HYPERGLYCEMIA INDUCED COGNITIVE AND BEHAVIORAL CHANGES IN TYPE 1 DIABETES MELLITUS OF EARLY ONSET

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Abstract: Central nervous system is not spared by the deleterious effects of diabetes mellitus, a metabolic catastrophe. Central effects are less well documented and studied than peripheral deficits. Long-standing concern about the hazardous effects of diabetes on CNS has enhanced with the increasing incidence of T1DM in children. Diabetic encephalopathy, in the younger age group will have serious consequences on healthcare, education and their performance during the productive life span. A meta-analysis showed cognitive impairment and behavioral changes, mainly reflecting in diminished mental activity and elevated levels of anxiety, depression and fear complex in Type 1 diabetic rats as well as in humans. This may have an important implication for school performance of children with early onset type of IDDM, in whom hyperglycemia induced impairment of complex cognitive function is seen. The questions that still remain unresolved are contribution of different disease variables such as duration of diabetes, levels of glycemic control and development of neuropsychological impairment. There is a need for elaborative research on the issue of hyperglycemia induced diabetic encephalopathy. Molecular studies may bring more focus on pathogenicity and hence, the line of treatment for such cognitive deficits. There is a necessity for the identification of active fractions or phytochemical constituents of nootropic herbs. Further studies are required to understand the mode of action of putative neurocognitive enhancers. The knowledge gathered in the present article may facilitate the researchers to explore more into diabetic encephalopathy related studies.

Key words: diabetic encephalopathy, learning and memory, anxiety, herbs, mazes, cognition

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Introduction: Diabetes is reported to be associated with cognitive disruption. The impact of diabetes mellitus, type 1 in particular, on the CNS has gained more attention in the recent past. A number of clinical observations suggest that, "CNS is not spared by diabetes"[1]. Cognitive deficits are frequently seen in patients with T1DM. The most common cognitive deficits identified are slowing of information processing speed[2] and worsening psychomotor efficiency[3]. Deficits in motor speed[4], vocabulary[5], general intelligence[6], visuo construction, attention[5], motor strength, memory[3] and executive function[6] have also been noted. In addition, slowing of all cognitive function, an increased number of mental subtraction errors[7], loss of inhibition and focus[8], impaired speed of information processing, decreased attention and working memory[9] have been observed during acute hyperglycemic phase in diabetic patients.

The brain is a fascinating organ, accounting for only 2 percent of our body weight but utilizes roughly 20 percent of our daily calories. Glucose is the only fuel normally used by brain cells. Brain depends on the bloodstream to deliver a constant supply of this precious fuel. Hence, cerebral glucose dysmetabolism in diabetes results in impairment of cognitive and behavioral functions. Severe hypoglycemia as well as chronic hyperglycemia affects cerebral glucose metabolism and neurotransmitter profiles in certain areas of the brain. Diabetes can impair the cerebral blood flow[7] affecting the neural structures irreversibly. These vascular insults leads to cerebrovascular diseases, which in turn will cause selective neuropsychological deficits, especially impaired learning and reduced memory[10]. Many studies link the cognitive deficits in diabetes to hyperglycemia induced end organ neuronal damage, dyslipidemia, amyloidopathy andTaupathy[11-13].Many

studies have stated that the cerebral dysmetabolism also affects the behavioral functions. The raised anxiety levels with the increasing duration of diabetic state in the rats could be attributed to 5HT (5-hydroxytryptamine), AC 8 (adenylyl cyclase type VIII) and TIP 39 (Tubero-infundibular peptide of 39 residues) deficiencies[14-17].

Sima *et al.,* (2009) provided conceptual depiction of temporal inter-relationship of pathogenetic mechanisms emanating from hyperglycemia and insulin deficiency in type 1 diabetic encephalopathy. Hyperglycemia leads to activation of thepolyol pathway and advanced glycated end products (AGEs), with up regulation of receptors for AGE (RAGE) and activation of innate inflammatoryfactors. Suppressed insulin signaling leads to defective expression of insulin like growth factor (IGF), nerve growth factor (NGF) and their respective receptors.Withdrawal of trophic factors results in early neurobehavioral deficits due to neurite degeneration and loss of presynaptic connections. Innate inflammatory activities and suppressed insulin signaling result in oxidative and apoptotic stresses, eventually resulting in apoptosis and cell loss of both neurons and oligodendroglial cells, with consequent gray and white matter atrophy and cognitive deficits[15].

However, the contribution of disease duration in inducing cognitive dysfunction has not been studied extensively, despite patient's reports on negative effects with respect to chronicity of hyperglycemia[7]. There is a need for understanding the hyperglycemia induced neuronal injury over a period of time. The clinical implication of such studies shows the importance of diagnosis and effective management of juvenile diabetes at its initial stage itself to prevent irreversible CNS damage in young children.

Learning, memory and emotional behavior

There has been a knowledge explosion about the cellular and molecular basis of learning and memory in several species, including animals and humans. However, much has to be explored in this area, as we still do not know comprehensively how new information is perceived, stored, consolidated, retrieved or forgotten over a period of time. The next couple of decades are likely to bring much greater understanding of learning and memory and hence, our ability to manipulate these pathways by various cognitive enhancers will undoubtedly increase. The central mechanism thought to underpin memory is synaptic plasticity with a well-balanced interplay of neurotransmitters. In a nutshell, the learning, memory and behavioral modifications are generally attributed to new synapse formation (synaptogenesis) or loss, the proliferation of new neurons (neurogenesis) or neuronal cell death (neurotoxicity and apoptosis) or synaptic plasticity. Each process provides the important possible target for early therapeutic intervention to enhance cognition in disease-associated cognitive decline.

1. Definitions

Learning is the process of acquisition of knowledge and skills, while memory is the process by which the acquired information is encoded, stored and later retrieved. Consolidation is nothing but the transformation of newly acquired short memories into more stable long term memories[18]. Behavior is the result of the interaction between genes and the environment. Learning and memory can be enhanced by behavioral experiences. In humans the most important mechanisms by which the environment alters behavior are learning and memory. The capability of turning the experience of either aversive or rewarding events into long lasting memories is important for the survival of an organism.

2. Classification of memory

Memories (m) can be classified according to many different criteria; function (working vs.reference m.), content (declarative/explicit vs. procedural/implicit m.), duration (immediate or short-term vs. long-term or remote m.), nature (associative vs.non-associative m.), or motivation (appetitive/reward vs. aversive m.)[19]. However, many cognitive psychologists have emphasized on implicit memory and explicit memory[20]. Implicit or non-declarative memory is the procedural information about how to perform something. It is a memory

that is recalled unconsciously and is not stored with respect to time and place. Hence, training reflexive motor or perceptual skills are based upon typical implicit memory. Skills, habits and priming are some of the examples of implicit form of memory. Explicit memory is the memory of facts and events, which is recalled by a deliberate, conscious effort. Factual knowledge of people, places, things and their meaning can be verbally declared, so it is also referred as declarative memory. Explicit memory is highly flexible and involves the association of multiple chunks of information. In contrast, implicit memory is more rigid and tightly connected to the original stimulus conditions under which the learning occurred. The psychologist Endel Tulving further classified explicit memory as episodic (a memory for events and personal experience) or semantic (facts).

3. Specific brain areas associated with memory

In the mid nineteenth century, clinical neurologists studied brain lesions at autopsy to discover where particular brain functions are located. They regarded their experiences with patients as "natural experiments" in brain function, as most of the early evidence relating cognitive functions to the association areas came from clinical studies of brain-damaged patients. Many studies using experimental animals have provided important insight into the neural mechanisms at systems, cellular and molecular level, that underlie the complex phenomenon of memory. Experimental animals can be studied both by stimulating or ablating a specific area and also by using genetically modified rodents such as knockout mice.

Sir Wilder Penfield, a neurosurgeon, was the first person to present evidences that memory processes might be localized to specific regions of the human brain. He found that electrical stimulation of the temporal lobes produced what he called an "experiential response" a coherent recollection of an earlier experience. Brenda Milner, a colleague of Penfield, studied the effects of bilateral removal of temporal lobes in a patient. The removal of the medial temporal lobes left him with a quite specific memory deficit. This type of memory deficit is popular as amnesia. Such deficits in explicit memory are usually in lesions number of regions, including the temporal lobe, the ventral and medial temporal cortex, the amygdala and the hippocampal formation (the hippocampus proper, the subiculum and the dentate gyrus) as well as the surrounding entorhinal, perirhinal, and parahippocampal cortices[21].

4.Neuronal circuits in memory

The master of neuronal orchestra is "hippocampal learning system", consisting of sub sectors - cornuammonis (CA1-CA4), dentate gyrus and entorhinal cortex. The knowledge stored as explicit memory is first acquired through processing in one or more of the three polymodal association cortices (prefrontal, limbic, and parieto-occipital-temporal cortices) that synthesize visual, auditory and somatic information. From there, the information is conveyed in series to the parahippocampal and perirhinal cortices, then to the entorhinal cortex, dentate gyrus, hippocampus, subiculum, and finally, back to entorhinal cortex. From the entorhinal cortex, the information is sent back to the parahippocampal and perirhinal cortices and finally back to the polymodal association areas of the neocortex.

Thus, in processing information for explicit memory storage, the entorhinal cortex has dual functions. First, it is the main input to the hippocampus. The entorhinal cortex projects to the dentate gyrus via the perforant pathway and by this, provides the critical input pathway through which the polymodal information from the association cortices reaches the hippocampus. Second, the entorhinal cortex is also the major output of the hippocampus. The information coming to the hippocampus from the polymodal association cortices and that coming from the hippocampus to the association cortices converge in the entorhinal cortex. Hippocampus is one of the most important cerebral structures for almost all cognitive phenomena such as, spatial learning and memory[22], declarative memory, contextual processing and episodic memory[23], long-term memory and relational processing[24].

Hippocampus is also an important component in the control of autonomic and vegetative functions such as adrenocorticotropin secretion[25].

e. Role of hippocampus in spatial learning and memory

The archicortical structure is termed as hippocampus by the great anatomist G. C. Aranzi, because of its close visual resemblance to a sea horse. A century agoin 1900, the Russian scientist, Vladimir Bekhterevfor the first time, highlighted the possible role of hippocampus in memory, based on his observation that a patient with a lesion around the hippocampus has profound memory deficits. Hippocampus has received most attention from the neurocognitive scientists, as it has got a pivotal role in spatial learning[22]. In mice and rats, lesions of the hippocampus interfere with memory for space and context, whereas single cells in the hippocampus encode specific spatial information. The right hippocampus seems to be greatly involved in this representation and the left hippocampus is concerned with verbal memory. An experimental rodent with a lesion in hippocampus was found to show impaired performance in Morris water maze with a hidden platform[26].

Spatial learning is the ability to encode, store and retrieve information about spatial locations, configuration or routes. Rats learn to perform a given spatial task by using so called “cognitive maps”. In 1978, O’ Keefe and Nadel, proposed a cognitive map theory, which postulates that a mental representation of allocentric space was created by hippocampus. This observation was later supported by the extensive studies on place cells of hippocampus, which fire rapidly during the place learning by the animals[24]. Many neuroscientists attributed memory processing to the hippocampus. Hippocampal theta rhythm has been implicated in synaptic plasticity, memory encoding and retrieval of information.It was predicted that hippocampal-dependent memories are encoded in the neocortex during REM sleep. The hippocampal-neocortical dialogue during sleep was found to be essential for the transfer of hippocampal- dependent memories in to hippocampal-independent one[28].

Field potential studies do provide the useful information about the role of supporting structures like subiculum and entorhinal cortex[29] in enhancing the regularity and amplitude of theta activity in CA1 area of the hippocampus, following spatial learning in rats. Thus, the enhancement of theta power could be associated with information processing in the form of a spatial map in hippocampal dependent spatial navigation tasks[30].

In summary, memory processes for many types of learning involve several brain structures. For example, learned changes of the vestibulo-ocular reflex appear to involve at least two different sites in the brain. Explicit learning involves neocortical structures as well as the hippocampal formation.Long-term storage of explicit memory requires the temporal lobe system. Implicit memory involves the cerebellum, amygdala and specific sensory and motor systems recruited for the task being learned.

f. Long term potentiation

The hippocampal tri-synaptic pathway consists of three major neuronal paths namely; Perforant pathway, Mossy fiber pathway and Schaffer collateral pathway. These pathways allow information to flow in from the entorhinal cortex and out to either the subiculum or the fornix[21]. In 1973, Timothy Bliss and Terje Lom, discovered that each of these pathways is remarkably sensitive to the history of previous activity. The mammalian brain slice preparation, hippocampal slice in particular, is widely used to study synaptic plasticity mechanisms such as long term potentiation (LTP) and long term depression. LTP can be studied in the intact animal, where it can last for days and even weeks. It can also be examined in cell culture for several hours. A brief high-frequency train of stimuli to any of the three major synaptic pathways increases the amplitude of the excitatory postsynaptic potentials in the target hippocampal neurons. The facilitation is called “long-term potentiation”. The LTP inducing stimulus is referred to as “Theta burst stimulation” consisting of two trains of

burst, each burst consisted of 100 pulses (each pulse of 100 msec. duration, 100 Hz with 200msec. inter-burst interval)[31]. LTP is a synaptic mechanism for maintaining a coherent spatial map over time and so, defects in LTP interfere with spatial memory.

The perforant fiber pathway from the entorhinal cortex forms excitatory connections with the granule cells of the dentate gyrus. The granule cells give rise to axons that form the Mossy fiber pathway, which connects with the pyramidal cells in area CA3 of the hippocampus. The pyramidal cells of the CA3 region project to the pyramidal cells in CA1 by means of the Schaffer collateral pathway. LTP is non-associative in the Mossy fiber pathway and associative in the other two pathways.

g. Recent advances in cognition enhancers

Many different strategies are proposed to enhance cognition. Most interventions target eitherdisease pathologies or the processes underlying normal cognition, particularly synaptic plasticity.Strategies and treatments for cognitive enhancement include general measures such as exercise and environmental enrichment, nutrients, herbal medicines, pharmaceuticals and electromagnetic interventions like trans-cranial magnetic stimulation and brain-computer interfaces.

i **Neurochemicals**

Many neurochemicals play apivotal role in cognitive and behavioral modifications. Some of the extensively studied chemicals include glutamate, acetyl choline, dopamine, serotonin, histamine and GABA. Cholinergic transmission dominates among all the other neuronal pathways involved in cognition. Many new cognitive enhancer drugs in development target acetylcholine. MKC231 represents a new class of agent thought to enhance cholinergic neurotransmission by increasing choline uptake and by reversing cholinergic deficits. It also offers protection against calcium induced neurotoxicity. The cholinesterase inhibitor phenserine, which also may reduce toxic β-amyloid[32] is in human trials. The combined cholinesterase inhibitor and monoamine oxidase inhibitor ladostigil, which may have neuroprotective, antidepressant and cognition-enhancing properties[33,34]. Another theoretical approach to increasing cholinergic transmission is the stimulation of muscarinic receptors, especially with M1 agonists[35].

ii Other molecular targets

Several other strategies targeting molecular messengers that are involved in cognitive processes inside neurons might prove useful in states other than neurodegeneration. These include agents acting on the protein kinase C that modulate effects of stress on working memory[36]. CEP1347 and AS601245 inhibit certain protein kinases, thereby enhancing cognition especially in Alziemer's disease. CPI1189 inhibits the potentially damaging immune chemical tumor necrosis factor (TNF)-α. One key strategy aims to mimic or enhance the activity of neurotrophic factors such as NGF, glial-cell-line-derived neurotrophic factor, and neuroimmunophilin ligands (e.g. GPI1485 for PD)[37]. One action of antidepressants is proposed to be neural growth due to release of neurotrophic factors like BDNF and FGF[38].One of several strategies is to inhibit amyloid formation, which depends on the breakdown of amyloid precursor protein by β- and γ-secretase enzymes. R-flurbiprofen lowers levels of β-amyloid, perhaps by altering secretase activity [39].

iii Genome and stem cells

The potential is immense for therapeutic strategies that target the genome, use cell replacement, or both [40]. In the next two decades, science in this area is likely to make major advances, although few successful therapies are expected, given the poor success rate over the past decade or so. Currently, the patients with Alzheimer's disease (AD) are treated either with their own re-implanted skin cells engineered to carry the NGF gene, or with a virus to deliver the gene directly into the body. Various strategies

are under study to use stem cells to replace dead neurons in neurodegenerative disease.

iv Dietary supplements and pharmaceuticals

Some researchers have recommended dietary supplements to improve cognition, including 'nutraceuticals' – dietary components or similar that act like drugs. The summary of specific dietary supplements reviewed by Cochrane Dementia and Cognitive Improvement Group (CDCIG) includes folate, thiamine, lecithin, dehydroepiandrosterone (DHEA), alpha-lipoic acid and acetyl-L-carnitine.The CDCIG also recommends certain pharmaceuticals that act on cognition and those include donepezil, galantamine, rivastigmine, nicotined-cycloserine, memantine, nimodipine, propentofylline, selegiline, piracetam, hydergine, nicergoline and vinpocetine [41].

v. Herbal preparations

Several studies have shown the potent nootropic activity of herbs. Many of these herbs are also mentioned in Ayurvedic and Chinese literature [41] (Table 1).

Table 1 : Some putative cognition-enhancing herbs [41]

Acorus calamas	*Embelia ribes*	*Nicotiana tabacum*
Angelica archangelica	*Emblica officinalis*	*Paeonia emodi*
Asparagus racemosus	*Eugenia caryophyllus*	*Panax ginseng*
Bacopa monniera	*Evodiarutaecarpa*	*Piper longum*
Biota orientalis	*Galanthusnivalis*	*Polygala tenuifolia*
Boerhavia diffusa	*Ginkgo biloba*	*Polygonum multiflorum*
Celastrus paniculatus	*Glycyrrhiza glabra*	*Pongamia pinnata*
Centella asiatica	*Huperzia serrata*	*Rosmarinus officinalis*
Clitoria ternatea	*Hydrocotyl asiatica*	*Salvia lavandulifolia*
Codonopsi spilosula	*Lawsonia inermis*	*Salvia miltiorrhiza*
Convolvulus pluricaulis	*Lycoris radiate*	*Schizandra chinensis*
Coptis chinensis	*Magnolia officinalis*	*Terminalia chebula*
Crocus sativus	*Melissa officinalis*	*Tinospora cordifolia*
Curcuma longa	*Nardostachys jatamansi*	*Withania somnifera*

Role of amygdala in behavioral modification

Extensive lesion studies suggest that the amygdala plays a crucial role in fear conditioning, anxiety, attention and neurotransmission. It is mainly mediated through N-methyl D-aspartate (NMDA) and α-amino – 3 – hydroxyl – 5 – methyl-4-isoxazolepropionic acid(AMPA) receptors [42]. The amygdala's activity was studied either by manipulation of its actions or by observation of different methods such as lesions, electrical brain stimulation, neurochemical intra amygdaloid injections, and single-unit recordings.

It is a well-established fact that the amygdala is crucial in various kinds of motivated and emotional behavior and related autonomic responses, which critically depend on learning and memory. Amygdala is an important structure in acquiring and storing associative memory by which animals recognize and evaluate the biological significance of a stimulus. This information is then transferred to the brainstem executing system.The baso-lateral and central nuclei are key portionsin amygdala. Here various sensory modalities converge and perform critical functions in acquiring and storing long-term associative memory [43].

Amygdala is structurally diverse, comprising of approximately 13 nuclei. The multinuclear complex is located at the medial edge of the temporal lobe. Each amygdaloid nucleus is different from another in their cytoachitecture, chemoarchitecture and connection. In 1987, Price et al., has classified amygdaloidnucei in to three major groups such as; the deep or basolaterlal group, including lateral nucleus, basal nucleus and accessory basal nucleus; the superficial or cortical- like group, which includes cortical nuclei and nucleus of the lateral olfactory tract; the centromedial group composed of the medial and central nuclei [44]. However, the intercalated cell masses and amygdalo-hippocampal area do not fall into any of these three groups and are listed separately. The amygdala is involved in certain types of learning and memory as well as emotional and motivational aspects of behavior. The amygdala and hippocampus govern two independent memory systems that interact when emotions meets memory. Amygdala plays a major role in memory, attention, interpretation of emotional significance of sensory stimuli, perception of the body movements and generation of emotional aspects of dream[45]. Amygdala also plays a pivotal role in the enhancement of memory formation of emotionally arousing events[46].

Monkeys with temporal lobe lesions exhibited an absence of anger and fear, increased exploration, visual agnosia, hyperorality, hypersexuality and loss of social interactions. These emotional disturbances are collectively known as Kluver-Bucy syndrome[47]. Amygdaloid lesions disrupt the acquisition, but not the retention of both active avoidance and passive avoidance conditioned responses in rabbits. In addition to the direct role of the amygdala in learning and memory, activation of the amygdala also has a modulatory effect on the acquisition and consolidation of memories that evoke an emotional response [48]. The cascade of events in memory modulation by emotionally relevant sensory stimuli is known to occur in interconnecting pathways between amygdala, hippocampus and parahippocampal region[46].

Many studies suggest the possible role of neural inputs from the amygdala in modulation of synaptic plasticity in the hippocampus. This is based on the observation that effects of lesions in the amygdala impair the long term potentiation in hippocampus. The magnitude of LTP following tetanic stimulation in ipsilateral lesion of the basolateral nuclei was significantly smaller than that of the intact control rats and also dentate gyrus. LTP was attenuated by lesion of the basomedial amygdaloid nucei [49]. Thus, many studies have shown that the amygdala enhances the memory formation when associated with meaningful emotional responses.

Methods used for assessing cognitive and behavioral functions

Many experimental apparatus have been designed and developed to assess cognitive and behavioral functions in animals since the early 20th century. Most widely accepted ones are mazes. Rats are particularly gifted at exploring mazes and their ability comes from their evolutionary history. Rats are small burrowing rodents that have spent millennia digging and finding their way around underground tunnels. It is no wonder they have a knack with mazes.

Thousands of studies have examined how animal perform in different types of mazes, from elevated plus maze to radial arm maze to water maze. Maze studies helped to uncover general principles about learning, memory and behavior that can be applied to many species, including humans. Mazes are used to determine whether different treatments or conditions affect learning and memory in rats. These maze studies are used to study spatial learning and memory in rats. Some mazes like elevated plus maze is also used to assess anxiety levels. Ethological measures such as rearing, grooming and boli of excreta help to evaluate other behavioral changes in animals. Many researchers have developed several experimental apparatus to study cognitive and behavioral changes[110] (Table 2).

Elevated plus maze (EPM) is a widely accepted test in the study of anxiety in rodents and other animal models[50]. The EPM

is sensitive enough to detect deficits in spatial learning and memory in rats.

Passive avoidance (PA) test is a widely accepted test to investigate the associative learning and memory trace for an aversive event [51]. Inhibitory avoidance involves learning to suppress a natural response in order to avoid an aversive stimulus. Learning session involves multiple trials and animal is punished for natural exploratory drive with a non-lethal, electric footshock. PA involves both an explicit, associative component and an operant-like conditioning component (to the shock) of implicit memory to certain extent. In PA, ethological parameters such as rearing, grooming and boli of excreta suggest behavioral changes in animals.

Table 2: Methods used for assessing cognitive and behavioral functions[19]

Memory (Implicit)	Habituation, sensitization	Tone conditioning
	Classical conditioning	Fear conditioning
	Operant conditioning	Active avoidance test, Passive avoidance test
Memory (Explicit)	Spatial memory	Morris water maze, 8-arm radial maze
	Item memory	Object recognition test
Behavior	Habituation	Open field test
	Aversive task	Step-down Inhibitory, Passive avoidance apparatus
	Anxiety	Elevated plus maze , Light –dark arena
Miscellaneous	Motor performance	Rot rod test, Pole climbing
	Pain sensitivity	Tail flick test Hot Plate and/or Paw Pressure test

The MWM is a well-established and widely used spatial memory test for rats and mice. Small rodents are natural swimmers and also noticeable for their spatial learning abilities, supposedly dependent upon visual cues. Water Maze and Radial Maze have been widely accepted as major spatial learning paradigms[52,53]. Several variants of each of these tasks may be used in order to obtain abundant behavioral indexes of contextual/spatial habituation, cue-driven navigation, operant-like navigation responses learning, and/or decision-taking. In MWM task, the animal learns to swim in a water tank, guided by external cues, and find a submerged platform[26]. Based upon spatial information, this animal learns how to escape to a platform, so this task may be classified as explicit, associative memory with operant-like spatial learning. When released at a certain location around the pool, the animal must use contextual (spatial) cues; markings on the walls of the room in which the pool is located, to find the hidden platform. This task requires the hippocampus and the animal with normal, intact hippocampus is expected to find the platform earlier than the animal with a lesion/damage to hippocampus. Mice that lack the NMDA receptor in the CA1 region of the hippocampus have a defect in LTP and in spatial memory.Thus, parameters such as reduced transfer latency and more time spent in the target quadrant are suggestive of improvement in the memory[54].

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