Journal of Alzheimer's Disease 85 (2022) 47–53
DOI 10.3233/JAD-215206
IOS Press

Hypothesis

The Auditory Afferent Pathway as a Clinical Marker of Alzheimer's Disease

Kaneez Fatima Shad[a,d,*], Wissam Soubra[c,d] and Dennis John Cordato[b,d]
[a]*School of Life Sciences, University of Technology Sydney, NSW, Australia*
[b]*Department of Neurophysiology, Liverpool Hospital, NSW, Australia*
[c]*A Healthy Step Clinic, NSW, Australia*
[d]*Ingham Institute for Applied Medical Research, Liverpool, NSW, Australia*

Accepted 6 October 2021
Pre-press 8 November 2021

AUTHOR COPY

Abstract. Brain stem neural tracts and nuclei may be disturbed prior to observable neuronal atrophy in AD. In this perspective, we discuss the notion of functional deficits presenting prior to structural abnormalities in Alzheimer's disease (AD). Imaging of inferior colliculi using magnetic resonance spectroscopy (MRS) shows significant decrease in the neuronal markers, N acetyl aspartate/creatine ratio and increase in the glial marker myo-Inositol, in subjects with Mini-Mental State Examination scores greater than 24 and with no signs of atrophy in their MRI of the medial temporal lobe. Abnormalities in components of the auditory event-related potentials (ERPs) are described in cognitive impairment including AD. We observed a significant decrease in amplitude and increase in latency during the first 10 ms of auditory evoked potentials measured on electroencephalography (EEG) indicating slow auditory response of the brainstem. EEG spectral power recorded at the cortex is also associated with neural activity at the level of the inferior colliculi. We postulate that a functional examination of auditory afferent pathways, using non-invasive techniques, such as MRS, brain stem auditory evoked potentials (BAEPs) and ERPs may improve diagnostic accuracy of AD. Functional changes precede structural changes and it is important to further understand the relationship between biochemical and electrophysiological measures such as MRS, BAEPs and EEG.

Keywords: Alzheimer's disease, brain stem auditory potentials, electroencephalography, magnetic resonance spectroscopy

INTRODUCTION

Dementia, in particular Alzheimer's disease (AD), poses a substantial economic burden of direct and indirect costs in Australia which exceeded 14.6 billion in 2016 and are predicted to rise to 36.85 billion AUD by 2056 [1]. Globally we are facing a pandemic of AD with 9.2 million cases predicted for the year 2050, such that 1 in 85 people on our planet will be living with this disease [2]. According to the World Health Organization (WHO) there are nearly 10 million new cases of dementia every year, with AD contributing to 60 to 70% of those cases [3].

AD has traditionally been a clinical diagnosis with standardized memory tests performed contemporaneously with an initial clinical assessment. The diagnosis can be supported by neuropsychological testing and structural imaging modalities, the latter of which are performed to exclude alternative diagnoses as well as characterize regional abnormalities, for example, by performing cross sectional magnetic resonance imaging (MRI) with hippocampal volumetry. These modalities are limited in their ability to accurately determine the underlying etiology in subjects presenting with mild cognitive impairment (MCI) [4].

*Correspondence to: Kaneez Fatima Shad, School of Life Sciences, University of Technology Sydney, 15 Broadway, Ultimo, NSW 2007, Australia. Mailing address: PO Box 123, Broadway NSW 2007, Australia. Tel.: +61432064886; E-mails: Kaneez.FatimaShad@uts.edu.au; ftmshad@gmail.com

ISSN 1387-2877/$35.00 © 2022 – IOS Press. All rights reserved.

This may potentially influence the findings of clinical trials as was found in the solanezumab EXPEDITION and EXPEDITION2 phase III studies in which 25% of the study population did not have imaging evidence of amyloid at baseline [5]. Recent modalities, such as amyloid and tau positron emission tomography (PET) and cerebrospinal fluid analysis (CSF) of amyloid-β (Aβ) 42/40 ratio and CSF tau [6], are not readily available for the general community and relatively expensive. Peripheral blood tests that measure the ratio of the two isoforms of Aβ are a promising future alternative to these more complex measures [7].

More recently, it has been postulated that various brain stem neural tracts and nuclei may be disturbed prior to observable neuronal atrophy in AD [8–10]. It follows that a functional examination of such pathways, using non-invasive techniques, such as magnetic resonance spectroscopy (MRS) [11], brain stem auditory evoked potentials (BAEPs), and event-related potentials (ERPs) [2] may improve diagnostic accuracy, particularly if structural abnormalities not observable using traditional imaging modalities, can be detected by observable functional deficits. A hybridization of MRS, BAEPs, and ERPs may be of value in identifying patients who are at risk of cognitive decline. It does not require use of a radiopharmaceutical compound and is non-invasive when compared to PET and/or CSF studies.

Hearing in patients with dementia is a focus of growing clinical interest, with increasing evidence that hearing loss may predict or accelerate cognitive deterioration [12, 13] and alterations of hearing may manifest as complex cognitive and behavioral symptoms relevant to the differential diagnosis of dementias [14–19]. The proposition that neural tracts and nuclei reacting before any identifiable atrophy of the cortex is a rather new hypothesis which is supported by neuropathological studies of brain sections of patients with AD [9]. The inferior and superior colliculi and medial geniculate body have been found to exhibit senile plaques and neurofibrillary tangles, respectively, in the brains of patients with AD [9]. Morphological changes in these two regions including neuronal loss and synaptic alterations, prior to the appearance of senile plaques or neurofibrillary tangles, have also been reported in early cases of AD [10]. It seems appropriate to investigate the anatomical structure of the brain stem, which has a high content of neural tracts.

Neuropathological studies in AD have demonstrated involvement of brain stem nuclei. One of these nuclei, the Tegmentopontine reticular nucleus, is affected in early stages during the development of AD (preclinical AD) before the neuropathological changes affect the limbic system (composed of the thalamus, hypothalamus, hippocampus, and the amygdala) and cerebral cortex [19]. The solitary tract and nucleus as well as dorsal nucleus of the vagus nerve are also affected in the early stages of AD. Histologically, most of these affected nuclei exhibit neurofibrillary tangles or senile plaques in the brains of patients with AD [9].

MAGNETIC RESONANCE SPECTROSCOPY

Patients with amnestic mild cognitive impairment (MCI) have a higher risk of progression to AD compared with their cognitively normal peers, and proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive biomarker, in such conditions, that can be diagnostically useful through its ability to measure numerous metabolites in the human brain [20].

There is evidence of progressive chemical changes that involve multiple brain regions during the progression of AD such as decreased neuronal integrity marker; N acetyl aspartate (NAA); or NAA/creatine ratio in the parietal and occipital cortex, gray matter, hippocampus, and posterior cingulate and increased glial marker myoinositol in the parietal and occipital cortex, gray matter, and posterior cingulate [21]. Elevated myoinositol/creatine and choline/creatine ratios and reduced NAA/creatine ratios in MCI and pre-symptomatic AD suggests that ^{1}H-MRS is valuable in predicting future development of dementia and monitoring early disease progression for preventive therapies [22].

No neuroimaging study has yet dealt with the anatomical structure of the brain stem nuclei concerning pathological changes caused by AD. We evaluated the ^{1}H-MRS of inferior colliculus findings in 54 males (27 healthy controls, 27 patients with MCI; aged 50–70 years). All patients underwent neuropsychological testing using Mini-Mental State Examination (MMSE) [23] and Clinical Dementia Rating (CDR) [24]. ^{1}H-MRS of the inferior colliculus was performed by the Point Resolved Spectroscopy (PRESS) system for sequencing, using both multi and single voxel with different voxel sizes (from 7–15) to obtain reproducible results with minimum noise. The study confirmed the feasibility of using ^{1}H-MRS in MCI for tracking neuronal changes in the brain stem (Figs. 1 and 2).

AUTHOR COPY

THE ASCENDING AUDITORY PATHWAY

Alteration of hearing may predict future onset of dementia such as AD. A relevant starting point in the examination of auditory neural tract disturbances would be the primary afferent pathways, more specifically the associated brain stem and midbrain nuclei as cortex activity is informed and governed by these structures including cochlear nuclei, inferior colliculi, and the medial geniculate nuclei.

We have selected to focus on the auditory pathway as it is the most external of the sensory pathways and it is also generally one of the last sensory pathways to be clinically detected as being disturbed in AD. It could be inferred that if damage is found in the auditory pathway, that other brain stem pathways, for example the nucleus tractus solitarius [25] and locus coeruleus [26], may already be damaged more severely.

Processing of sound begins in the ascending auditory pathway extending from the cochlea to the primary auditory cortex in Heschl's gyrus (transverse temporal gyrus) and involves complex signal processing at each of the different levels of the pathway [27]. A meta-analysis concluded that hearing loss impacts on multiple domains of cognition and that there is a correlation between cognition and hearing impairment [28] that is not simply attributable to hearing loss confounding speech-based cognitive tasks [29] and has been observed in those with and without dementia [30]. Histopathological involvement of auditory cortices has been described in major neurodegenerative dementias [31] and deficits of auditory cognition are early features of these diseases. Limited histopathological data is available for the role of auditory system in common dementias, indicating that the major auditory relay nuclei are involved in the pathology of AD [9, 31] and abnormalities of auditory cortical evoked potentials precede the clinical symptoms in young carriers of pathogenic AD mutations [32]. Relatively few studies, on the role of hearing in dementia, have addressed cortical auditory processing specifically, perhaps due to the wide variation in the reported frequency of hearing impairment in AD [13].

Patients with dementia may have reduced perception of sound, disproportionate to any damage

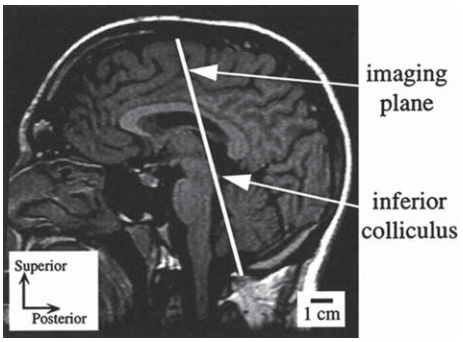

Fig. 1. The ^{1}H-MRS imaging plane used for the inferior colliculus.

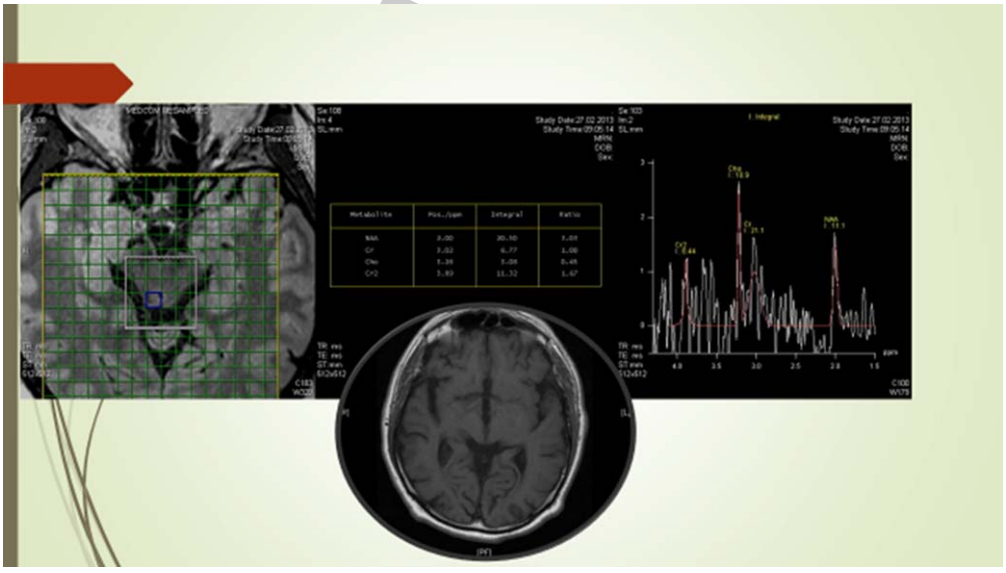

Fig. 2. A normal MRI image from a mild congitive impairment patient, and a ^{1}H-MRS image from the same patient showing abnormal biochemical changes.

AUTHOR COPY

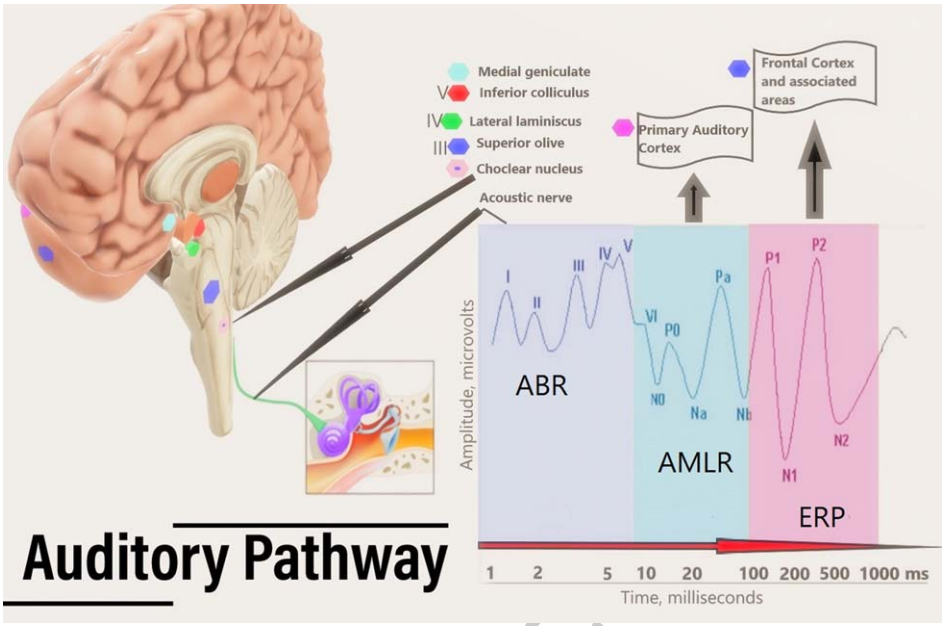

Fig. 3. This figure shows voltage changes to auditory stimuli captured during an electroencephalography (EEG) recording. Auditory brain stem response (ABR) of less than 10 ms, followed by the auditory middle latency response (AMLR) of less than 100 ms and event related potentials (ERPs) of up to 1000 ms.

involving the cochlea or the ascending auditory pathways, which may manifest as cortical deafness syndrome [33] with peri-Sylvian degeneration [34]. Patients with clinically typical AD commonly report difficulty following conversations and other sounds against background noise which may contribute to avoidance of social situations and a general dislike of busy auditory environments [35]. Such symptoms are attributed to a nonspecific memory or attentional deficit that may signify AD-associated impairments of auditory scene with disintegration of a parieto-temporal network [14, 17, 18] in an unfamiliar accent [16]. A neuroanatomical substrate may be present in the posterior peri-Sylvian cortices [35].

It may be of value to measure BAEPs not only for auditory dysfunction in general but also for patients with MCI or suspected diagnosis of AD. Previous literature suggests that central auditory dysfunction may precede the onset of clinical dementia [36]. There is also growing evidence of vestibular loss as a contributing factor to the development of MCI and AD.

EVENT-RELATED POTENTIALS AND QUANTITATIVE EEG

ERPs comprise of voltage changes to sensory stimuli, for example auditory (Fig. 3), captured during an electroencephalogram (EEG) [37]. The sequence of 7 auditory evoked potentials (Fig. 3), as described by Starr and Achor [38], are directly related to neural activity within the inferior colliculi [39]. The inferior colliculi provide input to the medial geniculate nucleus of the thalamus which subsequently relay to the cortex for processing, directly influencing cortex activity more broadly. Abnormalities in interpeak latency and/or amplitude ratios of the BAEP may be present in patients with MCI. It is also plausible that EEG spectral power recorded at the cortex is associated with neural activity at the level of the inferior colliculi. Abnormalities in components of the auditory ERPs have been recently described in aging, depression, and cognitive impairment including AD [40]. There may also be a role for evaluating other pathways including visual ERPs and vestibular evoked myogenic potentials in MCI and AD [41].

The P300 component of an auditory ERP is a positive deflection occurring 300 ms and the N400 component is a negative component peaking at 400 ms following a stimulus [42]. Research has demonstrated that EEG spectral power within the delta, theta, alpha, and beta frequency bands of pre- and post-auditory stimulus EEG is associated with both the amplitude and latency of various auditory ERP components [42]. The P300 amplitude has been shown to be reduced across the whole head and its

AUTHOR C

distribution is altered in patients with AD with maximums found at frontal sites as opposed to parietal sites in healthy controls [43]. The P300 latency has also been shown to be increased in patients with AD [44] whereas the N400 component is diminished [45]. The P400 amplitude has also been shown to be significantly higher in the posterior head regions in patients with AD who are performing a memory workload task [46]. Mismatch negativity has been found to have a decreased amplitude in AD [47].

Research indicates that both broad and event specific brain activity changes may precede and possibly predict early cognitive decline [2]. Changes in beta and gamma activities are generally linked to cognitive decline [48]. Domain specific cognitive decline may also influence other EEG activities across all frequency bands. An increase in delta and theta frequency band activity on quantitative EEG is well recognized as a manifestation of cognitive impairment [49]. Changes in higher frequency EEG activity including decreased upper alpha band activity [50] and alpha reactivity [51] have also been correlated to changes in cognitive performance. Alterations in gamma oscillatory synchrony [52] and in beta [2] and gamma activity including increased theta/gamma ratios [53] have also been implicated.

FUTURE DIRECTIONS, SUGGESTIONS, AND CONCLUSIONS

Despite the plausible relationship between ^{1}H-MRS based investigations of neural degeneration with similarly based BAEP and ERP quantitative electroencephalography research, future confirmatory studies that directly compare and/or hybridize these measures are required. Such research could lead to the future development of a unique hybrid algorithm that could function as a novel non-invasive biomarker of early cognitive decline and which may be further utilized to identify individuals at risk of dementia, in particular AD.

ACKNOWLEDGMENTS

The authors would like to acknowledge scholarly contributions from Associate Professor Sara Lal from University of Technology Sydney, Australia, Professor Bodo Kress and Dr. Yashar Aghazadeh from Chefarzt des Instituts für Neuroradiologie, Krankenhaus Nordwest, Frankfurt, Germany, and Dr. Ty Lees from Edna Bennett Pierce Prevention Research Center, The Pennsylvania State University, University Park, PA, USA.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/21-5206r1).

REFERENCES

[1] Brown L, Hansnata E, La HA. Economic cost of dementia in Australia 2016-2056. The Institute for Governance and Policy Analysis. Copyright University of Canberra, Canberra 2017. http://www.canberra.edu.au/centres/ucigpa Accessed on 3/6/2021. https://www.dementia.org.au/sites/default/files/NATIONAL/documents/The-economic-cost-of-dementia-in-Australia-2016-to-2056.pdf

[2] Jackson CE, Snyder PJ (2008) Electroencephalography and event-related potentials as biomarkers of mild cognitive impairment and mild Alzheimer's disease. *Alzheimers Dement* **4(1 Suppl 1)**, S137-S143.

[3] Rocca WA, Petersen RC, Knopman DS, Hebert LE, Evans DA, Hall KS, Gao S, Unverzagt FW, Langa KM, Larson EB, White LR (2011) Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. *Alzheimers Dement* **7**, 80-93.

[4] Yin C, Li S, Zhao W, Feng J (2013) Brain imaging of mild cognitive impairment and Alzheimer's disease. *Neural Regen Res* **8**, 435-444.

[5] Siemers ER, Sundell KL, Carlson C, Case M, Sethuraman G, Liu-Seifert H, Dowsett SA, Pontecorvo MJ, Dean RA, Demattos R (2016) Phase 3 solanezumab trials: Secondary outcomes in mild Alzheimer's disease patients. *Alzheimers Dement* **12**, 110-120.

[6] Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P (2019) Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's disease. *Alzheimers Res Ther* **11**, 34.

[7] Giudici KV, de Souto Barreto P, Guyonnet S, Li Y, Bateman RJ, Vellas B; MAPT/DSA Group (2020) Assessment of plasma amyloid-β42/40 and cognitive decline among community-dwelling older adults. *JAMA Netw Open* **3**, e2028634.

[8] Lee JH, Ryan J, Andreescu C, Aizenstein H, Lim HK (2015) Brainstem morphological changes in Alzheimer's disease. *Neuroreport* **26**, 411-415.

[9] Parvizi J, Van Hoesen GW, Damasio A (2001) The selective vulnerability of brainstem nuclei to Alzheimer's disease. *Ann Neurol* **49**, 53-66.

[10] Baloyannis SJ, Mauroudis I, Manolides SL, Manolides LS (2009) Synaptic alterations in the medial geniculate bodies and the inferior colliculi in Alzheimer's disease: A Golgi and electron microscope study. *Acta Otolaryngol* **129**, 416-418.

[11] Maul S, Giegling I, Rujescu D (2020) Proton magnetic resonance spectroscopy in common dementias-current status and perspectives. *Front Psychiatry* **11**, 769.

[12] Lin FR, Ferrucci L, Metter EJ, An Y, Zonderman AB, Resnick SM (2011) Hearing loss and cognition in the Baltimore Longitudinal Study of Aging. *Neuropsychology* **25**, 763-770.

[13] Lin FR, Metter EJ, O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L (2011) Hearing loss and incident dementia. *Arch Neurol* **68**, 214-220.

[14] Goll JC, Kim LG, Ridgway GR, Hailstone JC, Lehmann M, Buckley AH, Crutch SJ, Warren JD (2012) Impairments of auditory scene analysis in Alzheimer's disease. *Brain* **135(Pt 1)**, 190-200.

AUTHOR COPY

[15] Goll JC, Kim LG, Hailstone JC, Lehmann M, Buckley A, Crutch SJ, Warren JD (2011) Auditory object cognition in dementia. *Neuropsychologia* **49**, 2755-2765.

[16] Hailstone JC, Ridgway GR, Bartlett JW, Goll JC, Crutch SJ, Warren JD (2012) Accent processing in dementia. *Neuropsychologia* **50**, 2233-2244.

[17] Golden HL, Nicholas JM, Yong KX, Downey LE, Schott JM, Mummery CJ, Crutch SJ, Warren JD (2015) Auditory spatial processing in Alzheimer's disease. *Brain* **138(Pt 1)**, 189-202.

[18] Golden HL, Agustus JL, Goll JC, Downey LE, Mummery CJ, Schott JM, Crutch SJ, Warren JD (2015) Functional neuroanatomy of auditory scene analysis in Alzheimer's disease. *Neuroimage Clin* **7**, 699-708.

[19] Rüb U, Del Tredici K, Schultz C, Thal DR, Braak E, Braak H (2001) The autonomic higher order processing nuclei of the lower brain stem are among the early targets of the Alzheimer's disease-related cytoskeletal pathology. *Acta Neuropathol* **101**, 555-564.

[20] Kantarci K, Petersen RC, Przybelski SA, Weigand SD, Shiung MM, Whitwell JL, Negash S, Ivnik RJ, Boeve BF, Knopman DS, Smith GE, Jack CR Jr (2008) Hippocampal volumes, proton magnetic resonance spectroscopy metabolites, and cerebrovascular disease in mild cognitive impairment subtypes. *Arch Neurol* **65**, 1621-1628.

[21] Penner J, Rupsingh R, Smith M, Wells JL, Borrie MJ, Bartha R (2010) Increased glutamate in the hippocampus after galantamine treatment for Alzheimer disease. *Prog Neuropsychopharmacol Biol Psychiatry* **34**, 104-110.

[22] Kantarci K (2007) ^{1}H magnetic resonance spectroscopy in dementia. *Br J Radiol* **80(S2)**, S146-S152.

[23] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[24] Berg L (1988) Clinical Dementia Rating (CDR). *Psychopharmacol Bull* **24**, 637-639.

[25] Daulatzai MA (2012) Dysfunctional nucleus tractus solitarius: Its crucial role in promoting neuropathogenetic cascade of Alzheimer's dementia–a novel hypothesis. *Neurochem Res* **37**, 846-868.

[26] Olivieri P, Lagarde J, Lehericy S, Valabrègue R, Michel A, Macé P, Caillé F, Gervais P, Bottlaender M, Sarazin M (2019) Early alteration of the locus coeruleus in phenotypic variants of Alzheimer's disease. *Ann Clin Transl Neurol* **6**, 1345-1351.

[27] Cope TE, Baguley DM, Griffiths TD (2015) The functional anatomy of central auditory processing. *Pract Neurol* **15**, 302–308.

[28] Taljaard DS, Olaithe M, Brennan-Jones CG, Eikelboom RH, Bucks RS (2016) The relationship between hearing impairment and cognitive function: A meta-analysis in adults. *Clin Otolaryngol* **41**, 718-729.

[29] Panza F, Solfrizzi V, Seripa D, Imbimbo BP, Capozzo R, Quaranta N, Pilotto A, Logroscino G (2015) Age-related hearing impairment and frailty in Alzheimer's disease: Interconnected associations and mechanisms. *Front Aging Neurosci* **7**, 113.

[30] Uhlmann RF, Larson EB, Rees TS, Koepsell TD, Duckert LG (1989) Relationship of hearing impairment to dementia and cognitive dysfunction in older adults. *JAMA* **261**, 1916-1919.

[31] Sinha UK, Hollen KM, Rodriguez R, Miller CA (1993) Auditory system degeneration in Alzheimer's disease. *Neurology* **43**, 779-785.

[32] Golob EJ, Ringman JM, Irimajiri R, Bright S, Schaffer B, Medina LD, Starr A (2009) Cortical event-related potentials in preclinical familial Alzheimer disease. *Neurology* **73**, 1649-1655.

[33] Otsuki M, Soma Y, Sato M, Homma A, Tsuji S (1998) Slowly progressive pure word deafness. *Eur Neurol* **39**, 135-140.

[34] Grube M, Bruffaerts R, Schaeverbeke J, Neyens V, De Weer AS, Seghers A, Bergmans B, Dries E, Griffiths TD, Vandenberghe R (2016) Core auditory processing deficits in primary progressive aphasia. *Brain* **139(Pt 6)**, 1817-1829.

[35] Fletcher PD, Downey LE, Golden HL, Clark CN, Slattery CF, Paterson RW, Schott JM, Rohrer JD, Rossor MN, Warren JD (2015) Auditory hedonic phenotypes in dementia: A behavioural and neuroanatomical analysis. *Cortex* **67**, 95-105.

[36] Gates GA, Beiser A, Rees TS, D'Agostino RB, Wolf PA (2002) Central auditory dysfunction may precede the onset of clinical dementia in people with probable Alzheimer's disease. *J Am Geriatr Soc* **50**, 482-488.

[37] Vecchio F, Määttä S. (2011) The use of auditory event-related potentials in Alzheimer's disease diagnosis. *Int J Alzheimers Dis* **2011**, 653173.

[38] Starr A, Achor J (1975) Auditory brain stem responses in neurological disease. *Arch Neurol* **32**, 761-768.

[39] Starr A, Hamilton AE (1976) Correlation between confirmed sites of neurological lesions and abnormalities of far-field auditory brainstem responses. *Electroencephalogr Clin Neurophysiol* **41**, 595-608.

[40] Ruohonen EM, Kattainen S, Li X, Taskila AE, Ye C, Astikainen P (2020) Event-related potentials to changes in sound intensity demonstrate alterations in brain function related to depression and aging. *Front Hum Neurosci* **14**, 98.

[41] Fernandez R, Monacelli A, Duffy CJ (2013) Visual motion event related potentials distinguish aging and Alzheimer's disease. *J Alzheimers Dis* **36**, 177-183.

[42] Başar E, Başar-Eroglu C, Rosen B, Schütt A (1984) A new approach to endogenous event-related potentials in man: Relation between EEG and P300-wave. *Int J Neurosci* **24**, 1-21.

[43] Holt LE, Raine A, Pa G, Schneider LS, Henderson VW, Pollock VE (1995) P300 topography in Alzheimer's disease. *Psychophysiology* **32**, 257-265.

[44] Polich J, Ladish C, Bloom FE (1990) P300 assessment of early Alzheimer's disease. *Electroencephalogr Clin Neurophysiol* **77**, 179-189.

[45] Castañeda M, Ostrosky-Solis F, Pérez M, Bobes MA, Rangel LE (1997) ERP assessment of semantic memory in Alzheimer's disease. *Int J Psychophysiol* **27**, 201-214.

[46] Beuzeron-Mangina JH, Mangina CA (2000) Event-related brain potentials to Memory Workload and 'Analytical-Specific Perception' (Mangina-Test) in patients with early Alzheimer's disease and in normal controls. *Int J Psychophysiol* **37**, 55-69.

[47] Pekkonen E, Jousmäki V, Könönen M, Reinikainen K, Partanen J (1994) Auditory sensory memory impairment in Alzheimer's disease: An event-related potential study. *Neuroreport* **5**, 2537-2540.

[48] van Deursen JA, Vuurman EF, Verhey FR, van Kranen-Mastenbroek VH, Riedel WJ (2008) Increased EEG gamma band activity in Alzheimer's disease and mild cognitive impairment. *J Neural Transm (Vienna)* **115**, 1301-1311.

[49] Rossini PM, Del Percio C, Pasqualetti P, Cassetta E, Binetti G, Dal Forno G, Ferreri F, Frisoni G, Chiovenda P, Miniussi

AUTHOR COPY

C, Parisi L, Tombini M, Vecchio F, Babiloni C (2006) Conversion from mild cognitive impairment to Alzheimer's disease is predicted by sources and coherence of brain electroencephalography rhythms. *Neuroscience* **143**, 793-803.

[50] Pijnenburg YA, v d Made Y, van Cappellen van Walsum AM, Knol DL, Scheltens P, Stam CJ (2004) EEG synchronization likelihood in mild cognitive impairment and Alzheimer's disease during a working memory task. *Clin Neurophysiol* **115**, 1332-1339.

[51] van der Hiele K, Vein AA, Reijntjes RH, Westendorp RG, Bollen EL, van Buchem MA, van Dijk JG, Middelkoop HA (2007) EEG correlates in the spectrum of cognitive decline. *Clin Neurophysiol* **118**, 1931-1939.

[52] Tallon-Baudry C (2009) The roles of gamma-band oscillatory synchrony in human visual cognition. *Front Biosci (Landmark Ed)* **14**, 321-332.

[53] Moretti DV, Frisoni GB, Fracassi C, Pievani M, Geroldi C, Binetti G, Rossini PM, Zanetti O (2011) MCI patients' EEGs show group differences between those who progress and those who do not progress to AD. *Neurobiol Aging* **32**, 563-571.

AUTHOR COPY