

# **Corpus callosum size correlates with asymmetric performance on a dichotic listening task in healthy aging but not in Alzheimer's disease**

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## ABSTRACT

Alzheimer's disease (AD) involves not only gray matter but also white matter pathology, as reflected by atrophy of the corpus callosum (CC). Since decreased CC size may indicate reduced functional interhemispheric connectivity, differences in callosal size may have cognitive consequences that may become specifically apparent in neuropsychological tasks that tap hemispheric laterality. In the present study, we examined callosal functioning with a dichotic listening task in 25 Alzheimer patients, 20 healthy elderly and 20 healthy elderly with subjective memory complaints. We found decreased performance, increased ear asymmetry, and decreased callosal size in the AD group compared to healthy elderly. As expected, in the healthy elderly, we found significant negative correlations between ear asymmetry and callosal size, specifically in the anterior and posterior callosal subareas. While the association with the posterior subareas (isthmus and splenium) points at involvement of temporal areas mediating language processing, the association with the anterior subarea (the rostrum and genu) points at involvement of frontal areas mediating attention and executive functions. Remarkably however, in contrast to the healthy elderly, callosal size was not related to ear asymmetry in the AD group. The absence of an association between callosal atrophy and ear asymmetry implies that other pathological processes, next to reduced callosal functioning, attribute to ear asymmetry in AD. Difficulties to attend specifically to the left ear during dichotic listening in some of the AD patients, points at decreased attention and executive functions and suggests that pathology of specifically the frontal areas is involved.

Keywords: ear asymmetry, MRI, callosal functioning, hemispheric laterality, subjective memory complaints

## INTRODUCTION

Alzheimer's disease (AD) is generally considered to involve predominantly degeneration of gray matter. However, neuropathological studies (Brun & Englund, 1986; Englund & Brun, 1990; Scheltens et al., 1995) indicate that white matter pathology is also involved in the disease. Several neuroimaging studies (Kawamura et al., 1993; Scheltens et al., 1992; Scheltens et al., 1995) found increased lesions of the subcortical fiber system in AD patients compared to age matched healthy elderly. Additionally, the corpus callosum (CC), the largest white matter tract in the human brain, is reduced in size in AD patients compared to healthy elderly (Biegon et al., 1994; Black et al., 2000; Cuenod et al., 1993; Hampel et al., 1998; Hensel et al., 2002; Janowsky, Kaye, & Carper, 1996; Lyoo, Satlin, Lee, & Renshaw, 1997; Pantel et al., 1998; Vermersch, Scheltens, Barkhof, Steinling, & Leys, 1993; Vermersch et al., 1996; Yamauchi et al., 1993).

The CC is specifically involved in interhemispheric exchange of sensory, motor and higher-order cerebral information and thereby plays an important role in the communication between the two hemispheres (Gazzaniga, 2000). The two hemispheres are known to be differentially involved in several higher cognitive functions, a phenomenon known as hemispheric laterality. For example, the left hemisphere is more strongly involved in language functions while the right hemisphere is more strongly involved in visuospatial functions and attention. The CC allows integration of the functions and activity of the separate hemispheres. Since decreased CC size may indicate less callosal fibers and reduced functional connectivity between the hemispheres, differences in the size of the CC may have cognitive consequences.

Dichotic listening is an important method for the study of interhemispheric interaction and callosal function (Hugdahl, 2003). Dichotic listening procedures involve simultaneous presentation of different auditory stimuli to the separate ears, after which the participant is asked to report as many stimuli as possible. Typically, verbal stimuli presented to the right ear (RE) are reported more accurately than verbal stimuli presented to the left ear (LE) (Kimura, 1967). According to structural models, originally proposed by Kimura, this right-ear-advantage (REA) can be attributed to the functional anatomical organization of the central auditory system and the cerebral representation of language functions (Kimura, 1967). During dichotic stimulation, auditory information is thought to be processed in the brain primarily along contralateral pathways (Kimura, 1967). Thus, information from the RE, which reaches the language-dominant left hemisphere directly, would be processed faster and more accurately than information from the LE that has to be transferred from the right hemisphere across the CC to the left hemisphere, thereby inducing a REA. Callosal involvement in dichotic listening also comes forward from studies in patients in whom the CC is affected. As a consequences of partial lesions of the CC, specifically in the posterior part, these patients showed decreased performance of the LE (Gazzaniga, 2000; Pollmann, Maertens, von Cramon, Lepsien, & Hugdahl, 2002; Sugishita et al., 1995). Moreover, in patients suffering from multiple sclerosis decreased CC size was found to be associated with decreased dichotic performance of the LE (Gadea et al., 2002; Barkhof et al., 1998; Reinvang, Bakke, Hugdahl, Karlsen, & Sundet, 1994).

AD patients show decreased performance on dichotic listening tasks compared to age matched elderly (Claus & Mohr, 1996; Grady et al., 1989; Grimes, Grady, Foster, Sunderland, & Patronas, 1985; Mohr, Cox, Williams, Chase, & Fedio, 1990; Strouse, Hall, III, & Burger, 1995). Furthermore, performance of the LE is found to decrease more strongly than performance of the

RE, which results in increased ear asymmetry in this group (Bouma, 1998; Claus et al., 1996; Mohr et al., 1990; Strouse et al., 1995). Decreased dichotic performance in AD has been attributed to cortical dysfunction, specifically in the temporal lobe (Grady et al., 1989; Grimes et al., 1985). Bilateral atrophy in the anterior temporal lobes and reduced glucose metabolism in the left superior temporal region were found to be related to decreased dichotic performance in AD (Grady et al., 1989). In line with Kimura's structural model (Kimura, 1967), neuroimaging studies using PET (O'Leary et al., 1996; O'Leary et al., 1997) and fMRI (Jancke, Buchanan, Lutz, & Shah, 2001; Jancke & Shah, 2002; Hashimoto, Homae, Nakajima, Miyashita, & Sakai, 2000) underscore the importance of the temporal areas in dichotic listening. However, some of these studies also point at involvement of the parietal and frontal areas (Hashimoto et al., 2000; Jancke et al., 2002; O'Leary et al., 1997) which are postulated to be specifically involved in auditory attention in dichotic listening. Attention processes strongly influence ear asymmetry in dichotic listening as already mentioned by Kinsbourne (Kinsbourne, 1970). Moreover, auditory attention has been found to play a major role in increased ear asymmetry in focussed attention conditions in both AD (Bouma, 1998; Claus et al., 1996) and healthy aging (Bouma, 1998; Gootjes, Van Strien, & Bouma, 2004a; Hugdahl, 2000). Since attention processes are thought to be mediated by the frontal areas, these areas may play a role in decreased LE performance during dichotic listening in AD as well.

The finding that different cortical areas are involved in dichotic listening, suggests that regional subareas of the CC might be differentially involved as well. The CC is topographically organized with anterior callosal regions connecting the frontal areas and the posterior callosal regions connecting the posterior areas (Pandya & Seltzer, 1986). Thus, anterior regions of the CC might

be involved in auditory attention effects in dichotic listening, while the posterior regions might be more strongly involved in transmission of auditory information (Alexander & Warren, 1988).

Although earlier studies (Grady et al., 1989; Grimes et al., 1985) did examine the relation between gray matter pathology and dichotic listening performance, to our knowledge no study on AD patients has examined the contribution of white matter pathology to performance and ear asymmetry in dichotic listening. The aim of the present study was to see whether asymmetrical performance on a dichotic listening task (DLT) in Alzheimer's disease and aging is related to white matter pathology as reflected by callosal atrophy. Increased ear asymmetry on DLT in the AD group might be related to reduced CC size. More specifically, strongest relations are expected with regional atrophy of the posterior part of the CC, the isthmus, that is reported to transmit auditory information (Alexander et al., 1988). To test these hypotheses, we examined ear performance and ear asymmetry on DLT and correlated it with midsagittal callosal areas measured using MRI scans in 25 AD patients, 20 healthy elderly and 20 healthy elderly with subjective memory complaints (SMC). Although SMC are common in the elderly population, healthy elderly with SMC have been found to have a higher risk to develop cognitive decline (Dik et al., 2001) or even dementia (St John & Montgomery, 2002). Neuropsychological testing might not be sensitive enough to reveal decrease of memory in these elderly, but anatomical changes might already be present. Since decrease in callosal size might have cognitive consequences, it might be interesting to examine whether the presence of SMC, which may predict cognitive decline, affects callosal size and / or ear asymmetry in dichotic listening in otherwise healthy aging.

## METHODS

### **Subjects**

Twenty-five patients with the clinical diagnosis of probable AD according to NINCDS-ADRDA criteria (McKhann et al., 1984), and 20 healthy controls with subjective memory complaints (HC-SMC) but no objective cognitive symptoms were selected from the Memory Clinic, Department of Neurology, *Vrije Universiteit* Medical Center Amsterdam, the Netherlands. In addition, 20 healthy controls (HC) without subjective memory complaints were recruited from among spouses of the AD patients. Subject characteristics and inferential statistics of pair-wise comparisons between groups are presented in Table 4.1. Severity of dementia was determined according to Mini-Mental-Status Examination (MMSE) score (Folstein, Folstein, & McHugh, 1975). One patient was severely demented (MMSE <10), 8 patients were moderately demented ( $9 < \text{MMSE} < 21$ ), and 12 patients were mildly demented (MMSE > 20). Cognitive performance was examined with the Amsterdam Dementia Screening Test-3 (ADS-3) (Lindeboom & Jonker, 1988) that includes testing of visual memory, orientation, and verbal fluency. AD patients only received the ADS-3 if they had a MMSE score higher than 13. Participants also received the Visual Association Test (VAT) (Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002) that is a brief learning task based on imagery mnemonics with a high specificity to detect AD. All subjects were native Dutch speakers. Premorbid IQ was estimated by the Dutch Adult Reading Test (DART) (Schmand, Bakker, Saan, & Louman, 1991). Since the DART may underestimate premorbid IQ in demented patients, observed IQ was corrected on basis of the MMSE score in the AD group (Schmand, Geerlings, Jonker, & Lindeboom, 1998). Hand preference was examined with a Dutch handedness questionnaire with 10-items (van Strien, 1992). In order to examine possible asymmetries in age-related peripheral hearing loss, auditory screening was

used to examine hearing threshold at 1000, 1500, 2000, 3000 and 4000 Hz. Repeated measures ANOVAs for these frequencies revealed that decrease of hearing was bilaterally symmetrical in all three groups. Analyses of group differences revealed that the AD and the HC group did not differ in mean hearing thresholds at any frequencies. Hearing might be slightly better in the HC-SMC group compared to the HC group, although this was only significant at 2000 Hz ( $P = .032$ ). Informed written consent was asked and received from all patients and healthy subjects. The ethical committee of the *Vrije Universiteit* Amsterdam, The Netherlands approved of the study.

### **Dichotic listening task**

Ten monosyllabic Dutch digits (1-6, 8, and 10-12) were spoken by a female voice and were digitally recorded. The duration of each digit was digitally equated to 450 ms. Digits were arranged in dichotic pairs in such a way that two consecutive digits in a pair were not allowed. Each trial consisted of three pairs in such manner that two consecutive digits were not allowed to follow after each other in one channel. The interval between pairs within a trial was 50 ms and the inter-trial interval was 9.5 s. All digit combinations were counterbalanced between the two channels within the test trials of each condition. Each trial was preceded by a 550 ms 400 Hz tone that was presented to one ear selectively and a 900 ms silence interval. The subject was instructed to focus attention to the ear in which the tone was presented. The DLT consisted of 2 conditions: in one condition the tone was presented to the LE and attention had to be focussed to the LE (ATT-LE) while in the other condition the tone was presented to the RE and attention had to be focussed to the RE (ATT-RE). Trials were presented through earphones (ME 70 noise-excluding headset fitted with TDH 39 receivers, Madsen Electronics, Copenhagen) at a mean sound pressure level of 85 dB. All participants were explicitly asked whether this level was audible and comfortable. Each condition was composed of two warm-up trials and 20 test trials.



The order of the ATT-LE condition and ATT-RE condition was pseudo-randomly assigned to participants in each group: half started with the ATT-LE condition, while the other half started with the ATT-RE condition. Participants had to recall first as many digits as possible from the ear to which the tone was presented and then as many digits as possible from the other ear.

Participants had to indicate verbally when they switched reporting digits from the attended ear to reporting digits from the unattended ear. A short practice session of five trials was done prior to each condition to make sure the participants understood the instructions and felt comfortable with the task. For each ear (LE or RE) the total number of correctly recalled digits was determined. Maximal score for each ear was 60. For each condition (ATT-LE and ATT-RE), an absolute laterality quotient (|LQ|) was calculated according the following formula  $|LQ| = |(RE-LE)/(RE+LE)|$ .

## **MRI**

Fifty-eight subjects were examined on a 1.0 T Siemens Magnetom Impact MRI scanner and seven subjects (5 AD and 2 HC-SMC) were examined with a 1.5 T Siemens Magnetom Vision MRI scanner (both scanners from Siemens, Erlangen, Germany). All subjects had a volumetric T1 weighted axially oriented MRI sequence (for both scanners: TR = 15 ms, TE = 7 ms, resolution = 0.98 by 0.98 by 1.0 mm). Each volumetric sequence was resliced in 0.5 mm thick sagittal images. In case the subject's head was not positioned exactly perpendicular in the head coil, head tilt was corrected by rotating the brain in both axial and coronal direction before reslicing.

Corpus callosum measurements were performed on the sagittal slice that best represented the midsagittal section (Fig. 1A). The criteria for selecting this slice were, in hierarchical order, no or minimal white matter around the CC, the smallest size of the thalamus and intersection of the

cerebral aqueduct. Based on a previously described method (Hampel et al., 1998), Total Corpus callosum Area (TCA) and areas of callosal subregions were measured using in-house-developed software for region-of-interest measurement. TCA was obtained by tracing the outer edge of the corpus callosum semi-automatically using a boundary-detection algorithm with a Canny Edge Filter (Canny, 1986) to indicate high-low intensity edges (Fig. 1D). To divide the CC into subregions, first a rectangle was placed over the CC. The lower side of the rectangle cut tangentially the two lowest points of the anterior and posterior parts of the CC. The rectangle's length was determined by two lines, perpendicular to this lower side, that cut the most anterior and most posterior points of the CC. Subsequently, from the midpoint on the lower side of the rectangle, 4 radial lines, equiangular from each other, divided the CC in five callosal subregions (labeled C1, C2, C3, C4 and C5 in rostral-occipital direction) (Fig. 1E). The number of pixels within each region was summed automatically and multiplied by the pixel size to obtain absolute values (mm<sup>2</sup>).

To examine the intrarater reliability of CC measurements on the two scanners with different degree of field strength, intra-class correlation coefficient (ICC) was determined from scans of an independent group of 8 healthy subjects that were scanned twice, once at each scanner. The ICC for TCA was 0.98 and the ICC for the callosal subregions ranged from 0.99 for C4 and C5 to 0.88 for C1. The average TCA of the 8 subjects was 767.7 mm<sup>2</sup> measured on the 1.0 T scan and 760.8 mm<sup>2</sup> on the 1.5 T scan, which reflects 0.9 % smaller TCA measured by the 1.5 T scan. This is in the same range as the difference between repeated measurement of TCA on the same 1.0 T scan, which is 0.7 %. Since the CC measure is two-dimensional, also a two-dimensional measure of intracranial volume was estimated by tracing intracranial area (ICA) on the midsagittal slice in order to control for differences in brain size. Midsagittal ICA included area of cerebral hemispheres and cerebellum. In order to ascertain that variability is primarily caused

by variation in CC area and not by variation in the brain, we used ICA as a covariate in our analyses (Dorion, Capron, & Duyme, 2001).

All CC and ICA measurements were performed by an investigator (L.G.) blinded to clinical diagnosis.

## **Statistics**

To analyze DLT performance, ANOVAs with repeated measures were done with Condition (ATT-LE and ATT-RE) and Ear (LE and RE) as within-subject variables and Group (AD, HC-SMC and HC) as between-subject variable. To analyze asymmetric ear performance, absolute LQ scores were compared across groups by means of univariate ANOVAs with Condition (ATT-LE and ATT-RE) as within-subject variables and Group (AD, HC-SMC and HC) as between-subject variable. Overall group effects were further analyzed with post-hoc Bonferroni tests. Analyses were repeated with gender as a covariate to control for potential effects of gender distribution.

TCA was compared between groups using univariate ANOVA with gender as covariate. Areas of callosal subregions were compared between groups using repeated measures ANOVA with gender as covariate. Contrast analyses were performed to determine group differences.

Associations between CC areas and |LQ| were examined using partial correlations with gender as covariate. We assumed negative correlations between CC size and |LQ|, therefore we tested one-sided. All analyses involving callosal measures were repeated with ICA as a covariate to control for potential effects of head size. *Since a subgroup of AD patients showed difficulties to attend to the LE, we examined post hoc correlational analyses between callosal size and ear asymmetry in the ATT-LE condition in patients who had these difficulties and in patients without these difficulties.*

## RESULTS

### *DLT*

Mean recall scores are presented in Table 4.2 by group, ear, and condition. The ANOVA yielded significant main effects for Group,  $F(2, 62) = 8.51, P < .001$ . The AD group had significant lower recall scores compared to the HC-SMC ( $P < .001$ ) and to the HC ( $P < .05$ ). There was no difference in recall performance between the HC-SMC and the HC group. An overall Ear effect,  $F(1, 62) = 8.17, P < .01$ , showed a REA, that is, recall performance was better for the RE in all three groups. In addition to an Condition x Ear effect,  $F(1, 62) = 153.83, P < .001$ , a Condition x Ear x Group interaction,  $F(2, 62) = 3.46, P < .05$ , was found. In the HC-SMC and HC group, we found increased performance of the attended ear, namely, a REA in the ATT-RE condition and a LEA in the ATT-LE condition. However, in the AD group we only found a REA in the ATT-RE condition, but we did not find a LEA in the ATT-LE condition (Fig. 2). No significant effects were found for Condition, Ear x Group, and Condition x Group. Analyses of  $|LQ|$  revealed a main effect for Group,  $F(2, 62) = 5.66, P < .01$ , and for Condition,  $F(1, 62) = 6.81, P < .05$ .  $|LQ|$  was significantly higher in the AD group compared to the HC-SMC ( $P < .01$ ), and to the HC group ( $P < .05$ ). In all three groups,  $|LQ|$  was higher in the ATT-RE condition compared to  $|LQ|$  in the ATT-LE condition (Table 4.2). The results remained unchanged when analyses were repeated with gender as a covariate to control for potential effects of gender distribution.

### *CC*

Mean TCA and areas of callosal subregions are presented in Figure 3. Mean TCA differed significantly between the groups,  $F(2,61) = 3.69, P < .05$ . Post-hoc Bonferonni test showed that TCA was decreased in the AD group compared to the HC group ( $P < .01$ ). TCA in the HC-SMC

group was intermediate between the AD and HC group, but there was no significant difference in TCA between the AD group and the HC-SMC group or between the HC and the HC-SMC group. Although callosal atrophy in the AD group seems to be strongest in C1 and C5, there was no significant interaction between group and callosal subareas. The results remained unchanged when analyses were repeated ICA as a covariate to control for potential effects of head size.

#### *Correlation |LQ| and CC*

|LQ| in the ATT-LE condition was negatively correlated with TCA in the HC-SMC group ( $r = -.54, P < .01$ ). In the HC group there was a tendency to a significant correlation between |LQ| in the ATT-LE condition and TCA ( $r = -.33, P = .08$ ). At the level of the callosal subareas, we found |LQ| in the ATT-LE condition was negatively correlated with C1 ( $r = -.52, P < .05$ ) and C5 subareas ( $r = -.61, P < .01$ ) in the HC-SMC group. In the HC group, |LQ| in the ATT-LE condition and in the ATT-RE condition was negatively correlated with C5 subarea ( $r = -.41, P < .05$  and  $r = -.43, P < .05$ , respectively). |LQ| scores were not correlated with TCA nor with any subregion in the AD group. Figure 4 illustrates the correlation between |LQ| in the ATT-LE condition and TCA in the three groups. When analyses were repeated with ICA as a covariate to control for potential effects of head size, analyses involving the AD and HC-SMC group remained unchanged. In the HC group, significant correlation between callosal areas and |LQ| in the ATT-RE remained unchanged but correlation between callosal areas and |LQ| in the ATT-LE condition turned non-significant when analyses were repeated with ICA as covariate.

#### *Post hoc analyses on AD group*

Some AD patients showed moderate ( $n = 6$ ) or profound ( $n = 5$ ) difficulties to attend to the LE in the ATT-LE condition as shown by a high LQ in favor of the RE in this condition ( $0 < LQ < 0.5$

or  $LQ > 0.5$ , respectively). The subgroup of AD patients that showed such difficulties did not differ in mean dichotic listening performance,  $F(1,23) = 0.07$ ,  $p = .794$ , or in callosal size,  $F(1,23) = 0.24$ ,  $p = .628$ , compared to the subgroup of patients that did not show these difficulties. After excluding the AD patients that did have difficulties to attend to the LE, we did not find significant negative correlations or indications for a trend towards negative correlations between LQ and callosal size.

## DISCUSSION

In the present study, we related dichotic listening performance of AD patients and healthy elderly with white matter pathology as reflected by decreased CC area. We found an overall decrease in performance and an increased ear asymmetry on DLT in the AD group. Furthermore, we found significant decrease of callosal size in the AD group compared to healthy elderly. As expected, we found significant negative correlations between callosal size and ear asymmetry in the healthy elderly. Remarkably however, in contrast to the healthy elderly, we found no correlation between callosal size and ear asymmetry on the DLT in the AD group.

### *DLT*

Compared to the healthy elderly, AD patients showed reduced recall performance. This is in agreement with other studies that found reduced dichotic performance in AD (Bouma, 1998; Claus et al., 1996; Grady et al., 1989; Grimes et al., 1985; Mohr et al., 1990; Strouse et al., 1995). Furthermore, a significant Condition x Ear x Group interaction indicates that group differences in ear asymmetry are only present in the ATT-LE (Fig. 2). In the ATT-RE condition, both the control groups and the AD group showed increased recall for the attended RE compared to the unattended LE. However, in the ATT-LE condition, the control groups showed strongly increased performance for the attended LE compared to the unattended RE, while in AD group the difference in mean performance for the attended LE and the unattended RE was minimal.

The group differences that we found are not due to differences in asymmetrical hearing loss or to differences in hearing loss between the groups. Hearing threshold was bilateral symmetrical over the three groups. Also, average hearing threshold in the AD and HC group did not differ from each other. Only the HC and HC-SMC group exhibited a subtle difference in

average hearing threshold, but this is not reflected in differences in dichotic listening performance or in ear asymmetry.

It has been suggested that decreased LE performance in AD can be attributed to a deficit to intentionally shift attention to the LE (Bouma, 1998; Claus et al., 1996). Focussed attention conditions require the participant to focus attention to one ear selectively and involve accurate executive functioning. Impaired executive functions in AD have been reported earlier (Binetti et al., 1996; Duke & Kaszniak, 2000) and might result in an inability to respond accurately to the instruction to focus attention to the LE. Since the efficiency of executive functions like inhibitory control of attention responses is thought to be mediated by frontostriatal systems (Elliott, 2003), changes in the frontal areas may play a role in decreased LE performance during dichotic listening as well. Given this suggestion of an inability to focus attention to the LE, it might seem contradictory that the |LQ| in the ATT-LE condition was higher in the AD group than in the control groups. However, analyses at an individual level showed that a number of AD patients had moderate or profound difficulties attending to the LE: they reported more or mainly RE stimuli and had a high LQ score in favor of the RE despite the instructions to attend to the LE.

Attention problems in early AD have been reported in other studies as well (Dorion et al., 2002). Moreover, it has been suggested that deficits in dividing and shifting attention are one of the earliest indicators of cortical dysfunction in the disease (Parasuraman & Haxby, 1993). In our study, attention problems seem to be specific for the condition in which attention had to be focussed to the LE, which might indicate impaired executive functioning. The role of executive functioning in dichotic listening has been pointed out earlier by Hugdahl (Hugdahl, 2000; Hugdahl et al., 2003) who described dichotic listening in terms of bottom-up (stimulus driven) and top-down (instruction driven) processing. Stimulus driven processing of verbal dichotic stimuli would rely strongly on hemispheric differences in language processing and would result



in a REA [in line with Kimura's structural model (Kimura, 1967)]. Instruction driven processing would be affected by executive abilities to shift attention and would result either in a REA or in a LEA depending on the attention instructions [in line with Kinsbourne's attentional model (Kinsbourne, 1970)]. In focussed attention conditions, instruction driven processing would have a stronger impact on the observed ear asymmetry than in free attention conditions. However, only when attention has to be focussed to the LE, as in the ATT-LE in our study, stimulus driven processing and instruction driven processing have opposite effects. The ability to overcome stimulus driven processing in favor of instruction driven processing might strongly depend on executive inhibitory function. Failure of response inhibition in the AD group might result in increased stimulus driven processing compared to the control groups. In the ATT-LE condition this would result in an inability to focus to the LE while focusing attention in the ATT-RE is relatively unaffected due to stimulus driven processing in favor of the RE.

Additionally, pathology of specifically the right temporal areas might contribute to the observed inability to attend to the LE. Traditionally, patients with lesions restricted to the right hemisphere have been found to show decreased LE performance (Kimura, 1961). Indeed hemispheric asymmetry has been found in cortical pathology in AD, but there is no general agreement on the direction of this asymmetry. There are indications that this asymmetry is rather due to faster left hemisphere cortical degeneration than right hemisphere (e.g. Thompson et al., 2003). The direction of asymmetry in frontal pathology might have a smaller impact on ear asymmetry than asymmetry in temporal pathology since laterality of function disturbed by frontal-lobe lesions is thought to be less striking than lateralized lesions in the temporal and more posterior lobes. Frontal pathology may lead to decreased attentional and executive functions and impaired executive functions would lead to stronger deficits to attend to the LE than to the RE.

Namely, in the condition in which the subject has to focus attention to the LE, stronger demands are put on executive functions (as described in the previous paragraph).

*CC*

TCA was smallest in the AD group and largest in the HC group. This is in line with literature that found reduced callosal size in AD (Biegon et al., 1994; Black et al., 2000; Hampel et al., 1998; Hensel et al., 2002; Janowsky et al., 1996; Lyoo et al., 1997; Teipel et al., 1998; Teipel et al., 1999; Vermersch et al., 1993; Yamauchi et al., 1993). Although decreased callosal size appears to be strongest in subareas C1 and C5 (Fig. 3), repeated measures ANOVA showed no significant interaction between groups and callosal subareas. Findings on regional callosal atrophy in AD have been inconsistent. One study reported selective atrophy of the anterior CC (Biegon et al., 1994), another selective atrophy of the midbody of the CC (Weis, Jellinger, & Wenger, 1991), and again others reported selective atrophy of the smaller posterior CC (Lyoo et al., 1997; Yamauchi et al., 1993). Although these discrepant findings may be partly due to methodological differences in defining callosal subregions, differences between the investigated subjects are likely to attribute as well. Hampel et al. (Hampel et al., 1998) found greatest decrease in the anterior CC (rostrum) and posterior CC (splenium), while the midbody (truncus) was relatively spared, using almost the same method for defining callosal subregions as we did. However, callosal atrophy in AD was more pronounced in their study than in ours, which might be due to increased dementia severity as indicated by a mean MMSE score of 11.4 in their study compared to a MMSE score of 20.1 in our study. Regional differences in callosal atrophy might be too mild at early stages of dementia and might only become clear at the more severe stages. Moreover, regional differences might be masked by premorbid neuroanatomical variability between individuals at early stage of AD.

CC size of the HC-SMC group was intermediate between AD and HC, but did not differ significantly from any of these two groups. Since individuals with SMC have higher risk to develop cognitive decline (Dik et al., 2001), it might be that the HC-SMC group is partly composed of individuals that are in some kind of pre-stage to cognitive decline or even dementia. It has been found earlier that CC size in patients with questionable dementia (Hensel et al., 2002) and in elderly with cognitive decline (Janowsky et al., 1996) is intermediate between AD patients and healthy controls, but our results indicate that mean CC size in healthy elderly with SMC already shows a tendency to be reduced in the absence of objective cognitive decline. Subsequent follow-up examination of our HC-SMC group might reveal whether CC size is really related to the development of cognitive decline or even dementia.

#### *DLT and CC*

In the two healthy elderly groups, we found an association between decreased callosal size and increased ear asymmetry. Specifically decreased size of callosal subarea C5, the most posterior area of the CC in our method, was related to ear asymmetry. Area C5 represents the isthmus and the splenium. Since the isthmus is thought to facilitate the contralateral auditory pathways of the association cortex (Alexander et al., 1988), reduced size of the isthmus would affect interhemispheric transfer of auditory information and is thus likely to exert an effect on ear asymmetry. Both lesions in the isthmus (Alexander et al., 1988) and the splenium (Sugishita et al., 1995, Pollmann et al., 2002) have been suggested to be involved in ear asymmetry in dichotic listening. Furthermore, areas of posterior CC have been found to be negatively correlated with laterality indices of verbal dichotic listening performance in children with closed head injury (Benavidez et al., 1999).

In the HC-SMC group, we also found an association between reduced size of callosal subarea C1 and increased ear asymmetry. Area C1, the most anterior callosal subarea in our method, represents the rostrum and genu that are thought to connect frontal regions of the hemispheres. Neuroimaging research using fMRI has demonstrated that dichotic listening involves activation not only of temporal areas but also of frontal areas (Jancke et al., 2002). Moreover, the frontal areas, involved in attention processes and executive functions, are hypothesized to be involved in age-related increased ear asymmetry on dichotic listening (Gootjes et al., 2004a). Decreased LE performance in elderly compared to young participants specifically in a condition in which attention had to be focussed at the LE, might be attributed to a relative inability of the elderly group to intentionally shift attention to the LE, pointing at diminished frontal lobe functioning in elderly. Indeed, it has been found that the frontal lobes in particular are most susceptible to age-related brain changes (Coffey et al., 1992; Cowell et al., 1994)

The finding of an association between C1 size and ear asymmetry in the HC-SMC group but not in the HC group might be due to increased involvement of frontal areas in the HC-SMC group. Although the two control groups had comparable dichotic performance, it might be that the task was more demanding for the HC-SMC group and that increased frontal involvement might play a compensatory role in this group.

In contrast to our hypothesis, callosal size was not associated with increased ear asymmetry in dichotic performance in AD, even though TCA was decreased. *It might be that heterogeneity in dichotic listening performance in the AD group masks possible associations. A number of patients had profound difficulties to attend to the LE, and the attentional deficits of this subgroup might contaminate possible associations. To examine this possibility we performed post-hoc correlation analyses in a subgroup of AD patients were capable to attend to the left ear.*

No significant or near-significant negative correlations between LQ scores and TCA or any of the callosal subregions were found. However, the absence of such a relation might be due to the relative small number of patients included in this post hoc analyses.

In addition, possible associations might be masked by increased heterogeneity in neuropathological processes in AD. Both gray matter and white matter pathology are involved in AD. Moreover, white matter pathology not only involves reduced CC size but also increased lesions of the subcortical fiber system (Awad, Johnson, Spetzler, & Hodak, 1986; Barber et al., 1999; Erkinjuntti et al., 1994; Eulitz, Diesch, Pantev, Hampson, & Elbert, 1995). Decreased integrity of cortical areas and subcortical fiber tracts is very likely to contribute to decreased dichotic performance and increased ear asymmetry in AD. Indeed, intrahemispheric connectivity of specifically the frontal areas is found to be related to dichotic performance and ear asymmetry in young adults as well (Gootjes, Bouma, Van Strien, Scheltens, & Stam, submitted for publication). The frontal areas are thought to mediate inhibitory executive functions and are found to be most strongly affected in subcortical white matter pathology in AD (Gootjes et al., 2004b). Specifically the ATT-LE condition puts strong demands on inhibitory executive functioning and it is this condition in which AD patients show strongest decrease of left ear performance. Reduced inhibitory executive functioning and thus reduced top-down processing might allow bottom-up processes in favor of right ear performance to have a stronger effect on ear asymmetry in dichotic listening. A possible association between reduced callosal size (indicating reduced interhemispheric connectivity) and decreased recall performance and increased ear asymmetry in AD might be masked by the influence of subcortical white matter pathology (indicating reduced intrahemispheric connectivity) in specifically the frontal areas. Examination of a possible association between subcortical lesions and dichotic listening performance in AD might shed more light on this issue.

### *Conclusion*

Taken together, our results on increased ear asymmetry in dichotic listening performance in AD in the focussed attention condition, suggests that executive inhibitory functioning might be declined in AD. Although CC size was decreased in AD, the absence of an association between CC atrophy and ear asymmetry implies that next to reduced callosal functioning, other pathological processes attribute to ear asymmetry in AD. Profound difficulties to attend specifically to the left ear during dichotic listening in the AD group, points at decreased attention and executive functions and suggests that pathology of specifically the frontal areas is involved. Callosal functioning is strongly involved in ear asymmetry in healthy aging as indicated by the association between ear asymmetry and total callosal size and specifically size of the anterior and posterior callosal subareas. While the association with the two most posterior subareas, the isthmus and splenium, points at involvement of temporal functions, like language processing, the association with the most frontal subarea, the rostrum and genu points at involvement of frontal functions, like attention and executive functions.

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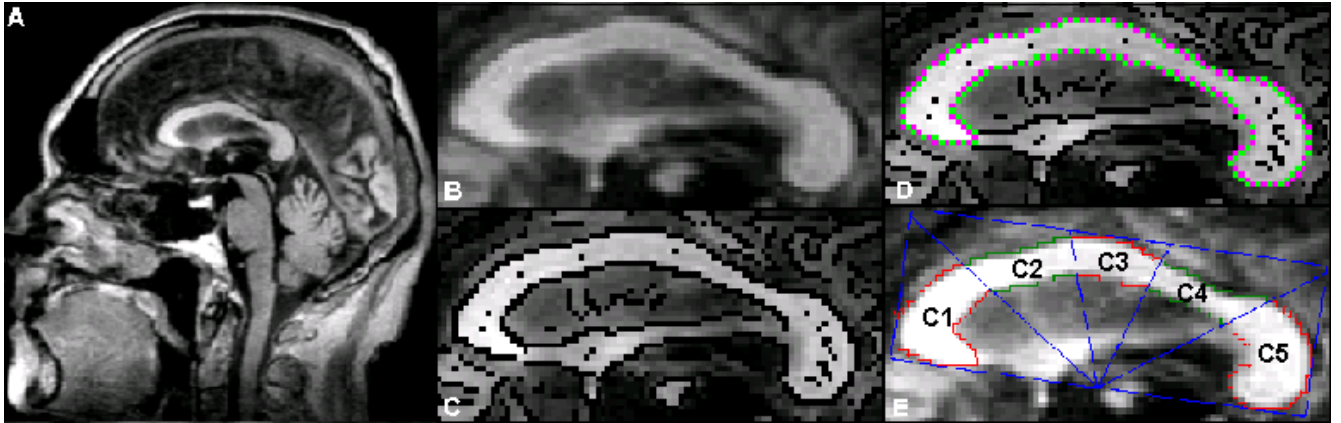
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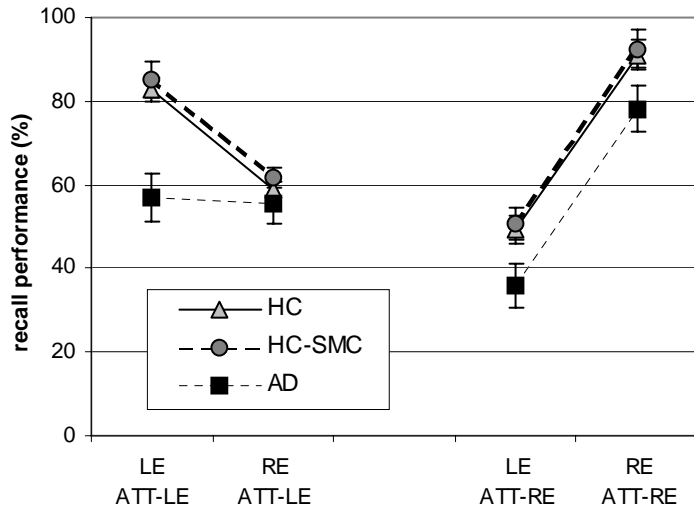
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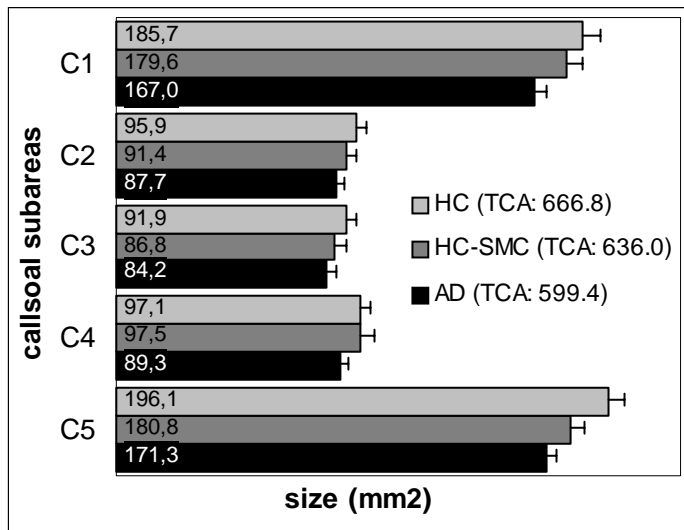
**Figure 1.** MRI scan, showing midsagittal section of the brain (A), zoomed in at the corpus callosum (B), black pixels indicating optimal border between pixels with high intensities and low intensities (C), corpus callosum semi-automatically traced (D), callosal subareas (E).



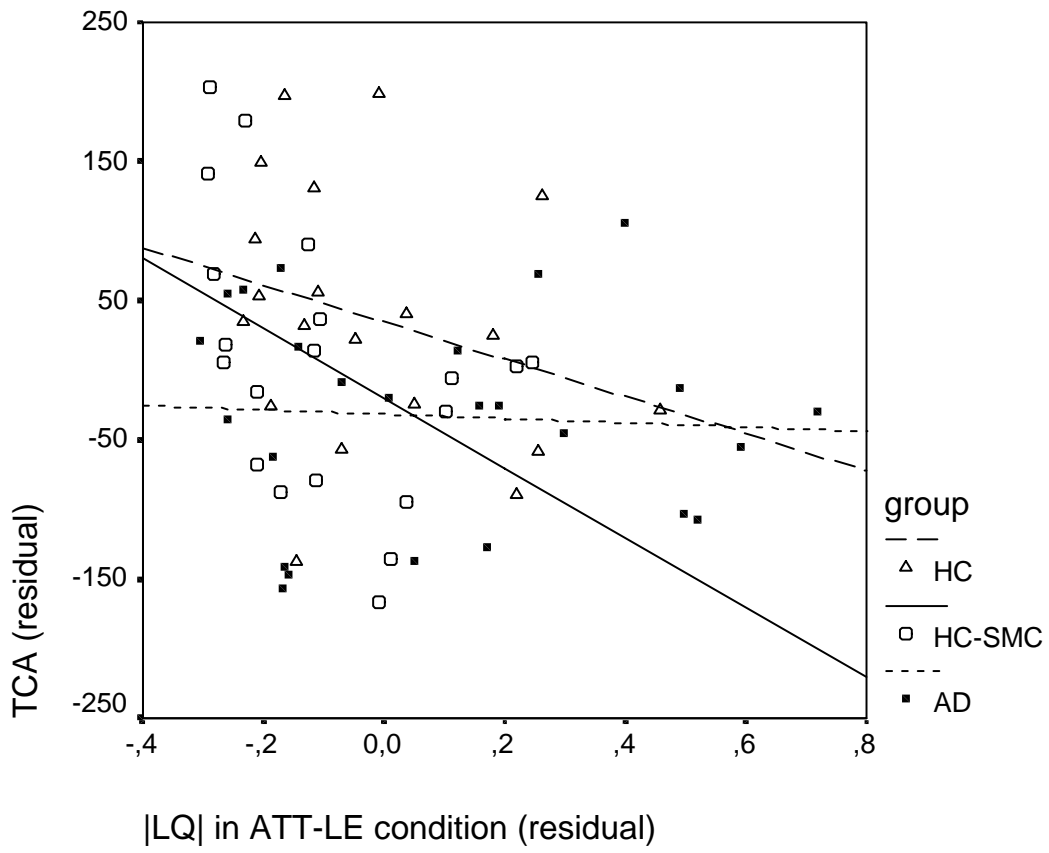
**Figure 2.** Mean recall performance ( $\pm$  SEM) per condition, ear, and group.



**Figure 3.** Mean ( $\pm$  SEM) areas of callosal subregions (mm<sup>2</sup>).



**Figure 4.** Scatter plot with regression lines for  $|LQ|$  in the ATT-LE condition and TCA corrected for gender.



**Table 1.** Subjects' characteristics and pair-wise comparisons between groups.

	<b>AD</b>	<b>HC-SMC</b>	<b>HC</b>	<b>AD vs. HC-SMC</b>	<b>AD vs. HC</b>	<b>HC vs. HC-SMC</b>
	<b>mean ± SD (range)</b>	<b>mean ± SD (range)</b>	<b>mean ± SD (range)</b>			
<b>Age in years</b>	69.3 ± 8.7 (54-83)	66.1 ± 9.3 (51-78)	68.6 ± 9.1 (50-81)	<i>ns</i>	<i>ns</i>	<i>ns</i>
<b>Gender (male/female)</b>	18/7	13/7	9/11	$\chi^2 = .25, ns$	$\chi^2 = 3.38, P < .07$	$\chi^2 = 1.62, ns$
<b>Handedness (right/left)</b>	21/4	15/5	18/2	$\chi^2 = .56, ns$	$\chi^2 = .35, ns$	$\chi^2 = 1.56, ns$
<b>MMSE</b>	20.1 ± 5.5(7-26)	28.6 ± 1.5 (25-30)	28.2 ± 1.6 (24-30)	$P < .001$	$P < .001$	<i>ns</i>
<b>VAT</b>	4.1 ± 4.6 (0-12) <sup>1)</sup>	11.7 ± .66 (10-12)	11.7 ± .49 (11-12)	$P < .001$	$P < .001$	<i>ns</i>
<b>ADS-3</b>	1.2 ± 3.3 (-7-6) <sup>1)</sup>	6.85 ± .37 (6-7)	6.7 ± .73 (4-7)	$P < .001$	$P < .001$	<i>ns</i>
<b>Prem. IQ</b>	104.9 ± 12.4 (82-127) <sup>1)</sup>	107.7 ± 11.2 (81-124)	107.8 ± 8.4 (88-118)	<i>ns</i>	<i>ns</i>	<i>ns</i>

<sup>1)</sup> only examined in subgroup of AD patients with a MMSE score > 13 (n = 17)



**Table 2.** Mean recall performance per ear as a function of group and condition.

	<b>AD</b>			<b>HC-SMC</b>			<b>HC</b>		
	LE	RE	LQ	LE	RE	LQ	LE	RE	LQ
ATT-LE	17.7	16.8	.420	25.6	18.5	.224	24.4	15.6	.291
ATT-RE	11.3	23.3	.510	15.3	27.8	.303	13.5	26.3	.347
total	29.0	40.1		40.9	46.3		37.9	41.9	