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RELATIONSHIPS BETWEEN COGNITION AND ACTIVITIES OF DAILY LIVING IN ALZHEIMER'S DISEASE DURING A 5-YEAR FOLLOW-UP: ALSOVA STUDY

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Abstract

Background: Impaired cognition and activities of daily living (ADL) are core symptoms of Alzheimer's disease (AD), but their relationship is unclear.

Objectives: To explore relationships between cognitive domains and functional ability during 5-year follow-up in persons with AD.

Methods: We analysed ALSOVA study data from 236 individuals with very mild or mild AD at baseline. The CERAD Neuropsychological Battery (CERAD-NB) was used as a cognitive measure and Alzheimer's Disease Cooperative Study ADL (ADCS-ADL) as a functional measure, analysing the IADL and BADL sub-scores separately. Annual regression models and linear mixed-effect models (LMMs) covering a 5-year follow-up period were used.

Results: Annually, The CERAD-NB total and especially Verbal Fluency, Clock Drawing, and Constructional Praxis were associated with the total ADCS-ADL and IADL scores increasingly yet modestly, and to a lesser extent the BADL score. In the LMMs, the same measures and MMSE were associated with ADL.

Conclusion: Measures of executive function and visuoconstructive skills appear to be associated with caregiver-interview based ADL measure during the progression of AD.

Keywords: Alzheimer's disease; dementia; follow-up study; activities of daily living; cognition; functional ability

1 INTRODUCTION

Episodic memory deficit is the initial clinical symptom of typical Alzheimer's disease (AD). In addition to cognitive problems, AD is associated with functional impairment, and both are required for a diagnosis of dementia due to AD [1, 2]. Early symptoms may also include deficits in visual skills, language, or executive function [1, 3].

In mild cognitive impairment (MCI), a person has cognitive impairment but only minimal or no impairment in instrumental activities of daily living (IADL) [4, 5]. IADL are considered to require a variety of cognitive domains, such as managing finances or preparing a meal, which explains their vulnerability to even minor changes in cognition. Basic activities of daily living (BADL) are functions associated with self-care, such as bathing or eating. BADL are more modestly associated with memory and executive function [6], possibly due to their smaller cognitive strain.

Longitudinal relationships between cognition and functional ability have not been studied extensively, despite their clinical importance. Comparisons of the results from studies on relationships between cognition and functional ability in AD are challenging due to differences in measures and study designs [6, 7]. Regarding assessment of functional ability, caregivers have been found to rate IADL and BADL decline as more severe than the persons with AD [8], which may reflect caregiver burden [9, 10] or stress [11]. Further, caregivers may base their functional evaluations on cognitive rather than functional status [12].

A review concluded that cognition accounts for a surprisingly modest amount of variance in activities of daily living (ADL), but the contributions of different cognitive domains to functional ability are not equivalent [6]. Executive function has been shown to correlate moderately with complex IADL functions, although the association between IADL and global cognition screening methods, such as MMSE, is stronger [6, 13]. In mild to moderate AD, executive function has been proposed to account for 17% of the variance in IADL, 9% in BADL [14]. Furthermore, memory, visual, and motor skills are associated with ADL, in addition to executive function [7].

Farias et al. demonstrated that memory has a similar and independent effect as executive function on IADL [15]. In a study with a 6-year follow-up, functional ability was related to memory and language skills in AD [16], which suggests that a decline in cognition precedes and leads to a decline in ADL. However, in that study, the measures used to assess cognition (modified MMSE, memory and language composites) were not psychometrically ideal for differentiating specific cognitive domains. In another longitudinal study with a 20-month follow-up, caregivers reported ADL decline while simultaneously reporting stability in memory in persons with early-stage dementia [17].

Liu-Seifert et al. reported that cognitive decline predicts subsequent functional decline in mild AD, suggesting that the effect of disease-modifying treatments can be driven primarily by the effects in cognition [18, 19]. Longitudinal studies on the relationship between cognition and ADL seem to favour MCI and mild AD samples [20]. During moderate and severe stages of AD, the relationship between cognition and functional ability becomes stronger and impairments in BADL emerge. The moderate stage shows almost a comparable decline in both IADL and BADL, differing from the mild stage when deficits in only IADL are prevalent [21]. A study using the total scores from a neuropsychological battery and performance-based measure of ADL found a significant relationship between the two scores in a sample of persons with moderate or severe AD [22]; however, the specifics of cognitive and functional impairment in the later stages are yet to be elucidated.

The aim of the present study was to investigate which cognitive domains assessed with the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB) are associated with BADL, IADL, and total ADL in a 5-year follow-up study of persons with mild or very mild AD.

2 METHODS

2.1 Participants and study design

This study utilized data from the ALSOVA follow-up study of persons diagnosed with very mild or mild AD. The participants and their caregivers were recruited in 2002–2006, and followed for five years up to 2011. Diagnosis was made in accordance with the DSM-IV [23] and NINCDS-ADRDA [24] criteria, including neuroimaging (CT or MRI), laboratory assessment, and clinical and neuropsychological evaluation. At baseline, the participants had very mild or mild AD; no co-morbid conditions influencing cognition; and were capable of completing the CERAD-NB. Voluntary participants were recruited from three memory clinics in Central and Eastern Finland. The final study population consisted of 236 participants. The end-points for follow-up were institutionalization or death. Of the 236 participants, 72 remained in the fifth and final annual follow-up. At the end of follow-up, most participants had mild or moderate AD, and some had proceeded to the severe stage of the disease [25]. The detailed study protocol was published previously [26, 27].

2.2 Measures

2.2.1 CERAD-NB. The CERAD-NB [28] is a widely used neuropsychological measure for AD-related cognitive deficits, especially screening for mild AD and MCI [29, 30]. In addition to assessing domain-specific cognitive performance, the total CERAD-NB score can be used to assess global cognition [26, 31].

The Finnish CERAD-NB [32] consists of nine previously published subtests. Two subtests have been added to the Finnish version: the Clock Drawing Test and the Constructional Praxis Recall. Each CERAD subtest is described in detail in Table 1. The total CERAD-NB score, a measure of global cognition, was calculated in accordance with Chandler et al. [31].

2.2.2 ADCS-ADL. A commonly used measure of ADL, the Alzheimer's Disease Cooperative Study Activities of Daily Living inventory (ADCS-ADL), is an informant-based method of measuring the patient's ability to perform BADL and IADL [41]. The ADCS-ADL consists of 23 questions regarding the patient's performance on ADL in the past 4 weeks, and the majority of the questions specify whether the patient performed the activity independently, with supervision, or with physical help [41]. Though the original ADCS-ADL does not explicitly differentiate between IADL and BADL items, a two-factor structure was proposed by Kahle-Wrobleski et al. [42] and utilized in the present study. BADL comprise the first seven items: eating, walking, toileting, bathing, grooming, and dressing. IADL comprise the remaining 17 items (using the telephone, watching television, conversation, clearing dishes, finding personal belongings, obtaining a drink, cooking a snack, disposing of litter, travelling outside of home, shopping, keeping appointments, being alone, talking about current events, reading, writing, performing hobbies, using appliances). The Cronbach's alpha reliability scores from baseline through the fifth annual follow-up visit were: .81, .95, .96, .96, .96, and .96 for IADL and .62, .96, .96, .97, .97, and .97, for BADL, respectively. The total ADCS-ADL score (0–78), measuring overall functional ability, includes the BADL sub-score (0–22) and IADL sub-score (0–56), higher scores indicating better functional ability.

2.3 Statistical analysis

The data were analysed using the SPSS for Windows 21.0 software package. Univariate regression analysis was used separately for each of the annual CERAD-NB subtests and the total CERAD-NB score on the corresponding total ADCS-ADL score and IADL and BADL sub-scores. Backwards regression analysis was applied to discover which CERAD-NB subtests, age, gender, and education are associated with the total ADCS-ADL score and IADL and BADL sub-scores separately at each of the six measurement points. Variables were set to remain in the backwards regression models if $P < .05$. Missing cases were excluded list-wise, i.e., only cases with available data on all variables were included.

A linear-mixed effect model (LMM) for repeated measures was used to analyse the association of CERAD-NB subtests with the total ADCS-ADL score and the IADL and BADL sub-scores during the whole 5-year follow-up period. The association of all CERAD-NB subtests was analysed with separate univariate analyses, followed by multivariate analyses, which were conducted by reducing least significant variables one by one to reveal the best symptom combination. The same analyses were performed separately for all three dependent variables.

The model with correlated residuals within the random effects and unstructured covariance type was selected based on information criteria. The advantage of LMM is the possibility to use all available longitudinal data, including that of dropouts. $P < .05$ was considered significant.

2.4 Ethical considerations

The ethics committee of Kuopio University Hospital (64/00) gave a favourable opinion of the study, and the study was approved by the Finnish Supervisory Authority for Welfare and Health and the Finnish Ministry of Social Affairs and Health. The study was performed in accordance with the Helsinki Declaration. Participants were provided with written and oral information about the study. Participation was voluntary and confidentiality assured. A consent form was signed by both the caregiver and the person with AD. Ethics required that proxy consent was obtained for people with a memory disorder who were not able to provide informed consent themselves. In this study, informed consent was always obtained from the person with AD, but in addition the caregiver also provided proxy consent on behalf of the person with AD.

3 RESULTS

3.1 Clinical and demographic characteristics

At baseline, two participants were unable to complete all CERAD-NB subtests. At the first to fifth follow-up visits 4, 5, 2, 7, and 10 participants were unable to complete all CERAD-NB subtests. These participants were omitted from the regression models as the missing data were not random; higher frequencies of completion were observed in the tasks administered earlier in the procedure. Table 2 represents the demographic characteristics and CERAD-NB and ADCS-ADL scores of the persons with AD in this 5-year follow-up study.

3.2 Total CERAD-NB score and associations with ADL scores

The total CERAD-NB score was associated ($P < .01$) with corresponding total ADCS-ADL score and IADL and BADL sub-scores except for BADL at baseline ($P = .10$; Appendix A). The β-values increased annually in a trend-wise fashion, indicating an increasing global functional change attributed to the global cognitive change peaking at the fifth follow-up visit. However, though the total CERAD-NB score was almost equally associated with the annual total ADCS-ADL score and IADL sub-score, it accounted for less of the variance in BADL.

3.3 CERAD-NB subtests and associations between total ADCS-ADL and IADL and BADL sub-scores

In the univariate regression analyses (data not shown), almost all CERAD-NB subtests were associated ($P < .05$) with the total ADCS-ADL score and IADL sub-score. Only Verbal Fluency, Boston Naming Test (BNT), and Word List Recognition at baseline and Constructional Praxis Recall in the fifth year were not significantly associated with the corresponding total ADCS-ADL scores. BNT and Word List Recognition at baseline and Constructional Praxis Recall in the fifth year were not significantly associated with the IADL sub-score.

The BADL sub-score was not associated with CERAD-NB subtest performance as often as the IADL sub-score or the total ADCS-ADL score in the univariate analysis. Consequently, Verbal Fluency, BNT, Word List Recall, Word List Recognition, and Constructional Praxis Recall were not associated with the corresponding BADL sub-scores ($P > .05$) at baseline; Word List Recall and Word List Recognition in the first year; Word List Recognition in the second year; BNT, Word List Recall, Word List Recognition, and Constructional Praxis Recall in the third year; Word List Recall and Word List Recognition in the fourth year; and Word List Recall and Constructional Praxis Recall in the fifth year.

Appendices B, C, and D present the annual backwards regression models with significant demographic variables and CERAD-NB subtests as explanatory measures. Gender remained in five, Verbal Fluency in four, Constructional Praxis in three, and Clock Drawing Test and Constructional Praxis Recall in two out of six regression models on total ADCS-ADL score.

Word List Learning Sum in the fifth year was associated with the total ADCS-ADL score (R^2 = .64, $P < .001$) and IADL sub-score (R^2 = .66, $P < .001$), more so than the other CERAD subtests, with the most significant association with the above-mentioned ADL scores of all of the analysed variables. Gender remained in the five first models of ADCS-ADL, IADL, and BADL, whereas age did not remain in any model after year 2 and education after year 1.

Collinearity indicators were within commonly acceptable boundaries in all backwards regression models [43].

3.4 Linear mixed-models of CERAD-NB subtests, age, gender, and education on the total ADCS-ADL score and IADL and BADL sub-scores

In the LMM univariate analyses, all CERAD subtests were associated with the total ADCS-ADL, IADL, and BADL scores (*P* < .05). Tables 3, 4, and 5 present the CERAD subtests and adjusted variables included in the LMMs. In the multivariate analyses, all CERAD subtests, except Word List Learning and Recognition, were significantly associated with the total ADCS-ADL score (*P* < .05). If Constructional Praxis Delayed Recall task was removed, the Word List Recognition task was included. All CERAD subtests except Word List Learning, Recognition, or Constructional Praxis Recall were associated with IADL (*P* < .05). MMSE, Constructional Praxis, and Clock Drawing Test were associated with BADL (*P* < .001).

4 DISCUSSION

4.1 Evaluation of the results

In this longitudinal, 5-year study we found that cognition measured by CERAD-NB associates increasingly yet modestly with functional ability (total ADCS-ADL, IADL and BADL sub-scores) in persons with very mild or mild AD at baseline and mild to moderate or severe disease at the end of the study. We were able to evaluate the functional relevance of cognitive domains at each visit and over the 5-year follow-up by utilizing both annual regression models and LMMs.

Our results confirm results from previous studies. The IADL and total ADCS-ADL scores were associated with similar cognitive domains due to IADL items accounting for the majority of the total score. As the disease progressed, IADL, BADL, and ADL total scores were associated with both the total CERAD-NB score and sub-scores in an increasing fashion. Liu-Seifert et al. [19] also reported that cognition and global functional ability relate more strongly as AD progresses. Based on previous research, global cognition and different cognitive domains, particularly executive function [6, 13, 44], are expected to be associated with IADL and global ADL. However, BADL is thought to remain relatively unimpaired before the moderate stage [18] and to be linked more modestly to cognition [6, 14]. In our study, BADL was more modestly linked to global and domain-specific cognitive measures than IADL through the follow-up period, possibly due to the performance of routine self-care functions requiring less cognitive effort [45] and the BADL measures being less sensitive to changes in persons with mild AD than IADL measures [41, 46].

Measures of executive function (Verbal Fluency, Clock Drawing Test) and visuoconstructive skills (Clock Drawing Test, Constructional Praxis) were significantly associated with global, basic, and instrumental functions annually. Furthermore, when analysing the whole follow-up period with LMMs, the same measures were associated with global and instrumental functions, and visuoconstructive skills with basic functions. When examining global function or IADL, a decline in Verbal Fluency or Clock Drawing Test temporally preceded deterioration in Constructional Praxis, whereas BADL was impaired if the participants had poor performance in Constructional Praxis. This finding was already noted at baseline. These findings may be explained by earlier impairment in executive function compared to visuoconstructive skills [47] and the performance of BADL items requiring basic visual perceptive capabilities and unimpaired praxis. Interestingly, Verbal Fluency and Constructional Praxis are regarded as having limited value in screening mild AD but being useful in the later stages [48]; yet, they appeared to be significant predictors of functional status across the follow-up period.

Visuospatial deficits in AD have received less attention in research than those of memory and executive function. However, visuoconstructive skills [7, 49] and more fundamental visual functions [50; 51] have been associated with global functional or IADL decline. As Glosser et al. [51] pointed out, many common ADL items can be considered to include a component of visual perception (e.g., grooming, reading, writing). Executive function and memory may be subordinate to more fundamental visual abilities in performing a variety of ADLs and be associated with functional decline only if the decline is not already accounted for by visual performance. In our study, a combination of visuoconstructive skills and executive function measures were associated with ADL in several models, leading to the suggestion that the integrity of these lower- and higher-order cognitive domains is a prerequisite for unassisted living.

Our results also revealed that difficulties in verbal and visual delayed recall are associated with a decline in global functional ability and impairments in verbal delayed recall with deteriorated IADL skills when analysing the whole 5-year study period in LMMs. Furthermore, while naming ability was not a significant predictor of function in annual analyses, it was included in LMMs, affecting functional ability during the disease process. The results are in line with a 6-year follow-up study by Zahodne et al. [16], who found that memory composites, including a delayed recall task, and language composites, including BNT, predicted functional decline in AD. In addition, the brief measure of global cognition, MMSE, was significantly associated with the total ADCS-ADL score and IADL and BADL sub-scores in LMMs.

Interestingly, Word List Learning was the only significant non-visual measure associated with the total ADCS-ADL score and IADL sub-score during the final follow-up year. Word List Learning or other measures of non-visual learning and memory, such as Word List Recall and Recognition, were not significantly associated with ADL in the annual follow-ups, perhaps due to the floor-effect on memory scores caused by characteristic early memory decline in typical AD. Additionally, caregiver-rated ADL performance may decline even in the presence of memory stability [17]. Recall task was also included in LMMs, which may reflect the importance of the retrieval of information pertinent to ADL performance. In previous studies, contradictory results regarding the role of memory deficits have been shown, and they may independently contribute to functional decline [15] or memory decline may be associated with functional status only with subsequent executive function deficits [52].

Males had lower ADL scores over the follow-up period. The applicability of ADCS-ADL items to different cultures and cohorts must be evaluated with some reservations, particularly regarding items possibly considered gender-related in the population (e.g., preparation of meals, using home appliances). Thus, lower IADL scores for males may be explained, in part, by the content of ADL items themselves instead of functional decline [53, 54] because gender-relatedness was not as evident in BADL.

4.2 Strengths and limitations

The merits of this study include the longitudinal design, broad neuropsychological assessment with validated measurements, such as CERAD-NB, and the differentiation between IADL, BADL, and total ADL performance. These factors facilitated the observation of relationships between different cognitive domains and function in a well-defined sample of persons with AD. Moreover, the longitudinal design may detect clinically important information about progression of relationships compared to cross-sectional studies as well as allowed the observation of changes in cognition-ADL relationships as AD progressed.

The study also revealed that the Clock Drawing Test can be considered a welcome addition to the Finnish CERAD-NB [32] based on it being a significant predictor of functional ability in several models.

We used LMMs accounting for the whole 5-year follow-up period, as well as the data from drop-outs, to explore associations between cognitive domains and daily functions. Furthermore, using regression analyses we were able to investigate how the associations change as the disease progresses.

This study contained some methodological limitations. First, the CERAD-NB is primarily used as a screening test to detect mild AD and MCI [29, 30, 48] and some of the CERAD-NB measures may 'bottom-out' quickly as the disease progresses [55]. However, the total CERAD-NB score has been shown to correlate with AD progression as measured by the clinical dementia rating (CDR) [56]. Second, as discussed above, some IADL items may be less applicable for males [53, 54] and longitudinal inconsistencies may be present for the applicability of certain IADL items [46].

Additionally, as caregivers may underestimate patients' functional ability [12] and as patients are perhaps capable of assessing their functional ability in mild to moderate AD [8, 12], it must be considered that caregiver ratings may be inconsistent with self-rated or objective ADL performance. These inconsistencies may be due to caregivers interpreting the cognitive decline as functional or reflecting caregiver stress [11] and burden [9, 10], among other reasons. However, the ADCS-ADL is validated and widely used to describe functional ability in AD.

Third, the ability of Verbal Fluency and Clock Drawing tasks to measure executive function is limited. Moreover, it has been suggested that the associations between executive functions and IADL may be better explained by what executive functions and other cognitive domains have in common, i.e. general intelligence (Spearman's g) [57]. It is possible that if cognitive measures were adjusted for g, their individual contributions to different ADL measures would have been more modest.

Fourth, backwards regression models from follow-up years 4 and 5 must be interpreted carefully, as statistical regression is thought to be prone to overfitting data in model construction [43]. However, the use of LMMs reduces the relevance of this issue because they use all available data. Fifth, underlying factors, such as AD severity and rate of decline, may affect both neuropsychological and functional performance [45]. Non-cognitive changes during the follow-up period may have also affected ADL performance.

Finally, remarkable drop-out rates were observed due to institutionalization and death. This is expected in longitudinal studies of community-dwelling persons with AD (see [45]). Some participants were unable to complete some CERAD-NB subtests and were omitted from the regression models because higher frequencies of completion were observed in the tasks administered earlier in the procedure, indicating possible terminations of assessment due to patient fatigue or irritability.

4.3 Implications

As resources are often limited, it is not always feasible to perform a comprehensive functional and neuropsychological assessment. Royall et al. [6] suggested that future assessments should avoid redundancy by using cognitive measures associated with functional ability. Using the CERAD-NB measures of executive function and visuoconstructive skills may allow some insight to be gained into functional ability with only cognitive measures. The CERAD-NB measures implicated in this study are also easy and quick to administer, and they can be used in addition to common screening measures, such as MMSE, to enhance the assessment of both cognition and functional ability.

4.4 Conclusion

In conclusion, the total CERAD-NB score was modestly yet increasingly associated with functional ability in persons with AD as measured by the total ADCS-ADL score and its sub-scores over a 5-year follow-up. Measures of executive function and visuoconstructive skills (Verbal Fluency, Clock Drawing Test, and Constructional Praxis) were most significantly associated with the IADL sub-score and ADCS-ADL global score. The same subtests were significant, to a lesser extent, for BADL. The results suggest that measures of executive function and visuoconstructive skills are associated with caregiver-interview based ADL measure, and give information about functional capability during the progression of AD.

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Contributions

All authors participated in the design of this study.

Toni Saari conducted the analyses, interpreted the results, and drafted the manuscript.

Ilona Hallikainen collected the data, interpreted the results, and drafted the manuscript.

Tuomo Hänninen interpreted the results and revised the manuscript.

Hannu Räty interpreted the results and revised the manuscript.

Anne M. Koivisto monitored data collection, interpreted the results, and drafted and revised the manuscript. She is the primary investigator of the study.

All of the authors have reviewed and approved the manuscript.

References

[1] American Psychiatric Association. 2013. Diagnostic and statistical manual of mental disorders. 5th ed. Washington: American Psychiatric Publishing.

[2] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. *Alzheimers Dement* **3**, 263–269.

[3] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 270–279.

[4] Dubois B, Feldman HH, Jacova C, Cummings JL, DeKosky ST, Barberger-Gateau P, et al. 2011. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* **9**, 1118–1127.

[5] Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund L-O, et al. 2004. Mild cognitive impairment: beyond controversies, towards a consensus – report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* **256**, 240–46.

[6] Royall DR, Lauterbach EC, Kaufer D, Malloy P, Coburn KL, Black KJ. 2007. The cognitive correlates of functional status: a review from the Committee on Research of the American Neuropsychiatric Association. *J Neuropsychiatry Clin Neurosci* **19**, 249–265.

[7] Farias ST, Harrell E, Neumann C, Houtz A. 2003. The relationship between neuropsychological performance and daily functioning in individuals with Alzheimer's disease. *Arch Clin Neuropsychol* **18**, 655–672.

[8] Kiyak HA, Teri L, Borson S. 1994. Physical and functional health assessment in normal aging and in Alzheimer's disease: Self-reports vs family reports. *Gerontologist*, **34**, 324–330.

[9] Mangone CA, Sanguinetti RM, Baumann PD, Gonzalez Pereyra S, Bozzola FG, Gorelick PB, et al. 1993. Influence of feelings of burden on the caregiver's perception of the patient's functional status. *Dement Geriatr Cogn Disord* **4**, 287–293.

[10] Razani J, Kakos B, Orieta-Barbalace C, Wong JT, Casas R, Lu P, et al. 2007. Predicting caregiver burden from daily functional abilities of patients with mild dementia. *J Am Geriatr Soc* **55**, 1415–1420.

[11] Martyr A, Nelis SM, Clare L. 2014. Predictors of perceived functional ability in early-stage dementia: self-ratings, informant ratings and discrepancy scores. *Int J Geriatr Psychiatry* **29**, 852–862.

[12] Martyr A, Clare L. 2018. Awareness of functional ability in people with early-stage dementia. *Int J Geriatr Psychiatry,* **33**, 31–38.

[13] Martyr A, Clare L. 2012. Executive function and activities of daily living in Alzheimer's disease: a correlational meta-analysis. *Dement Geriatr Cogn Disord* **33**, 189–203.

[14] Boyle PA, Malloy PF, Salloway S, Cahn-Weiner DA., Cohen R, Cummings JL. 2003. Executive dysfunction and apathy predict functional impairment in Alzheimer disease. *Am J Geriatr Psychiatry* **11**, 214–221.

[15] Farias ST, Cahn-Weiner DA, Harvey DJ, Reed BR, Mungas D, Kramer JH, et al. 2009. Longitudinal changes in memory and executive functioning are associated with longitudinal change in instrumental activities of daily living in older adults. *Clin Neuropsychol* **23**, 446–461.

[16] Zahodne LB, Manly JJ, MacKay-Brandt A, Stern Y. 2013. Cognitive declines precede and predict functional declines in aging and Alzheimer's disease. *PLoS ONE* **8**, doi:10.1371/journal.pone.0073645.

[17] Clare L, Nelis SM, Martyr A, Whitaker CJ, Marková IS, Roth I, et al. 2012. Longitudinal trajectories of awareness in early-stage dementia. *Alzheimer Dis Assoc Disord* **26**, 140–147.

[18] Liu-Seifert H, Siemers E, Sundell K, Price K, Baoguang H, Selzler K, et al. 2015. Cognitive and functional decline and their relationship with mild Alzheimer's dementia. *J Alzheimers Dis* **43**, 949–955.

[19] Liu-Seifert H, Siemers E, Price K, Han B, Selzler KJ, Henley D, et al. 2015. Cognitive impairment precedes and predicts functional impairment in mild Alzheimer’s disease. *J Alzheimers Dis* **47**, 205–214.

[20] Snyder PJ, Kahle-Wrobleski K, Brannan S, Miller DS, Schindler RJ, DeSanti S, et al. 2014. Assessing cognition and function in Alzheimer’s disease clinical trials: Do we have the right tools? *Alzheimers Dement* **10**, 853–860.

[21] Liu-Seifert H, Siemers E, Selzler K, Sundell K, Aisen P, Cummings, J, et al. 2016. Correlation between cognition and function across the spectrum of Alzheimer’s disease. *J Prev Alz Dis* **3**, 138-144

[22] Wajman JR, Oliveira FF, Marin SMC, Schultz RR, Bertolucci, PHF. 2014. Is there correlation between cognition and functionality in severe dementia? The value of a performance-based ecological assessment for Alzheimer’s disease. *Arq Neuropsiquiatr* **72**, 845–850.

[23] American Psychiatric Association. 1994. Diagnostic and statistical manual of mental disorders. 4th ed. Washington: American Psychiatric Publishing.

[24] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM, et al. 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939–944.

[25] Hongisto K. 2016. Quality of life and neuropsychiatric symptoms in patients with Alzheimer’s disease – The Alsova follow-up study [dissertation]. University of Eastern Finland.

[26] Hallikainen I, Hänninen T, Fraunberg M, Hongisto K, Välimäki T, Hiltunen A, et al. 2013. Progression of Alzheimer’s disease during a three-year follow-up using the CERAD-NB total score: Kuopio ALSOVA study. *Int Psychogeriatr* **25**, 1335–1344.

[27] Koivisto A, Hallikainen I, Välimäki T, Hongisto K, Hiltunen A, Karppi P, et al. 2015. Early psychosocial intervention does not delay institutionalization in persons with mild Alzheimer

disease and has impact on neither disease progression nor caregivers' well-being: ALSOVA 3-year follow-up. *Int J Geriatr Psychiatry* **31**, 273–283.

[28] Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, et al. 1994. The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology* **44**, 609–614.

[29] Paajanen T, Hänninen T, Tunnard C, Mecocci P, Sobow T, Tsolaki M, et al. 2010. CERAD neuropsychological battery total score in multinational mild cognitive impairment and control populations: the AddNeuroMed study. *J Alzheimers Dis*, **22**, 1089–1097.

[30] Sotaniemi M, Pulliainen V, Hokkanen L, Pirttilä T, Hallikainen I, Soininen H, et al. 2012. CERAD-neuropsychological battery in screening mild Alzheimer’s disease. *Acta Neurol Scand* **125**, 16–23.

[31] Chandler MJ, Lacritz LH, Hynan LS, Barnard HD, Allen G, Deschner M, et al. 2010. A total score for the CERAD neuropsychological battery. *Neurology* **65**, 102–106.

[32] Hänninen T, Pulliainen V, Salo J, Hokkanen L, Erkinjuntti T, Koivisto K, et al. 1999. Kognitiiviset testit muistihäiriöiden ja alkavan dementian varhaisdiagnostiikassa: CERAD-tehtäväsarja. *Suom Laakaril* **54**, 1967–75.

[33] Suhonen N-M. 2017. Cognitive and behavioral characteristics of frontotemporal lobar degeneration [dissertation]. *Acta Universitatis Ouluensis D Medica*, **1423**.

[34] Isaacs B, Kennie TA. 1973. The set test as an aid to the detection of dementia in old people. *Br J Psychiatry* **123**, 467–470.

[35] Kaplan E, Goodglass H, Weintraub S. 1983. Boston naming test. Philadelphia: Lea & Febiger.

[36] Folstein MF, Folstein SE, McHugh, PR. 1975. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189–198.

[37] Morris JC, Heyman A, Mohs R, Hughes JP, van Belle G, Fillenbaum G, et al. 1989. The Consortium to Establish a Registry for Alzheimer's Disease. Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* **39**, 1159–1165.

[38] Rosen WG, Mohs RC, Davis KL. 1984. A new rating scale for Alzheimer's disease. *Am J Psychiatry* **141**, 1356–64.

[39] Fillenbaum GG, Burchett BM, Unverzagt FW, Rexroth DF, Welsh-Bohmer K. 2011. Norms for CERAD Constructional Praxis Recall. *Clin Neuropsych* **25**, 1345–1358.

[40] Hazan E, Frankenburg F, Brenkel M, Shulman K. 2018. The test of time: a history of clock drawing. *Int J Geriatr Psychiatry,* **33**, e22–e30.

[41] Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, et al. 1997. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. *Alzheimer Dis Assoc Disord* **11**(Suppl 2), 33–39.

[42] Kahle-Wrobleski K, Coley N, Lepage B, Cantet C, Vellas B, Andrieu, S. 2014. Understanding the complexities of functional ability in Alzheimer's disease: more than just basic and instrumental factors. *Curr Alzheimer Res* **11**, 357-366.

[43] Tabachnick BG, Fidell LS. 2013. Using multivariate statistics. 5th ed. Boston: Pearson.

[44] Marshall GA, Rentz DM, Frey MT, Locascio JJ, Johnson KA, Sperling RA. 2011. Executive function and instrumental activities of daily living in MCI and AD. *Alzheimers Dement* **7**, 300–308.

[45] Galasko D, Edland SD, Morris JC, Clark C, Mohs R, Koss E. 1995. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part XI. Clinical milestones in patients with Alzheimer's disease followed over 3 years. *Neurology* **45**, 1451–1455.

[46] Green CR, Mohs RC, Schmeidler J, Moshen AMA, Davis KL. 1993. Functional decline in Alzheimer's disease: a longitudinal study. *J Am Geriatr Soc* **41**, 654–661.

[47] Baudic S, Dalla Barba G, Thibauder MC, Smagghe A, Remy P, Traykov L. 2006. Executive function deficits in early Alzheimer's disease and their relations with episodic memory. *Arch Clin Neuropsychol* **21**, 15–21.

[48] Welsh K, Butters N, Hughes JP, Mohs RC, Heyman A. 1992. Detection and staging of dementia in Alzheimer's disease: use of the neuropsychological measures developed for the Consortium to Establish a Registry for Alzheimer's Disease. *Arch Neurol* **49**, 448–452.

[49] Willis SL, Allen-Burge R, Dolan MM, Bertrand R, Yesavage J, Taylor JL. 1998. Everyday problem solving among individuals with Alzheimer's disease. *Gerontologist* **38**, 569–577.

[50] Jefferson AL, Barakat LP, Giovannetti T, Paul RH, Glosser G. 2006. Object perception impairments predict instrumental activities of daily living dependence in Alzheimer's disease. *J Clin Exp Neuropsychol* **28**, 884–897.

[51] Glosser G, Gallo J, Duda N, de Vries JJ, Clark CM, Grossman M. 2002. Visual perceptual functions predict instrumental activities of daily living in patients with dementia. *Neuropsychiatry Neuropsychol Behav Neurol* **15**, 198–206.

[52] Royall DR, Palmer R, Chiodo LK, Polk MJ. 2005. Executive control mediates memory's association with change in instrumental activities of daily living: the Freedom House study. *J Am Geriatr Soc* **53**, 11–17.

[53] Lawton MP, Brody EM. 1969. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179–186.

[54] Lechowski L, de Stampa M, Denis B, Tortrat D, Chassagne P, Robert P, et al. 2008. Patterns of loss of abilities in instrumental activities of daily living in Alzheimer's disease: the REAL cohort study. *Dement Geriatr Cogn Disord* **25**, 46–53.

[55] Welsh K, Butters N, Hughes J, Mohs R, Heyman A. 1991. Detection of abnormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures. *Arch Neurol* **48**, 278–281.

[56] Hallikainen I, Martikainen J, Lin P, Cohen JT, Lahoz R, Välimäki T, et al. 2014. The progression of Alzheimer's disease can be assessed with a short version of the CERAD

neuropsychological battery: the Kuopio ALSOVA study. *Dement Geriatr Cogn Dis Extra* **4**, 494–508.

[57] Royall D, Palmer RF. 2014. “Executive functions” cannot be distinguished from general intelligence: two variations on a single theme within a symphony of latent variance. *Front Behav Neurosci* **8**, 1–10.

Table 1 CERAD-NB subtests used in the study (modified from Suhonen, 2017 [33])

Subtest	Administration	Cognitive functions	Reference
Verbal Fluency	The participant is asked to produce the names of as many animals (exemplars of a semantic category) as possible in 60 seconds.	Executive function, language functions, semantic memory	Isaacs & Kennie, 1973 [34]
Abbreviated Boston Naming Test	Three series of five objects each are presented sequentially to the participant, who is asked to name the objects. The series increase in difficulty based on the infrequent usage of the objects in the language.	Language functions	Kaplan, Goodglass, & Weintraub, 1983 [35]
MMSE	Brief instrument, in which the participant is asked to complete instructed tasks and to answer questions regarding orientation and cognition	Global cognition	Folstein, Folstein, & McHugh, 1975 [36]

Word List Learning, Word List Recall and Word List Recognition	In Word List Learning the participant is presented 10 words sequentially, after which he or she is asked to freely recall as many words as possible. Two more free recall trials are given. The participant is asked to recall as many of the 10 words as possible after a delay in Word List Recall, and in Word List Recognition he or she is asked to recognize the 10 words when grouped with 10 distractor words.	Verbal memory, verbal learning	Morris et al., 1989 [37]
Constructional Praxis	The participant is asked to copy four increasingly complex figures, one at a time.	Visuoconstructive skills	Rosen, Mohs, & Davis, 1984 [38]
Constructional Praxis Recall	After a delay, the participant is asked to produce the figures in Constructional Praxis relying on free recall.	Visual memory	Fillenbaum et al., 2008 [39]
Clock Drawing Test	The participant is asked to draw a clock, setting the hands at 10 past 11.	Executive function, visuoconstructive skills	Hazan et al., 2017 [40]

Table 2. The clinical and demographic characteristics of persons with very mild or mild Alzheimer's Disease at baseline during the five-year follow-up

	Baseline n=236	Year 1 n=198	Year 2 n=168	Year 3 n=126	Year 4 n=83	Year 5 n=72
Age	75.15±6.52 (53–90)					
Education	7.58±3.29 (1–20)					
Female, %	51.2	53	53.6	56.3	56.6	56.9
Verbal Fluency	13.49±5.19 (2–34)	11.88±4.89 (1–31)	10.16±5.11 (0–28)	9.26±5.37 (0–27)	8.33±4.97 (0–21)	8.00±5.82 (0–26)
Abbreviated BNT (0–15)	9.89±2.68 (2–15)	9.05±3.05 (2–15)	8.32±3.42 (0–15)	7.78±3.47 (0–15)	7.33±3.78 (0–15)	6.72±4.13 (0–15)
MMSE (0–30)	21.50±3.44 (12–30)	19.33±4.30 (8–30)	17.78±5.01 (4–29)	16.76±4.71 (4–28)	15.01±6.34 (0–28)	13.83±6.79 (0–29)
Word List Learning	12.36±3.85 (2–27)	11.40±4.28 (0–25)	10.46±4.95 (0–28)	9.59±5.04 (0–25)	8.91±5.53 (0–23)	9.41±6.11 (0–26)
Constructional Praxis (0–11)	8.36±1.86 (2–11)	8.02±2.18 (0–11)	7.63±2.79 (0–11)	7.72±2.34 (0–11)	7.45±2.36 (1–11)	6.89±2.26 (2–11)
Word List Recall (0–10)	2.07±1.80 (0–9)	1.65±1.70 (0–8)	1.17±1.65 (0–8)	1.11±1.54 (0–7)	0.64±1.17 (0–5)	0.88±1.41 (0-5)
Word List Recognition (0–20)	15.51±2.77 (9–20)	14.82±2.90 (8–20)	13.91±3.00 (1–20)	13.75±2.82 (8–20)	13.31±3.64 (0–20)	12.82±3.40 (0–20)
Constructional Praxis Recall (0–11)	3.54±3.01 (0–11)	3.00±2.82 (0–10)	2.10±2.56 (0–10)	1.97±2.36 (0–11)	1.78±2.49 (0–11)	1.35±2.12 (0–11)
Clock Drawing Test (0–6)	4.00±1.73 (0–6)	3.28±1.89 (0–6)	2.96±1.92 (0–6)	2.90±1.77 (0–6)	2.37±1.84 (0–6)	1.95±1.70 (0–6)
CERAD-NB Total Score (0–100)	51.58±11.85 (22–96)	46.90±13.01 (16–92)	42.09±14.77 (4–92)	39.49±15.74 (3–91)	37.83±15.76 (5–82)	36.78±18.18 (2–84)
ADCS-ADL BADL Score (0–22)	20.81±1.87 (10–22)	19.72±3.13 (6–22)	17.98±4.31 (3–22)	16.75±5.49 (0–22)	16.14±5.59 (2–22)	14.60±6.33 (0–22)
ADCS-ADL IADL Score (0–56)	43.85±7.68 (17–56)	38.43±10.39 (7–56)	33.42±12.35 (3–53)	29.26±13.44 (1–50)	27.42±13.19 (1–51)	23.26±14.32 (1–51)
ADCS-ADL Total Score (0–78)	64.57±8.88 (33–78)	58.08±12.74 (17–78)	51.26±15.92 (8–75)	46.05±18.37 (4–72)	43.58±17.91 (3–73)	37.95±19.66 (1–71)

*Values presented are mean ± standard deviation. Ranges of values are presented in parentheses.

Table 3 Associations of the CERAD-NB subtests and demographic variables with ADCS-ADL total score during the 5-year follow-up in the adjusted LMM model.

Variables	Univariate				Multivariate			
	B	SE	β	*p*	B	SE	β	*p*
Verbal Fluency	0.35	0.07	0.11	< 0.001	0.22	0.07	0.07	< 0.001
Abbreviated Boston Naming Test	0.69	0.15	0.14	< 0.001	0.37	0.16	0.07	0.020
MMSE	1.12	0.09	0.35	< 0.001	0.83	0.10	0.26	< 0.001
Word List Learning	0.59	0.09	0.17	< 0.001				
Constructional Praxis	0.83	0.16	0.11	< 0.001	0.50	0.17	0.07	0.004
Word List Recall	1.14	.20	0.11	< 0.001	0.64	0.22	0.06	0.004
Word List Recognition	0.51	0.11	0.09	< 0.001				
Constructional Praxis Recall	0.67	0.11	0.11	< 0.001	0.25	0.13	0.04	0.048
Clock Drawing Test	1.12	0.19	0.13	< 0.001	0.54	0.20	0.06	0.009
Gender, ref = male	-5.37	1.08	-0.32	< 0.001	-6.74	1.09	-.40	< 0.001
Age, years	-0.21	0.09	-0.08	0.019				
Education, years	0.78	0.16	0.15	< 0.001				

*CERAD-NB = Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory; LMM = linear mixed-effect model; MMSE = mini-mental state examination, ref = reference category

Table 4 Associations of the CERAD-NB subtests and demographic variables with IADL score during the 5-year follow-up period in the adjusted LMM model

Variables	Univariate				Multivariate			
	B	SE	β	*p*	B	SE	β	*p*
Verbal Fluency	0.37	0.06	0.16	< 0.001	0.23	0.06	0.10	< 0.001
Abbreviated Boston Naming Test	0.74	0.13	0.19	< 0.001	0.41	0.13	0.11	0.002
MMSE	1.06	0.07	0.43	< 0.001	0.79	0.09	0.32	< 0.001
Word List Learning	0.53	0.08	0.20	< 0.001				
Constructional Praxis	0.74	0.14	0.13	< 0.001	0.43	0.15	0.08	0.002
Word List Recall	1.08	0.18	0.14	< 0.001	0.72	0.19	0.09	< 0.001
Word List Recognition	0.44	0.09	0.10	< 0.001				
Constructional Praxis Recall	0.57	0.10	0.12	< 0.001				
Clock Drawing Test	1.03	0.16	0.15	< 0.001	0.42	0.17	0.06	0.019
Gender, ref = male	-4.38	0.94	-0.33	< 0.001	-5.69	0.96	-0.43	< 0.001
Age, years	-0.20	0.08	-0.10	0.010				
Education, years	0.69	0.14	0.17	< 0.001				

*CERAD-NB = Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory; LMM = linear mixed-effect model; MMSE = mini-mental state examination, ref = reference category

Table 5 Associations of the CERAD-NB subtests and demographic variables with BADL score during the 5-year follow-up period in the adjusted LMM model.

Variables	Univariate				Multivariate			
	B	SE	β	*p*	B	SE	β	*p*
Verbal Fluency	0.05	0.02	0.06	0.004				
Abbreviated Boston Naming Test	0.12	0.04	0.09	0.002				
MMSE	0.22	0.02	0.25	< 0.001	0.17	0.03	0.20	< 0.001
Word List Learning	0.14	0.02	0.15	< 0.001				
Constructional Praxis	0.28	0.04	0.14	< 0.001	0.20	0.05	0.10	< 0.001
Word List Recall	0.18	0.05	0.07	0.001				
Word List Recognition	0.10	0.03	0.06	< 0.001				
Constructional Praxis Recall	0.13	0.03	0.08	< 0.001				
Clock Drawing Test	0.30	0.05	0.13	< 0.001	0.15	0.06	0.06	0.008
Gender, ref = male	-0.95	0.23	-0.21	< 0.001	-1.15	0.23	-0.25	< 0.001
Age, years	-0.03	0.02	-0.04	0.106				
Education, years	0.11	0.04	0.08	0.002				

*CERAD-NB = Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory; LMM = linear mixed-effect model; MMSE = mini-mental state examination, ref = reference category

Appendix A β-values of annual univariate regression analyses of CERAD-NB total scores on corresponding ADCS-ADL total scores and IADL and BADL sub-scores.

	ADCS-ADL Total Score				IADL Score				BADL Score			
	B	SE B	β	*p*	B	SE B	β	*p*	B	SE B	β	*p*
Baseline	0.18	0.05	0.24	< 0.001	0.16	0.04	0.25	< 0.001	0.02	0.01	0.11	0.095
Year 1	0.36	0.07	0.37	< 0.001	0.29	0.05	0.37	< 0.001	0.08	0.02	0.34	< 0.001
Year 2	0.50	0.07	0.48	< 0.001	0.40	0.06	0.48	< 0.001	0.11	0.02	0.38	< 0.001
Year 3	0.53	0.09	0.49	< 0.001	0.43	0.07	0.50	< 0.001	0.13	0.03	0.38	< 0.001
Year 4	0.63	0.10	0.58	< 0.001	0.50	0.08	0.59	< 0.001	0.16	0.04	0.46	< 0.001
Year 5	0.62	0.10	0.62	< 0.001	0.50	0.08	0.63	< 0.001	0.16	0.04	0.47	< 0.001

*B = unstandardized coefficient, SE B = standard error of unstandardized coefficient**,** β = standardized coefficient

Appendix B Annual multiple regression models of the CERAD-NB sub-tests, gender, age and education on corresponding ADCS-ADL total scores.

	B	SE B	β	*p*
Baseline (R^2 = .51, p < .001†)				
Constructional Praxis Recall	.56	.18	.19	.002
Clock Drawing Test	.90	.31	.18	.004
Gender, ref = male	-.54	1.00	-.31	< .001
Education, years	.63	.16	.23	< .001
Year 1 (R^2 = .55, p < .001†)				
Gender, ref = male	-8.73	1.55	-.35	< .001
Constructional Praxis Recall	.73	.31	.16	.020
Clock Drawing Test	1.11	.47	.17	.019
MMSE	.60	.23	.20	.009
Year 2 (R^2 = .64, p <. 001†)				
Gender, ref = male	-8.40	1.92	-.27	< .001
Age, years	-.36	.14	-.16	.011
Verbal Fluency	.62	.22	.21	.005
Constructional Praxis	2.08	.40	.37	< .001
Word List Recall	1.34	.62	.14	.032
Year 3 (R^2 = .60, p < .001†)				
Gender, ref = male	-7.56	2.55	-.22	.004
Verbal Fluency	1.16	.26	.37	< .001
Constructional Praxis	2.03	.59	.28	.001
Year 4 (R^2 = .68, p < .001†)				
Gender, ref = male	-7.50	3.10	-.21	.018
Verbal Fluency	1.51	.38	.42	< .001
Constructional Praxis	2.23	.81	.29	.008
Year 5 (R^2 = .64, p < .001†)				
Word List Learning Sum	1.96	.32	.64	< .001

† = Model *p*-values were significant at the Bonferroni adjusted level p = .0083,
ref = reference category

Appendix C Annual multiple regression models of the CERAD-NB subtests, gender, age and education on corresponding IADL scores.

	B	SE B	β	*p*
Baseline (R^2= .51, p < .001†)				
Gender, ref = male	-4.45	.88	-.29	< .001
Education, years	.55	.14	.24	< .001
Constructional Praxis Recall	.50	.16	.20	.002
Clock Drawing Test	.78	.27	.18	.004
Year 1 (R^2= .53, p < .001†)				
Gender, ref = male	-7.36	1.29	-.36	< .001
MMSE	.56	.18	.23	.002
Constructional Praxis	.77	.31	.16	.015
Word List Recall	.85	.42	.14	.046
Year 2 (R^2= .62, p < .001†)				
Gender, ref = male	-5.86	1.51	-.24	< .001
Age, years	-.24	.11	-.14	.033
Verbal Fluency	.45	.17	.19	.010
Constructional Praxis	1.56	.32	.35	< .001
Word List Recall	1.42	.49	.20	.004
Year 3 (R^2= .61, p < .001†)				
Gender, ref = male	-5.22	1.88	-.21	.006
Verbal Fluency	.88	.19	.38	< .001
Constructional Praxis	1.53	.44	.29	.001
Year 4 (R^2= .67, p < .001†)				
Gender, ref = male	-4.98	2.35	-.19	.037
Verbal Fluency	1.12	.29	.42	< .001
Constructional Praxis	1.61	.61	.29	.010
Year 5 (R^2= .65, p < .001†)				
Word List Learning Sum	1.50	.23	.65	< .001

† = Model *p*-values were significant at the Bonferroni adjusted level p = .0083, ref = reference category

Appendix D Annual multiple regression models of the CERAD-NB subtests, gender, age and education on corresponding BADL total scores.

	B	SE B	β	*p*
Baseline (R^2= .37, $p < .001$†)				
Gender, ref = male	-.92	.23	-.24	< .001
Education, years	.08	.04	.14	.027
Constructional Praxis	.21	.06	.21	.001
Year 1 (R^2= .51, $p < .001$†)				
Gender, ref = male	-1.72	.40	-.27	< .001
Education, years	.16	.06	.18	.005
Verbal Fluency	.14	.05	.21	.003
Clock Drawing Test	.32	.12	.20	.006
Year 2 (R^2= .60, $p < .001$†)				
Gender, ref = male	-2.39	.53	-.29	< .001
Age, years	-.11	.04	-.19	.004
MMSE	.14	.06	.17	.027
Constructional Praxis	.60	.12	.39	< .001
Year 3 (R^2= .52, $p < .001$†)				
Gender, ref = male	-2.21	.80	-.22	.007
Verbal Fluency	.26	.08	.28	.002
Constructional Praxis	.56	.19	.26	.003
Year 4 (R^2= .62, $p < .001$†)				
Gender, ref = male	-2.54	1.02	-.24	.015
Verbal Fluency	.40	.12	.37	.002
Constructional Praxis	.62	.27	.27	.023
Year 5 (R^2= .64, $p < .001$†)				
Verbal Fluency	.51	.14	.52	< .001
Constructional Praxis Recall	1.03	.32	.39	.002
Clock Drawing Test	1.06	.45	.32	.022

† = Model *p*-values were significant at the Bonferroni adjusted level $p = .0083$, ref = reference category