Bacterial Contamination and the Transport Vial Material Affect Cerebrospinal Fluid Concentrations of β-Amyloid and Tau Protein as Determined by Enzyme Immunoassay

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Key Words
β-Amyloid 1–42 · Tau protein · Pseudomonas aeruginosa · Stenotrophomonas maltophilia · Polyethylene · Polypropylene

Abstract
Background/Aims: Determination of marker proteins of neuronal degeneration in cerebrospinal fluid (CSF) is of increasing importance. However, preanalytical problems may compromise the results. Methods: We studied the influence of the transport tube material and shaking at room temperature on the CSF concentrations of β-amyloid and tau protein determined by enzyme immunoassays. Results: The materials of the transport tube moderately influenced the CSF concentrations of β-amyloid and tau protein. Polyethylene and polypropylene tubes were well suited, but glass, polycarbonate and polystyrene tubes caused a decrease in the CSF β-amyloid and tau protein concentrations. The strongest impact, however, was caused by bacterial contamination of samples. Contamination with high concentrations of Pseudomonas aeruginosa and related species rendered β-amyloid undetectable and strongly diminished tau protein concentrations. The effects of several Gram-positive bacteria were less pronounced. Addition of 0.1% sodium azide prior to bacterial contamination increased the interval at which CSF could be kept at room temperature without a substantial reduction of the β-amyloid or tau protein concentration. Conclusion: Polyethylene or polypropylene tubes are suitable transport vessels for CSF samples. Bacterial contamination during sampling and portioning must be avoided. Addition of sodium azide may be an option when transport of the sample is delayed.

Introduction
Cerebrospinal fluid (CSF) analysis has become increasingly important in the differential diagnosis of dementia. Most clinical data on CSF in dementia are based on measurements of β-amyloid 1–42, total tau protein and phosphorylated tau protein concentrations using various commercially available enzyme immunoassays (EIAs).

Large clinical studies have documented the high sensitivity and specificity of a combined measurement of β-amyloid 1–42 and tau protein for the differentiation between patients suffering from Alzheimer dementia (AD) and cognitively normal persons [1]. Comparison of CSF analysis with brain autopsy findings revealed a high con-
gruence between the combined β-amyloid1–42 and tau protein measurements and the histological findings when differentiating AD from aged healthy brains [2]. In patients with mild cognitive impairment, measurements of β-amyloid and tau protein were highly predictive of the development of AD [3].

In several studies, CSF was frozen immediately after lumbar puncture and then thawed out for assaying [e.g. 4–8]. Since this is impractical in the clinical routine, present guidelines recommend that CSF samples should rapidly be sent to the laboratory without freezing, preferably in polypropylene tubes (see for example www.uke.de/extern/dgln/demenz.htm; www.dgn.org/images/stories/dgn/leitlinien/ll_demenz/ll-demenz-lang-170210.pdf).

In the Laboratory for Clinical Neurochemistry of the University of Göttingen, a nationwide reference laboratory of the Deutsche Gesellschaft für Liquordiagnostik and Klinische Neurochemie, which analyzes CSF samples from many clinical departments and physicians in private practice, we observed that 0.35% of the samples sent to us for the determination of β-amyloid1–42, total tau protein and phosphorylated tau protein concentrations within 2 years contained implausibly low CSF concentrations of these proteins. Since such low concentrations were most frequently observed in samples sent by outside hospitals, we studied preanalytical problems which might be responsible for these low levels. Since CSF is a body fluid with a low protein content, thus increasing the risk of the binding of β-amyloid1–42 and tau protein to the transport vessel walls, we investigated a possible influence of the material of the transport tube on the sample. We discovered that bacteria, mostly Stenotrophomonas and Sphingomonas spp., grew in many of the samples in which degeneration markers were below the quantification limit. Therefore we also studied the effect of bacterial contamination during CSF sampling or portioning for transport.

**Materials and Methods**

This study was part of quality control measures to increase the accuracy of the determination of marker proteins of neuronal degeneration in CSF. The Ethics Committee of the University of Göttingen gave its approval of the study. After completion of the CSF analysis as requested by the treating physicians, remnants of routine CSF samples were collected, particularly from patients who underwent a spinal tap for suspected normal pressure hydrocephalus. At lumbar puncture, the CSF was primarily collected in polypropylene tubes. Remnants were frozen and stored at –20°C. After thawing, they were aliquoted to different test tubes. The levels of CSF β-amyloid1–42 and tau protein were determined using sandwich EIA kits (Innogenetics, Hannover, Germany) in accordance with the manufacturer’s instructions. Briefly, we filled 75 μl of conjugate working solution 1 and 25 μl of undiluted CSF into 96-well plates coated with the antibodies. After incubation for 30 min, the plates were washed. 100 μl of conjugate working solution 2 was then added and incubated for 30 min. After washing the plates again, 100 μl substrate working solution was added and incubated again for 30 min. The extinction at 450 nm was measured by a TECAN Spectra Rainbow EIA reader. The limit of quantification was 125 pg/ml for β-amyloid1–42 and 75 pg/ml for tau protein. All samples from an individual experiment were assayed on the same ELISA plate to avoid inter-assay variation.

In a first series of experiments, either 5 ml or 0.25 ml of CSF (both groups n = 11, 4× pooled CSF, 7× CSF from one individual) was filled into tubes made of polyethylene (order number 55.220), polypropylene (order number 55.518), polystyrene (order number 55.468), polycarbonate (order number 71.9923.610 PC) by Sarstedt, Nümbrecht, Germany, or glass tubes (order number LP 45.1; Carl Roth GmbH & Co KG, Karlsruhe, Germany). Different volumes were chosen to mimic transport conditions with high and low sample volumes. The tubes were then shaken for 12 h and 60 h at room temperature on a shaking water bath (GFL, Burgwedel, Germany) which did not contain water, in order to mimic the conditions of a transport by mail. β-Amyloid1–42 and tau protein concentrations were then immediately determined by EIA. In 4 of the 11 5-ml and 0.25-ml CSF samples, both β-amyloid1–42 and tau protein were below the limit of quantification, and a turbidity of these samples was noted. Bacteriological analysis revealed growth of Pseudomonas aeruginosa in 3 samples. A probable reason for the high rate of contamination with bacteria in this series was the use of pooled CSF. Hence, in the following experiments we used CSF samples from individual patients only.

In the second series of experiments with polypropylene tubes, we studied the effect of the addition of live bacteria previously grown in tryptic soy broth and then harvested with 0.9% NaCl and stored at –20°C until use. The bacteria were thawed and diluted in 0.9% NaCl to obtain final concentrations in CSF of 104 or 106 colony-forming units (CFU)/ml of Escherichia coli ATCC 25922, *P. aeruginosa* ATCC 27853, Streptococcus pneumoniae D39, *Staphylococcus aureus* ATCC 25923, or *Staphylococcus epidermidis* ATCC 12228.

We did not include phospho-tau in our analysis since it is not used in all routine laboratories. Measurement of phospho-tau would have increased the amount of CSF necessary by 50% and entailed the use of pooled CSF for most of the experiments.

Statistical comparisons were carried out using the program GraphPad InStat. When the data were normally distributed, a two-tailed paired t test was used for the comparison of two groups, and for more than two groups, repeated measures ANOVA followed by Dunnett’s or Bonferroni’s correction for repeated testing were used. In the absence of normal distribution (particularly when measurements were below the limit of quantification) for the comparison of two groups, the Mann-Whitney U test, and for more than two groups, non-parametric repeated measures ANOVA (Friedman test) followed by Dunn’s multiple comparisons test to correct for repeated testing were used. If all measurements in one group were below the quantification limit, Fisher’s exact test was used instead of the U test. A p value ≤0.05 was considered statistically significant.
Results

Series 1

The median CSF concentrations of β-amyloid$_{1-42}$ were lower in all CSF samples shaken for 12 h or 60 h than in the sample assayed before shaking (Table 1). At 60 h, the β-amyloid$_{1-42}$ concentrations measured in polystyrene (p < 0.05), polycarbonate (p < 0.01) and glass tubes (p < 0.001) were significantly lower than those measured prior to shaking (Friedman test, correction for repeated testing by Dunn’s multiple comparisons test). After 12 h of shaking, the concentrations measured in polycarbonate (0.25 ml, p < 0.05) and glass tubes (5 ml, p < 0.05 and 0.25 ml, p < 0.01) were significantly lower than those determined prior to shaking (Friedman test, correction for repeated testing by Dunn’s multiple comparisons test).

When the 4 samples below the quantification limit were not included, after 60 h of shaking, only the β-amyloid$_{1-42}$ concentrations measured in glass tubes (5 and 0.25 ml) were significantly lower (p < 0.01) than those measured prior to shaking (medians 91% and 80% of the initial median concentrations, n = 7, repeated measures ANOVA, correction for repeated testing by Dunnett’s multiple comparisons test). At 60 h (5 ml CSF), the median β-amyloid$_{1-42}$ concentrations in polystyrene and polycarbonate tubes were 90 and 91% of the median concentrations measured at the beginning of the experiment (p > 0.05).

The median tau protein concentrations were also lower in all CSF samples shaken for 12 h or 60 h than in the sample assayed prior to shaking (Table 1). At 60 h, the tau protein concentrations measured in polycarbonate (5 ml, p < 0.01; 0.25 ml, p < 0.001) and glass tubes (5 ml, p < 0.01;

### Table 1. β-Amyloid$_{1-42}$ and tau protein CSF concentrations after 12 and 60 h of shaking at room temperature to mimic transport in different tubes

| Group (n = 11) | Volume ml | 12 h median | 12 h minimum | 12 h maximum | 60 h median | 60 h minimum | 60 h maximum |
|----------------|-----------|-------------|--------------|--------------|-------------|--------------|--------------|
| β-Amyloid$_{1-42}$, pg/ml | Start | 633 | 350 | 1,002 | 633 | 350 | 1,002 |
| | Polyethylene 5 | 597 | <125 | 1,016 | 597 | <125 | 1,112 |
| | Polyethylene 0.25 | 621 | <125 | 1,009 | 588 | <125 | 1,079 |
| | Polypropylene 5 | 631 | <125 | 1,019 | 597 | <125 | 978 |
| | Polypropylene 0.25 | 617 | <125 | 1,008 | 603 | <125 | 1,023 |
| | Polystyrene 5 | 579 | <125 | 1,102 | 605 | <125 | 917a |
| | Polystyrene 0.25 | 618 | <125 | 993 | 604 | <125 | 984a |
| | Polycarbonate 5 | 582 | <125 | 946 | 567 | <125 | 937b |
| | Polycarbonate 0.25 | 539 | <125 | 917b | 507 | <125 | 922b |
| | Glass 5 | 508 | <125 | 937b | 497 | <125 | 912c |
| | Glass 0.25 | 478 | <125 | 875b | 499 | <125 | 796c |
| Tau protein, pg/ml | Start | 140 | 106 | 1,035 | 140 | 106 | 1,035 |
| | Polyethylene 5 | 119 | <75 | 1,100 | 119 | <75 | 1,017 |
| | Polyethylene 0.25 | 120 | <75 | 1,051 | 119 | <75 | 1,039 |
| | Polypropylene 5 | 109 | <75 | 1,019 | 119 | <75 | 1,009 |
| | Polypropylene 0.25 | 120 | <75 | 1,079 | 121 | <75 | 1,103 |
| | Polystyrene 5 | 118 | <75 | 1,007 | 127 | <75 | 1,014 |
| | Polystyrene 0.25 | 121 | <75 | 997 | 112 | <75 | 1,100 |
| | Polycarbonate 5 | 117 | <75 | 1,017a | 109 | <75 | 964b |
| | Polycarbonate 0.25 | 102 | <75 | 946b | 106 | <75 | 912c |
| | Glass 5 | 113 | <75 | 903a | 109 | <75 | 809b |
| | Glass 0.25 | 98 | <75 | 800c | 111 | <75 | 762c |

a p ≤ 0.05; b p ≤ 0.01; c p ≤ 0.001.
0.25 ml, \( p < 0.001 \)) were significantly lower than the concentrations measured prior to shaking (Friedman test, correction for repeated testing by Dunn’s multiple comparisons test). After 12 h of shaking, the concentrations measured in polycarbonate (5 ml, \( p < 0.05 \), 0.25 ml, \( p < 0.001 \)) and glass tubes (5 and 0.25 ml, \( p < 0.05 \) and 0.001) were significantly lower than those determined prior to shaking (Friedman test, correction for repeated testing by Dunn’s multiple comparisons test).

When the samples below the quantification limit (\( n = 4 \)) were not included, no significant differences were observed after 60 h of shaking. In the remaining 7 samples, after 12 h of shaking, tau protein concentrations measured in glass tubes (sample volume 0.25 ml) were significantly lower (median 76% of the initial median concentration, \( p < 0.01 \)) than those measured prior to shaking (\( n = 7 \), repeated measures ANOVA, correction for repeated testing by Dunnett’s multiple comparisons test). At 60 h, the median tau concentrations in glass tubes (5 and 0.25 ml CSF) were 91 and 80% of the median concentrations measured at the beginning of the experiment (\( p > 0.05 \)).

In the majority of samples, the concentrations measured in the tubes with sample volumes of 0.25 ml were slightly lower than those measured in the tubes with the high sample volumes of 5 ml. These differences, however, failed to reach statistical and clinical significance (repeated measures ANOVA, correction for repeated testing by Bonferroni’s multiple comparisons test).

**Series 2**

The addition of a low number of bacteria (\( S. pneumoniae, S. aureus, S. epidermidis, E. coli, P. aeruginosa \), final concentration in the CSF sample \( 10^4 \) CFU/ml, 12 h co-incubation with and without shaking) to CSF in polypropylene tubes did not substantially affect the CSF \( \beta \)-amyloid and tau protein concentrations.

Conversely, the addition of a higher number of \( P. aeruginosa \) (final concentration in the CSF sample \( 10^6 \) CFU/ml, 16 h of co-incubation with and without shaking) to CSF in polypropylene tubes decreased the \( \beta \)-amyloid and tau protein concentrations below the limit of quantification with and without shaking (fig. 1A, B). The average CSF concentra-
tions of tau protein were decreased by approximately 50% after the addition of 10⁶ CFU/ml *P. aeruginosa* and shaking, but did not fall below the quantification limit in 2 out of 4 samples (fig. 1C). Addition of 10⁶ CFU/ml *P. aeruginosa* in the absence of shaking led to a slight decrease of CSF tau protein content, which failed to reach statistical significance (fig. 1D). Co-incubation of CSF with a high concentration of *P. aeruginosa* (10⁹ CFU/ml) for the short interval of 1 h did not lead to a substantial reduction of *H9252*-amyloid 1–42 and tau CSF concentrations.

The addition of gentamicin or sodium azide to CSF samples did not interfere with the EIA (fig. 2). When CSF was heavily contaminated with 10⁶ CFU/ml *P. aeruginosa*, this procedure was not effective at preventing the disappearance of *H9252*-amyloid 1–42 from CSF over 12 h (fig. 3A, B). Median concentrations fell by ≥80%. After addition of gentamicin or sodium azide, CSF tau protein concentrations were still measurable in CSF, but median concentrations were 33% (gentamicin, both with and without shaking), 31% (sodium azide, without shaking) and 33% (sodium azide, with shaking) lower than those measured in the absence of bacterial contamination (fig. 3C, D).

Shaking CSF samples for 48 h at room temperature without addition of bacteria led to a 7% decrease in the median *H9252*-amyloid 1–42 concentration (n = 20, p < 0.05, repeated measures ANOVA followed by Dunn’s multiple comparisons test). This was prevented by the addition of 0.1% sodium azide. In the absence of sodium azide, the median CSF tau concentration decreased by 30% (n = 20, p < 0.001). In the presence of sodium azide, the median CSF tau concentration was still 9% below the respective value measured prior to shaking for 48 h at room temperature (n = 20, p < 0.001).

Shaking CSF samples for 72 h at room temperature caused a reduction in the median tau protein concentrations by 24% (n = 22, p < 0.001, repeated measures ANOVA followed by Dunn’s multiple comparisons test), which could be prevented by the addition of 0.1% sodium azide. Under these conditions, the reduction of the median *H9252*-amyloid 1–42 concentration was 9% (n = 16, p > 0.05), which was also prevented by the addition of sodium azide.

Shaking CSF samples for 7 and 14 days at room temperature caused a reduction in *H9252*-amyloid 1–42 and tau concentrations, which were only partially prevented by 0.1% sodium azide (fig. 4A–D) (median reductions: *H9252*-amyloid 1–42 7 days 18 vs. 2%, 14 days >80 vs. 33%; tau protein 7 days 44 vs. 7%, 14 days >50 vs. 44%).

**Discussion**

In clinical practice, the value of *H9252*-amyloid 1–42 and tau protein measurements in CSF strongly depends on the preanalytical processing of the material. *H9252*-amyloid 1–42 and tau protein are very stable when frozen at −80°C. At room temperature in polypropylene tubes, *H9252*-amyloid 1–42 CSF concentrations decreased by approximately 20%, whereas tau protein was stable at 4 and 18°C for up to 12 days [9].

In the present study, mimicking transport conditions by shaking the samples at room temperature revealed that tubes made from polyethylene and polycarbonate are the most suitable transport vessels for unfrozen CSF samples. According to our results, polystyrene and polycarbonate should be avoided, and glass tubes are not feasible. Similar to our findings, Lewczuk and co-workers [4] reported a reduction of approximately 30% of the *H9252*-amyloid 1–42 and *H9252*-amyloid 1–40 CSF concentrations when CSF was stored in polystyrene compared to polypropyl-
Proteins are known to bind to glass and polystyrene surfaces. On glass, the rate of adhesion depended strongly on protein charge [10].

Because of the low overall CSF protein content, we hypothesized that the decrease in β-amyloid_{1–42} and tau protein concentrations after shaking should be stronger with a small than with a large sample volume. Contrary to our expectations, the sample volume (0.25 vs. 5 ml) only had a small effect on the CSF concentrations of markers of neurodegeneration.

Fig. 3. β-Amyloid_{1–42} and tau protein concentrations in CSF after addition of 10^6 CFU/ml *P. aeruginosa* plus 0.1% sodium azide or 100 μg/ml gentamicin and 12 h of co-incubation with and without shaking (each group n = 9, median, minimal and maximal values, statistical comparisons by nonparametric repeated measures ANOVA followed by Dunn’s multiple comparisons test). Neither sodium azide nor gentamicin was able to prevent a strong reduction of β-amyloid_{1–42} as measured by EIA. Under these conditions, sodium azide or gentamicin were partially effective in protecting tau protein. A β-Amyloid_{1–42} concentrations without shaking: most values measured in samples contaminated by bacteria were below the level of quantification (uncontaminated CSF vs. bacteria only, p < 0.001; uncontaminated CSF vs. bacteria plus 0.1% sodium azide, p < 0.01; uncontaminated CSF vs. bacteria plus 100 μg/ml gentamicin, p < 0.05). B β-Amyloid_{1–42} concentrations with shaking: all except one value in the sodium azide and gentamicin group were below the quantification limit (all groups contaminated with bacteria vs. the uncontaminated group: p < 0.01, nonparametric repeated measures ANOVA followed by Dunn’s multiple comparisons test). C Tau protein concentrations without shaking: the presence of *P. aeruginosa* led to a strong reduction of the tau concentrations measured (p < 0.001). Co-incubation of bacteria with 0.1% sodium azide (p < 0.05) or 100 μg/ml gentamicin (p < 0.05) reduced the CSF tau concentrations by approximately 30% compared to the sterile controls. D Tau protein concentrations with shaking: the presence of *P. aeruginosa* caused a strong reduction of the concentrations measured (all measurements below the quantification limit, p < 0.001). Co-incubation of bacteria with 0.1% sodium azide (p > 0.05) or 100 μg/ml gentamicin (p < 0.05) reduced the CSF tau concentrations by approximately 33%. 
The reason for most of the implausible measurements turned out to be bacterial contamination, particularly by P. aeruginosa and related species (Stenotrophomonas maltophilia, Sphingomonas paucimobilis), Staphylococcus epidermidis and Micrococcus luteus. CSF is not the ideal substrate for bacteria, but it contains glucose, lactate, pyruvate, amino acids, lipids and proteins [for details see 11]. Frequency and causes of the contamination of blood cultures have been studied [e.g. 12–14]. However, systematic studies on the frequency and causes of bacterial contamination of CSF samples are scarce. One report on false-positive detection of bacteria by Gram staining identified funnels of the cytocentrifuge contaminated by Bacillus spp. and crystal violet staining solution containing Flavimonas oryzae as the sources [15]. In a study on 2,091 CSF specimens, 182 bacterial strains from 129 patients were isolated. 100 isolates from 97 patients, i.e. a rate of 5%, were classified as contaminated [16]. The main reason for bacterial contamination of CSF in this study was the lumbar puncture itself. Other reasons for bacterial contamination include the use of unsterile transport tubes and, in laboratories specialized in

![Graphs](image)

**Fig. 4.** β-Amyloid$_{1–42}$ and tau protein concentrations in CSF after 7 and 14 days of shaking at room temperature to mimic long transports in the absence and presence of 0.1% sodium azide [each group n = 20 (A, B), n = 19 (C) or n = 18 (D), median, minimal and maximal values, statistical comparisons by nonparametric repeated measures ANOVA followed by Dunn’s multiple comparisons test]. A After 7 days of shaking, the median β-amyloid$_{1–42}$ was reduced by approx. 20% (p < 0.01). Sodium azide prevented this reduction (p > 0.05). B 7 days of shaking strongly reduced the CSF tau protein concentrations. This reduction was partially prevented by 0.1% sodium azide (both groups: p < 0.001 vs. the values measured prior to shaking at room temperature). C 14 days of shaking strongly reduced the β-amyloid$_{1–42}$ CSF concentrations. 15 of 19 measurements were below the quantification limit (p < 0.001). 0.1% sodium azide was only partially able to prevent this effect, the median β-amyloid$_{1–42}$ CSF concentration still was 36% lower than that of the concentrations measured before shaking (p < 0.001). D 14 days of shaking strongly reduced the tau protein CSF concentrations. 13 of 18 measurements were below the quantification limit (p < 0.001). Despite the addition of 0.1% sodium azide, the median tau CSF concentration dropped to 56% of the median of the respective concentrations measured before shaking (p < 0.001).
the analysis of the chemical composition and not in the microbiology of CSF samples, unsterile tips and tubes used when the CSF is portioned for further analyses. Shaking of samples as well as the use of pooled samples in the present study probably contributed to the relatively high rate of contaminated CSF specimens. Frequently, pipetting results in unstability of the rim of the tube or the sealing plug, and by subsequent shaking bacteria reach the CSF. In our study, the most frequent problem leading to implausible results of β-amyloid1–42 and tau protein measurements was bacterial contamination by P. aeruginosa and related species. Contamination by other bacterial strains investigated including S. epidermidis, the most frequent contaminant from the skin [16], appeared not to disturb the analysis by EIA at bacterial densities of up to 10^6 CFU/ml and co-incubation times of up to 16 h. The presence of bacteria in CSF may explain why in acute purulent bacterial meningitis, CSF β-amyloid1–42 levels were reduced by 28% of that in controls, whereas no change was found in viral meningitis, and why after successful treatment the CSF β-amyloid1–42 increased [17]. Conversely, in the presence of brain parenchymal damage elevated CSF tau protein levels were observed in patients with meningocencephalitis, suggesting that neuronal destruction outweighed the presence of bacteria [18].

In conclusion, for the transport of CSF samples, polyethylene and polypropylene are ideal transport vessel materials, polystyrene and polycarbonate should be avoided, and glass is most inappropriate. Measures must be taken to avoid bacterial contamination of the CSF specimen during lumbar puncture and during portioning of the CSF for the various analytical procedures, and CSF should be sent unfrozen as rapidly as possible to the analyzing laboratory (www.uke.de/extern/dgln/demenz.htm; www.dgn.org/images/stories/dgn/leitlinien/ll_demenz/ll-demenz-lang-170210.pdf). In the present study, for transports up to 72 h at room temperature, sodium azide proved to be effective for preventing bacterial overgrowth leading to a reduction of β-amyloid1–42 and tau protein concentrations in CSF. Since 0.1% of sodium azide does not interfere with the routine CSF analysis, this procedure may serve as an alternative to freezing the samples when transport is delayed.

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Disclosure Statement

The authors declare that they have no commercial interests in this study and no conflicts of interests. They have no commercial relations in connection with Innogenetics, Hannover.

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Citations

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Erratum

The name of one of the authors was misspelled in the article ‘Dementia Risk Score Predicts Cognitive Impairment after a Period of 15 Years in a Nondemented Population’ by Reijmer et al. [Dement Geriatr Cogn Disord 2011;31:152–157]. The correct name is ‘L. Jaap Kappelle’, instead of ‘Jaap L. Kappelle’.