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Verfaillie, S.C.J.

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CHAPTER 8

Amyloid accumulation is associated with fewer specific words during spontaneous speech in subjective cognitive decline

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

submitted

"Language is a process of free creation; its laws and principles are fixed, but the manner in which the principles of generation are used is free and infinitely varied."(N. Chomsky)

ABSTRACT

Background. Individuals with subjective cognitive decline (SCD) often experience word-finding problems, which could be indicative of Alzheimer's Disease (AD) and underlying amyloid-β pathology. Our aim was to investigate whether amyloid-β is associated with semantic complexity in spontaneous speech.

Methods. We included 63 individuals with SCD (age 64±8, MMSE 29±1) with available amyloid status (PET scans n=59, Aβ1-42 CSF n=4) and spontaneous speech recordings. Spontaneous speech was recorded using three open-ended tasks (description of cookie theft picture, abstract painting and a regular Sunday) and linguistic parameters were extracted using T-scan computational software. For specific words, we used: content words, frequent, concrete and abstract nouns, and fillers. For lexical diversity, we used: lemma frequency, Type-Token-Ratio. For syntactic complexity, we used the Developmental Level scale (D-level). In addition, we performed Boston naming test, phonemic and category fluency.

Results. Nineteen individuals had abnormal amyloid-β accumulation. We found no group differences on language tests (all $p>0.05$). When analyzing spontaneous speech using multinomial regression (all linguistic parameters in tertiles), amyloid-β was 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). For abstract nouns, we found an interaction between amyloid-β and education ($p<0.05$), showing that highly educated individuals with abnormal amyloid-β used more abstract nouns than those with a lower education (OR_{lowest}: 48.5(2.7-868.4)). We did not find any associations between amyloid and fillers, lexical diversity or syntactic complexity.

Discussion. Abnormal amyloid-β accumulation was associated with fewer specific words, suggesting that subtle changes in spontaneous speech occur very early in the AD continuum.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease related to amyloid plaques and neurofibrillary tangles, which start to aggregate 10-20 years before the onset of dementia.[1–3] AD is characterized by gradual deterioration in various cognitive domains, including language.[4] In spontaneous speech, the degree of lexical diversity (e.g. vocabulary variation) and content words are impaired in AD.[5–11] 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.[12]

Subjective cognitive decline (SCD) can be caused by various conditions, such as preclinical AD which is defined as abnormal amyloid accumulation but normal cognition.[13–18] Individuals with SCD often experience word-finding problems, but these self-perceived deficits are difficult to objectify 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 diversity in spontaneous speech and written output as early signs of AD up till decades before clinical symptoms became manifest.[12,19–21]

It is currently unknown whether deficits in spontaneous speech could reveal subtle decline in language, even in absence of impairment on conventional neuropsychological testing. In the current study, we investigated whether altered use of specific words, lexical diversity or syntactic complexity, derived from spontaneous speech, are associated with amyloid accumulation in individuals with SCD. Based on the existing literature we expected that individuals with abnormal amyloid will use *fewer* specific words and display *less* lexical diversity.

METHODS

Participants. We included 63 individuals with SCD and known amyloid status from the ongoing Subjective Cognitive ImpairmeNt Cohort (SCIENCe). 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.[22] Prior to SCIENCe enrollment, all patients underwent a standardized dementia screening according to the procedures of the Amsterdam Dementia Cohort.[23] 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).[16,24] Amyloid positron emission tomography (PET) scans and lumbar puncture were offered as part of research. 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 minutes), and Boston naming test- short version. The medical ethics committee of the VU University Medical Center approved the study. All patients provided written informed consent.

Linguistic parameters. Spontaneous speech was recorded using three open-ended questions: Could you provide descriptions of; 1) the cookie theft picture, 2) an abstract painting (Figure 1; Van Gogh "Tree roots", 1890, https://www.vangoghmuseum.nl/en/collection/s0195V1962) and 3) "describe your regular Sunday". 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 one meter 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/), and subsequently linguistic parameters were extracted using the computational linguistics package software package T-scan.[25,26] T-Scan is a fully automated software package for analyzing 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.[27] We extracted eight parameters that reflect three language characteristics impaired in AD[5–7]; i. specific words, ii. lexical diversity and iii. syntactic complexity. For specific words, we extracted the following parameters: 1) content words (ratio nouns/ pronouns; lower values reflect a lower proportion of content words), 2) frequent nouns (top1000 most frequent nouns for adult language use; higher frequency reflects higher proportion of common words), 3) density (i.e. 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). For lexical diversity, we extracted the following parameters: 5) lemma frequency (number of unique words which can be found in a dictionary irrespective of affixes; lower values reflect a lower number of unique words), 6) 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 a lower information density). For syntactic complexity, we used 7) 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).[28] The following words were considered content words: nouns, names, adjectives, adverb, verbs (no link or auxiliary verbs). In addition, we used in-house developed python scripts to extract the number of predefined fillers (e.g. ehm, uhm, uhh), all transcribed in a similar fashion (i.e. uhm). The following parameters were inverted so that a higher score reflects a better performance: density of nouns referring to abstract events or actions, fillers, and frequent nouns. 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.[29] 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 statistics and as 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.[30] This analysis showed a high inter-rater reliability (F_1 score= 0.84).[31]

Amyloid. PET and CSF were used to define preclinical AD,[18] and if both were available, we determined amyloid status based on amyloid PET. Amyloid status (yes/no) was determined based on visual reading of amyloid PET scans (n=59), or cerebrospinal fluid (CSF) Aβ1-42 (n=4) (<1 year of speech recording date). All participants were invited to undergo an additional amyloid PET Positron Emission Tomography (PET) scan, with either [^{18}F]florbetapir (Amyvid; n=52) or [^{18}F]florbetaben (Neuraceg; n=7) radiotracers.[32,33] For florbetapir, 90 minutes 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 370MBq [^{18}F]florbetapir. For [^{18}F]florbetaben, 20 minutes static acquisitions (PET/MR, Philips Medical Systems, Best, The Netherlands) were collected 90 minutes after a bolus injection of approximately 250MBq [^{18}F]florbetaben. All standardized uptake value (SUV) ([^{18}F]florbetapir 50-70 minutes and [^{18}F]florbetaben 90-110 minutes post-injection) PET scans were visually inspected by an experienced nuclear medicine physician (BvB). During the standardized screening lumbar puncture was performed, and CSF Aβ1-42 was measured using ELISA (Innogenetics-Fujirebio, Ghent, Belgium) at the Neurochemistry Laboratory.[34] Our center cut-off for CSF Aβ1-42 indicating AD pathology is <813 ug/L.[35]

Quantitative image analysis. Dynamic [^{18}F]florbetapir PET scans (n=52) allowed the quantification of specific tracer binding to amyloid using parametric images.[36,37] Images were acquired in dynamic mode with a matrix size of 128x128x90 dimensions (2x2x2 mm^3), and 22 frames were reconstructed using 3D-RAMLA. PET images were corrected

for attenuation, scatter, random, decay and dead time. 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.[38,39] 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, while using cerebellum gray matter as a reference region. Finally, we calculated volume-weighted mean cortical amyloid load.

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

Demographic/ clinical data	**No preclinical AD (n=43)**		**Preclinical AD (n=19)**	
Age	61.5	(7.4)	68.2	(8.1)
Education (range 1-7)[40]	5.6	(1.4)	5.7	(.92)
Sex distribution (n males [%])	25	(61%)	11	(55%)
MMSE	28.7	(1.4)	28.6	(1.19)
Language complaints (n "yes" [%])[1]	34	(31%)	18	(44%)
Phonemic fluency – D-A-T (average 3 trials)	13.2	(4.0)	13.3	(2.7)
Category fluency – animals	24.2	(5.7)	23.6	(4.7)
Boston naming test (short version)	79.1	(10.3)	82.0	(3.3)
Text characteristics				
Average word length	5.09	(0.69)	5.29	(1.08)
Sentences	55.07	(11.82)	53.37	(12.17)
Specific words	% proportion lowest/middle/highest tertiles			
Content words (ratio nouns/ pronouns)	30/26/44		40/50/10	
Concrete nouns	21/42/37		60/15/25	
Abstract nouns	21/19/61		50/10/40	
Conversation fillers	35/35/30		40/30/30	
Lexical diversity				
1000 most frequent nouns	30/37/33		40/30/30	
Lemma (frequency)	35/37/28		30/25/40	
Type Token Ratio	37/26/37		25/50/25	
Syntactic complexity				
D-level	40/33/28		20/35/45	

Data are presented as mean (SD) or n (%). Linguistic are presented as % tertiles per group. [1], 12 cases missing

Statistics. Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS, IBM v22). To investigate differences in demographics between subjects with and without abnormal amyloid accumulation, we used χ2-tests for discrete variables, and analyses of variance (ANOVA) for continuous data. Because linguistic variables remained non-normal distributed after Log- and Z-transformations, we ranked them into tertiles (lowest/middle/highest). To allow comparison between different outcome measures, we also transformed neuropsychological 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, sex, and education (median split [low/high]) (model 1).[40] As language ability is inherently connected with educational attainment, we additionally tested for education*amyloid 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 additionally adjusted for phonemic fluency (model 2).[41] We report Odds ratios (OR) with corresponding 95% confidence intervals (CI). Positive OR (>1) reflect the likelihood for individuals with abnormal amyloid to have worse language performance (reference: highest tertile). Finally, to investigate whether quantitative amyloid load is associated with spontaneous speech, we performed linear regression analyses between mean cortical amyloid load (independent variable, continuous) and linguistic parameters (dependent variables in tertiles, separate models). Analyses were adjusted for age, sex, education. Additionally, interaction effects between education and amyloid status were tested.

Figure 1. Painting "Tree Roots" by Vincent van Gogh (1853-1890), Auvers-sur-Oise, July1890 oil painting on canvas, 50.3 cm x 100.1 cm, which was used as one of the stimuli for speech recordings. Van Gogh Museum, Amsterdam, The Netherlands (Vincent van Gogh Stichting). Reprinted with permission of the Van Gogh museum, (https://www.vangoghmuseum.nl/en/collection/s0195V1962)

Table 2. Amyloid positivity in association with linguistic parameters and neuropsychological tests

Linguistic parameters				
	Model 1		**Model 2**	
Specific words	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)*
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	2.9 (0.4-21.1)	4.0 (1.0-16.0)	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 diversity				
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	2.1 (0.3-12.5)	0.9 (0.2-4.6)	2.2 (0.4-13.3)	1.1 (0.2-6.1)
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. Positive odds ratios (>1) reflect the likelihood for individuals with abnormal amyloid 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.

RESULTS

Demographic, clinical and linguistic data are presented in Table 1. Nineteen (30%) out of sixty-three individuals with SCD had evidence for abnormal amyloid accumulation, and those individuals were older ($F(61,1)=17.67$, $p<0.000$: normal amyloid levels (age)=61.5, abnormal amyloid=68.2). Sex and education levels, MMSE and conventional neuropsychological language tests, including Boston naming test, category fluency and phonemic fluency did not differ between groups (all $p<0.05$).

Table 2 shows amyloid positivity 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. When we analysed spontaneous speech, individuals with abnormal amyloid 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 abnormal amyloid and higher levels of 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 diversity (i.e. top 1000 most frequent nouns, lemma frequency and TTR). These results remained essentially unchanged after additional adjustment for phonemic fluency (Table 2; model 2).

To explore whether spontaneous speech is associated with quantitative cortical amyloid load, we performed linear regression analyses between amyloid load and conventional language tests and linguistic parameters (Figure 2). We did not find any associations between amyloid load and conventional neuropsychological language tests. Linear regression analyses confirmed negative associations between amyloid load and content words (beta= -0.54, p=0.003) and abstract nouns (beta= -0.69, p=0.004). In addition, we found that higher amyloid load was associated with increased syntactic complexity (beta=0.48, p=0.008). Finally, there was a significant interaction between education and amyloid for lemma frequency. Subsequent stratification for education showed that increased amyloid load was associated with lower lemma frequency for individuals with higher levels of education (beta= -0.63, p=0.013), but not for those with lower education.

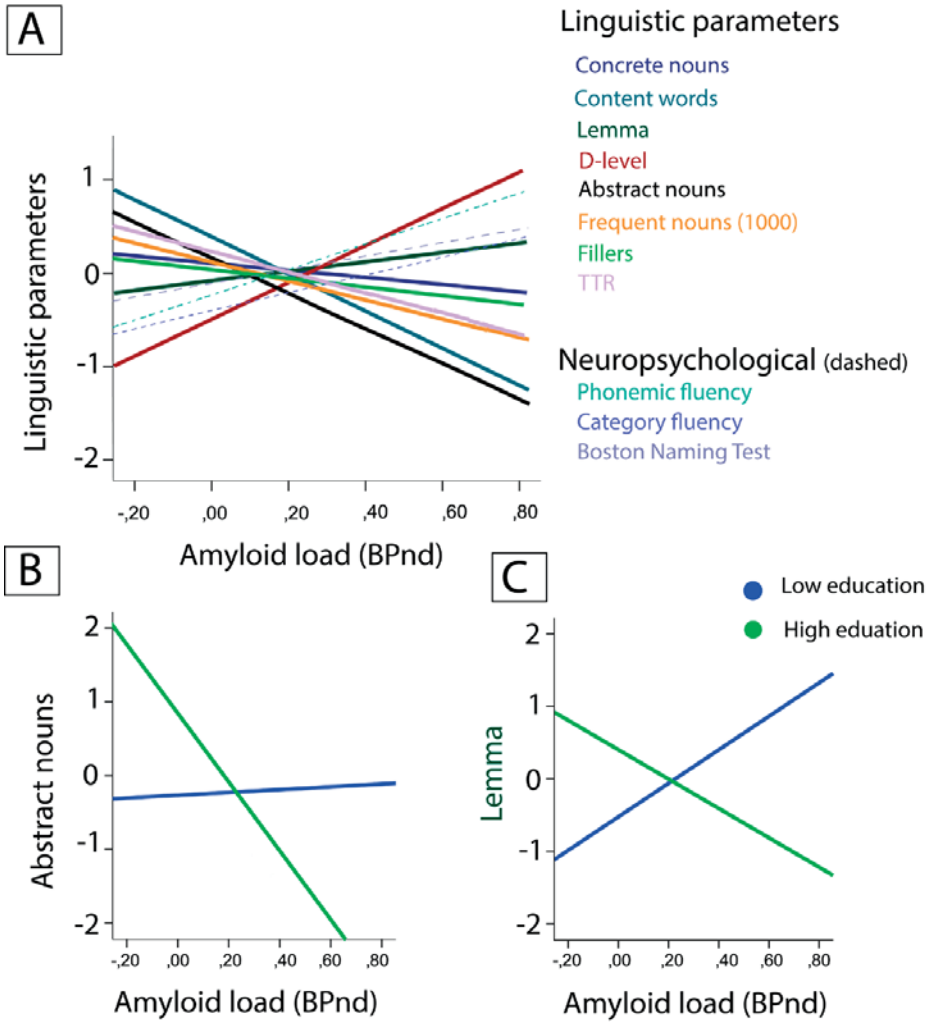

Figure 2. Associations between mean amyloid load (BP_{nd}) and linguistic parameters and conventional neuropsychological language tests. Panel A shows the effects between amyloid load and concrete nouns (beta= -0.09, p=0.56), content words (beta= -0.31, p=0.03), Lemma (beta= 0.05, p=0.74), D-level (beta=0.10), abstract nouns (beta= -0.28, p=0.05), 1000 most frequent nouns (beta = -0.21, p=0.19), fillers (beta= -0.09, p=0.55), TTR (beta= -0.19, p=0.20), phonemic fluency (beta= 0.21, p=0.17), category fluency (beta= 0.16, p=0.26) and Boston naming test (beta=0.11, p=0.46). Panel B shows an interaction effect for education between abstract nouns and amyloid load (p=0.004: high education beta= -0.69; low education beta= 0.03), and panel C shows an interaction effect for education between lemma (p=0.01: high education beta= -0.35; low education beta= 0.33) and amyloid load. Negative values reflect worse performance, higher binding potential (BP_{nd}) reflects more amyloid load. Effects were plotted using standardized residuals (std res) for each variable (adjusted for age, sex, and education) with a fitted linear line.

DISCUSSION

The main finding of the present study is that abnormal amyloid accumulation in SCD was associated with the use of fewer specific words, but not with lexical diversity or syntactic complexity, or conventional language test performance, particularly in those individuals with higher levels of education.

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.[13–17] In keeping with prior results,[42] we did not find associations between abnormal amyloid accumulation 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. Spontaneous speech is a complex source of information encompassing of various hierarchical levels of language organization. For this reason, it is conceivable that spontaneous speech, at some organization level, could be affected by early pathophysiological processes. In the present study we investigated three semantic characteristics of spontaneous speech: specific words, lexical diversity and syntactic complexity.

Others have shown that compared to controls, patients with AD dementia show reduced lexical diversity and use fewer specific words.[5–9,11] It is not yet clear whether changes in spontaneous speech are related to abnormal amyloid accumulation in individuals with SCD (i.e. preclinical AD).[18] 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.[12] A substantial part of our SCD sample had abnormal amyloid accumulation as evidenced by PET or CSF,[43] and we predominantly found associations between amyloid status and linguistic parameters within the domain of specific words. More specifically, we observed that individuals with abnormal amyloid accumulation 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 abnormal amyloid accumulation, while these have been reported in an earlier case study.[12] One explanation could be that conversation fillers in preclinical stages are relatively subtle. On the other hand, we found that increased quantitative amyloid load was associated with higher syntactic complexity, and increased use of abstract nouns particularly in individuals with higher levels of education. The previous suggests that language may indeed become more vague in relation to abnormal amyloid accumulation. A potential explanation could be that individuals with SCD and

underlying AD pathology may compensate for their self-perceived decline which could result in more syntactically complex sentences and abstract nouns (e.g. circumlocution).

Contrary to our expectations, we did not find any association between amyloid status and measures of lexical diversity. 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.[5,8] Our study is the first to focus on spontaneous speech in cognitively normal individuals with SCD, and one explanation is that TTR becomes abnormal in later – symptomatic – stages. Others showed that lexical diversity, measured by text analyses of famous novelists, declined over time and coincided with a self-reported forgetfulness.[21] 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 abnormal amyloid and specific words and lexical diversity among individuals with higher levels of education, which suggests that educational attainment influences speech deficits following amyloid pathology.

SCD is a heterogeneous label which could be caused by a myriad of factors other than preclinical AD, including mental illness or normal aging.[44] 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,[4,7,45] 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.

Whilst spontaneous speech recordings could be a promising way to reveal subtle AD-related language deficits some limitations merit attention. First, the majority of our linguistic parameters were not associated with amyloid, or showed opposite effects (i.e. D-level). Notwithstanding, we did find a relationship between amyloid 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, we investigated SCD patients who visited a memory clinic, which reduces the generalizability of our results to the general population. Individuals with SCD are, however, a clinically relevant population since they seek help for their complaints and are at increased risk for clinical progression.[17,46] Our results indicate that subtle language deficits in this group could be indicative of underlying preclinical AD. Third, 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. Notwithstanding, amyloid status was determined using state-of-the-art (imaging) techniques, and baseline abnormal amyloid was previously found to be associated with six to nine-fold increased risk of clinical progression to AD in SCD.[47]

In sum, in a memory clinic sample of individuals with SCD, we found associations between abnormal amyloid accumulation and fewer specific words during spontaneous speech, particularly in those individuals with 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 precede cognitive impairment.

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