Corpus Callosum Tissue Loss and Development of Motor and Global Cognitive Impairment: The LADIS Study

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Key Words

Dementia · Corpus callosum · Motor function · Magnetic resonance imaging · Self-perceived memory impairment · Cognitive impairment

Abstract

Objective: To examine the impact of corpus callosum (CC) tissue loss on the development of global cognitive and motor impairment in the elderly. **Methods:** This study was based on the Leukoaraiosis and Disability (LADIS) study. Assessment of cognitive and motor functions and magnetic resonance imaging (MRI) were done at baseline and at a 3-year follow-up in nondemented elderly subjects. **Results:** 328 of 639 LADIS subjects had MRIs at baseline and at the 3-year follow-up, which allowed for assessment of CC. Logistic regression revealed differential tissue loss rates in posterior

CC in subjects converting to dementia, compared to nonconverters ($p < 0.05$). Anterior and posterior CC tissue loss was significantly correlated with self-perceived memory impairment in nonconverters ($p < 0.05$). CC tissue loss was also significantly associated with impaired single leg stance time ($p < 0.01$). **Conclusion:** The present longitudinal study on CC supports the role of callosal tissue loss in the development of global cognitive as well as motor impairment.

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Introduction

Preserved cognitive abilities and motor control are essential for maintaining functional independence with advancing age. The neural structures involved in age-related motor deficits have not been explored extensively,

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whereas global cortical and hippocampal atrophies are well-established pathological correlates of cognitive decline and dementia. So far no studies have provided a definite conclusion regarding the role of corpus callosum (CC) atrophy. This may partly be attributed to a sparseness of longitudinal studies which are necessary to elucidate a potential causal relationship between CC tissue loss and the gradual development of cognitive and motor deficits.

In cross-sectional studies, CC atrophy has been associated with both cognitive and motor deficits in the elderly [1, 2], with the presence of Alzheimer's disease (AD) [3, 4] and vascular dementia (VaD) [5]. In a recent study we found CC to be a predictor of subsequent cognitive and motor decline [6]. To our knowledge, only one longitudinal study has reported elevated rates of callosal tissue loss in AD [7]. Therefore, it is of importance to study the progression of CC tissue loss in elderly subjects without dementia in a longitudinal design, in order to establish the potential association with clinical symptoms.

Based on the Leukoaraiosis and Disability (LADIS) study (see Appendix), the objective of this longitudinal study was to examine the role of callosal tissue loss in the development of global cognitive and motor impairment. We hypothesized that greater rates of tissue loss were associated with self-perceived memory impairment, global cognitive impairment and conversion to dementia, as well as with motor impairment.

Methods

Design and Subjects

Data for the present study were obtained from the LADIS study. A detailed description of design, methods and rationale has been published previously [8]. The aim of the LADIS study was to investigate the role of age-related white matter changes (ARWMC) in the transition to disability in a population of independent elderly subjects. Patients were enrolled if they were independent in daily living activities; they could have minor neurological, cognitive, mood or motor complaints, or incidental findings on cranial imaging caused by nonspecific events, or otherwise volunteers. Six hundred and thirty-nine subjects with varying degrees of ARWMC load were included. Subjects were stratified according to the degree of ARWMC as rated on the modified Fazekas scale [9] (mild, moderate, severe). Follow-up was carried out for 3 years, and magnetic resonance imagings (MRIs) were obtained at baseline and at the 3-year follow-up. Inclusion criteria were: age 64–85 years, no or only minor disability as indicated by a score of 1 or less on the Instrumental Activities of Daily Living Scale [10], presence of ARWMC on MRI or CT, and informed consent. Exclusion criteria comprised the presence of severe illnesses such as cardiac failure, cancer or other relevant systemic disease which was likely to cause dropout, severe unrelated neurological

diseases, leukoencephalopathy of nonvascular origin (immunological, demyelinating, metabolic, toxic, infectious, other) or severe psychiatric disorders.

At the 3-year follow-up, 73 dropouts and 43 deaths had occurred. Furthermore, for the present study only subjects for whom baseline and 3-year follow-up MRIs of sufficient quality were available could be included, leaving a total of 328 subjects. The present study was based on data from baseline and 3-year follow-up.

Magnetic Resonance Imaging

Baseline and follow-up MRIs were conducted according to the same standard scan protocol. For baseline scans 10 centers used 1.5-tesla scanners, and 1 center 0.5 T, whereas for follow-up 3 centers had acquired new scanners, so only 1.5-tesla scanners were used. The MRI protocol included the following sequences: T₁-weighted magnetization prepared rapid-acquisition gradient echo (MPRAGE; scan parameters: coronal or sagittal plane, TE: 2–7 ms, TR: 9–26 ms, flip angle: 15–30°, voxel size 1·1·1–1.5 mm³), T₂-weighted fast spin echo (scan parameters: axial plane, TE: 100–130 ms, TR: 4,000–6,600 ms, voxel size 1·1·5 mm³, 19–31 slices), and fluid-attenuated inversion recovery (scan parameters: axial plane, TE: 100–160 ms, TR: 6,000–10,000 ms, TI: 2,000–2,400 ms, voxel size 1·1·5 mm³, 19–31 slices).

Corpus Callosum Area

For assessment of CC, MPRAGE images were reoriented to standard Montreal Neurological Institute template orientation, using a 6-parameter rigid transformation SPM5 software package (<http://www.fil.ion.ucl.ac.uk/spm/spm5.html>), after which baseline MPRAGE images were coregistered to follow-up MPRAGE images.

CC was localized in a semiautomatic way on the midsagittal section of the MPRAGE data set using learning-based active appearance models [11]. In short, active appearance models parameterize object variability from a training set of manually annotated CCs, creating a constrained deformation basis for localization of objects similar to the training set based on a computational framework described elsewhere [2, 12]. A trained reviewer, unaware of the clinical status, subsequently corrected the data for inaccuracies. Finally, the CC was automatically divided into 5 subregions using a modification of the Witelson Partitioning scheme [2, 13]: rostrum and genu (CC1), rostral body (CC2), mid-body (CC3), isthmus (CC4) and splenium (CC5). This partitioning scheme has been applied in previous studies in the same cohort [1, 2, 6]. The areas of each segment were calculated automatically and adjusted for head size, i.e. skull size, by registration (12-parameter affine) of the MPRAGE to a standard brain template (Montreal Neurological Institute template) from which scaling parameters along the y- and z-axes were derived. Each CC area was subsequently multiplied by the individual parameters.

Assessment of White Matter Hyperintensities and Lacunes

Visual rating of ARWMC progression was done using the modified Rotterdam Progression Scale [14]. The scale scores progression in 9 brain areas (no progression = 0, progression = 1) yielding a score between 0 and 9 for each subject. Scoring of scans was carried out in a side-by-side manner by a single rater blinded to clinical status. To identify lacunes, fluid attenuation inversion recovery, MPRAGE and T₂ images were used.

Assessment of Medial Temporal Lobe Atrophy

Medial temporal lobe atrophy (MTA) was visually assessed at baseline according to the MTA scale [15]. Assessment was done on the coronal T₁-weighted sequence with a possible score of 0–4: 0 = no atrophy; 1 = widening of the choroid fissure; 2 = widening of the choroid fissure and temporal horn; 3 = widening of the choroid fissure and temporal horn and diminishing height of the hippocampus; 4 = severe atrophy. The mean of the left and the right scores was used.

Assessment of Clinical Status

Global Cognitive Assessment

The Mini Mental State Examination (MMSE) was used to assess global cognitive function. Furthermore, subjects were asked about self-perceived memory impairment (yes/no) at baseline and at the 3-year follow-up.

Diagnosis of Dementia

At the 3-year follow-up, subjects who fulfilled the criteria for dementia, according to the Diagnostic and Statistical Manual of Mental Disorders IV criteria for dementia, were identified. For diagnosis of dementia subtypes the following criteria were used: NINDS-AIREN criteria for VaD [16], the criteria of Erkinjuntti et al. [17] for subcortical VaD, NINCDS-ADRDA criteria for AD [18], the criteria of McKhann et al. [19], for frontotemporal dementia, and those of McKeith et al. [20] for Lewy body dementia.

Assessment of Motor Functions

Motor function was assessed using a test battery including the Short Physical Performance Battery (SPPB), single leg stance time (SLS) and walking speed. Furthermore, history of falls (yes/no) was noted.

In detail, the SPPB assesses balance, gait and lower extremity in 5 different tests. The test battery has previously been described [21]. Each area of testing was scored on a scale from 0 to 4 points yielding a composite score of 0–12 points. Walking speed was calculated using timed walks on an 8-meter course, which participants were asked to complete twice at their normal walking speed. SLS was measured by asking participants to stand on one leg with their hands on their hips. This was carried out a total of 4 times (twice for each leg). A maximum limit of 30 s was applied. As for walking speed the best times were used.

Statistical Analysis

Annual percent change in CC areas was calculated using the following formula: $[(CC_{fu}) - (CC_b)/(CC_b \cdot ISI)] \cdot 100\%$, where CC_{fu} = CC area at follow-up, CC_b = CC area at baseline and ISI = interscan interval.

Multiple linear regression analysis was performed with MMSE scores at the 3-year follow-up as dependent variables, and annual percent CC tissue loss as an independent variable with relevant covariates (baseline MMSE, age, gender, modified Rotterdam progression scale score, MTA score, incident lacunes, presence of diabetes). Logistic regression analysis was carried out with self-perceived memory impairment (yes/no) and a diagnosis of dementia at 3 years as outcomes in 2 separate analyses (covariates: baseline MMSE, age, gender, modified Rotterdam progression scale score, MTA score, incident lacunes, presence of diabetes). For analysis of self-perceived memory impairment, the presence of self-perceived memory impairment at baseline was entered as

Table 1. Summary of demographic and clinical characteristics of the total study population (n = 328)

Age at baseline (mean $\pm$ SD), years	73.8 $\pm$ 5.0
Female/male, %	53 (174)/47 (154)
MMSE at baseline (mean $\pm$ SD)	27.7 $\pm$ 2.4
ARWMC severity at baseline, %	
Mild	44 (145)
Moderate	33 (109)
Severe	23 (74)

Figures in parentheses indicate patient numbers.

covariate, together with Geriatric Depression Scale 15-item score at the 3-year follow-up, since depression has been associated with self-perceived memory impairments [22].

To better assess clinical relevance of the predictive value of CC tissue loss, 3-year follow-up scores on tests assessing motor function were dichotomized according to previously published pre-specified cutoff values [21–23] into ‘physiological’ (SLS >15 s; walking speed ≥ 1.2 m/s, SPPB >10) and ‘pathological’ groups. Moreover, this enabled entering the dichotomized test scores into a logistic regression analysis as dependent variables (covariates: age, gender, modified Rotterdam progression scale score, MTA score, incident lacunes).

Statistical analysis was carried out using statistical software from STATA version 9.2. Results were considered statistically significant at $p < 0.05$ (2-tailed).

Results

Summary characteristics of the study population are displayed in table 1. The median Rotterdam progression scale score was 2 (range 0–8). The median MTA rating score was 1 (range 0–3.5).

The total CC mean area for the entire cohort was 681.2 mm² (SD: ± 92.0 mm²) at baseline with a mean change of -16.3 mm² (SD: ± 39.4 mm²) and an annual change of -0.70% (SD: $\pm 1.9\%$).

Diagnosis of Dementia

Forty-four (13.4%) patients had received a diagnosis of dementia at the 3-year follow-up. Of these, 13 patients were diagnosed as having AD, 30 patients VaD and 1 frontotemporal dementia. Due to the relatively small numbers, statistical analysis was conducted on the total group of converters, not on subtypes. Clinical data on the presence or absence of dementia were missing for 9 subjects. The mean MMSE at 3 years was 20.1 (SD: ± 4.8) for subjects who converted to dementia. Logistic regression

Table 2. Annual percent tissue loss by diagnostic group at 3-year follow-up

	Subjects without dementia (n = 275)		Subjects with dementia (all causes; n = 44)	
	mean	95% CI	mean	95% CI
tCC	-0.6	-0.8 to -0.4	-1.1	-1.8 to -0.4
CC1	-0.9	-1.2 to -0.7	-1.5	-2.3 to -0.6
CC2	-0.4	-0.8 to 0	-0.3	-1.3 to 0.8
CC3	-0.2	-0.6 to 0.2	-0.5	-1.9 to 0.9
CC4	-0.1	-0.4 to 0.3	0	-0.9 to 0.9
CC5	-0.7	-0.9 to -0.5	-1.5*	-2.5 to -0.5

* $p < 0.05$, converters to dementia (all causes) versus nonconverters. tCC = Total CC.

analysis revealed a significant predictive value for CC5 [odds ratio (OR): 0.81; 95% confidence interval (CI): 0.69–0.96; $p < 0.05$; table 2].

Global Cognitive Function

MMSE scores were available for 319 (97.3%) subjects. Regression analysis revealed a significant relationship between MMSE and CC5 ($\beta = 0.21$; 95% CI: 0.05–0.38; $p < 0.05$) indicating that severer CC atrophy was associated with a lower score. There was no significant relationship when the analysis was carried out in subgroups of converters and nonconverters.

Self-Perceived Memory Impairment

At the 3-year follow-up, a total of 189 (68.7%) subjects who had not converted to dementia reported memory complaints. Logistic regression analysis indicated a significant predictive value of tissue loss in the total CC (OR = 0.77; 95% CI: 0.64–0.93; $p < 0.01$), CC1 (OR = 0.84; 95% CI: 0.74–0.97; $p < 0.05$) and CC5 (OR = 0.83; 95% CI: 0.70–0.98; $p < 0.05$) for the presence of self-perceived memory impairment in nonconverters (table 3).

Motor Function

For SLS, logistic regression analysis revealed a predictive value of the total CC (OR = 0.70; 95% CI: 0.55–0.88; $p < 0.01$), CC1 (OR = 0.80; 95% CI: 0.68–0.95; $p < 0.01$), CC3 (OR = 0.86; 95% CI: 0.76–0.97; $p < 0.05$) and CC5 (OR = 0.72; 95% CI: 0.59–0.88; $p < 0.01$). There was no significant predictive value of CC tissue loss on other motor test scores (SPPB, walking speed), or on the history of falls.

Table 3. Annual percent CC tissue loss in subjects without dementia at 3 years, stratified by presence of self-perceived memory impairment

	No self-perceived memory impairment (n = 86)		Presence of self-perceived memory impairment (n = 189)	
	mean	95% CI	mean	95% CI
tCC	-0.3	-0.6 to 0.1	-0.8**	-1.1 to -0.5
CC1	-0.5	-1.1 to 0.1	-1.1*	-1.4 to -0.8
CC2	-0.1	-0.6 to 0.4	-0.5	-1.0 to 0
CC3	0.1	-0.5 to 0.7	-0.4	-0.9 to 0.1
CC4	0.2	-0.4 to 0.8	-0.2	-0.6 to 0.3
CC5	-0.4	-0.7 to 0	-0.8*	-1.1 to -0.7

* $p < 0.05$; ** $p < 0.01$. tCC = Total CC.

Discussion

In this longitudinal study, we employed 2 MRIs at 3-year intervals to chart the role of callosal tissue loss in the development of global cognitive and motor impairment in elderly subjects with ARWMC. This is to the best of our knowledge the first study to do so. Subjects who converted to dementia had a higher rate of tissue loss in the splenium compared to nonconverters, and in subjects who did not develop dementia callosal tissue loss was significantly associated with self-perceived memory impairment. The impact of CC tissue loss was independent of the presence of MTA, a hallmark pathological finding in dementia, and of ARWMC and incident lacunes.

In the only other longitudinal study known to us, Teipel et al. [7] investigated callosal tissue loss rates in a small group of AD patients and found greater rates of anterior and posterior callosal tissue loss, as compared with healthy subjects. In our cohort, both anterior and posterior CC areas exhibited an increased rate of tissue loss in subjects who developed dementia, although only the posterior area reached significance. The authors also reported very high rates of tissue loss in relatively advanced AD (–7.3%), as compared to our findings in patients with incident dementia (–1.5%). This further supports that CC tissue loss may develop early and accelerate with progression of disease during the course of neurodegenerative dementia disease.

Although anterior and posterior callosal atrophy has been the most consistent finding in cross-sectional studies examining CC in patients with dementia [4, 24–26], divergent results have been reported. Specifically, in mild

AD and mild cognitive impairment, several studies have been unable to find atrophy in CC subregions [27, 28]. Our results are in contrast to this and indicate that degenerative processes in the CC are ongoing in very early stages of dementia processes. This is supported by previous findings that cross-sectional measures of CC atrophy may predict conversion to dementia [6]. It is also of note that in our study the group which developed dementia consisted of both AD patients and patients with VaD. Although similar patterns of anterior and posterior CC atrophy have been reported in AD and VaD [25, 27], it may be speculated that different patterns of CC atrophy may exist, possibly due to different underlying mechanisms of CC tissue loss. One model of callosal atrophy hypothesizes that cortical degeneration (i.e. neurofibrillary tangles and plaques) cause wallerian degeneration of interhemispheric neurons passing through the CC. In contrast to this, in VaD subcortical ischemic pathology, such as lacunar infarcts and leukoaraiosis, is a predominant pathological feature [29]. In a previous study it was shown that ARWMC is another possible mechanism involved in CC atrophy [30]. Therefore, in contrast to AD, these subcortical changes may be the primary mechanism of CC tissue loss in VaD.

We examined structure-function relationships and found that the MMSE score at the 3-year follow-up was associated with tissue loss in CC5 in the entire cohort, but not when the analysis was carried out in converters to dementia or in nonconverters, separately.

In previous cross-sectional studies subregions in the middle and posterior areas of the CC have been reported to be correlated with the MMSE score in mild AD [7, 25–27]. Our findings indicate a similar relationship, but only when examining the entire cohort, as no association was found in converters and nonconverters when analyzed separately. This may reflect that the patients in the present study were in earlier disease stages than patients in previous studies, and furthermore that callosal tissue loss most likely contributes to cognitive decline to a far lesser degree than for example MTA. Moreover, the MMSE score may not be a suitable cognitive test for assessing the relationship between callosal tissue loss and cognition in very early stages of dementia.

The presence of self-perceived memory impairment at the 3-year follow-up was significantly associated with an increased rate of tissue loss in the total CC, genu and splenium in nonconverters. Self-perceived memory impairment may represent a preclinical phase in the AD spectrum [31] and may predict development of AD [32], but it has also been associated with depressive symptoms [22,

33] and cognitive decline [34], which we controlled for in the analysis. The present findings indicate that callosal tissue loss may be present in a preclinical phase of dementia. In addition, corresponding CC areas with increased tissue loss rates in both nonconverters with self-perceived memory impairment and converters to dementia may indicate that occipital white matter circuitry is involved in both conditions.

We found that increased callosal tissue loss in the entire CC and anterior, middle and posterior subregions was associated with a pathological score on a single motor test. The SLS is a measure of postural control and balance, and may be indirectly related to the risk of falling [35]. Based on studies in callosotomized patients and patients with extensive callosal lesions, the CC has been linked to bimanual coordination and motor skill learning [36]. Our findings of a global effect of the CC may reflect that balance and postural control require integrating sensorimotor information including visual and proprioceptive input and may also involve a considerable cognitive component involving frontal circuits [37]. This may apply especially in elderly subjects in whom central control mechanisms play an important role in maintaining postural control [38].

This study has some limitations. The LADIS study was not designed specifically to examine the effects of CC tissue loss in relation to dementia and cognition. One of the possible effects of this may be an exacerbation of variability in longitudinal measures of callosal tissue loss possibly obscuring significant associations. This could also explain the small positive change in CC3 and CC4 in nonconverters without self-perceived memory impairment. Likewise, the multicenter design resulting in the use of different MRI scanners may also contribute to this. However, phantoms were used, and previous investigations have found that it is possible to combine morphometric data of the CC across different field strengths and scanner sequences [39]. Moreover, a flexible CC segmentation method was developed specifically for a multicenter setting, which has been applied several times in the LADIS study cohort [1, 2, 6]. We used a modification of the Witelson partitioning scheme for the subdivision of the CC, which is the most widely used in the CC literature. Although diffusion tensor imaging-based tractography studies indicate that the fiber organization of the CC may merit a different subdivision, these results show discrepancies as to the specific boundaries of the projections from the CC to cortical areas across studies and need further evaluation in larger cohorts [40, 41]. We were not able to control for whole-brain atrophy rates, which would

have improved the specificity of our findings. Moreover, a relatively small number converted to dementia. Therefore, analysis of the effects of callosal tissue loss in relation to subtypes was not carried out. Finally, most subjects were recruited from hospitals and all had ARWMC, which limits extrapolation of the findings to the general population.

The strengths of the present study were that we were able to include a very large number of dementia-free subjects who had MRI twice, and in that sense it represents a unique data set, also in regard to the ability to detect conversion to dementia. In addition, subjects were well characterized and examined at both baseline and 3-year follow-up, and possible confounders such as MTA and progression of ARWMC could be controlled for.

In conclusion, the present findings have important implications. Firstly, they indicate that in preclinical/early stages of dementia, degenerative processes in the CC are ongoing, independent of the presence of MTA. Secondly, disruption in frontal and occipital white matter circuitry, in which the anterior and posterior CC is a part, may play a role in self-perceived memory impairment. Thirdly, callosal tissue loss may be involved in age-related motor deficits, particularly balance and postural control. The findings in this study warrant further study of callosal tissue loss in dementia and its role as a possible biomarker. Further longitudinal studies of callosal changes are needed in both patients with dementia and healthy elderly populations.

Appendix: Participating Centers and Personnel in the LADIS Study

Helsinki, Finland (Memory Research Unit, Department of Clinical Neurosciences, Helsinki University): Timo Erkinjuntti, MD, PhD; Tarja Pohjasvaara, MD, PhD; Pia Pihanen, MD; Raija Ylikoski, PhD; Hanna Jokinen, PhD; Meija-Marjut Somerkoski, MPsych; Riitta Mäntylä, MD, PhD; Oili Salonen, MD, PhD.

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The Coordinating Center is in Florence, Italy (Department of Neurological and Psychiatric Sciences, University of Florence): Domenico Inzitari, MD (study coordinator); Luciano Bartolini, PhD; Anna Maria Basile, MD, PhD; Eliana Magnani, MD; Monica Martini, MD; Mario Mascalchi, MD, PhD; Marco Moretti, MD; Leonardo Pantoni, MD, PhD; Anna Poggesi, MD; Giovanni Pracucci, MD; Emilia Salvadori, PhD; Michela Simoni, MD. The LADIS Steering Committee is formed by Domenico Inzitari, MD (study coordinator); Timo Erkinjuntti, MD, PhD; Philip Scheltens, MD, PhD; Marieke Visser, MD, PhD, and Peter Langhorne, MD, BSC, PhD, FRCP, who replaced in this role Kjell Asplund, MD, PhD, beginning in 2005.

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Disclosure Statements

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Dr. Philip Scheltens receives no personal compensation. He serves on advisory boards of Genentech, GE Healthcare, Pfizer,

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Dr. Franz Fazekas serves on scientific advisory boards for Bayer Schering, Biogen Idec, Merck Serono, Novartis and Teva Pharmaceutical Industries Ltd./Sanofi-Aventis; he serves on the editorial boards of *Cerebrovascular Diseases*, *Multiple Sclerosis*, the *Polish Journal of Neurology and Neurosurgery*, *Stroke*, and the *Swiss Archives of Neurology and Psychiatry*, and has received speaker honoraria from Biogen Idec, Bayer Schering, Merck Serono and Sanofi-Aventis.

Dr. Timo Erkinjuntti serves on scientific advisory boards for Johnson & Johnson and Servier; he has also served on speakers' bureaus for and has received speaker honoraria from Janssen Spain during the past 2 years.

Dr. Hanna Jokinen has received research funding from the Clinical Research Institute and the Medical Research Fund of the Helsinki University Central Hospital, and the Ella and Georg Ehrnrooth Foundation.

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Leonardo Pantoni is editor of the section Vascular Cognitive Impairment of *Stroke* and member of the Editorial Board of *Acta Neurologica Scandinavica*, *Cerebrovascular Diseases*, and *International Journal of Alzheimer Disease*.

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Gunhild Waldemar serves on the editorial board of *Alzheimer's Disease and Associated Disorders*, *Dementia and Geriatric Cognitive Disorders*, *Journal of Alzheimer's Disease*, *European Journal of Neurology*, and *Practical Neurology*; he receives royalties from the publication of *Alzheimer's Disease* (Oxford University Press, 2009), serves on a scientific advisory board for Lundbeck Inc., has received speaker honoraria from Novartis and Pfizer Inc., and receives research support from the Danish Ministry of Health, the Danish Health Foundation, the Danish Strategic Research Council, the Lundbeck Foundation and the Spies Foundation.

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