DISCUSSION
A. RATIONALE OF ALTERNATED DUAL TASK

The purpose of this thesis is to consider whether learning of two things together (by alternating) better than learning one by one, and does learning of one task influence other? The concept of dual task prevailing in animal and human studies are different from the one considered in the present study. In animal studies dual tasks are rarely used, and in human studies mainly dual task includes a combination of a primary task and subsidiary task (Dorn and Sanders, 1989) or a mental arithmetic task added either early or late in practice either as an independent task (Bahrick et al., 1964) etc. When people try to carry out two separate choice response tasks at nearly the same time, responses to one or both tasks are usually delayed. According to this hypothesis, central operations (response selection and perhaps other operations) can take place on only one task at a time (Ruthruff et al., 2001). But in our study, the two tasks included were of similar background i.e. both (T-maze and radial arm maze) involves spatial learning and memory. It is generally agreed that radial arm maze (RAM) task and spontaneous learned alternation behavioral task in T maze (TM) are hippocampus dependent spatial tasks. Also it is important to mention that, either of the two tasks was not considered as a primary task and the other one as a subsidiary task. However, the difficulty to learn a task depending on the time taken was different and hence one task was considered as simple and the other as complex. The present and other previous experiments revealed that number of trials required for acquisition and retention of TM task is significantly less than RAM task. This gave the basis for considering TM task as a simple task & RAM task as a complex one.

The two tasks adopted in the present study were all arm baited procedure in RAM, which mainly assess the working memory aspect of spatial learning and memory, and the other task was learned alternation procedure in TM. In T-maze rats tend to alternate their choices spontaneously; that is, when given two successive trials they tend to choose first one arm then the other, rather than the same arm on both trials. They alternate even when no choice has been made on the first trial; thus, if put directly into the goal box at the end of one arm of a previously explored T-maze, and then given a choice between the two maze arms, they will tend to choose the arm leading to the other goal box. In general there is a tendency to go to the part of the environment that has been least recently explored. Not only in spontaneous alternation, but also in learned left-right spatial alternation, where a learning criterion is established for the purpose of specifying the time when the task has been acquired, the phenomenon of choosing least explored environment can be observed (Latomis, 2002). In the present study TM task was based on a learned alternation procedure and learning criteria was also specified. Similarly for RAM task also learning criteria was specified. This allowed the calculation of number of trials to criteria rather than days to criteria in the present study. We expect more accuracy when number of trials is considered, because more than one trial is done per day, and criteria may be achieved in the middle of a day.

II. NOVELTY AS CAUSE OF BETTER LEARNING & MEMORY IN ADT

In the alternated dual task (ADT) groups the number of trials required for acquisition and retention of RAM task was similar to TM task, in contrast to other groups. This indicates that the rats learning ability has increased when the task was alternated. The probable reason for this may be novel learning conditions given alternately. A novel environment represents a stressful condition, and the first exposure to it causes pronounced behavioral activation (Aiosi et al., 1997; Cieccarelli et al., 1999), which provides one of the most elementary forms of learning. As stated by Dember, & Fowler, in 1958, rats tend to choose the environment that has been least recently explored. This could have increased the curiosity, and curiosity tends to increase the ability of alternation behavioral tasks (Dember, & Earl, 1957). It was pointed out that rats prefer (over repeated trials) a path leading to a goal box containing complex stimuli over a blind alley or an empty goal box respectively (Berlyne, & Slater, 1957). So when rats were alternated between TM and RAM their learning ability enhanced. Also when rats were learning both the task without alternation, the novelty drive hypothesis (Berlyne, & Slater, 1957) was lacking and be the reason why they behaved similar to single task groups for having a significant difference between the number of trials required for TM task and RAM task.

The fact that rats in both the modes of ADT procedure [TRAM-ADT and RAMT-ADT] behaved similarly was not surprising when the novelty drive hypothesis is considered. Because starting with TM or with RAM
maze doesn’t make any difference for the degree of novelty and exposure to a new environment simultaneously, or it doesn’t decrease the level of curiosity and no change in motivation levels. So we can expect both these ADT groups to behave similarly and thus the exploration for dropping one of them from the further experiments. Also in non alternated dual task groups [TRAM-NADT and RAMT-NADT] need for two modes were not felt.

Interference is a key word that is discussed in the literature that normally uses dual tasks. Prior to a seminal paper by Benton Underwood in 1967, it was widely believed that retroactive interference was a major cause of forgetting. Retroactive interference refers to forgetting caused by conflicting memories acquired between original acquisition and subsequent testing of the target memory. Retroactive interference may be represented symbolically as learn A, then learn B, and then test A. What Underwood demonstrated was that far more potent cause of forgetting was associated with proactive interference rather than retroactive interference. Proactive interference refers to forgetting caused by conflicting memories acquired prior to the acquisition of the target memory. Proactive interference may be represented as learn B, then learn A, and then test A (Capaldi and Neath, 1995).

In the dual task procedures adopted in this study, presence of retroactive interference and proactive interference can be considered. For NADT and ADT procedures the forgetting effects of interference was not observed. This probably is because of the similar non conflicting tasks used in the dual task procedure. In both TM task and RAM task food restriction is used and rats have to go to the arms of the maze and collect food, with the difference that in simpler TM task only two arms whereas in complex RAM task eight arms are to be explored by the rat.

When ADT procedure is used, it is seen that a complex task can be learned easily. Moreover the long term memory for the complex task learned is better, and that the task learned faster is not easily forgotten. So this principle of “alternated dual task” can be made use when a complex task is to be learned by a rat within a short period of time. We have no clear explanation for the finding that learning ability of only complex task is increased due to ADT procedure. Langias, & Savage, n 1996 provided evidence for the fact that high levels of spontaneous alternation are consistent with good spatial memory performance. Here in our experiment also as the complexity in alternation increased by using alternated dual task, the spatial memory performance also enhanced. Since RAM task involve more use of spatial cues than TM task, probably by ADT, spatial memory performance may be enhanced and thus better performance of RAM task.

Another possibility that can be considered for the fact that TM task is not enhanced by ADT could be that there was a ceiling effect in the acquisition of TM task – i.e., the rat just could not acquire it faster, given ADT or not. Indeed, in the ADT procedure, the learning of the TM task goes hand in hand with learning of the RAM task, and it is shown in Fig. R 1 as well as other figures that the number of trials to criterion for the TM task and the RAM task in the ADT procedure are almost exactly the same. It strengthens the possibility that what the ADT procedure did was to “build” the RAM task on the TM task and then reactivates and reconsolidates it. Here we mean to say that in ADT when rats do one task and then forced to learn the new second task, it reactivates what the rat have learned in the first task and then apply the rules in the second task and reconsolidates the skills such that they perform better in retention or reacquisition tests which follow. Hence better performance in ADT, but may be because of a ceiling effect in TM task, only RAM task is more influenced by ADT procedure.

C. IN ADT, TASK LEARNED FASTER IS NOT EASILY FORGOTTEN, PROBABLY BECAUSE OF METAPLASTICITY THAT OCCURRED IN HIPPOCAMPUS.

All the groups showed significant difference between acquisition and retention. Retention of task after 10 days took always less number of trials for all the rats. This prompted us to calculate a memory score which gave a clear idea about memory capacity of rats. Only the alternated groups showed a significantly higher memory score, in contrast to the non alternated group. It can be assumed that the alternated groups had a novelty drive and also a higher load on short term memory and working memory compared to non alternated groups. As the short term memory load was more a better long term memory formation may be possible. In 1968 Atkinson-Shifrin model described the structure of memory and mentioned the need for rehearsal to transfer short term memory to long term memory. Recently also it was shown that regular rehearsal helps in consolidation of long
term memory (Mild et al., 2006). In our study alternated groups received regular rehearsal for complex task
interspersed with simple task, whereas non-alternated groups received continuous rehearsal for a particular
task. So a better retention capacity is possible in alternated groups, as indicated over here by an increased
memory score in this group.

Another possible explanation for enhanced memory in ADT group of rats can be obtained when we consider
more recently introduced term “metaplasticity”. Metaplasticity, the plasticity of synaptic plasticity, is thought to
have a pivotal role in activity-dependent modulation of synaptic connectivity, which underlies learning and
memory. The idea is that the synapse’s previous history of activity determines its current plasticity. Predisposition
for activity-induced strengthening and weakening of synaptic connections is highly dependent on the history of
the synapse. It has been suggested that this phenomenon, termed metaplasticity, strongly affects long-term
synaptic modifications that underlie learning and memory. Metaplasticity may play a role in some of the underlying
mechanisms thought to be important in memory and learning such as LTP, LTD and so forth. Recently, it has
become clear that the prior history of synaptic activity is an additional variable that influences the synaptic state,
and thereby the degree, of LTP or LTD produced by a given experimental protocol. Hippocampus is considered
one of the major sites of metaplasticity to occur especially underlying rule learning (Avraham and Bear, 1996;
Zeigler et al., 2009).

Metaplasticity is usually attributed to activity-induced changes in glutamate receptors, triggered by calcium
current through the NMDA channels (Crum et al., 2001; Castellani et al., 2001; Giubellato et al., 2003; Mockett
et al., 2002; Phipot et al., 2003; Sawtell et al., 2003; Tompa and Friedrich, 1998; Van Dann et al., 2004). In ADT,
learning of one task stimulated activity-induced changes, and when the second task was learned in alternation
with first one, it might have caused enhanced neuronal excitability in hippocampal neurons, which underlies the
induction of metaplasticity. Moreover, Zeigler et al., 2008; also showed that when metaplasticity is induced in
hippocampus, the behavioral consequences of these modifications are far more reaching. In ADT protocol
adopted here, both tasks are hippocampal dependent. Enhanced neuronal excitability in hippocampal neurons
enables a general enhancement of hippocampus-dependent learning by enhancing the creation of rule learning
of novel tasks. In the presence of such enhanced neuronal excitability, the hippocampal network enters into a
‘learning mode’ in which a variety of hippocampus-dependent skills are acquired rapidly and efficiently. So we
can consider metaplasticity as one of the possible mechanisms that has enhanced spatial learning and memory
in ADT rats.

Spontaneous alternation has been labeled a hippocampal – dependent task (Isaacson, 2002; McIntyre et
al., 2002; McIntyre et al., 2003; Lalonde, 2002). It has assumed considerable popularity in studies of spatial
memory as a quick and simple measure of retention that avoids the need for extensive training and the use of
conventional reinforcers (Roberts, 2004). Even though spontaneous alternation can be a useful index of
responsiveness to novelty, its value as a measure of retention is less certain especially when used as a measure
of short term memory. In the ADT such a deficit in the measure of retention is not observed. It can be considered
that when ADT is used, a complex task can be learned easily and acquired faster. Moreover the long term
memory for the complex task learned is better, and that the task learned faster is not easily forgotten. So this
principle of “alternated dual task” can be made use when a complex task is to be learned by a rat within a short
period of time.

The exploration of novel environmental stimuli is dependent on the integrity of limbic and non-limbic pathways,
including the basal forebrain, the hippocampus, the thalamus, the prefrontal cortex, and the dorsal striatum, as
well as the vestibular system and cerebellum. Neurochemical pathways using acetylcholine, GABA, and dopamine
in the hippocampus and septum have been implicated in the exploration of novelty (Lalonde, 2002). Understanding
the neurobiological basis of ADT will delineate the way by which the brain reacts more generally to sources of
novelty. As an approach to do this the lesion and pharmacological manipulation of brain is adopted in the
present study.

D. POSITIVE MODIFICATION OF CHOLINERGIC NEURONS PROJECTING TO THE HIPPOCAMPUS MAY OCCUR BY ADT PROCEDURE

Anticholinergic drug scopolamine (SC) was administered to evaluate the role of hippocampus and cholinergic
system in alternated dual task. While it is often assumed that poorer learning following systemic treatment with
scopolamine is due to memory impairments, there is longstanding evidence to suggest that such changes can arise from disrupted sensory/attentional processes (Brown and Warburton, 1971; Cheal, 1981; Milar et al., 1978) or performance deficits (Smith and Calhoun, 1972). In some cases, it is also possible that motivational factors independent of central cholinergic activity might play some part since scopolamine has been shown to lead to novelty avoidance (in the absence of effects on memory) possibly because of the drug's aversive peripheral action (Hughes, 1982; Hamburgh and Hughes, 1981). Drug-induced novelty avoidance is particularly relevant to the interpretation of spontaneous alternation behaviour outcomes since the phenomenon is widely accepted as involving responsiveness to the more novel of two maze arms on any binary choice occasion (Dember and Riehn, 1989). In the present study also novelty is considered to be one of the factors that caused betterment of learning and memory in ADT group of rats.

In the ADT groups even when SC was administered, the number of trials required for acquisition and first retention of a complex task (RAM task) was similar to a simple task (TM task) within each group, in contrast to NADT groups with SC treatment. This indicates that the rats learning ability has increased when the task was alternated. But this phenomenon was not observed during second retention phase, probably because by second retention phase the memory was well consolidated and was in long term memory. So it shows that the long term memory retrieval was not influenced by alternated dual task, and it can be considered that the ADT influences the learning ability and makes it faster. But once learned thoroughly the memory retention is not getting influenced by alternated dual task.

The effects of scopolamine on the retention of well learned maze habits are ambiguous since Dener and Schueler in 1980 found it to produce a deficit whereas Pazzaglia and Pepeu (1964) failed to demonstrate a scopolamine induced deficit. In the present study both acquisition and first retention of TM and RAM tasks was impaired by SC, probably because, after acquisition the memory may not be well consolidated in long term memory store. The fact that SC appears to be less disruptive to long term memory storage could not be established at this level, as first retention was equally affected by SC similar to acquisition. So we introduced the second retention phase as an approach to break the ambiguity. SC administration did not influence the second retention phase. It has been already shown that once a memory has been consolidated, it may no longer be susceptible to disruption by scopolamine (Nancy, 1986). So our study also supports this view. Pazzaglia and Pepeu (1964) also failed to demonstrate a SC induced deficit for a well learned maze habit. In our study it may be that rats tend to use more of allocentric cues rather than egocentric cues, especially in alternated dual tasks.

Number of trials required for first retention phase when compared to corresponding second retention phase, no significance was observed in ADT groups, except when SC was administered during first retention phase. This is in contrast with NADT groups, indicating that, by the first retention phase itself the memory is well consolidated in ADT groups compared to NADT groups. It again supports the fact that ADT groups learn faster.

Another key observation in our study is that there was significant difference between the number of trials for first retention phase of group ADT with SC during 1st retention and NADT with SC during 1st retention. Here NADT group took almost double the number of trials than ADT group. This indicates that the ADT group is able to counteract the deficits caused by SC. The influence of SC on ADT group is less than on NADT group.

But this difference was not so prominently featured when acquisition was considered. In other words, when SC was administered during acquisition in ADT and NADT groups, both the groups took significantly more number of trials than control, but between them the difference was not so significant. This was especially true for a simple task like TM task, but the complex task, i.e. RAM task, took significantly more number of trials in NADT group than ADT group with SC administration during acquisition. This observation is in parallel to the observation in control group, where also simple task like TM task is not much influenced by the alternated dual task procedure, in contrast to the complex task (RAM task) which was decreased for number of trials for acquisition in alternated dual task control group compared to non alternated dual task control group.

RAM is more susceptible to impairment by scopolamine (SC) than Morris water maze (Dorman et al., 1996). But in the present study both TM and RAM task showed almost similar deficit with SC. This is probably because both tasks involve similar rewarded behavioral strategies and neuronal network involved may also be similar.
Activation of the forebrain cholinergic system has been demonstrated in many tasks and conditions in which the environment requires the analysis of novel stimuli that may represent a threat or offer a reward (Pepeu & Giovannini, 2004). Scopolamine interferes with memory and cognitive function in humans (Beatty et al., 1986) and experimental animals (Steevens, 1981; Sutherland et al., 1982) by blocking muscarinic receptors mainly in these brain regions. In ADT also we consider the novel stimuli to be the key factor. This explains the memory impairment, even though less, caused by SC in ADT procedure.

Rivastigmine (RVM) alone clearly reduces the number of trials to criteria in both the tasks by different groups. It was able to antagonize the amnesia produced by SC in all the groups. Also, when the rats were under the influence of a combination of RVM and SC during the acquisition trial, their memory in the retention test was unimpaired. So all these results show that RVM is an effective antagonist of the SC induced deficits in spatial memory and this view is also supported by other works (Boeije et al., 1999). The present study compared the effects of this relatively novel cholinesterase inhibitor, RVM, with that of ADT procedure against SC induced memory impairments in the RAM task and spontaneous alternation behavioural task in TM. In RAM task both RVM and ADT could restrict the impairment caused by SC, but in TM task only RVM could do it efficiently.

Rats placed in novel environments, showed a 150%–200% increase in acetylcholine (ACh) release from the cortex and hippocampus (Pepeu and Giovannini, 2004). Hippocampal ACh release increases during performance of a learned spatial memory task (Ragazzino et al., 1989; Stancampiano et al., 1999), and, interestingly, the improvement in RAM performance is positively correlated to the increase in ACh release during 12 days of task learning (Fadda et al., 2000). These results show that the learning of the spatial task modifies the function of cholinergic neurons projecting to the hippocampus, which become progressively more active. In ADT group of rats probably there is a better positive modification of cholinergic neurons projecting to the hippocampus, compared to other groups, and this may be the explanation for reduced effect of SC in ADT group of rats.

We have already discussed the role of interference in the present study. Acetylcholine plays an important role in associative learning by decreasing proactive interference (Hassebroek and Bower, 1993). Experimental data and computational models suggest that blockade of muscarinic cholinergic receptors impairs paired-associate learning and increases proactive interference (DeRosa and Hassebroek, 2000; Hassebroek and Bower, 1993). It is also shown that scopolamine prevents memory interference (Boeije et al., 2007). Probably by ADT procedure acetylcholine has increased or cholinergic neurons stimulations might have increased and this may be one of the reasons for not observing the forgettting effects of interference in the present study.

It may be stated that “alternated dual task” help to learn a complex task faster than learning it in isolation from other tasks. An anticholinergic drug, scopolamine showed similar decrement in both T maze and radial arm maze tasks. But this decrement can be decreased by adopting procedures like “alternated dual task”, especially for complex task. The influence of “alternated dual task” on scopolamine treated rats were similar to the effects of rivastigmine. But this similarity was restricted to radial arm maze task and T maze task was less influenced by “alternated dual task” procedure.

**E. ADRENERGIC SIGNALING CRITICAL FOR RETRIEVAL OF SPATIAL MEMORIES MAY BE STIMULATED BY ADT PROCEDURE**

In all the alternated groups even when MPD was administered, the number of trials to criteria required for acquisition and retention of a complex task (RAM task) was similar to a simple task (TM task) within each group, in contrast to all non alternated groups, except for retention in groups where MPD was administered during retention phase. This again confirms that the rats learning ability has increased especially for a complex task, when the task was alternated.

Some existing evidence indicates that MPD may reduce rats’ preference for novelty (Dyne and Hughes, 1970; Hughes and Syme, 1972). However, no indication of such an effect was found in the present experiments. It is a well known fact that RAM and TM induces activation of memory formation processes involved in the hippocampus. It has been recently shown that neural circuit involving hippocampus and prefrontal cortex is a part through which spatial information acquired before a delay is used, subsequently to locate food on a RAM.
In the present study also, both ADT and NADT rats probably use this pathway to solve both RAM and TM tasks. Some studies have shown that higher doses MPD can impair prefrontal cortex dependent memory formation (Arnsten, 2001). But in the present study any impairment in this regard could not be established, as performance was enhanced in both ADT and NADT rats by using MPD. This is probably because of a comparable low dose of MPD used in this study. Many reasons have been suggested by previous workers for this enhancement, including an increase in histamine release in prefrontal cortex by MPD, so keeping the rat vigilant and wakeful, resulting in better performance (Horner et al., 2007); an increase in synaptic levels of dopamine and nor epinephrine (NE) by MPD can increase overall attention and may contribute towards better performance (Arnsten, 2001); and, an increase in cortical and hippocampal acetylcholine release by MPD significantly improves performance in RAM and TM (Tzavara et al., 2006).

The NE release in hippocampus increases during spontaneous alternation behavior (SAB) testing, supporting role of NE in SAB (Men et al., 1999). Also it is believed that optimal dopamine is required for SAB (Lattonde, 2002). In the present study also the SAB testing procedure has been used as a learned alternation procedure for TM task. As such ADT involves a higher degree of alternation procedure and it can be assumed that, when MPD increased NE and dopamine release, improvement in spatial learning of ADT rats is due to this factor. When compared to NADT the complexity of alternation is more in ADT and the amelioration caused by MPD is thus more in ADT groups. The fact that ADT is more ameliorated by MPD is clear from the results that shows a higher number of trials to criteria for NADT groups than ADT groups for acquisition when MPD was administered during acquisition.

Adrenergic signaling is critical for the retrieval of intermediate-term spatial and contextual memories but not for retrieval of emotional memories in general (Murphy, 2004). In Morris water maze, knockout rats for NE, exhibit a deficit in retaining spatial memory two days after last training. But no deficit was found when it was after two hours (Thomas and Palmer, 1997). Studies have also shown that spatial memory consolidation (retention) using aversive stimuli depend on adrenergic signaling, but acquisition does not depend on adrenergic signaling (Thomas and Palmer, 1997). But in the present study both acquisition and retention has been enhanced by MPD. So it may be assumed that NE increase caused by MPD might have ameliorated the retention capacity and enhancement in acquisition may be due to increase in histamine release (Horner et al., 2007) or acetylcholine release (Tzavara et al., 2006) or due to some other factors like increased attention or increased locomotor activity that is normally seen associated with MPD administration (McDougall et al., 1999).

In 2007 Ning Zhu et al. showed improvement in spatial learning and memory by oral methylphenidate administration. But in their experiment number of days to criteria for a RAM task did not show a change, which is in contrast to the present study, where number of trials to criteria in RAM test has decreased significantly by MPD administration. The probable reason for this difference may be due to the consideration between number of days to criteria and number of trials to criteria.

It may be stated that the amelioration attained for retention of complex task by ADT procedure, could be achieved by NADT rats only by administration of drugs like MPD. The influence of ADT on acquisition and retention of TM and RAM tasks were similar to the effects of MPD, especially for the RAM task. MPD at low dose is found to enhance the learning and memory capacity in rats, than deteriorating it, supporting the use of MPD as a drug to treat attention deficit hyperactive disorder (Arnsten, 2001). The recent reports (Thomas and Palmer, 1997) suggesting the effect of MPD only on retention and not on acquisition could not be confirmed, as enhancement for both acquisition and retention was found in this study.

F. HIPPOCAMPAL LESIONED RATS PROBABLY USED EGOCENTRIC STRATEGY FOR LEARNING SPATIAL TASKS.

Results of lesion study showed that in all the hippocampal lesioned groups' rats took more number of trials to learn the tasks. But the fact that lesioned rats were able to learn the task is important even though more number of trials was required. Previous studies have shown that hippocampal system lesion typically disrupt allocentric spatial learning but leave egocentric learning intact. (Aggleton et al., 1995; Rasmussen et al., 1989;
Neave et al., 1997). So in the present study, probably the control groups of rats were using allocentric strategy, but lesioned groups might have used egocentric strategy to learn the tasks.

Previous studies have shown that learning egocentric responses is enhanced by hippocampal damage. On some tasks, more than one learning/memory system in the brain can provide a solution. For example, many spatial tasks can be solved either by learning to make particular egocentric body turns (which would depend on the caudate putamen) or by allocentric navigation (which requires the hippocampus). Whether the caudate or hippocampal strategy dominates usually depends on the amount of training and the time elapsed since beginning training. However, inactivation of the hippocampus results in caudate-dependent response learning being seen at all stages in training (Packard and McGaugh, 1996; Schroeder et al., 2002), thereby speeding the development of a response strategy. In the present study single task and dual tasked groups took more number of trials, indicating that hippocampal damage did not enhance the learning. Instead it points towards the idea that hippocampus was essential for both single task and dual task learning. The acquisition of several other tasks can be speeded by hippocampal lesions. These include performance on a two-way active avoidance task that requires the animal to return to a place in which it has been shocked (Olton and Nadel, 1978), and a win-stay radial maze task which requires the animal to revisit the area from which it has removed food in order to receive another food reward (McDonald and White, 1993; Packard and White, 1989). This suggests that the hippocampus and other memory/learning systems may sometimes interact competitively. The fact that the hippocampus inhibits the acquisition or expression of information in other regions is very important. These points suggest that in our study rats were clearly depending on hippocampus for learning and memory of spatial tasks.

Tasks that are best served by egocentric strategies may be acquired faster after hippocampal lesions, which suggest that the hippocampus may initially suppress learning in that system. That means in our experiments control rats were using allocentric strategy to complete the tasks.

Some tasks may be performed faster after hippocampal damage. Femoral and ventral hippocampus lesioned rats have been shown to be superior on some measures of learning (such as the latency to find a platform, Bannerman et al., 1999). This appears to be dependent on lesion-induced hyperactivity and increased swim speed under stress. But such a phenomenon of rats going faster in the mazes was not observed in this study.

Another observation was that neither ADT nor NADT group of rats showed any advantage over single tasked rats when hippocampus was lesioned. This indicates that ADT and NADT group of rats were equally depending on hippocampus as that of single tasked groups.

When the dentate gyrus (DG) was lesioned, in both single and dual tasked groups, they behaved similar to other dorsal hippocampal sub region lesioned groups. That means DG lesion had similar effect as complete dorsal hippocampal lesion. Previous studies have also supported this. Rats with lesions in DG have been tested on a working memory version of the radial eight-arm maze. The results demonstrated that lesion of the DG resulted in deficits similar to complete hippocampal lesions (Eimerich and White, 1989; McLamb et al., 1988; Tilton et al., 1987; White et al., 1988). In addition, rats with DG lesions were tested on the Morris water maze task and showed deficits comparable to rats with complete hippocampal lesions when the start location varied on each trial (Nunn et al., 1989; Sutherland et al., 1983; Xavier et al., 1999).

Based on characteristics of the mossy fiber system, Rolls (1989 and 1996) suggests that spatial pattern separation may be a function of the DG and its mossy fiber projections to CA3. A study by Lassalle et al., in 2000, conducted in mice showed that the mossy fiber projections to CA3 are essential for the encoding of spatial information but are not necessary for retrieval. Lee and Kesner, 2004, have also shown that the mossy fiber input to CA3 is critically involved in encoding of spatial information in rats, but may not be involved in retrieval. The present study also showed that the acquisitions of the tasks are mainly affected by the DG and other hippocampal lesions and retention of the task is spared. That is to say that hippocampus is essential for acquiring new information, especially in this context spatial information, but once it is formed it is not abolished by hippocampal lesions.

One of the mnemonic processes suggested for CA3 is the rapid acquisition of novel information (Mear 1971). Present study also suggests this fact. In the present study not only single tasked groups, but also acquisition in ADT and NADT groups were impaired by CA3 lesioning. Lee and Kesner, 2002, strongly suggest that rapid plastic changes in the CA3 network are essential in encoding novel information quickly into the hippocampal

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memory system and NMDA receptor mediated plasticity mechanisms appear to play a significant role in the process.

During retrieval of information, Marr 1971 suggested that the CA3 recurrent collaterals should play a major role in the hippocampus in retrieving originally stored information patterns in the face of partial inputs to the hippocampus (‘collateral effect’ or pattern completion). But in the present study evidence for this fact was not obtained. Here retention of learned spatial task was not affected when CA3 was lesioned. But in the present study when rats learn a task after hippocampal lesion, probably by using egocentric strategy, we can see that it was not well consolidated in the long term memory. Because during retention of the task done after 10 days in these rats similar number of trials as acquisition was required. That means even though the hippocampal lesioned rats are able to learn using other brain regions, such information regarding spatial environment is unable to be stored properly in long term memory in the neocortex.

Ramos in 2001 showed that 3 days after the end of the training, hippocampal lesioned rats remembered as well as control rats, but this was no longer true 6 or 12 days after the training. These results suggest that, in certain training procedures, the hippocampus is not necessary for the learning of a place task but is required for the formation of long-term spatial memory. This study also supports our result that retention of the task done after 10 days in lesioned rats, took similar number of trials as acquisition.

CA3, but not DG or CA1, supports paired associate learning when a stimulus must be associated with a spatial location. Support for the above mentioned statement comes from the observation that CA3 lesions do not disrupt an object-trace-odor (non spatial) paired associate learning task (Kesner et al., 2005). But in the present study not only CA3, but also DG and CA1 lesion caused impairment in dual task learning. So it can be seen that the phenomenon of paired associate learning is different from the phenomenon of dual task adopted in the present study. In dual task the principle of rule learning is applicable. Here rats learn a rule in one task and apply it to the subsequent task and reconsolidates it faster.

CA1 can compress the input patterns from CA3 to facilitate the transfer of hippocampal information to neocortex Rolls, (1996). So we can assume that when CA1 is lesioned hippocampal dependent task cannot be stored in the long term memory. In our experiments we also have observed the fact that both single and dual task group of rats were unable to store the information learned after the CA1 lesion. It was suggested that CA1 involves the mediation of temporal processing of information chunking and temporally separating information to endow spatial or non spatial contexts with a temporal structure of the information to be remembered Rolls, (1996). Functions of CA1 might be to encode the temporal order of events and store one event as separate from another event in time. Also Gilbert et al., 2001, suggest that when CA1 sub region is lesioned rats are unable to remember the order of specific events. This may be the reason that in ADT group of rats rule learning and its application to the subsequent task was not carried out as in control when CA1 was lesioned, resulting in similar number of trials for single and dual task groups.

In addition to the processing of temporal information, the CA1 is likely to be intrinsically involved in processing information within an intermediate-term memory system based on cellular consolidation and subsequent retrieval with a time frame of minutes to hours after learning has taken place. NMDA dependent plasticity in the CA1 may be critical for intermediate, but not short-term memory (Lee and Kesner, 2003). This again supports why ADT groups behaved similar to control group when CA1 lesion was made. That is to say that an intermediate-term memory was essential to apply the rule of a task learned on to the second task and also when inter trial interval was one hour intermediate-term memory might have involved.

There are several well-known problems with the traditional lesion approach, some of which are likely to be especially problematic for hippocampal studies. The most obvious of these is that lesion studies can only tell us what the brain can do in the absence of an area, not what that area does in an intact brain; and many of the tasks commonly used to probe hippocampal function can be solved using several different strategies dependent on different brain areas. Even though it is clear that reliable specificity of function exists among the three sub regions of the dorsal hippocampus, there also appears to be extensive cooperation for each of these sub regions. In the light of the fact that all the three dorsal hippocampal lesioned groups behaved similarly in the present study, we can say that cooperation among the sub regions is essential for total functioning of hippocampus. But it can also be considered that when one region of hippocampus is lesioned cellular damage
G. IMPAIRMENT DUE TO VENTRAL SUBICULAR LESION WAS LESS PROBABLY BECAUSE VENTRAL HIPPOCAMPUS IS NOT CRITICAL FOR SPATIAL MEMORY

Subiculum acts as the major output structure of hippocampus. The projections from subiculum to the entorhinal cortex terminate primarily in the deeper layers of entorhinal cortex (Brown et al., 1978; Finch et al., 1986; van Groen and Lopes da Silva, 1986). Dorsal subiculum projects to cortical structures such as prefrontal cortex, which has been implicated in cognitive processing of spatial and non-spatial tasks (Lay and Noser, 1991). Besides this the perirhinal and lateral entorhinal cortices receive major projections from the proximal subiculum, and postrhinal and medial entorhinal cortices receive projections from the distal subiculum (O'Mara et al., 2001). Connections have been traced from ventral subiculum (VSub) to prelimbic, infralimbic and anterior cingulated cortices (Finch et al., 1986). Also to subcortical structures like mammillary bodies and hypothalamus, septal complex nucleus accumbens, nucleus reuniens of the thalamus, anterior thalamic complex and interanteromedial nucleus of thalamus (Aylward and Totterdell, 1993; Canteras and Swanson, 1992; Kossai et al., 1993; Narrera et al., 1994; van Groen and Lopes da Silva, 1986; Witter et al., 1990; Witter and Amaral, 1991; Wouterlood et al., 1989; Zheng, 1994). From these data one may assume that ventral subiculum have less significance in spatial learning and memory.

But, the present study and many previous studies have shown impairment in spatial learning and memory due to VSub lesion. In the present study in all the VSub lesioned groups, including single and dual tasking groups, took more number of trials than control groups. Studies from other labs with selective lesion of VSub have also demonstrated impairment in the acquisition of operant and spatial learning tasks (Govindaiah et al., 1997; Lawrie et al., 1999; Morris et al., 1990) have shown impairment in the maze task in rats after subicular lesion; the same results were also obtained with the hippocampal lesions. Other studies reported that the lesioning of the entire retro-hippoccampal area, including the subicular complex and entorhinal cortex, caused impairment in a T-maze task (Good et al., 1989), whereas discrete and selective ibotenate lesions of entorhinal cortex or subiculum also impaired the animal’s capacity to memorize a single spatial location in an eight-arm radial maze Cho and Jaffard, (1995).

Lesion analysis of subiculum demonstrates that it plays an imperative role in spatial representation and spatial navigation. The first study conducted by Schenk and Morris (1965) on lesion of the subicular complex revealed a profound impairment in spatial learning task. (Morris et al., 1990) found that both hippocampal and subicular lesion caused impairment in the initial acquisition but not in eventual learning. However they exhibited impairment during the retention test. Hippocampal lesioned rats employed a circling strategy in the water maze whereas subicular lesioned rats behaved like naïve rats. They suggested that hippocampal lesion may cause dual deficit – a slower rate of learning and separate navigational impairment, while subicular lesion may cause an impairment of long term spatial learning but little impairment in spatial processing or short term memory. Together with these results and the results of the present study suggests that the subiculum is important area for spatial information coding and processing.

Oswald and Good (2000) have observed severe impairment in the water maze performance following entorhinal cortex lesion in rats. Cho et al., 1999 showed that mice with ibotenate lesion of entorhinal cortex or subiculum were impaired in post operative acquisition of the spatial discrimination task. Behavioural results indicated that selective lesioning of VSub alone produced significant impairment in variety of learning tasks; in operant learning task and on a continuous reinforcement paradigm for food reward (Govindaiah et al., 1997; Nutan and Math, 1998). Maren (1999) examine the effect of neurotoxic lesion of ventral subiculum on Pavlovian fear conditioning. Freezing was measured in rats following conditioning by number of tone foot shock trials in a novel chamber. VSub lesion made prior to training produced a severe deficit in acquired freezing to tone but modest context freezing deficits, whereas post training lesion produced severe deficits in freezing to both tone
and context. Subsequently, botenate lesion of the ventral subiculum produced impairment in the acquisition of reward alternation test in a T-maze with no impairment in retention of the task (Laerri et al., 1996). Devi et al. (2003) reported significant impairment in both acquisition and retention of the eight arm radial maze task following bilateral ventral subiculum lesion in rats. They suggested that combined effect of subiculum lesion with associated neurodegeneration of hippocampal structures were responsible for spatial learning impairment. The present study also adds to the existing information that VSub cause impairment in T-maze task, radial arm maze task, and also in dual tasks. Adopting of dual task procedure did not cause any added advantage in lessening the impairment.

The present study revealed that VSub lesion caused as impairment in the acquisition of the spatial tasks, but not the retention. Many other studies have also shown this phenomenon. Govindaiah et al. in 1997 suggest that the subiculum might be involved in the acquisition of new information rather than in retention. Laerri et al., (1999), noted that the rats with selective lesions of the subiculum were not able to learn the rewarded alternation task in T-maze but were normal in acquiring stored spatial information. Apparently, the normal retention may be possible because animals can use an alternative strategy that involves the learning to approach the correct area of the maze using the neocortical regions. The impairment in acquiring new information may be due to the selective damage in the areas, which may participate in transferring the processed hippocampal information to the neocortex.

The rats with damage to both the hippocampus and subiculum displayed impairments that were greater than those produced by either hippocampus or subiculum lesions alone (Janard, 1989). Thus, the connections between the hippocampal formation and other cortical and subcortical brain structures mediated through subiculum are also important for hippocampal-dependent memory (Olton et al., 1982). However, in the present study there was a significant difference between the dorsal hippocampal lesions and VSub lesion. VSub lesion had less impairment probably because ventral hippocampus as such is less involved in mediating spatial learning and memory.

The dorsal, but not ventral hippocampus is critical for spatial memory. The existence of relatively direct connections between hypothalamic nuclei and ventral hippocampus suggests that the ventral hippocampus may be involved in acquisition of information regarding internal cues (hunger). Dorsal hippocampus lesion impairs the formation of spatial memory (Bryan and Michael, 1998). This may be one of the reasons for less impairment observed in VSub lesioned rats.

Another possible reason is that when VSub is lesioned existence of an intact dorsal hippocampus is possible, and it can still help the acquisition of spatial learning and memory. When we consider this issue we also need to see the possibility of cellular damage that can occur in CA1 and slightly less in CA3 areas due to VSub lesion (Govindaiah et al., 1997; Rao et al., 2001). So this cellular damage in CA1, CA3 and associated areas may be responsible for the impairment seen in VSub lesioning. But this impairment can be less than a direct lesion in the CA1 or CA3 areas, because during direct lesion not only cells but also fiber tract passing through will also be damaged, especially in electrical lesioning, which is adopted in the present study. Also when CA1, CA3 and associated areas are damaged it will also in turn cause cellular damage in subiculum. All these factors considered together gives a possible explanation for decreased impairment in VSub lesioned rats compared to dorsal hippocampal lesioned rats.

In conclusion for this subsection, the present study suggests that the subiculum is found to be an important area for spatial information coding and processing during the early stages of learning in rats. Also adopting of dual task procedure did not provide any advantage to counteract the lesion effects.

With this section we wrap up the discussion of the thesis. Conclusions derived from this thesis is listed in the next section.