Tablet-based sensorimotor home-training system for amnestic mild cognitive impairments in the elderly: design of a randomised clinical trial

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ABSTRACT

Introduction Dementia (particularly Alzheimer’s disease, AD) is a major cause of impaired cognitive functions in the elderly. Amnestic mild cognitive impairment (aMCI) is a prodromal stage of AD, if substantiated by Alzheimer biomarkers. A neuroscientific model of pathological ageing emphasises the loss of brain plasticity, sensorimotor capacities and subsequent cognitive decline. A mechanistic treatment targeting dysfunctional plastic changes associated with ageing should be efficacious in delaying AD. In this trial, we aim to evaluate the effectiveness of a newly developed sensorimotor training, delivered at home, combined with personalised reinforcement, on the progression of aMCI-related cognitive impairments.

Methods and analysis In a randomised trial, we will compare two aMCI groups (30 subjects each), randomly allocated to a sensorimotor or a cognitive control training. Both trainings consist of an adaptive algorithm, and will last 3 months each. We hypothesise that both trainings will have positive effects on cognitive function with the sensorimotor training being superior compared with the control training based on its improvement in basic perceptual skills underlying memory encoding and retrieval. The primary outcome is episodic memory function, improved hippocampal function during memory encoding and retrieval. The primary outcome is episodic memory function, improved hippocampal function during memory tasks will be a secondary outcome. As further exploratory outcomes, we expect improved segregation in sensory and motor maps, better sensory discrimination only in the sensorimotor training and reduced transition to dementia (examined after completion of this study). We expect the experimental training to be evaluated more positively by the users compared with the cognitive training, resulting in reduced rates of discontinuation.

Ethics and dissemination The Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, approved the study (2015–543N-MA), which adheres to the Declaration of Helsinki. The results will be published in a peer-reviewed journal. Access to raw data is available on request.

Trial registration number DRKS00012748.

INTRODUCTION

Dementia in Alzheimer’s disease (AD) is a major cause of impaired cognition, everyday functioning and mobility in the elderly. Amnestic mild cognitive impairment (aMCI) is a prodromal stage of AD, particularly in subjects who have been tested positive for AD biomarkers. A neuroscientific model of pathological ageing recently emphasised the loss of sensorimotor capacities and the development of maladaptive plastic changes and subsequent cognitive, mental, and physical decline. An especially important variable in this process is ‘disuse’ of the brain by reduced sensory and motor input, which is thought to lead to a loss of connectivity and reduced growth of new connections and a lack of further learning capacity and plasticity. Noisy processing in sensory and motor systems is believed to lead to maladaptive behaviours and greatly affects sensorimotor brain maps and motor input, which is thought to lead to a loss of connectivity and reduced growth of new connections and a lack of further learning capacity and plasticity. Noisy processing in sensory and motor systems is believed to lead to maladaptive behaviours and greatly affects sensorimotor brain maps and motor maps, 2, 3 aided by faulty compensatory behaviours and reduced modulatory capacity of transmitters. These maladaptive plasticity processes are thought to contribute to pathological ageing and specifically to aMCI, due to Alzheimer pathophysiology (MCI due to AD). On the other hand, brain plasticity is still considerable in older age and may confer resilience to pathological...
processes. Thus, a complex interaction of pathologies (for example, AD) and maladaptive plastic changes with resilience factors (such as neuronal plasticity) is hypothesised to determine the actual cognitive functioning in the elderly.

**Importance of impaired sensorimotor processing**

It has been shown that older adults display a decline in neural plasticity with physiological ageing, especially in the sensorimotor cortex. In healthy humans, sensory training aimed at reversing this maladaptive plasticity was found to yield significant improvements in key neurocognitive processes that decline with age.

In patients with aMCI, cognitive or pharmacological interventions have so far only yielded limited success and have not been shown to generalise to other domains. Pathological plasticity, however, can be slowed down or even reversed. Emotional and motivational processes as well as implicit learning processes seem to be less affected by maladaptive brain plasticity and thus provide a target sensorimotor training could be based on. However, up to now, there is no indication that a sensorimotor training, which is specifically tailored for elderly people and combines sensorimotor elements with motivational and emotional reinforcers, can improve maladaptive brain changes in early stages of dementia. Thus, we describe a randomised clinical trial in which we will apply a new long-term tablet-based multimodal sensory and sensorimotor home-training for the elderly.

**Study objectives**

In the present project, we will conduct a randomised controlled trial to evaluate the effectiveness of a newly developed tablet-based sensorimotor training (tbSMT), delivered at home, on the negative progression of aMCI. We will compare two patient groups using a) tbSMT or b) a computerised cognitive training. Both trainings will consist of an adaptive algorithm, and the training will last for 3 months in both groups. Based on the evidence reviewed above, we hypothesise that tbSMT will have superior effects on cognitive functioning compared with the computerised cognitive training.

Thus, the primary outcome is episodic memory function. Secondary outcomes will be 1) effects on neurobiology in terms of hippocampal function during memory tasks as well as hippocampal volume and 2) sustained effects on both, memory and neurobiology at follow-up after 6 months. As further exploratory outcomes, we hypothesise that sensory and sensorimotor functions will improve only in the tbSMT condition, which will be also reflected in perceptual maps in the brain. Finally, we expect that tbSMT will be evaluated more favourably compared with the computerised cognitive training, resulting in reduced rates of discontinuation of the training. Further follow-ups after completion of the study will examine transition to dementia.

**METHODS**

This protocol was written in line with the Standard Protocol Items: Recommendations for Interventional Trials statement (online supplementary appendix 1), detailing recommendations for a minimum set of scientific, ethical and administrative elements that should be addressed in a clinical trial. The information relies on protocol V.2. The full data collection forms can be requested from the corresponding author.

**Patient and public involvement**

Patients and the public were involved in the development of the research question, outcome measures, study design and recruitment in informal discussion circles. In the pilot phase, participants were asked to provide personal feedback after the intervention. After study completion, participants will be informed orally or in writing about key findings of the investigation. Burden of the intervention will be assessed by interviewing the participants after study participation. The results of the trial will be submitted for publication in a peer-reviewed journal on geriatric psychiatry and presented at relevant international conferences.

**Study population and diagnostics**

MCI (International Classification of Diseases, Tenth Revision code: F06.7—mild cognitive disorder) participants with an amnestic component in neuropsychological testing will be recruited from a consecutive clinical sample of the memory clinic of the Central Institute of Mental Health (CIMH), Mannheim, Germany; they are referred for workup of cognitive complaints and cognitive deficits. According to clinical guidelines, a detailed clinical workup including comprehensive laboratory assessments, MRI/CT and (in a majority of cases) cerebrospinal fluid (CSF) analysis will be performed to rule out other causes of cognitive impairment. CSF will further be used to analyse AD biomarkers. Detailed neuropsychological testing (the CERAD-Plus test battery, particularly the verbal and visual delayed recall tests and the logical memory subtests of the Wechsler Memory Scale-Revised) will be used to document an amnestic component in MCI. On the basis of patient self-reports of memory impairments, medical history, neuropsychiatric examination and further neuropsychological testing, all subjects will be classified having aMCI, using Petersen’s diagnostic criteria. All included subjects with aMCI will be rated on the Clinical Dementia Rating (CDR) and will only be included if the CDR score equals 0.5.

AD biomarkers include semi-quantitative ratings for neurodegeneration (Scheltens scale) and subcortical vascular degeneration (Fazekas scale), using FLAIR images on 3T MRI scans, which will be rated by an experienced neuroradiologist. CSF biomarkers are measured using the following commercially available kits: total tau INNOTEST hTAU Ag, pTau INNOTEST PHOSPHO-TAU (P181), Aβ 1–42 INNOTEST βAMYLOID 1–42 by Fujirebio, and Aβ 1–40 Amyloid-beta CSF ELISA by IBL, as described previously. MCI due to AD is defined by clinical state and by evidence of amyloid-pathology (Aβ42<550 pg/mL or Aβ40/42-ratio<0.5) and/
or neuronal injury (Tau-protein >450 pg/dL or pTau >61 pg/mL in CSF) or Scheltens scale rating >1. Exclusion criteria will comprise inability to complete the written forms, current dementia, other neurodegenerative diseases, stroke and other neurological disorders with neurocognitive impairments as a major feature, myocardial infarction within the last 2 years, a deficit in vitamin B12, folate or thyroid-stimulating hormone, which is not substituted for at least 3 months, life-time prevalence of certain severe mental disorders (schizophrenia and other psychotic disorders, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder), current severe major depression and other axis I mental disorders. All patients will have a Fazekas scale rating <2 to rule out relevant cerebrovascular pathology. Current intake of benzodiazepines, high doses of neuroleptics or tricyclic and anticholinergic antidepressants, and antidiabetes medication is not allowed, which would be off-label use in the stage of aMCI anyway. Furthermore, we will test for severe disturbances in sensory capabilities (ie, glaucoma and cataracts; visual acuity <0.1; von-Frey hair threshold >512 mN; WHO hearing loss ≥3; severe tinnitus symptomatology), which render the present sensorimotor training impossible, as well as frailty as defined by the Fried criteria,26 and will exclude all subjects who fulfil these criteria. Since there is no validated and successful non-pharmacological intervention for delaying progression from aMCI to AD dementia so far, no restrictions were made in this point. However, during and after the treatment, participants will be asked for any ‘interventions’ (medication, ‘brain jogging’, etc) they could have performed.

Sample size

To our knowledge, there is no study that investigated the effect of a sensory training on progression of aMCI. However, previous studies based on brain plasticity-based interventions in elderly healthy humans achieved moderate to large effect sizes on cognitive functions compared with a no training or active control condition,8 9 27 but did not contain motivational and emotional enhancement. Computerised cognitive trainings yielded inconclusive to small effects on memory in controlled trials.28 In our study, we expect a large effect size of at least Cohen’s $f=0.4$ for the sensorimotor, and a medium effect size of Cohen’s $f=0.25$ for the computerised cognitive training. Thus, assuming 95% statistical power, a correlation of 0.50 between the dependent measurements, and an alpha error level of 0.05, we would need 22 participants per group,29 based on a repeated measures design with one between-factor with two groups and one within-factor with three assessment points. Allowing for an expected loss of 25%, we will include 30 participants per group to obtain sufficient power. The participant flow is depicted in figure 1.

Randomisation and blinding

Participants will be randomised on a 1:1 ratio as per an electronically generated randomisation schedule. At least three researchers are involved in the procedure of allocation, assessment and support during training: a trained study physician who is blinded for the treatment allocation and the results is performing the aMCI assessment, based on medical and psychological assessments in the context of the memory outpatient clinic, while a trained psychological researcher will perform the pretraining and post-training data assessments. This researcher remains blind to the treatment allocation. A second researcher (also a trained psychologist) is performing the training instructions and training support, but remains blinded for predata and post-data.

Intervention arms

Experimental training

The tbSMT will progressively engage the experimental group’s participants in unimodal (visual, auditory and tactile), bimodal (visual-auditory, visual-tactile and auditory-tactile) and sensorimotor tasks (visual-auditory regulated cycling, visual-tactile controlled grasping and auditory-visual hands coordination). Each task consists of a perceptual discrimination task requiring an explicit answer on the tablet touch screen or a predefined and feedback-driven motor activity. Unimodal, bimodal and sensorimotor discrimination activities will be scheduled consecutively with a duration of 30 days each (90 days in total). The tasks are part of a container application which schedules the required activity (lasting 30 min) in a daily manner. The participants will be asked to execute the daily training activity in order to earn tickets for a two-dimensional virtual journey across European cities. External peripheral and wireless components (two Braille cells of 4×6 pins, one customised ergometer and one handgrip strength measurement device) will be connected to the tablet to engage the participants in the tasks involving the tactile domain, the cycling and the grasping exercises. All remaining tasks will be controlled by the tablet itself. The modulation of the physical properties of the stimuli (or of the required motor response) will be controlled by an adaptive algorithm to progressively engage each participant close to his/her sensory and sensorimotor capabilities. Methods of skill learning, engagement of implicit processes and shaping will be used for motivational purposes. In order to further enhance motivation, personally chosen reinforcers (pictures, feedback sounds and background colours) will be implemented and presented for correct responses. Performance data pertaining to each task will be collected daily and sent to a dedicated server for monitoring and analysis purposes.

Control training

As a standardised computerised cognitive control training, we will use CogniPlus (V.CC 2730; Schuhfried GmbH, Moedling, Austria) that has been shown to improve cognitive functioning in elderly with mild cognitive deficits before,30 at least if combined with physical exercises. The CogniPlus training battery consists of 15 training programmes aiming at improving cognitive functions.
For our purpose, we selected those training programmes with the least sensory elements; instead, attention, executive functions and working memory will be trained. In all selected training programmes, the principle of adaptation is implemented and the difficulty level of the respective task can be gradually increased and decreased based on the abilities of the performer. In contrast to the tbSMT, the CogniPlus training programme has no individualised motivational feedback system included. As in the sensorimotor training the training period of 3 months will be split into three phases (30 days each), including two CogniPlus training programmes per phase lasting 15 min each.

Outcome measures

Memory function
We are focusing on different memory functions assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB)\(^{31}\), a computer-based cognitive assessment system consisting of a battery of neuropsychological tests. Here, we selected the paired associates learning paradigm, the delayed matching to sample test and the pattern recognition memory paradigm which in combination have been shown to differentiate between subjects with and without aMCI with a predictive accuracy of 80%.\(^{32}\) Furthermore, we include the spatial recognition memory test, since deficits of performances in visuospatial modality seem to be of memory origin.\(^{33}\) Since early forms of dementia are often accompanied by attentional impairments,\(^{33}\) we further include the reaction time and rapid visual information processing test for controlling for unspecific training effects. Besides the CANTAB tests, we further include the California Verbal Learning Test (CVLT)\(^{34}\), which is a measure of episodic verbal learning and memory by assessing encoding, recall and recognition in the auditory-verbal modality. The CVLT is designed to measure how much the subjects learn and to show the strategies they use and ultimately what kind of errors they make. The CVLT measures free and cued recall (short and long delay), serial position effects (including primacy and recency), semantic clustering, intrusions, interference and recognition have been shown to significantly predict the transition from aMCI to dementia.\(^{35}\)

Sensory testing
We will assess visual, auditory and tactile capabilities. For visual testing, we will use the Freiburg Visual Acuity Test\(^{36}\) (https://michaelbach.de/fract/index.html), an
 automated procedure for self-administered measurement of visual acuity. In separate trials, Landolt Cs (with different size, orientation and contrast), Snellen Es and gratings with different orientations and level of contrast are presented on a screen in a pre-defined distance and standardised lighting conditions. To estimate the acuity threshold, a Best Parameter Estimation by Sequential Testing procedure is used to assess visual capabilities in terms of a psychometric function.

For testing tactile acuity, we will use grating domes (JVP Domes, Stoelting Europe, Dublin, Ireland), being a set of 15 plastic gratings (with a width of 0.35–12 mm), which are used for the assessment of cutaneous spatial resolution. During the assessment, the experimenter presses the domes against the patient’s skin (right index finger pad, ring finger pad and lower lip, in a randomised order) in one of two orthogonal directions. The selection of these regions permits to test for learning effects on the trained finger (the right index finger) and a potential generalised effect for the hand (fourth digit) or even across body parts (lower lip), according to the representation of body parts in primary somatosensory cortex. The patient’s task is to report the orientation (vertical, horizontal) of the grating.

By using a screening audiometer (MA 25, MAICO Diagnostics GmbH, Berlin, Germany), we will create an audiogram, covering the frequency range from 125 Hz to 8 kHz, separately for the left and the right ear in counterbalanced order, using a staircase method for finding the respective threshold.

Sensorimotor processing
We will use the Purdue Pegboard Test (PPT), a neuropsychological assessment of manual dexterity and bimanual coordination, which consists of a board with two parallel rows with holes into which metal pegs can be placed by the participants either with the dominant, the non-dominant or both hands simultaneously at a set time. In a fourth trial, participants have to combine pegs, washers and small tubes to a predefined pattern. Thus, the test involves both gross movements of arms, hands and fingers, and fine motor dexterity. Poor PPT performance is a sign of deficits in complex, visually coordinated movements.40

Magnetic resonance imaging
We will implement a functional MRI (fMRI) paradigm39 for episodic memory-associated brain activity in patients with aMCI before and after intervention. In this task, we will present computer-generated stimuli, comprising every day indoor objects as well as empty indoor scenes. Stimuli will be displayed in pairs in which every stimulus either consists of two identical or two similar versions. Stimuli will be presented on an MR-compatible high-resolution screen and participants will watch them through a mirror attached to the MR head coil.

We will use a 3T Magnetom Trio MRI system (Siemens, Erlangen, Germany) and a 32-channel head coil. Prior to the fMRI session, we will obtain a whole-head 3D-MPRAGE with 1 mm isotropic resolution, field of view (FOV)=256×256 mm², repetition time (TR)/echo time (TE)/inversion time (TI)=2500/4.37/1100 ms, flip angle (FA)=7°. Subsequently, two fMRI runs will be recorded using gradient-echo echo-planar imaging with 2x2 mm² in-plane resolution, FOV=208x208 mm², TR/TE=2400/30 ms, 40 slices with 4.4 mm slice thickness (10% slice gap). One run will last for about 12 min.

For mapping of the somatosensory representation of the hand prior to and after training as a marker of sensory processing, we will use two short stimulation protocols applying soft touches using a custom-made pneumatic device.41 In the first trial, the five finger pads of the right hand will be equipped with pneumatic tactors and the fingers will be stimulated in randomised order in a block design consisting of on-blocks and off-blocks. In another run, the fingers will be continuously stimulated without the implementation of off-blocks. The second sequence, implementing a well-validated phase-encoding paradigm, will enable us to reveal highly reproducible maps of individual digits in primary somatosensory cortex, with relative position of individual digit representations.41

The two fMRI runs will be recorded using gradient-echo echo-planar imaging with 2x2 mm² in-plane resolution, FOV=220x220 mm², TR/TE=1500/22 ms, 22 slices with 1.8 mm slice thickness.

Treatment expectation/evaluation
Treatment expectation and evaluation will be assessed by five questions each asking for motivational aspects and expectations related to the experimental or control treatment before training (formulated in future tense) and after the training (evaluation, formulated in past tense; adapted from Borkovec and Nau42). In combination with a qualitative interview after the intervention about the participants’ treatment evaluation and the drop-out rate, these measures will serve to answer the question whether or not our training is perceived superior compared with the computerised cognitive training.

Procedure
Participants who fulfill the diagnostic criteria will be informed about the trial by the study physician who also collects written informed consent in the participants who are willing to participate. One researcher, who is blinded for the treatment, will then perform pre-measurements on sensory and cognitive functioning (see above). Only after these assessments, a second researcher, who is blinded for the tests results, will randomly assign participants to the experimental or the control treatment. Since adequate sensory capabilities are a key requirement for performing the tbSMT, participants who show deficits in the auditory and/or visual assessment are required to visit an acoustician and/or optician for potential (re)supply with hearing and/or visual aid prior to the experimental procedure.

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treatment. In order to prevent any time effects, participants assigned to the control treatment will also have to wait a similar period before starting the training. The second researcher will do the support during the treatment. He or she will call participants on a regular basis (about once per week) paying attention to not preferring any group. Furthermore, the second researcher is monitoring the data that will be sent daily from both trainings, and will intervene if peculiarities occur. After 8 weeks (ie, after unimodal and bimodal tasks in the experimental training), the second researcher will visit participants to provide the devices necessary for the sensorimotor tasks. Furthermore, he or she will repeat the CANTAB tests (repeated tests will be always performed with parallelised versions) as an interim assessment. Although no supply of new devices is required in the control training, he or she will also visit these participants after 8 weeks of training and will do the CANTAB testing. After another 4 weeks, all participants will be re-invited and the tests on sensory and cognitive functioning will be repeated by the first researcher who also conducted pre-assessments. We will do a follow-up after an additional 6 months where we will a) again assess cognitive functioning using the CANTAB test and b) re-evaluate the current state of the participants using the CERAD-Plus test battery in order to detect a potential transition to AD. The procedure of the trial is given in figure 1. After the trial has ended, participants will receive as usual medical care of the CIMH’s memory clinic and will be further followed up. First enrolment was in August 2017, and the study is still ongoing (completion of data acquisition is expected by the end of 2020).

Analysis
In line with the BMJ and Consolidated Standards of Reporting Trials guidelines, data analysis will be intent-to-treat. All participants who have been enrolled in a randomised manner will be included in analyses, including those who drop out. The main outcomes are a) episodic memory functioning and b) progress of aMCI and its potential transition to dementia. Thus, we will compare both groups for differences in these key variables as well as secondary outcomes. Although our focus is on MCI due to AD, we might have to include also other types of MCI; thus, we will further compare these subgroups in order to evaluate the specificity of the intervention. The problem of missing data will be handled by a multiple imputation approach.

Adverse events
We do not expect any adverse events caused by any of our treatment protocols; however, participants will be monitored by a physician experienced in geriatric psychiatry who could intervene if any unintended effects occur during the treatment. All spontaneously reported adverse events will be systematically documented.

Ethics and dissemination
Informed consent forms can be obtained from the corresponding author. The study has been registered at the German Clinical Trials Register, part of the German Cochrane Center and the Clinical Trials Unit of the University of Freiburg (DRKS00012748; see online supplementary appendix 2). The entry in the trial registry will be updated for any important changes of the trial protocol. The CIMH’s data monitoring committee will monitor the trial. The trial adheres to the General Data Protection Regulation of the European Union in its most recent form. Electronic or paper-pencil personal information of study participants is protected and monitored by the department’s data protection commissioner. Direct access to data will only be granted to authorised representatives from the host institution and the regulatory authorities.

Collaborations
Technical support for the tbSMT will be provided by one of its developers, Stefano Tamascelli (XTeam Software Solutions, Rovigo, Italy). The fMRI memory paradigm will be discussed with Emrah Düzel, head of the Institute of Cognitive Neurology and Dementia Research at the Magdeburg University, Germany.

DISCUSSION
Dementia, with AD being at the top of the list, ranks among the most urgent health problems in the world. At the beginning of the 21st century, the worldwide direct costs for dementia were estimated at US$156 billion, which might increase rapidly related to the increasing numbers of older persons. Although there has been much progress on the mechanisms of the disorder in the recent past, the breakthrough in terms of effective treatments has not yet been achieved.

With the present project, we follow a yet underexplored approach in countering cognitive decline in the early stages of dementia. Our tbSMT is expected to target the well-documented disruption of sensorimotor processing characterising pathological ageing. This approach could offer new treatment opportunities. Moreover, such results would implicate that maintaining sensorimotor functions across the lifespan could be an effective strategy in preventing age-related cognitive decline and dementia.

Methodological considerations
Our study has several strengths. First, the trial aims at evaluating the effects of a new potentially mechanism-based intervention for early stages of AD in comparison to a standard intervention with moderate success. Second, the state-of-the-art assessment process for detecting MCI due to AD, involving both neuropsychological variables and biomarkers, will potentially strengthen the interpretation of results. Third, the treatments have been conceived as a home-delivery intervention, lowering the threshold for implementation in daily care, particularly for the elderly.
Some limitations of the present study should also be noted. The study sample cannot be considered stochastic and representative for the population of patients with aMCI. First, we will recruit patients from the local memory clinic, which makes the included sample different to community-based samples. On the other hand, the stability of symptoms has been shown to be higher in clinical samples which is advantageous for the purposes of the present study. However, the conversion rate from MCI to AD in clinical populations is rather high (10%–15%). Although the current study is only funded up to 6 months post-training, we expect to be able to follow the patients in 6-month cycles to evaluate a potential delayed progression into dementia in the experimental versus the control condition.

CONCLUSION
In our clinical trial, we will test the hypothesis that age-related cognitive decline can be positively modulated by a sensorimotor training compared with a cognitive training. This type of treatment might offer new avenues for research as well as for preventing early forms of dementia in the future.

Contributors
HF conceived the study and obtained funding for the clinical trial. RBB, AL, SS, LF, LH, SD, DK and HF contributed to the conception and design of the study. RBB, AL and LH are involved in acquisition of data. RBB drafted the first version of the manuscript and AL, SS, LF, LH, SD, DK and HF edited and revised it and have approved its final version.

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Competing interests
None declared.

Patient consent for publication
Not required.

Ethics approval
The Medical Ethics Committee II of the Medical Faculty Mannheim, Heidelberg University, approved the study protocol (2015–543N-MA) which adhered to the Declaration of Helsinki in its current version.

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