Figure 2.1 Mean number of visits to baited arms expressed as a percentage of the total number of all arm visits, the day prior to the injection (white) and the day of the injection (black) for the lidocaine and saline groups during the training phase and test phase of Experiment 2a. Standard errors are represented by vertical bars........................................................................................................34

Figure 2.2 Mean number of arm visits made by the saline group (shaded) and lidocaine group (black) to retrieve each of four pellets during the training phase of Experiment 2a, on the day of the injection. Standard errors are represented by vertical bars........................................................................................................36

Figure 2.3 Mean number of visits to baited arms expressed as a percentage of the total number of all arm visits, the day prior to the injection (white) and the day of the injection (black) for the lidocaine and saline groups during the test phase of Experiment 2b. ** denotes statistical significance at p<0.01. Standard errors are represented by vertical bars........................................................................................................38

Figure 2.4 Mean number of across-delay (hatched) and within-trial (shaded) errors made by the lidocaine and saline groups during the test phase of Experiment 2b the day of the injection (see text for details). Standard errors are represented by vertical bars........................................................................................................40
Figure 2.5 Mean number of arm visits made by the saline group (shaded) and
lidocaine group (black) to retrieve each of four pellets during the test phase of
Experiment 2b, the day of the injection. * denotes a statistically significant
difference from chance at p<0.05. Standard errors are represented by vertical
bars. 42

Figure 2.6 Number of arm visits necessary to retrieve 4 pellets on an eight arm
maze, by chance (values were mathematically generated). 44

Figure 2.7 Schematic representation of the infusion sites for all subjects included in
Experiment 2. Black dots represent the location of the cannulae tips. Infusions
spread approximately 0.5mm from the cannulae tips (see text). Illustrated brain
sections are computer generated adaptations of plates found in Paxinos and
Watson (1982). Histological abbreviations, N.Acc.=nucleus accumbens, cc=corpus
callosum, ac=anterior commisure, CPu=caudate putamen. 46

Figure 3.1 Mean number of visits to baited arms expressed as a percentage of the
total number of all arm visits, the day prior to the injection (white) and the day of the
injection (black) for the lidocaine and saline groups during the random foraging task
(Experiment 3). ** denotes statistical significance at p<0.01. Standard errors are
represented by vertical bars. 53

Figure 3.2 Mean number of revisits to baited arms (cross hatched) and non-baited
arms (horizontal lines) for the saline and lidocaine groups during the random
foraging task (Experiment 3) the day of the injection. Standard errors are
represented by vertical bars. 55

Figure 3.3 Mean number of arm visits made by the saline group (shaded) and
lidocaine group (black) to retrieve each of four pellets during the random foraging
task (Experiment 3), the day of the injection. * denotes a statistically significant
difference from chance at p<0.05. Standard errors are represented by vertical
bars. 57

Figure 3.4 Schematic representation of the infusion sites for all subjects included in
Experiment 3. Black dots represent the location of the cannulae tips. Infusions
spread approximately 0.5mm from the cannulae tips (see text). Illustrated brain
sections are computer generated adaptations of plates found in Paxinos and
Watson (1982). Histological abbreviations, N.Acc.=nucleus accumbens, cc=corpus
callosum, ac=anterior commisure, CPu=caudate putamen. 59

Figure 4.1 Mean number of visits to baited arms expressed as a percentage of the
total number of all arm visits for the saline and lidocaine groups during the training
phase and test phase in Experiment 4 following pre-training (hatched) and pre-test
(black) injections. ** denotes statistical significance at p<0.01. Standard errors are
represented by vertical bars. 66
Figure 4.2  Mean number of across-delay (hatched) and within-trial (shaded) errors made by the lidocaine and saline groups during the test phase of Experiment 4, the day of the injection (see text for details). * denotes a statistically significant difference at p<0.05. Standard errors are represented by vertical bars.................68

Figure 4.3  Mean number of arm visits made by the saline group (shaded) and lidocaine group (black) to retrieve each of four pellets during Experiment 4, the day of the injection. * denotes a statistically significant difference from chance at p<0.05. Standard errors are represented by vertical bars..................................70

Figure 4.4  Schematic representation of the infusion sites for all subjects included in Experiment 4. Black dots represent the location of the cannulae tips. Infusions spread approximately 0.5mm from the cannulae tips (see text). Illustrated brain sections are computer generated adaptations of plates found in Paxinos and Watson (1982). Histological abbreviations, N.Acc.=nucleus accumbens, cc=corpus callosum, ac=anterior commissure, CPu=caudate putamen..................................72
ACKNOWLEDGMENTS

Special thanks goes to my thesis supervisor, Dr. Tony Phillips, for his support, guidance and extreme patience in helping me with the preparation of this thesis. I would also like to thank Stan Floresco and Tim Bussey for their involvement in some of the experiments described in this thesis. Finally, I would like to thank my thesis committee members, Dr. D. Wilkie and Dr. E. Eich for their helpful comments and insights.
Introduction:
Limbic-Striatal Interactions in Motivated Behaviors

The ventral striatum or nucleus accumbens (N.Acc.) lies at a crossroads between the limbic system and motor output regions of the brain (Nauta & Domesick 1978). This structure receives input from the amygdala, hippocampus and prefrontal cortex, and sends indirect projections through the pallidum and "mesencephalic locomotor region (MLR)" to motor output regions in the spinal chord (Groenewegen, Berendse, Meredith & Haber, 1991; Mogenson & Yang, 1991). Electrophysiological data have demonstrated that activity of the N.Acc. is affected by hippocampal stimulation, while activity in the MLR is influenced by stimulation of the N.Acc. (Mogenson & Yang 1991; Pennartz, Dolleman-Van Der Weel, Katai & DaSilva 1992; Pennartz & Katai 1991; Yang & Mogenson 1984). The functional importance of this pathway is indicated by behavioral data demonstrating that stimulation of the glutamate NMDA receptor in the hippocampus, or injection of the dopamine (DA) agonist, d-amphetamine into the N.Acc. cause increases in locomotor behavior which can be attenuated by procaine injections into the subpallidal region or the MLR (Mogenson & Neilson 1984; Mogenson & Yang 1991). Based on these and other findings, Gordon Mogenson and his colleges have proposed that the N.Acc. acts as a limbic-motor interface, allowing limbic inputs to gain access to motor output areas of the brain (Mogenson & Yang 1987; Mogenson & Yang 1991).

While this theory has been very influential, there is a growing body of evidence suggesting that the N.Acc. is more than simply a relay site for limbic input. Heimer, deOlmos, Alhied and Zaborsky (1991) have advanced the idea that the N.Acc. and related areas make up the "extended amygdala" which is essential for gating the ascending and descending output of the entire limbic
system. While it is still unclear as to the nature of this gate, one possibility is that DA activity in the N.Acc. has a "gain amplifying" effect on afferent input from the amygdala (Cador, Robbins, Everitt, Simon, LeMoal & Stinus 1991). Cador et al. (1991) and Cador, Everitt and Robbins (1989) have shown that lesions of the basolateral nucleus of the amygdala impair the ability to acquire a new operant response with conditioned reinforcement, while having a relatively minor effect on operant responding for primary reinforcement. Relative to control subjects, animals with amygdala lesions respond less frequently on a lever which delivers a conditioned stimulus. However, injections of d-amphetamine into the N.Acc. of animals with amygdala lesions leads to an increase responding specifically for the presentation of a conditioned stimulus. Therefore enhanced DA transmission in the N.Acc. may selectively modulate input received from the amygdala.

Electrophysiological data suggest that DA in the N.Acc. may play a similar role in modulating hippocampal input. Stimulation of discrete areas of the hippocampus activates certain cells in the N.Acc. (DeFrance, Sikes & Chronister, 1985; Pennartz & Katai 1991; Pennartz et al. 1992; Yang & Mogenson 1984). Microinjection of DA into the N.Acc., or stimulation of the ventral tegmental area (which causes DA release in the N.Acc.), inhibits these excitatory responses in a use-dependent manner. When the hippocampus is stimulated at 0.5Hz, DA inhibits approximately 75% of the elicited activity in the N.Acc. Conversely, when the hippocampus is stimulated at 6 Hz there is no decrease in the evoked activity (DeFrance et al. 1985). DeFrance et al. (1985) have suggested that DA in the N.Acc. may act to "increase the signal to noise ratio" of hippocampal input. The "signal" is hypothesized to be information arriving at the N.Acc. in the 6 Hz range. Activity in this range is observed in the hippocampus naturally when an animal actively explores it's environment (Bland & Vanderwolf 1972).
Furthermore, tetanic stimulation at 6Hz induces long-term potentiation (a synaptic model of memory) in the hippocampus (Bliss & Lynch 1988). Thus, DA activity in the N.Acc. may selectively enhance the transmission of information gathered during exploration and learning by inhibiting the transfer of other types of information. If this theory is expanded to incorporate the hypothesis that the N.Acc. acts as a "limbic-motor interface" (Mogenson & Yang 1991), then information acquired during exploration may have a preferential influence over ongoing behavior. Hence, the interaction between the hippocampus and N.Acc. may be crucial for updating behavior based on newly acquired information. Indeed it has been suggested that the hippocampus and N.Acc. may act together to guide flexible modes of responding in the face of environmental change (Isaacson 1982 and 1984; Scheel-Kruger & Wilner 1991). Much of the evidence supporting this claim comes from the findings that inflexible stereotyped modes of responding similar to those observed following hippocampal damage can also be produced by altering DA activity in the N.Acc.

It is quite clear that damage to the hippocampus reduces the variety of behavioral responses. Lesions of the hippocampus inhibit spontaneous alternation (for review see Isaacson 1982), and produce a tendency to exhibit win-stay behavior in the radial arm maze (Packard, Hirsh & White, 1989). Animals with hippocampal damage also sample fewer arm choices in a radial maze than control subjects and show a decrease in vigilant behaviors, indicating "fewer shifts in behavior and attention away from routine" (Devenport, Hale & Stidham 1988). Furthermore, such animals respond over a restricted range of inter-response intervals in operant paradigms and tend to respond in a rhythmic manner (Devenport, Devenport & Holloway 1981; Devenport et al. 1988; ). Finally, hippocampal damage produces an inability to inhibit responding during
periods of non-reward in a DRL paradigm (Isaacson 1982; Schmaltz & Isaacson 1966).

Hippocampal damage also alters DA activity in the N.Acc. (Isaacson 1984; Mittleman et al. in press). Hence it follows that many of the impairments that occur following hippocampal lesions may be due in part to secondary changes in the DA system at the level of the N.Acc. This theory is supported by the findings that 6-OHDA lesions of the N.Acc. cause impairments in spontaneous alternation, spatial alternation, reduced exploration of objects or environments and great difficulty in reversing previously learned habits (Taghzouti et al. 1985a, 1985b). While the exact interaction between the hippocampus and N.Acc. in guiding flexible modes of responding remains unclear, it has been suggested that hippocampal damage may lead to an inability to assess properly the relevance of external stimuli which provide signals for an animal to change its current mode of behavior (Devenport et al. 1981; Douglas & Pribram 1969; Isaacson 1982). Likewise, decreased DA activity in the N.Acc. may also result in an inability to change current modes of responding based on external cues (Scheel-Kruger & Wilner 1991; van den Bos, Charria Oritz, Bergman & Cools 1991).

The interactive roles of the N.Acc. and hippocampus in guiding flexible modes of behavior and in the control of locomotion raise the question as to whether the N.Acc. participates in other functions thought to be mediated by the hippocampus. The most extensively studied behavioral function of the hippocampus is its role in learning and memory. This work began in the 1950's with the discovery that bilateral removal of the medial temporal lobes produces a severe anterograde amnesia, and relatively mild retrograde amnesia (for review see Corkin 1984; Scoville & Milner 1957). Since that time there has been a
great deal of interest in the memory-related functions of medial temporal lobe structures and in particular the hippocampus.

In the early 1970's O'Keefe and Dostrovsky (1971) demonstrated the existence of "place cells" in the hippocampus. These cells fire when an animal is in a place in its environment as specified by the combination of allocentric cues that surround the animal (O'Keefe & Speakman 1987). The integrated activity of a network of place cells in the hippocampus has been hypothesized to form the basis of an enduring internal representation of an animal's environment (O'Keefe & Nadel 1978). In accordance with this theory, hippocampal lesions produce impairments in a variety of tasks that require an ability to acquire knowledge about spatial locations (Goodlett, Nichols, Holloran & West 1989; Jarrard 1983; Nadel & McDonald 1980). Taken together, these data suggest that the hippocampus is involved in spatial learning and memory.

A second view of hippocampal function was put forward by Olton, Becker & Handelmann (1980), who suggested that the hippocampus is involved in working memory, whether it be for spatial or non-spatial information. In one experiment, Olton reported that rats with hippocampal lesions, were unable to learn which arms of a radial maze contained food and which did not based solely on the patterns of the arms (Olton & Feustle 1981). A second task required animals to learn that certain arms of a radial maze always contained food, and others never contained food. The location of these arms were signaled by their relationship to extra-maze cues. Hence, it was a spatial task, with two components which Olton termed "working memory" (WM) and "reference memory" (RM). The working memory component assessed the ability to remember which arms were visited within a trial, while the reference memory component assessed the ability to remember which four arms always contained food across many trials. Rats with hippocampal lesions were able to learn the
reference memory component but not the working memory component, thereby demonstrating that although these animals had a memory deficit they could acquire some types of spatial information (Davis, Baranowski, Pulsinelli & Volpe 1986; Olton et al. 1980; Olton & Papas 1979). These data have been supported by other demonstrations that rats with hippocampal lesions are impaired in specific non-spatial cued radial arm maze tasks which involve a working memory component (Jarrard Okaichi, Steward & Goldschmidt 1984). Furthermore, lesions of the hippocampus in monkeys have produced impairments in non-spatial tasks such as delayed non-matching to sample, concurrent object discrimination and object-reward association tasks (Squire 1992). Taken together, these data demonstrate that the role of the hippocampus in memory appears to extend beyond the ability to learn about and utilize spatial features of an external environment.

Specific regions of the hippocampal formation are also involved in certain aspects of learning and memory. Patients with CA1 damage resulting from an ischemic episode have severe memory impairments, especially in learning new material (Zola-Morgan, Squire & Amaral 1986). Animals with this type of damage are deficient on spatial navigation tasks, such as the spatial win-shift task, described below and in a delayed non-matching to sample task (Auer, Murray & Whishaw 1989; Wood, Bussey & Phillips 1992; Wood, Mumby, Pinel & Phillips 1991). Damage to the subiculum, or its main output pathway, the fornix (Brodal 1968) also causes spatial navigation and working memory impairments in the radial arm maze (Goodlett et al. 1989; Jarrard et al. 1984). Lesions of the fornix produce deficits that are often very similar to deficits produced by damage to the entire hippocampus, namely problems in spatial navigation and working memory (Becker, Walker & Olton 1980; Jarrard et al. 1984: Meck, Church & Olton 1984; Olton et al. 1980; Olton, Walker & Wolf 1982; Olton & Werz 1978).
Damage to the anterior columns of the fornix in humans may be partially responsible for the pathology of the amnesic syndrome of Korsakoff (Heilman & Sypert 1977). Patients with this disorder show a marked anterograde amnesia and possibly a temporally graded retrograde amnesia (Albert, Butters & Levin 1979). Finally cortical areas closely related to the hippocampus also play important roles in learning and memory processes. Zola-Morgan, Squire, Amaral & Suzuki (1989) have demonstrated that lesions of the perirhinal, parahippocampal, or entorhinal cortices in monkeys produce impairments in the performance of delayed non-matching to sample and concurrent object discrimination tasks. It is therefore quite evident that the hippocampus and related regions of the overlying cortex play a critical role in many types of memory processes.

Anatomical evidence demonstrates that the N.Acc. receives either direct or indirect input from most of the medial temporal lobe regions discussed above. The dorsolateral or "core" area of the N.Acc. receives input from intermediary areas of the subiculum, the perirhinal cortex, and the anterior entorhinal cortex while the more ventral medial "shell" region receives input from the ventral subiculum, temporal regions of the CA1 subfield, medial and posterior regions of the entorhinal cortex, prelimbic cortex, and anterior cingulate cortex (Groenewegan, Beredse, Wolters & Loman 1990; Groenewegan, Vermeulen-Van Der Zee, Kortscot & Witter 1987; Kelly & Domesick 1982; McGeorge & Faull 1989; Newman & Winas 1980; Swanson & Cowan 1977; Walaas 1981). These anatomical data therefore raise the possibility that the N.Acc. may indeed play a role in the memory-related functions of the hippocampus. However the behavioral data supporting this speculation are sparse and in many cases inconclusive.
Two tasks which are impaired by hippocampal lesions, namely acquisition of the spatial Morris water maze task and spatial reversal in the T-maze are also impaired by excitotoxic lesions of the N.Acc. (Annett, McGregor & Robbins 1989; Sutherland & Rodriguez 1989; Brandes, Brandys & Yehuda 1989; Goodlett et al. 1989; Isaacson 1982). Scheel-Kruger & Wilner (1991) have also shown that microinjections of glutamate antagonists into the N.Acc. produce impairments in a spatial water maze task both during initial training and when the task is well learned. While these data suggest a functional interaction between the hippocampus and N.Acc. with regards to learning and memory processes, other data do not support this hypothesis. Microinjection of a glutamate antagonist into the N.Acc. produces impairments in the reference memory component of the WM/RM radial arm maze described previously, whereas hippocampal lesions do not (Davis et al. 1986; Olton & Papas 1979; Schacter, Yang, Innis & Mogenson 1989). The reference memory component of this task is however sensitive to damage of the caudate nucleus (Packard & White 1990; Colombo, Davis & Volpe 1989). Furthermore disruption of dorsal striatal function also results in impairments in spatial reversal in the T-maze (Divac 1971) and spatially mediated behavior in the Morris water maze (Whishaw, Mittleman, Bunch & Dennett 1987; Scheel-Kruger & Wilner 1991). Therefore, based on these data it may be argued that the N.Acc. is involved in memory processes mediated by either the caudate nucleus or the hippocampal formation.

Any attempt to explore the role of the N.Acc. in behaviors linked to hippocampal function, must use tasks which are sensitive to lesions of the hippocampal formation and not to damage to other areas of the brain. One candidate is the spatial win-shift 8-arm radial maze task developed by Packard et al. (1989) and Packard and White (1991). The task consists of a training phase and test phase separated by a delay period. During the training phase
four arms are blocked and the animal must explore four open arms of the maze to find food in each. During the test phase the animal must avoid the arms it visited during the previous training phase and visit the four remaining arms. This task has an inherent working memory component in that the animal must remember previous arm choices both within a test phase and across a delay. It also requires a knowledge of spatial locations as the location of the arms are signaled by the constellation of allocentric spatial cues surrounding the maze. Finally the task requires an ability to respond in a flexible manner as the animal must explore a novel set of arms each day as well as avoid arms previously visited both within a trial and across a delay. This task therefore encompasses many of the functions ascribed to the hippocampus discussed above. Perhaps the most important feature of the spatial win-shift task is its sensitivity to lesions of the hippocampus but not to damage of the caudate nucleus or amygdala (McDonald & White 1993).

As noted above, hypotheses concerning the function of the N.Acc. must also pay particular attention to its possible involvement in the memory-related functions of the caudate nucleus. Indeed anatomists have suggested that the N.Acc. is in a position to influence the activity of the caudate nucleus indirectly by affecting the activity of the substantia nigra, the main source of DA input to the caudate nucleus (Groenewegen et al. 1991; Groenewegen & Russchen 1984; Fallon 1988; Nauta, Smith, Faull & Domesick 1978). If disruption of neural activity in the N.Acc. results in the modification of striatal function, this may be manifested by disrupted behavior on a task sensitive to lesions of the caudate nucleus, such as the cued win-stay task also developed by Packard et al. (1989) and Packard and White (1991). In this task the animal must learn to approach arms on a radial maze which are illuminated in order to obtain food reward. The cued win-stay task appears to be sensitive to several functions ascribed to the
striatum, including the association of a response with a stimulus, reference memory, habit learning, and memory for a visual stimulus (Columbo et al 1989; Cook & Kesner 1988; Hikosaka 1986; Mitchell, Channell & Hall 1985; Packard et al 1989; Packard & McGaugh 1992; Packard & White 1990). Importantly, the cued win-stay task is disrupted by lesions of the caudate nucleus but not of the hippocampus or amygdala (McDonald & White 1993). Therefore the cued win-stay task serves as viable behavioral test for memory functions thought to be mediated by the dorsal striatum.

Purpose of Present Research

The purpose of the present series of experiments was to examine the possible contribution of the N.Acc. to behaviors controlled by the hippocampus and the caudate nucleus, using the spatial win-shift and win-stay procedures just described. In contrast to the majority of lesion studies referred to above, the present study employed transient lesions of the N.Acc. produced by intracranial injections of the local anesthetic lidocaine. Local anesthetics, such as lidocaine or procaine have been used by electrophysiologists to block temporarily the activity of a brain area under investigation. As discussed above, Mogenson and Yang (1991) have used this technique to examine the role of the hippocampal-MLR pathway in locomotion. This technique has also been used to block the activity of cerebellar nuclei transiently during the performance of a conditioned eye blink task (Chapman, Steinmetz, Sears & Thompson 1990; Knowlton & Thompson 1988; Welsh & Harvey 1991).

There are a number of reasons for choosing this technique over methods which produce permanent lesions. First lidocaine lesions can be made quickly and easily therefore the animals do not have to forgo training for many days to allow time for surgery and recovery. Furthermore, permanent lesions cause changes in other structures which receive projections from the lesioned area,
making it difficult to make accurate structure/function assessments (Isaacson 1984). Although, at present there is no direct evidence that similar effects do not occur with lidocaine lesions, this technique does not produce any long-term impairments in the performance of a variety of responses on the radial arm maze (personal observations). Finally the use of permanent lesions poses difficulty in assessing accurately which component of memory has been affected by the lesion, i.e. rule acquisition, versus the acquisition, storage, and/or retrieval of within-trial information.

The choice of the reversible lesion technique focused my experiments on the ability to acquire and use trial-unique information. Animals, with indwelling canulae aimed at the N.Acc. were trained daily on the spatial win-shift and cued win-stay tasks. Once the behaviors were well learned, lidocaine injections were made into the N.Acc. of these animals, at different points of the daily learning trials. Electrophysiological data indicate that the time necessary for the anesthetic effects of lidocaine on neural tissue to commence is approximately 2 min while the effects dissipate in approximately 20-30 min (Crawford, Hallock, Truant & Wilder 1960; Sandkuhler, Maish & Zimmerman 1987; Welsh & Harvey 1991). This technique therefore allowed animals to be trained with a transient N.Acc. lesion and tested drug-free or trained drug-free and tested with a N.Acc. lesion, thereby permitting a dissociation of the role of the N.Acc. in the acquisition as compared to the retrieval of information that was unique to a given trial.

The present study was divided into four experiments. Experiment 1 examined the effects of intra-N.Acc. lidocaine infusions on the performance of a spatial win-shift task and a cued win-stay task, while all subsequent experiments addressed the role of the N.Acc. in specific aspects of spatial win-shift behavior. In Experiment 2, transient N.Acc. lesions were delivered prior to the training
phase (2a) or prior to the test phase (2b) of this task to determine whether the N.Acc. is involved in the acquisition and/or use of newly acquired information. Experiment 3 examined the effects of transient N.Acc. lesions on a random foraging task. As this task was identical to the test phase of the spatial win-shift task, it permitted an assessment of the effects of transient N.Acc. lesions on acquisition and/or use of information solely within the test phase. Experiment 4 provided a necessary control for a state-dependency phenomenon, given that the animals in Experiments 1 and 2 were either trained in a drug free state and tested under the influence of lidocaine or vice versa.
General Methods

Subjects

The subjects were 104 male Long Evans rats (350-550 g), housed individually in a temperature and light-controlled (12:12-hr light-dark cycle) colony. All subjects were given free access to water and were reduced to 80% of their free feeding weight, prior to the first day of food training. Once the rats began to eat on the maze, they were maintained at 85% of their free-feeding weight by providing approximately 25-30g of Purina lab chow pellets once daily. All animals were tested during their light cycle between 2-8 pm daily.

Surgery

Prior to surgery animals were anesthetized with 1 mg/kg ketamine hydrochloride and 0.33 mg/kg xylazine. Twenty two gauge stainless steel guide cannulae were aimed at the N.Acc. bilaterally using standard stereotaxic procedures. The cannulae were aimed at the ventromedial region of the N.Acc. This area was choosen because it receives a large input from medial temporal lobe structures, as discussed above. The stereotaxic coordinates obtained from Paxinos and Watson (1982) were, AP=+1.9 mm, ML=1.4 mm, from bregma and DV=-6.3 mm from cortex. Solid steel 26 gauge stylets, the same length as the guide cannulae, were inserted and left in place until the injections were made. After surgery animals were allowed to recover for at least 10 days prior to behavioral testing.

Injection Procedure

The injections for all experiments were made only on the day after each animal attained criterion performance. All animals were injected in their home cages in the rooms which contained the test apparatus. For each injection the solid steel stylets were removed and a 26 gauge inner cannulae was inserted which extended .8mm beyond the end of the guide. 1μl of Lidocaine
hydrochloride (2%, Astra Phamaceuticals) or 1μl of isotonic saline was delivered at a rate of 1μl / 2 min by a Sage instruments model 341 syringe pump. The injection cannulae were left in place for an additional 60 s to allow for diffusion. Animals were allowed an additional 120 s in their home cages prior to being placed on the maze to ensure sufficient tissue anesthetization.

Apparatus

Two similar 8-arm radial mazes were used for all behavioral testing. Both mazes had octagonal center platforms measuring 40cm in diameter. Radiating out from these platforms were eight arms each 50cm x 9cm, with 1cm (height) x 3cm (diameter) cylindrical food cups at the ends of maze 1 and 0.5cm (depth) x 1cm (diameter) food wells at the ends of maze 2. Maze 1 had eight six watt light bulbs mounted on Plexiglas sheets (6cm x 10cm) located directly above the food cups. Metal doors 9cm (width) x 13cm (height) which laid flat against each arm, could be raised to block the entrance to each arm of maze 1 while arms were blocked in maze 2 using 9cm (width) x 13cm (height) pieces of removable opaque plastic.

In Experiment 1, maze 1 was used for both the spatial win-shift and cued win-stay tasks. For the spatial win-shift task the maze was elevated 40cm off the ground and surrounded by several extra maze cues. For the cued win-stay task, the maze was placed on a large opaque cylindrical platform, surrounded on all sides by curtains to obscure the animal's view of extra-maze cues. Animals were monitored by an overhead video camera. The lights at the ends of the arms were operated by a remote switch box. All other experiments were conducted using maze 2. This maze was elevated 40 cm off the ground and surrounded by several extra maze cues.
**Histology**

After behavioral testing the animals were sacrificed in a carbon dioxide chamber. Brains were removed and fixed in a 10% formalin solution. The brains were then frozen and sliced in 40μm sections prior to being mounted and stained using the Kluver-Barrera method (Luna 1960). Cannulae placements were verified with reference to the stereotaxic atlas of Paxinos and Watson (1982). Histological results are shown in Fig. 1.3 for Experiment 1, Fig. 2.7 for Experiment 2, Fig. 3.4 for Experiment 3 and Fig. 4.4 for Experiment 4. These figures show the location of the cannulae tips for each animal included in Experiments 1 through 4. Albert and Madryga (1980) demonstrate that the functional spread of lidocaine in the occlulomotor nucleus is approximately 0.5 mm from the site of infusion. However Welsh & Harvey (1991) have shown that lidocaine has a functional spread of up to 1.4 mm in the cerebellum. Based on histological analysis in the present study, tissue damage resulting from lidocaine infusions into the N.Acc. extended no greater than 1 mm from the tip of the injection cannulae. Subjects whose injections diffused out of the N.Acc. were not included in the above figures or data analysis. The placements were largely confined within the N.Acc. with the exception of two animals in Experiment 1, four animals in Experiment 2 and four animals in Experiment 4.
Experiment 1:
The Effects of Intra-N.Acc. Lidocaine Infusions on Spatial Win-Shift and Cued Win-Stay Behavior.

As discussed in the introduction, the N.Acc. participates in tasks thought to be mediated by the hippocampus and caudate nucleus. A number of behavioral investigations have shown that damage to, or inhibition of DA or glutamatergic transmission in the N.Acc., impairs performance on the spatial Morris water maze task and spatial reversal in a T-maze (Annett et al. 1989; Scheel-Krugar & Wilner 1991; Taghoutzi, Simon Louilot, Herman & LeMoal 1985a, Taghoutzi, Louilot, Herman, LeMoal & Simon 1985b; Sutherland & Rodriguez 1989). However, as these tasks are sensitive to both hippocampal lesions (Brandesis et al. 1989; Goodlett et al. 1989; Isaacson 1982) and lesions of the caudate nucleus (Divac 1971; Scheel-Krugar & Wilner 1991; Whishaw et al. 1987) it is difficult to conclude whether the N.Acc. interacts specifically with the hippocampus or caudate nucleus in guiding these behaviors. Recently Packard et al. (1989), Packard and White (1991) and McDonald and White (1993) have shown that the memory-related functions of the hippocampus and caudate nucleus can be dissociated using two radial arm maze tasks. They demonstrated that performance of a spatial win-shift task was sensitive to lesions of the hippocampus but not the caudate nucleus while performance of the cued win-stay task was impaired by lesions of the caudate nucleus, but not the hippocampus. These tasks therefore provide viable behavioral assays of the memory-related functions of the hippocampus and caudate nucleus. The purpose of the present experiment was to examine the effects of transient N.Acc. lesions on the spatial win-shift and cued win-stay tasks, in an attempt to gain
insight into as to whether this structure interacts with the hippocampus or caudate nucleus in guiding radial arm-maze behavior.

Methods

The spatial win-shift and cued win-stay paradigms used in the present study were variations of tasks used by Packard et al. (1989), and Packard and White (1991) with a 5 min inter-phase interval. The procedure for the spatial win-shift task was as follows. On the first two days of behavioral testing, animals were placed on the maze for 10 min, with no food available. Upon returning to their home cages they were given five Bioserv pellets (Holton Industries Co., Frenchtown, NJ). Daily learning trials were divided into a training phase and a test phase separated by a delay. Prior to the training phase a set of four arms chosen quasi-randomly were blocked and a food pellet was placed in the food cups of the four remaining open arms. During the training phase the animal was required to retrieve the four pellets from the four baited arms within 10 min. On the first day of training four pellets were also placed on the center platform and one pellet was placed in the center as well as on the food cup of the four open arms during the training phase. After the first training session, food was only placed in the food cups. During the test phase of each daily trial, all arms were open, but only the arms that were blocked during the training phase were baited. The animals were given 10 min to retrieve the four pellets during the test phase. A 5 min delay separated the training and test phases in this experiment. Criterion performance was attained when the animals could retrieve all 4 pellets during the training phase, and 4 pellets in 5 or fewer choices during the test phase, for 3 consecutive days.

The day after criterion performance was attained the animals were again allowed to retrieve all 4 pellets during the training phase, but were then removed from the maze to receive injections of either saline or lidocaine, into the N.Acc.
as described above. After a 5 min delay, the animals were placed on the maze for the test phase. The percentage of correct arm choices out of the total number of all arm choices during the test phase was computed for the day prior to the injection and the day of the injection. A correct choice was scored as an entry into a baited arm and consumption of the food pellet.

While the cued win-stay task used the same maze as the spatial win-shift task, the maze was placed on a large circular platform surrounded by curtains, with lights at the ends of the arms to signal the presence of food. The initial two days of training for the cued win-stay task were similar to the spatial win-shift task, in that the animals were allowed to explore the maze for 10 min with no food available and were given 5 pellets in their home cages after being removed from the maze. Each subsequent day of training consisted of two similar sessions separated by a 5 min delay. This procedure was used to mimic the temporal design of the spatial win-shift task, as well as to allow time for an injection between identical training sessions. This procedure therefore allowed a direct comparison of performance during a transient N.Acc. lesion to drug-free performance 5 min. earlier. During the first daily session the lights of four arms chosen quasi-randomly were turned on and the food cups located beneath these lights, were baited. Each rat was given 10 min. to retrieve the pellets from the food cups of the four lit arms. Once a pellet was retrieved the light located above it, was turned off. The animals were then removed from the maze and placed in their home cages for 5 min. After the delay the procedure outlined above was repeated.

Criterion performance was attained when eight pellets over 2 daily sessions could be obtained in 10 or fewer choices, for 3 consecutive days. The day after criterion performance was demonstrated, the animals were injected with either saline or lidocaine, in the manner described above, between the two
training sessions. Arm choices were recorded, and the number of correct choices (visits to lit arms) as a percentage of the total number of choices was calculated for the drug-free and injection trial.

Results

Transient lidocaine induced lesions of the N.Acc. produce severe impairments in test phase performance of the spatial win-shift task while leaving cued win-stay behavior intact. The effects of intra-N.Acc. lidocaine injections on spatial win-shift and cued win-stay behavior is shown in Fig. 1.1 and 1.2 respectively. A two-way repeated measures ANOVA was performed on the scores obtained the during the test phase of the spatial win-shift task on the day prior to the injection, and on the day of the injection. A significant group effect (sal \( \bar{x} = 84\% \), lido \( \bar{x} = 69.5\% \), \( F(1,18) = 9.05, p = 0.008 \)) and a day x group interaction effect (\( F(1,18) = 24.91, p < 0.05 \)), was observed and followed by simple main effect analysis which yielded no significant difference between the groups the day prior to the injection (sal \( \bar{x} = 88\% \), lido \( \bar{x} = 94\% \), \( F(1,18) = 1.8, p = 0.19 \)) but a significant difference between the groups the day of the injection, (sal \( \bar{x} = 74\% \), lido \( \bar{x} = 45.2\% \), \( F(1,18) = 25.37, p < 0.001 \)). A two-way repeated measures ANOVA was computed on the choice scores for the two trials, the day of the injection for the cued win-stay task. No significant difference was observed between the saline ( \( \bar{x} = 83.6\% \)) and lidocaine ( \( \bar{x} = 90\% \)) groups \( F(1,14) = 1.68 \), \( p = 0.298 \) overall or between the trial prior to the injection versus the trial immediately following the injection \( F(1,14) = 0.331 \), \( p = 0.574 \) for either saline or lidocaine groups.

Histological results for all animals included in the spatial win-shift and cued win-stay tasks in Experiment 1 are shown in Fig. 1.3.
Figure 1.1 Mean number of visits to baited arms expressed as a percentage of the total number of all arm visits, the day prior to the injection (white) and the day of the injection (black) for the lidocaine and saline groups during the test phase of the spatial win-shift task in Experiment 1. ** denotes statistical significance at p<0.01. Standard errors are represented by vertical
4.

Lidocaine Group

Saline Group

day prior to injection
day of injection
Figure 1.2  Mean number of visits to lit arms expressed as a percentage of all arm visits, the day prior to the injection (white) and the day of the injection (black) for the lidocaine and saline groups during the cued-win-stay task of Experiment 1. Standard errors are represented by vertical bars.
prior to injection
injection

Percent Correct

Lidocaine Group  Saline Group
Figure 1.3  Schematic representation of the infusion sites for all subjects included in Experiment 1. Black dots represent the location of the cannulae tips. Infusions spread approximately 0.5mm from the cannulae tips (see text). Illustrated brain sections are computer generated adaptations of plates found in Paxinos and Watson (1982). Histological abbreviations, N.Acc.=nucleus accumbens, cc=corpus callosum, ac=anterior commisure, CPu=caudate putamen.
Discussion

The results of this experiment demonstrate that intra-N.Acc. lidocaine infusions spare cued win-stay behavior. In contrast, this manipulation produced a severe impairment in performance on the test phase of the spatial win-shift task. In view of the results obtained by Packard et al. 1989, the present data suggest that the N.Acc. is involved preferentially in tasks thought to be mediated by the hippocampus rather than those linked to the caudate nucleus. However, Schacter et al. (1989) report that microinjections of a glutamate antagonist into the N.Acc. impairs the the reference memory component but not the working memory component of the WM/RM radial arm maze task (described above). A similar impairment is observed following permanent lesions of the caudate nucleus, while hippocampal lesions impair only the working memory component (Colombo et al. 1989; Davis et al. 1986; Olton 1982; Packard & White 1990) suggesting that the N.Acc. is involved in tasks mediated by the caudate nucleus rather than the hippocampus. A second interpretation of these data is that the N.Acc. is involved in spatially mediated tasks. Given that the cued win-stay task is not spatially mediated, transient N.Acc. lesions would be expected to have little effect on this behavior.

Although animals with permanent or transient N.Acc. lesions are impaired on the initial acquisition of the spatial Morris water maze task, they can eventually learn to find a hidden platform using spatial cues (Annett et al. 1989; Seamans, Floresco & Phillips in preparation). Therefore N.Acc. lesions do not seem to abolish completely the ability to form a spatial map (O'keefe & Nadel 1978). These lesions may however impair the ability to use newly acquired information about specific aspects of a spatial environment. This interpretation is in accordance with the results of the present experiment demonstrating an impairment in the ability to use newly acquired information about the location of
four food pellets on an 8-arm spatially cued maze following transient N.Acc. lesions.

A second major difference between the cued win-stay and spatial win-shift task is that the former does not require a flexible mode of responding. In this task the animal must, under all circumstances, visit arms that are illuminated. Conversely, in the spatial win-shift task the animal must use a variety of cues to navigate among arms in a non-repetitive manner. Transient N.Acc. lesions may therefore produce an impairment in the ability to respond in a flexible manner. Taghzouti et al. (1985a, 1985b) have reported that 6-OHDA lesions of the N.Acc. impair the ability to perform spatial reversals in a T-Maze, as lesioned animals tend to perseverate in their previous response tendencies. However it is unlikely that such an impairment is responsible for the deficits observed in the present investigation as the animals were responding randomly and rarely revisited the same arm or arm sequence in succession (personal observations). Annett et al. (1989) have observed random modes of responding in a spatial T-maze paradigm following excitotoxic lesions of the N.Acc. These authors suggest that N.Acc. lesions impair the ability to choose the correct response strategy necessary to solve the task. It is possible that the animals receiving transient N.Acc. lesions in the present experiment were unable to use the correct or well learned behavioral strategy (i.e. win-shift) and as a result began to respond in a random manner. Moreover, it is clear that this type of impairment is limited to win-shift radial arm maze behavior as no such impairment is observed in employing a win-stay strategy.

Finally, the amount of new information acquired daily is clearly different for the spatial win-shift and cued win-stay tasks. In the former case, up to eight previous arm choices must be remembered, whereas no previous daily information must be retained in the latter task. In contrast the cued win-stay task
requires an ability to use the well learned rule that a light signals the location of food. Lights are turned off following a visit, and thus information about previously visited arms can be forgotten. Hence trial-unique information must be acquired and used only in spatial win-shift task and not the cued win-stay task. Therefore, the deficit produced by transient N.Acc. lesions may be attributed to an inability to acquire and/or use trial-unique information efficiently.
Experiment 2: The Effects of Pre-Training and Pre-Test Intra-N.Acc. Lidocaine Infusions on Spatial Win-Shift Behavior.

Transient lesions of the N.Acc. delivered prior to the test phase of the spatial win-shift task in Experiment 1 impaired test phase performance. However the results of Experiment 1 provided little insight into the role of the N.Acc. in the acquisition as opposed to the use of trial-unique information in the spatial win-shift task. Experiment 2a was designed to address this issue by exploiting the transient anesthetic properties of lidocaine on neuronal tissue. Intra-N.Acc. lidocaine infusions were delivered prior to the training phase of the spatial win-shift task. In this experiment the test phase followed 30 min. later when the anesthetic effects of the drug had dissipated, hence the animals were trained under the influence of the drug, but tested drug free. This procedure permitted an analysis of the role played by the N.Acc. specifically in the acquisition of trial-unique information during the training phase of the spatial win-shift task. The role of the N.Acc. in the ability to use information acquired previously during the training phase of the spatial win-shift task was addressed in Experiment 2b. In this experiment a transient N.Acc. lesion was delivered at the end of the 30 min. inter-phase interval, prior to the commencement of the test phase. Collectively Experiments 2a and 2b were conducted in an attempt to gain insight into the role of the N.Acc. in the acquisition as opposed to the retrieval of information obtained during the training phase of the spatial win-shift task.

Methods

The behavioral procedure for this experiment was similar to that outlined above for the spatial win-shift task. However, injections were made the day after
an animal successfully retrieved four pellets during the training phase and four pellets in five or fewer choices during the test phase for two consecutive days at a five min. inter-phase interval, then at a 30 min. inter-phase interval. In Experiment 2a, the day after criterion performance was demonstrated, the animals received either a saline or lidocaine injection, in the manner described above, prior to the training phase. After the injection, the animals completed both the training phase and the test phase 30 min. later. A 30 min. post-injection interval is sufficient time for the anesthetic effects of lidocaine to dissipate (Crawford et al. 1960; Sandkuhler et al. 1987; Welsh & Harvey 1991). Hence the animals acquired information during the training phase under the influence of lidocaine but were tested drug free during the test phase.

Experiment 2b used the same procedure as Experiment 2a. However an intra-N.Acc. infusion of saline or lidocaine was delivered prior to the test phase rather than prior to the training phase. On the day of the injections, the animals were required to complete the training phase as usual. They were then returned to their home cages, where 25 min. later they were given intra-N.Acc. lidocaine or saline injections, in the manner described above (the injections took 5 min, making a total delay of 30 min). After the injections the animals were placed back on the maze for the test phase.

The number of correct choices (visits to baited arms) expressed as a percentage of the total number of arm choices was calculated for the training phase and test phase of Experiment 2a and the test phase of Experiment 2b. The type of errors made, i.e. across-delay errors (revisits to arms visited during the training phase), and within-trial errors (revisits to arms visited previously during the test phase) was calculated for the test phase of Experiment 2b. Finally the number of choices required to retrieve each pellet was obtained for the training phase of Experiment 2a and test phase of Experiment 2b.
Results

In Experiment 2a transient lidocaine-induced lesions of the N.Acc. delivered prior to the training phase of the spatial win-shift task, did not impair training phase performance or test phase performance 30 min. later when the anesthetic effects of the drug had dissipated (Fig. 2.1, Fig. 2.2). In contrast pre-test intra-N.Acc. lidocaine infusions disrupted performance during the test phase of the spatial win-shift task in Experiment 2b (Fig. 2.3). Animals receiving this manipulation made an equal number of across-delay and within trial errors (Fig. 2.4). Furthermore their performance was similar to the saline group in retrieving the first two pellets but approached chance when they attempted to retrieve pellets 3 and 4 (Fig. 2.5, Fig. 2.6).

A two-way repeated measures ANOVA was computed on the number of errors made during the training phase of Experiment 2a. There was no significant difference between the day prior to the injection versus the day of the injection F(1,14)=1.79, p=0.20 or between the lidocaine (\(\bar{x}=96\%\)) and saline groups (\(\bar{x}=93.3\%\)) F(1,14)=0.27, p=0.61. A two-way repeated measures ANOVA was computed on the performance scores during the test phase of Experiment 2a. Again there was no significant difference in the percentage of correct choices made by the lidocaine (\(\bar{x}=84.9\%\)) and saline (\(\bar{x}=85.7\%\)) groups (F(1,14)=0.01, p=0.92). Fig. 2.2 shows the mean number of arm visits made by the lidocaine and saline groups to retrieve pellets 1 to 4 during the training phase of Experiment 2a. No differences were observed between the groups on the choices taken to retrieve each pellet (pellet 1, \(\bar{x}=1\), pellet 2, \(\bar{x}=1.08\), pellet 3, \(\bar{x}=1\), pellet 4 \(\bar{x}=1.48\), F(3,42)=1.47, p=0.236).

A two-way repeated measures ANOVA was computed on the performance scores during the test phase of Experiment 2b. A significant group effect (sal \(\bar{x}=82.5\%\), lido \(\bar{x}=63.5\%\)) and day x group interaction effect
F(1,14)=7.36 p<0.05 was observed. This was followed by simple main effect analyses which yielded no significant difference between the groups on the day prior to the injection F(1,14)=2.333, p=0.149, but a significant difference was observed between the groups on the day of the injection (saline $\bar{x}=74\%$, lidocaine $\bar{x}=41.75\%$) F(1,14)=17.69, p=0.001.

A two-way repeated measures ANOVA conducted on the types of errors made by the saline and lidocaine groups revealed a significant overall group difference (sal $\bar{x}=1.4$, lido $\bar{x}=3$, F(1,14)=10.8, p=0.005). No differences were observed in the types of errors made by the lidocaine group (across-delay errors $\bar{x}=3$, within-trial errors $\bar{x}=4.8$, F(1,7)=2.16, p=0.185) while the saline group made slightly more across-delay errors ($\bar{x}=1.54$) than within-trial errors ($\bar{x}=0.32$) (F(1,7)=4.667, p=0.06).

Fig. 2.5 shows the number of arm choices (visits) required to retrieve each pellet (choices are non-cumulative) while chance values are shown in Fig. 2.6. The chance values generated mathematically are: 2 choices to retrieve the first pellet, 2.67 to retrieve the second, 4 to retrieve the third, and 8 choices to retrieve the final pellet. Two chi-square analyses were conducted on the number of arm visits taken to retrieve pellet 1 and 2 and the number arm visits taken to retrieve pellet 3 and 4. There was no significant difference from chance levels on the number of choices necessary to retrieve pellet 1 and 2 for the saline group (pellet 1, $\bar{x}=1.5$, pellet 2, $\bar{x}=1.13$, $\chi^2$(1)=0.88, p>0.1) or lidocaine group (pellet 1, $\bar{x}=1.25$, pellet 2, $\bar{x}=2$, $\chi^2$(1)=0.38, p>0.1). The saline group was significantly different from chance in retrieving pellets 3 ($\bar{x}=1.25$) and 4 ($\bar{x}=1.88$) ($\chi^2$(1)=6.58, p<0.05), whereas the lidocaine group was not (pellet 3, $\bar{x}=2.38$, and pellet 4, $\bar{x}=5.125$, $\chi^2$(1)=1.657, p>0.1).

Histological results for all subjects included in Experiments 2 are shown in Fig. 2.7
Figure 2.1 Mean number of visits to baited arms expressed as a percentage of the total number of all arm visits, the day prior to the injection (white) and the day of the injection (black) for the lidocaine and saline groups during the training phase and test phase of Experiment 2a. Standard errors are represented by vertical bars.
34 day prior to injection

34 day of injection

Percent Correct

0 20 40 60 80 100

training  test  training  test

Lidocaine Group  Saline Group

day prior to injection
day of injection
Figure 2.2  Mean number of arm visits made by the saline group (shaded) and lidocaine group (black) to retrieve each of four pellets during the training phase of Experiment 2a, on the day of the injection. Standard errors are represented by vertical bars.
Pellet Number

Choices

pellet 1  pellet 2  pellet 3  pellet 4

saline group
lidocaine group
Figure 2.3. Mean number of visits to baited arms expressed as a percentage of the total number of all arm visits, the day prior to the injection (white) and the day of the injection (black) for the lidocaine and saline groups during the test phase of Experiment 2b. ** denotes statistical significance at p<0.01. Standard errors are represented by vertical bars.
day prior to injection

day of injection

Percent Correct

Lidocaine Group

Saline Group

**
Figure 2.4  Mean number of across-delay (hatched) and within-trial (shaded) errors made by the lidocaine and saline groups during the test phase of Experiment 2b the day of the injection (see text for details). Standard errors are represented by vertical bars.
across delay errors
within trial errors

Number of Errors

Lidocaine Group
Saline Group
Figure 2.5 Mean number of arm visits made by the saline group (shaded) and lidocaine group (black) to retrieve each of four pellets during the test phase of Experiment 2b, the day of the injection. * denotes a statistically significant difference from chance at p<0.05. Standard errors are represented by vertical bars.
Figure 2.6: Number of arm visits necessary to retrieve 4 pellets on an eight arm maze, by chance (values were mathematically generated).
Figure 2.7  Schematic representation of the infusion sites for all subjects included in Experiment 2. Black dots represent the location of the cannulae tips. Infusions spread approximately 0.5mm from the cannulae tips (see text). Illustrated brain sections are computer generated adaptations of plates found in Paxinos and Watson (1982). Histological abbreviations, N.Acc.=nucleus accumbens, cc=corpus callosum, ac=anterior commisure, CPu=caudate putamen.
Discussion

Experiment 2a demonstrates that pre-training intra-N.Acc. lidocaine injections have no effect on foraging behavior on a four arm maze (training phase). Furthermore, this manipulation has no effect on acquisition of new information during the training phase, as this information can be used effectively during the test phase, when the anesthetic effects of lidocaine have dissipated. Experiment 2b demonstrates that intra-N.Acc. lidocaine infusions prior to the test phase of the spatial win-shift task, produce a severe impairment in test phase performance.

The error distribution shown in Fig. 2.4, illustrates two points. 1) The saline group made significantly fewer errors overall than the lidocaine group. 2) The saline group made slightly more across-delay errors than within-trial errors, while the lidocaine group made an equal number of both. Therefore the lidocaine group was equally impaired at using information acquired prior to a delay, as in using information acquired earlier within a trial.

The number of arm visits necessary to retrieve each pellet during the test phase of Experiment 2b, shown in Fig. 2.5, illustrates that the performance of the lidocaine group departed from the saline group and approached chance levels during the retrieval of pellets 3 and 4. The chance values shown in Fig. 2.6 indicate that there is a lower probability of retrieving pellets 3 and 4 by chance than pellets 1 and 2. Hence the impairment following a transient N.Acc. lesion may be dependent on task difficulty. This hypothesis is supported by the observation that the lidocaine group performed above chance during the training phase of Experiment 2a (Fig. 2.2) which is much easier than the test phase. During the test phase in which eight arms are open, and only four are baited the animal must potentially remember many more previous arm choices than during the training phase and must use this information to navigate through twice as
many arms. Optimal performance during the test phase also requires the animal to use information acquired across a delay. As the lidocaine group made an equal number of across-delay and within-trial errors in Experiment 2b (Fig. 2.4), it is difficult to determine whether the lidocaine-induced deficit is attributable to an inability to acquire and/or use information within a trial or in the ability to use information acquired prior to a delay.
Experiment 3:
The Effects of Intra-N.Acc. Lidocaine Infusions on Random Foraging Behavior.

As noted, it was unclear as to whether the inefficient retrieval of four pellets on an 8-arm maze observed in Experiment 2b was the result of an inability to use information acquired prior to a delay or an inability to use information acquired within a trial. The present random foraging task was designed to address this question. In this task animals were required to forage for four randomly placed pellets, on an 8-arm maze. Hence it was identical to the test phase of the spatial win-shift task used in Experiments 1 and 2 above. However, since there was no training phase the animals were not required to use information acquired prior to a delay. Thus, this task permitted an investigation of the effects of transient N.Acc. lesions solely on the ability to acquire and/or use within-trial information to forage for four pellets on an 8-arm maze.

Methods

Each day the animals were allowed to explore the maze freely to retrieve a food pellet from four quasi-randomly chosen arms. The animals were trained in this manner for 15 days, approximately the same amount of training received by the animals in Experiment 2. Criterion performance was attained when the animals could retrieve the 4 pellets in 5 or fewer choices, for 3 consecutive days. The day after criterion were attained, a saline or lidocaine intra-N.Acc. infusion, was delivered to the animals in the manner described above, prior to being placed on the maze.

Three measures of performance were calculated for the day prior to the injection and the day of the injection, 1) the number of visits to baited arms expressed as a percentage of total arm visits, 2) the number of revisits to baited
arms versus the number of revisits to non-baited arms and 3) the number of arm
visits required to obtain each pellet.

Results

In this experiment transient lidocaine-induced lesions of the N.Acc.
produced impairments in the ability to forage for four randomly placed pellets on
an eight arm maze (Fig. 3.1). Furthermore, the lidocaine group revisited
previously baited and previously non-baited arms equally (Fig. 3.2). Finally, the
lidocaine group and saline groups made a similar number of arm visits when
retrieving the first two pellets but the lidocaine group approached chance levels
when they attempted to retrieve pellets 3 and 4 (Fig. 3.3, Fig. 2.6).

A two way repeated measures ANOVA was computed on the number of
visits to baited arms expressed as a percent of the total number of arm choices,
and revealed a significant difference between the groups on the day of the
injection (sal ̅x=56%, lido ̅x=34% F=16.82, p=0.001).

These data were also compared to the results obtained in Experiment 2b
(exp 2b) (Fig. 2.3) using a four way repeated measures ANOVA. The overall
test revealed a significant group difference (sal ̅x=69%, lido ̅x=55%,
F(3,26)=18.605, p=0.000) and a significant day x group interaction effect
(F(3,26)=4.657, p<0.05). This was followed by two, two-way repeated measures
ANOVA. A significant difference was found between the saline group from
Experiment 2b (̅x=82.5%) and the saline group from Experiment 3 (̅x=56%)
(F(1,13)=20.173, p=0.001). A significant overall difference was also found
between the lidocaine groups (exp 2b ̅x=63.5%, exp 3 ̅x=48.5%,
(F(1,13)=17.203=0.001) as was a significant day x experiment interaction effect
(F(1,13)=4.46, p=0.05). This interaction effect was followed by two simple main
effect analyses which yielded a significant difference between the lidocaine
groups on the day prior to the injection (exp 2b ̅x=85%, exp 3 ̅x=61%
$$F(1,13=21.137, p<0.01)$$ but no significant difference on the day of the injection (exp 2b $\bar{x}=42\%$, exp 3 $\bar{x}=34\%$ $F(1,10)=1.93$, $p=0.189$).

A two way repeated measures ANOVA was computed on the number of revisits to baited and non-baited arms (Fig. 3.2) and revealed a significant overall difference in the mean number of errors made by the lidocaine ($\bar{x}=2.14$) and saline groups ($\bar{x}=0.71$) ($F(1,12)=22.64$, $p<0.01$), but no significant overall difference in the number of revisits to baited arms versus the number of revisits to non-baited arms ($F(1,12)=0.049$, $p=0.828$) and no group x error interaction effect ($F(1,12)=0.049$, $p=0.828$).

Fig. 3.3 shows the mean number of choices to retrieve each pellet, (chance values are shown in Fig. 2.6). A Chi-square analysis on the mean number of choices to retrieve pellets 1 and 2 showed no significant difference from chance for the saline group (pellet 1 $\bar{x}=2.14$, pellet 2 $\bar{x}=1.43$, $\chi^2(1)=0.58$, $p>0.05$) or lidocaine group (pellet 1 $\bar{x}=2.57$, pellet 2 $\bar{x}=2$, $\chi^2(1)=0.32$, $p>0.05$). However a similar analysis on the mean number of choices to retrieve pellets 3 and 4 revealed a significant difference from chance for the saline group (pellet 3 $\bar{x}=2.1$, pellet 4 $\bar{x}=2.03$ $\chi^2(1)=5.35$, $p<0.05$) but no significant difference from chance for the lidocaine group (pellet 3 $\bar{x}=2.86$, pellet 4 $\bar{x}=4.14$ $\chi^2(1)=2.18$, $p>0.1$).

Histological results for all subjects included in the random foraging experiment are shown in Fig. 3.4.
Figure 3.1 Mean number of visits to baited arms expressed as a percentage of the total number of all arm visits, the day prior to the injection (white) and the day of the injection (black) for the lidocaine and saline groups during the random foraging task (Experiment 3). ** denotes statistical significance at p<0.01. Standard errors are represented by vertical bars.
Percent Correct

Lidocaine Group  Saline Group

day prior to injection
day of injection
Figure 3.2 Mean number of revisits to baited arms (cross hatched) and non-baited arms (horizontal lines) for the saline and lidocaine groups during the random foraging task (Experiment 3) the day of the injection. Standard errors are represented by vertical bars.
Within Trial Errors

- Revisits to baited arms
- Revisits to nonbaited arms

Number of Errors

- Saline group
- Lidocaine group
Figure 3.3 Mean number of arm visits made by the saline group (shaded) and lidocaine group (black) to retrieve each of four pellets during the random foraging task (Experiment 3), the day of the injection. * denotes a statistically significant difference from chance at p<0.05. Standard errors are represented by vertical bars.
Figure 3.4  Schematic representation of the infusion sites for all subjects included in Experiment 3. Black dots represent the location of the cannulae tips. Infusions spread approximately 0.5mm from the cannulae tips (see text). Illustrated brain sections are computer generated adaptations of plates found in Paxinos and Watson (1982). Histological abbreviations, N.Acc.=nucleus accumbens, cc=corpus callosum, ac=anterior commisure, CPu=caudate putamen.
Discussion

The results of the random foraging experiment demonstrate that intra-N.Acc. lidocaine infusions impaired the ability to retrieve four randomly placed pellets on an 8-arm maze. Hence this manipulation impairs the ability to use information acquired within a trial. Furthermore, the foraging behavior of the lidocaine group in the present experiment and Experiment 2b was similar. This indicates that subjects in that experiment were completely unable to use information acquired 30 min previously during the training phase. Therefore, transient lesions of the N.Acc. impair both the ability to use of information acquired prior to a delay and within a trial to forage for 4 pellets on an 8-arm maze.

Despite differences in the frequency of errors, the types of errors made by control animals and animals receiving intra-N.Acc. lidocaine infusions are similar in that they equally likely to be revisits to an arm which previously contained food as one that did not. Therefore, although the lidocaine group visited more non-baited arms overall than the saline group their pattern of responding was similar. Thus these data demonstrate that transient N.Acc. lesions do not cause animals to perseverate in previously reinforced choices as is the case following 6-OHDA lesions of the N.Acc. (Taghoutzi et al.1985a, 1985b).

Both the saline and lidocaine groups made the same number of choices to retrieve pellets 1 and 2. However, the performance of the lidocaine group differed from the saline group and began to approach chance levels during the retrieval of pellets 3 and 4. As already discussed (see Fig. 2.6) there is a much lower probability of retrieving pellets 3 and 4 by chance than pellets 1 and 2. Thus the retrieval of the final two pellets is a more difficult task than retrieval of the first two pellets. As the random foraging task progresses there are greater demands placed on the animal as it must remember an increasing number of
subsequent arm choices. The large number of errors made by the lidocaine group in retrieving pellets 3 and 4 therefore supports the conclusion reached in Experiment 2 that the impairments produced by transient N.Acc. lesions are related to task difficulty.

The results of the present experiment are very similar to those obtained in Experiment 2b and together they suggest that transient N.Acc. lesions impair the ability use within-trial and across-delay information to forage on an 8-arm maze.
Experiment 4:
The Effects of Combined Pre-Training and Pre-Test Intra-N.Acc. lidocaine Injections on Spatial Win-Shift Behavior: A Test For State-Dependency

Conger (1951) postulates that alterations on tasks assessing memory functions following single pre-training or pre-test drug administrations may be attributable to an impairment in stimulus generalization resulting from a change in drug state between training and test. Conger's theory of state-dependent learning is now a well established phenomenon (see Overton 1991 for review) and should be considered in any learning experiment employing single drug administration. The deficits observed in Experiments 1, 2b, and 3 above, may therefore have been due to a state-dependency effect, as the animals learned new information in one drug-state and were tested in another. To eliminate this possibility, animals were trained and tested on the spatial win-shift task in the same drug state.

Methods

In the present experiment animals were trained in an identical manner to that used in Experiment 2. However on the day after criterion performance was demonstrated, intra-N.Acc. lidocaine or saline infusions were delivered prior to both the training phase and the test phase. The animal's behavior was assessed the day of the injection using three measures; 1) percent correct performance during the training phase and test phase, 2) the number of across-delay errors versus the number of within-trial errors during the test phase, and 3) the number of arm visits required to obtain each pellet, during the test phase.
**Results**

Experiment 4 demonstrates that pre-training intra-N.Acc. lidocaine infusions do not impair training phase performance, while pre-test infusions severely impair test phase performance on the spatial win-shift task (Fig. 4.1). These results argue against the suggestion that state dependent learning was responsible for the impairments observed in Experiments 1-3. In the present experiment the saline group made more across-delay than within-trial errors while the lidocaine group made an equal number of both (Fig. 4.2). Furthermore, the performance of the lidocaine group was similar to that of the saline group in retrieving the first two pellets but approached chance when they attempted to retrieve pellets 3 and 4 (Fig. 4.3, Fig. 2.6).

A two-way repeated measures ANOVA was conducted on the data shown in Fig. 4.1 and revealed an overall group effect (sal $\bar{x}=79\%$, lido $\bar{x}=59\%$, $F(1,10)=14.76$, $p=0.003$) and a significant phase x group interaction effect ($F(1,10)=11.32$, $p<0.05$). This was followed by simple main effect analysis which yielded no significant difference between the groups for the training phase (sal $\bar{x}=90\%$, lido $\bar{x}=82\%$, $F(1,10)=1.364$, $p=0.27$), but a significant difference during the test phase (sal $\bar{x}=67\%$, lido $\bar{x}=36\%$, $F(1,10)=15.07$, $p=0.003$).

A two way repeated measure ANOVA was computed on the number of across-delay and within-trial errors made by the lidocaine and saline groups (Fig. 4.2). A significant group effect (sal $\bar{x}=0.81$, lido $\bar{x}=2.38$ $F(1,10)=7.9$, $p=0.016$) was observed as was a significant interaction effect ($F(1,10)=4$, $p=0.06$). Simple main effect analysis revealed that the lidocaine group made an equal number of both types of errors (across-delay errors $\bar{x}=3.14$, within-trial errors $\bar{x}=4$ ($F(1,6)=0.76$, $p=0.42$), whereas the saline infused group made significantly more across-delay errors ($\bar{x}=1.9$) than within-trial errors ($\bar{x}=0.57$) ($F(1,6)=9.346$, $p=0.02$).
Two chi-square analyses were computed on the mean number of choices taken to retrieve pellets 1 and 2 and the mean number of choices to retrieve pellets 3 and 4 (Fig. 4.3). Chance values are represented in Fig. 2.6. Neither the saline ($\chi^2(1)=0.73$, $p>0.05$) or lidocaine ($\chi^2(1)=0.66$, $p>0.05$) groups differed from chance performance in retrieving pellets 1 and 2. The saline animals differed from chance in retrieving pellets 3 ($\bar{x}=1.71$ choices) and 4 ($\bar{x}=1.86$ choices) ($\chi^2(1)=6$, $p<0.05$), whereas the lidocaine animals did not (pellet 3 $\bar{x}=3$ and pellet 4 $\bar{x}=5.14$, $\chi^2(1)=1.27$, $p>0.05$).

Histological results for all animals included in Experiment 4 are shown in Fig. 4.4.
Figure 4.1. Mean number of visits to baited arms expressed as a percentage of the total number of all arm visits for the saline and lidocaine groups during the training phase and test phase in Experiment 4 following pre-training (hatched) and pre-test (black) injections. ** denotes statistical significance at p<0.01. Standard errors are represented by vertical bars.
Lidocaine Group

Saline Group

% Correct

---

pretraining injection
pretest injection

---

* * *
Figure 4.2 Mean number of across-delay (hatched) and within trial (shaded) errors made by the lidocaine and saline groups during the test phase of Experiment 4, the day of the injection (see text for details). • denotes a statistically significant difference at p<0.05. Standard errors are represented by vertical bars.
across delay errors

Within trial errors

Number of Errors

Lidocaine Group

Saline Group
Figure 4.3  Mean number of arm visits made by the saline group (shaded) and lidocaine group (black) to retrieve each of four pellets during Experiment 4, the day of the injection. * denotes a statistically significant difference from chance at p<0.05. Standard errors are represented by vertical bars.
pellet 1  
pellet 2  
*pellet 3  
*pellet 4  

Pellet Number

10
9
8
7
6
5
4
3
2
1
0

Choices

- saline
- lidocaine

* indicates significant difference
Figure 4.4  Schematic representation of the infusion sites for all subjects included in Experiment 4. Black dots represent the location of the cannulae tips. Infusions spread approximately 0.5mm from the cannulae tips (see text). Illustrated brain sections are computer generated adaptations of plates found in Paxinos and Watson (1982). Histological abbreviations, N.Acc.=nucleus accumbens, cc=corpus callosum, ac=anterior commisure, CPu=caudate putamen.
Discussion

The results of this experiment demonstrate that pre-training lidocaine injections do not have a significant effect on training phase performance, while subsequent pre-test infusions in these animals do affect test phase performance. These results argue against a state-dependency interpretation of the deficits reported in the previous experiments, as the animals in this experiment were trained and tested in the same drug state. The results of this experiment also replicate the findings of Experiment 2a & 2b demonstrating that pre-training intra-N.Acc. infusions do not impair training phase performance whereas pre-test injections impair test phase performance.

The lidocaine group made more errors than the saline group overall, but made the same number of across-delay errors as within-trial errors. The saline group however made significantly more across-delay errors than within-trial errors. As discussed in Experiment 2, animals receiving transient N.Acc. lesions are equally deficient at using information acquired within the test phase, as they are at using information acquired 30 min. earlier during the training phase. However, the deficits in the ability to use information acquired within a trial seem to be severe enough to mask additional impairments in the ability to use information acquired prior to a delay (see Experiment 3). Finally as observed in Experiment 2 and 3 the performance of the lidocaine group approaches chance levels when retrieving pellets 3 and 4, but not pellets 1 and 2. Taken together, the results of the present experiment are in accordance with those reported in Experiments 1-3. Furthermore the present experiment demonstrates that a state-dependency phenomenon cannot account for the results of those experiments.
The Effects of Intra-N.Acc. Lidocaine Infusions on Locomotor Behavior

There are numerous reports that the N.Acc. plays an important role in locomotor behavior (Mittleman et al. in press; Mogenson & Neilson 1984; Mogenson & Yang 1991; Schacter et al. 1989). However, the N.Acc. does not seem to be involved in all types of motoric behavior, but rather plays a specific role in goal-directed locomotion (Kelley & Stinus 1985; Salamone 1992; Whishaw & Kornelsen in press). In an attempt to gain insight into the impact of intra-N.Acc. lidocaine infusions on goal-directed locomotion, approach latencies were compared between experimental and control groups in each experiment. Approach latency was defined as the time (in seconds) required to reach the food cup of the first arm visited by the animal after being placed on the maze. Hence this measure was used to assess the latency to reach a goal location rather than simply the time to initiate any type of locomotor behavior. Table 1 illustrates that lidocaine infusions produced a significant increase in the latency to approach a food well in the spatial win-shift task of Experiment 1, Experiment 2b and Experiment 3 (F(1,44)=5.55, p<0.05). A two-way ANOVA revealed that the lidocaine groups in the cued win-stay task of Experiment 1 and Experiment 2a did not differ from the control groups in approach latency (F(1,28)=3.7, p>0.05), or in task performance (see Experiment 1 and 2a above). Collectively, these data indicate that when task performance was impaired by transient N.Acc. lesions, approach latency was also increased whereas when task performance was unimpaired, approach latency was unaffected. One interpretation of these results is that enhanced approach latency may reflect a state of confusion in the animal that is manifested in impaired task performance. However as approach latencies are highly variable (as shown by the large standard errors in Table 1), this interpretation should be taken with caution.
Table 1  Mean latency to approach a food well for tasks which the lidocaine group made numerous errors (left column) versus tasks which the lidocaine group made no more errors than controls (right column). The left column shows the mean approach latency for the lidocaine (top) and saline (bottom) groups during the test phase of the spatial win-shift task in Experiment 1 and Experiment 2b and the random foraging task (Experiment 3). The right column shows the mean approach latency for the lidocaine (top) and saline (bottom) groups during the training phase of Experiment 2a and the cued win-stay task of Experiment 1. * denotes significance at p<0.05. Standard errors are shown in brackets.
<table>
<thead>
<tr>
<th></th>
<th>Pre-test Inj. (Exp 1-3)</th>
<th>Pre-training Inj. (Exp 2a)</th>
<th>Cued win-stay (Exp 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lidocaine</strong></td>
<td>$\bar{x}=88 \ (\pm22.8)^* \text{ sec.}$</td>
<td>$\bar{x}=23 \ (\pm9) \text{ sec.}$</td>
<td></td>
</tr>
<tr>
<td><strong>Saline</strong></td>
<td>$\bar{x}=36.9 \ (\pm9.6) \text{ sec.}$</td>
<td>$\bar{x}=68.6 \ (\pm21) \text{ sec.}$</td>
<td></td>
</tr>
</tbody>
</table>
General Discussion

The results of the present study demonstrate that lidocaine injections into the N.Acc. have no effects on cued win-stay behavior or the ability to forage for, and learn the spatial location of 4 pellets on a 4-arm radial maze. This manipulation does, however, cause severe impairments in test phase performance of the spatial win-shift task.

As discussed above, there is a selective effect of the transient N.Acc. lesions on locomotor behavior. The results of the present series of experiments indicate that if task performance is impaired by the lesions so too is approach latency, whereas if task performance is unimpaired no such increase in approach latency is observed. However once the animals showing enhanced approach latencies initiate movement toward a food cup they are able to move about the radial arm maze environment with little or no difficulty, and in fact visit many more arms than control animals. Therefore, a generalized locomotor impairment cannot account for the impairments observed in Experiment 1-4.

Numerous authors have proposed a role for the N.Acc. in motivated behaviors (Mogenson, Jones & Yim 1980; Phillips et al. 1991; Salamone 1992). Thus it may be argued that the lesioned animals in the present study were less motivated to retrieve the food pellets and as a result entered arms in a random manner. This is unlikely as animals receiving transient N.Acc. lesions retrieved and consumed all the food pellets in every task, despite making numerous errors. Furthermore lesioned animals were unimpaired on the cued win-stay task and the training phase of the spatial win-shift task in which they had to retrieve the same number of pellets (i.e. 4) as during the test phase of the spatial win-shift task. Therefore, impairments in goal-directed behavior following the
transient N.Acc. lesions are dependent on task complexity and the cues used to navigate towards a goal.

A generalized perceptual impairment also cannot account for the impairment in test phase performance, as lesioned animals performed the cued win-stay task adequately, as well as the training phase of the spatial win-shift task which required them to use spatial cues to navigate on the maze.

Finally, based on the results from Experiment 4, poor performance by the lidocaine-treated animals on the test phase of the spatial win-shift task cannot be attributed to state-dependent learning. Animals receiving both pre-training and pre-test infusions were impaired only during the test phase, thereby indicating that this manipulation does not induce a "state" that must be re-established during the test phase in order to use previously acquired information.

No impairments were observed in the cued win-stay task following transient N.Acc. lesions suggesting that this structure is not involved in the ability to recognize and respond to specific non-spatial cues which have been previously and consistently associated with reward. Past work has demonstrated that lesions of the caudate nucleus but not of the hippocampus or amygdala produce impairments in cued win-stay behavior (McDonald & White; 1993; Packard et al 1989). Therefore the results of Experiment 1 suggest that the N.Acc. does not act synergistically with the caudate nucleus to guide cued win-stay behavior. In contrast, lesions of the N.Acc. or caudate nucleus produce impairments on tasks such as spatial reversal in the T-maze, reference memory performance on the radial arm maze, and the spatial Morris water maze (Taghoutzi et al. 1985a, 1985b; Divac 1971; Packard & White 1990; Colombo et al. 1989; Schacter et al. 1989; Scheel-Krugar & Wilner 1991; Whishaw et al 1987). As each of these tasks has a spatial component that is not present in the
cued win-stay task, it may be argued that the N.Acc. is involved preferentially in spatially-mediated behaviors.

This conclusion is supported by data demonstrating that ibotenic acid or electrolytic lesions of the N.Acc. impair the acquisition of a spatial Morris water maze task (Annett et al. 1989; Sutherland & Rodriguez 1989). However while this task is mediated by spatial cues, decrements in task performance following N.Acc. lesions may not be the result of an impairment in the ability to form a spatial map (O'Keefe & Nadel 1978). If an animal is unable to learn its position in space relative to surrounding extra-maze cues, then performance of the spatial Morris water maze task would be severely affected. However, exocitoxic N.Acc. lesions do not completely abolish the acquisition of the task, as lesioned animals are eventually able to swim to the hidden platform in a manner that does not differ from controls (Annett et al.; 1989). Furthermore, although Sutherland & Rodriguez (1989) reported that electrolytic lesions of the N.Acc produced an initial deficit in task performance, they also demonstrated that pre-trained rats could find a hidden platform as accurately as controls, following electrolytic lesions of the N.Acc. Taken together these data suggest that animals with N.Acc. lesions are able to localize their position in space relative to a set of consistent extra-maze cues. Hence it is unlikely that the impairments in spatial win-shift behavior following transient N.Acc. lesions observed in the present series of experiments were the result of an inability to acquire a spatial map. This is supported further by the observation that no impairments were observed during the training phase of the spatial win-shift task in Experiment 2a following transient N.Acc. lesions. Although fewer arms are used in the training phase than in the test phase, animals must still be able to forage for four pellets using a consistent set of extra-maze cues. However, the impairment in test phase performance observed in Experiments 1-4 may have been the result of an
inability to learn, store or use daily information regarding the location of food in a familiar environment.

The results of Experiment 2a argue against the possibility that transient N.Acc. lesions produced a specific impairment in the acquisition of new information. Lidocaine-induced N.Acc. lesions delivered prior to the training phase did not disrupt performance 30 min. later during the test phase when the anesthetic effects of the drug had dissipated. This suggests that these lesions spared the ability to learn about and encode the location of four randomly placed pellets on a 4-arm maze.

Another possibility that must be considered is that the deficits in test phase performance may be attributed to an impairment in the consolidation of newly acquired information. There is evidence that the mesolimbic DA system (the source of DA input to the N.Acc.) is involved in the processes underlying memory consolidation, as delivery of peripheral or intra-hippocampal infusions of DA receptor agonists post-training, improves test phase performance on the spatial win-shift task (Packard & White 1991; White, Packard & Seamans in press). It is therefore possible that the lidocaine infusions interfered with the activity of the mesolimbic DA system in the N.Acc. and impaired some aspect of the consolidation of newly acquired information. However this possibility is not supported by the results of Experiment 2b. Here the saline group rarely entered the previously baited arms during the test phase, suggesting that 25 min. is sufficient time for consolidation of newly acquired information. Therefore, it may be assumed that the lidocaine group had also consolidated the information acquired during the training phase prior to receiving the injection. This suggests that unless the transient N.Acc. lesions altered the processes underlying consolidation in a retroactive manner, it is unlikely that this manipulation had any effect on memory consolidation.
Conversely, the lidocaine-induced impairment in test phase performance during the spatial win-shift task may have been the result of a deficit in memory retrieval. This hypothesis cannot be refuted by the present data set. Infusions of lidocaine into the N.Acc. prior to the test phase reliably and consistently produced an impairment in test phase performance in all experiments reported here. Test phase data from Experiments 1-4 demonstrated that the animal's behavior approaches chance levels following transient N.Acc. lesions. Furthermore, Figs. 2.4, 4.2 show that these animals made an equal number of across-delay and within-trial errors suggesting that they were unable to use recently acquired information regarding the location of baited and unbaited arms to guide their subsequent choices of arms that may contain food.

This inability to use previously acquired information following transient N.Acc lesions is not absolute, as it is dependent on task complexity. Transient N.Acc. lesions produced no impairments in training phase performance (Experiment 2a) but caused severe impairments in test phase performance (Experiments 1, 2b, 3, & 4). The training phase differs from the test phase in several important respects. In contrast to the test phase, the training phase does not assess the ability to use information acquired prior to a delay. A comparison of Figs. 2.3 and 3.1 shows that animals given transient N.Acc. lesions were as impaired on the random foraging task as they were during the test phase of Experiment 2b. Hence information that was acquired during the training phase was of no use to the lidocaine group during the test phase of Experiment 2b. A second difference between the training and test phase relates to the use of four out of four baited arms in the former condition and four out of eight baited arms in the latter. The effects of transient lesions of the N.Acc. are only manifested in the more complex 8-arm situation. Therefore it is conceivable that the observed deficits are related to the amount of information that must be
either processed or retained in order to forage efficiently when encountering four randomly baited arms on an 8-arm maze. If transient N.Acc. lesions impair the ability to remember a large number of arm choices then impairments in test phase performance should be most apparent at the end of the trial. This pattern may be seen in Figs. 2.5, 3.3, 4.3 where both saline and lidocaine-infused animals do not differ when retrieving pellets 1 and 2, but performance of the lidocaine group falls dramatically when retrieving pellets 3 and 4. These results suggest that when the amount of newly acquired information exceeds a certain limit, the capacity to use this information is severely impaired by transient N.Acc. lesions. It therefore follows that the failure to observe disruptive effects following transient N.Acc. lesions during the training phase of Experiment 2a may be related to the fact that these animals required fewer choices to retrieve the four pellets and hence did not exceed their reduced working memory capacity.

A final possibility that must be considered is that the lidocaine-induced deficit in test phase performance may not only produce an inability to retrieve previously acquired information but also an inability to select information that is relevant to the current situation. During the training phase the animal is faced with 4 open arms rather than 8 during the test phase. Hence in the latter case there is a greater number of non-baited arms that must be avoided. As the behavior of the lidocaine-treated animals was random during the test phase, it suggests that these animals were incapable of directing their responding to the correct subset of baited arms. The failure to observe similar impairments during the training phase of Experiment 2a may be related to the fact that the blockade of four arms provided proximal cues indicating which arms were to be attended to. Purves (1993) proposes that the "N.Acc. is part of a general spatial processing system and that this system is distinct from that used to process proximal cues". As no such proximal cues were available during the test phase,
the animals had to use previously acquired knowledge about the spatial location of arms which previously contained food to direct their responding to the correct subset of newly baited arms. Therefore, the transient N.Acc. lesions may have impaired the process through which the specific information regarding the location of the correct subset of baited arms, comes to influence responding in a complex spatial environment. According to this interpretation, the N.Acc. is involved in the process through which relevant information influences current modes of behavior.

This interpretation is in accordance with clinical literature suggesting that "an inherited or acquired deviation in ventral straital circuitry, might result in a grave disturbance in cognitive or emotional filtering processes" (Swerdlow & Koob 1987 pg 203). Furthermore, without the inhibitory influence of the N.Acc. on its efferent connections "appropriate filtering and amplification of cortical information cannot occur at the level of the N.Acc, and irrelevant and relevant cognitive or emotional activity are not segregated" (Swerlow & Koob 1987, pg 204). While Swerdlow & Koob suggest that these effects are due to excessive DA activity in the N.Acc. which inhibits GABAergic output neurons to the ventral pallidum, lidocaine may have the same effect, in that it also inhibits N.Acc. output neurons. Hence transient lidocaine-induced lesions of the N.Acc. could block the flow of limbic input and cause ungated activity in the efferents of this structure.

Swerdlow & Koob's theory is quite similar to that of Margulies (1985) who has hypothesized that while the hippocampus may detect noteworthy or salient environment cues, the N.Acc is involved in "the integration of new noteworthy events into ongoing thought or behavior" (pg 254). Taken together these clinically based theories suggest that the N.Acc. modulates the flow of limbic input, allowing only some types information to influence behavior.
These clinical theories are supported by electrophysiological data demonstrating such a modulatory role for the N.Acc. Stimulation of the fornix causes excitatory post synaptic potential (EPSP)/ inhibitory post synaptic potential (IPSP) sequences in N.Acc. cells (Pennartz & Katai 1991). It is hypothesized that the IPSP sequences in the N.Acc. limit the impact of hippocampal input. DA in the N.Acc. also modulates the effects of hippocampal input by inhibiting both the elicited EPSP and IPSP (Pennartz et al. 1992). However the magnitude of this modulation is dependent on the frequency of hippocampal stimulation. If 6 Hz stimulation is delivered to the fornix, there is very little signal modulation by DA in the N.Acc., while the effects of 0.5Hz stimulation are greatly reduced (DeFrance et al. 1985). This is a noteworthy finding as the hippocampus fires at 6 Hz when an animal is actively exploring its environment (Bland & Vanderwolf 1972). Furthermore tetanic stimulation in the 6 Hz range is effective in inducing long-term potentiation (a synaptic model of learning and memory) in the hippocampus (Bliss & Lynch 1988). This suggests that information processed by the hippocampus during exploration or learning may be selectively enhanced by the N.Acc. relative to information processed by the hippocampus at other times.

As well as playing a role in modulating limbic input, the N.Acc. may also be crucial to the process through which this input comes to influence behavior. Various manipulations of the pathway from the hippocampus, through the N.Acc to the ventral pallidum and MLR can selectively enhance or inhibit locomotion (for review see Mogenson & Yang 1991). Furthermore, enhanced locomotion due to hippocampal lesions can be blocked by inhibition of DA activity in the N.Acc. (Mittleman, LeDuc & Whishaw, in press). In the present series of experiments, the transient N.Acc. lesions may have impaired the ability of this structure to allow information, processed by limbic structures, regarding the
location of previously visited arms of the maze, to guide the animals' ongoing responding.

Given the role of the hippocampal formation in spatial navigation and in spatial win-shift behavior, the discussion thus far has emphasized that the hippocampus is critical to the role played by the N.Acc. in guiding behavior. However, it is also possible that the transient N.Acc. lesions altered the effects that input from the frontal cortex has on behavioral output. The N.Acc. receives a direct projection as well as an indirect projection, through the subiculum, from the medial prefrontal cortex (Alexander, Crutcher & Delong 1990; Groenewegen et al. 1987; Groenewegen et al. 1991; Heimer et al. 1991; McGeorge & Faull 1989). Damage to the prefrontal cortex in humans, causes memory deficits on spatial and non-spatial conditional learning tasks, memory for temporal order and in planning (Joyce & Robbins 1991; Milner 1982; Milner & Petrides 1984; Milner, Petrides & Smith 1985; Petrides 1989; Shallice 1981). In rats, lesions of the frontal cortex can cause impairments on various spatial learning tasks, delayed response learning, response flexibility, delayed alternation behavior, foraging on an 8-arm maze and tasks requiring memory for frequency of stimulus presentation (Divac 1971; Kesner 1990; Kesner & Holbrook 1987; Kesner, Farnsworth & DiMattia 1989; Kolb 1984; Kolb, Pittman, Sutherland & Whishaw 1982; Kolb, Sutherland & Whishaw 1983; Winocour 1991). It is clear that many of these processes are necessary for optimal performance on the spatial win-shift task, and hence the role of the frontal-N.Acc. pathway may be of utmost importance in this regard.

Robbins (1990 & 1991) suggests that the frontal cortex mediates the generation of plans based on previously acquired and currently available information, while the N.Acc. translates this information into a sequences of responses. Therefore, these two areas act to guide purposive, or goal-oriented
behaviors. One effect of transient N.Acc. lesions may be to disrupt this coordinated activity and thereby cause a shift to random responding. Therefore, an alternative explanation for the random performance of lidocaine-treated animals in the present study may be that they are unable to translate the response strategies generated by the frontal cortex into the proper sequences of responses. Validation of this hypothesis along with the more general theory that the N.Acc. is involved in processes by which previously acquired information is used to direct responding towards relevant aspects of a spatial environment, await future investigation.
References


Mittleman, G. LeDuc, P.A. & Whishaw, I.Q. The role of d1 and d2 receptors in the heightened locomotion induced by amphetamine in rats with hippocampal damage: an animal analogue of schizophrenia. Manuscript submitted for publication.


limbic inputs to the shell region of the rat nucleus accumbens studied in vitro.  
Journal of Neurophysiology, 67, 1325-1334.

Petrides, M. Frontal Lobes and Memory. (1989). In Boller, F. & Grafman, J.  
Handbook of Neuropsychology, (vol 3) Elsevier Science Publishers B.V.,  
Amsterdam.

insights provided by in vivo analyses. In: Willner, P & Scheel-Kruger, J. (Eds)  
The Mesolimbic Dopamine System: From Motivation to Action. John Wiley and  
Sons Ltd., U.K., pp 199-223.

Purves, D.G. (1993). Involvement of the nucleus accumbens in distal but not in  
proximal cue directed behavior on a radial arm maze. Canadian Society For  

neural basis and the role of dopamine. In: Willner, P & Scheel-Kruger, J. (Eds)  
The Mesolimbic Dopamine System: From Motivation to Action, John Wiley and  
Sons Ltd., U.K. pp 497-528.


Salamone, J.D. (1992). Complex motor and sensorimotor functions of striatal and  
accumbens dopamine: involvement in instrumental behavioral processes.  


White, N.M. Packard, M.G. & Seamans, J.K. Memory enhancement by post-training peripheral administration of low doses of dopamine agonists: possible autoreceptor effect. Manuscript submitted for publication.


excitatory responses by the mesolimbic dopaminergic system. *Brain Research*, 324, 69-84.


