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ABSTRACT

Introduction:

A growing body of evidence suggests that hearing loss is a significant and potentially modifiable risk factor for cognitive impairment. Additionally, hearing aid use has been associated with improved cognition. Although the mechanisms underlying the associations between cognitive decline and hearing loss are unclear, listening effort, has been posited as one of the mechanisms involved with cognitive decline in older age. To date, there has been a lack of research investigating this association, particularly among adults with Mild Cognitive Impairment (MCI).

Methods and analysis:

15-25 cognitively healthy participants and 15-25 patients with MCI (ages 40-85) will be recruited to participate in an exploratory study investigating the association between cognitive functioning and listening effort. Both behavioural and objective measures of listening effort will be investigated. The Sentence-Final Word Identification and Recall test in varying levels of background noise will be administered while monitoring pupil dilation. Evaluation of cognitive function will be carried out in a clinical setting using a battery of neuropsychological tests. Participants will use Oticon Opn S 1 miniRITE hearing aids for six weeks and will be re-tested on both listening effort and cognitive function measures. Independent sample t-tests will be used to test the significance between groups in cognitive function and listening effort, and dependent sample t-tests between baseline and re-testing after the

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hearing aid trial. Regression analysis will be applied to investigate the association between cognitive functioning and listening effort scores. This study is considered proof-of-concept, with information taken to help decide the validity of larger-scale trials.

Ethics and Dissemination

Written approval exemption was obtained by the Scientific Ethics Committee in the Central Region of Denmark (De Videnskabsetiske Komiteer i Region Hovedstaden), refernce 19042404, and the project is registered at clinicaltrials.gov, identifier NCT04593290. Study results will be disseminated in peer-reviewed journals and conferences.

ARTICLE SUMMARY

Strength and limitations of this study

- This is to our knowledge the first study to examine both behavioural and objective measures of listening effort and cognitive function in participants with and without cognitive dysfunction.
- A growing body of evidence suggests that an early intervention relating to hearing impairment may be valuable for the identification, management and prevention of cognitive decline.
- Enabling representatives from cognitive management and hearing health care fields to combine their expertise to support the execution of this study.
- Limited by the lack of previous studies in the area the sample size for this study is not based on prior estimation of effect size or statistical powering.

INTRODUCTION

Research suggests an association between hearing loss and cognitive decline, with even mild levels of hearing loss being associated with the long-term risk of cognitive decline and dementia.[1–3] A seminal report in The Lancet has also suggested that hearing loss is one of the most prominent modifiable risk factors for dementia in mid-to-late stages of life.[3,4] Age-related hearing loss is also a marker for frailty in older age.[5–7] Despite increasing research in the fields of hearing loss and cognitive decline, there is little known about the underlying mechanisms between these processing difficulties. One possible

pathway involves listening effort, defined by McGarrigle et al.[8] and the British Society of Audiology Cognition in Hearing (BSA) as "the mental exertion required to attend to, and understand, an auditory message" (pp. 2). This has been explained alongside the notion of cognitive compensation, where a decline in sensory processing occurs alongside an increase in the recruitment and use of other cognitive areas.[9–11] This requires an increased reliance top-down mechanisms, and is supported by neuroimaging research that demonstrates the association between patterns of overactivation and age-equivalent performance. Over time, these compensatory effects decrease and may no longer able to offset the further deterioration of cognitive function.[5,12–15] Previous research investigating hearing and cognition have primarily demonstrated associations with processing speed, executive function and memory.[2,16,17] Mild Cognitive Impairment (MCI) generally refers to a stage of cognitive dysfunction that lies between normal cognitive function and dementia. Those with MCI have preserved function in daily activities; however, they may have minor impairment in complex instrumental functions and all score below normative levels on objective cognitive tasks. Those with MCI are also at higher risk for further cognitive decline and the later onset of dementia. For those with MCI who are later diagnosed with dementia, functions such as memory, attention, perceptual speed and executive functioning are further impaired.[18] Speech perception, particularly in noisy environments, requires processes such as inhibitory control, attention and working memory.[11] Therefore, it is particularly relevant to investigate the association between these related functions in a population with mild cognitive dysfunction and increased risk for further cognitive decline. This will provide insight that may guide the design and development of a future complex healthcare intervention aimed at slowing or mitigate the negative impact of cognitive decline in this population.[19]

The assessment of hearing loss has traditionally focused on pure-tone and speech audiometry as measurements of speech and sound recognition at standardised thresholds. However, this does not, account for the effort that is exerted or the fatigue that is experienced in complex listening situations – a common patient complaint within audiology.[11] In a study by Jayakody et al.,[20] older adults with moderately-severe hearing loss performed significantly worse non-verbal tests of spatial working

memory, episodic visuospatial memory, learning and association ability and psychological function in comparison to older adults with normal hearing. A recent meta-analysis and systematic review demonstrated that a combined cognitive and auditory training approach was most optimal for improving cognition among adults with hearing loss.[21] Although no causal links have been established, research has also found that hearing rehabilitation in the form of hearing aid use is associated with improved cognition and a delayed dementia diagnosis.[22–24] Hearing aid use has also been associated with improved word recall and dual-task response times in those with mild to severe hearing loss.[25] Thus far, little research has investigated hearing aid use among individuals without a demonstrable hearing loss. In this study, we investigate the association between listening effort and cognitive functioning among older adults without cognitive dysfunction and with MCI – all without significant levels of hearing loss. Furthermore, we investigate subsequent listening effort and cognitive functioning after six weeks of hearing aid use. A significant association between listening effort and cognitive function may act as an entry point for future research into listening effort and cognitive decline. The insights gained from our current research are also aimed at assessing potential barriers and benefits of hearing aid use for a population at risk for cognitive decline – particularly those who have begun to experience increased listening effort without clear signs of peripheral hearing loss.

Research Questions

Overall research question

The aim of this study is to investigate the association between cognitive functioning and listening effort among older healthy adults and in older memory clinic patients with MCI.

Secondary research questions

- To determine whether there is a significant difference in listening effort between older healthy adults and MCI patients.
- To determine whether hearing aid use has a significant impact on both listening effort and cognitive function in older healthy adults and MCI patients.

METHODS AND ANALYSIS

Research design

This is an exploratory proof-of-concept study and an exploratory intervention study with hearing aids in the context of listening effort. With a case (MCI) and control group (cognitively healthy), we will investigate the associations between listening effort and cognitive function and assess the effect of hearing aid use on both listening effort and cognitive function after a period of six weeks.

Study procedures

We will recruit 30-50 participants. Half of these participants (n=15-25) will be individuals who have been diagnosed with MCI. They will be recruited at the Danish Dementia Research Centre, Rigshospitalet Denmark and will be diagnosed by a multi-disciplinary team after comprehensive diagnostic work-up including neurological examination, blood tests, neuropsychological assessment, structural imaging (Magnetic Resonance Imaging) and in most cases functional imaging (FDG-PET) and lumbar puncture. The control group of participants (n=15-25) will be cognitively healthy individuals, recruited via advertisements in local newspapers, community centres in and around Copenhagen and a website for recruiting research participants in Denmark (forsoegsperson.dk). All participants will undergo both listening effort testing,[26] coupled with pupillometry,[27] and cognitive performance testing, based on a battery of neuropsychological tests (see Table 1). After six weeks of hearing aid use, participants will be retested on these measures. There is not sufficient literature to support a sample size calculation for this association study; however, this study may guide power calculations in future studies.

Study sample

Eligibility

MCI participants: inclusion criteria

- MCI diagnosis, according to recommendations in Winblad et al.[18]
    - Not normal, not fulfilling diagnostic criteria for dementia

- Functional activities are mainly preserved
- Evidence of cognitive decline, measured by self-report in conjunction with deficits on objective cognitive tasks, operationalised as test scores below -1.5 standard deviation below age and education adjusted normative data

- Mini Mental State Examination score ≤ 26;
- 40-85 years old;
- No other significant neurological or psychiatric disease;
- Normal hearing, defined as a pure tone threshold of ≤ 20 decibels (dB) 250 hertz (Hz) - 1 kilohertz (kHz); ≤ 25 dB between 2-3 kHz; ≤ 30 dB at 4 kHz (one five dB increase in one ear, one frequency is accepted);
- Clinical Dementia Rating = 0.5;
- Danish as native language;
- Has live-in informant.

Cognitively healthy participants: inclusion criteria

- 40-85 years old;
- Mini Mental State Examination score ≥ 26;
- CDR Global score = 0;
- No significant neurological or psychiatric disease;
- Normal hearing; defined as a pure tone threshold of ≤ 20 decibels (dB) 250 hertz (Hz) - 1 kilohertz (kHz); ≤ 25 dB between 2-3 kHz; ≤ 30 at 4 kHz (one five dB increase in one ear, one frequency is accepted);
- Danish as a native language.

Exclusion criteria: all participants

- Medication or treatment that could impact the pupillary dilation: eye drops (e.g. atropine or phenylephrine);

- Medication that could impact cognitive function;
- Alcohol or drug abuse;
- Unable to comply with study procedures.

Pure Tone Audiometry

During screening, hearing will be assessed using Pure Tone Audiometry. This measure involves the peripheral and central auditory systems, identifying the hearing threshold levels of an individual and providing a basis for traditional hearing loss diagnosis and management.[28]

Mini Mental Status Examination

The Mini Mental State Exam includes tests of orientation, attention, memory, language and visual-spatial skills. It is a widely used test of cognitive dysfunction.[29,30]

Clinical Dementia Rating

The Clinical Dementia Rating is a 5-point scale used to assess cognitive function through a semi-structured interview with both the patient and a reliable informant, such as a family member. This 0-3 scale covers six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care.[31,32]

Measures

Cognitive function

Assessment scores for cognitive function will be recorded in a clinical setting, and will be based on a battery of neuropsychological tests (see Table 1).

Table 1 Neurocognitive tests used to measure cognitive function

Test	**Cognitive abilities measured**
Stroop Test[33]	Processing speed, selective attention, automaticity, inhibition

Trail Making Test [34]	Visual search speed, scanning, speed of processing, mental flexibility
Symbol-Digit Modalities Test [35,36]	Attention, processing speed, oculomotor scanning, working memory, motor persistence, visuomotor coordination
Verbal Fluency Tests (category, lexical)	Language representations of semantic concepts, central executive component of working memory, mental speed
Rey Complex Figure Test[37]	Visuospatial abilities, non-verbal memory, planning
Logical Memory (part A)[38]	Narrative episodic verbal memory, delayed recall, verbal recognition

The Stroop test is a demonstration of cognitive interference where a delay in the reaction time of a task occurs due to a mismatch in stimuli. A 40-item version will be applied, which will assesses processing speed, selective attention and automaticity.[33]

The Trail Making Test (part A & B) measures visual attention and task-switching. It consists of two parts, whereby the subject is instructed to connect a set of 25 numbers and number/letters as quickly as possible while still maintaining accuracy.

The Symbol-Digit Modalities Test is a symbol substitution test that examines attention and speed of processing. This test requires a person to substitute geometric symbols for numbers while scanning a response key.[35]

Verbal fluency tests are widely used as measures of language and executive functions. Category fluency tasks rely on language representations of semantic concepts, whereas lexical and action word tasks rely more on the central executive component of working memory.[39]

The Rey Complex Figure Test is an assessment where examinees are asked to reproduce a line drawing, first by copying it freehand and then drawing it from recall.[37]

The Logical Memory test is a subtest of the Wechsler Memory Scale—Third Edition, and is a standardised assessment of narrative episodic memory.[38] A short story is orally presented and the

examinee is asked to recall the story verbatim (immediate recall). Approximately 20 minutes later, free recall of the story is again elicited (delayed recall) and recognition is also measured. Only part A is administered in this study.

Sentence-final word identification and recall test

The objective measure of listening effort, pupil dilation, will be recorded as a measure of task performance accuracy. This will be measured during a sentence-final word identification and recall test, a dual-task behavioural test used to measure the effect of listening on performance on a secondary memory task.[26,40] The test consists of two tasks which are performed in series. The participants are asked to report the final word of each of seven sentences right after each sentence has been played (identification task), and they are encouraged to guess if they are unsure of the word. After reporting the final word of the seventh sentence of a list, they are asked to recall, in any order, all the words that they had previously reported (free recall task). The order of sentence presentation within each set is randomised between participants. Prior to the test, participants undergo an adaptive Danish Hearing in Noise Test (HINT)[41], comprising a list of equally intelligible sentences to be repeated in varying levels of background noise. The individual's speech reception threshold will be set at 80% correct responses which we hypothesise should load working memory enough for inter-individual differences in effort to become apparent while maintaining attentional engagement.[42,43]

Pupillometry

Physiological measures have the benefit of increased, time-bound insight into cognitive load changes during the process of understanding. Pupil dilation has been shown to fluctuate with changes in cognitive task load, and that these changes reflect the variation in cognitive demands and the cognitive load required to perform these tasks.[23,24] Pupillometry is increasingly being used as an objective indicator of effort allocation for listening. memorising and auditory conflict tasks.[27,44–46] In this study, the participant is fitted with PupilLabs' eye-tracking add-on for the HTC Vive virtual reality head-mounted display. To prevent floor and ceiling effects that are independent to baseline pupil size, the illumination

within the display is individually adapted to the individual's pupil size midpoint prior to data collection between dim (~30 lux) and bright (~230 lux), with an average illuminance of 110 lux. A software suite allows the capture and post-processing of the data feed, including pupil diameter. For the purpose of this study, the PupilLabs software is controlled via a MATLAB interface.

Hearing aid intervention

Participants will be administered Oticon Opn S 1 miniRITE hearing aids for a period of six weeks. All cognitively healthy participants will be invited to participate, while only MCI patients with a live-in informant will receive this intervention. Hearing aid fitting will occur wirelessly using the Oticon Genie 2 fitting software. The fitting protocol uses open domes, a speaker level of 60 dB and the National Acoustic Laboratories Nonlinear 2 (NAL-NL2) gain prescription procedure. For soft and moderate input levels between 750 Hz and 4 kHz, an average of 5-10 dB gain will be added to the NAL-NL2 prescribed gain for the respective hearing threshold deviation from 0 dB of hearing loss. The open sound transition in the OpenSound Navigator feature of the Opn S 1 hearing aids will be set to 'high' and the adaptive microphone settings will be set to 'Open Automatic'. This multi-microphone beamforming algorithm selectively attenuates noise sources and preserves access to a wider range of speech and sounds while removing noise between words.[47] The background noise reduction in both simple environments, with low reverberation and few disturbing sound sources, and complex environments, with high sound levels and multiple sound sources, will be set to a maximum (-9 dB and -3 dB, respectively). By providing amplification with noise reduction and directionality, the signal-to-noise ratio can be increased for speech signals in a wider range of environments, which is hypothesised to provide a more comfortable listening experience and an ease of listening effort.

Data analysis

Independent sample t-tests will be used to test the significance between groups in cognitive function and listening effort, and dependent sample t-tests between baseline and re-testing after the hearing aid trial. Regression analysis will be applied to investigate the association between cognitive functioning and

listening effort scores. This study is considered proof-of-concept, with information taken to help decide the validity of larger-scale trials.

Participant and patient involvement

There was no direct patient or public involvement in the study design. Input and feedback from participants during hearing aid use will be taken into consideration during the planning of future research and will contribute to knowledge surrounding the motivators and barriers towards hearing aid use among an older population and an MCI patient group. The Listen Carefully research project has been presented to potential future stakeholders within the municipality, such as those working within dementia care coordination and welfare innovation. Those who have been consulted and collaborated with throughout the research will receive a summary of results. Patients and participants will also be provided with a summary of results upon request.

Study timeline

Recruitment for the study began in July 2020. The first participant, first visit took place in August 2020 and the last participant, last visit is planned for June 2021.

DISCUSSION

Despite increasing research in the fields of hearing loss and cognitive decline, little is known about the mechanisms linking hearing loss to cognitive decline, and whether some of these mechanisms may account for some of the cognitive challenges observed in individuals with MCI, who do not demonstrate significant hearing loss. In particular, if listening effort does play a role in the association between hearing loss and cognitive decline, it may be reasonable to expect that individuals with MCI exhibit different patterns of listening effort, compared to normal cognition controls. With increased amplification in higher frequencies and improved signal-to-noise ratio, our investigation of the influence of using hearing aids in these cohorts may reveal benefits (reduction) in listening effort that could well translate into benefits in cognitive functioning over a longer time period. The insights gained from this study should therefore help

refine our understanding of factors that could later inform complex hearing and cognitive healthcare interventions.[19]

ETHICS AND DISSEMINATION

Written approval exemption was obtained by the Scientific Ethics Committee in the Central Region of Denmark (De Videnskabsetiske Komiteer i Region Hovedstaden), case number 19042404 and the project is registered at clinicaltrials.gov, identifier NCT04593290. Access to study records will be limited to the study team, which includes the relevant researchers at the Memory Clinic in Copenhagen. This includes source documents, regulatory documents, data collection instruments and study data.

Only the investigators will have access to the data and will be responsible for data processing. This will not include the participant's contact or identifying information. Rather, individual participants and their personal data will be identified by a unique study identification number. Only fully anonymised data will be published in reports, scientific publications or clinical study outcomes. Regardless of findings, the results of the research will be published.

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Author's contributions

The concept and design were constructed and refined by AF, FP, MB, GW, AM, and AV. Study coordination and data collection will be conducted by AF, OJ and AB. Analysis will be performed by PYH and AF. AF composed the first draft of the manuscript. All authors provided feedback, guidance, and academically relevant insight towards the final draft.

Competing interests

Authors Monika Baumann and Francois Patou are affiliated with Demant subsidiaries, of which Oticon A/S provided hearing aids audiometric testing equipment for the purposes of this study.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents* (addressed in full protocol document, referred to in listed page numbers)

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	17
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	Footer
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 13
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	(see 9)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	(see 8-9)
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17-20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17-20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	28-31
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The Listen Carefully protocol: An exploratory study of the association between listening effort and cognitive function

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The Listen Carefully protocol: An exploratory study of the association between listening effort and cognitive function

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The Listen Carefully protocol: An exploratory study of the association between listening effort and cognitive function

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ABSTRACT

Introduction:

A growing body of evidence suggests that hearing loss is a significant and potentially modifiable risk factor for cognitive impairment. Although the mechanisms underlying the associations between cognitive decline and hearing loss are unclear, listening effort, has been posited as one of the mechanisms involved with cognitive decline in older age. To date, there has been a lack of research investigating this association, particularly among adults with mild cognitive impairment (MCI).

Methods and analysis:

15-25 cognitively healthy participants and 15-25 patients with MCI (ages 40-85) will be recruited to participate in an exploratory study investigating the association between cognitive functioning and listening effort. Both behavioural and objective measures of listening effort will be investigated. The Sentence-Final Word Identification and Recall (SWIR) test will be administered with single talker non-intelligible speech background noise while monitoring pupil dilation. Evaluation of cognitive function will be carried out in a clinical setting using a battery of neuropsychological tests. This study is considered exploratory and proof-of-concept, with information taken to help decide the validity of larger-scale trials.

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Ethics and Dissemination

Written approval exemption was obtained by the Scientific Ethics Committee in the Central Region of Denmark (De Videnskabsetiske Komiteer i Region Hovedstaden), reference 19042404, and the project is registered at clinicaltrials.gov, identifier NCT04593290. Study results will be disseminated in peer-reviewed journals and conferences.

ARTICLE SUMMARY

Strength and limitations of this study

- This is to our knowledge the first study to examine both behavioural and objective measures of listening effort and cognitive function in participants with and without cognitive dysfunction.
- A growing body of evidence suggests that an early intervention relating to hearing impairment may be valuable for the identification, management and prevention of cognitive decline.
- Enabling representatives from cognitive management and hearing health care fields to combine their expertise in support of the execution of this study.
- Limited by the lack of previous studies conducted listening effort testing using pupillometry among MCI patients, the sample size for this study is not based on prior estimation of effect size or statistical powering.

INTRODUCTION

Research suggests an association between hearing loss and cognitive decline, with even mild levels of hearing loss being associated with the long-term risk of cognitive decline and dementia.[1–3] A seminal report in The Lancet has also suggested that hearing loss is one of the most prominent modifiable risk factors for dementia in mid-to-late stages of life.[3,4] Age-related hearing loss is also a marker for frailty in older age.[5–7] Despite increasing awareness of the links between sensory and cognitive deterioration as well as increasing research in the fields of hearing loss and cognitive decline, little is known about the mechanisms linking hearing loss to cognitive decline or about whether any of these mechanisms may account for some of the cognitive challenges observed in individuals with mild cognitive impairment

(MCI).[8,9] Beyond audiometric variations in hearing, research increasingly shows that cognitive factors such as attention and memory also play an important role in speech understanding.[10–12] Even if individuals achieve the same level of speech intelligibility, they may disproportionately distribute cognitive resources in order to do so.

One possible pathway involves listening effort, defined by McGarrigle et al.[13] and the British Society of Audiology Cognition in Hearing (BSA) as "the mental exertion required to attend to, and understand, an auditory message" (pp. 2). Speech understanding depends on phonological and semantic factors which are reliant on working memory capacity.[14–16] When the speech input doesn't easily match an individual's phonological representation, explicit and deliberate working memory processes are engaged. When the signal is distorted or presented alongside increased noise, for example, increased capacity is required to reach understanding. As the signal is maintained in working memory, fewer cognitive resources remain for retention.

In the Framework for Understanding Effortful Listening, listening effort is separated from pure intelligibility and is described as a deliberate allocation of mental resources. This dimension varies over time as a function of an individual's capacity to meet the demand and their motivational arousal.[17,18] Described as intentional attentional engagement, the motivation dimension reflects the individual assessment of arousal and fatigue on the valuation of the task in relation to the expenditure of available resources. In Strauss and Francis' taxonomic model of attention in effortful listening, sensory processing relies on the interaction between externally directed perceptual attention and internally directed central attention that employs executive functions such as working memory.[12]

Listening effort has also been explained alongside the notion of cognitive compensation, where a decline in sensory processing occurs alongside an increase in the recruitment and use of other cognitive areas.[17,19,20] The decline requires an increased reliance top-down mechanisms, and is supported by neuroimaging research that demonstrates the association between patterns of overactivation and age-equivalent performance. Over time, these compensatory effects decrease and may no longer able to offset

the further deterioration of cognitive function. This not only increases fatigue, but also decreases the amount of resources available to meet the demands of a given task.[5,21–24]

Previous research investigating hearing and cognition have primarily demonstrated associations with processing speed, executive function and memory.[2,25,26] Speech perception, particularly in noisy environments, requires processes such as inhibitory control, attention and working memory.[17] The assessment of hearing loss has traditionally focused on pure-tone and speech audiometry as measurements of speech and sound recognition at standardised thresholds. However, the effort exerted or the fatigue experienced in complex listening situations—a common patient complaint within audiology—is not assessed.[17]

Jayakody et al.,[27] found that older adults with moderately severe hearing loss performed significantly worse on nonverbal tests of spatial working memory, episodic visuospatial memory, learning and association ability and psychological function than did older adults with normal hearing. A recent meta-analysis and systematic review demonstrated that a combined cognitive and auditory training approach was most optimal for improving cognition among adults with hearing loss.[28] Although no causal links have been established, research has also found that hearing rehabilitation in the form of hearing aid use is associated with improved cognition and a delayed dementia diagnosis.[29–31]

Mild cognitive impairment (MCI) generally refers to a stage of cognitive dysfunction that lies between normal cognitive function and dementia. Those with MCI have preserved function in daily activities; however, they may have minor impairment in complex instrumental functions and all score below normative levels on objective cognitive tasks. Those with MCI are also at higher risk for further cognitive decline and the later onset of dementia. For those with MCI who are later diagnosed with dementia, functions such as memory, attention, perceptual speed and executive functioning are further impaired.[32]

In this study, we investigate the association between listening effort and cognitive functioning among older adults without cognitive dysfunction and with MCI—all without significant levels of hearing loss. A significant association between listening effort and cognitive function may act as an entry point for future research into listening effort and cognitive decline. The insights gained from our current research are

aimed at assessing a population at risk for cognitive decline—particularly those who have begun to experience increased listening effort without clear signs of peripheral hearing loss. This study is the first to examine both behavioural and objective measures of listening effort and cognitive function in participants both with and without cognitive dysfunction.

Research Questions

Overall research question

The aim of this study is to investigate the association between cognitive functioning and listening effort among older healthy adults and in older memory clinic patients with MCI.

Secondary research question

- To determine whether there is a significant difference in listening effort between older healthy adults and MCI patients.

METHODS AND ANALYSIS

Research design

This is an exploratory proof-of-concept study with a case (MCI) and control group (cognitively healthy), where we will investigate the associations between listening effort and cognitive function.

Study procedures

Study sample

We will recruit 30-50 participants over a one-year interval. As we are investigating a potential factor in early stages of cognitive decline, potentially occurring in mid-stages of life, a wide age range is used (40-85 years) to ensure external validity for participants both with and without cognitive dysfunction. Half of these participants (n=15-25) will be individuals who have been diagnosed with MCI (see table 1). They will be recruited at the Danish Dementia Research Centre, Rigshospitalet Denmark and will be diagnosed by a multi-disciplinary team after comprehensive diagnostic work-up including neurological examination, blood tests, neuropsychological assessment, structural imaging (Magnetic Resonance Imaging) and in

most cases functional imaging (FDG-PET) and lumbar puncture. The control group of participants (n=15-25) will be cognitively healthy individuals, recruited via advertisements in local newspapers, community centres in and around Copenhagen and a website for recruiting research participants in Denmark (forsoegsperson.dk). Table 1 shows the inclusion and exclusion criteria for MCI and cognitively healthy participants. All participants will undergo both listening effort testing, coupled with pupillometry, and cognitive performance testing, based on a battery of neuropsychological tests (see table 2).

Table 1 Inclusion/exclusion criteria

	MCI participants	Cognitively healthy participants

Inclusion criteria	• MCI diagnosis, according to recommendations in Winblad et al.[32]
	  ○ Not normal, not fulfilling diagnostic criteria for dementia
	  ○ Functional activities are mainly preserved
	  ○ Evidence of cognitive decline, measured by self-report in conjunction with deficits on objective cognitive tasks, operationalised as test scores below -1.5 standard deviation below age and education
		▪ 40-85 years old;
		▪ Mini Mental State Examination score ≥ 26;
		▪ CDR Global score = 0;
		▪ No significant neurological or psychiatric disease;
		▪ Normal hearing; defined as a pure tone threshold of ≤ 20 decibels (dB) 250 hertz (Hz) - 1 kilohertz (kHz); ≤ 25 dB between 2-3 kHz; ≤ 30 at 4 kHz (one five dB increase in one ear, one frequency is accepted);
		▪ Danish as a native language.

	adjusted normative data • Mini Mental State Examination score ≤ 26; • 40-85 years old; • No other significant neurological or psychiatric disease; • Normal hearing, defined as a pure tone threshold of ≤ 20 decibels (dB) 250 hertz (Hz) - 1 kilohertz (kHz); ≤ 25 dB between 2-3 kHz; ≤ 30 dB at 4 kHz (one five dB increase in one ear, one frequency is accepted); • Clinical Dementia Rating = 0.5; • Danish as native language; • Has live-in informant.
Exclusion criteria (all)	▪ Medication or treatment that could impact the pupillary dilation: eye drops (e.g. atropine or phenylephrine); ▪ Medication that could impact cognitive function; ▪ Alcohol or drug abuse; ▪ Unable to comply with study procedures.

Eligibility

Pure Tone Audiometry

During screening, hearing will be assessed using Pure Tone Audiometry, a pure-tone air conduction audiometric test method that matches the International Standards Organization (ISO) 8253-1:2010 guidelines.[33] This measure involves the peripheral and central auditory systems, identifying the hearing threshold levels of an individual and providing a basis for traditional hearing loss diagnosis and management. Otoscopy will also be used to examine the ear canal for impacted cerumen. We define normal hearing based on the World Health Organization's hearing impairment grading system, and have adapted thresholds above 25 dB at 4 kHz to account for the average hearing levels for men and women in older age groups, as described by ISO-7029.[34,35]

Mini Mental Status Examination

The Mini Mental State Exam includes tests of orientation, attention, memory, language and visual-spatial skills. It is a widely used test of cognitive dysfunction.[36,37]

Clinical Dementia Rating

The Clinical Dementia Rating is a 5-point scale used to assess cognitive function through a semi-structured interview with both the patient and a reliable informant, such as a family member. This 0-3 scale covers six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care.[38,39]

Measures

Cognitive function

Assessment scores for cognitive function will be recorded in a clinical setting, and will be based on a battery of neuropsychological tests (see Table 1).

Table 2 Tests used to measure cognitive function

Test	Cognitive abilities measured
Stroop Test[40]	Processing speed, selective attention, automaticity, inhibition
Trail Making Test [41]	Visual search speed, scanning, speed of processing, mental flexibility
Symbol-Digit Modalities Test [42,43]	Attention, processing speed, oculomotor scanning, working memory, motor persistence, visuomotor coordination
Verbal Fluency Tests (category, lexical)	Language representations of semantic concepts, central executive component of working memory, mental speed
Rey Complex Figure Test[44]	Visuospatial abilities, non-verbal memory, planning
Logical Memory (part A)[45]	Narrative episodic verbal memory, delayed recall, verbal recognition

The Stroop test is a demonstration of cognitive interference where a delay in the reaction time of a task occurs due to a mismatch in stimuli. A 40-item version will be applied, which will assesses processing speed, selective attention and automaticity.[40]

The Trail Making Test (part A & B) measures visual attention and task-switching. It consists of two parts, whereby the subject is instructed to connect a set of 25 numbers and number/letters as quickly as possible while still maintaining accuracy.

The Symbol-Digit Modalities Test is a symbol substitution test that examines attention and speed of processing. This test requires a person to substitute geometric symbols for numbers while scanning a response key.[42]

Verbal fluency tests are widely used as measures of language and executive functions. Category fluency tasks rely on language representations of semantic concepts, whereas lexical and action word tasks rely more on the central executive component of working memory.[46]

The Rey Complex Figure Test is an assessment where examinees are asked to reproduce a line drawing, first by copying it freehand and then drawing it from recall.[44]

The Logical Memory test is a subtest of the Wechsler Memory Scale—Third Edition, and is a standardised assessment of narrative episodic memory.[45] A short story is orally presented and the examinee is asked to recall the story verbatim (immediate recall). Approximately 20 minutes later, free recall of the story is again elicited (delayed recall) and recognition is also measured. Only part A is administered in this study.

Listening effort

The Framework for Understanding Effortful Listening, the Ease of Language Understanding model and Strauss and Francis'[12] taxonomic model of attention in effortful listening outline a number of cognitive and linguistic factors that moderate both effort and performance hearing ability.[12,15,17] Beyond subjective and behavioural measures, physiological measures have the benefit of time-bound insight into cognitive load changes and resource allocation during the process of understanding.[47] They may also allow more deeper insight into the neurocognitive mechanisms underlying listening effort.[12] Pupil dilation has been shown to fluctuate with changes in cognitive task load, indicating the variation in cognitive demands and the cognitive load required to perform these tasks.[48] Dilation of the pupil is also associated with the locus coeruleus-noradrenergic system, suggesting its ability to both control the muscles of the iris and reflect wider changes in attention.[49] Pupillometry is increasingly being used as an objective indicator of effort allocation for listening, memorising and auditory conflict tasks.[47,50–52]

Pupillometry hardware and software

In this study, the participant is fitted with PupilLabs' eye-tracking add-on for the HTC Vive virtual reality head-mounted display. To prevent floor and ceiling effects that are independent to baseline pupil size, the illumination within the display is individually adapted to the individual's pupil size midpoint prior to data collection between dim (~30 lux) and bright (~230 lux), with an average illuminance of 110 lux. A software suite allows the capture and post-processing of the data feed, including pupil diameter, dilation

at sentence baseline and latency between sentence onset and peak pupil diameter. The PupilLabs software is controlled via a MATLAB interface. Participants will be instructed not to drink coffee at least four hours before testing, and will be asked to wash off or refrain from wearing any eye makeup. Real-time monitoring of the eye during pupil measurement will occur to check for eye closures and head movements, and the confidence interval on the PupilLab's software will be regularly observed. After measurement, all data will undergo a subjective quality check with a sampling rate of 60 Hz, blink span removal below 35 and above 75 milliseconds, moving average span 0.5 seconds, baseline from 4.2 to 5.2 seconds and peak pupil diameter range from 5.2 to 9.7 seconds. To detect dilation speed outliers, the median absolute deviation will be used. If the ratio of missing pupil data in a list exceeds 40% after deblinking, it will be discarded from analysis.

Sentence-Final Word Identification and Recall (SWIR) test

The objective measure of listening effort, task-evoked pupil dilation, will be recorded during a Sentence-Final Word Identification and Recall (SWIR) test, a dual-task behavioural test used to measure the effect of listening on performance on a secondary memory task.[53,54] The test consists of a single condition of two tasks performed in a seven-sentence series. The participants are asked to report the final word after each sentence has been played (identification task), and they are encouraged to guess if they are unsure of the word. After reporting the final word of the seventh sentence, there is a 0.5 second beep tone and they are instructed to recall, in any order, all the words that they had previously reported (free recall task). The order of sentence presentation within each set is randomised between participants. Playing from a loudspeaker placed at 0° azimuth, the target speech (sentences), spoken by a male speaker, is set at 65 dB and played simultaneously with the International Speech Test Signal (noise), a single female talker which includes non-intelligible speech properties from American English, Arabic, Chinese, French, German and Spanish.[55] This masker signal begins two seconds before sentence onset and ends two seconds after sentence onset (see Figure 1).

Prior to the test, participants undergo an adaptive Danish Hearing in Noise Test (HINT) to determine the appropriate level of background noise during the SWIR test.[56] The HINT contains a list of equally

intelligible sentences to be repeated in varying dB levels of white noise. This results in the individual's speech reception threshold, set at 80% correct responses (see Figure 2). This value is used to set the SWIR masker level either above or below the 65 dB level of the target track. Listening effort changes as a function of the signal-to-noise ratio, and based on the framework for understanding effortful listening, is moderated by both the demands of the task and individual motivation. Previous research using the SWIR test with pupillometry has been administered to a population without cognitive dysfunction. Based on FUEL, it is possible that fatigue, motivation and/or the evaluation of demands on available capacity may influence the allocation of effort during recall, and thereby the pupil dilation response.[17] Given previous research using older adults both with and without hearing loss, we expect a speech reception threshold at 80% to load working memory without overloading its capacity, making inter-individual differences in effort apparent while maintaining attentional engagement.[51,57–60]

Data analysis

Group by group comparisons will be applied to assess significant differences in listening effort and its association with cognitive function between normal cognition controls and MCI patients. To assess the presence of a significant association between cognitive functioning and listening effort, a data analysis plan will be used. As several measures of cognitive function and listening effort are administered, this will limit the effect of multiplicity.

The primary analysis will use three neuropsychological variables: 1) Stroop Test (time on incongruent version), 2) Symbol-Digit Modalities Test and 3) Logical Memory Test (recall score part 1). Correlation analysis with these measures and the following listening effort measures will be administered: 1) average peak pupil diameter, 2) average pupil size during baseline (during noise before sentence onset), 3) average latency between sentence onset and peak pupil diameter.

Correlation analyses (e.g. Pearson correlation coefficient) will be completed for the entire participant group on all measures. If significant associations are found, further analysis will be conducted separately

in the two participant groups. If significant, linear regression will be performed using the significant cognitive test scores as dependent variables and listening effort outcomes as independent variables (together with relevant co-variates, e.g. gender and age). If significant associations are demonstrated between the three selected neuropsychological tests and the listening effort parameters, additional cognitive measures will be included for further analysis. If no significant associations are found in the initial analysis, further analysis will not be conducted.

Participant and patient involvement

There was no direct patient or public involvement in the study design. Input and feedback from participants during hearing aid use will be taken into consideration during the planning of future research and will contribute to knowledge surrounding the motivators and barriers towards hearing aid use among an older population and an MCI patient group. The Listen Carefully research project has been presented to potential future stakeholders within the municipality, such as those working within dementia care coordination and welfare innovation. Those who have been consulted and collaborated with throughout the research will receive a summary of results. Patients and participants will also be provided with a summary of results upon request.

Study timeline

Recruitment for the study began in July 2020. The first participant, first visit took place in August 2020 and the last participant, last visit is planned for December 2021.

DISCUSSION

Despite increasing research in the fields of hearing loss and cognitive decline, little is known about the mechanisms linking hearing loss to cognitive decline, and whether some of these mechanisms may account for some of the cognitive challenges observed in individuals with MCI, who do not demonstrate significant hearing loss. In particular, if listening effort does play a role in the association between hearing and cognitive decline, it may be reasonable to expect that individuals with MCI exhibit different patterns

of listening effort compared to those without cognitive dysfunction, particularly in relation to working memory and internally directed central attention.[12] This may aid the understanding of which cognitive factors are influenced by effortful listening. Furthermore, the sensitivity of pupillometry may allow us to assess the engagement and the experience of fatigue among a group with cognitive dysfunction when completing the dual-task behavioural SWIR test. In particular, it is expected that the will provide valuable insights for its future use among those with cognitive dysfunction, and the insights gained from this study should therefore help refine our understanding of factors that could later inform complex hearing and cognitive healthcare interventions.[61]

ETHICS AND DISSEMINATION

Written approval exemption was obtained by the Scientific Ethics Committee in the Central Region of Denmark (De Videnskabsetiske Komiteer i Region Hovedstaden), case number 19042404 and the project is registered at clinicaltrials.gov, identifier NCT04593290. Access to study records will be limited to the study team, which includes the relevant researchers at the Memory Clinic in Copenhagen. This includes source documents, regulatory documents, data collection instruments and study data.

Only the investigators will have access to the data and will be responsible for data processing. This will not include the participant's contact or identifying information. Individual participants and their personal data will be identified by a unique study identification number. Only fully anonymised data will be published in reports, scientific publications or clinical study outcomes. Regardless of findings, the results of the research will be published.

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family members for their support. We also thank Hysse Forchhammer for early dialogue preparing the project and project title.

Author's contributions

The concept and design were constructed and refined by AF, FP, MB, GW, AM, and AV. First draft was written by AF, and all authors provided feedback, guidance, and academically relevant insight towards the final draft.

Competing interests

Authors Monika Baumann and Francois Patou are affiliated with Demant subsidiaries, of which Oticon A/S provided audiometric testing equipment for the purposes of this study.

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Figure legend

Figure 1 SWIR test procedure. For the purpose of this figure, sentence and final word examples are translated from Danish to English.

Figure 2 HINT procedure. For the purpose of this figure, the sentence example has been translated from Danish to English.

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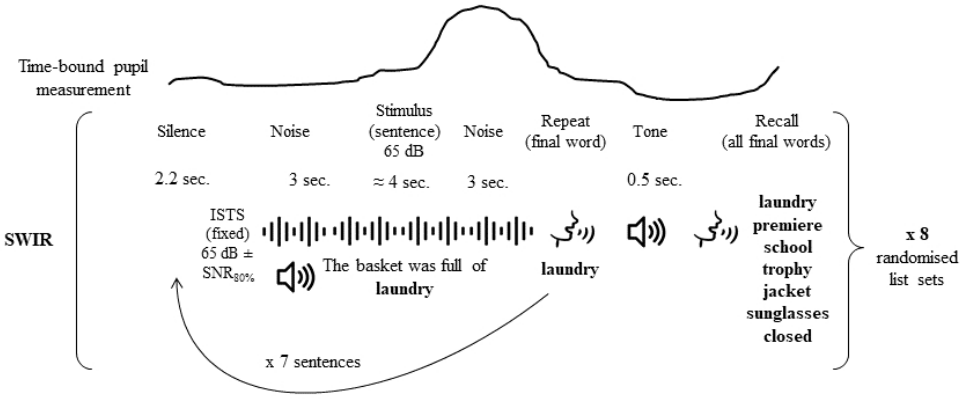

Figure 1 SWIR test procedure. For the purpose of this figure, sentence and final word examples are translated from Danish to English.

577x385mm (38 x 38 DPI)

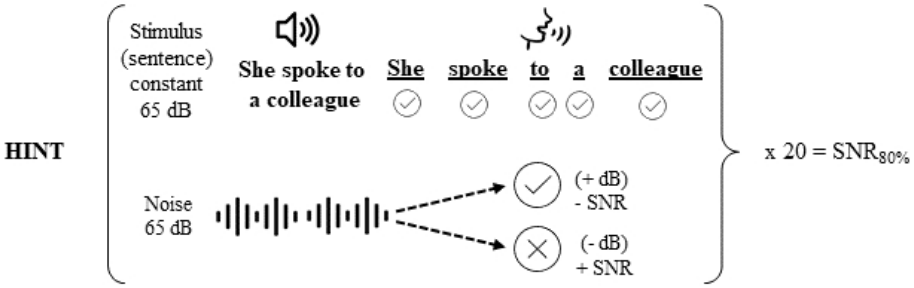

Figure 2 HINT procedure. For the purpose of this figure, the sentence example has been translated from Danish to English.

449x256mm (38 x 38 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents* (addressed in full protocol document, referred to in listed page numbers)

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	17
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	Footer
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 13
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	(see 9)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	(see 8-9)
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17-20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17-20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	28-31
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The Listen Carefully protocol: An exploratory study of the association between listening effort and cognitive function

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The Listen Carefully protocol: An exploratory study of the association between listening effort and cognitive function

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The Listen Carefully protocol: An exploratory study of the association between listening effort and cognitive function

Alix Feldman[1], François Patou[1,2], Monika Baumann[3], Anders Stockmarr[4], Gunhild Waldemar[5], Anja Maier[1,6], Asmus Vogel[7]

ABSTRACT

Introduction:

A growing body of evidence suggests that hearing loss is a significant and potentially modifiable risk factor for cognitive impairment. Although the mechanisms underlying the associations between cognitive decline and hearing loss are unclear, listening effort, has been posited as one of the mechanisms involved with cognitive decline in older age. To date, there has been a lack of research investigating this association, particularly among adults with mild cognitive impairment (MCI).

Methods and analysis:

15-25 cognitively healthy participants and 15-25 patients with MCI (ages 40-85) will be recruited to participate in an exploratory study investigating the association between cognitive functioning and listening effort. Both behavioural and objective measures of listening effort will be investigated. The Sentence-Final Word Identification and Recall (SWIR) test will be administered with single talker non-intelligible speech background noise while monitoring pupil dilation. Evaluation of cognitive function will be carried out in a clinical setting using a battery of neuropsychological tests. This study is considered exploratory and proof-of-concept, with information taken to help decide the validity of larger-scale trials.

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Ethics and Dissemination

Written approval exemption was obtained by the Scientific Ethics Committee in the Central Region of Denmark (De Videnskabsetiske Komiteer i Region Hovedstaden), reference 19042404, and the project is registered at clinicaltrials.gov, identifier NCT04593290. Study results will be disseminated in peer-reviewed journals and conferences.

ARTICLE SUMMARY

Strength and limitations of this study

- This is to our knowledge the first study to examine both behavioural and objective measures of listening effort and cognitive function in participants with and without cognitive dysfunction.
- A growing body of evidence suggests that an early intervention relating to hearing impairment may be valuable for the identification, management and prevention of cognitive decline.
- Enabling representatives from cognitive management and hearing health care fields to combine their expertise in support of the execution of this study.
- Given literature documenting the high prevalence of hearing loss among an older age group, the number of eligible participants may be limited.

INTRODUCTION

Research suggests an association between hearing loss and cognitive decline, with even mild levels of hearing loss being associated with the long-term risk of cognitive decline and dementia.[1–3] A seminal report in The Lancet has also suggested that hearing loss is one of the most prominent modifiable risk factors for dementia in mid-to-late stages of life.[3,4] Age-related hearing loss is also a marker for frailty in older age.[5–7] Despite increasing awareness of the links between sensory and cognitive deterioration as well as increasing research in the fields of hearing loss and cognitive decline, little is known about the mechanisms linking hearing loss to cognitive decline or about whether any of these mechanisms may account for some of the cognitive challenges observed in individuals with mild cognitive impairment (MCI).[8,9] Beyond audiometric variations in hearing, research increasingly shows that cognitive factors

such as attention and memory also play an important role in speech understanding.[10–12] Even if individuals achieve the same level of speech intelligibility, they may disproportionately distribute cognitive resources in order to do so.

One possible pathway involves listening effort, defined by McGarrigle et al.[13] and the British Society of Audiology Cognition in Hearing (BSA) as "the mental exertion required to attend to, and understand, an auditory message" (pp. 2). Speech understanding depends on phonological and semantic factors which are reliant on working memory capacity.[14–16] When the speech input doesn't easily match an individual's phonological representation, explicit and deliberate working memory processes are engaged. When the signal is distorted or presented alongside increased noise, for example, increased capacity is required to reach understanding. As the signal is maintained in working memory, fewer cognitive resources remain for retention.

In the Framework for Understanding Effortful Listening, listening effort is separated from pure intelligibility and is described as a deliberate allocation of mental resources. This dimension varies over time as a function of an individual's capacity to meet the demand and their motivational arousal.[17,18] Described as intentional attentional engagement, the motivation dimension reflects the individual assessment of arousal and fatigue on the valuation of the task in relation to the expenditure of available resources. In Strauss and Francis' taxonomic model of attention in effortful listening, sensory processing relies on the interaction between externally directed perceptual attention and internally directed central attention that employs executive functions such as working memory.[12]

Listening effort has also been explained alongside the notion of cognitive compensation, where a decline in sensory processing occurs alongside an increase in the recruitment and use of other cognitive areas.[17,19,20] The decline requires an increased reliance top-down mechanisms, and is supported by neuroimaging research that demonstrates the association between patterns of overactivation and age-equivalent performance. Over time, these compensatory effects decrease and may no longer able to offset the further deterioration of cognitive function. This not only increases fatigue, but also decreases the amount of resources available to meet the demands of a given task.[5,21–24]

Previous research investigating hearing and cognition have primarily demonstrated associations with processing speed, executive function and memory.[2,25,26] Speech perception, particularly in noisy environments, requires processes such as inhibitory control, attention and working memory.[17] The assessment of hearing loss has traditionally focused on pure-tone and speech audiometry as measurements of speech and sound recognition at standardised thresholds. However, the effort exerted or the fatigue experienced in complex listening situations—a common patient complaint within audiology—is not assessed.[17]

Jayakody et al.,[27] found that older adults with moderately severe hearing loss performed significantly worse on nonverbal tests of spatial working memory, episodic visuospatial memory, learning and association ability and psychological function than did older adults with normal hearing. A recent meta-analysis and systematic review demonstrated that a combined cognitive and auditory training approach was most optimal for improving cognition among adults with hearing loss.[28] Although no causal links have been established, research has also found that hearing rehabilitation in the form of hearing aid use is associated with improved cognition and a delayed dementia diagnosis.[29–31]

Mild cognitive impairment (MCI) generally refers to a stage of cognitive dysfunction that lies between normal cognitive function and dementia. Those with MCI have preserved function in daily activities; however, they may have minor impairment in complex instrumental functions and all score below normative levels on objective cognitive tasks. Those with MCI are also at higher risk for further cognitive decline and the later onset of dementia. For those with MCI who are later diagnosed with dementia, functions such as memory, attention, perceptual speed and executive functioning are further impaired.[32]

In this study, we investigate the association between listening effort and cognitive functioning among older adults without cognitive dysfunction and with MCI—all without significant levels of hearing loss. A significant association between listening effort and cognitive function may act as an entry point for future research into listening effort and cognitive decline. The insights gained from our current research are aimed at assessing a population at risk for cognitive decline—particularly those who have begun to

experience increased listening effort without clear signs of peripheral hearing loss. This study is the first to examine both behavioural and objective measures of listening effort and cognitive function in participants both with and without cognitive dysfunction.

Research Questions

Overall research question

The aim of this study is to investigate the association between cognitive functioning and listening effort among older healthy adults and in older memory clinic patients with MCI.

Secondary research question

- To determine whether there is a significant difference in listening effort between older healthy adults and MCI patients.

METHODS AND ANALYSIS

Research design

This is an exploratory proof-of-concept study with a case (MCI) and control group (cognitively healthy), where we will investigate the associations between listening effort and cognitive function.

Study procedures

Study sample

We will recruit 30-50 participants over a one-year interval. As we are investigating a potential factor in early stages of cognitive decline, potentially occurring in mid-stages of life, a wide age range is used (40-85 years) to ensure external validity for participants both with and without cognitive dysfunction. Half of these participants (n=15-25) will be individuals who have been diagnosed with MCI (see table 1). They will be recruited at the Danish Dementia Research Centre, Rigshospitalet Denmark and will be diagnosed by a multi-disciplinary team after comprehensive diagnostic work-up including neurological examination, blood tests, neuropsychological assessment, structural imaging (Magnetic Resonance Imaging) and in most cases functional imaging (FDG-PET) and lumbar puncture. The control group of participants (n=15-

25) will be cognitively healthy individuals, recruited via advertisements in local newspapers, community centres in and around Copenhagen and a website for recruiting research participants in Denmark (forsoegsperson.dk). Table 1 shows the inclusion and exclusion criteria for MCI and cognitively healthy participants. All participants will undergo both listening effort testing, coupled with pupillometry, and cognitive performance testing, based on a battery of neuropsychological tests (see table 2).

Table 1 Inclusion/exclusion criteria

	MCI participants	Cognitively healthy participants
Inclusion criteria	• MCI diagnosis, according to recommendations in Winblad et al.[32] o Not normal, not fulfilling diagnostic criteria for dementia o Functional activities are mainly preserved o Evidence of cognitive decline, measured by self-report in conjunction with deficits on objective cognitive tasks, operationalised as test scores below -1.5 standard deviation below age and education adjusted normative data	▪ 40-85 years old; ▪ Mini Mental State Examination score ≥ 26; ▪ CDR Global score = 0; ▪ No significant neurological or psychiatric disease; ▪ Normal hearing; defined as a pure tone threshold of ≤ 20 decibels (dB) 250 hertz (Hz) - 1 kilohertz (kHz); ≤ 25 dB between 2-3 kHz; ≤ 30 at 4 kHz (one five dB increase in one ear, one frequency is accepted); ▪ Danish as a native language.

	• Mini Mental State Examination score ≤ 26; • 40-85 years old; • No other significant neurological or psychiatric disease; • Normal hearing, defined as a pure tone threshold of ≤ 20 decibels (dB) 250 hertz (Hz) - 1 kilohertz (kHz); ≤ 25 dB between 2-3 kHz; ≤ 30 dB at 4 kHz (one five dB increase in one ear, one frequency is accepted); • Clinical Dementia Rating = 0.5; • Danish as native language; • Has live-in informant.
Exclusion criteria (all)	▪ Medication or treatment that could impact the pupillary dilation: eye drops (e.g. atropine or phenylephrine); ▪ Medication that could impact cognitive function; ▪ Alcohol or drug abuse; ▪ Unable to comply with study procedures.

Eligibility

Pure Tone Audiometry

During screening, hearing will be assessed using Pure Tone Audiometry, a pure-tone air conduction audiometric test method that matches the International Standards Organization (ISO) 8253-1:2010 guidelines.[33] This measure involves the peripheral and central auditory systems, identifying the hearing threshold levels of an individual and providing a basis for traditional hearing loss diagnosis and management. Otoscopy will also be used to examine the ear canal for impacted cerumen. We define normal hearing based on the World Health Organization's hearing impairment grading system, and have adapted thresholds above 25 dB at 4 kHz to account for the average hearing levels for men and women in older age groups, as described by ISO-7029.[34,35]

Mini Mental Status Examination

The Mini Mental State Exam includes tests of orientation, attention, memory, language and visual-spatial skills. It is a widely used test of cognitive dysfunction.[36,37]

Clinical Dementia Rating

The Clinical Dementia Rating is a 5-point scale used to assess cognitive function through a semi-structured interview with both the patient and a reliable informant, such as a family member. This 0-3 scale covers six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care.[38,39]

Measures

Cognitive function

Assessment scores for cognitive function will be recorded in a clinical setting, and will be based on a battery of neuropsychological tests (see Table 1).

Table 2 Tests used to measure cognitive function

Test	Cognitive abilities measured
Stroop Test[40]	Processing speed, selective attention, automaticity, inhibition
Trail Making Test [41]	Visual search speed, scanning, speed of processing, mental flexibility
Symbol-Digit Modalities Test [42,43]	Attention, processing speed, oculomotor scanning, working memory, motor persistence, visuomotor coordination
Verbal Fluency Tests (category, lexical)	Language representations of semantic concepts, central executive component of working memory, mental speed
Rey Complex Figure Test[44]	Visuospatial abilities, non-verbal memory, planning
Logical Memory (part A)[45]	Narrative episodic verbal memory, delayed recall, verbal recognition

The Stroop test is a demonstration of cognitive interference where a delay in the reaction time of a task occurs due to a mismatch in stimuli. A 40-item version will be applied, which will assesses processing speed, selective attention and automaticity.[40]

The Trail Making Test (part A & B) measures visual attention and task-switching. It consists of two parts, whereby the subject is instructed to connect a set of 25 numbers and number/letters as quickly as possible while still maintaining accuracy.

The Symbol-Digit Modalities Test is a symbol substitution test that examines attention and speed of processing. This test requires a person to substitute geometric symbols for numbers while scanning a response key.[42]

Verbal fluency tests are widely used as measures of language and executive functions. Category fluency tasks rely on language representations of semantic concepts, whereas lexical and action word tasks rely more on the central executive component of working memory.[46]

The Rey Complex Figure Test is an assessment where examinees are asked to reproduce a line drawing, first by copying it freehand and then drawing it from recall.[44]

The Logical Memory test is a subtest of the Wechsler Memory Scale—Third Edition, and is a standardised assessment of narrative episodic memory.[45] A short story is orally presented and the examinee is asked to recall the story verbatim (immediate recall). Approximately 20 minutes later, free recall of the story is again elicited (delayed recall) and recognition is also measured. Only part A is administered in this study.

Listening effort

The Framework for Understanding Effortful Listening, the Ease of Language Understanding model and Strauss and Francis'[12] taxonomic model of attention in effortful listening outline a number of cognitive and linguistic factors that moderate both effort and performance hearing ability.[12,15,17] Beyond subjective and behavioural measures, physiological measures have the benefit of time-bound insight into cognitive load changes and resource allocation during the process of understanding.[47] They may also allow more deeper insight into the neurocognitive mechanisms underlying listening effort.[12] Pupil dilation has been shown to fluctuate with changes in cognitive task load, indicating the variation in cognitive demands and the cognitive load required to perform these tasks.[48] Dilation of the pupil is also associated with the locus coeruleus-noradrenergic system, suggesting its ability to both control the muscles of the iris and reflect wider changes in attention.[49] Pupillometry is increasingly being used as an objective indicator of effort allocation for listening, memorising and auditory conflict tasks.[47,50–52]

Pupillometry hardware and software

In this study, the participant is fitted with PupilLabs' eye-tracking add-on for the HTC Vive virtual reality head-mounted display. To prevent floor and ceiling effects that are independent to baseline pupil size, the illumination within the display is individually adapted to the individual's pupil size midpoint prior to data collection between dim (~30 lux) and bright (~230 lux), with an average illuminance of 110 lux. A software suite allows the capture and post-processing of the data feed, including pupil diameter, dilation

at sentence baseline and latency between sentence onset and peak pupil diameter. The PupilLabs software is controlled via a MATLAB interface. Participants will be instructed not to drink coffee at least four hours before testing, and will be asked to wash off or refrain from wearing any eye makeup. Real-time monitoring of the eye during pupil measurement will occur to check for eye closures and head movements, and the confidence interval on the PupilLab's software will be regularly observed. After measurement, all data will undergo a subjective quality check with a sampling rate of 60 Hz, blink span removal below 35 and above 75 milliseconds, moving average span 0.5 seconds, baseline from 4.2 to 5.2 seconds and peak pupil diameter range from 5.2 to 8.5 seconds. To detect dilation speed outliers, the median absolute deviation will be used. If the ratio of missing pupil data in a list exceeds 40% after deblinking, it will be discarded from analysis.

Sentence-Final Word Identification and Recall (SWIR) test

The objective measure of listening effort, task-evoked pupil dilation, will be recorded during a Sentence-Final Word Identification and Recall (SWIR) test, a dual-task behavioural test used to measure the effect of listening on performance on a secondary memory task.[53,54] The test consists of a single condition of two tasks performed in a seven-sentence series. The participants are asked to report the final word after each sentence has been played (identification task), and they are encouraged to guess if they are unsure of the word. After reporting the final word of the seventh sentence, there is a 0.5 second beep tone and they are instructed to recall, in any order, all the words that they had previously reported (free recall task). The order of sentence presentation within each set is randomised between participants. Playing from a loudspeaker placed at 0° azimuth, the target speech (sentences), spoken by a male speaker, is set at 65 dB and played simultaneously with the International Speech Test Signal (noise), a single female talker which includes non-intelligible speech properties from American English, Arabic, Chinese, French, German and Spanish.[55] This masker signal begins two seconds before sentence onset and ends two seconds after sentence onset (see Figure 1).

Prior to the test, participants undergo an adaptive Danish Hearing in Noise Test (HINT) to determine the appropriate level of background noise during the SWIR test.[56] The HINT contains a list of equally

intelligible sentences to be repeated in varying dB levels of white noise. This results in the individual's speech reception threshold, set at 80% correct responses (see Figure 2). This value is used to set the SWIR masker level either above or below the 65 dB level of the target track. Listening effort changes as a function of the signal-to-noise ratio, and based on the framework for understanding effortful listening, is moderated by both the demands of the task and individual motivation. Previous research using the SWIR test with pupillometry has been administered to a population without cognitive dysfunction. Based on FUEL, it is possible that fatigue, motivation and/or the evaluation of demands on available capacity may influence the allocation of effort during recall, and thereby the pupil dilation response.[17] Given previous research using older adults both with and without hearing loss, we expect a speech reception threshold at 80% to load working memory without overloading its capacity, making inter-individual differences in effort apparent while maintaining attentional engagement.[51,57–60]

Data analysis

Group by group comparisons will be applied to assess significant differences in listening effort and its association with cognitive function between normal cognition controls and MCI patients. To assess the presence of a significant association between cognitive functioning and listening effort, a data analysis plan will be used. The primary analysis will use three neuropsychological variables: 1) Stroop Test (time on incongruent version), 2) Symbol-Digit Modalities Test and 3) Logical Memory Test (recall score part 1). Correlation analysis with these measures and the following listening effort measures will be administered: 1) average peak pupil diameter (on a per sentence measure, across lists), 2) average slope of the pupil curve (averaged across lists), and 3) proportion of correctly recalled final words from the SWIR list (averaged across lists).

Correlation analyses (e.g. Pearson correlation coefficient) will be completed for the entire participant group on all measures. If significant associations are found, further analysis will be conducted separately in the two participant groups. If significant, linear regression will be performed using the significant cognitive test scores as dependent variables and listening effort outcomes as independent variables

(together with relevant co-variates, e.g. gender, age and case/control). If significant associations are demonstrated between the three selected neuropsychological tests and the listening effort parameters, additional cognitive measures will be included for further analysis. If no significant associations are found in the initial analysis, further analysis will not be conducted.

Collinearity is a consideration when interpreting regression analyses using the measures of cognitive function and listening effort, as the resultant confidence intervals and standard errors will be wider.[61] Moderate to high collinearity could influence statistical power and would preclude the assumption that listening effort predicts the score on particular measures of cognitive functioning. In this case, it is important to interpret the results of coefficient estimates in accordance with the overlap between certain cognitive measures. We have identified a subset of three neuropsychological tests for the initial analysis to limit the effect of multiplicity.

Power estimation

The power is exemplified by the relationship between the subset of three neuropsychological tests and one listening effort measure, average peak pupil diameter. The formula for the estimating the relationship between the cognitive scores (Y) for the Symbol-Digit Modalities test, Logical Memory test and Stroop test, age and peak pupil diameter is given by $Y=\alpha+\beta Age+\gamma PPD+\varepsilon$. The mean, standard deviation and coefficients with age are stated in table 3.

Table 3 Mean and standard deviations of independent and dependent variables

Measure	**μ**	**σ**	**Correlation with age**
Symbol-Digit Modalities test[40]	45.5	7.1	-0.55
Logical Memory test[62]	15.8	4.1	-0.24
Stroop test[40]	19.8	4.9	-0.14
Peak pupil diameter[63,64]	0.1	0.012	0.06 (not used in analysis)

The peak pupil diameter values for cases are estimated to be 30% higher than those for healthy participants, explained by the increase in cognitive load for patients with cognitive dysfunction. The coefficients in the equation $Y=\alpha+\beta Age+\gamma PPD+\varepsilon$ are determined from the values in Table 3, and the varying correlation between Y and peak pupil parameter. The β is the same for all choices of correlation with peak pupil parameter, while γ varies.

Using these coefficients, we simulated our defined sample size of 25 healthy control participants and 25 patients with cognitive dysfunction from a normal distribution, and performed a linear regression on the simulated data. For each correlation between Y and peak pupil diameter, and for each Y (Symbol-Digit Modalities test, Logical Memory test and Stroop test), the procedure is repeated 10,000 times. For each Y each and correlation value, the power was determined as the average frequency of statistical significance from the above procedure. The power is presented graphically, whereby power is depicted as a function of the correlation (see figures 4-6). The values of the correlations between peak pupil diameter and the cognitive test scores that may be detected with 80% and 50% statistical power are listed in table 4. Given the high negative correlation between Symbol-Digit Modalities test and age (see table 3), we expect to see an effect on this variable with a higher power.

Table 4 Correlations with peak pupil dilation estimated for statistical power

Cognitive test	80% power	50% power
Symbol-Digit Modalities test	0.49	0.32
Logical Memory test	0.48	0.33
Stroop test	0.48	0.33

Participant and patient involvement

There was no direct patient or public involvement in the study design. Input and feedback from participants during hearing aid use will be taken into consideration during the planning of future research

and will contribute to knowledge surrounding the motivators and barriers towards hearing aid use among an older population and an MCI patient group. The Listen Carefully research project has been presented to potential future stakeholders within the municipality, such as those working within dementia care coordination and welfare innovation. Those who have been consulted and collaborated with throughout the research will receive a summary of results. Patients and participants will also be provided with a summary of results upon request.

Study timeline

Recruitment for the study began in July 2020. The first participant, first visit took place in August 2020 and the last participant, last visit is planned for December 2021.

DISCUSSION

Despite increasing research in the fields of hearing loss and cognitive decline, little is known about the mechanisms linking hearing loss to cognitive decline, and whether some of these mechanisms may account for some of the cognitive challenges observed in individuals with MCI, who do not demonstrate significant hearing loss. In particular, if listening effort does play a role in the association between hearing and cognitive decline, it may be reasonable to expect that individuals with MCI exhibit different patterns of listening effort compared to those without cognitive dysfunction, particularly in relation to working memory and internally directed central attention.[12] This may aid the understanding of which cognitive factors are influenced by effortful listening. Furthermore, the sensitivity of pupillometry may allow us to assess the engagement and the experience of fatigue among a group with cognitive dysfunction when completing the dual-task behavioural SWIR test. In particular, it is expected that the will provide valuable insights for its future use among those with cognitive dysfunction, and the insights gained from this study should therefore help refine our understanding of factors that could later inform complex hearing and cognitive healthcare interventions.[65]

ETHICS AND DISSEMINATION

Written approval exemption was obtained by the Scientific Ethics Committee in the Central Region of Denmark (De Videnskabsetiske Komiteer i Region Hovedstaden), case number 19042404 and the project is registered at clinicaltrials.gov, identifier NCT04593290. Access to study records will be limited to the study team, which includes the relevant researchers at the Memory Clinic in Copenhagen. This includes source documents, regulatory documents, data collection instruments and study data.

Only the investigators will have access to the data and will be responsible for data processing. This will not include the participant's contact or identifying information. Individual participants and their personal data will be identified by a unique study identification number. Only fully anonymised data will be published in reports, scientific publications or clinical study outcomes. Regardless of findings, the results of the research will be published.

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Author's contributions

The concept and design were constructed and refined by AF, FP, MB, GW, AM, and AV. Statistical guidance and power estimates were conducted by AS. First draft was written by AF, and all authors provided feedback, guidance, and academically relevant insight towards the final draft.

Competing interests

Authors Monika Baumann and François Patou are affiliated with Demant subsidiaries, of which Oticon A/S provided audiometric testing equipment for the purposes of this study.

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Figure legend

Figure 1 SWIR test procedure. For the purpose of this figure, sentence and final word examples are translated from Danish to English.

Figure 2 HINT procedure. For the purpose of this figure, the sentence example has been translated from Danish to English.

Figure 3 Power estimate for listening effort. Percentage increase in peak pupil dilation between those with and without cognitive dysfunction.

Figure 4 Power for Symbol-Digit Modalities test. Correlation needed to detect of an effect of peak pupil diameter for moderating performance.

Figure 5 Power for Logical Memory test. Correlation needed to detect of an effect of peak pupil diameter for moderating performance.

Figure 6 Power for Stroop test. Correlation needed to detect of an effect of peak pupil diameter for moderating performance.

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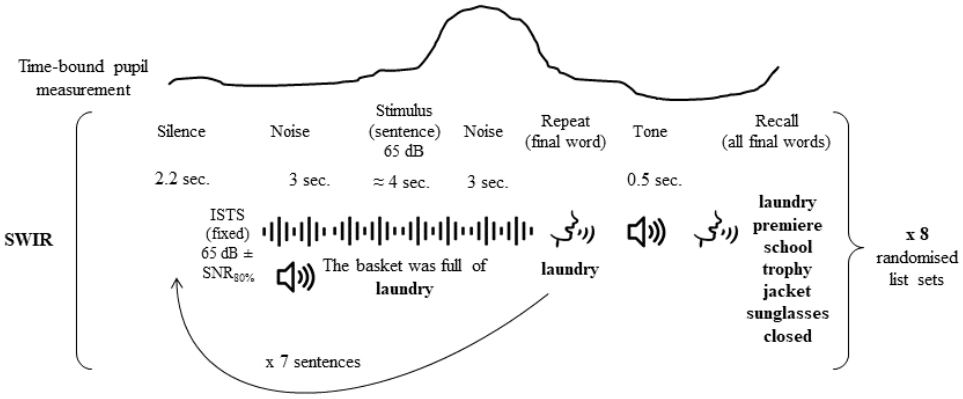

Figure 1 SWIR test procedure. For the purpose of this figure, sentence and final word examples are translated from Danish to English.

577x385mm (38 x 38 DPI)

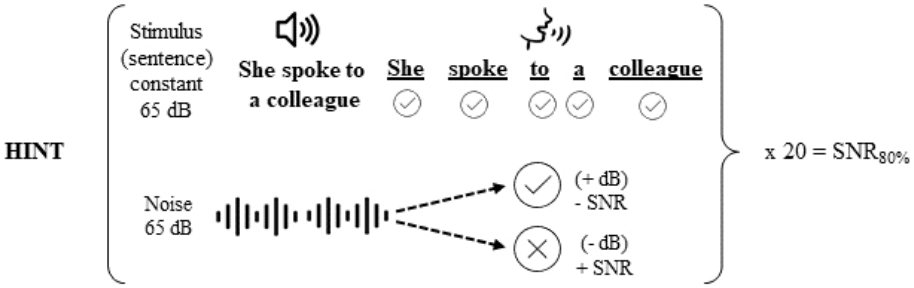

Figure 2 HINT procedure. For the purpose of this figure, the sentence example has been translated from Danish to English.

449x256mm (38 x 38 DPI)

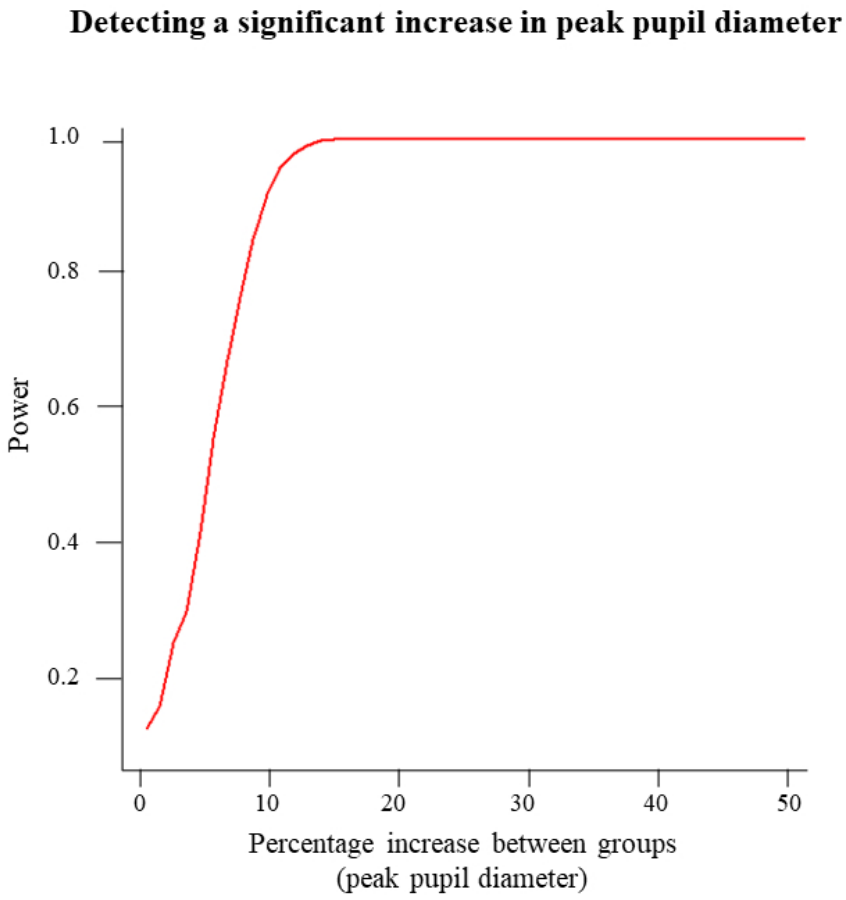

Figure 3 Power estimate for listening effort. Percentage increase in peak pupil dilation between those with and without cognitive dysfunction.

190x190mm (96 x 96 DPI)

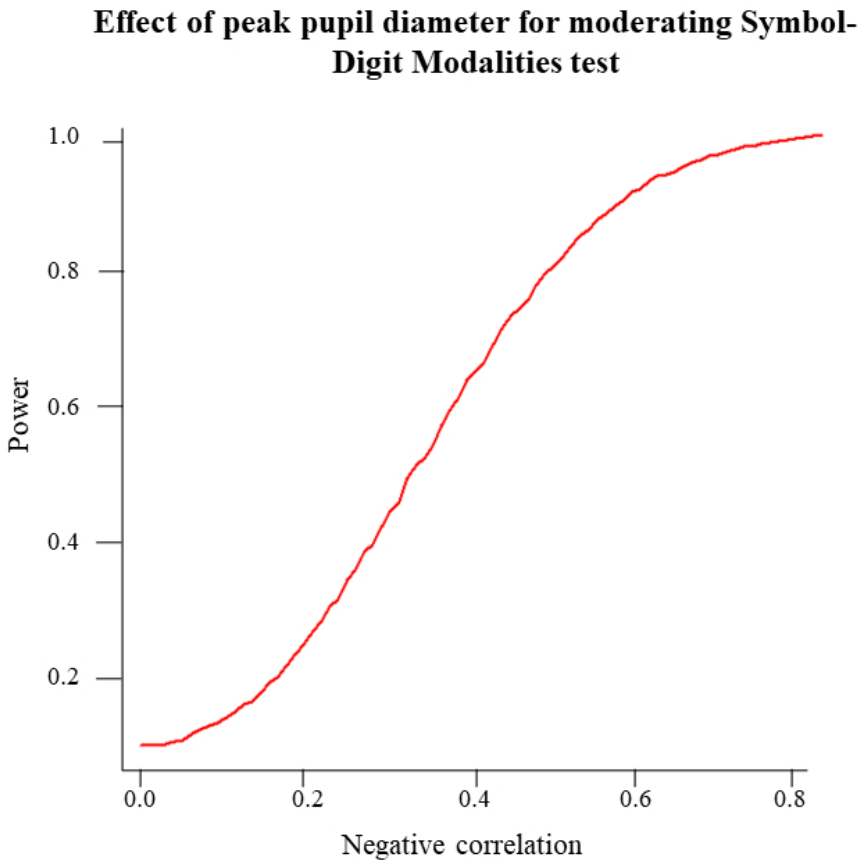

Figure 4 Power estimate for Symbol-Digit Modalities test. Correlation needed to detect of an effect of peak pupil diameter for moderating performance.

190x190mm (96 x 96 DPI)

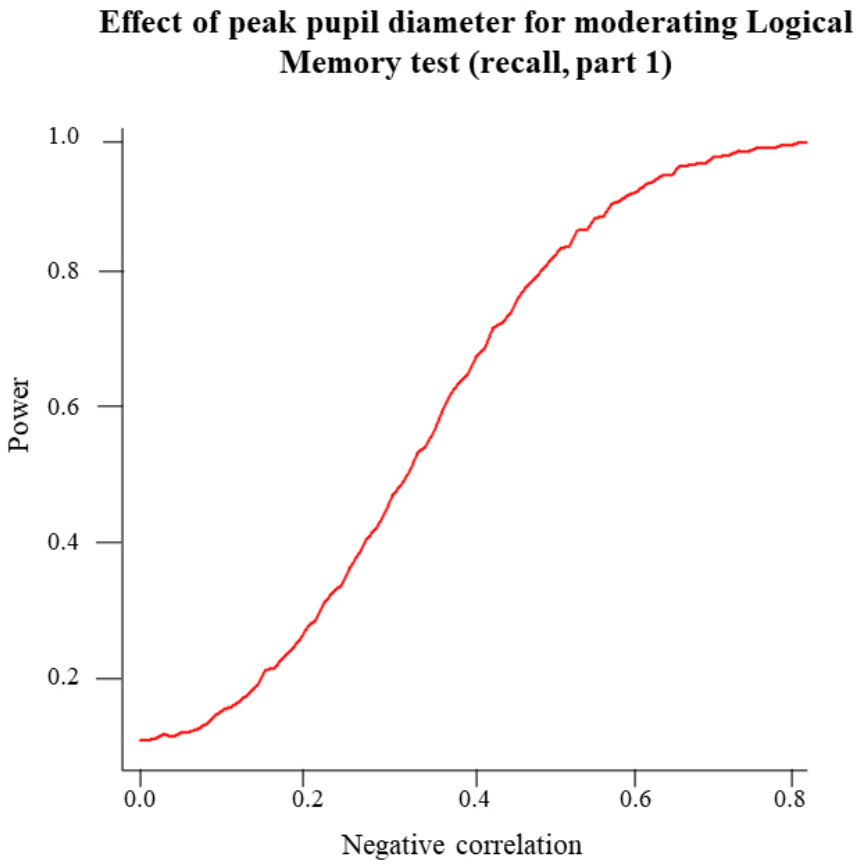

Figure 5 Power estimate for Logical Memory test. Correlation needed to detect of an effect of peak pupil diameter for moderating performance.

190x190mm (96 x 96 DPI)

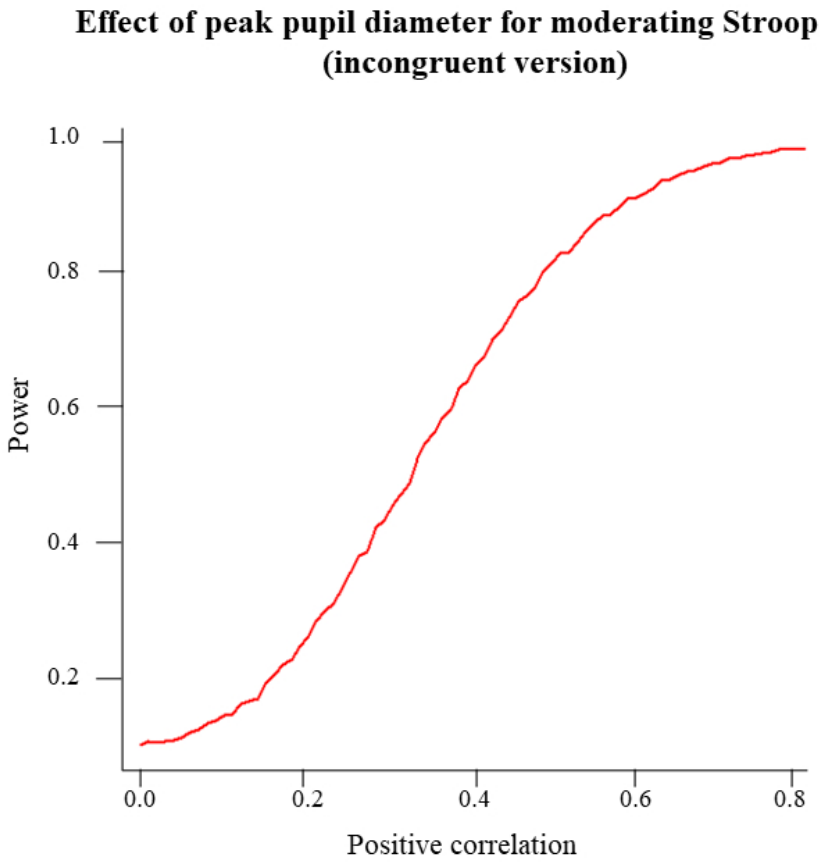

Figure 6 Power estimate for Stroop test. Correlation needed to detect of an effect of peak pupil diameter for moderating performance.

190x190mm (96 x 96 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents* (addressed in full protocol document, referred to in listed page numbers)

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	17
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	Footer
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 13
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	(see 9)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	(see 8-9)
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17-20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17-20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	28-31
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The Listen Carefully protocol: An exploratory proof-of-concept case-control study of the association between listening effort and cognitive function

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The Listen Carefully protocol: An exploratory proof-of-concept case-control study of the association between listening effort and cognitive function

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The Listen Carefully protocol: An exploratory proof-of-concept case-control study of the association between listening effort and cognitive function

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ABSTRACT

Introduction:

A growing body of evidence suggests that hearing loss is a significant and potentially modifiable risk factor for cognitive impairment. Although the mechanisms underlying the associations between cognitive decline and hearing loss are unclear, listening effort, has been posited as one of the mechanisms involved with cognitive decline in older age. To date, there has been a lack of research investigating this association, particularly among adults with mild cognitive impairment (MCI).

Methods and analysis:

15-25 cognitively healthy participants and 15-25 patients with MCI (ages 40-85) will be recruited to participate in an exploratory study investigating the association between cognitive functioning and listening effort. Both behavioural and objective measures of listening effort will be investigated. The Sentence-Final Word Identification and Recall (SWIR) test will be administered with single talker non-intelligible speech background noise while monitoring pupil dilation. Evaluation of cognitive function will be carried out in a clinical setting using a battery of neuropsychological tests. This study is considered exploratory and proof-of-concept, with information taken to help decide the validity of larger-scale trials.

Contact Alix Feldman (afeld@dtu.dk) 2

Ethics and dissemination

Written approval exemption was obtained by the Scientific Ethics Committee in the Central Region of Denmark (De Videnskabsetiske Komiteer i Region Hovedstaden), reference 19042404, and the project is registered at clinicaltrials.gov. Study results will be disseminated in peer-reviewed journals and conferences.

ARTICLE SUMMARY

Strength and limitations of this study

- This exploratory proof-of-concept study will be the first to examine both behavioural and objective measures of listening effort and cognitive function in participants with and without cognitive dysfunction.
- This is the first study to integrate pupillometry, an objective measure of listening effort, into a cognitive care setting.
- With the inclusion of patients with mild cognitive impairment, we are able to investigate the cognitive processes underlying a patient group who are at a higher risk for further cognitive decline yet have preserved function in daily activities.
- Given the high prevalence of hearing loss among an older age group, the number of eligible participants may be limited.

INTRODUCTION

Research suggests an association between hearing loss and cognitive decline, with even mild levels of hearing loss being associated with the long-term risk of cognitive decline and dementia.[1–3] A seminal report in The Lancet has also suggested that hearing loss is one of the most prominent modifiable risk factors for dementia in mid-to-late stages of life.[3,4] Age-related hearing loss is also a marker for frailty in older age.[5–7] Despite increasing awareness of the links between sensory and cognitive deterioration as well as increasing research in the fields of hearing loss and cognitive decline, little is known about the mechanisms linking hearing loss to cognitive decline or about whether any of these mechanisms may

account for some of the cognitive challenges observed in individuals with mild cognitive impairment (MCI).[8,9] Beyond audiometric variations in hearing, research increasingly shows that cognitive factors such as attention and memory also play an important role in speech understanding.[10–12] Even if individuals achieve the same level of speech intelligibility, they may disproportionately distribute cognitive resources in order to do so.

One possible pathway involves listening effort, defined by McGarrigle et al.[13] and the British Society of Audiology Cognition in Hearing (BSA) as "the mental exertion required to attend to, and understand, an auditory message" (pp. 2). Speech understanding depends on phonological and semantic factors which are reliant on working memory capacity.[14–16] When the speech input doesn't easily match an individual's phonological representation, explicit and deliberate working memory processes are engaged. When the signal is distorted or presented alongside increased noise, for example, increased capacity is required to reach understanding. As the signal is maintained in working memory, fewer cognitive resources remain for retention.

In the Framework for Understanding Effortful Listening, listening effort is separated from pure intelligibility and is described as a deliberate allocation of mental resources. This dimension varies over time as a function of an individual's capacity to meet the demand and their motivational arousal.[17,18] Described as intentional attentional engagement, the motivation dimension reflects the individual assessment of arousal and fatigue on the valuation of the task in relation to the expenditure of available resources. In Strauss and Francis' taxonomic model of attention in effortful listening, sensory processing relies on the interaction between externally directed perceptual attention and internally directed central attention that employs executive functions such as working memory.[12]

Listening effort has also been explained alongside the notion of cognitive compensation, where a decline in sensory processing occurs alongside an increase in the recruitment and use of other cognitive areas.[17,19,20] The decline requires an increased reliance top-down mechanisms, and is supported by neuroimaging research that demonstrates the association between patterns of overactivation and age-equivalent performance. Over time, these compensatory effects decrease and may no longer able to offset

the further deterioration of cognitive function. This not only increases fatigue, but also decreases the amount of resources available to meet the demands of a given task.[5,21–24]

Previous research investigating hearing and cognition have primarily demonstrated associations with processing speed, executive function and memory.[2,25,26] Speech perception, particularly in noisy environments, requires processes such as inhibitory control, attention and working memory.[17] The assessment of hearing loss has traditionally focused on pure-tone and speech audiometry as measurements of speech and sound recognition at standardised thresholds. However, the effort exerted or the fatigue experienced in complex listening situations—a common patient complaint within audiology—is not assessed.[17]

Jayakody et al.,[27] found that older adults with moderately severe hearing loss performed significantly worse on nonverbal tests of spatial working memory, episodic visuospatial memory, learning and association ability and psychological function than did older adults with normal hearing. A recent meta-analysis and systematic review demonstrated that a combined cognitive and auditory training approach was most optimal for improving cognition among adults with hearing loss.[28] Although no causal links have been established, research has also found that hearing rehabilitation in the form of hearing aid use is associated with improved cognition and a delayed dementia diagnosis.[29–31]

Mild cognitive impairment (MCI) generally refers to a stage of cognitive dysfunction that lies between normal cognitive function and dementia. Those with MCI have preserved function in daily activities; however, they may have minor impairment in complex instrumental functions and all score below normative levels on objective cognitive tasks. Those with MCI are also at higher risk for further cognitive decline and the later onset of dementia. For those with MCI who are later diagnosed with dementia, functions such as memory, attention, perceptual speed and executive functioning are further impaired.[32]

In this study, we investigate the association between listening effort and cognitive functioning among older adults without cognitive dysfunction and with MCI—all without significant levels of hearing loss. A significant association between listening effort and cognitive function may act as an entry point for future research into listening effort and cognitive decline. The insights gained from our current research are

aimed at assessing a population at risk for cognitive decline—particularly those who have begun to experience increased listening effort without clear signs of peripheral hearing loss. This study is the first to examine both behavioural and objective measures of listening effort and cognitive function in participants both with and without cognitive dysfunction.

Research Questions

Overall research question

The aim of this study is to investigate the association between cognitive functioning and listening effort among older healthy adults and in older memory clinic patients with MCI.

Secondary research question

- To determine whether there is a significant difference in listening effort between older healthy adults and MCI patients.

METHODS AND ANALYSIS

Research design

This is an exploratory proof-of-concept study with a case (MCI) and control group (cognitively healthy), where we will investigate the associations between listening effort and cognitive function.

Study procedures

Study sample

We will recruit 30-50 participants over a one-year interval. As we are investigating a potential factor in early stages of cognitive decline, potentially occurring in mid-stages of life, a wide age range is used (40-85 years) to ensure external validity for participants both with and without cognitive dysfunction. Half of these participants (n=15-25) will be individuals who have been diagnosed with MCI (see table 1). They will be recruited at the Danish Dementia Research Centre, Rigshospitalet Denmark and will be diagnosed by a multi-disciplinary team after comprehensive diagnostic work-up including neurological examination, blood tests, neuropsychological assessment, structural imaging (Magnetic Resonance Imaging) and in

most cases functional imaging (FDG-PET) and lumbar puncture. The control group of participants (n=15-25) will be cognitively healthy individuals, recruited via advertisements in local newspapers, community centres in and around Copenhagen and a website for recruiting research participants in Denmark (forsoegsperson.dk). Table 1 shows the inclusion and exclusion criteria for MCI and cognitively healthy participants. All participants will undergo both listening effort testing, coupled with pupillometry, and cognitive performance testing, based on a battery of neuropsychological tests (see table 2).

Table 1 Inclusion/exclusion criteria

	MCI participants	Cognitively healthy participants

Inclusion criteria	• MCI diagnosis, according to recommendations in Winblad et al.[32]
	  ○ Not normal, not fulfilling diagnostic criteria for dementia
	  ○ Functional activities are mainly preserved
	  ○ Evidence of cognitive decline, measured by self-report in conjunction with deficits on objective cognitive tasks, operationalised as test scores below -1.5 standard deviation below age and education
		▪ 40-85 years old;
		▪ Mini Mental State Examination score ≥ 26;
		▪ CDR Global score = 0;
		▪ No significant neurological or psychiatric disease;
		▪ Normal hearing; defined as a pure tone threshold of ≤ 20 decibels (dB) 250 hertz (Hz) - 1 kilohertz (kHz); ≤ 25 dB between 2-3 kHz; ≤ 30 at 4 kHz (one five dB increase in one ear, one frequency is accepted);
		▪ Danish as a native language.

	adjusted normative data • 40-85 years old; • Mini Mental State Examination score ≤ 26; • Clinical Dementia Rating = 0.5; • No other significant neurological or psychiatric disease; • Normal hearing, defined as a pure tone threshold of ≤ 20 decibels (dB) 250 hertz (Hz) - 1 kilohertz (kHz); ≤ 25 dB between 2-3 kHz; ≤ 30 dB at 4 kHz (one five dB increase in one ear, one frequency is accepted); • Danish as native language; • Has live-in informant.
Exclusion criteria (all)	▪ Medication or treatment that could impact the pupillary dilation: eye drops (e.g. atropine or phenylephrine); ▪ Medication that could impact cognitive function; ▪ Alcohol or drug abuse; ▪ Unable to comply with study procedures.

Eligibility

Pure Tone Audiometry

During screening, hearing will be assessed using Pure Tone Audiometry, a pure-tone air conduction audiometric test method that matches the International Standards Organization (ISO) 8253-1:2010 guidelines.[33] This measure involves the peripheral and central auditory systems, identifying the hearing threshold levels of an individual and providing a basis for traditional hearing loss diagnosis and management. Otoscopy will also be used to examine the ear canal for impacted cerumen. We define normal hearing based on the World Health Organization's hearing impairment grading system, and have adapted thresholds above 25 dB at 4 kHz to account for the average hearing levels for men and women in older age groups, as described by ISO-7029.[34,35]

Mini Mental Status Examination

The Mini Mental State Exam includes tests of orientation, attention, memory, language and visual-spatial skills. It is a widely used test of cognitive dysfunction.[36,37]

Clinical Dementia Rating

The Clinical Dementia Rating is a 5-point scale used to assess cognitive function through a semi-structured interview with both the patient and a reliable informant, such as a family member. This 0-3 scale covers six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care.[38,39]

Measures

Cognitive function

Assessment scores for cognitive function will be recorded in a clinical setting, and will be based on a battery of neuropsychological tests (see Table 1).

Table 2 Tests used to measure cognitive function

Test	Cognitive abilities measured
Stroop Test[40]	Processing speed, selective attention, automaticity, inhibition
Trail Making Test [41]	Visual search speed, scanning, speed of processing, mental flexibility
Symbol-Digit Modalities Test [42,43]	Attention, processing speed, oculomotor scanning, working memory, motor persistence, visuomotor coordination
Verbal Fluency Tests (category, lexical)	Language representations of semantic concepts, central executive component of working memory, mental speed
Rey Complex Figure Test[44]	Visuospatial abilities, non-verbal memory, planning
Logical Memory (part A)[45]	Narrative episodic verbal memory, delayed recall, verbal recognition

The Stroop test is a demonstration of cognitive interference where a delay in the reaction time of a task occurs due to a mismatch in stimuli. A 40-item version will be applied, which will assesses processing speed, selective attention and automaticity.[40]

The Trail Making Test (part A & B) measures visual attention and task-switching. It consists of two parts, whereby the subject is instructed to connect a set of 25 numbers and number/letters as quickly as possible while still maintaining accuracy.

The Symbol-Digit Modalities Test is a symbol substitution test that examines attention and speed of processing. This test requires a person to substitute geometric symbols for numbers while scanning a response key.[42]

Verbal fluency tests are widely used as measures of language and executive functions. Category fluency tasks rely on language representations of semantic concepts, whereas lexical and action word tasks rely more on the central executive component of working memory.[46]

The Rey Complex Figure Test is an assessment where examinees are asked to reproduce a line drawing, first by copying it freehand and then drawing it from recall.[44]

The Logical Memory test is a subtest of the Wechsler Memory Scale—Third Edition, and is a standardised assessment of narrative episodic memory.[45] A short story is orally presented and the examinee is asked to recall the story verbatim (immediate recall). Approximately 20 minutes later, free recall of the story is again elicited (delayed recall) and recognition is also measured. Only part A is administered in this study.

Listening effort

The Framework for Understanding Effortful Listening, the Ease of Language Understanding model and Strauss and Francis'[12] taxonomic model of attention in effortful listening outline a number of cognitive and linguistic factors that moderate both effort and performance hearing ability.[12,15,17] Beyond subjective and behavioural measures, physiological measures have the benefit of time-bound insight into cognitive load changes and resource allocation during the process of understanding.[47] They may also allow more deeper insight into the neurocognitive mechanisms underlying listening effort.[12] Pupil dilation has been shown to fluctuate with changes in cognitive task load, indicating the variation in cognitive demands and the cognitive load required to perform these tasks.[48] Dilation of the pupil is also associated with the locus coeruleus-noradrenergic system, suggesting its ability to both control the muscles of the iris and reflect wider changes in attention.[49] Pupillometry is increasingly being used as an objective indicator of effort allocation for listening, memorising and auditory conflict tasks.[47,50–52]

Pupillometry hardware and software

In this study, the participant is fitted with PupilLabs' eye-tracking add-on for the HTC Vive virtual reality head-mounted display. To prevent floor and ceiling effects that are independent to baseline pupil size, the illumination within the display is individually adapted to the individual's pupil size midpoint prior to data collection between dim (~30 lux) and bright (~230 lux), with an average illuminance of 110 lux. A software suite allows the capture and post-processing of the data feed, including pupil diameter, dilation

at sentence baseline and latency between sentence onset and peak pupil diameter. The PupilLabs software is controlled via a MATLAB interface. Participants will be instructed not to drink coffee at least four hours before testing, and will be asked to wash off or refrain from wearing any eye makeup. Real-time monitoring of the eye during pupil measurement will occur to check for eye closures and head movements, and the confidence interval on the PupilLab's software will be regularly observed. After measurement, all data will undergo a subjective quality check with a sampling rate of 60 Hz, blink span removal below 35 and above 75 milliseconds, moving average span 0.5 seconds, baseline from 4.2 to 5.2 seconds and peak pupil diameter range from 5.2 to 8.5 seconds. To detect dilation speed outliers, the median absolute deviation will be used. If the ratio of missing pupil data in a list exceeds 40% after deblinking, it will be discarded from analysis.

Sentence-Final Word Identification and Recall (SWIR) test

The objective measure of listening effort, task-evoked pupil dilation, will be recorded during a Sentence-Final Word Identification and Recall (SWIR) test, a dual-task behavioural test used to measure the effect of listening on performance on a secondary memory task.[53,54] The test consists of a single condition of two tasks performed in a seven-sentence series. The participants are asked to report the final word after each sentence has been played (identification task), and they are encouraged to guess if they are unsure of the word. After reporting the final word of the seventh sentence, there is a 0.5 second beep tone and they are instructed to recall, in any order, all the words that they had previously reported (free recall task). The order of sentence presentation within each set is randomised between participants. Playing from a loudspeaker placed at 0° azimuth, the target speech (sentences), spoken by a male speaker, is set at 65 dB and played simultaneously with the International Speech Test Signal (noise), a single female talker which includes non-intelligible speech properties from American English, Arabic, Chinese, French, German and Spanish.[55] This masker signal begins two seconds before sentence onset and ends two seconds after sentence onset (see Figure 1).

Prior to the test, participants undergo an adaptive Danish Hearing in Noise Test (HINT) to determine the appropriate level of background noise during the SWIR test.[56] The HINT contains a list of equally

intelligible sentences to be repeated in varying dB levels of white noise. This results in the individual's speech reception threshold, set at 80% correct responses (see Figure 2). This value is used to set the SWIR masker level either above or below the 65 dB level of the target track. Listening effort changes as a function of the signal-to-noise ratio, and based on the framework for understanding effortful listening, is moderated by both the demands of the task and individual motivation. Previous research using the SWIR test with pupillometry has been administered to a population without cognitive dysfunction. Based on FUEL, it is possible that fatigue, motivation and/or the evaluation of demands on available capacity may influence the allocation of effort during recall, and thereby the pupil dilation response.[17] Given previous research using older adults both with and without hearing loss, we expect a speech reception threshold at 80% to load working memory without overloading its capacity, making inter-individual differences in effort apparent while maintaining attentional engagement.[51,57–60]

Data analysis

Group by group comparisons will be applied to assess significant differences in listening effort and its association with cognitive function between normal cognition controls and MCI patients. To assess the presence of a significant association between cognitive functioning and listening effort, a data analysis plan will be used. The primary analysis will use three neuropsychological variables: 1) Stroop Test (time on incongruent version), 2) Symbol-Digit Modalities Test and 3) Logical Memory Test (recall score part 1). Correlation analysis with these measures and the following listening effort measures will be administered: 1) average peak pupil diameter (on a per sentence measure, across lists), 2) average slope of the pupil curve (averaged across lists), and 3) proportion of correctly recalled final words from the SWIR list (averaged across lists).

Correlation analyses (e.g. Pearson correlation coefficient) will be completed for the entire participant group on all measures. If significant associations are found, further analysis will be conducted separately in the two participant groups. If significant, linear regression will be performed using the significant cognitive test scores as dependent variables and listening effort outcomes as independent variables

(together with relevant co-variates, e.g. gender, age and case/control). If significant associations are demonstrated between the three selected neuropsychological tests and the listening effort parameters, additional cognitive measures will be included for further analysis. If no significant associations are found in the initial analysis, further analysis will not be conducted.

Collinearity is a consideration when interpreting regression analyses using the measures of cognitive function and listening effort, as the resultant confidence intervals and standard errors will be wider.[61] Moderate to high collinearity could influence statistical power and would preclude the assumption that listening effort predicts the score on particular measures of cognitive functioning. In this case, it is important to interpret the results of coefficient estimates in accordance with the overlap between certain cognitive measures. We have identified a subset of three neuropsychological tests for the initial analysis to limit the effect of multiplicity.

Power estimation

The power is exemplified by both the difference between groups and the relationship between the subset of three neuropsychological tests and one listening effort measure, average peak pupil diameter. The formula for the estimating the relationship between the cognitive scores (Y) for the Symbol-Digit Modalities test, Logical Memory test and Stroop test, age and peak pupil diameter is given by $Y=\alpha+\beta Age+\gamma PPD+\varepsilon$. The mean, standard deviation and coefficients with age are stated in table 3.

Table 3 Mean and standard deviations of independent and dependent variables

Measure	μ	σ	Correlation with age
Symbol-Digit Modalities test[40]	45.5	7.1	-0.55
Logical Memory test[62]	15.8	4.1	-0.24
Stroop test[40]	19.8	4.9	-0.14
Peak pupil diameter[63,64]	0.1	0.012	0.06 (not used in analysis)

The peak pupil diameter values for cases are estimated to be 30% higher than those for healthy participants, explained by the increase in cognitive load for patients with cognitive dysfunction. The estimated power for peak pupil diameter between groups is presented graphically in Figure 3. The coefficients in the equation $Y=\alpha+\beta Age+\gamma PPD+\varepsilon$ are determined from the values in Table 3, and the varying correlation between the cognitive score Y and peak pupil diameter. The β is the same for all choices of correlation with peak pupil parameter, while γ varies.

Using these coefficients, we simulated our defined sample size of 25 healthy control participants and 25 patients with cognitive dysfunction from a normal distribution, and performed a linear regression on the simulated data. For each correlation between Y and peak pupil diameter, and for each cognitive score Y (Symbol-Digit Modalities test, Logical Memory test and Stroop test), the procedure is repeated 10,000 times. For each Y and each correlation value, the power was determined as the average frequency of statistical significance from the above procedure. The power is presented graphically, whereby power is depicted as a function of the correlation (see figures 4-6). The values of the correlations between peak pupil diameter and the cognitive test scores that may be detected with 80% and 50% statistical power are listed in table 4. Given the high negative correlation between Symbol-Digit Modalities test and age (see table 3), we expect to see an effect on this variable with a higher power.

Table 4 Correlations with peak pupil dilation estimated for statistical power

Cognitive test	80% power	50% power
Symbol-Digit Modalities test	0.49	0.32
Logical Memory test	0.48	0.33
Stroop test	0.48	0.33

Participant and patient involvement

There was no direct patient or public involvement in the study design. Input and feedback from participants during hearing aid use will be taken into consideration during the planning of future research and will contribute to knowledge surrounding the motivators and barriers towards hearing aid use among an older population and an MCI patient group. The Listen Carefully research project has been presented to potential future stakeholders within the municipality, such as those working within dementia care coordination and welfare innovation. Those who have been consulted and collaborated with throughout the research will receive a summary of results. Patients and participants will also be provided with a summary of results upon request.

Study timeline

Recruitment for the study began in July 2020. The first participant, first visit took place in August 2020 and the last participant, last visit is December 2021.

DISCUSSION

Despite increasing research in the fields of hearing loss and cognitive decline, little is known about the mechanisms linking hearing loss to cognitive decline, and whether some of these mechanisms may account for some of the cognitive challenges observed in individuals with MCI, who do not demonstrate significant hearing loss. In particular, if listening effort does play a role in the association between hearing and cognitive decline, it may be reasonable to expect that individuals with MCI exhibit different patterns of listening effort compared to those without cognitive dysfunction, particularly in relation to working memory and internally directed central attention.[12] This may aid the understanding of which cognitive factors are influenced by effortful listening. Furthermore, the sensitivity of pupillometry may allow us to assess the engagement and the experience of fatigue among a group with cognitive dysfunction when completing the dual-task behavioural SWIR test. In particular, it is expected that the will provide valuable insights for its future use among those with cognitive dysfunction, and the insights gained from this study

should therefore help refine our understanding of factors that could later inform complex hearing and cognitive healthcare interventions.[65]

ETHICS AND DISSEMINATION

Access to study records will be limited to the study team, which includes the relevant researchers at the Memory Clinic in Copenhagen. This includes source documents, regulatory documents, data collection instruments and study data.

Only the investigators will have access to the data and will be responsible for data processing. This will not include the participant's contact or identifying information. Individual participants and their personal data will be identified by a unique study identification number. Only fully anonymised data will be published in reports, scientific publications or clinical study outcomes. Regardless of findings, the results of the research will be published.

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Author's contributions

The concept and design were constructed and refined by AF, FP, MB, GW, AM, and AV. Statistical guidance and power estimates were conducted by AS. First draft was written by AF, and all authors provided feedback, guidance, and academically relevant insight towards the final draft.

Competing interests

Authors Monika Baumann and François Patou are affiliated with Demant subsidiaries, of which Oticon A/S provided audiometric testing equipment for the purposes of this study.

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Figure legend

Figure 1 SWIR test procedure. For the purpose of this figure, sentence and final word examples are translated from Danish to English.

Figure 2 HINT procedure. For the purpose of this figure, the sentence example has been translated from Danish to English.

Figure 3 Power estimate for listening effort. Percentage increase in peak pupil dilation between those with and without cognitive dysfunction.

Figure 4 Power for Symbol-Digit Modalities test. Correlation needed to detect of an effect of peak pupil diameter for moderating performance.

Figure 5 Power for Logical Memory test. Correlation needed to detect of an effect of peak pupil diameter for moderating performance.

Figure 6 Power for Stroop test. Correlation needed to detect of an effect of peak pupil diameter for moderating performance.

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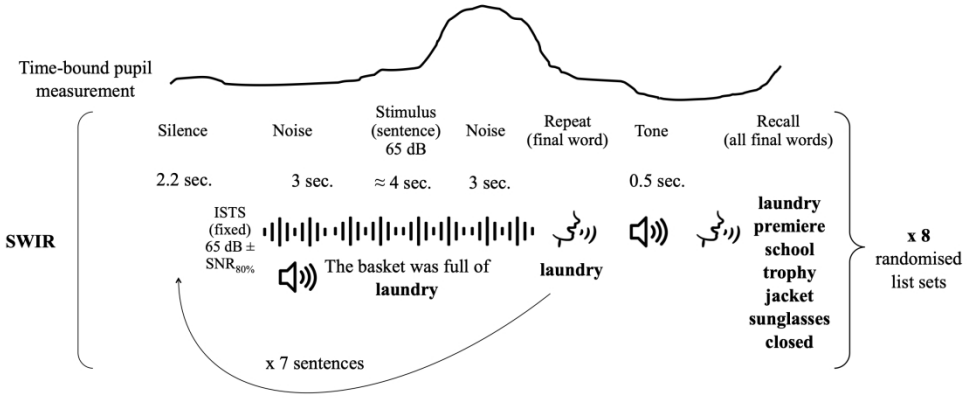

Figure 1 SWIR test procedure. For the purpose of this figure, sentence and final word examples are translated from Danish to English.

228x152mm (300 x 300 DPI)

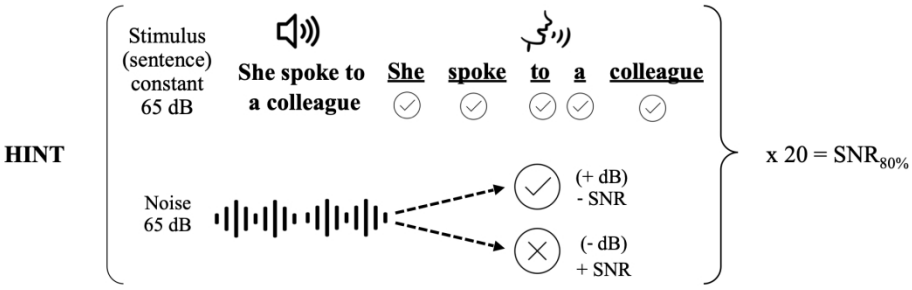

Figure 2 HINT procedure. For the purpose of this figure, the sentence example has been translated from Danish to English.

177x101mm (300 x 300 DPI)

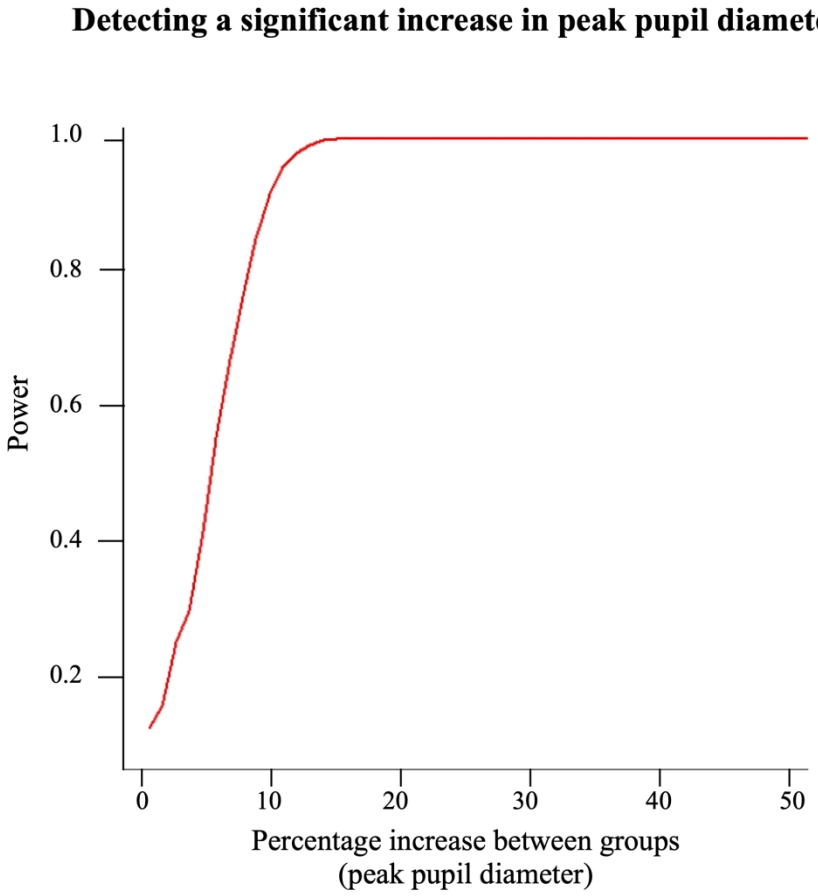

Figure 3 Power estimate for listening effort. Percentage increase in peak pupil dilation between those with and without cognitive dysfunction.

190x190mm (300 x 300 DPI)

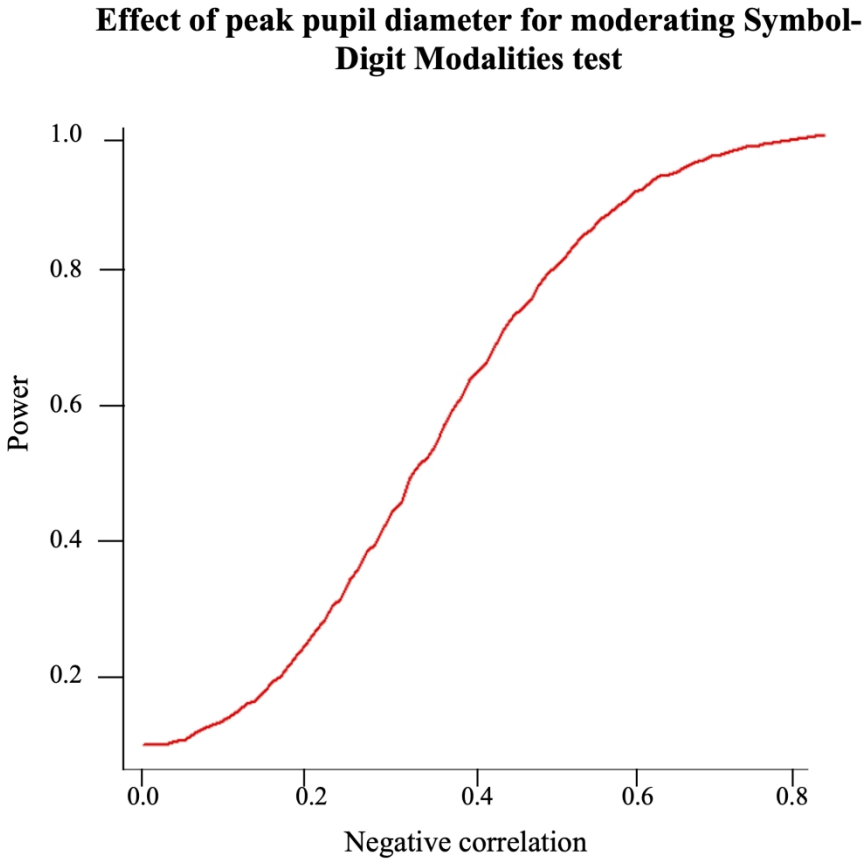

Figure 4 Power estimate for Symbol-Digit Modalities test. Correlation needed to detect of an effect of peak pupil diameter for moderating performance.

190x190mm (300 x 300 DPI)

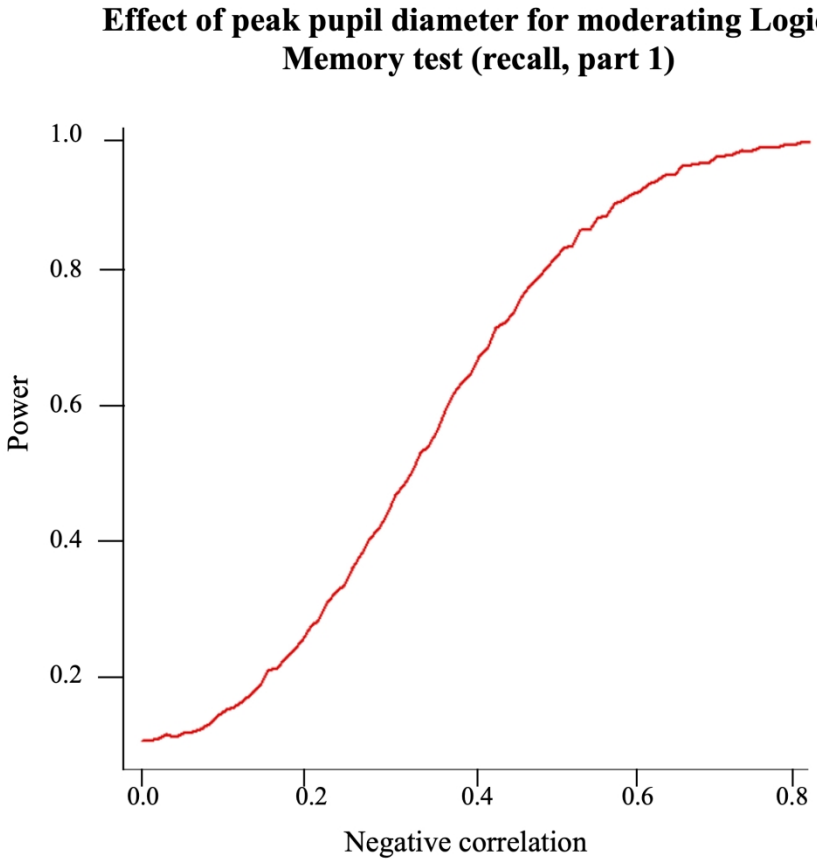

Figure 5 Power estimate for Logical Memory test. Correlation needed to detect of an effect of peak pupil diameter for moderating performance.

190x190mm (300 x 300 DPI)

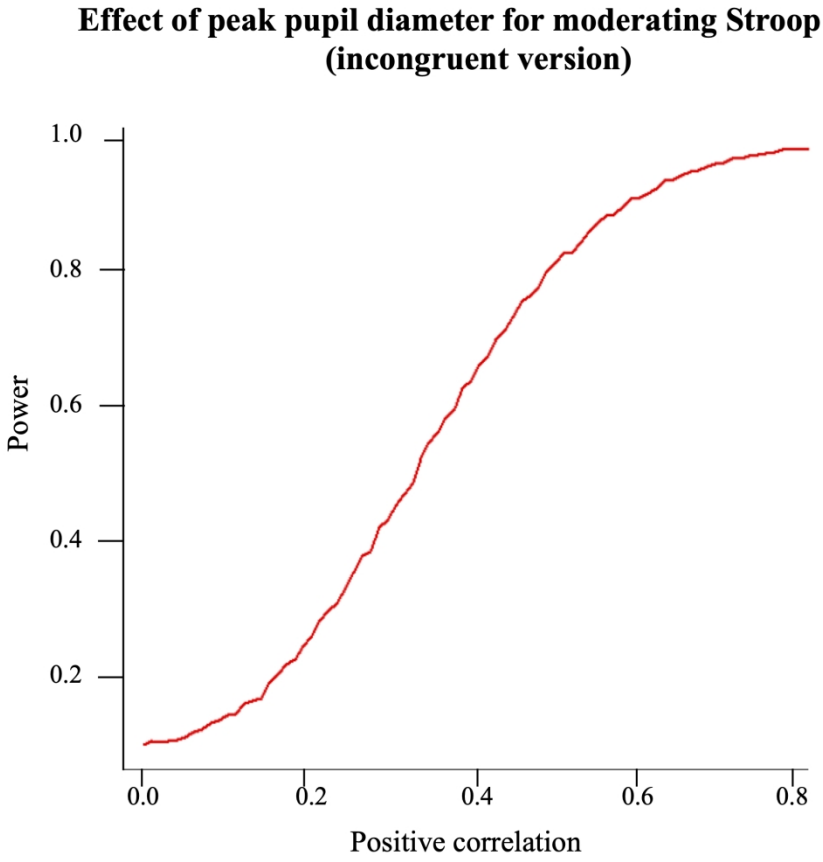

Figure 6 Power estimate for Stroop test. Correlation needed to detect of an effect of peak pupil diameter for moderating performance.

190x190mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents* (addressed in full protocol document, referred to in listed page numbers)

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	17
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	Footer
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 13
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	(see 9)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	(see 8-9)
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17-20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17-20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	28-31
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.