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Auditory function in Alzheimer's disease

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**Article abstract**—The pattern of cerebral degeneration in Alzheimer's disease (AD) patients suggests that basic auditory capacities should be normal in AD, whereas progressively higher levels of auditory function should be increasingly impaired. To test this hypothesis, we administered tests of auditory capacities associated with primary auditory cortex (sound localization and perception of complex tones) and auditory association cortex (phoneme discrimination, timbre discrimination, and tonal memory) to 19 mildly to moderately demented AD patients, 21 elderly control subjects (ECS), and 14 young control subjects (YCS). The results showed significant differences between YCS and ECS on phoneme discrimination with synthetic speech and on tonal memory. The AD group differed from the ECS group on sound localization, one measure of synthetic speech discrimination, and timbre discrimination. Performance did not correlate with age, dementia severity, or duration of illness on any test condition. These findings indicate that although AD is accompanied by specific auditory deficits, the increase in neuropathologic change between primary auditory and auditory association cortices is not reflected in an increased impairment of functions that are mediated by these areas. Degraded aural language comprehension, which is characteristic of AD, likely reflects disruption of language processes, rather than dysfunction specific to auditory circuits.

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Several studies have indicated that cortical pathology in Alzheimer's disease (AD) is minimal in primary sensory areas and increases progressively in successively higher areas. Within the auditory system, Esiri et al. found only an occasional neurofibrillary tangle (NFT) and few neuritic plaques in primary auditory cortex (Brodmann's areas 41 and 42). Lewis et al. described substantial increases in the number of NFT in auditory association cortex (Brodmann's area 22) compared with primary auditory cortex in patients with AD. Hyman et al. found that areas 41 and 42 in AD patients were least affected by NFT and that pathologic changes became increasingly dense in primary, secondary, and tertiary auditory association cortices; and Arnold et al. found more NFT in area 22 than in areas 41 and 42.

Given the differential vulnerability of auditory cortices, we hypothesized that AD patients would perform normally on tests mediated by primary auditory cortex but would show deficits in capacities mediated by modality-specific auditory association cortex. To test this hypothesis, we compared the performance of AD patients with that of elderly control subjects (ECS) on several aspects of auditory perception. We also compared the performance of ECS with young control subjects (YCS) in order to document the effects of aging on these auditory capacities. The selection and categorization of tests was based upon results from independent studies that examined the anatomic substrates of specific auditory capacities in animals and in humans. These studies (described below) provided evidence that primary auditory cortex is necessary and sufficient for the processing of sound localization and pitch perception of complex tones, whereas auditory association cortex is required for the processing of phoneme discrimination, timbre discrimination, and tonal memory. We did not assess high-level language abilities (aural comprehension), but instead focused on basic auditory capacities and on the interface between audition and language.

**Methods. Subjects.** The 104 participants in the study included 39 patients with probable AD, 47 ECS, and 14 YCS. Of this original group, 20 AD patients and 26 ECS were excluded from testing because of hearing loss (described below), reducing the number of participants to 19 AD, 21 ECS, and 14 YCS. The diagnosis of AD was...
Audiometry. Pure-tone air conduction audiometric thresholds were measured in all subjects at 125, 250, 500, 1,000, 2,000, 4,000, 6,000, and 8,000 Hz. Measurements were made with a clinical audiometer (Maico MA 39) calibrated to specifications of the American National Standards Institute. Test-retest reliability was 5 dB or less in all cases.

General procedure. Testing was conducted in a private room with reduced ambient noise. To avoid the possibility of systematic changes in performance due to practice or fatigue, we varied the order of test presentation across subjects. Each test was explained in detail and demonstrated. If an AD patient did not understand the test instructions, testing was suspended for that test. With the exception of the sound localization test (in which stimuli were presented in a sound isolation chamber through speakers), subjects listened to stimuli from a recording played through headphones at 50 dB relative to the pure-tone average at each ear.

Auditory capacities mediated by primary auditory cortex. The two measures of auditory capacities mediated by primary auditory cortex were sound localization and pitch perception of complex tones.

Free-field sound localization. Primary auditory cortex appears to be critical for free-field sound localization. Unilateral lesions of primary auditory cortex in cats and monkeys cause permanent deficits in the localization of sound sources in the contralateral auditory hemisphere. In fact, massive lesions of nonprimary auditory cortex that spare primary auditory cortex, or patients with left temporal lobe lesions. Pitch discrimination of tones that spared primary auditory cortex, or patients with left temporal lobe lesions. Pitch discrimination of tones that contained the fundamental frequency was unimpaired.

Pitch perception of complex tones. When a series of harmonic tones is presented simultaneously without the presence of the fundamental frequency, listeners typically perceive the pitch corresponding to the missing fundamental. This phenomenon has been linked to the functional integrity of primary auditory cortex in the right hemisphere. Patients with right temporal lobe lesions that invaded primary auditory cortex made more errors on a pitch discrimination task based on a missing fundamental than patients with right temporal lobe lesions that spared primary auditory cortex, or patients with left temporal lobe lesions. Pitch discrimination of tones that contained the fundamental frequency was unimpaired. These results are consistent with Whitfield's demonstration that cats could not be retrained to discriminate pitch based on a "missing fundamental" after bilateral ablation of auditory cortex, although they could be retrained to respond to individual frequencies of complex tones. We therefore chose pitch perception of complex tones as the second test of basic auditory capacity.

Stimuli for the missing fundamental test were constructed via digital synthesis on a personal computer and recorded onto a cassette. On each trial, two tones either ascended or descended in pitch. In all cases, the pitch change corresponded to 200 versus 300 Hz (low-tone condition) or 600 versus 900 Hz (high-tone condition). In the missing fundamental conditions, the pitch change was produced by a series of consecutive harmonics of the desired fundamental frequency but contained no energy at the fundamental itself. For example, for the 200/300 Hz pair, stimuli consisted of the sixth through ninth harmonics of 200 Hz (1,200, 1,400, 1,600, and 1,800 Hz), and the fourth through sixth harmonics of 300 Hz (1,200, 1,500, and 1,800 Hz). The mean and the range of spectral energy within the elements of a pair were chosen to be similar, but the perceived fundamental frequency differed; thus, in order to hear a rising or falling pitch, the (missing) fundamental frequency had to be perceived. The stimuli in the control series were identical to those in the missing fundamental conditions in all respects except that the control stimuli contained an additional prominent tonal component at the fundamental frequency.

Each complex tone was 500 msec in duration, with a 200 msec inter-tone interval. We presented the two control conditions (low or high tones) first, consisting of 18 trials each (nine ascending pairs and nine descending pairs in random order). We then presented the two missing fundamental conditions, consisting of 18 trials each, for a total of 72 trials in the entire series. Subjects indicated whether complex tones with fundamental frequencies (control conditions) or without fundamental frequencies (experimental conditions) ascended or descended in pitch by responding orally ("up" or "down") or by pointing to an upright or a downward arrow.

Auditory capacities mediated by auditory association cortex. Tests of phoneme discrimination with natural and with synthetic speech, timbre discrimination, and tonal memory were given to examine the integrity of auditory association cortex.

Phoneme discrimination. Several lines of evidence have indicated that auditory association cortex and other associative cortical areas mediate some aspects of phoneme discrimination. For example, Ojemann reported that patients receiving electrical stimulation to the superior temporal gyrus (area 22) during surgery made errors on a phonemic identification task. Basso et al. and Blumstein et al. found that, in contrast to normal
subjects, some aphasic patients with lesions invading the perisylvian association cortex were unable to discriminate pairs of computer-generated consonant-vowel syllables (CVs) differing in voice-onset time (VOT) across a category boundary. Similarly, patients with auditory agnosias for speech sounds had difficulty discriminating CV pairs that differed in their initial consonants.\textsuperscript{18} Cerebral blood flow changes elicited by speech syllables have also been described in the superior temporal gyrus.\textsuperscript{19,20}

Based on these findings, our subjects received three tests of phoneme perception: natural speech identification, synthetic speech identification, and synthetic speech discrimination. Subjects whose first language was not English (two AD patients and one ECS) were excluded from the phoneme discrimination tests.

**Natural speech identification.** The stimuli consisted of the following spoken CV pairs: BA, DA, GA, HA, KA, MA, NA, PA, TA, and VA. Each CV occurred six times in a semirandomized order in six blocks of nonrepeating items, for a total of 60 trials. Subjects responded by pointing to one item in a list of the 10 CV pairs.

**Synthetic speech identification.** The stimuli were synthesized sounds of the stimuli “DA,” “TA,” and several intervening acoustic forms. The sounds had VOTs of 0, 10, 15, 20, 25, 30, 35, 40, 50, or 60 msec. Each VOT was presented six times in a semirandomized order, for a total of 60 trials. For each trial, subjects heard one CV and responded by choosing “DA” or “TA” as printed on a card.

**Synthetic speech discrimination.** The stimuli consisted of two synthesized speech CV pairs. Relative VOTs defined the difference between the two CVs. The possible VOT combinations were 25/25, 20/30, 15/35, 10/40, 5/45, and 0/50 msec, thereby establishing possible VOT differences of 0, 10, 20, 30, 40, and 50 msec. Each VOT difference bracketed 25 msec, which is the normal phonetic boundary between “DA” and “TA.” Subjects indicated whether the pairs sounded the same or different by responding “same” or “different,” or by pointing to the written words SAME or DIFFERENT. In addition, subjects heard pairs of CV combinations with relative VOTs of 10/10, 20/20, 30/30, 40/40, and 50/50 msec. The addition of these CV pairs improved the balance between the number of trials with physically identical CVs and those with physically disparate CVs, thereby improving the balance between the number of trials in which stimuli were perceived as “same” and “different.” Each combination of two CV pairs was presented eight times in semirandom order, yielding a total of 80 trials.

**Timbre discrimination.** The ability to discriminate complex sounds that differ only in harmonic structure is altered in patients with right anterior temporal lobectomy, even in cases where primary auditory cortex is spared.\textsuperscript{21} This ability may be assessed in a subtest of the Seashore Measures of Musical Talents.\textsuperscript{22}

The stimuli consisted of pairs of tones that were either identical or different in timbre. Four blocks of 10 trials each yielded a total of 40 trials. The difference in timbre lessened with each consecutive block, thereby progressively increasing the task difficulty. Subjects indicated whether or not they distinguished a difference between the two tones by responding “same” or “different,” or by pointing to the written words SAME or DIFFERENT.

**Tonal memory.** The ability to discriminate brief melodies is altered in patients with right temporal lobectomy, even with sparing of primary auditory cortex.\textsuperscript{21,23} Short-term retention of pitches is also impaired following right temporal lobectomy.\textsuperscript{24} These results are consistent with those of Colombo et al,\textsuperscript{25} who studied auditory short-term memory in monkeys with lesions of auditory association cortex. We assessed this ability using the Tonal Memory subtest of the Seashore test.

The stimuli consisted of a three- to five-tone melody played twice, with one of the tones changed in pitch on the second playing. Subjects indicated the new tone in the sequence by either responding verbally or by pointing to a written number. The three successive blocks of trials presented pairs of melodies containing, respectively, three, four, and five tones.

**Results. Analyses of test results.** A comparison of the scores for the YCS and ECS showed the effects of age; a comparison of the scores for the ECS and AD patients showed effects specific to AD. Statistical comparisons were made for each test condition by means of ANOVA or, if sample distributions deviated significantly \(p < 0.05\) from normality, with the Kruskal-Wallis test. Where significant group differences occurred, Tukey’s Studentized Range Test was used, or in the case of the Kruskal-Wallis test, pairs of groups were compared using a Mann-Whitney \(U\)-test with the Bonferroni correction for multiple test chance effects. Further, the scores on each test were correlated with the subjects’ age (for each group separately) and with dementia severity (BDS) and duration of illness (for the AD patients).

**Auditory.** Subjects with pure-tone audiometric thresholds of greater than 45 dB (HL, ANSI\textsuperscript{8})\textsuperscript{x} in either ear at any frequency tested were classified as having hearing loss and were therefore excluded from subsequent testing. A similar percentage of individuals from the ECS (55%) and AD (61%) groups demonstrated hearing loss. No YCS demonstrated hearing loss. Abnormal thresholds were generally found at high frequencies (\(>4,000\) Hz).

The group with hearing loss was significantly older than the group with normal hearing for ECS \(F[1,45] = 7.12; p < 0.05\) as well as AD patients \(F[1,37] = 11.53; p < 0.01\). An analysis of covariance adjusting for age indicated that AD patients with hearing loss did not differ significantly from those with normal hearing in dementia severity \(F[1,36] = 1.78; p = 0.19\) or duration of illness \(F[1,36] = 0.03; p = 0.87\). For subjects classified as having normal hearing, one or more audiometric thresholds fell within the range of 26 to 40 dB for 16 of 19 AD patients, 16 of 21 ECS, and no YCS.

**Auditory capacities mediated by primary auditory cortex.** Age-related decline in function was not observed on either test of basic auditory capacities. AD patients were inferior to ECS on sound localization but not on pitch perception of complex tones.

**Sound localization.** Localization accuracy was measured for each speaker in terms of mean localization error (figure 1). One-way ANOVAs indicated a significant effect of group at localizing the two most lateral speaker positions: 85° to the left \(F[2,30] = 4.38; p < 0.05\) and right \(F[2,30] = 9.75;
p < 0.001) of center. Localization errors for these speakers were made in the medial direction. Post hoc analysis indicated YCS did not differ significantly (p > 0.1) from ECS, whereas AD patients were significantly (p < 0.05) inferior to ECS.

Pitch perception of complex tones. For test conditions in which the fundamental frequency was present, all groups identified the direction of pitch change with greater than 98% accuracy. When the fundamental frequency was missing, most subjects made no more than one error on the low- (100% of YCS, 90% of ECS, and 79% of AD) as well as the high- (100% of YCS, 81% of ECS, and 64% of AD) pitch series. Despite a trend indicating poor performance by the AD subjects, no statistically significant (p > 0.10) group differences were found.

Auditory capacities mediated by auditory association cortex. YCS differed from ECS on synthetic speech identification, synthetic speech discrimination, and tonal memory. The performance of AD patients was significantly less accurate than that of ECS on timbre discrimination. Although AD patients differed significantly from ECS on one measure of synthetic speech identification, the performance of AD patients on this condition resembled that of YCS. Contrary to the hypothesis, AD patients and ECS did not differ significantly (p > 0.10) on any other test of high-order auditory capacity except timbre discrimination.

Natural speech identification. Most subjects made no more than one error (99% for YCS, 95% for ECS, and 89% for AD) on any measure of natural speech identification. The groups did not differ significantly (p > 0.1) at identifying any CV pair.

Synthetic speech identification. A qualitative assessment of the data indicated that all subjects demonstrated strong evidence for categoric identification of synthetic speech, with an abrupt transition between perceived phonemes.

Three characteristics of performance were analyzed: identification at each VOT, categoric crossover point, and phonetic boundary zones. The responses of two ECS fell beyond three standard deviations from the ECS group mean and were therefore not included in the statistical analysis. Comparison of phonetic identification at each VOT (figure 2) indicated that the YCS group differed significantly (p < 0.05) from the ECS group at 20 and 30 msec VOT. AD patients did not differ significantly from ECS except at the 20 msec VOT condition, where the performance of the AD group was superior to that of the ECS group and did not differ significantly from the YCS group.

Figure 1. Free-field sound localization. Mean localization error for six speaker positions differing in azimuth. Speaker location is relative to center. Localization errors in the medial direction were significantly greater for AD patients than elderly control subjects (ECS) at ±85°.

Figure 2. (Top) Synthetic speech identification. Mean percentage of trials in which computer-generated speech was identified as “DA.” Speech was varied along a VOT continuum from 0 to 60 msec. At 20 msec, the performance of the elderly control subjects (ECS) differed from that of the other two groups. Groups did not differ significantly in phoneme crossover point or in the extent of the boundary zone between phonemes. (Bottom) Synthetic speech discrimination. Mean percentage of trials in which a pair of computer-generated sounds were identified as being the same. Difference in VOT between pairs was varied from 0 to 50 msec. Young control subjects (YCS) differed significantly from ECS at VOT difference of 10 msec. The ECS and AD groups did not differ significantly.
the boundary zone, calculated for each subject, did not differ significantly (p > 0.1) among groups.

**Synthetic speech discrimination.** The mean percentage of trials in which subjects did not discriminate a difference was calculated as a function of the difference in VOT between the two CV pairs (figure 2). At a difference of 10 msec, YCS perceived a difference significantly (p < 0.05) more often than ECS. ECS and AD patients did not differ significantly (p > 0.1) at any VOT difference.

**Timbre discrimination.** The performance of YCS and ECS did not differ significantly (p > 0.1). AD patients, however, were significantly (p < 0.05) less accurate than the ECS at the third level of difficulty, and there was a trend in that direction at level two (although the difference did not reach significance). A ceiling effect at difficulty level one and a floor effect at difficulty level four (chance = 50% correct responses) may have obscured further differences between groups (figure 3).

**Tonal memory.** YCS demonstrated significantly (p < 0.05) superior performance to ECS on the three- and five-tone series. No significant differences (p > 0.1) were found between ECS and AD patients (figure 3).

**Discussion.** The results indicate that certain high-order auditory functions decline with normal aging; the decline is presumably central in origin. Performance differences between the YCS and ECS groups is likely due to central factors because all subjects had normal pure-tone audiometric thresholds between the frequencies of 125 and 8,000 Hz. However, the majority of ECS had one or more audiometric thresholds within the range of 26 to 40 dB, whereas all YCS had thresholds of less than 26 dB. Since even small decreases in pure-tone threshold may decrease phonetic discrimination, we cannot conclusively exclude the influence of peripheral factors to the diminished performance by ECS. Contrary to our expectation based on the differential vulnerability of auditory cortices in AD, the results indicate that mild to moderate AD is not associated with a differential impairment of high-order auditory functions, as measured here. Although the performance of AD patients differed from that of ECS on timbre discrimination, the pattern of impairment (impairment of sound localization and preservation of phoneme discrimination and tonal memory) did not resemble that expected from the density of neuropathologic changes in auditory areas.

**Audiometry.** All participants in the study demonstrated normal audiometric thresholds, based on the criterion described above. Although YCS in general had lower audiometric thresholds than ECS, stimuli were presented at about 50 dB above mean audiometric thresholds for each subject. The percentage of subjects in the ECS and AD groups demonstrating hearing loss was similar and was comparable with the prevalence of hearing loss.
in elderly adults (age greater than 70 years) living at home. Comparing AD patients who demonstrated hearing loss with those with normal hearing, we found no group differences in level of dementia or duration of illness. In two studies that specifically examined the relation between hearing loss and dementia, there was an association between the degree of hearing impairment in AD patients, the rate of cognitive decline, and the level of dementia. Differences between our results and these studies may reflect the use of different criteria for the classification of hearing loss. In the Peters et al. study and Uhlmann et al. studies, the degree of hearing loss was based on pure-tone audiometric thresholds at frequencies of 4,000 Hz or less, as recommended for the evaluation of hearing handicap. In our study, the evaluation of hearing impairment avoided potential confounding affects of peripheral impairment on central auditory function. Our designation of subjects as hearing impaired was usually based on abnormal thresholds at 4,000, 6,000, and 8,000 Hz, which is consistent with the well-documented finding that hearing loss due to aging is usually characterized by greater impairment at higher frequencies. Because of procedural differences, our study and those of Peters et al. and Uhlmann et al. are not directly comparable.

Age-related performance. Comparable performance between YCS and ECS in free-field sound localization is consistent with previous reports of preserved ability in elderly subjects in sound localization based on interaural amplitude differences and interaural temporal differences. The sparing of the basic auditory functions of sound localization and pitch perception of complex tones is consistent with a preservation of the mainline lemniscal auditory pathways from the brainstem through primary auditory cortex in the normal aging process.

Performance deficits by ECS on phoneme discrimination and tonal memory indicate changes in central auditory function due to the normal aging process. These observed deficits could reflect the decreases in neuronal density in the auditory cortex of the superior temporal gyrus that have been found in the normal aging brain. Degraded performance by elderly subjects in understanding speech cannot be accounted for solely on the basis of pure-tone sensitivity loss. Elderly subjects with normal audiometric thresholds were less accurate at discriminating natural and synthetic speech than young subjects, which is consistent with the results of the present study of impaired synthetic speech identification and discrimination by ECS. Although there were no group differences on the natural speech identification test, errorless performance by many subjects created a ceiling effect that may have obscured group differences. Increasing the sensitivity of these tests may demonstrate further age-related decline in speech perception at the phonemic level.

Auditory deficit in AD relative to level of processing. AD patients' pattern of deficit on auditory tests did not correspond to the distribution of neuropathologic changes in auditory cortex. The gradual progression of neuropathologic changes in AD probably affects cognitive functions mediated by the heteromodal association cortex (such as language, memory, and spatial abilities) before affecting the high-order (modality-specific) auditory functions tested here. Accordingly, patients in more advanced stages of AD than our subjects may be more impaired in high-order auditory function. Nevertheless, the characteristics of auditory capacities found here, with regard to degradation and preservation of function, elucidate several details of sensory function in mildly to moderately demented AD patients.

Auditory localization of central positions was normal in AD, whereas mislocalization in the mediolateral direction became increasingly pronounced for more lateral sound sources, producing a restriction in the lateral extent of the auditory spatial field. This pattern of mislocalization was bilaterally symmetric, reflected by group mean values as well as measures from individual subjects. It is uncertain whether this pattern of response reflects a perceptual abnormality or resulted from a response bias possibly resulting from a restriction in the attentional field. A narrowed field of attention is likely to be centered upon the mean stimulus location, thereby reducing the relative attention directed to lateral areas. One could explore this possibility further by manipulating attentional variables over space while measuring auditory localization. A spatial field restriction may reflect a more global restriction of egocentric space that extends across sensory modalities. Our results of abnormal auditory localization, as well as reported abnormalities in visuospatial perception, may reflect a more general deficit of heteromodal spatial perception in AD rather than a deficit in basic auditory function.

Auditory (aural) language comprehension is clearly compromised in AD. The performance of AD patients did not differ significantly from ECS on synthetic speech discrimination or on synthetic speech identification (the crossover point and boundary zone). In the single phonemic test condition in which AD patients differed from ECS, the performance of AD patients resembled that of YCS. Results from the phoneme discrimination tests are consistent with the report of Bayles that the degree of impairment in AD patients was minimal on phonologic tasks, moderate on morphologic tasks, and severe on semantic tasks. Also, Grimes et al. reported degraded performance by AD patients on dichotic speech recognition, a task that places demands on relatively complex cognitive function. In their study, deficits could not be accounted for by peripheral dysfunction but were associated with cerebral atrophy on CTs in anterior and posterior temporal lobes. The preservation of phoneme discrimination in AD in
the present study supports evidence that impaired aural comprehension in AD results from a degradation of higher-order language function and not from an impairment of modality-specific auditory capacities.

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