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Hadeel Y. Tarawneh

Wilhelmina H.A.M. Mulders

Hamid R. Sohrabi
Edith Cowan University, h.sohrabi@ecu.edu.au

Ralph N. Martins
Edith Cowan University, r.martins@ecu.edu.au

Dona M.P. Jayakody

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Auditory electrophysiological assessments of Alzheimer's disease and preclinical stages: protocol for a systematic review and meta-analysis

Hadeel Y Tarawneh [1,2,3] Wilhelmina H A M Mulders,[1] Hamid R Sohrabi,[4,5] Ralph N Martins,[4,5] Dona M P Jayakody[2,3]

For numbered affiliations see end of article.

Correspondence to
Hadeel Y Tarawneh;
hadeel.tarawneh@research.uwa.edu.au

ABSTRACT

Introduction Investigating auditory functions in populations at risk of developing Alzheimer's disease (AD) using auditory neurophysiological measurements can potentially identify a crucial and sensitive diagnostic window of opportunity in preclinical AD. Auditory electrophysiological assessments have gained interest as possible tools for early diagnosis of AD. This paper outlines the protocol that will be used to systematically review the published literature currently available on auditory electrophysiological assessments that have been used to assess the auditory functions of adults over the age of 60 years diagnosed with AD or its preclinical stages.

Methods and analysis All full-length peer-reviewed publications of original data that use auditory electrophysiological assessments in AD and its preclinical stages (subjective cognitive decline (SCD) and mild cognitive impairment (MCI)) will be considered in this review. The search will be performed on major electronic databases (Ovid MEDLINE, Ovid Embase, PsycINFO, PubMed, Scopus and CINAHL Plus) using keywords alone or in combination with Medical Subject Headings divided into two domains; (i) auditory tests and (ii) AD. The database search will be conducted on the 7th of May 2019. Data analysis will be completed and reported in the full review. A random effects meta-analysis will also be conducted using the Comprehensive Meta-Analysis software, V.3. This review will describe which auditory electrophysiological tests have been found to be useful in assessing the auditory function in cognitively impaired adults (MCI and AD) or adults with serious complaints about their cognition (SCD). This review will also identify and describe which auditory electrophysiological test demonstrates the most sensitivity in differentiating people at different stages of cognitive decline.

Ethics and dissemination This systematic review focusses on analysing already available literature. Therefore, there will be no requirement for ethical approval. The systematic review findings will be disseminated through peer-reviewed publication as well as relevant media platforms, for example, conferences.

Systematic review registration PROSPERO CRD42019133553.

Strengths and limitations of this study

► This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.
► This protocol outlines the procedure for a systematic review which will reduce the possibility of duplication of the methods and allows for peer review of the procedure.
► This will offer highest level evidence for informed decisions.
► The detailed keyword and Medical Subject Headings term search methods offer a more comprehensive search of relevant publications.
► The exclusion of papers that are not published in English may mean some important additional findings are not taken into consideration.

INTRODUCTION

Worldwide, someone develops dementia every 3 seconds, and in 2017 the number of people estimated to be living with dementia globally was close to 50 million people.[1] Without a medical breakthrough the number of dementia cases is expected to double every 20 years, with it estimated to be over 152 million cases by 2050.[2] Contributing to a total of 5.4% of deaths in males and 10.6% of deaths in females each year, dementia is the second leading cause of death of Australians.[3] Everyday approximately 250 Australians are diagnosed with dementia, and this number is expected to increase to 650 people a day by 2056.[1]

Dementia of the Alzheimer's disease (AD) type accounts for 60% to 80% of all dementia cases.[4] It is characterised by loss of episodic memory as well as loss of other cognitive functions.[5] Cognitive decline has been shown to be strongly associated with hearing loss with the probability of incident dementia log-linearly increasing with the severity of hearing loss.[6]

In addition, results from a number of longitudinal studies suggest that changes in central auditory processing skills, even in the absence of severe peripheral hearing loss, are associated with high incidence of cognitive decline and AD.[7 8] Changes in the human auditory system can be objectively measured which can provide an avenue in differentiating normal age-related cognitive dysfunction from AD and its prodromal states.[9–11]

Investigating peripheral and central auditory functions in populations at risk of developing AD using auditory neurophysiological measurements combined with audiological assessments can potentially identify a crucial and sensitive diagnostic window of opportunity in preclinical AD. Auditory electrophysiological assessments have gained interest as possible tools for early diagnosis of AD. The present paper outlines the protocol used to systematically review the published literature currently available on auditory electrophysiological assessments that have been used to assess the auditory functions of adults over the age of 65 years diagnosed with AD and its preclinical stages including those with mild cognitive impairment (MCI) and subjective cognitive decline (SCD). The aims of the systematic review and meta-analysis are; (i) to determine the magnitude of auditory electrophysiological component amplitude and/or latency abnormalities present in AD, MCI and SCD when compared with controls, (ii) to determine which auditory electrophysiological component can be used to differentiate between the different study groups (ie, AD, MCI, SCD and controls) and (iii) to determine which auditory electrophysiological assessments can yield a possible diagnostic tool for preclinical AD.

METHODS
This systematic review will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[12] This protocol is reported in accordance with the PRISMA-Protocols (PRISMA-P) 2015 checklist.[13] This systematic review is registered in the PROSPERO; International Prospective Register of Systematic Reviews, (http://www.crd.york.ac.uk/PROSPERO/).

Eligibility criteria
All full-length peer-reviewed publications of original data related to auditory electrophysiological assessments in AD or its preclinical stages available on the selected databases published between 1985 and May 2019 will be considered in this review.

The eligibility criteria (table 1) illustrate the inclusion and exclusion criteria for publications based on four categories; publication type, population type, assessment type and reported outcome. Only publications of original data that are reported in English will be included in this review, publication of non-original data such as reviews or editorials will not be included in this review. In order to be included in this review all studies must have one or more subject groups with cognitive impairment associated with

AD and its preclinical stages. The studies must also have used auditory electrophysiological assessments either as a tool for assessing hearing abilities in cognitively impaired adults or as a diagnostic tool for cognitive impairment. Studies using a non-human subject pool and subject groups under the age of 60 will be excluded from this review. The full inclusion and exclusion criteria is illustrated in table 1.

Information sources
The search will be conducted on the following major databases in medicine, neuroscience and psychology: Ovid Embase, Ovid MEDLINE, PsycINFO, PubMed, Scopus and CINAHL Plus. A hand search of references and citations of the included publications will also be conducted using Google Scholar. In addition, a grey literature search will be conducted using Google Scholar to identify any relevant studies that would not be found through the major database searches.

Search strategy
Medical Subject Headings (MeSH) in exploded mode in conjunction with keyword searches will be used to maximise the sensitivity of the search strategy in the Embase, MEDLINE and PsycINFO databases. Keyword searches with synonyms, abbreviations, truncations and different spellings (see table 2) will also be used in the PubMed, Scopus and CINAHL Plus databases. The search terms are divided in two domains; (i) auditory tests and (ii) Alzheimer's disease, refer to table 2.

Data management and study selection
All results from database and hand searches will be exported into EndNote X7 software (Thomson Reuters, 2016), where the duplicate publications will be removed. The study selection will then be undertaken in two stages; first, the titles and abstracts will be screened against the eligibility criteria to confirm whether they are suitable for the final review; second, the full-texts for the eligible publications will be analysed against the eligibility criteria. The search strategy and publication screening will be conducted by two authors (HYT and DMPJ) assisted by Covidence,[14] a systematic review publication organisational tool (http://www.covidence.org). Any discrepancies between the two authors where a consensus could not be reached will be resolved through discussion and consultation with a third reviewer (WHAMM).

Data items and collection process
Data extracted from publications for this review will include the following:
1. Publication characteristics: authors, year of publication, journal of publication, title, study objective, study design.
2. Participant characteristics: geographical location of the study, number of participants, age of subject groups, diagnosis method of the disease (SCD or MCI or AD), Mini-Mental State Examination score (if reported).

Table 1	Eligibility criteria	
Eligibility criteria	Include	Exclude
Publication type	► Peer-reviewed, full-length publications of original data.	► Non-original data publications; editorials, reviews, letters, opinion pieces, miscellaneous reports, non-empirical studies.
	► Publications written in English.	► Publications in any language other than English.
	► All articles on the topic published between 1985 and May 2019.	
Population type	► Studies that include participants with dementia of the Alzheimer's type and/or its prodromal states.	► Studies that only address non-cognitively impaired adults or adults without memory complaints.
	► Studies with participants that are healthy and participants with cognitive impairment or memory complaints if the data for cognitively impaired participants is reported.	► Studies with no age matched comparison (control) group.
	► Studies conducted on humans only.	► Studies on children or adults with the mean age under 60.
	► Studies conducted on humans and other animals if data for humans is reported.	
	► Studies with an age matched comparison (control) group.	
	► Studies on elderly adult participants; mean age of 60 years old or older (If mean age not specified the age range for the subject must start at 60 years old).	
Assessment type	► Studies that use auditory electrophysiological assessments either as a tool for assessing hearing abilities in cognitively impaired adults or as a diagnostic tool for cognitive impairment.	► Studies that only use auditory assessments that are not electrophysiological.
	► Studies that use a recognised diagnostic criteria, neuropsychological evaluation or medical imaging to diagnose/classify the AD or MCI groups.	► Non-human studies.
	► Studies that use non-auditory electrophysiological assessments as well as auditory electrophysiological assessments, if the data for the auditory electrophysiological assessments is reported.	
Reported outcome	► Latency and amplitude measures of the auditory electrophysiological assessments.	► Self-reported outcomes.

AD, Alzheimer's disease; MCI, mild cognitive impairment.

3. Assessment characteristics: testing methods applied, for example, auditory electrophysiology assessment task/paradigm.
4. Outcome characteristics: which auditory electrophysiological measures were used, major findings on components latency and/or amplitude, major conclusions and limitations or difficulties of testing procedures.

The data extracted will be analysed qualitatively to identify any particular patterns, similarities or differences between studies. The data extracted from the publications will provide information about any gaps in knowledge and the future direction of research on auditory electrophysiology in AD and its preclinical stages.

Quality assessment

All articles will be assessed to address the risk of; selection bias, performance bias, analysis bias and reporting bias. A quality assessment tool developed by Thomas et al[15] will be used to evaluate the methodological quality of the quantitative studies included in the systematic review. The quality assessment findings will be analysed, and the evidence will be tabulated in order to grade the recommendations based on the American Society of Plastic Surgeons' Evidence Rating Scale for Therapeutic Studies scale for grading recommendations.

Meta-analytic approach

The meta-analysis will be conducted using the Comprehensive Meta-Analysis (V.3) software developed by Biostat.[16] The data in each study will be refined for the meta-analysis; (1) grand averages of multiple electrode site measures will be pooled into a single mean for each group, (2) measures reported in subgroups (eg, male and female separately) will be pooled and analysed as a single group, (3) event-related potential (ERP) components reported as subcomponents (eg, P300 as P3a and

Table 2 Keywords and Medical Subject Headings (MeSH) terms (explode) applied per domain in search databases

Domain	Keywords	MeSH terms
Auditory tests	psychoacoustic test* OR auditory test OR central auditory test OR electrophysiological assessment OR electrophysiology OR electroencephalography OR ECochG OR ECOG OR event related potential OR ERP OR AEP OR evoked auditory response OR acoustic* evoked response OR acoustic* evoked potential OR auditory event related potential OR AERP OR auditory brainstem response OR ABR OR auditory brainstem responses OR ABRs OR speech-evoked ABR OR complex ABR OR cABR OR brainstem auditory evoked potential OR frequency following response OR FFR OR frequency following potential OR FFP OR envelope following response OR EFR OR auditory middle latency response OR AMLR OR auditory MLR OR middle latency response OR middle-latency response OR MLR OR middle latency responses OR MLRs OR transient middle latency response OR middle latency auditory evoked potentials OR MLPs OR Na OR Pa OR Nb OR Pb OR slow vertex potential OR slow-vertex potential OR SVP OR slow vertex response OR SVR OR V potential OR late cortical response OR long latency auditory evoked potential OR cortical event-related potentials OR P1 OR P100 OR N1 OR N100 OR P2 OR P200 OR N2 OR N200 OR P50 OR late positive component OR late positive complex OR LPC OR late latency response OR LLR OR slow latency auditory evoked potentials OR SLAEPs OR late latency auditory evoked potentials OR LLAEPs OR P300 OR P3 OR mismatched negativity OR MMN OR mismatched field OR MMF OR contingent negative variation OR CNV OR N4 OR N400 OR P6 OR P600 OR auditory steady-state response OR ASSR OR multiple auditory steady-state response OR MASTER OR multiple-frequency ASSR OR multiple-ASSR OR steady state evoked response OR SSER OR Steady state evoked potential OR SSEP OR 4 kHz response	Hearing tests OR Auditory evoked potentials OR Audiometry
Alzheimer's disease	Alzheimer* disease OR Alzheimer* OR Dementia OR AD OR cognitive impairment OR cognitive decline OR cognitive processing OR cognitive ability dementia OR Alzheimer* type dementia OR mild cognitive impairment OR MCI OR amnestic MCI OR amnestic mild cognitive impairment OR minimal cognitive impairment OR moderate cognitive impairment OR severe cognitive impairment OR subjective memory complainers OR SMC OR subjective cognitive decline OR SCD	Dementia OR Cognitive dysfunction, impairment OR Cognition disorders

P3b) will be combined as a single mean for each group and (4) only baseline measures of the ERP components will be included in the meta-analysis. Standard difference in mean with 95% CIs will be reported as synthesised measure of effect size. The standard mean difference reflects the difference between the means of two groups divided by their pooled SD. The data for the meta-analysis will be entered as continuous outcomes under the random effects model. The random effects model will be used to account for variation between study methodologies. The q-value statistic will be performed to test heterogeneity of the studies and the I^2 statistic will indicate heterogeneity as a percentage. A p value <0.05 will be considered statistically significant for all analyses.

Synthesis of results

The data extracted from the studies will be tabulated to illustrate the overall methodological quality, the main findings, the main conclusions and the level of evidence for each study. The findings will be analysed based on the patient group (SCD, MCI or AD) and the clinical testing approach (type of auditory electrophysiological assessment and type of outcome measures) in order to synthesise the evidence. An understanding of the feasibility, efficiency, effectiveness and quality of the use of each auditory electrophysiological assessment in the patient groups will be developed through the synthesis of the results.

Patient and public involvement

Patient and public involvement is not required for this systematic review.

ETHICS AND DISSEMINATION

The aim of this review is to investigate and describe the different auditory electrophysiological tests that have been used in clinical studies in participants with SCD, MCI and AD. This review will provide information about which auditory electrophysiological tests have been found to be useful in assessing auditory function in cognitively impaired adults. Additionally, the review will identify the strengths and limitations of each auditory electrophysiological test and identify which auditory electrophysiological test demonstrates most sensitivity in differentiating subject groups; that is, between those at different stages

of cognitive impairment. This review will also contribute to the study design of clinical studies looking at auditory evoked potentials in patients with AD and its preclinical stages. The full review and meta-analysis will be submitted for publication in a peer-reviewed journal and the results will be presented at conferences and meetings relevant to the field. Ethical approval is not required as no primary data will be collected.

Author affiliations
[1]School of Human Sciences, University of Western Australia, Crawley, Western Australia, Australia
[2]Ear Science Institute Australia, Subiaco, Western Australia, Australia
[3]Ear Science Centre, School of Surgery, University of Western Australia, Crawley, Western Australia, Australia
[4]School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia
[5]Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Macquarie, New South Wales, Australia

ORCID iD
Hadeel Y Tarawneh http://orcid.org/0000-0003-1860-9167

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