Neuropsychologia 131 (2019) 184–192

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

High amyloid burden is associated with fewer specific words during spontaneous speech in individuals with subjective cognitive decline

Sander C.J. Verfaillie[a,b,d,*], Jurriaan Witteman[e,f], Rosalinde E.R. Slot[a,d], Ilanah J. Pruis[a,d], Lieke E.W. Vermaat[a,d], Niels D. Prins[a,d], Niels O. Schiller[e,f], Mark van de Wiel[c], Philip Scheltens[a,d], Bart N.M. van Berckel[b,d], Wiesje M. van der Flier[b,c,d], Sietske A.M. Sikkes[b,c,d]

[a] Department of Neurology and Alzheimer Center, Amsterdam University Medical Center, location VUmc, Vrije Universiteit, de Boelelaan 1118, 1081HZ, Amsterdam, the Netherlands
[b] Department of Radiology & Nuclear Medicine, Amsterdam University Medical Center, location VUmc, Amsterdam, the Netherlands
[c] Department of Epidemiology & Biostatistics, Amsterdam University Medical Center, location VUmc, Amsterdam, the Netherlands
[d] Amsterdam Neuroscience, Amsterdam, the Netherlands
[e] Leiden University Centre for Linguistics, Leiden, the Netherlands
[f] Leiden Institute for Brain and Cognition, Leiden, the Netherlands

ARTICLE INFO

Keywords:
Amyloid burden
Spontaneous speech
Linguistics
Subjective cognitive decline
Early diagnosis
Alzheimer's disease
Preclinical AD

ABSTRACT

Self-perceived word-finding difficulties are common in aging individuals as well as in Alzheimer's Disease (AD). Language and speech deficits are difficult to objectify with neuropsychological assessments. We therefore aimed to investigate whether amyloid, an early AD pathological hallmark, is associated with speech-derived semantic complexity. We included 63 individuals with subjective cognitive decline (age 64 ± 8, MMSE 29 ± 1), with amyloid status (positron emission tomography [PET] scans n = 59, or $A\beta_{1\text{-}42}$ cerebrospinal fluid [CSF] n = 4). Spontaneous speech was recorded using three open-ended tasks (description of cookie theft picture, abstract painting and a regular Sunday), transcribed verbatim and subsequently, linguistic parameters were extracted using T-scan computational software, including specific words (content words, frequent, concrete and abstract nouns, and fillers), lexical complexity (lemma frequency, Type-Token-Ratio) and syntactic complexity (Developmental Level scale). Nineteen individuals (30%) had high levels of amyloid burden, and there were no differences between groups on conventional neuropsychological tests. Using multinomial regression with linguistic parameters (in tertiles), we found that high amyloid burden is associated with fewer concrete nouns (OR_{middle} (95%CI): 7.6 (1.4–41.2), OR_{lowest}: 6.7 (1.2–37.1)) and content words (OR_{lowest}: 6.3 (1.0–38.1). In addition, we found an interaction for education between high amyloid burden and more abstract nouns. In conclusion, high amyloid burden was modestly associated with fewer specific words, but not with syntactic complexity, lexical complexity or conventional neuropsychological tests, suggesting that subtle spontaneous speech deficits might occur in preclinical AD.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease related to amyloid beta plaques and neurofibrillary tangles, which start to aggregate 10–20 years before the onset of dementia (Braak and Braak, 1991; Bateman et al., 2012; Scheltens et al., 2016). AD is characterized by gradual deterioration in various cognitive domains, including language (Manenti et al., 2004). In spontaneous speech, the degree of lexical complexity (e.g. vocabulary variation) and content words are impaired in AD, whereas syntactic complexity is affected only until later stages of the disease (Kemper et al., 1994, 2001; Emery, 2000; Gayraud et al., 2011; Roark et al., 2011; Ahmed et al., 2013; Fraser et al., 2015). Moreover, a recent case study showed that increased use of conversational fillers and decreased number of content words can be observed years before onset of dementia (Berisha et al., 2015).

Subjective cognitive decline (SCD) can be caused by various conditions, such as preclinical AD which is defined as high levels of amyloid burden but normal cognition (Sperling et al., 2011; Jessen et al., 2014; Jack et al., 2018). Compared to other cognitive domains,

* Corresponding author. Department of Radiology & Nuclear Medicine and Department of Neurology and VUmc Alzheimer center, Amsterdam University Medical Center, location VUmc, P.O. Box 7057, 1007 MB Amsterdam, the Netherlands.
E-mail address: s.verfaillie@vumc.nl (S.C.J. Verfaillie).

https://doi.org/10.1016/j.neuropsychologia.2019.05.006
Received 30 August 2018; Received in revised form 3 May 2019; Accepted 6 May 2019
Available online 07 May 2019

language functioning shows a relatively steep decline over time in individuals with SCD (Verfaillie et al., 2017, 2018). Individuals with SCD often experience word-finding problems, but these self-perceived deficits are difficult to initially capture with conventional neuropsychological assessments. Evaluation of spontaneous speech is a closer approximate of real-world use of language, with high ecological validity and potentially higher sensitivity to subtle language deficits. Retrospective case studies detected fewer content words and decreased lexical complexity in spontaneous speech and written output as early signs of AD up till decades before clinical symptoms became manifest (Garrard et al., 2005; van Velzen and Garrard, 2013; Van Velzen et al., 2014; Berisha et al., 2015).

It is currently unknown whether amyloid pathology could reveal deficits in spontaneous speech, even in absence of impairment on conventional neuropsychological assessment. Neuroanatomically, spontaneous speech relies on the complex interplay of many brain regions with critical areas being Broca's and Wernicke's, angular gyrus, medial and superior frontal cortex (Mesulam, 1990; Indefrey and Levelt, 2004; Grande et al., 2012). Spontaneous speech is a complex source of information encompassing of various hierarchical levels of language organization, and a recent literature review indicated that phonetic, phonological, morpho-syntactic and lexico-semantic levels are to some extent affected in AD (Boschi et al., 2017). For this reason, it is conceivable that spontaneous speech, at some organization level, could be affected by early pathophysiological processes such as amyloid accumulation (Wilson and Petkov, 2011).

At what level, however, could we specifically expect AD-induced deficits in verbal processing? It has been proposed previously that there is a hierarchy of language decline in AD, with the most complex layers of language (particularly semantics) being most vulnerable to disturbance by progression of the disease (Emery, 2000), resulting in reduced complexity in the semantic domain (for instance, as expressed in the number of different words that are used in spontaneous speech). Furthermore, such semantic level processing difficulty has been proposed to result in 'empty speech' characterized by a lack of content words and imprecise expressions using generic terms (such as 'animal') rather than a more specific (such as 'dog') term (Rohrer et al., 2008). Two (non-mutually exclusive) explanations from the neurolinguistics literature have been put forward to account for semantic-level deficits in spontaneous speech among AD patients. First, there might be a primary semantic processing deficit in (early) AD (Rohrer et al., 2008), resulting in 'word-finding difficulty'. Indeed, a prevailing neurolinguistics model of speech production suggests that lexical selection during speech production takes place in the left (posterior) middle temporal gyrus (Indefrey and Levelt, 2004). Since neuropathology has been observed in the left lateral temporal lobe in AD (Villeneuve et al., 2015), empty speech AD may be caused by interfering of AD neuropathology with lexical selection. Alternatively, others have suggested that semantic processing disturbance in AD is secondary to a working memory deficit, resulting in rapid decay of semantic features and in the production of more general ('empty') speech (Almor et al., 1999). Recent evidence for accumulation of AD neuropathology in key nodes of the working memory network (i.e., the medial prefrontal cortex and precuneus) in prodromal AD is compatible with such an account (Villeneuve et al., 2015).

In the current study, we investigated whether amyloid burden in individuals with SCD is associated altered use of specific words, lexical complexity or syntactic complexity, derived from spontaneous speech, and we hypothesized that individuals with high levels of amyloid burden will use *fewer* specific words and display *less* lexical diversity.

2. Experimental procedure

2.1. Participants

We included 63 individuals with SCD from the ongoing Subjective Cognitive ImpairmeNt Cohort (SCIENCe) (Slot et al., 2018b). All participants were born in the Netherlands and had adequate proficiency in Dutch. SCD was defined based on spontaneous report by patients and subsequent referral to the memory clinic (Molinuevo et al., 2017). Prior to SCIENCe enrollment, all patients underwent a standardized dementia screening according to the procedures of the Amsterdam Dementia Cohort (Van Der Flier et al., 2014). Screening included extensive neuropsychological assessment, physical and neurologic examination as well as laboratory tests, and brain MRI. Clinical diagnosis was established by consensus in a multidisciplinary team. Patients were labelled as having SCD when they presented with cognitive complaints, and results of clinical investigations were within normal range. Criteria for MCI, dementia, or any other neurological or major psychiatric (e.g. major depression) disorders known to cause cognitive complaints were not met (i.e. cognitively intact) (Jessen et al., 2014; Molinuevo et al., 2017). Amyloid PET scans and lumbar puncture were offered as part of research, and these results were not used for diagnostic decision making. In addition, information about amyloid status was not disclosed to the participants. Our neuropsychological test battery included tests that measured cognitive functioning in the domains of memory, attention, executive functioning and language. For the current study, we only used tests in the latter domain: category fluency animals, phonemic fluency (i.e. average word generation to letter D-A-T over 3 min), and Boston naming test (BNT, short version). Finally, we used a structured interview to assess the nature of cognitive complaints. We used the following question "What complaints do you report?". Based on the individuals' spontaneous response the following cognitive domains were scored "yes/no": memory, attention, organization, language (Verfaillie et al., 2019). The medical ethics committee of the VU University Medical Center approved the study. All patients provided written informed consent.

2.2. Spontaneous speech recording and transcription

Spontaneous speech was recorded using three open-ended questions: Could you provide descriptions of; 1) the cookie theft picture, 2) an abstract painting (Fig. 1; Van Gogh "Tree roots", 1890, https://www.vangoghmuseum.nl/en/collection/s0195V1962) and 3) "describe your regular Sunday". All questions were administered in the same order for all subjects under similar conditions. Participants were instructed to talk freely for a minimum of 1 minute for each question, and a portable voice recorder (Tascam DR-05 V2) was positioned on a desk approximately 1 m in front of the participant with preconfigured settings. Verbatim transcription of speech recordings was done by two trained raters (IP, LV) using PRAAT (v.6.0.30) software (http://www.fon.hum.uva.nl/praat/), both of whom were blinded for participants' amyloid status.

2.3. Linguistic parameters

Linguistic parameters were extracted using the computational linguistics package software package T-scan (Kraf et al., 2009; Maat et al., 2014). T-Scan is a fully automated software package to quantify the complexity of Dutch text, particularly to extract text features that relate to genre and text complexity, which outputs a total of 253 linguistic parameters. T-scan makes use of a large Dutch lexicon (i.e. *Referentie Bestand Nederlands*) consisting of approximately 50.000 words, and 90.000 fixed and flexible syntactic relationships (Martin and Maks, 2005). We extracted eight parameters that reflect three language characteristics impaired in AD (Kemper et al., 2001; Gayraud et al., 2011; Roark et al., 2011); i. specific words, ii. lexical diversity and iii. syntactic complexity. For specific words classes, we extracted the following parameters: 1) content words (ratio nouns/pronouns; lower values reflect a lower proportion of content words), 2) frequent nouns (top 1000 most frequent nouns for adult language use; higher frequency reflects higher proportion of common words), 3) density (i.e.

Fig. 1. Painting "Tree Roots" by Vincent van Gogh (1890) which was used as one of the stimuli for speech recordings. Reprinted with permission of the Van Gogh museum, Amsterdam, The Netherlands (https://www.vangoghmuseum.nl/en/collection/s0195V1962).

standardized frequency of words per transcript) of nouns referring to concrete events or actions (e.g. respiration, caress; lower values reflect a lower density of concrete nouns), 4) density of nouns referring to abstract events or action (e.g. crisis, reduction; higher values reflect a higher density of abstract nouns), 5) conversation fillers (predefined, e.g. ehm, uhm, uhh). Fillers were extracted using in-house developed python scripts and these were all transcribed in a similar fashion (i.e. uhm). For lexical complexity, we extracted the following parameters: 6) lemma frequency (frequency of words referring to a concept of ideas irrespective of affixes; lower values reflect a higher number of unique ideas or unusual word stems and therefore a higher lexical complexity [this metric is in logarithmic scale]), 7) Type-Token-Ratio (TTR) of content words (unique [type] words, excluding closed-class (e.g. function) words, divided by the total number of words [tokens]; lower TTR reflects lower unique words or lexical diversity). For syntactic complexity, we used 8) the Developmental Level scale (i.e. D-level: 0(min)-7(max). D-level is an automated syntactic complexity metric based on the Developmental Level scale, which reflects the degree of syntactic complexity per utterance; e.g. 0 = elliptical sentence "over there", 4 = "I saw him walking his dog", 7 = "James thought that he had seen Marie, who dyed her hair red, walking on the streets recently) (Covington et al., 2006). The following words were considered content words: nouns, names, adjectives, adverb, verbs (no link or auxiliary verbs). The following parameters were inverted so that a higher score reflects a better performance: density of nouns referring to abstract events or actions, fillers, frequent nouns and lemma frequency. Please see the supplementary materials (Table S1) for an overview and more information on the interpretation of the linguistic parameters. Transcripts with a minimum of 300 words, based on the total word count of three consecutive recorded questions, were used in order to get a reliable linguistic parameter estimation (Prins and Bastiaanse, 2004). Two subjects were excluded from analyses due to insufficient number of words (n = 1) and poor recording quality (n = 1). Average word length and number of sentences were extracted for descriptive purposes (parameters of no interest). A random sample of repeated verbatim transcriptions (n = 12), performed by both raters, was drawn to estimate inter-rater reliability. Interrater reliability was computed by first aligning the texts of both raters using Needleman-Wunsch algorithm implemented in Python and then computing the F1 measure of similarity between the texts (i.e., the harmonic mean of the recall and precision) with a Needleman-Wunsch algorithm (McCowan et al., 2005). This analysis showed a high inter-rater reliability (F_1 score = 0.84) (Garrard et al., 2011). Speech transcripts were used if the recording took place < 1 year of the amyloid measurement.

2.4. Amyloid measures

Either PET or CSF were used to define the level of amyloid burden, and if both were available, we determined amyloid status based on amyloid PET. Either of the two amyloid PET were used [^{18}F]florbetaben (n = 7) or [^{18}F]florbetapir (n = 52), which depended on if PET scans were acquired during diagnostic screening or when individuals entered the SCIENCe cohort (after diagnostic screening). If both [^{18}F]florbetaben and [^{18}F]florbetapir were available, [^{18}F]florbetapir was used because it could be used for further quantitative image analysis. For [^{18}F]florbetapir, 90 min dynamic PET emission scans (PET/CT Ingenuity TF or Gemini TF, Philips Medical Systems, Best, The Netherlands) were acquired immediately following bolus injection of approximately 370 MBq [^{18}F]florbetapir. For [^{18}F]florbetaben, 20 min static acquisitions (PET/MR, Philips Medical Systems, Best, The Netherlands) were collected 90 min after a bolus injection of approximately 250 MBq [^{18}F]florbetaben. For CSF (n = 4), standardized screening lumbar puncture was performed, and CSF Aβ1-42 was measured using ELISA (Innogenetics-Fujirebio, Ghent, Belgium) at the Neurochemistry Laboratory (Mulder et al., 2010).

2.5. Amyloid positivity

Amyloid status (yes/no) was determined based on visual reading of amyloid PET scans ([^{18}F]florbetapir 50–70 min and [^{18}F]florbetaben 90–110 min post-injection) or CSF Aβ1-42 < 813 μg/L (center cut-off for amyloid positivity) (Tijms et al., 2017). FDA guidelines for both amyloid PET tracers were used to determine the degree of amyloid burden by an experienced and trained nuclear medicine physician (BvB) resulting in amyloid positive scans (i.e. high amyloid burden) and amyloid negative scans (i.e. low amyloid burden).

2.6. Quantitative amyloid load

Dynamic 90 min [^{18}F]florbetapir PET scans (n = 52) allowed the quantification of specific tracer binding to amyloid-β using parametric images (Lammertsma and Hume, 1996; Golla et al., 2018). Images were acquired in dynamic mode with a matrix size of 128 × 128 × 90 dimensions (2 × 2x2 mm^3), and 22 frames were reconstructed using 3D-RAMLA. PET images were corrected for attenuation, scatter, random, decay and dead time using standardized scanner software provided by Philips Healthcare. T1-weighted MRI scans were co-registered to the PET scans. Regions of interest (ROI), according to the Hammers template, were delineated on the MRI scan and superimposed onto the dynamic PET scan to obtain regional time activity curves (TACs), and using PVElab (Hammers et al., 2003; Svarer et al., 2005). Next, to

obtain non-displaceable binding potential (BP_{ND}) images, we used a reference tissue approach with optimized settings, i.e. receptor parametric mapping (RPM, settings: basis exponential (start-end) 1/0.01–1/0.1min with 50 basis functions) computed with in-house developed software (i.e. PPET), while using cerebellum gray matter as a reference region. Finally, we calculated volume-weighted mean cortical amyloid-β load, including all cortical regions (i.e. frontal, temporal, parietal, occipital and cingulate cortex) based on the Hammers brain atlas.

2.7. Statistics

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS, IBM v22). To investigate differences in demographics between individuals with low and high amyloid burden, we used $\chi 2$-tests for discrete variables, and analyses of variance (ANOVA) for continuous demographic and neuropsychological data, and Mann-Whitney U tests for (raw) linguistic data. To investigate the relationship between each linguistic parameters and demographic (age, sex, education) and neuropsychological data we performed Spearman Rho correlations and T-tests (for linguistic parameters and sex). Because linguistic variables remained non-normal distributed after Log- and Z-transformations, we ranked them into tertiles, and used the highest tertile as reference group. To allow comparison between different outcome measures, we also transformed neuropsychological language test scores into tertiles. We used multinomial regression analyses to investigate the associations between amyloid status (dichotomous; independent variable) and linguistic parameters (dependent variables in tertiles, in separate models). All analyses were adjusted for age (continuous), sex, and education (median split [low/high]) (model 1) (Verhage, 1965). We did not have a continuous measure for education level, therefore we have used the Verhage scale, which we have transformed into low/high to be consistent with our interaction terms and improve interpretation. As language ability is inherently connected with educational attainment, we additionally tested for education*amyloid status interaction. If there was a significant interaction, we stratified the analysis for education. If there was no interaction, the interaction term was removed from the model. Because fluency could influence semantic processing we adjusted for phonemic fluency (model 2) (Papp et al., 2015) in addition to age, sex, and education. We report Odds ratios (OR) with corresponding 95% confidence intervals (CI). Positive OR (> 1) reflect the likelihood for individuals with high levels of amyloid burden to have worse language performance (reference: highest tertile). Finally, to investigate whether quantitative amyloid-β load is associated with spontaneous speech, we performed linear regression analyses between mean cortical amyloid-β load (independent variable, continuous) and linguistic parameters (dependent variables in tertiles, separate models). Analyses were adjusted for age, sex and education. Additionally, interaction effects between education and amyloid load were tested. In addition, the false discovery rate (FDR) procedure was used to correct for multiple comparisons to the three domains of specific words, lexical diversity and syntactic complexity (Benjamini and Yekutieli, 2001).

3. Results

Demographic, clinical and linguistic data are presented in Table 1. Nineteen (30%) out of sixty-three individuals with SCD had evidence for high amyloid burden, and those individuals were older (68.2) than those with low amyloid burden (age = 61.5, $F\ (1,61) = 17.67$, $p < 0.001$). Sex, education levels and MMSE scores did not differ between groups (all $p > 0.05$). Correlations between demographic, conventional neuropsychological tests and linguistic parameters are presented in Table 2. Age was not correlated to the linguistic parameters (Table 2; all $p > 0.05$), and males (fillers = 23.4) used more conversation fillers than females (fillers = 16.9, $F\ (1,61) = 1.51$, $p = 0.047$). Education was positively correlated to lemma frequency, but not with any other linguistic parameters. Lemma frequency, D-level and content words were correlated with the BNT (Spearman Rho = 0.343, $p = 0.006$), category fluency (Spearman Rho = 0.25, $p = 0.046$) and phonemic fluency (Spearman Rho = −0.299 $p = 0.016$) respectively.

Table 3 shows amyloid burden in association with conventional neuropsychological language tests and linguistic parameters derived from spontaneous speech. We did not find any association between amyloid status and conventional neuropsychological language tests including BNT, category fluency and phonemic fluency (all $p > 0.05$). When we analysed spontaneous speech, individuals with high amyloid burden used fewer specific words (concrete nouns (OR_{middle} (95%CI): 7.6 (1.4–41.2), OR_{lowest}: 6.7 (1.2–37.1)), and content words (OR_{middle} (95%CI): 1.2 (0.3–6.1), OR_{lowest}: 6.3 (1.0–38.1)). There was a significant interaction between education and amyloid status for abstract nouns, but not for any of the other linguistic parameters. After stratification for education, we found that individuals with high levels of amyloid burden and higher education used more abstract nouns (OR_{lowest}: 48.5 (2.7–868.4)), but this effect was not observed in individuals with lower education. There were no associations between amyloid status and conversation fillers, syntactic complexity (i.e. D-level) or lexical complexity (i.e. top 1000 most frequent nouns, lemma frequency and TTR). These results remained essentially unchanged after additional adjustment for phonemic fluency (Table 3; model 2), but none of the linguistic parameters did survive FDR adjustments for multiple comparisons to the three domains of specific words, lexical complexity and syntactic complexity.

To explore whether spontaneous speech is associated with quantitative cortical amyloid load (i.e. [^{18}F]florbetapir BP_{ND}), we performed linear regression analyses between amyloid load and conventional language tests and linguistic parameters (Fig. 2B–E). Again, we did not find any associations between amyloid load and conventional neuropsychological language tests. Linear regression analyses confirmed negative associations between high amyloid load and fewer content words (beta = −0.54, $p = 0.003$) and more abstract nouns (beta interaction effect = 0.69, $p = 0.004$). In addition, we found that high amyloid load was associated with increased D-level (Fig. 2C; beta = 0.48, $p = 0.008$). Finally, there was a significant interaction between education and amyloid load for lemma frequency. Subsequent stratification for education showed that increased amyloid load was associated with lower lemma frequency for individuals with lower levels of education, but not for those with higher education (beta = 0.63, $p = 0.013$).

4. Discussion

The main finding of the present study is that high levels of amyloid burden in individuals with SCD were modestly associated with the use of fewer specific words, particularly in those individuals with higher levels of education, but not with lexical or syntactic complexity, or conventional neuropsychological language tests.

It takes 10–20 years from early pathophysiological changes until clinical manifestation of dementia. Nonetheless, amyloid deposition may insidiously affect cognitive functions prior to symptom onset (Jessen et al., 2010, 2014; Amariglio et al., 2012; Snitz et al., 2015; Perrotin et al., 2016). In keeping with prior results, (Baker et al., 2017) we did not find associations between amyloid burden and conventional neuropsychological language tests. In contrast to conventional language tests, the ecological validity of spontaneous speech is high, as it is a much closer approximate of real-world word-finding difficulties. In the present study we investigated three semantic characteristics of spontaneous speech: specific words, lexical and syntactic complexity.

Others have shown that compared to controls, patients with AD dementia show reduced lexical complexity and use fewer specific words (Kemper et al., 1994, 2001; Gayraud et al., 2011; Roark et al., 2011; Ahmed et al., 2013; Fraser et al., 2015). It is not yet clear whether

Table 1
Semantic complexity in individuals with SCD according to amyloid status.

Demographic/clinical data	Low amyloid burden (n = 44)		High amyloid burden (n = 19)		p-values
Age	61.5	(7.4)	68.2	(8.1)	< 0.001
Education (range 1–7) (Verhage, 1965)	5.6	(1.4)	5.7	(.92)	0.51
Sex distribution (n males [%])	25	(61%)	11	(55%)	0.53
MMSE	28.7	(1.4)	28.6	(1.19)	0.75
Language complaints (n "yes" [%])[1]		(31%)		(44%)	0.37
Memory complaints (n "yes" [%])[1]		(71%)		(63%)	0.54
Organization complaints (n "yes" [%])[1]		(5%)		(0%)	0.35
Attention complaints (n "yes" [%])[1]		(24%)		(19%)	0.69
Phonemic fluency – D-A-T (average)	13.2	(4.0)	13.3	(2.7)	0.84
Category fluency – animals	24.2	(5.7)	23.6	(4.7)	0.30
Boston naming test (short version)	79.1	(10.3)	82.0	(3.3)	0.27
Text characteristics					
Average word length	5.09	(0.69)	5.29	(1.08)	0.59
Sentences	55.07	(11.82)	53.37	(12.17)	0.75
Specific words	% tertiles median (range)				
Content words (ratio nouns/pronouns)	27/29/43	0.005 (0.004–0.009)	37/47/16	0.004 (0.004–0.005)	0.02
Concrete nouns	21/41/39	6.7 (3.3–9.9)	53/26/21	3.3 (0.0–6.7)	0.01
Abstract nouns	21/18/61	0 (0.0–3.3)	53/11/37	3.3 (0.0–6.5)	0.03
Conversation fillers	34/36/30	18.5 (12.0–24.75)	42/26/32	16.0 (8.0–33.0)	0.89
Lexical complexity					
1000 most frequent nouns	32/36/32	0.26 (0.22–0.33)	37/32/32	0.27 (0.22–0.32)	0.91
Lemma (frequency)	23/43/35	5.1 (5.0–5.3)	47/21/32	5.21 (5.01–5.27)	0.53
Type Token Ratio	36/27/36	0.63 (0.56–0.66)	26/47/26	0.61 (0.59–0.67)	0.91
Syntactic complexity					
D-level	39/30/32	0.96 (0.79–1.22)	16/42/42	1.01 (0.86–1.28)	0.32

Data are presented as mean (SD) or n (%). Linguistic are presented as % tertiles (lowest/middle/highest) per group together with median (25%–75% percentile range) of the original data. Chi-Square tests were used to investigate between group differences for linguistic parameters. Between group analyses for linguistic data (raw) were performed with Mann-Whitney U tests (not adjusted for any covariates). [1], 12 cases missing.

changes in spontaneous speech are related to amyloid burden in individuals with SCD (i.e. preclinical AD) (Sperling et al., 2011). A case study investigating conference speeches of two former U.S. presidents, showed that at least 6 years before AD diagnosis former president Reagan already used fewer specific words than president George H.W. Bush, who has no known diagnosis of AD (Berisha et al., 2015). Here, we predominantly found associations between amyloid status and linguistic parameters within the domain of specific words. More specifically, we observed that individuals with high amyloid burden use fewer concrete nouns and content words, and particularly individuals with higher levels of education used more abstract nouns. These findings were corroborated by our quantitative amyloid analyses, underlining the robustness of our finding that amyloid deposition is associated with fewer specific words. Contrary to our hypothesis, we did not observe a higher use of conversation fillers in individuals with high levels of amyloid burden, while these have been reported in an earlier case study (Berisha et al., 2015). One explanation could be that conversation fillers in preclinical stages are relatively subtle. We furthermore found that increased quantitative amyloid load was associated with higher syntactic or grammatical complexity (i.e. D-level), and increased use of abstract nouns particularly in individuals with higher levels of education. Most studies has shown a relative stability of syntactic complexity during normal aging (Glosser and Deser, 1992; Marini et al., 2005), and a syntax preservation until fairly advanced stages in AD dementia (Kempler, 1995; Garrard et al., 2005) because it is considered a more automatic linguistic function (Almor et al., 1999). Notwithstanding, we found opposite patterns of higher syntactical complexity in relation to high amyloid load. While it needs to be interpreted with caution, the previous may be explained by the effects of amyloid on higher level linguistic functions, such as an altered use of specific words, which may in turn requires a slight syntax remodeling or different use of grammar. The previous could furthermore be in line with the clinical observation of empty speech and circumlocution in AD dementia patients (Berisha et al., 2015). Future studies are, however, necessary to fully elucidate the syntactical changes in relation to higher level linguistic functions in preclinical AD.

Contrary to our expectations, we did not find any association between amyloid status and measures of lexical complexity. Our study is the first to focus on spontaneous speech in cognitively normal individuals with SCD, and one potential explanation for our findings is

Table 2
Correlations between demographic, conventional neuropsychological tests and linguistic parameters.

Linguistic parameters	Demographic variables		Conventional neuropsychological tests		
	Education	Age	Phonemic fluency	Category Fluency	Boston Naming Task
Abstract Nouns	0.034 (0.787)	0.112 (0.379)	0.025 (0.847)	0.125 (0.324)	−0.060 (0.639)
Concrete Nouns	0.053 (0.680)	−0.113 (0.374)	0.037 (0.772)	−0.083 (0.515)	0.146 (0.253)
Content Words	−0.201 (0.111)	−0.105 (0.407)	**−0.299 (0.016)**	−0.187 (0.139)	0.170 (0.184)
Fillers	0.140 (0.270)	−0.205 (0.104)	0.000 (0.999)	−0.116 (0.362)	0.087 (0.496)
1000 Frequent nouns	−0.092 (0.470)	0.002 (0.987)	−0.031 (0.808)	0.054 (0.672)	0.014 (0.911)
Type Token Ratio	0.002 (0.986)	0.228 (0.070)	−0.122 (0.338)	0.036 (0.776)	−0.001 (0.993)
Lemma Frequency	**0.309 (0.013)**	0.065 (0.612)	−0.067 (0.599)	0.073 (0.569)	**0.343 (0.006)**
D-level	0.031 (0.809)	−0.021 (0.871)	0.072 (0.574)	**0.249 (0.047)**	−0.174 (0.173)

Correlations were performed between demographic and conventional neuropsychological data and untransformed (raw) linguistic data using Spearman's rho. Of note, the following parameters were inverted so that a higher score reflects a better performance: density of nouns referring to abstract events or actions, fillers, frequent nouns and lemma frequency. Verhage classification (range 1–7) was used for education. Values represent correlation coefficients (p-values).

Table 3
Amyloid burden (low versus high) in association with linguistic parameters and neuropsychological tests.

Linguistic parameters				
Specific words	Model 1		Model 2	
	Middle	Lowest	Middle	Lowest
Content words	1.2 (0.3–6.1)	6.3 (1.0–38.1)*	1.0 (0.2–5.2)	8.3 (1.1–62.7)*
Low education	100.1 (0.40–25423.0)	1024.6 (2.7–394011.5)*	*No model convergence*	*No model convergence*
High education	4.1 (0.5–31.4)	41.7 (0.6–2759.9)	0.41 (0.0–4.3)	1.1 (0.1–12.9)
Concrete nouns	7.6 (1.4–41.2)*	6.7 (1.2–37.1)*	7.8 (1.4–44.4)*	7.3 (1.2–42.8)*
Low education	5.0 (0.5–49.3)	*No model convergence*	7.8 (0.4–168.5)	*No model convergence*
High education	21.5 (1.1–418.4)*	*2.6 (0.3–22.0)*	24.0 (1.1–512.2)*	2.5 (0.3–21.7)
Abstract nouns	2.4 (0.3–18.8)	3.8 (0.9–15.3)	3.3 (0.4–24.9)	4.8 (1.1–20.7)*
Low education	*No model convergence*	0.75 (0.1–5.6)	*No model convergence*	0.8 (0.1–8.6)*
High education	*No model convergence*	48.5 (2.7–868.4)*	*No model convergence*	49.4 (2.7–904.5)*
Fillers	1.5 (0.3–7.7)	3.2 (0.6–18.6)	1.3 (0.3–7.0)	2.9 (0.5–17.0)
Lexical complexity				
1000 most frequent nouns	1.0 (0.2–4.6)	1.0 (0.2–4.6)	1.1 (0.2–4.8)	1.1 (0.2–5.4)
Lemma frequency	3.0 (0.4–21.2)	1.3 (0.3–6.7)	2.5 (0.4–18.1)	1.1 (0.2–5.6)
Type Token Ratio	0.4 (0.1–2.0)	2.7 (0.5–15.7)	0.4 (0.1–1.8)	2.1 (0.4–12.8)
Syntactic complexity				
D-level	0.2 (0.0–1.3)	0.2 (0.0–1.1)	0.3 (0.0–1.6)	0.2 (0.0–1.4)
Neuropsychological language tests				
Letterfluency D-A-T	0.3 (0.1–1.6)	0.4 (0.1–2.5)	n.a.	n.a.
Category fluency – animals	0.85 (0.2–3.7)	1.2 (0.2–6.1)	1.3 (0.2–8.3)	2.0 (0.3–14.2)
Boston Naming Test	1.0 (0.2–5.5)	0.3 (0.0–1.7)	0.9 (0.2–5.0)	0.2 (0.0–1.5)

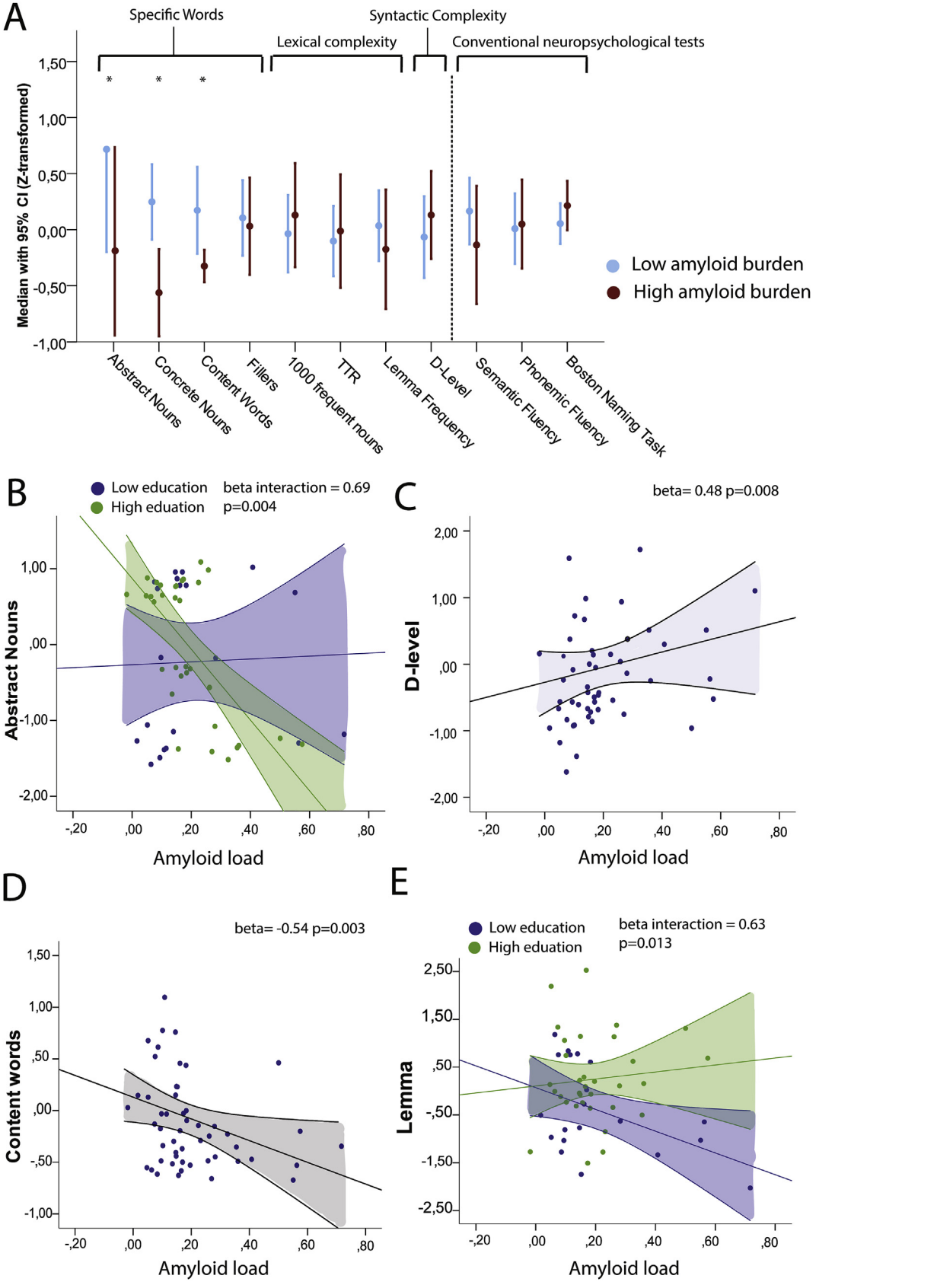
Lowest tertiles (i.e. worst linguistic scores of the distribution, < 33.33%), middle and highest categories represent the consecutive 33.33–66.66% and > 66.66% linguistic scores. Of note, the following parameters were inverted so that a higher score reflects a better performance: density of nouns referring to abstract events or actions, fillers, frequent nouns and lemma frequency. Positive odds ratios (> 1) reflect the likelihood for individuals with high amyloid burden to be in the lowest tertile indicating worse performance (reference: highest tertile). Significant odds ratios (95% confidence intervals) are marked with *. If interaction effects between amyloid*education were significant, odds ratios are additionally presented separately for low and high education levels. Model 1 is adjusted for age, sex, education. Model 2 is additionally adjusted for phonemic fluency. n.a.; not applicable.

that TTR becomes abnormal in later – symptomatic – stages. Former studies investigating transcribed speech found a reduced number of clauses per sentence and type-token ratio (TTR) in patients with AD or MCI compared to controls (Kemper et al., 1994; Roark et al., 2011). Others showed that lexical complexity, measured by text analyses of famous novelists, declined over time and coincided with a self-reported forgetfulness (Van Velzen et al., 2014). An explanation could be that novels are different than spontaneous speech in the sense that these are a result of elaborate manuscript drafting rather than an immediate reflection of spontaneous thought. In addition, it could be argued that novelists have a special linguistic talent, that will likely devolve in different ways from the average population. In the present study we found evidence for differential associations between high amyloid burden and specific words and lexical complexity among individuals with higher levels of education, which suggests that educational attainment influences speech deficits following amyloid pathology. The previous may also be explained by cognitive reserve (Stern, 2002), which indicates that individuals with higher education are able to tolerate greater levels of pathology while (relatively) maintaining cognitive function (Oh et al., 2018). At a high amyloid burden, more educated subjects may therefore perform as well as less educated subjects with low amyloid burden (https://www.ncbi.nlm.nih.gov/pubmed/29237798).

SCD is a heterogeneous label which could be caused by a myriad of factors other than preclinical AD, including mental illness or normal aging (Jonker et al., 2000). Of note, we deliberately adjusted for age, and individuals with a current psychiatric diagnosis (e.g. depression) were not included in our cohort. Reduced prosody and processing speed are usually affected by depression and normal aging respectively, (Alpert et al., 2001; Kemper et al., 2001; Manenti et al., 2004) but not the number of specific words. Therefore, it seems unlikely that associations between amyloid status and reduced number of specific words could be attributed to these factors. In addition, there were limited correlations between conventional neuropsychological language tests, age, education, and linguistic parameters, which indicates that linguistic parameters might measure different languages competencies.

Some limitations merit attention. First, the majority of our linguistic parameters were not associated with amyloid burden. Notwithstanding, in contrast to conventional neuropsychological language tests, we did find a relationship between amyloid load and several linguistic parameters within the domain of specific words, which suggests that at least one aspect of spontaneous speech could be affected in preclinical AD. Second, our study had a cross-sectional design. Therefore, we cannot make any inferences about whether a lower number of specific words is associated with actual clinical progression to symptomatic stages of AD. Future longitudinal studies should include repeated linguistic measures to investigate which parameter is mostly associated with disease progression while taking into account individuals' relatively variable starting positions. Third, we investigated SCD patients who visited a memory clinic and have not included individuals without SCD, which reduces the generalizability of our results to the general population. Our individuals with SCD did, however, have a comparable cognitive performance to peers based on extensive neuropsychological assessment, and evidenced by comparable conventional neuropsychological language test scores. In addition, individuals with SCD are a clinically relevant population because they often report language complaints and are at increased risk for clinical progression (Geerlings et al., 1999; Jessen et al., 2010; R.E. Slot et al., 2018a), particularly if they exhibit high levels of amyloid burden (Van Harten et al., 2013). Finally, the present analyses required transcription of speech to text by human transcribers because currently automatic speech-to-text-to is relatively inaccurate. Manual transcription and the need for specific linguistic software (including in-house developed scripts) may limit the clinical utility. However, we note that speech-to-text technology is improving fast, perhaps making fully automated speech-to-text transcription with high accuracy possible in the near future, allowing feasible (automated) speech-based analysis of language complexity.

In sum, in a memory clinic sample of individuals with SCD, we found associations between high amyloid burden and fewer specific words during spontaneous speech, particularly in those individuals with



(caption on next page)

Fig. 2. Panel A shows the Z-transformed median scores (with 95% confidence intervals) of the linguistic parameters and neuropsychological language tests for individuals with low and high amyloid burden (based on amyloid status yes/no). A higher linguistic parameter score reflects a better performance. * = $p < 0.05$ based on Mann-Whitney U tests. **Panel B** shows associations between amyloid load (quantitative amyloid PET or [18F]florbetapir BP_{ND}) and abstract nouns with an interaction effect for education. **Panel C** shows associations between amyloid load and D-level (i.e. syntactical complexity). **Panel D** shows a scatterplot with the association between amyloid load and content words, and **panel E** shows an interaction effect for education level between amyloid load and lemma frequency. Scatterplots in Panel B–E are displayed with mean confidence intervals. Of note, the following parameters were inverted so that a higher score reflects a better performance: density of nouns referring to abstract events or actions, fillers, frequent nouns and lemma frequency.

higher levels of education. Compared to conventional neuropsychological assessment, spontaneous speech recordings could be a promising way to reveal subtle AD-related language deficiencies which could foreshadow cognitive impairment.

Funding

Research of the VUmc Alzheimer center is part of the neurodegeneration research program of the Amsterdam Neuroscience. The VUmc Alzheimer Center is supported by Alzheimer Nederland and Stichting VUmc Fonds. Wiesje van der Flier is recipient of a research grant for the SCIENCe project from Gieske-Strijbis Fonds. Sander Verfaillie and Rosalinde Slot are supported by a research grant from Gieske-Strijbis Fonds. Sietske Sikkes is supported by grants from JPND and Zon-MW. [^{18}F]florbetapir PET scans were made possible by Avid Radiopharmeuticals Inc., a wholly owned subsidiary of Eli Lilly and Company (NYSE: LLY). [^{18}F]florbetaben PET scans were performed in the context of a research grant by Piramal Neuroimaging.

Conflicts of interest

SCJV, JW, RERS, IP, LEWV, NOS, MvdW, BNMvB report no disclosures. NDP serves on the advisory board of Boehringer Ingelheim and Probiodrug, and on the DSMB of Abbvie's M15–566 trial; has provided consultancy services for Sanofi, Takeda, and Kyowa Kirin Pharmaceutical Development; receives research support from Alzheimer Nederland (project number WE.03–2012-02); and is CEO and co-owner of the Alzheimer Research Center, Amsterdam, the Netherlands. PS has received grant support for the institution Alzheimer Center, VU University Medical Center from GE Healthcare and MERCK; has received speaker's fees paid to the institution Alzheimer Center, VU University Medical Center, from Lilly, GE Healthcare, and Roche; and serves as editor in chief of Alzheimer's Research and Therapy. SAMS provided consultancy services in the past 2 years for Nutricia and Takeda; all fees were paid to her institution. WMVdF has received research funding and speaker honorarium from Boehringer Ingelheim; research programs have been funded by ZonMW, NWO, EU-FP7, Alzheimer Nederland, CardioVasculair Onderzoek Nederland, stichting Dioraphte, Gieskes-Strijbis fonds, Boehringer Ingelheim, Piramal Neuroimaging, Roche BV, Janssen Stellar, and Combinostics; and all funding is paid to her institution.

Acknowledgements

We would like to acknowledge the participants of the SCIENCe cohort for dedicating their time and energy to help us collecting this data. We thank Richard Forsyth for kindly sharing the python implementation of the Needleman-Wunsch algorithm. Finally, we would like to thank the Van Gogh museum (Amsterdam, the Netherlands) for their permission to reprint "Tree Roots".

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2019.05.006.

References

Ahmed, S., Haigh, A.-M.F., de Jager, C.A., Garrard, P., 2013. Connected speech as a marker of disease progression in autopsy-proven Alzheimer's disease. Brain 136, 3727–3737 [Internet].

Almor, A., Kempler, D., MacDonald, M.C., Andersen, E.S., Tyler, L.K., May 1999. Why do Alzheimer patients have difficulty with pronouns? Working memory, semantics, and reference in comprehension and production in Alzheimer's disease. Brain Lang. 67 (3), 202–227.

Alpert, M., Pouget, E.R., Silva, R.R., 2001. Reflections of depression in acoustic measures of the patient's speech. J. Affect. Disord. 66, 59–69.

Amariglio, R.E., Becker, J.A., Carmasin, J., Wadsworth, L.P., Lorius, N., Sullivan, C., et al., 2012. Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. Neuropsychologia 50, 2880–2886.

Baker, J.E., Lim, Y.Y., Pietrzak, R.H., Hassenstab, J., Snyder, P.J., Masters, C.L., et al., 2017. Cognitive impairment and decline in cognitively normal older adults with high amyloid-β: a meta-analysis. Alzheimer's Dement. Diagn. Assess. Dis. Monit. 6, 108–121.

Bateman, R.J., Xiong, C., Benzinger, T.L.S., Fagan, A.M., Goate, A., Fox, N.C., et al., 2012. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N. Engl. J. Med. 367, 795–804.

Benjamini, Y., Yekutieli, D., 2001. The control of the false discovery rate in multiple testing under dependency by Yoav Benjamini 1 and Daniel Yekutieli 2. Ann. Stat. 29, 1165–1188.

Berisha, V., Wang, S., LaCross, A., Liss, J., 2015. Tracking discourse complexity preceding Alzheimer's disease diagnosis: a case study comparing the press conferences of presidents ronald reagan and George herbert walker bush. J. Alzheimer's Dis. 45, 959–963.

Boschi, V., Catricalà, E., Consonni, M., Chesi, C., Moro, A., Cappa, S.F., 2017. Connected speech in neurodegenerative language disorders: a review. Front. Psychol. 8.

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82, 239–259.

Covington, M. a., He, C., Brown, C., Naçi, L., Brown, J., 2006. How Complex Is that Sentence? A Proposed Revision of the Rosenberg and Abbeduto D-Level Scale. [Internet].

Emery, V.O., 2000. Language impairment in dementia of the Alzheimer type: a hierarchical decline? Int. J. Psychiatry Med. 30, 145–164.

Fraser, K.C., Meltzer, J.A., Rudzicz, F., 2015. Linguistic features identify Alzheimer's disease in narrative speech. J. Alzheimer's Dis. 49, 407–422.

Garrard, P., Maloney, L.M., Hodges, J.R., Patterson, K., 2005. The effects of very early Alzheimer's disease on the characteristics of writing by a renowned author. Brain 128, 250–260 [Internet].

Garrard, P., Haigh, A.M., de jager, C., 2011. Techniques for transcribers: assessing and improving consistency in transcripts of spoken language. Lit. Ling. Comput. 26, 389–405.

Gayraud, F., Lee, H., Barkat-Defradas, M., 2011. Syntactic and lexical context of pauses and hesitations in the discourse of Alzheimer patients and healthy elderly subjects. Clin. Linguist. Phon. 25, 198–209.

Geerlings, M.I., Jonker, C., Bouter, L.M., Adèr, H.J., Schmand, B., 1999. Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. Am. J. Psychiatry 156, 531–537.

Glosser, G., Deser, T., Jul 1992. A comparison of changes in macrolinguistic and microlinguistic aspects of discourse production in normal aging. J. Gerontol. 47 (4), P266–P272.

Golla, S.S.V., Verfaillie, S.C.J., Boellaard, R., Adriaanse, S.M., Zwan, M.D., Schuit, R.C., et al., Jun 2018. Quantification of [18F]florbetapir: a test – retest tracer kinetic modelling study. J. Cereb. Blood Flow Metab. https://doi.org/10.1177/0271678X18783628. 13:271678X18783628, epub ahead of print.

Grande, M., Meffert, E., Schoenberger, E., Jung, S., Frauenrath, T., Huber, W., et al., 2012. From a concept to a word in a syntactically complete sentence: an fMRI study on spontaneous language production in an overt picture description task. Neuroimage 61, 702–714.

Hammers, A., Allom, R., Koepp, M.J., Free, S.L., Myers, R., Lemieux, L., et al., 2003. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. Hum. Brain Mapp. 19, 224–247.

Indefrey, P., Levelt, W.J.M., Oct 12 2004. The spatial and temporal signatures of word production components. Cognition 2, 255. https://doi.org/10.3389/fpsyg.2011.00255.

Jack, C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., et al., Apr 2018. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimer's Dement. 14 (4), 535–562. https://doi.org/10.1016/j.jalz.2018.02.018.

Jessen, F., Wiese, B., Bachmann, C., Eifflaender-Gorfer, S., Haller, F., Kölsch, H., et al., 2010. Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. Arch. Gen. Psychiatr. 67,

414–422.
Jessen, F., Amariglio, R.E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., et al., 2014. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimer's Dement. 1–9.
Jonker, C., Geerlings, M.I., Schmand, B., 2000. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int. J. Geriatr. Psychiatry 15, 983–991.
Kemper, S., Anagnopoulos, C., Lyons, K., Heberlein, W., 1994. Speech accommodations to dementia. J. Gerontol. 49, P223–P229 [Internet].
Kemper, S., Marquis, J., Thompson, M., Marquis, J., 2001. Longitudinal change in language production: effects of aging and dementia on grammatical complexity and propositional content. Psychol. Aging 16, 600–614.
Kempler, D., 1995. Language changes in dementia of the Alzheimer's type. Dement. Commun. Res. Clin. Implica 98–114.
Kraf, R., Maat, H.P., Cito, D., 2009. Leesbaarheidsonderzoek: oude problemen, nieuwe kansen. [Internet] Tijdschr. Taalbeheers. 31, 97–123. Available from: papers://53a564bf-cd27-4bf5-aaf7-76e13e37c82d/Paper/p35.
Lammertsma, A.A., Hume, S.P., 1996. Simplified reference tissue model for PET receptor studies. Neuroimage 4, 153–158.
Maat, H.P., Kraf, R., Van Den Bosch, A., Dekker, N., Van Gompel, M., Kleijn, S., et al., T-Scan, 2014. A new tool for analyzing Dutch text. In: Computational Linguistics in the Netherlands Journal, pp. 53–74.
Manenti, R., Repetto, C., Bentrovato, S., Marcone, A., Bates, E., Cappa, S.F., 2004. The effects of ageing and Alzheimer's disease on semantic and gender priming. Brain 127, 2299–2306.
Marini, A., Boewe, A., Caltagirone, C., Carlomagno, S., Sep 2005. Age-related differences in the production of textual descriptions. J. Psycholinguist. Res. 34 (5), 439–463.
Martin, W., Maks, I., 2005. Referentiebestand Nederlands - Documentatie. pp. 108.
McCowan, I., Moore, D., Dines, J., 2005. On the Use of Information Retrieval Measures for Speech Recognition Evaluation. IDIAP Institut Dalle.
Mesulam, M.-M., 1990. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann. Neurol. 28, 597–613.
Molinuevo, J.L., Rabin, L.A., Amariglio, R., Buckley, R., Dubois, B., Ellis, K.A., et al., 2017. Implementation of subjective cognitive decline criteria in research studies. Alzheimer's Dement. 13, 296–311.
Mulder, C., Verwey, N a, van der Flier, W.M., Bouwman, F.H., Kok, A., van Elk, E.J., et al., 2010. Amyloid-beta(1-42), total tau, and phosphorylated tau as cerebrospinal fluid biomarkers for the diagnosis of Alzheimer disease. Clin. Chem. 56, 248–253.
Oh, H., Razlighi, Q.R., Stern, Y., Jan 16 2018. Multiple pathways of reserve simultaneously present in cognitively normal older adults. Neurology 90 (3), e197–e205. https://doi.org/10.1212/WNL.0000000000004829.
Papp, K.V., Mormino, E.C., Amariglio, R.E., Munro, C., Dagley, A., Schultz, A.P., et al., 2015. Biomarker validation of a decline in semantic processing in preclinical Alzheimer's disease. Neuropsychology 30, 624–630.
Perrotin, A., La Joie, R., de La Sayette, V., Barré, L., Mézenge, F., Mutlu, J., et al., May 2016. Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: differential affective and imaging correlates. Alzheimer's Dement. 13 (5), 550–560. https://doi.org/10.1016/j.jalz.2016.08.011.
Prins, R., Bastiaanse, R., 2004. Analysing the spontaneous speech of aphasic speakers. Aphasiology 18, 1075–1091.
Roark, B., Mitchell, M., Hosom, J.P., Hollingshead, K., Kaye, J., 2011. Spoken language derived measures for detecting mild cognitive impairment. IEEE Trans. Audio Speech Lang. Process. 19, 2081–2090.
Rohrer, J.D., Knight, W.D., Warren, J.E., Fox, N.C., Rossor, M.N., Warren, J.D., Jan 2008. Word-finding difficulty: a clinical analysis of the progressive aphasias. Brain 131 (Pt 1), 8–38 Epub 2007 Oct 18.
Scheltens, P., Blennow, K., Breteler, M.M.B., de Strooper, B., Frisoni, G.B., Salloway, S., et al., 2016. Alzheimer's disease. [Internet] Lancet (London, England) 6736, 1–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26921134.
Slot, R.E., Sikkes, S.A., Berkhof, J., Brodaty, H., Buckley, R., 2018a. Subjective cognitive decline and rates of incident Alzheimer's disease and non-Alzheimer's disease dementia. [Internet] Alzheimer's Dement. 1–12. Available from: https://doi.org/10.1016/j.jalz.2018.10.003.
Slot, R.E., Verfaillie, S.C., Overbeek, J.M., Timmers, T., Wesselman LM, P., Teunissen, C.E., et al., 2018b. Subjective cognitive impairment cohort (SCIENCe): study design and first results. [internet] Alzheimer's Res. Ther. 1–13 Available from: https://doi.org/10.1186/s13195-018-0390-y.
Snitz, B.E., Weissfeld, L.A., Cohen, A.D., Lopez, O.L., Nebes, R.D., Aizenstein, H.J., et al., 2015. Subjective cognitive complaints, personality and brain amyloid-beta in cognitively normal older adults. Am. J. Geriatr. Psychiatry 23, 985–993.
Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., et al., 2011. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 7, 280–292.
Stern, Y., Mar 2002. What is cognitive reserve? Theory and research application of the reserve concept. J. Int. Neuropsychol. Soc. 8 (3), 448–460.
Svarer, C., Madsen, K., Hasselbalch, S.G., Pinborg, L.H., Haugbøl, S., Frøkjær, V.G., et al., 2005. MR-based automatic delineation of volumes of interest in human brain PET images using probability maps. Neuroimage 24, 969–979.
Tijms, B.M., Willemse, E.A.J., Zwan, M.D., Mulder, S.D., Visser, P.J., van Berckel, B.N.M., et al., Mar 2017. Unbiased approach to counteract upward drift in cerebrospinal fluid amyloid-β 1-42 analysis results. [Internet]. Clin. Chem. 64 (3), 576–585. https://doi.org/10.1373/clinchem.2017.281055. clinchem.2017.281055, Epub 2017 Dec 5.
Van Der Flier, W.M., Pijnenburg, Y.A.L., Prins, N., Lemstra, A.W., Bouwman, F.H., Teunissen, C.E., et al., 2014. Optimizing patient care and research: the Amsterdam dementia cohort. J. Alzheimer's Dis. 41, 313–327.
Van Harten, A.C., Visser, P.J., Pijnenburg, Y.A.L., Teunissen, C.E., Blankenstein, M.A., Scheltens, P., et al., 2013. Cerebrospinal fluid Ab42 is the best predictor of clinical progression in patients with subjective complaints. Alzheimer's Dement. 9, 481–487.
van Velzen, M., Garrard, P., 2013. From hindsight to insight – retrospective analysis of language written by a renowned Alzheimer's patient. Interdiscip. Sci. Rev. 33, 278–286 [Internet].
Van Velzen, M.H., Nanetti, L., De Deyn, P.P., 2014. Data modelling in corpus linguistics: how low may we go? Cortex 55, 192–201.
Verfaillie, S.C.J., Slot, R.E., Tijms, B.M., Bouwman, F., Benedictus, M.R., Overbeek, J.M., et al., Jan 2017. Thinner cortex in patients with subjective cognitive decline is associated with steeper decline of memory. Neurobiol. Aging 61, 238–244. https://doi.org/10.1016/j.neurobiolaging.2017.09.009. Epub 2017 Sep 20.
Verfaillie, S.C.J., Slot, R.E.R., Dicks, E., Prins, N.D., Overbeek, J.M., Teunissen, C.E., et al., Aug 2018. A more randomly organized grey matter network is associated with deteriorating language and global cognition in individuals with subjective cognitive decline. Hum. Brain Mapp. 39 (8), 3143–3151. https://doi.org/10.1002/hbm.24065. Epub 2018 Mar 30.
Verfaillie, S.C.J., Timmers, T., Slot, R.E.R., van der Weijden, C.W.J., Wesselman, L.M.P., Prins, N.D., et al., 2019. Amyloid-β load is related to worries, but not to severity of cognitive complaints in individuals with subjective cognitive decline: the SCIENCe project. Front. Aging Neurosci.
Verhage, F., 1965. Intelligence and age in a Dutch sample. Hum. Dev. 8, 238–245.
Villeneuve, S., Rabinovici, G.D., Cohn-Sheehy, B.I., Madison, C., Ayakta, N., Ghosh, P.M., et al., 2015. Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: Statistical and pathological evaluation. Brain 138, 2020–2033.
Wilson, B., Petkov, C.I., 2011. Communication and the primate brain: insights from neuroimaging studies in humans, chimpanzees and macaques. Hum. Biol. 83, 175–189 [Internet].