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Abstract

This study investigated perseverative behavior, attention, and exploratory behaviors via discrete lesions of the rat hippocampal formation. It was hypothesized that lesions which interrupted input to the hippocampus and output to cortical and subcortical regions would induce these behaviors. Forty-four male Long-Evan rats were randomly divided into four treatment groups: cerebral spinal fluid, and three colchicine lesioned groups, 10-COL, 15-COL, and 25-COL. The animals were compared based upon performance in a standard T-maze to test perseveration. Behaviors were also observed in an activity chamber to measure locomotion, attention, and exploration. Animals in the 25-COL group demonstrated a significant increase in activity and perseveration as well as a decrease in exploration and attention compared to all other groups. Disrupting the convergence of information to the hippocampal formation interferes with output to subcortical and cortical regions, inducing behavioral changes associated with the structures of the hippocampal system.

Alzheimer's Disease (AD) is a progressive degenerative brain disorder which primarily effects elderly people. It is estimated to affect approximately 20 to 30 percent of individuals who live to their mid-eighties (Papalia & Olds, 1990). The disease is characterized by symptoms including a decreased awareness of the environment, resulting from spatial disorientation and confusion, as well as memory loss which initially affects short-term memory. As the disease progresses remote memories also deteriorate resulting in failure to recognize family members (Papalia & Olds). AD patients frequently experience a locomotor dysfunction, manifestations of which may surface as a behavior called wandering. Wandering is usually associated with increased motor activity, restlessness, and spatial disorientation (Snyder, Ruppercht, Pyrek, Brekus, & Moss, 1978). Observations of nursing home patients who demonstrate this psychomotor abnormality have identified three types of wanderers: goal-directed searching, goal-directed industrious, and nongoal-directed (Snyder, et al.). The goal-directed searching patient attempts to reach an impossible goal or finish an impossible task. The goal-directed industrious patient is motivated to occupy themselves continuously with one or more tasks. The nongoal-directed wanderer walks indiscriminately about and is easily distracted from one stimulus only to be attracted to another. Wandering is reported as a primary problem among caregivers (Cummings & Victoroff, 1990); treatments for the problem, such as neuroleptic drugs and physical restraint, are generally ineffective. Despite the problematic nature of the behavior, wandering is one of the least understood and minimally investigated behaviors in AD.

Ryan, Saxby, Donahue, McBain, Kunkel, Hoffmann, Brown, and Stewart (1990), developed an animal model of wandering in AD characterized by neuropathological, neuroanatomical, neurochemical, and neurobehavioral changes which mimic the disease state in human beings. In AD the neuropathology involves neurofibrillary tangles and senile plaques. Neurofibrillary tangles can be produced in the rat brain through the use of the neurotoxin colchicine. Colchicine disrupts the microtubules in the neurons causing irreversible cell loss to the area of injection (Mundy & Tilson, 1990). Senile plaques do not occur in animals and can only be produced through gene manipulation involving embryonic cells.

Therefore, research conducted thus far with animal models of AD has not successfully replicated both markers of the disease. Neurochemical changes in AD involve a decrease in Acetylcholine (Ach). Cochicine administered to the rat hippocampus decreases Ach levels (Nakagawa, Makamura, Kase, Noguchi, & Ishihara, 1987). Colchicine also induces some of the neurobehavioral changes in AD such as memory impairments and spatial disorientation (Nakagawa, et al., 1987; Ryan, et al., 1990).

Intrahippocampal postmortem examination of AD patients' brains reveal cell loss in the hippocampus and the cerebral cortex. These areas also exhibit the characteristic plaques and tangles of the disease (Chui, 1989). The hippocampus is believed to be critical for short-term memory as well as spatial orientation (Mandybur & Chuirazzi, 1990). In AD the hippocampus becomes isolated from other brain structures due to excessive cell loss, separating the input to the hippocampus and output from the hippocampus to other regions of the brain (Hyman, Van Hoesen, Demasio, & Barnes, 1984). Through colchicine injections into the rat hippocampal formation Ryan and colleagues (1990) have attempted to mimic the functional isolation of the hippocampus as reported in the human disease state.

The sites chosen for injection are located at areas which involve input from cortical and subcortical regions of the brain and output to other structures of the hippocampal system: orbito-frontal cortex, nucleus accumbens, and caudate nucleus. The hippocampus receives efferents from the septal and brainstem regions of the brain via the dentate gyrus. These regions are responsible for remaining attentive and oriented toward a stimulus. The CA1 region of the hippocampus sends glutamatergic efferents by way of the fornix to the caudate nucleus and the nucleus accumbens. The caudate participates in both attention and task-switching behavior and the nucleus accumbens participates in locomotor activity and exploratory behavior (Ryan, 1994).

Evidence of neurotransmitter changes distal to the hippocampal colchicine lesion site have been demonstrated in several studies. Middleton (1992) through the use of *in vivo* microdialysis of the nucleus accumbens found reduced dopamine levels in animals with colchicine lesions of the hippocampal formation as compared to control animals. The reduction of dopamine may be related to the loss of glutamatergic hippocampal efferents to the nucleus accumbens. Lesions of the rat hippocampus have been reported to result in the reduction of these glutamatergic efferents from the hippocampus to the nucleus accumbens (Schacter, Yang, Innis, & Mogenson, 1989).

Changes in neurotransmitter levels following colchicine injections have also been supported through a series of studies involving dopamine receptor drugs (Markham, 1992). It was shown that the abnormal behavior demonstrated by the lesioned animals could be corrected through injections of dopamine agonist drugs suggesting that (1) colchicine lesions have the effect of altering the dopamine levels of the brain as the behavior of the non-lesioned animals was unaltered, and (2) lesions to the dentate gyrus decrease the levels of dopamine resulting in the amelioration or exacerbation of the abnormal behavior using a dopamine agonist (Ryan, Markham, Woods, & Metroka,1992). Markham then demonstrated an interaction between the dopamine and cholinergic systems. He found that the D2 agonist drug used in conjunction with a cholinergic blocker improved the animals spatial deficits to an even greater degree than if the D2 agonist was used alone. The cholinergic blocker when used alone was shown to further impair the animals' behavior. This suggests that there is a neurochemical interaction between the dopamine and cholinergic systems as cited in the literature (Museo & Wise, 1990).

In addition to alteration in neurotransmitters, the animal model also sought to produce certain behavioral changes which have been observed to

occur in wandering AD patients. These have included examining spatial memory deficits, spatial disorientation, and increased activity levels. Similar behaviors could be elicited in animals through the utilization of specific apparati such as the Morris water maze and the Wahmann running wheel. Ryan et al. (1992), demonstrated cognitive impairments in the water maze following discrete colchicine lesions of the rat dorsal hippocampal formation replicating general findings, as well as showing that intradentate colchicine lesions induce spatial memory, learning, and orientation impairments. The study also demonstrated that higher doses of colchicine induce a perseverative type of behavior as shown in the circumference swimming patterns of the lesioned animals. Douglas (1989) proposed that this type of behavior is the result of the loss of the hippocampal inhibitory mechanism in brain regions involved in locomotion (e.g., nucleus accumbens). Ryan (1994) proposed that the behavioral abnormalities observed in the water maze may be related to increased activity levels of the lesioned rats. This hypothesis was examined using the Wahmann wheel as a measure of increased activity levels. The results indicated that animals with lesions demonstrated higher activity levels during the nocturnal period as compared to their pre-surgical baseline data and non-lesioned control group (Woods, 1992). Recently, Ryan, Bliven, and Moon (1993) suggest that performance in the water maze has a psychomotor component in addition to a spatial memory component.

Animals with large lesions of the hippocampus exhibit an inability to remain attentive to one stimulus for any length of
time, an increase in locomotor activity, and a decrease in exploratory behavior. The attention deficit is apparent when animals with lesions of the hippocampus are given a hole poking test. Non-lesioned rats will place their heads into a hole and investigate the area for a longer length of time than animals with hippocampal damage and will explore a greater number of holes, avoiding already examined holes (Isaacson, 1982). Conversely, rats with hippocampal cell damage spend less time inspecting each hole and show a propensity to re-examine already checked holes, thereby examining fewer holes and exploring their environment less (Isaacson).

Animals with eighty percent of their hippocampus removed also exhibit another aberrant behavior referred to as perseverative behavior. Douglas (1989) proposed that perseveration is a result of the disruption in the hippocampal system which involves other brain regions, such as the caudate nucleus, which participates in regulating attention and task-switching behavior (Ryan, 1994). One way to examine this is through the T-maze, a task which measures spontaneous alternating behavior. Spontaneous alternating behavior (SAB) can be operationally defined according to the following:

A rat is placed in the start stem of a T-maze and given two trials with a brief interval. On trial 1 (t1) it enters one of the goal arms; gently removed from the maze and returned for its second trial, the animal on trial 2 (t2) enters the other goal arm. This pattern of entering first one arm and then the alternate arm, if exhibited with significant frequency by a given animal over multiple testings or on tests of many animals, has been called spontaneous alternating behavior (SAB). Alternating for obvious reasons and spontaneous because the animal has not been trained through differential reinforcement to behave that way (Douglas, 1989).

Spontaneous alternating behavior has been linked to several areas of the brain, however, the hippocampus and related structures have been shown to be particularly important in SAB. The converse of SAB is perseverative behavior. In the T-maze, perseverative behavior is defined as choosing one arm repeatedly, below chance levels (20-30%). Animals with hippocampal lesions exhibit an impairment in alternating behavior, that is, they exhibit perseverative behavior (Douglas, 1989). Douglas also reported that lesions within the corpus striatum and, in particular, to the caudate nucleus,

also abolish SAB behavior and induce perseverative behavior. These findings have been replicated by several research labs (Douglas). Tagzhouti (cited in Douglas) has also revealed that lesions of the nucleus accumbens abolish SAB. Both the caudate nucleus and the nucleus accumbens participate in the hippocampal system. Disruptions to one or more components of the system will induce behavioral anomalies, such as perseveration, increased activity and deficits in exploration.

The present study investigated exploratory behavior, activity and attention with a computerized chamber. It was hypothesized that animals with marked dorsal hippocampal formation lesions involving CA1 and dentate gyrus would demonstrate increased movement and decreased attention in comparison to animals with limited lesions to the dentate gyrus or CA1 and nonlesioned control animals. It was also hypothesized that perseverative behavior using a standard T-maze would be greater in animals with significant lesions of CA1 and dentate gyrus, and that changes in exploratory behavior and SAB would result from the disruption of the input to the hippocampus and output to other brain regions, including structures of the hippocampal system.

Method

Subjects

Forty-four male Long-Evans rats, each eight weeks old, were purchased from the Charles River Animal Farm. The animals weighed between 250 and 350 grams at the time of surgery, and were housed in a sanitary colony room with ad lib food and a twelve hour light-dark cycle.

Surgery

Forty-four Long-Evans hooded rats were randomly divided into one of four groups (n=11): a cerebral spinal fluid (CSF) control group, a 10ug CA1 pyramidal cell colchicine lesioned group (10-COL), a 15ug dentate gyrus granule cell colchicine lesioned group (15-COL), and a 25ug CA1 and dentate gyrus colchicine lesioned group (25-COL). The CSF group was further subdivided into three injection groups as a control for each colchicine injection site.

Ketamine (75mg/kg) followed by Xylazine (60mg/kg) was administered intramuscularly (IM) to anesthetize the animals. Their scalps were then shaved and the animals were placed into a stereotaxic instrument using aseptic surgical procedures. After fully exposing the skull, the stereotaxic coordinates of the dorsal hippocampal formation were marked: -3.6mm posterior to bregma, and +/- 1.5mm lateral to saggital suture. Holes were then made to allow for the injection of colchicine or CSF into the dorsal hippocampal formation.

The 15-CSF control subgroup (n=4), and the 15-COL group (n=11), were injected bilaterally by lowering the Hamilton syringe -4.8mm dorsal-ventral into the dentate gyrus. One microliter of CSF or 15-COL dissolved in 1ul of CSF was delivered bilaterally over a four minute interval using a Kopf microinjector unit. A two minute interval was allowed before the needle was raised and lowered into the other site to ensure proper placement of the neurotoxin. The 25-CSF control subgroup (n=4), and the 25-COL lesioned group (n=11), received the CSF or colchicine dissolved in 1ul of CSF. The syringe was lowered -4.8mm dorsal-ventral into the granule cell layer and 0.6ul of CSF or 15ug colchicine dissolved in 0.6ul CSF was injected. After two minutes the syringe was raised 0.8mm, and the remaining 0.4ul of CSF or 10ug of colchicine dissolved in 0.4ul of CSF was injected into the CA1 region. The 10-CSF control subgroup (n=3), and the 10-COL group (n=11), were injected with 0.6ul of CSF or 10ug of colchicine dissolved in 0.6ul of CSF in the CA1 region only. The combination of the three CSF control subgroups created the entire CSF control group (n=11).

After suturing the incision, the animals were administered an intramuscular (IM) injection of Yohimbine (2mg/kg) to counteract the

anesthetic, followed five minutes later by 2cc of lactated ringers solution administered subcutaneously in the animal's dorsal neck area. The animal was then eartagged and received a .005mg/kg (IM) dose of the analgesic buprenorphin followed 12 hours later by another dose if necessary. The animal was allowed to fully recover in a holding room before being returned to the colony room. The protocol for surgical procedures was approved by the Institutional Animal Care and Use Committee (IACUC).

Behavioral Apparatus

T-Maze. The T-maze consisted of a long arm of 57cm in length which attached to the middle of a 36cm cross arm with alleys measuring 10cm x 10cm. The start box consisted of the first 18cm of the long arm and was separated from the alley by a sliding door. The maze was covered with clear plexiglass and rested on a tray of sawdust for easy cleanup after each animal. The dependent variable measured was the percent of spontaneous alternating behavior exhibited by the animals.

Activity Chamber. The activity chamber used for this study was the Digiscan Animal Activity Monitor. Any vertical or horizontal activity demonstrated by the animals was detected by infrared photocells. The information was computer collected, analyzed and recorded on a printout. A red light was used during testing. The following dependent variables were measured during the 60 minutes that the animal was in the activity chamber: total distance (TD), movement time (MT), speed (TD/MT), margin time (MGT), vertical activity (VA), number of vertical movements (VM), and vertical time (VT). Total distance (cm) indicates the distance travelled by the animal in a given time interval. Movement time (seconds) measures the amount of time that the animal is in continuous motion. Speed is calculated by dividing the total distance by the movement time. Margin time is the amount of time the animal is within 1cm of the walls of the chamber. Vertical activity is the number of times the vertical beam below the hole-poke board is interrupted. The number of vertical movements is determined as the number of times that the animal breaks the vertical beam below the hole-poke board for > 1 second. Vertical time is the total amount of time that the vertical beam is broken by the animal placing its head into any hole of the hole-poke board.

Behavioral Testing Procedure

Each animal was placed into the activity chamber with the hole-poke board prior to surgery to obtain a baseline activity rate. The animals then underwent the surgical procedure and were allowed ten days to recover before subsequent behavioral testing. On the eleventh day following surgery the animals were returned to the activity chamber for their first postsurgical activity testing (Post-1) with researchers blind to the group membership of each animal. On days 12-15 the animals were placed in the T-maze to measure their SAB and their behavior was recorded. Each animal was placed in the start box of the T-maze with the two sliding doors to both alleys opened. Timing then began as the initial sliding door of the start box was lifted. After 30 seconds, if the rat had not yet moved, its tail was stroked. If the animal still did not move then it was placed back into its cage for two minutes and then given another trial. When the subject moved, it was monitored to see which alley it chose to enter. After entering the alley, a door was shut behind it preventing it from leaving and allowing the observer to record which side it had entered. On the 16th postsurgical day the animals were again returned to the activity chamber for the final activity measure (Post-2).

Testing using the activity chamber with the hole-poke board involved placing each animal in the activity chamber alone for one hour. The 60 minutes was divided into six ten minute intervals with data being printed in an adjacent room at the end of each interval. The animals were left undisturbed during this time as all activity was being processed by the

Digiscan Analyzer.

Euthanasia

On postsurgery day 19 each animal was euthanized with an interperitoneal (IP) injection of 25mg/ml of urethane and intra-
cardially profused with physiological saline followed by a fixative solution. Immediately after the animals were profused their brains were removed.

Histology

After the brains were removed the tissue was cryoprotected in a series of sucrose solutions. The brains were then blocked, frozen and sectioned at 40 microns using a sliding microtome. The sections were placed on gelatinized slides and stained with cresyl violet. Cellular damage was quantified via cell counting at 100x. Interrater reliability for cell counting (r =.95) was established prior to the start of the procedure. Researchers were blind to the treatment group of the tissue during cell counting.

Data Analysis

The dependent variables for the Activity Chamber were analyzed using a two factor analysis of Variance (ANOVA), mixed design. There were four levels of factor one (group), [CSF, 10-COL, 15-COL, and 25-COL] and three levels of factor two (day), [presurgery, Post-1, and Post-2]. Multiple comparisons were conducted using Tukey's protected t-test. T-maze testing was analyzed using one way ANOVAs for each Dorsal Hippocampal Formation region (CA1, CA2, CA3, and DG).

Results

A total of 39 subjects were entered into analysis: CSF (n=10), 10-COL (n=10), 15-COL (n=9), and 25-COL (n=10). One subject from the 15-COL group and two subjects from the 10-COL group were removed because the cells were not able to be counted due to inadequate staining. Two subjects were removed from the 25-COL group, one with unilateral damage only and the other due to the lack of any lesion.

Animals in the 25-COL group demonstrated increased activity at both the Post-1 and Post-2 testing days as measured by Total Distance in comparison to the 10-COL, 15-COL and CSF group, $F(6,72) = 5.789$, $p<.0001$. The 10-COL group demonstrated a sign-

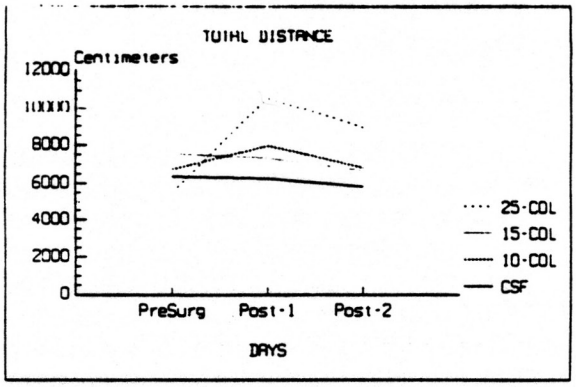

Figure 1. Total distance in the activity chamber measured in centimeters during three testing periods. The 25-COL group differs significantly from all three groups on postsurgical day 1 (Post-1) and postsurgical day 2 (Post-2) ($p<.01$). The 10-COL demonstrated significantly greater total distance than the CSF group on Post-1 ($p<.01$).

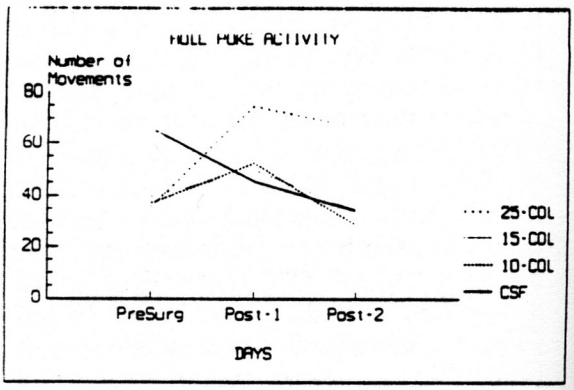

Figure 2. Hole-poke activity as measured by the number of vertical movements in the activity chamber. There is a significant difference between the CSF group and all three groups ($p<.05$). The 25-COL differs significantly from all groups on the postsurgical day 1 (Post-1) and postsurgical day 2 (Post-2).

ficant increase in activity at the Post-1 day as compared to the CSF control group only, t=2.78, $p<.01$. The data for each CSF subgroup were analyzed and were found to be nonsignificant for each variable; the data was then collapsed. The number of Vertical Movements or Hole-Pokes on postsurgical testing days exhibited by the 25-COL group were significantly greater as compared to all other testing groups, $F(6,72) = 3.81$, $p<.01$. The CSF control group showed a significant increase in activity at the presurgical testing time, $F(3,36) = 4.22$, $p<.05$, which was not present at Post-1 and Post-2. There were no significant differences between groups for vertical time, margin time, speed, and movement time. The 25-COL group exhibited a significant decrease in SAB on Day 1 in comparison to all other groups ($X^2=10.13$, $p<.01$) as illustrated in figure 3 and the 25-COL group performed at chance levels for days 2-4, similar to 10-COL, 15-COL, and CSF groups. The 25-COL group exhibited significant cell loss in the left

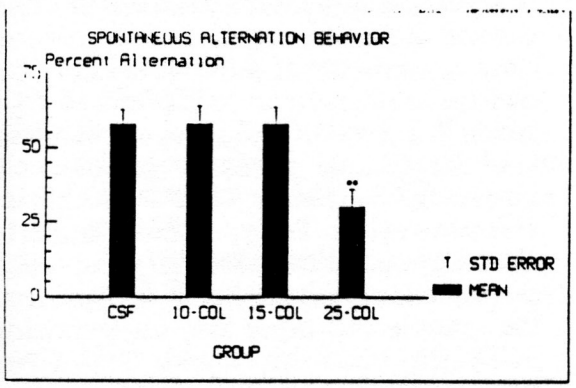

Figure 3. Spontaneous alternation behavior in the T-maze occured below chance levels for the 25-COL group and within chance levels for the CSF, 10-COL, and 15-COL.

and right dentate gyrus in comparison to the 10-COL, 15-COL, and CSF group, $F(3,31) = 7.49$, $p<.01$; $F(3,31) = 7.08$, $p<.01$, respectively. Both the 10-COL and 15-COL groups had significant cell loss in the dentate gyrus in comparison to CSF subjects. The left and right CA1 pyramidal cell layer was similar between the 10-COL and 25-COL groups and exhibited greater cell loss than the other

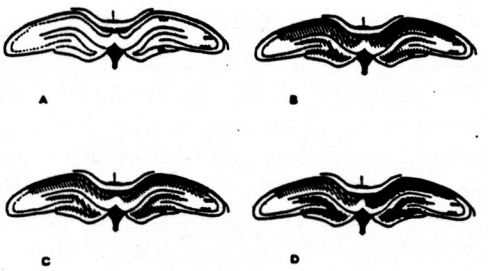

Figure 4. A schematic diagram of the representative lesions of each treatment group: CSF (A), 10-COL (B), 15-COL (C), and 25-COL (D). All groups differ from the CSF in the left CA1 region (LCA1), right CA1 region (RCA1), left dentate gyrus (LDG), and the right dentate gyrus (RDG). In the 25-COL group RCA1 differs significantly from the 15-COL RCA1 ($p<.05$). In the RCA1 there was no significant difference found between the 25-COL and the 10-COL. The 25-COL was found to have more damage than the 10-COL in both the RDG and LDG ($p<.05$).

groups, $F(3,31) = 6.76$, $p<.01$; $F(3,31) = 5.91$, $p<.01$, respectively. There were no differences in histology between CSF subgroups.

Discussion

The 25-COL group exhibited increased activity in the chamber as measured by total distance traversed. The 10-COL group differed significantly in total distance from the CSF group for the first post surgical day (Post-1) only. One explanation for the similarity in behavior between the 25-COL and the 10-COL groups on Post-1 may be found in the histology for both groups. Tissue from the 25-COL group showed marked cell loss in the dentate gyrus bilaterally and also in the left CA1 region of the hippocampus. The 10-COL group also showed marked cell loss in the CA1 region but only marginal cell damage in the dentate gyrus. Issacson (1982) reported that disruption of the CA1 region of the hippocampus prevents glutamatergic efferents from reaching the nucleus accumbens. It is well documented that this structure participates in the modulation of locomotor activity and that activity will be altered due to a disruption within the hippocampal system (Mogenson & Nelson, 1984).

Issacson (1982) found that non-lesioned rats showed normal attention when given the hole-poke test. Conversely, rats with hippocampal damage spend less time examining each hole. In a related study, Ryan (1994) proposed that hippocampal-caudate communication is disrupted following dorsal hippocampal formation colchicine lesions. We expected that animals with significant damage to the CA1 region would demonstrate a decrease in attention as measured by the hole-poke task. Our study found that the 25-COL group covered more distance and had an increased number of hole-pokes as measured by the number of vertical movements.

In measuring attention, we compared the number of hole-pokes to vertical time, which is the total amount of time an animal spends examining any hole. The 25-COL group exhibited an increase in the number of vertical movements in comparison to 10-COL, 15-COL and CSF groups but did not differ in vertical time between groups. The 25-COL group investigated significantly more holes in the same length of time as other groups indicating a marked decrease in attention. The 10-COL group which had similar damage to the 25-COL animals in the CA1 pyramidal cell region did not exhibit a significant decrease in attention. The difference in lesions between the two groups appeared in the dentate gyrus, suggesting that damage to both regions results in attention deficits.

By comparing the total distance and the number of vertical movements for each subject we examined the type of exploratory behavior exhibited by the animals. The only group to demonstrate an increase in both total distance and vertical movements was the 25-COL lesioned animals. Issacson (1982) found that animals exhibited increased activity, examine fewer holes and explore their environment less. These animals attend to each hole for a shorter duration and show a propensity to re-examine already checked holes. The output to the orbitofrontal cortex from the hippocampus may play a role in this behavior. The orbitofrontal cortex is responsible for maintaining order in exploratory behavior; when there is marked damage to the hippocampus there is no systematic exploration (Ryan, 1994).

The 25-COL group exhibited perseverative behavior as indicated by a significant decrease in SAB on the first day of testing only, with days 2-4 reaching chance levels. Contrary to expectations, we did not see a significant decrease in SAB across the testing days for this group. Douglas (1989), however, reported that lesioned animals will experience some learning across days in the T-maze. Crusio, Bertholet, and Schwegler (1990) reported that animals exhibit SAB behavior reaching chance levels on repeated test days. Although the 25-COL group did not differ from other groups after day one, their SAB was slightly below the chance level during repeated testing.

In this study the researchers attempted to induce discrete lesions of the CA1 or the dentate gyrus. Surprisingly, however, colchicine injections to either one of the areas resulted in significant damage to the other area. It is likely that damage to the granule cells of the 10-COL group is a result of diffusion of colchicine into the dentate gyrus as granule cells have an affinity for colchicine (Wisniewski & Terry, 1987). Similarly, CA1 damage in the 15-COL group could result from colchicine being dragged from the granule cell layer into the pyramidal cell layer when the cannula is removed from the brain.

One of the many roles of the hippocampus involves the inhibition of behaviors. The disruption of hippocampal modulation results in the behavioral manifestations which include increased activity, inability to attend, perseveration, and spatial disorientation. The present research supports the theoretical approach of hippocampal inhibition and leads to subsequent investigation in other regions of the hippocampal system.

One implication of this study is that the neurological focus of functional loss in AD may be too limited. The pathogenesis of cortical loss in AD

originates in the limbic system and spreads to cortical and subcortical regions (DeLacoste & White, 1993). Problematic behaviors in AD such as wandering may be related to unique patterns of degeneration in areas of the hippocampal system involved in movement, spatial orientation and attention. Expanding the conceptualization of the brain-behavior relationship in AD may offer new insights into more appropriate interventions and the development of new treatments.

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