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Central auditory function in early Alzheimer's disease and in mild cognitive impairment

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Abstract

Objective: to investigate auditory function in subjects with early Alzheimer's disease, mild cognitive impairment and with subjective memory complaints, in search of signs of central auditory processing dysfunction even in early stages of cognitive impairment.

Design and subjects: a consecutive group of men and women, referred to the Memory Clinic at the Karolinska University Hospital, was approached for inclusion in this prospective study. One hundred and thirty-six subjects, mean age 64 years (range 50–78 years), diagnosed with Alzheimer's disease ($n = 43$), mild cognitive impairment ($n = 59$) or with subjective memory complaints ($n = 34$), were included.

Methods: auditory function was assessed with pure tone audiometry, speech perception in quiet and in background noise and dichotic digits tests with two or three digits.

Results: pure tone audiometry and speech perception scores in quiet and in background noise were normal for age and without between-group differences. Dichotic digits tests showed strongly significant differences between the three groups, where the Alzheimer's disease group performed significantly poorer than the other two groups, with the mild cognitive impairment group in an intermediate position.

Conclusions: our results demonstrate that central auditory processing dysfunction is highly evident in subjects with Alzheimer's disease, and to a considerable extent even in subjects with mild cognitive impairment.

Keywords: age-related hearing impairment, central auditory processing, dementia, hearing, subjective memory complaints, elderly

Introduction

Central and peripheral auditory function interacts with impaired cognition in dementia, and this influence is enhanced by the development of age-related hearing impairment (ARHI). Alzheimer's disease (AD) is the most common form of dementia, develops gradually, and often goes undiagnosed until it has progressed to debilitating stages. AD is characterised by decline in cognition, memory and activities of daily life (ADL). The implications are profound, with benefits of early diagnosis [1]. At an early stage, AD should be separated from mild cognitive impairment (MCI). Persons with MCI are not demented and have intact ADL, but they have subjective memory problems greater than expected for their age, and objective cognitive decline [2]. The annual rate of progression to dementia is 6–10% in epidemiological studies, and 10–15% in clinical materials [2]. Over a 3-year period 20% of MCI-cases were diagnosed with dementia, of which 78% were AD [3].

The incidence of AD is strongly correlated to increasing age [4]. Central auditory processing (CAP) dysfunction also increases with age [5] but is more difficult to study in older persons as the increased incidence of age-related peripheral hearing impairment tends to obscure the interpretation of central auditory tests. CAP dysfunction has been described in AD and is evident even in mild memory impairment [6]. Studies of auditory function in AD and MCI can shed light on the interactions between cognitive impairment and central auditory function, and the influence of early ARHI. CAP dysfunction influences the processing of auditory input, often impaired by ARHI. It is therefore desirable to study central auditory function in early AD and MCI in relatively young individuals with normal or nearly normal peripheral hearing and only mild to moderate cognitive impairment in order to avoid contamination of processes related to ageing only.

The aim of this study was to assess some aspects of both peripheral and central auditory function in a well-defined sample of subjects with early AD and MCI. A group with subjective memory complaints (SMC) and normal cognition was included for reference purposes.

The results of this study provide the base-line for a prospective longitudinal investigation, intending to clarify if CAP dysfunction is a predictor of upcoming cognitive decline. If so, tests of central auditory function should be included in the early diagnostic procedure of memory complaints.

Methods

Subjects

A consecutive group of men and women aged 50–80 years with memory problems, referred to the Memory Clinic at the Karolinska University Hospital, was approached for inclusion in the study from May 2006 to January 2008. The Memory Clinic is a regional centre mainly focused on persons with memory complaints before retirement age. The proposed participants were examined with a comprehensive assessment battery consisting of an interview with a specialist in geriatrics, a general physical and neurological investigation, a detailed neuropsychological assessment with tests from various cognitive domains (language skills, visuospatial functions, psychomotor speed, executive function, short-term memory, verbal episodic memory), neuroimaging and cerebrospinal fluid investigation for biochemical markers. Patients were diagnosed as having either (i) early AD [7, 8], (ii) MCI [9] or (iii) SMC, i.e. persons who were referred because of SMC, but had no objective decline in memory or other cognitive functions. Inclusion criteria were, apart from having one of the three abovementioned diagnoses, a pure-tone average over 0.5, 1, 2 and 4 kHz (PTA4) not exceeding 70 dB HL and complying to the inclusion criteria of Hällgren *et al.* [10] (PTA of 0.5, 1 and 2 kHz <50 dB HL), and no previous use of hearing aid. Exclusion criteria were abnormal otoscopy or tympanometry, conductive hearing loss, other neurodegenerative diseases causing cognitive impairment or use of antipsychotic drugs.

Altogether 146 subjects were invited to participate in the study; 136 were included (response rate 93.2%). Ten subjects were excluded, due to only partial participation in the audiometric tests. For subject group characteristics including the mini-mental state examination (MMSE) scores see Table 1.

Audiometric assessment

Pure tone audiometry, including air conduction thresholds at 0.125–8 kHz and bone conduction thresholds at 0.5–4 kHz, was performed using a GN Resound Orbiter 922 version 2 audiometer, according to ISO 8253-1 [11] using Telephonics TDH-39 ear phones and a Radio Ear B71 bone conductor in a sound-attenuating booth complying with standards specified in ISO 8253-2 [12].

Table 1. Subject group characteristics and mini-mental state examination (MMSE) scores

	All	AD	MCI	SMC
Number of subjects	136	43	59	34
Age in years, mean (SD)	64.3 (6.4)	65.5 (6.4)	63.2 (7.1)	64.0 (5.1)
Male, <i>n</i> (%)	65 (47.8)	20 (46.5)	33 (55.9)	12 (35.3)
Female, <i>n</i> (%)	71 (52.2)	23 (53.5)	26 (44.1)	22 (64.7)
MMSE, median (range)	28 (11–30)	24.5 (11–30)	28 (22–30)	29 (26–30)

AD, Alzheimer's disease; MCI, mild cognitive impairment; SMC, subjective memory complaints.

Speech audiometry, phonemically balanced (PB) words in speech perception in quiet (SPQ) and in speech perception in background noise (SPN), consisted of PB monosyllabic words in Swedish with carrier phrases, according to ISO 8253-3 [13]. In the SPQ test, the phrases were presented through the same audiometer with the same headphones and in the same booth as in the pure tone audiometry. The subjects were instructed to repeat the last word in a sentence that was presented. In the SPN test fifty-sentence lists, using monosyllabic, PB words were presented through a CD-player at a comfortable level chosen by the subject in a fixed speech weighted background noise at a 4 dB S/N-ratio (signal to noise ratio) as described in detail by Magnusson [14].

Dichotic digits tests (DDT) were delivered through a CD player, an audiometer (Madsen OB922) and earphones (Telephonics TDH 39). The presentation level was adjusted to a comfortable level with the subjective sound level equal in both ears. Monosyllabic digits (1, 2, 3, 5, 6, 7) were presented in lists containing series of two and three digits, modified from a previously described Swedish test protocol [15]. The list with two digits contained 20 pairs of digits presented simultaneously in both ears in blocks of five. The list with three digits contained ten triplets presented in the same way as in the list with two digits.

Both the two and the three digit tests were performed under two different conditions: (i) direct report (DR), where the subject was asked to repeat what was heard only in the right or in the left ear, respectively and (ii) free report (FR), where the subject was asked to repeat all digits that were heard in both ears, without specifying in which ear it was heard. In both cases, the order of the digits was ignored. The results are presented as the percentage correctly repeated digits of all presented digits.

Ear advantage (EA) was calculated as the number of correctly repeated digits presented to the right ear minus the number of correctly repeated digits presented to the left ear divided by the total number of correctly repeated digits presented to either ear.

Statistical analysis

The *t*-test for independent samples was used to assess between-group differences in age. Medians and inter-

quartile ranges (P25-P75) for PTA4, speech tests and the DDT are presented. The Kruskal–Wallis analysis of variance (K–W) was used to assess between-group differences. If there was a statistically significant main effect, multiple comparisons of mean ranks for all groups were performed and the *P*-values were adjusted according to the Bonferroni procedure. One-way ANOVA was used to assess between group EA differences. If the *F*-test was significant, pairwise comparisons among the means were performed by the Tukey HSD test. Estimated means and 95% confidence intervals (CI) from the ANOVA are also presented. All statistical analyses were performed with the computer software program Statistica version 9 (StatSoft Scandinavia AB).

The study protocol was approved by the regional ethical review board at the Karolinska Institutet, 2005/914-31.

Results

Pure tone audiometry

The mean hearing thresholds in all three groups did not exceed 20 dB HL at any frequency between 0.125 and 2 kHz in any ear. A mean threshold elevation at 3–8 kHz, not greater than 50 dB HL in any ear, was demonstrated in all three groups. There were no significant between-group differences in hearing threshold levels at any frequencies, in any ear, and no significant interaural differences, thus only the results for the right ear are shown (Figure 1).

Speech perception in quiet

The median percentages of correct responses in both ears were 98% in the AD group and 100% for the MCI and SMC groups (Table 2).

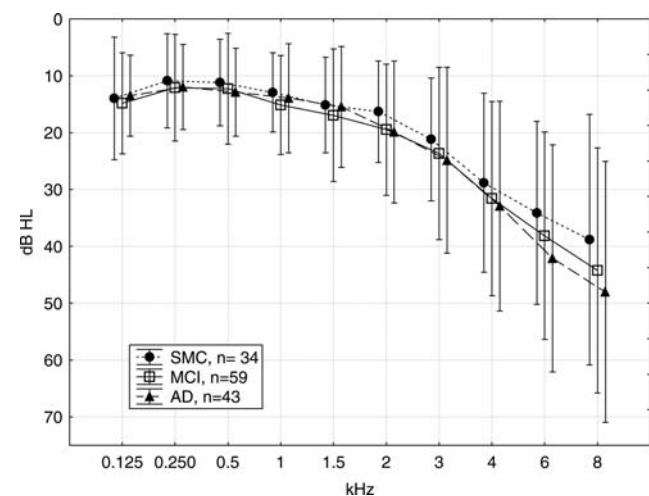


Figure 1. Mean hearing thresholds by group, ± 1 SD, right ear. SMC, subjective memory complaints, MCI, mild cognitive impairment, AD, Alzheimer's disease.

Table 2. Outcomes for the audiometric tests and EA-indexes

	All	Ear	AD	MCI	SMC	K-W	AD-MCI	AD-SMC	MCI-SMC
							and multiple comparisons		
PTA4 median (P25-P75)		RE	15 (10–25)	15 (11–21)	16 (10–21)	0.599			
		LE	15 (10–25)	15 (10–21)	14 (9–20)	0.662			
SPQ median (P25-P75)		RE	98 (96–100)	100 (96–100)	100 (98–100)	0.017	1.000	0.036	0.145
		LE	98 (94–100)	100 (96–100)	100 (98–100)	0.015	0.591	0.023	0.306
SPN median (P25-P75)		RE	78 (68–80)	76 (70–82)	79.5 (72–82)	0.347			
		LE	74 (64–80)	76 (70–80)	79 (72–82)	0.072			
DDT									
Two digits, median (P25-P75)	DR	RE	90 (75–100)	100 (90–100)	100 (95–100)	0.002	0.034	0.004	0.894
		LE	70 (30–90)	90 (80–95)	100 (90–100)	0.000	0.002	0.000	0.004
	FR	RE	85 (74–94)	95 (88–98)	95 (90–100)	0.002	0.019	0.003	1
		LE	66 (41–85)	86 (73–95)	95 (88–95)	0.000	0.001	0.000	0.199
Three digits, median (P25-P75)	DR	RE	93 (73–100)	100 (93–100)	100 (93–100)	0.003	0.078	0.007	0.738
		LE	67 (40–93)	93 (87–100)	100 (93–100)	0.000	0.000	0.000	0.026
	FR	RE	85 (70–93)	90 (82–97)	93 (80–97)	0.173			
		LE	63 (50–80)	80 (67–90)	83 (77–93)	0.000	0.005	0.000	0.590
EA-index							ANOVA (Tukey HSD)		
Two digits, mean ($\pm 95\%$ CI)	DR		0.22 (0.15–0.29)	0.05 (0.02–0.08)	0 (–0.04–0.03)		0	0	0.354
	FR		0.15 (0.08–0.22)	0.05 (0.02–0.09)	0.01 (–0.03–0.05)		0.04	0.002	0.497
Three digits, mean ($\pm 95\%$ CI)	DR		0.15 (0.08–0.22)	0.04 (0.01–0.08)	0 (–0.03–0.03)		0.007	0	0.495
	FR		0.11 (0.06–0.16)	0.05 (0.02–0.09)	0.01 (–0.02–0.05)		0.126	0.007	0.451

AD, Alzheimer's disease; DDT, dichotic digits test; DR, directed report; EA, ear advantage; FR, free report; K–W, Kruskal–Wallis analysis of variance; MCI, mild cognitive impairment; PTA4, pure tone average over 0.5, 1, 2 and 4 kHz; SMC, subjective memory complaints; SPN, speech perception in noise; SPQ, speech perception in quiet.

Speech perception in background noise

The median percentages of correct responses in both ears were between 74 and 79.5% (Table 2).

Dichotic digits tests

The median percentages of correct responses for all test conditions are presented in Table 2.

Two-digit test

The AD group demonstrated significantly poorer scores compared with both the MCI group and to the SMC group in all test situations. The MCI group demonstrated significantly poorer scores compared with the SMC group only in the DR situation in the left ear.

Three-digit test

The AD group demonstrated significantly poorer scores compared with the MCI group in the DR and FR situations only in the left ear. The AD group performed significantly poorer than SMC in the DR situations in both ears, and in the FR situation only in the left ear. The MCI group demonstrated significantly poorer scores compared with the SMC group only in the DR situation in the left ear.

Ear advantage in the dichotic digits tests

In the AD group, there was a highly significant right ear advantage (REA) in all test situations. In the MCI group, the REA was also significant in all test situations. In the

SMC group, there was no significant EA in any test situation. An index of 0 means that there is no EA, +1 indicates a 100% REA. Negative values mean a left EA (Table 2). Between group analyses revealed that the mean REA was stronger in the AD group than in the MCI group in all test situations except in the FR situation with three digits. The REA was stronger in the AD group than in the SMC group in all test situations. The EA in the MCI and the SMC groups did not differ significantly (Table 2).

Discussion

The median pure tone thresholds of all three study groups were age appropriate compared with reference materials [16]. There were no significant differences in median hearing thresholds between the three groups. Gates *et al.* [17] and Kurylo *et al.* [18] likewise could not demonstrate significant differences in hearing thresholds between older AD patients and non-demented controls.

All groups of the present study had normal median speech perception scores in quiet. There was a significant difference between the median scores of the AD group and the SMC group (98 versus 100%). Nevertheless, the hearing was, in general, so good that there are no foreseeable implications regarding hearing loss as a possible confounder.

Speech perception scores in background noise were also within predicted limits in all three groups, adjusting for age and high frequency hearing loss according to a reference model for this speech test as suggested by Barrenäs and Wikström [19]. These results indicate that this speech in noise test is unsuitable to identify CAP dysfunction in AD and MCI.

In the DDT, the AD group performed significantly poorer than the two other groups. However, there were also significant differences between the MCI and SMC groups, placing the MCI group in an intermediate position. These results are in accordance with the findings of Strouse *et al.* [20] and Gates *et al.* [6] who demonstrated that the AD group had poorer performance in CAP tests compared to the control group without memory loss. This implies a 'gradient' in CAP dysfunction between early AD, MCI and SMC, suggesting that DDT might serve as an indicator for early identification of being at risk for AD and/or MCI, in agreement with the findings of Gates *et al.* [21]. Gates *et al.* [6] have suggested central auditory testing in the evaluation of older persons with hearing complaints. In addition, Strouse *et al.* [20] support screening for central auditory dysfunction in AD. However, a test battery comprising many tests is not ideal for clinical studies of CAP in AD and other cognitive dysfunctions. Musiek *et al.* [22] advocated a short, time-efficient test battery for screening purposes. A simple screening test programme, including a CAP-test, provides a possibility to study early AD and MCI, and to monitor these conditions in a non-invasive and time-saving manner.

The outcome of the two-digits DDT was more decisive than that of the three-digits DDT, indicating that the former is more useful for identifying differences in central auditory function with varying degrees of cognitive deficit. This may be caused by the higher possibility of guessing a correct result in the three-digits test. The results of the DR did not differ from the FR to the same extent, implying that either one or both sub-tests could be applied.

A significant REA was demonstrated both in the AD and the MCI groups. Similar results were found by Strouse *et al.* [20], showing poorer performance in dichotic tests in the left ear in AD subjects compared with controls. Hällgren *et al.*, [10] also demonstrated a strong connection between age-related cognitive decline in the elderly and problems to perceive stimuli presented to the left ear. The SMC group, i.e. the clinical controls, showed no significant EA for any ear. This is not surprising in these subjects with a mean age of 64; Jerger *et al.* [23] showed an increasing left-ear deficit in dichotic listening with age, especially in the age group above 80 years. In the present study, both ears had equal, high DDT scores, implying that this test is simple to perform for subjects without CAP disturbances.

The relative mildness of cognitive decline in early AD, the lack of severe ARHI and the REA pattern indicate that the abnormal DDT results actually signal CAP dysfunction in AD, and to some extent also in MCI. Consequently, the DDT can be useful for testing CAP dysfunction during ageing in both audiological and gerontological practice.

Conclusions

Central auditory function was assessed with dichotic digit tests in a group of elderly with cognitive complaints and relatively well preserved peripheral auditory function. Our

results demonstrate that CAP dysfunction is evident in both AD and in MCI, however more prominent in AD. The two-digits DDT is more decisive than the three-digits DDT. An adequate evaluation of CAP might provide an auditory diagnostic complement in monitoring the progression of AD and MCI, or MCI to AD, in a non-invasive and time-saving manner.

Key points

- In AD central auditory dysfunction is striking.
- Central auditory dysfunction is apparent even in MCI.
- The DDT can be used in diagnostic screening of central auditory dysfunction.

Conflicts of interest

None declared.

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Use of NSAIDs for osteoarthritis amongst older-aged primary care patients: engagement with information and perceptions of risk

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Abstract

Background: non-steroidal anti-inflammatory drugs (NSAIDs) are used commonly to treat osteoarthritis in older patients.

Objective: to explore the understandings of risk that older-aged primary care patients have in the context of the use of oral NSAIDs to treat osteoarthritis.

Method: semi-structured interviews were conducted with 15 patients who were recruited from four general practices located in Sydney, Australia. Patients were aged at least 65 years and were currently taking, or in the past 2 years had taken, an NSAID for osteoarthritis. Emergent themes were identified from the transcripts and were compared within and across transcripts to develop more abstract concepts.