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Effect of Long term bilateral and unilateral vestibular stimulation in cognition in scopolamine-induced dementia

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ABSTRACT

The aim of the study is to provide preliminary evidence on beneficial effects of long term caloric vestibular stimulation as an alternative therapy for enhancement of cognition and motor activity as well as delay/prevent dementia symptoms in scopolamine induce dementia in a rat model. Adult male Wistar albino rats were chosen in the current study. Scopolamine was the drug of choice to induce dementia and donepezil was used as a standard drug in this study. Vestibular stimulation method was Caloric vestibular stimulation which was administered by injecting hot water of 45 degrees centigrade into the middle ear cavity with the help of syringe for 60 days (both bilaterally and unilaterally). In conclusion, bilateral and unilateral left vestibular stimulation had found to beneficial in improving spatial memory, motor control and various cognitive neurotransmitter levels in scopolamine-induced dementia rats. But the mechanism is largely unclear and unknown. Further detailed studies should be conducted in this area to explore mechanisms of action.



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INTRODUCTION

Dementia had always misunderstood with "age-associated memory impairment," which is considered a normal part of aging. Dementia is a group of neurodegenerative diseases which are entirely different from age-related memory loss. Dementia is an umbrella term that conceptualizes the symptoms associated with a decline of both short and long term memory together and the progressive disturbances in other cognitive functions such as

abstract thinking, judgement, language, recognition and personality too. Dementia-associated disturbances severely compromise all aspects of a person's life social life and family relationships (Feast et al.,2016). The patient is permanently disabled to do their own day to day activities. This disability progresses unlimitedly if leave unattended and gradually need full-time care giver's assistance. It causes great stress to families and caregivers Physically, emotionally and economically (Richard Schulz and Paula Sherwood,2008). According to WHO, "47.5 million people have dementia Worldwide", and it is expected to "increase to 75.6 million in 2030 and 135.5 million in 2050". The proportion is high over 85 years of age and which is 20-40% of people. Among dementia, Alzheimer's disease is most common which accounts 40-60% and followed by vascular dementia. Lack of proper treatments or preventive measures makes this disease more tragic. Currently, dementia is managed by pharmacological and few non-pharmacological interventions, which is only

symptomatic treatment. Medical research and development are continuing to evolve in this area. The journey towards discovering effective new treatments or alternative therapies for dementia are full of challenges. But the neurological scientists are committed to developing new or alternative therapies without any side effects in order to prevent/delay dementia. The making developments through natural therapies like music therapy, pet therapy, art therapy, massage etc. (Art and Music Therapy for Alzheimer's Disease). We are making significant headway towards healing /slowing down of this disease.

Vestibular stimulation is one of the old but not well-explored technique in dementia research. The vestibular system is called the sixth special sense which is essential to maintain equilibrium and balance with respect to environment and gravity. Vestibular system is the first system to develop in a human embryo and rocking motion of mother's womb indirectly stimulates this system which facilitates the development of nervous system including motor development (Sprouts Child Development Blog; Clark et al.,1977) In 17th century itself Greeks and Romans used various vestibular stimulation techniques to cure 'phrenesis' and calm the anxious and depressed patients (Sailesh et al.,2016). Through various experiments in animals and human's area of vestibular research bloomed despite the fact of limited understanding of the neurophysiological mechanisms. In this era, vestibular stimulation has found to possess countless benefits like decreased self-stimulation and hypersensitivity, increased postural security, concentration and attentiveness, balance and body awareness, calming effects, reduction of abnormal muscle tone, improving motor skills etc. But the beneficial effects of vestibular stimulation in cognitive research is even more encouraging. Vestibular stimulation has been found to increase learning and memory in both animals and human experiments. The massive and extensive connection of the vestibular system to various important cognitive brain areas especially hippocampus, fronto-temporo-parital cortex, regulating important cognitive neurotransmitters and capability to suppress stress axis are the key mechanisms to improve cognitive health (Hitier et al.,2014). Though its pathways this technique always keep the brain inactivated state which indirectly stabilizes neurotransmitters. A direct example is according to Tai and Stan Leung et al.; vestibular stimulation has found to increase Ach level thereby promoting long-term potentiation in septo-hippocampal cells in the hippocampus (Tai and Leung,2012). Vestibular impairment has always found to be associated with changes in cognition, high rates of anxiety, depression, personality changes, attention deficits

etc. and moreover with hippocampal atrophy and reduction in brain volume. These findings underline the importance of the vestibular system in improving cognition (Sang et al.,2006; Jáuregui et al.,2008). Studies regarding the application of vestibular stimulation in neurodegenerative diseases are quite sparse. Since vestibular stimulation is simple, natural, easy to adopt, economic, non-time consuming; qualities of this technique are endless so that it can be used as an alternative or adjunct therapy in neurodegenerative disorders like dementia. Our study was undertaken to provide preliminary evidence for beneficial effects of long term bilateral as well as unilateral caloric vestibular stimulation as an alternative or add on therapy for enhancement of cognition and motor activity in scopolamine induce dementia in Wistar albino rats.

MATERIAL AND METHODS

Animals: A total of 36 healthy, adult male Wistar albino rats with body weight ranging between 150-200 g were used in the current study. Rats were housed in polypropylene cages (30 × 22 × 14 cm), fed with standard-chow and water ad libitum. The animals were kept at a temperature of 22 ± 3°C and a 12 h light/dark cycle as well as a constant relative humidity throughout the experimental period.

Rats were randomly assigned into six groups.

- G1: (n=6) Negative control group
- G2: (n=6) Positive control group -Scopolamine induced dementia
- G3: (n=6) Scopolamine induced dementia+ Donepezil
- G4: (n=6) Scopolamine induced dementia +bilateral hot water vestibular stimulation (60days)
- G5: (n=6) Scopolamine induced dementia +Unilateral Left ear hot water vestibular stimulation (60days)
- G6: (n=6) Scopolamine induced dementia+ unilateral right ear hot water vestibular stimulation (60days)

Scopolamine administration: 3mg/kg scopolamine is administered intraperitoneally for 7 days to induce dementia in Wistar rats (Jae-chul et al.,2018). The drug was purchased from Sigma-Aldrich (Bangalore, India).

Donepezil hydrochloride administration: As standard drug donepezil is used in our study. It was administered orally at a dose of 5 mg/kg for 14 days (Srinivasa Rao,2016). Donepezil hydrochloride was purchased from Sigma-Aldrich (Bangalore, India).

Caloric vestibular stimulation: The technique we used to stimulate the vestibular system is caloric vestibular stimulation. The procedure consists of

irrigating the middle ear cavity with hot water with a temperature of 45°C with the help of a syringe. We have administered hot water stimulation for 60 days (Horii *et al.*, 1994). In the present study, apart from stimulating both the vestibular system, we implemented unilateral left and unilateral right vestibular stimulation as well (right and left ear individually).

Behavioural tests

Elevated plus maze: The elevated plus maze for rats consist of two open arms (50 cm × 10 cm × 40 cm) and two enclosed arms (50 cm × 10 cm × 40 cm) extended from a central platform (5 cm × 5 cm) and the maze was elevated to a height of 58 cm from the floor. Transfer latency is measured by the time taken by the animal to move from the open arm into one of the covered arms with all its four legs. If the animal did not enter into one of the covered arms within 3 min, it was gently pushed into one of the two covered arms and TL was assigned as 3 min. Since transfer latency (TL) has been validated as a cognitive measure, we have assigned as a cognitive parameter in our study. Zero-day values are recorded in all groups. Retention of this learned task (memory) was examined after scopolamine-induced, standard drug treatment and 60 days of bilateral and unilateral vestibular stimulation (Itoh *et al.*, 1990).

Morris Water Maze test: The Morris water maze (MWM) is a validated tool for assessing spatial learning and memory. The basic principle behind this test is how well rodents use the distal cues to navigate from start locations around the perimeter of an open swimming arena to locate a submerged escape platform. Richard Morris developed 'the water maze' in 1984. The main component of the water maze was an open circular pool of about 214 cm in diameter, about 91cm deep and 10cm² platform and filled approximately half-way with water. Water maze was filled up with tap water, and the temperature was maintained close to 26±1°C. Pre-training trials were done in order to "teach" the animals about these properties of the task. After pre-training Maze was filled up in such a way that the platform gets immersed one inch below the water. 125 millilitres of non-toxic white tempera paint were used to make the water opaque. Each animal was undergone three consecutive 3 trials/day for 4days. The water maze had 4 starting positions: north, south, east, or west. Based on the position of the platform start point is semi-randomly selected and made sure it is distal start positions. Rats were carefully lowered by supporting it with our hand and brought it down gently into the water by tail-end first so that no stress for the animal by dunking it in head first. The animal is allowed to swim for 120seconds. Experimentor remains stationary in a

constant location. If the animal couldn't found the hidden platform, it is recorded as 120 seconds, and the animal was placed in the platform for 15 seconds. 15 s has become common inter-trail interval and produced good learning. Eventually, as the trails continue, they learned to search the platform and climb up. Once the rodent reached the platform, recorded the time. Trails were done before the intervention, and a retention test was carried out after 60days of intervention (Bruno *et al.*, 2014).

Actophotometer: Locomotor behaviour is measured through actophotometer in our study. Horizontal locomotor activities of control and test animals were recorded for a period of 5 min using Medicraft actophotometer, model No: 600-40, S. No: PA-0149, India. Based on the beam breaks by movement of the rat's locomotor activity counted arbitrarily. Actophotometer test in rats "before and after administration of Scopolamine and 60days of caloric (both bilateral and unilateral) vestibular stimulation" was used to validate motor coordination activity (Dews, 2953).

Biochemical parameters: Acetylcholine and Acetyl Choline Esterase were measured by spectrophotometry. The animals were sacrificed after treatment by euthanasia. The whole brain was removed immediately and placed in ice-cold saline. The tissues weighing 0.5 g were homogenised with motor driven Teflon coated homogeniser with 5 mL of ice-cold 0.1 M phosphate buffer pH 8.0 to get 10% homogenate. The homogenate was centrifuged at 10,000 rpm for 20 min at 5°C. The supernatant was collected and used for the ex-vivo neurotransmitter estimation.

Estimation of brain acetylcholine esterase: The whole-brain activity Acetyl Choline Esterase was measured by spectrophotometry based on the method of Ellman *et al.*, 1961.

Procedure: 25 µL of tissue homogenate was mixed with 75 µL of phosphate buffer (0.1 M pH 8.0), and 75 µL of Dithiobisnitrobenzoic acid (DTNB) (0.01 M) and the absorbance is measured at 415 nm after 5 min of incubation at room temperature. 25 µL of the substrate, Acetylthiocholine iodide (ATCI) was then added, and the absorbance was measured again for 3 min at an interval of 1 min. Change in absorbance per minute was thus determined.

Estimation of brain acetylcholine levels: Acetylcholine content in all the tissues was estimated by the method of Hestrin. Ach reacts with ferric chloride, a brown colour developed was read at 540 nm against the reagent blank. The acetylcholine content was expressed as moles of acetylcholine/gram wet weight of tissue (Hestrin, 1949).

Study setting: The current study was conducted at Little Flower Medical Research Centre, Angamaly, Kerala, India.

Ethical consideration: The experimental protocol was approved by the Institutional Animals Ethics Committee (IAEC) of Little Flower Medical Research Centre. Animal care was taken as per the guidelines of CPCSEA.

Data analysis: Data was analysed by using SPSS 20.0 version. One-way analysis of variance was applied to observe the significance of the difference between the groups. Bartlett's test for equal variances was applied for post hoc analysis. A p value less than 0.05 was considered significant.

RESULTS

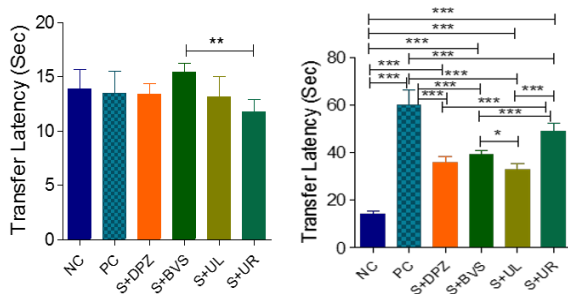


Figure 1: Transfer latency on elevated plus maze before and after treatment in scopolamine-induced dementia in Wistar albino rats. (Data was presented as Mean±SD. *P<0.05 is significant, **P<0.01 is significant, ***P<0.001 is significant). (NC: Negative Control; PC: Positive Control; S+DPZ: Scopolamine+ Donepezil group; S+BVS: Scopolamine+ Bilateral Vestibular Stimulation group; S+UL: Scopolamine+ Unilateral Left Vestibular Stimulation group; S+UR: Scopolamine+ Unilateral Right Vestibular Stimulation group)

Figure I explains the transfer latency on elevated plus maze before and after caloric vestibular stimulation in scopolamine-induced dementia in Wistar albino rats. There was no significant difference in transfer latency between the groups before the treatment. Transfer latency was significantly increased in positive control when compared with negative control (P<0.001). Transfer latency in the standard treatment group is significantly decreased in comparison with the positive control (P<0.001). But when compared with negative control there is still significant increment (P<0.001) in the standard treatment group. In all intervention groups, transfer latency is significantly reduced when compared to positive control (P<0.001). However, in comparison with the negative control, transfer latency is still significantly higher in all intervention groups (P<0.001). For Scopolamine+ bilateral vestibular stimulation group (60days) and unilateral left vestibular stim-

ulation group (60days), there is no significant difference with the standard treatment group. Whereas transfer latency in scopolamine+ unilateral left vestibular stimulation group is significantly reducing when compared with scopolamine+ bilateral vestibular stimulation group (P<0.05). In scopolamine+ Unilateral right, vestibular stimulation group transfer latency is significantly higher in comparison with standard treatment group, scopolamine+ bilateral vestibular stimulation and scopolamine+ unilateral left vestibular stimulation groups (P<0.001).

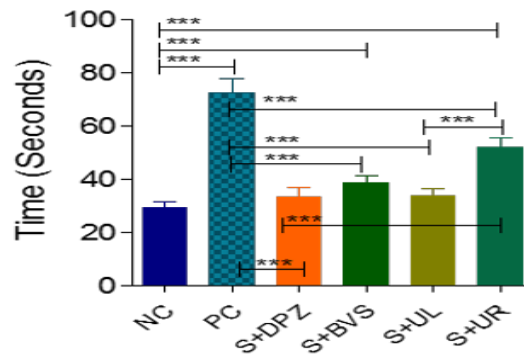


Figure 2: Escape latency in Morris water maze after intervention treatment in scopolamine-induced dementia in Wistar albino rats. (Data was presented as Mean±SD. *P<0.05 is significant, **P<0.01 is significant, ***P<0.001 is significant). (NC: Negative Control; PC: Positive Control; S+DPZ: Scopolamine+ Donepezil group; S+BVS: Scopolamine+ bilateral Vestibular Stimulation group; S+UL: Scopolamine+ unilateral Left Vestibular Stimulation group; S+UR: Scopolamine+ unilateral Right Vestibular Stimulation group)

Figure 2 explains escape latency in the Morris water maze test after caloric vestibular stimulation in scopolamine-induced dementia in Wistar albino rats. Escape latency is significantly increased in scopolamine treated rats when compared to negative control (P<0.001). All intervention groups including standard treatment group escape latency are significantly decreased in comparison with the positive control group (P<0.001). Scopolamine+ bilateral vestibular stimulation showed a significant increase in escape latency when compared to the negative control group whereas, no significant difference with the standard treatment group. Scopolamine+ unilateral left vestibular stimulation group has shown no significant difference with negative control as well as standard treatment groups. Escape latency in scopolamine+ unilateral right vestibular stimulation group is significantly high when compared to negative control, standard treatment group and scopolamine+ unilateral left vestibular stimulation group. Overall Scopolamine+ unilateral left vestibular stimulation group

found effective in decreasing escape latency among intervention groups.

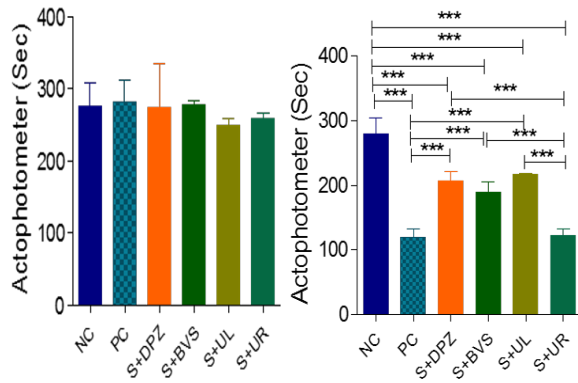


Figure 3: Actophotometer (sec) before and after treatment in scopolamine-induced dementia in Wistar albino rats. (Data was presented as Mean \pm SD. * $P < 0.05$ is significant, ** $P < 0.01$ is significant, *** $P < 0.001$ is significant). (NC: Negative Control; PC: Positive Control; S+DPZ: Scopolamine+ Donepezil group; S+BVS: Scopolamine+ Bilateral Vestibular Stimulation group; S+UL: Scopolamine+ Unilateral Left Vestibular Stimulation group; S+UR: Scopolamine+ Unilateral Right Vestibular Stimulation group)

Figure 3 explains locomotor activity score in Actophotometer before and after caloric vestibular stimulation in scopolamine-induced dementia in Wistar albino rats. There was no sign of locomotor scores before the intervention. Locomotor activity is significantly reduced in positive control in comparison with negative control ($P < 0.001$). Scores have significantly increased in the standard treatment group when compared to the positive control group ($P < 0.001$). However, in comparison with the negative control group, the score of scopolamine+ Donepezil is significantly lower ($P < 0.001$). Scopolamine+ bilateral vestibular stimulation and Scopolamine+ unilateral left vestibular stimulation groups show a significant increase in scores when compared to positive control ($P < 0.001$). But scopolamine+ unilateral right vestibular stimulation group didn't show any significant difference with the positive control group. However, compared with the negative control, scores were significantly lower in long term intervention groups ($P < 0.001$). Scopolamine+ bilateral vestibular stimulation and Scopolamine+ unilateral left vestibular stimulation groups show no significant difference from the standard treatment group. Scores in scopolamine+ unilateral right vestibular stimulation group were significantly lower when compared with negative control, scopolamine+ Donepezil, Scopolamine+ bilateral vestibular stimulation and Scopolamine+ unilateral left vestibular stimulation groups ($P < 0.001$) and showed no significant difference from positive control.

Figure 4 presents Acetylcholine levels in control and intervention groups. Acetylcholine level is expressed in mol/min/g of tissue. Acetylcholine level is significantly reduced in positive control followed by scopolamine administration in comparison with negative control ($P < 0.001$). In all intervention groups except scopolamine+ unilateral right vestibular stimulation group, acetylcholine level has found to increase significantly when compared with the positive control ($P, 0.001$). There is no significant difference between positive control and scopolamine +unilateral right vestibular stimulation group. Even with the negative control, all intervention groups except scopolamine +unilateral right vestibular stimulation group had no significant difference. In scopolamine+ unilateral right vestibular stimulation group acetylcholine level is significantly low when compared to negative control, scopolamine+ bilateral vestibular stimulation and scopolamine+ unilateral left vestibular stimulation groups ($P < 0.001$) and with standard treatment group p-value is 0.01 ($P < 0.01$).

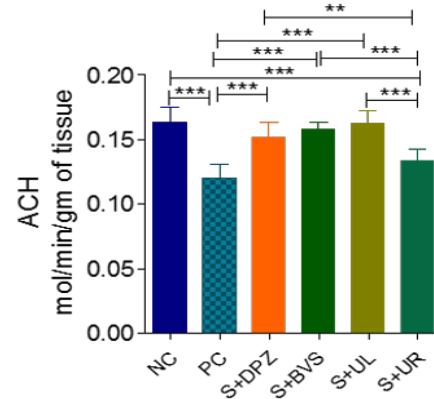


Figure 4: Acetylcholine levels in control and after treatment in scopolamine-induced dementia in Wistar albino rats. (Data was presented as Mean \pm SD. * $P < 0.05$ is significant, ** $P < 0.01$ is significant, *** $P < 0.001$ is significant). (NC: Negative Control; PC: Positive Control; S+DPZ: Scopolamine+ Donepezil group; S+BVS: Scopolamine + Bilateral Vestibular Stimulation group; S+UL= Scopolamine+ Unilateral Left Vestibular stimulation group; S+UR: Scopolamine+ Unilateral Right Vestibular Stimulation group)

Figure 5 explains the Acetylcholine esterase activity in Control and treatment groups. Acetylcholine esterase activity is significantly increased in Positive control when compared with negative control ($P < 0.001$). All intervention groups, Acetylcholine esterase activity is significantly reduced in comparison with the positive control ($P < 0.001$). Standard treatment group, scopolamine+ bilateral vestibular stimulation and scopolamine+ unilateral left vestibular stimulation groups had no significant difference with negative control. In scopolamine+ unilateral right vestibular stimulation

group acetylcholine esterase activity was significantly higher when compared with negative control, standard treatment, scopolamine+ bilateral vestibular and scopolamine+ unilateral left vestibular stimulation groups ($P < 0.001$).

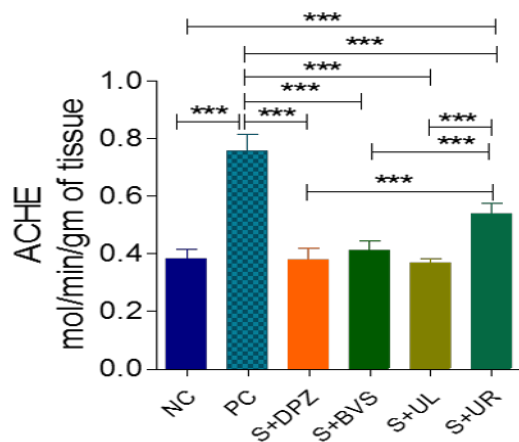


Figure 5: Acetylcholine esterase (AChE) activity in control and after treatment in scopolamine-induced dementia in Wistar albino rats. (Data was presented as Mean \pm SD. * $P < 0.05$ is significant, ** $P < 0.01$ is significant, *** $P < 0.001$ is significant). (NC: Negative Control; PC: Positive Control; S+DPZ: Scopolamine+ Donepezil group; S+BVS: Scopolamine+ Bilateral Vestibular Stimulation group; S+UL: Scopolamine+ Unilateral Left Vestibular Stimulation group; S+UR: Scopolamine+ Unilateral Right Vestibular Stimulation group)

DISCUSSION

The present study had carried out in order to give preliminary evidence of the beneficial effects of long term caloric vestibular stimulation in improving spatial cognition in scopolamine-induced dementia rats, especially unilateral left and bilateral vestibular stimulation. Though our study not only explored the extent of cognitive enhancement but also tried to extract the unique effects of unilateral vestibular stimulation. In our present study, we maintained six groups with selected cognitive behaviour as well as neurotransmitter assay as parameters. In our previous paper, it was explained the beneficial effects of short term (30days) caloric vestibular stimulation in cognition. Since the 30days of vestibular stimulation found to be effective in enhancing learning and memory in drug-induced dementia, we extended the duration to 60days in order to explore the long term effects. Even long term beneficial effects of vestibular stimulation are found even more promising in preventing dementia effects in rats

It has been found that 60 days of unilateral left and bilateral vestibular stimulation have significantly improved transfer latency, escape latency scores, Ach levels and decreased Acetyl Choline esterase

activity compared to positive control. But unilateral right vestibular stimulation had found not effective as unilateral left and bilateral vestibular stimulation. Unilateral Left ear stimulation was effective than bilateral as well as unilateral right ear vestibular stimulation in improving spatial memory and various neurotransmitter levels.

Vestibular stimulation has been using as a powerful and non-invasive therapy for a wide range of psychiatric and neurological conditions from ancient times by Greek and Roman physicians. Later on, by more and more understanding of the vestibular system, it has been revealed that vestibular stimulation extensively and massively connected to the cognitive areas of the brain especially hippocampus, basal ganglia, parieto-frontal cortices, cerebellum which creates its own neural network called vestibular cortices (Brandt and Dieterich, 1999). Especially the connection between the vestibular system and hippocampus is through four main pathways. Vestibular input has found to be vital for cognitive functions such as spatial functions, navigation and various types of memory in the hippocampus and cerebral cortex. As many lesion studies have proven that bilateral vestibular lesions lead to consequence like spatial memory deficits and atrophy of hippocampus itself (Brandt et al., 2005). The question might, therefore, be if, additional vestibular stimulation is provided, it can be beneficial in improving various functions. A large number of studies about vestibular stimulation had proven that this sensory organ is not just for equilibrium and balance but play a key role in various cognitive processes such as spatial cognition, memory, social cognition, decision making, space perception, attention etc. If we search the history of vestibular stimulation, it has already proven to enhance sensory and cognitive functions such as visual memory, verbal and spatial memory (Ferrè et al., 2013; Wilkinson et al., 2008; Falconer et al., 2012). Increases in blood flow had been found in many cortical regions including language areas by caloric vestibular stimulation (Bachtold et al., 2001; Fasold et al., 2002). There were Spontaneous improvements in repetition and comprehension is evident with caloric vestibular stimulation in brain-injured patients (Dieterich et al., 2003; Heiss et al., 2006). Various EEG studies in humans, as well as animals, underlines the proof of vestibular stimulation further improvises memory by the alteration in frontal beta power and hippocampal theta rhythm generation (Hamilton et al., 2011; Lee et al., 2014). Sharot and Phelps, 2004 reported that there is a positive effect on memory retention arousal by vestibular stimulation. (Sharot and Phelps, 2004; Leutgeb et al., 2005). Stochastic galvanic stimulation has been shown to alter the EEG synchrony patterns to enhance neural information

processing and computational goals (McDonnell *et al.*, 2011)). Aswathy *et al.* reported that caloric vestibular stimulation increases T-maze scores in dementia induced rats (Aswathy *et al.*, 2016). Repeated Noisy Galvanic vestibular stimulation enhanced water maze scores and hippocampal c-Fos-positive cells which is a neuronal activity marker in intracerebroventricular streptozotocin (ICV-STZ)-induced cognitive impairment rat model (Mansoureh *et al.*, 2016). Rotatory vestibular stimulation in a controlled way enhances spatial memory scores in the radial arm maze test (Devi *et al.*, 2017). These recent studies in rodents clearly reveal various types of vestibular stimulation could enhance learning and memory in dementia induced rats and healthy rats as well.

Acetylcholine is an ultimate neurotransmitter which involves in various functions like a wide range of cognitive functions, memory and arousal. (Jerusalinsky, 1997; Sarter *et al.*, 2005; Hasselmo *et al.*, 2006). The hippocampal cholinergic network is crucial for learning and long term memory formation and its retrieval (Mesulam, 1983). Ablation of septal cholinergic or systemic blockade abolishes dendritic long term potentiation and which impairs spatial learning and memory (Leung *et al.*, 2003; Walsh *et al.*, 1996; Shen *et al.*, 1996). Even the cholinergic theory of Alzheimer's disease supports the fact that the degeneration of cholinergic neurons in the hippocampus and basal forebrain including the medial septum play the main part in contributing to the cognitive deficits of Alzheimer's disease (Bartus *et al.*, 1982; Francis *et al.*, 1999). Running and walking had proven to enhance acetylcholine release and LTP of the basal dendritic synapses on hippocampal CA1 pyramidal cells compared immobility (Dudar *et al.*, 1979). Horii *et al.* have proven that caloric vestibular stimulation increases septohippocampal acetylcholine release by more than 100% of the basal rate (Horii *et al.*, 1994, 1995). Even Acetyl Choline esterase activity also highly altered in Alzheimer's and various forms of dementia. Acetyl Choline esterase activity has found abnormally high in Alzheimer's disease (Parihar *et al.*, 2004). Especially the hike of Acetyl Choline esterase levels around amyloid plaques and neurofibrillary tangles is a mystery, and it is a very common feature of AD neuropathology. Acetyl Choline esterase is known to promote A β aggregation. This A β -AChE complex increases the neurotoxicity of A β fibrils two fold than A β aggregates alone (Alvarez *et al.*, 1998; Ferrari *et al.*, 2001; Inestrosa *et al.*, 1996). But evidence suggests that as the diseases progress, there is a decline in Acetyl Choline esterase along with Ach and choline acetyltransferase (ChAT). But the current strategy for AD therapy is by inhibiting Acetyl Choline esterase ac-

tivity (AChE-I) (Kaduszkiewicz *et al.*, 2005). Vestibular stimulation is a natural therapy which improves learning and memory in normal as well as cognitive impairment subjects. In our laboratory experiments rotatory vestibular stimulation have found beneficial in decreasing the Acetyl Choline esterase level significantly in dementia rats (Devi *et al.*, 2017). In the current study also, caloric vestibular stimulation had found to be decreasing Acetyl Choline Esterase level significantly in scopolamine-induced dementia rats. There are not many studies conducted in order to explore the details of the mechanism behind this phenomenon.

Bilateral vestibular stimulation is used in almost all past studies in order to explore the vestibular connections and various beneficial aspects of brain function in neurodegenerative disorders. Mostly unilateral studies incorporated to establish areas of the brain is activated at the time of vestibular stimulation. Various fMRI and PET methods in humans and animals have proven that there is quite an asymmetry in handling vestibular information in two hemispheres. In fact, it depends on a number of factors like the subject's handedness, the side of the stimulated ear and the direction of the induced vestibular nystagmus (Dietrich *et al.*, 2003). The detailed explanation has been given in our previous paper. Even though vestibular processing structures are bilaterally represented how lateralisation of vestibular input happens in hemispheres are still unclear. Lateralisation of cortical functions was thought to be an exclusive feature of the advanced brain like humans, but recent studies established it in animals too. Best *et al.*, through a series of studies, provides primary evidence that in rodents, vestibular information processing handling is an exclusive function of the left hemisphere. He vividly explains the mechanism that there is a number of neuronal circuit handling the left vestibular information than the right vestibular information. So left-sided vestibular information appears to be considered dominant compared to the right-sided information processing (Best *et al.*, 2013). Advanced studies should be conducted in this field to explore unknown mechanisms. We recommend further detailed studies in this area to explore mechanisms of action.

To date, besides the research of new drugs able to combat age-related cognitive decline, the protection of neurons from damage and death associated with neurodegenerative disorders is a major challenge in neuroscience. The concept of neuroprotection has found increasing acceptance in neurology during the past decade and includes interventions aimed to slow or even halt the progress of neuronal degeneration. Vestibular stimulation is a natural therapy known to have endless beneficial effects in the cognitive neuroscientific area. The simplicity,

lack of side effects, less time consumption makes it easy to incorporate in routine day to day lifestyle not only to delay/ prevent neurodegenerative disorders but also to improve the quality of life. And it can be used as a simple, cost-effective intervention in dementia patients as an adjunct therapy.

REFERENCES

- Alexandra Feast, Martin Orrell, Georgina Charlesworth *et al.* Behavioural and psychological symptoms in dementia and the challenges for family carers: a systematic review. *Br J Psychiatry*. 2016; 208(5): 429-434.
- Alvarez, A.; Alarcón, R.; Opazo, C.; Campos, E.O.; Muñoz, F.J.; Calderón, F.H.; Dajas, F.; Gentry, M.K.; Doctor, B.P.; De Mello, F.G.; Inestrosa, N.C. Stable complexes involving acetylcholinesterase and amyloid- β peptide change the biochemical properties of the enzyme and increase the neurotoxicity of Alzheimer's fibrils. *J. Neurosci.*, 1998, 18(9): 3213-3223.
- Aswathy Gopinath, Archana R, Kumar sai Sailesh and Mukkadan J K. Effect of caloric vestibular stimulation on memory. *Int J Pharm Bio Sci*. 2015; 6(3): (B) 453 - 459.
- Bachtold, D., Baumann, T., Sandor, P.S., Kritos, M., Regard, M., Brugger, P. Spatial- and verbal-memory improvement by cold-water caloric stimulation in healthy subjects. *Exp Brain Res*. 2001;136: 128-32.
- Bartus RT, Dean 3rd RL, Beer B, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. *Science*. 1982; 217:408-14.
- Best C, Lange E, Buchholz HG. Left hemispheric dominance of vestibular processing indicates lateralisation of cortical functions in rats. *Brain Struct Funct*. 2014; 219: 2141-2158.
- Brandt T, Dieterich M. The vestibular cortex. Its locations, functions, and disorders. *Ann N Y Acad Sci* 1999; 871: 293-312.
- Bruno M. da Silva, Tobias Bast and Richard G.M. Morris. Spatial memory: behavioural determinants of persistence in the water-maze delayed matching-to-place task. Cold Spring Harbor Laboratory Press. 2014;21: 28-36.
- D L Clark, J R Kreutzberg, Chee. Vestibular stimulation influence on motor development in infants. *Science*.1977;196(4295):1228-9.
- De Ferrari, G.V.; Canales, M.A.; Shin, I. *et al.* structural motif of acetylcholinesterase that promotes amyloid β -peptide fibril formation. *Biochemistry*. 2001;40(35):10447-10457.
- Devi NP, Mukkadan JK. Impact of rotatory vestibular stimulation in memory boosting. *MOJ Anat& Physiol*. 2017; 9: 144-151.
- Dews PB. The measurement of the influence of drugs on voluntary activity in mice. *Br J Pharmacol Chemother*.1953; 8: 46-48.
- Dieterich M, Bense S, Lutz S, Drzezga A, Stephan T, Bartenstein P, Brandt T. Dominance for vestibular cortical function in the non-dominant hemisphere. *Cereb Cortex*. 2003; 13(9):994-1007.
- Dietrich M, Bense S. Dominance for vestibular cortical function in the non-dominant hemisphere. *Cereb Cortex*.2003; 13: 994-1007.
- Dudar JD, Whishaw IQ, Szerb JC. The release of acetylcholine from the hippocampus of freely moving rats during sensory stimulation and running. *Neuropharmacology*. 1979; 18:673-8.
- Ellman G.L, Courtney K.D, Andres V, Featherstone R.M. A new and rapid colourimetric determination of acetylcholinesterase activity. *Biochemical Pharmacology*. 1961;7,88-95.
- Falconer, C.J., Mast, F.W. Balancing the mind: vestibular induced facilitation of egocentric mental transformations. *Exp. Psychol*. 2012;59: 332-339.
- Fasold O, von Brevern M, Kuhberg M, Ploner CJ, Villringer A, Lempert T, Wenzel R. Human vestibular cortex as identified with caloric stimulation in functional magnetic resonance imaging. *Neuroimage*. 2002; 17(3):1384-93.
- Ferrè, E.R., Bottini, G., Iannetti, G.D., Haggard, P. The balance of feelings: vestibular modulation of bodily sensations. *Cortex J. Devoted Study Nerv. Syst. Behav*. 2013; 49:748-758.
- Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *Journal of Neurology, Neurosurgery and Psychiatry*. 1999; 66:137-47.
- Hamilton RH, Chrysikou EG, Coslett B. Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. *Brain Lang*. 2011; 118(1-2):40-50.
- Hasselmo ME. The role of acetylcholine in learning and memory. *Current Opinion in Neurobiology*. 2006;16;710-5.
- Heiss WD, Thiel A. A proposed regional hierarchy in the recovery of post-stroke aphasia. *Brain Lang*. 2006; 98(1):118-23.
- Hestrin S. The reaction of acetylcholine and other carboxylic acid derivatives with hydroxylamine, and its analytical application. *J Biol Chem*. 1949; 180:249-261.

- Hitier M, Besnard S, Smith PF. Vestibular pathways involved in cognition. *Front Integr Neurosci.* 2014; 23:8:59.
- Horii A, Takeda N, Mochizuki T et al. Vestibular modulation of the septohippocampal cholinergic system of rats. *Acta Oto-laryngological Supplement.* 1995;520(Pt 2):395–398.
- Horii A, Takeda N, Mochizuki T, Okakura-Mochizuki K et al. Effects of vestibular stimulation on acetylcholine release from rat hippocampus: an *in vivo* microdialysis study. *J Neurophysiol.* 1994; 72: 605-611.
- <http://sproutsdevelopment.com/what-is-the-vestibular-system>. SproutsChild Development Blog. Browsed on February 9th, at 12.30pm,2019.
- <https://www.webmd.com>. Art and Music Therapy for Alzheimer's Disease. Browsed on March 8th, at 12.30pm,2019.
- https://www.who.int/mental_health/neurology/dementia/en/.
- Inestrosa, N.C.; Alvarez, A.; Perez, C.A. et al. Acetylcholinesterase accelerates assembly of amyloid-peptides into Alzheimer's fibrils: possible role of the peripheral site of the enzyme. *Neuron.* 1996;16(4): 881- 891.
- Itoh J, Nabeshima T, Kameyama T. Utility of an elevated plus-maze for the evaluation of memory in mice: effects of nootropics, scopolamine and electroconvulsive shock. *Psychopharmacology.* 1990;101;27-33.
- Jae-Chul Lee, Joon ha park, Ji Hyeon Ahn et al. Effects of chronic scopolamine treatment on cognitive impairment and neurofilament expression in the mouse hippocampus. *Molecular medicine reports.* 2018; 17:1625-1632.
- Jáuregui-Renaud K, Ramos-Toledo V, Aguilar-Bolaños M et al. Symptoms of detachment from the self or from the environment in patients with an acquired deficiency of the special senses. *J Vestib Res.* 2008; 18(2-3):129-37.
- Jerusalinsky D, Kornisiuk E, Izquierdo I. Cholinergic neurotransmission and synaptic plasticity concerning memory processing. *Neurochemical Research.* 1997; 22:507–15.
- Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP et al. Cholinesterase inhibitors for patients with Alzheimer's disease: a systematic review of randomised clinical trials. *BMJ.* 2005;331(7512):321-7.
- Kumar Sai Sailesh, Archana R. Mukkadan J K. Impact of traditional vestibular stimulation on depression, anxiety and stress in college students. *Biomedical Research.* 2016; 27(2): 295-297.
- Lee, J.-W., Lee, G.-E., An, J.-H., Yoon, S.-W., Heo, M., Kim, H.-Y. Effects of galvanic vestibular stimulation on visual memory recall and EEG. *J. Phys. Ther. Sci.* 2014; 26:1333–1336.
- Leung LS, Shen B, Rajakumar N, Ma J. Cholinergic activity enhances long-term hippocampal potentiation in CA1 during walking in rats. *Journal of Neuroscience.* 2003; 23:9297–304.
- Leutgeb S, Leutgeb JK, Moser MB, Moser EI. Place cells, spatial maps and the population code for memory. *Curr Opin Neurobiol* 2005; 15: 738-746.
- M.S. Parihar, T. Hemnani Alzheimer's disease pathogenesis and therapeutic interventions. *J Clin Neurosci.* 2004; 11:456-467.
- Mansoureh Adel Ghahraman, Maryam Zahmatkesh, Akram Pourbakht et al. Noisy galvanic vestibular stimulation enhances spatial memory in cognitive impairment-induced by intracerebroventricular-streptozotocin administration. *Physiology & Behavior.* 2016; 157:217 – 224.
- McDonnell, M.D., Ward, L.M. The benefits of noise in neural systems: bridging theory and experiment. *Nat. Rev. Neurosci.* 2011;12: 415–426.
- Mesulam MM, Mufson EJ, Wainer BH, Levey AI. Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1-Ch6). *Neuroscience.* 1983; 10:1185–201.
- Richard Schulz and Paula R. Sherwood. Physical and Mental Health Effects of Family Caregiving. *Am J Nurs.* 2008;108(9): 23–27.
- Sang FY, Jáuregui-Renaud K, Green DA, Bronstein AM, Gresty MA. Depersonalisation/derealisation symptoms in vestibular disease. *J Neurol Neurosurg Psychiatry.* 2006; 77(6):760-6.
- Sarter M, Hasselmo ME, Bruno JP, Givens B. Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. *Brain Research Brain Research Reviews.* 2005; 48:98–111.
- Sharot, T., Phelps, E.A. How arousal modulates memory: disentangling the effects of attention and retention. *Cogn. Affect. Behav. Neurosci.* 2004;4: 294–306.
- Shen J, Barnes CA, Wenk GL, McNaughton BL. Differential effects of selective immunotoxic lesions of medial septal cholinergic cells on spatial working and reference memory. *Behavioural Neuroscience.* 1996; 110:1181–6.
- Srinivasa Rao (2016) Effect of hypocholesterolemic drugs for memory enhancement among animals. (Thesis submitted)

Tai SK, Leung SL. Vestibular stimulation enhances long-term hippocampal potentiation via activation of cholinergic septohippocampal cells. *Behav Brain Res*. 2012; 232: 174-182.

Thomas Brandt, Franz Schautzer, Derek A Hamilton. et al. Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans. *Brain*. 2005; 128(11):2732-2741.

Walsh TJ, Herzog CD, Gandhi C, Stackman RW, Wiley RG. Injection of IgG 192- asporin into the medial septum produces cholinergic hypofunction and dose-dependent working memory deficits. *Brain Research*. 1996;726:69-79.

Wilkinson, D, Nicholls, S, Pattenden, C, Kilduff P, Milberg, W. Galvanic vestibular stimulation speeds visual memory recall. *Exp. Brain Res*. 2008; 189:243-248.