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Effectiveness of vestibular therapy as an adjunct to cognitive therapy to improve cognition in elderly with mild cognitive impairment (MCI): study protocol for a randomized controlled trial

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ABSTRACT

The rapid global increase in aging populations is leading to a rise in age-related conditions like mild cognitive impairment (MCI), necessitating new treatment strategies. This study will conduct a double-blinded, three-arm, randomized controlled trial to evaluate the effectiveness of adding vestibular therapy to cognitive therapy (VT+CT) compared to cognitive therapy (CT) alone and a control group. Participants will be assigned to one of three groups: VT+CT, CT only, or a control group. The VT+CT group will receive vestibular rehabilitation exercises along with a computerized brain program, while the CT group will get only the computerized brain program. Primary outcomes will include electroencephalography (EEG), the Digit Symbol Substitution Test (DSST), and event-related potential (ERP-P300). Secondary outcomes will be the Stroop Color Word Test (SCWT), Trail-Making Test (TMT), and European Quality 5 Dimensions (EQ-5D-5L). This research aims to determine if VT+CT improves cognitive function in elderly individuals with MCI.

Keywords: mild cognitive impairment; vestibular therapy; cognitive therapy; cognition; quality of life

1. Introduction

The likelihood of aging-related illnesses, such as MCI rates rising quickly is expected to coincide with life expectancy becoming longer at older ages. MCI is a clinical disorder characterized by a deterioration in memory and/or other cognitive functions that are more significant than the cognitive decline linked to normal aging but not severe enough to be identified as dementia (Flak et al., 2014). MCI is a mental state that falls somewhere between normal cognition and dementia, essentially preserving functional abilities (Hugo & Ganguli, 2014), as a result, this condition is often overlooked. The global prevalence of MCI in the population aged ≥ 60 years is up to 38.60% (Alkhunizan et al., 2018), but it is approximately 8.8% in the elderly in North India (Sengupta et al., 2014). MCI is mostly diagnosed based on the patient's medical history and by administering cognitive screening tests (Knopman et al., 2014). MCI is a risk factor for dementia and is associated with a 6-fold increased risk of Alzheimer's disease (AD) (Bae et al., 2015). To promote targeted therapies, it has been more crucial in the field of gerontology during the past few decades to identify the characteristics that predict cognitive decline as researchers believe that early interventions for those who are at risk for cognitive decline and their implementation may be more successful in protecting cognitive functions (Lebedeva et al., 2015). Cognitive therapy has significant intervention effects in improving cognition domains including, memory, attention, spatial skills, information processing speed, executive functions, and improved capacity to perform instrumental activities of daily living (Akhoondzadeh et al., 2014).

Previous research has shown multiple anatomical connections between the vestibular system and cognitive regions like the hippocampus. Moreover, the vestibular system is essential for spatial learning and navigation, providing spatial representation information to the hippocampus through head direction and place cells (Smith, 2017). Through vestibular stimulation, the relationship between the vestibular system and hippocampal spatial memory has been established (Smith et al., 2009). The vestibular system is important for cognition, and vestibular abnormalities seen in MCI patients can cause cognitive problems in these individuals (Gurvich et al., 2013). Several studies have found vestibular system impairments in patients with AD and its preclinical stage, MCI, by using cervical methods, such as sound-evoked cervical muscle myogenic potentials to assess saccular function (Wei et al., 2019), and ocular methods (Cohen et al., 2022). Furthermore, vestibular loss may also be a contributing factor to AD, which is first characterized by the degradation of cholinergic networks in the posterior cingulate, middle temporal, and posterior parietal-temporal areas (Previc, 2013). Interventions involving the vestibular system may therefore enhance these individuals'

cognitive abilities in addition to their vestibular functions. Maximizing central nervous system compensation at the vestibular nucleus level and other levels of the vestibular pathways is the goal of Vestibular Rehabilitation (VR), an exercise-based approach to the treatment of vestibular disorders (Eleftheriadou et al., 2012). A study including patients with intractable dizziness who used vestibular rehabilitation (VR) three times a day for one to four months demonstrated improvements in their executive functions, attention, processing velocity, and visuospatial ability (Sugaya et al., 2018). Another study that used repeated 25-minute galvanic vestibular stimulation (GVS) sessions has been shown to improve cognitive performance in patients with unilateral spatial neglect (Wilkinson et al., 2014). Exercises for vestibular rehabilitation were proposed by Cawthorne-Cooksey (1946). This protocol involves exercises in lying down, sitting, standing, and moving with the eyes open and closed as well as repetitive motions of the head, trunk, and eyes (Ricci et al., 2016). Results from a recent randomized controlled trial (RCT) suggested that a combination of vestibular rehabilitation exercises and GVS significantly improved verbal and spatial memory in amnestic MCI patients (Kamali et al., 2023). The incremental effects of the addition of vestibular therapy to cognitive therapy are inconclusive in the literature. This study endeavors to create a treatment plan that enhances cognitive function and quality of life in the elderly with MCI. Consequently, it offers a significant understanding of the clinical association between the cognitive and vestibular systems.

2. Method

2.1 Study design and setting

This will be a double-blinded, three-armed randomized controlled trial, wherein the assessors and the participants will both be blinded. The subjects will be recruited from the Centre for Physiotherapy and Rehabilitation Sciences clinic, M.A. Healthcare Centre, Jamia Millia Islamia University, and referred cases from the community to maximize the generalizability effect of this program. The present study is conducted according to the principles indicated in the Declaration of Helsinki.

2.2 Participants, recruitment strategy and randomization

The inclusion criteria of this program are: (1) being aged 60 or above, (2) both males and females, (3) having basic knowledge of primary education, (4) being

diagnosed with MCI, (5) Addenbrooke's cognitive examination-III scale score of 83/100 (Pan et al., 2022), (6) Mini-Mental Status Examination (MMSE) score of <24/30 (Bertolucci et al., 1994), and (7) a minimum to no risk of falls according to short-falls efficacy scale with a score of <7/28 (Dewan & MacDermid, 2014), and (6) no prior history of neurological diseases and falling which could contribute to balance instability (Roh & Lee, 2019). The participants will not be eligible if they are: (1) taking medications affecting consciousness or indirectly cognitive system, (2) having a history of other neurological conditions that may alter cognition, (3) any significantly diagnosed visual and auditory impairment, (4) already engaged in other programs, and (5) medical contraindications for making the necessary head movements during vestibular rehabilitation (e.g., severe cervical disorder).

The SPIRIT statement is used as a guideline for this protocol paper (Chan et al., 2013). Identification of individuals that meet the inclusion criteria will be facilitated by the patients' register maintained at the Centre for Physiotherapy and Rehabilitation Sciences Clinic and M.A. Health Care Centre. A set of protocols, comprising information on the study and guidelines for making phone calls, will be given to all clinic staff members who are participating in the recruitment. The potential subjects who meet the criteria will be invited to participate in the study and those who agree will sign a consent form. The block randomization will be done using computer-generated software and allocation concealment will be done using a "sealed envelope." when block randomization occurs, the group assignments will be placed in sealed envelopes and revealed one at a time. A schematic overview of the study design has been shown in Figure 1. Efforts shall be made to ensure the blinding of each participant and unblinding may only be permitted in cases where participants' adherence to the protocol is challenged due to low motivation and/or if adverse events are reported. The CONSORT guidelines will be followed while conducting the randomized controlled trial (Schulz et al., 2010).

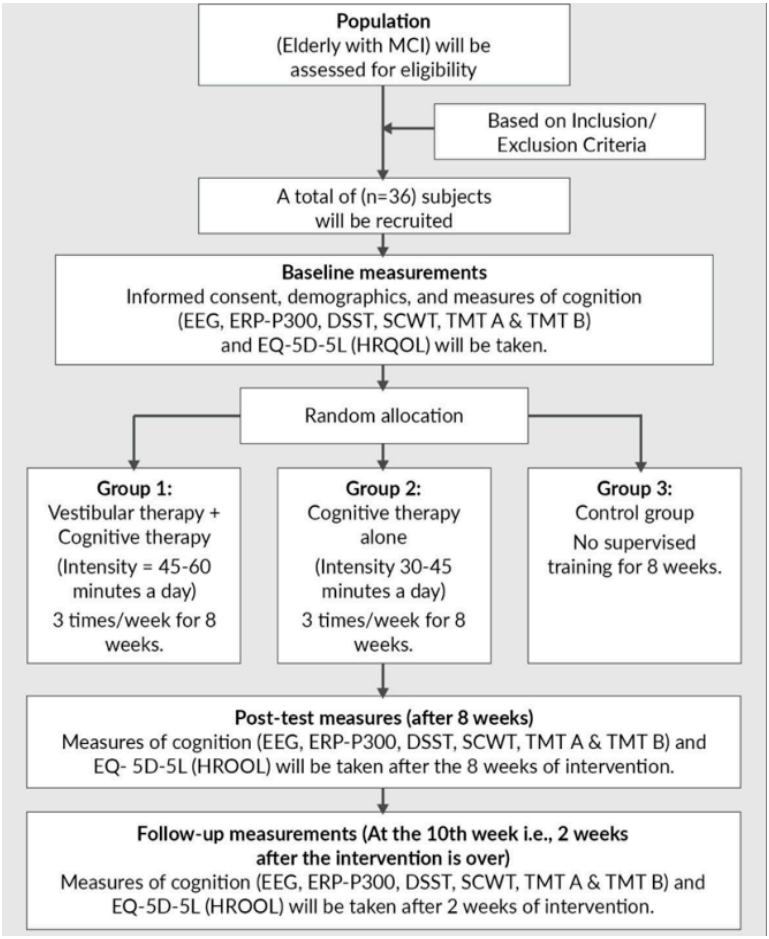

Figure 1. Schematic overview of study design

2.3 Intervention

2.3.1 Group A (vestibular therapy + cognitive therapy)

This group of participants will receive vestibular therapy as an adjunct to cognitive therapy (VT+CT): (1) Vestibular therapy will be administered using Cawthrone-Cooksey's vestibular rehabilitation exercises and, (2) Cognitive therapy will be given with a computerized brain program game software from Lumosity Inc. The intervention will be given for 45-60 minutes a day, 3 days a week for a total of 8 weeks. Previous studies have shown that 4-8 weeks is an adequate dose to bring about a change (Husseini et al., 2016; Kamali et al., 2023). The Multimodal Cawthrone-Cooksey's protocol for vestibular rehabilitation adds flexibility, cognition, sensory engagement, and muscle strength components to the exercises (Ricci et al., 2016). The protocol is composed of four progressive stages including specific exercises performed while lying down and sitting (1 week each) and, subsequently, standing and walking (3 weeks each). Cognitive therapy, beginning with 30 minutes on the first day and increasing to 45 minutes in the seventh and eighth weeks, will be given in an incremental regimen. The six major cognitive areas of Divided attention, Selective attention, Information processing speed, Memory, Logical reasoning, and Spatial reasoning will be the focus of the study. The difficulty level for each participant will be the same at the outset. When a predetermined performance standard is met during each exercise, the level of difficulty is raised (Finn & McDonald, 2011). In this study, only the participants with minimum to no risk of having vestibular impairments will be recruited (keeping vestibular-cognitive interactions at a minimum towards gain in vestibular function) to ensure that whatever the potential benefits are going to be achieved after the intervention is reflected in the improved cognitive functions. Also, the aim as already discussed is to examine the adjunct effects of VT on CT and not the direct effects of VT alone on cognition, and hence, the inclusion of the vestibular training alone group is not needed.

Although VT has no reported side effects in patients with no history of cervical disorders, should any difficulties arise such as dizziness or vomiting due to neck movements performed during the VT, the treatment shall be modified and/or discontinued as felt necessary and will be reported to the Trial participants, Ethical committee, CTRI, and Journal.

2.3.2 Group B (cognitive therapy alone)

This group of participants will only receive computerized cognitive therapy procured from Lumosity Inc. for (30-45) minutes a day, 3 days a week for a

total of 8 weeks. It will be an incremental regimen, beginning with 30 minutes on the first day and increasing to 45 minutes in the seventh and eighth weeks. The Six major cognitive areas of Divided attention, Selective attention, Information processing speed, Memory, Logical reasoning, and Spatial reasoning will be the focus of the study. The difficulty level for each participant will be the same at the outset. When a predetermined performance standard is met during each exercise, the level of difficulty is raised.

2.3.3 Group C (control group)

This group of participants will continue with their usual care activities and shall be given targeted therapy after the conclusion of this study.
The key features of the interventions for the 3 groups are summarized in Table 1.

Table 1. A summary of the key features of the interventions for 3 groups

Groups	Features	Details
VT+CT[a] group	Proactive case management with VT+CT	VT[b] - Multimodal Cawthrone and Cooksey protocol for Vestibular rehabilitation will be used in four progressive stages including specific exercises performed while lying down and sitting (1 week each) and, subsequently, standing and walking (3 weeks each). Exercise set 1- In bed or sitting: (Initial 1st week) Eye movement – Head immobile, looking up & down, etc. Head movement bending alternatively, forward & backward, left & right, and roll head & body. Exercise set 2 - Sitting position: (2nd week) Arm & body movements – shrugging & rotating shoulders, bending forward & picking objects from the floor, etc. Exercise set – 3 Standing position: (3rd, 4th, and 5th week) Switching from sitting to standing with eyes

		open & then closed, sitting to standing then turning around, etc. Exercise set –- 4 Walking position: (6th, 7th, and 8th week) Throwing & catching a ball while walking, climbing stairs up and down with head turned left and right, etc. CTc - A computerized brain program from Lumosity Inc. will deliver cognitive therapy, starting at 30 mins & increasing to 45 mins by the last week. The focus will be on divided attention, selective attention, processing speed, memory, and logical & spatial reasoning.
CT[c] alone group	A computerized brain program by Lumosity Inc.	The above-discussed cognitive areas will be the focus of the intervention.
Control group	Usual care	Participants will continue with their usual day activities & will get targeted therapies after the conclusion of this study.

[a] reflects vestibular therapy as an adjunct to cognitive therapy; [b] reflects vestibular therapy; [c] reflects cognitive therapy.

2.4 Data collection

Data will be collected at 3-time points – at baseline before intervention (T1), at 8 weeks (T2) when the program is completed, and at 2 weeks (T3) after the program is completed to test the sustained intervention effect. The baseline and follow-up data will be collected for all the outcome measures for each group.

2.4.1 Group C (control group)

There are 3 sets of outcome measures: demographics, measures related to cognition, and quality of life measures.

Primary outcome. The primary outcome is the measures related to cognition in the elderly with MCI. Cognitive domains of attention, information processing speed, executive functions, memory, logical reasoning, and spatial reasoning

will be assessed using electroencephalography (EEG), event-related potential (ERP-P300), Digit Symbol Substitution Test (DSST), and Digit Symbol Coding Test (WAIS-R).

The elderly with MCI and Alzheimer's disease (AD) often exhibit a shift towards increased power in the lower EEG frequencies (δ & θ) in their EEG patterns (The maximum intraclass correlation coefficient between the MMSE scores and model-predicted values was .757 with RMSE = 2.685 (Choi et al., 2019). Disorders of the brain that may affect the primary cognitive operations of attention allocation and immediate memory will have an impact on the measure of P300 by reducing amplitude and/or increasing latency (test-retest reliability ranging from .78-.81) (Williams et al., 2005). The DSST measures a range of cognitive operations, good performance on the DSST requires intact motor speed, attention, and visuo-perceptual functions, including scanning and the ability to write or draw (i.e., basic manual dexterity). The Digit Symbol Coding Test (WAIS-R) is used to evaluate information processing speed and has high test-retest reliability (Matarazzo & Herman, 1984). It consists of nine-digit symbol pairs (e.g. 1/β, 2/ Λ ... 7/ ⊥, 8/ =, 9/ X) pursued by a list of digits, under each digit the subject has to write down the related symbol as quickly as possible in 90 seconds (Brukner et al., 2004).

Secondary outcome. The secondary outcomes include measures related to cognition and client outcomes (quality of life). The Stroop Color Word Test (SCWT) assesses selective attention and inhibition and is a valid and reliable measure for the assessment of processing speed and executive functions in older adults with low formal education with a split-half coefficient of reliability showed high internal consistency > .900) (de Paula et al., 2017). Trail Making Test (TMT-A - TMT-B) is used to assess executive function and attentional abilities. Part A of TMT evaluates the information processing speed, while part B assesses cognitive flexibility or switching. TMT-B minus TMT-A, assess task switching (Test-retest reliability coefficients for TMT-A, TMT-B, with a congruous condition were estimated as .82, .93 respectively) (Wang et al., 2018). In part A, the task consists of connecting numbers (from 1 to 25) with straight lines as fast as possible. In part B, participants will have to alternate between letters in alphabetical order and numbers in ascending order (1-A-2-B-3-C, etc.) as fast as possible. The total times in seconds for Parts A and B represent the TMT-A and TMT-B direct scores. Elderly with MCI often experience a lower quality of life (QoL) due to the concern of getting dementia in later life if the degree of their memory loss exceeds what is typical for them. The European Quality of Life 5 Dimensions (EQ-5D) is a widely used generic Health-related quality of life (HRQoL) instrument and assesses a respondent's health status on the day of the survey in five dimensions: mobility, self-care,

usual activities, pain/discomfort, and anxiety/depression. As a self-administered generic scale, the EQ-5D will be a good tool for QoL assessment in the elderly with MCI with a Cronbach's alpha of .723 (Pérez-Ros & Martínez-Arnau, 2020). All outcome measures have been shown in Table 2.

Table 2. Outcome measures of the study

Outcome measures	Tools	Collection time	Methods of data collection
Attention, Executive functions, Information processing speed, Logical reasoning, and Working memory	Electroencephalography (EEG)	T1, T2, T3	Brain waveforms will be recorded using non-invasive surface EEG electrodes
Attention and Information processing speed	Event-related potential (ERP-P300)	T1, T2, T3	Specific brain waveform activities next to a stimulus will be recorded using non-invasive surface P-300 electrodes
Visuoperceptual functions and Attention	Digit Symbol Substitution Test (DSST)	T1, T2, T3	Data will be extracted from a pen-paper cognitive test presented on a single sheet of paper that requires subjects to match symbols to numbers
Selective attention	Stroop Color Word Test (SCWT)	T1, T2, T3	Data will be extracted from a cognitive test sheet having conflicting tasks to test inhibition ability to the irrelevant stimuli
Cognitive flexibility, Attention, and Executive	Trail Making Test (TMT-A and TMT-B)	T1, T2, T3	Data scores will be extracted from a cognitive test sheet having alphabets and numbers that require subjects to connect them

functions			in a given time
Health-related Quality of Life (HRQoL)	European Quality of Life 5-Dimensions (EQ-5D-5L)	T1, T2, T3	EQ-5D-5L is a generic HRQOL tool that assesses respondents' health status in five dimensions: mobility, self-care, usual activities, pain, and anxiety

Note. T1, at baseline before intervention; T2, at 8 weeks when the program is completed; T3, at 2 weeks after the program is completed.

2.5 Background demographic data

The demographic data, age, gender, marital status, education, accommodation, financial status, family members living in the same household, and caretaking support will be collected at baseline.

2.5.1 Sample

The sample size calculation is based on power analysis (Faul et al., 2009). Assuming a 2-tailed α of .05, a statistical power (1- β) of 95%, and an effect size of .264 after calculating for the same primary outcome measure (Digit symbol substitution test - WAIS-R) from the results of previous research studies that Thapa and colleagues provided (Thapa et al., 2020), 10 participants are required per group. Concerning the 10–15% attrition reported in previous programs for community-dwelling older adults, we assume a 20% dropout rate in this study, thus the total sample size needed is 12 participants per group, that is, a total of 36 participants.

2.6 Data processing and analysis

Data from the EEG, P300, DSST, DSCT (WAIS-R), Stroop Test, TMT-A & TMT-B, and EQ-5D will be entered into the SPSS software (version 26.0, IBM). Each of the variables in the data set will be screened by descriptive statistics to detect potential outliers.

The normality of data will be checked using the Shapiro-Wilk test. To meet the normality post hoc analysis with Bonferroni correction can be done. The sphericity assumptions can be checked through the Mauchly test for sphericity.

Greenhouse-Geisser correction can be made to meet the sphericity assumptions. Two-way Analysis of variance ANOVA statistics with repeated measures will be used to find between-group effects, the within-group (time) effects, and the interaction effects (group × time). Intention-to-treat will be used as the primary analysis in this study. A significant result is indicated when the p-value (level of significance) is < .05 for a 2-tailed test. The data shall be coded and presented in numeric form and restricted to the principal investigator and researcher to ensure confidentiality before, during, and after the trial.

2.6.1 Data management

One researcher will enter data into an Excel spreadsheet. The entered data will be double-checked for any errors. Paper materials related to each participant's assessment and intervention will be stored in a binder. The binders will be kept at the Centre for Physiotherapy and Rehabilitation Sciences, Jamia Millia Islamia, inside a lockable shelf.

2.6.2 Data monitoring

An independent research advisory committee, which is comprised of the study supervisor, co-supervisor, and three research team members part of the study, will get a six-monthly progress report on the status of the study from the researchers at all the stages of the data collection process i.e., screening, subject recruitment, before the intervention, evaluating the intervention, after the intervention and at follow up session.

3. Discussion

The objective of this proposed study is to determine the effectiveness of combined vestibular therapy as an adjunct to cognitive therapy in preventing MCI progression and improving cognition as well as quality of life among the elderly with MCI. To the best of our knowledge, this is the first trial that would investigate the direct effect of combined vestibular therapy and cognitive therapy to improve cognition and quality of life in this target population.

Given that the vestibular system is more widely distributed than any other system, and that it is thought to have a unique and significant vestibular pathway that primarily originates from the semicircular canals and ends in the medial temporal cortex, which includes the parahippocampal gyrus and the hippocampal region (Lopez & Blanke, 2011), we anticipate that using

Cawthorne-Cooksey exercises as a vestibular intervention would improve memory performance in elderly with MCI. Exercise-induced alterations in the hippocampus are highly responsive due to neurogenesis and cell proliferation. Physical activities, including vestibular therapy, lower levels of oxidative stress and neuroinflammation, boost the expression of brain-derived neurotrophic factor (BDNF), which is involved in cell growth, survival, and memory enhancement, raise calcium messenger RNA levels, which enhances transmission speed, and stimulate neuroplasticity (Huang et al., 2000).

Since the training sessions will last for eight weeks and a follow-up session 2 weeks after the intervention is over, we expect that finding participants and keeping them there for the duration of the intervention may prove to be a challenge. The researchers will be collaborating closely with the coordinators at the Centre for Physiotherapy and Rehabilitation Sciences clinic and M.A. Health Care Centre to invite and monitor subjects to address this. In addition, each participant will receive 2 familiarization sessions before the commencement of the study, which will motivate them to participate fully. The sample size was inflated by 20% since dropping out can occur for a variety of reasons, including a hectic schedule, relocation, insufficient motivation, or illness. Provisions for post-trial care will also be offered to participants who suffer from any harm as a result of the intervention.

To summarize, this trial will provide clinical insight into the effect of integrating vestibular therapy as an adjunct to cognitive therapy in preventing the progression of MCI and improving cognition as well as the quality of life in the elderly with MCI living in the community. Healthcare professionals and practitioners in the gerontology field will be provided with validated community-based interventions whose effect on MCI and MCI-related risk factors is scientifically evaluated.

Ethic Statement

The present study was approved by the Ethics Committee of the University (Proposal reference No.: 19/6/456/JMI/IEC/2023) and written informed consent will be obtained from the participants before the commencement of the program.

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Conflict of Interest

All authors have no conflicts of interest.

Authors' contribution

A.G. and C.A.S.: conceived the idea and developed the original study plan. M.M.N.: supported the development and implementation of the interventions. S..P and M.A.: verified the analytical methods, A.G.: wrote the content of the manuscript., C.A.S.: supervised the development of study protocol. All authors critically revised the draft manuscript and approved the final manuscript.

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