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Seija Pekkala

Debra Wiener

Jayandra Himali

Alexa Beiser

Loraine Obler
CUNY Graduate Center

See next page for additional authors

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Lexical retrieval in discourse: An early indicator of Alzheimer's dementia

SEIJA PEKKALA[1], DEBRA WIENER[2], JAYANDRA J. HIMALI[3,4,5], ALEXA S. BEISER[3,4,5], LORAINE K. OBLER[3,6,7], YULIN LIU[4], ANN McKEE[3,7], SANFORD AUERBACH[3,4], SUDHA SESHADRI[3,4], PHILIP A. WOLF[4,8], & RHODA AU[3,4]

[1]*Institute of Behavioural Sciences, University of Helsinki, Helsinki, Finland,* [2]*The Bromfield School, Harvard, MA, USA,* [3]*Department of Neurology, Boston University School of Medicine, Boston, MA, USA,* [4]*The Framingham Heart Study, Framingham, MA, USA,* [5]*Boston University School of Public Health, Department of Biostatistics, Boston, MA, USA,* [6]*Program in Speech-Language-Hearing Sciences, City University of New York Graduate Center, NY, USA,* [7]*VA Boston Health Care System, Boston, MA, USA, and* [8]*Department of Neurology, Medicine & Public Health, Boston University School of Medicine, Boston, MA, USA*

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Abstract
We examined the progression of lexical-retrieval deficits in individuals with neuropathologically determined Alzheimer's disease (AD; $n = 23$) and a comparison group without criteria for AD ($n = 24$) to determine whether linguistic changes were a significant marker of the disease. Our participants underwent multiple administrations of a neuropsychological battery, with initial administration occurring on average 16 years prior to death. The battery included the Boston Naming Test (BNT), a letter fluency task (FAS) and written description of the Cookie Theft Picture (CTP). Repeated measures analysis revealed that the AD-group showed progressively greater decline in FAS and CTP lexical performance than the comparison group. Cross-sectional time-specific group comparisons indicated that the CTP differentiated performance between the two groups at 7–9 years prior to death and FAS and BNT only at 2–4 years. These results suggest that lexical-retrieval deficits in written discourse serve as an early indicator of AD.

Keywords: Alzheimer's disease, discourse, early markers, naming, neuropathology

Introduction

Although some cognitive functions, such as episodic memory and visuo-spatial skills, decline in older age (e.g. Small, Fratiglioni, von Strauss, & Bäckman, 2003), language abilities remain relatively stable among older adults (e.g. Cruise, Worrall, & Hickson, 2000; Small, Stern, Tang, & Mayeux, 1999). Verbal knowledge (Singer, Verhaegen, Ghisletta, Lindenberger, & Baltes, 2003) and vocabulary (Rabbitt et al., 2004), in particular, have been found resistant to the effects of

Correspondence: Seija Pekkala, PhD, Institute of Behavioural Sciences, University of Helsinki, POB 9 (Siltavuorenpenger 3 A), 00014, Finland. Tel: +358 9 191 29676. E-mail: seija.pekkala@helsinki.fi

cognitive aging. Nevertheless, there is evidence showing that language changes, most commonly involving a decline in lexical retrieval, do take place in healthy aging (e.g. Au et al., 1995; Connor, Spiro, Obler, & Albert, 2004; Goral, Spiro, Albert, Obler, & Connor, 2007).

According to the National Institute on Aging's recently revised criteria for dementia, impaired language functions, including difficulties in speaking, reading and writing, are among the core clinical criteria of Alzheimer's disease (AD; McKhann et al., 2011). The presence of language impairment is evident in the symptomatic prodromal phase of AD, as well. These earliest stages have been labeled ''preclinical'' (Clark et al., 2009; Jacobs et al., 1995; Mickes et al., 2007; Saxton et al., 2004), ''incipient'' (Rubin et al., 1998), ''minimal'' (Forbes, Shanks, & Venneri, 2004) or ''mild cognitive impairment'' (MCI; Albert et al., 2011; Levinoff et al., 2006; Petersen et al., 1999; Östberg, Fernaeus, Hellström, Bogdanović, & Wahlund, 2005).

Among the language impairments seen in AD, as in healthy aging, are lexical retrieval problems. Cross-sectional (Levinoff et al., 2006) as well as longitudinal (Jacobs et al., 1995; Rubin et al., 1998) studies have demonstrated that confrontation naming performance measured by the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) was significantly worse among even those individuals who had MCI, than among matched healthy controls. Individuals who develop AD have demonstrated lexical retrieval deficits on a confrontation naming task 2–3 years prior to diagnosis (Chen et al., 2001; Mickes et al., 2007), as well as exhibiting a steady decline in confrontation naming ability during the progression of the disease once diagnosed (Locascio, Growdon, & Corkin, 1995; Salmon, Heindel, & Lange, 1999).

Word production is a high-speed, fairly automatic and errorless process. In normal speech, about two to five words per second are retrieved from the mental lexicon (Levelt, 1989; Levelt, Roelofs, & Meyer, 1999). Spoken word production can be approached from several perspectives that have their roots in different research traditions (for a review, see Laine & Martin, 2006). According to two current models, the discrete two-stage word production model (Levelt, 1999, 2001; Levelt et al., 1999) and the interactive connectionist model (Dell, 1986; Dell & O'Seaghda, 1992; Foygel & Dell, 2000), when a speaker visually perceives a target (e.g. an object or a picture of an object) in a confrontation naming test, the percept activates the corresponding conceptual-semantic information, the lemma consisting of conceptual-semantic and syntactic information of the target word, and the morpho-phonological form of the word before the phonetic plan of the word is formed and articulated. The models differ in the architecture of conceptual-semantic representation (i.e. non-decomposed nodes versus decomposed semantic features) and the direction and extent of spreading of activation within and between different levels of processing (i.e. unidirectional vs. interactive spread of activation).

In healthy elderly people, the lexical-retrieval difficulties have been taken to reflect weakening of the connections between the semantic and phonological levels of the mental lexicon, resulting in an omission or an instance in which a speaker does not find the phonological form for the target word (a tip-of-the-tongue state) or produces a phonologically related word-substitution error (Burke & Shafto, 2004). In AD, by contrast, as we detail below, the lexical-retrieval difficulties have been attributed primarily to impaired functioning at the semantic level of the mental lexicon. Typical word errors in a confrontation naming task are semantically related errors, such as superordinate category labels and category co-ordinates (Balthazar, Cendes, Pereira Damasceno, 2008; Bayles & Tomoeda, 1983; Martin & Fedio, 1983; Moreaud, David, Charnallet, & Pellat, 2001), descriptions of the target (Balthazar et al., 2008; Moreaud et al., 2001; Obler & Albert, 1981; Robinson, Grossman, White-Devine, & D'Esposito, 1996; White-Devine et al., 1996), as well as omissions and ''don't know'' responses (Robinson et al., 1996; White-Devine et al., 1996; Williamson, Adair, Raymer, & Heilman, 1998). As the disease advances, the error rate keeps increasing and unrelated words, non-words and utterances with empty syntax are produced (Bayles, Tomoeda, & Trosset, 1990; Obler & Albert, 1981; White-Devine et al., 1996).

Phonologically related errors may emerge but usually not until later in the course of the disease (Croot, Hodges, Xuereb, & Patterson, 2000; Williamson et al., 1998).

A number of word characteristics enter into determining the ease of lexical retrieval. Normal healthy elderly tend to name high- and low-frequency words relatively equally, whereas AD patients' accuracy of naming low-frequency words is remarkably affected (Kim & Thompson, 2001; Kirshner, Webb, & Kelly, 1984). Other factors, such as familiarity of the to-be-named target, as well as imageability and typicality, have also been shown to affect naming performance both among elderly and people with AD, with the higher familiarity, imageability, and category typicality corresponding to more accurate naming (Bird, Howard, & Franklin, 2000; Bird, Lambon Ralph, Patterson, & Hodges, 2000; Gainotti, Di Betta, & Silveri, 1996). The naming ability of AD patients may also be affected by word length, with shorter words better retrieved (Kirshner et al., 1984); as well, they do better naming nonliving items relative to living items (Almor et al., 2009; Silveri, Daniele, Giustolisi, & Gainotti, 1991; Whatmough et al., 2003). Additionally, it has been reported that syntactic features of a word can play a role in word production, however these results are controversial. According to some studies, naming of nouns is more difficult than naming of verbs (Bowles, Obler, & Albert, 1987; Cappa et al., 1998; Fung et al., 2001; Williamson et al., 1998), while verb superiority over nouns has been reported in other studies (Almor et al., 2009; Kim & Thompson, 2001; Masterson et al., 2007; Robinson et al., 1996; White-Devine et al., 1996).

Studies using different imaging techniques have indicated that impaired word retrieval in AD is associated predominantly with abnormalities in left temporal cortex which is known to be involved in semantic processing (Hirono et al., 2001; Melrose et al., 2009; Teipel et al., 2006). Behavioral studies have suggested that a breakdown or loss of semantic information (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006; Chertkow & Bub, 1990; Gainotti et al., 1996; Garrard, Lambon Ralph, Patterson, Pratt, & Hodges, 2005; Hodges, Salmon, & Butters, 1992; Martin & Fedio, 1983), difficulty in accessing semantic information (Smith, Murdoch, & Chenery, 1989) or a combination of the two (Balthazar et al., 2008; Chertkow & Bub, 1990; Kirshner et al., 1984; Martin & Fedio, 1983; White-Devine et al., 1996) underlie word retrieval problems in AD. Word retrieval problems can also arise as a consequence of a difficulty in interaction between the semantic and lexical level (lemma retrieval; Chertkow & Bub, 1990; Kirshner et al., 1984; Masterson et al., 2007; Moreaud et al., 2001) and impaired phonological processing (Croot et al., 2000; Williamson et al., 1998). Additionally, impaired attention, executive functions and working memory (Rogers, Ivanoio, Patterson, & Hodges, 2006), as well as impaired visual object recognition (Appell, Kertesz, & Fisman, 1982; Hajilou & Done, 2007; Kirshner et al., 1984; Martin & Fedio, 1983; Nicholas, Obler, Au, & Albert, 1996; Robinson et al., 1996; Rochford, 1971) can affect word retrieval in AD.

The other common measure of lexical retrieval in the normal aging and AD literature is the verbal fluency task (Benton & Hamsher, 1976). The letter fluency task measures a participant's ability to generate words beginning with a target letter (e.g. F, A and S) without the cue of a visual stimulus. The task requires a strategic search and access to phonological and orthographical information stored in the mental lexicon (Rascovsky, Salmon, Hansen, Thal, & Galasko, 2007). A number of factors underlie performance on the task: neuropsychological factors, psycholinguistic factors, as well as experiential factors (for a review, see Pekkala, 2012). Of the neuropsychological factors underlying the letter fluency task, the role of working memory is crucial, as it provides temporary storage and processing of information necessary to successfully perform the task (e.g. Baddeley, Logie, Bressi, Della Sala, & Spinnler, 1986; Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Bayles, 2003; Rende, Ramsberger, & Miyake, 2002; Rosen, & Engle, 1997). The central executive component of working memory both allows a systematic and effective search for words and allows flexibility to change a search strategy when necessary

(Rende et al., 2002; Rosen, 1980; Troyer, Moscovitch, & Winocur, 1997). Working memory also plays a role in monitoring the word retrieval processes to prevent speakers from repeating words that they have already generated for the task (Foldi, Helm-Estabrooks, Redfield, & Nickel, 2003; Rosen & Engle, 1997; Ruff, Light, Parker, & Levin, 1997; Weiss et al., 2006).

Some studies have indicated that the total number of correct words produced for the letter fluency tasks can be related to such psycholinguistic factors as the speed of word retrieval (Troyer et al., 1997; Vinogradov et al., 2003) and word length, with longer words taking more time and memory capacity to access and produce than shorter words (Cheung & Kemper, 1994; Hedden et al., 2002). Experiential factors, such as higher level of education (Troyer, 2000) and female gender (Weiss et al., 2006) have been found to positively affect letter fluency performance, while advancing age tends to have a negative effect on performance (Kavé, 2005; Troyer, 2000).

Studies examining letter fluency performance in individuals with MCI have revealed reductions as compared with healthy controls, both cross-sectionally (Clark et al., 2009; Doi, 2013; Levinoff et al., 2006; Nutter-Upham et al., 2008; Östberg et al., 2005) and longitudinally (Chen et al., 2001; Clark et al., 2009; Grober et al., 2008). Individuals with mild AD perform worse than healthy elderly adults (Adlam et al., 2006; Clark et al., 2009; Groves-Wright, Neils-Strunjas, Burnett, & O'Neill, 2004; Levinoff et al., 2006) and individuals with MCI (Adlam et al., 2006; Clark et al., 2009). However, the findings obtained from longitudinal studies are contradictory, suggesting the sensitivity of the letter fluency task in AD. Clark et al. (2009), for example, showed that, after an average follow-up period from 2.3 to 5.9 years, letter fluency performance among individuals who at baseline were diagnosed with AD or preclinical AD declined significantly faster than among cognitively normal individuals. Grober et al. (2008) revealed a significant decline in letter fluency performance on average at 2.5 years before AD diagnosis. On the other hand, Saxton et al. (2004), in their 8-year follow-up study, demonstrated that the letter fluency performance of individuals who developed AD remained stable during the follow-up. It has been suggested that the letter fluency task is robust against the changes caused by AD because of the strong involvement of the left anterior and prefrontal cortical regions of the brain (Baldo, Schwartz, Wilkins, & Dronkers, 2006; Kitabayashi et al., 2001; Melrose et al., 2009; see also Saxton et al., 2004). These regions are affected later in the progression of the disease and not in its preclinical phase (Braak & Braak, 1991; Delacourte et al., 1999).

Writing disorders are an early manifestation of AD (for reviews, see Croisile, 1999; Graham, 2000; Harnish & Neils-Strunjas, 2008). In written word production, the word meanings are first activated in response to a concept in the semantic system (Roeltgen, 2003; Whitworth, Webster, & Howard, 2005) or a picture (e.g. Forbes et al., 2004; Groves-Wright et al., 2004). Triggered by semantic and phonological information, the written word forms are activated in the orthographic output lexicon. The functioning of the graphemic buffer, a storage of graphemic representations associated with attention and working memory, is crucial as it holds the selected information for conversion into letter shapes or names (Caramazza, Miceli, Villa, & Romani, 1987; Lambert et al., 2007; Roeltgen, 2003). Next, the peripheral writing processes, such as selection of visuospatial features of letters (e.g. case and style of letters) and graphic motor patterns (direction, size, position and order of strokes) are called into play, and the graphic code is executed and controlled by neuromuscular commands (Lambert et al., 2007). Writing sentences and narratives requires simultaneous semantic and syntactic planning and organization, coherence, spelling, working memory and attention, as well as graphomotor functions (Ardila & Surloff, 2006; Groves-Wright et al., 2004; Harnish & Neils-Strunjas, 2008; Roeltgen, 2003), which place high demand on executive functions (Ardila & Surloff, 2006; Baddeley et al., 1986; Forbes et al., 2004; Goldberg, 2001) that are sensitive to brain pathologies involving frontal lobes (Ardila & Surloff, 2006).

The ability of people with AD to produce written narratives on such tasks as describing what is occurring in the Cookie Theft Picture (CTP), a portion of the Boston Diagnostic Aphasia

Examination (BDAE; Goodglass & Kaplan, 1983), can be impaired even at the early stage of the disease. Forbes et al. (2004) reported significantly worse written discourse production at the mild and moderate stages of AD compared to healthy controls. The participants with AD produced shorter and less complex sentences, incoherent and indefinite phrases, semantic and graphemic paraphasias, and fewer pictorial themes. Croisile et al. (1996), reported that, while the written narratives of individuals with mild-to-moderate AD showed simplified but relatively well preserved syntax, they produced significantly shorter descriptions with less information and more errors (e.g. neologisms, intrusions) and implausible details for the CTP than healthy controls. Groves-Wright et al. (2004) reported somewhat different findings, indicating that only at the moderate stage of the disease did individuals with AD perform significantly poorer on written discourse when compared with individuals with mild AD and healthy controls. In addition to the retrieval difficulties at the semantic-lexical level, individuals with AD have been found to have difficulties in the functioning of the graphemic buffer (Haslam, Kay, Tree, & Baron, 2009; Lambert et al., 2007) and with spelling (Carthery, de Mattos Pimenta Parente, Nitrini, Bahia, & Caramelli, 2005; Croisile et al., 1996; Haslam et al., 2009; Lambert et al., 2007), as well as with graphic motor patterns and handwriting (Forbes et al., 2004; Lambert et al., 2007; Werner, Rosenblum, Bar-On, Heinik, & Korczyn, 2006). Consequently, we conclude that difficulties in written word retrieval arise at multiple levels of the writing process.

Longitudinal studies in the literature investigating early indicators of language change in AD are limited to the examination of tasks requiring retrieval of individual lexemes. Furthermore, time of follow-up is usually no greater than a few years. Additionally, these studies rely on clinically diagnosed cases rather than pathologically defined ones, which can dilute findings, as mixed pathologies or inaccurate diagnoses are common for the elderly (Brunnström & Englund, 2009).

For over three decades, the Framingham Heart Study (FHS) has conducted prospective surveillance of a dementia-free cohort for incident dementia, and, since 1997, a brain autopsy program. Additionally, a neuropsychological battery that included the BNT, FAS and a written description of the CTP has been regularly administered. The purpose of this study was to find an early language marker of AD by comparing lexical retrieval on these three language tests in participants with clear cases of AD compared to that of participants who did not, post-mortem, meet neuropathological criteria for diagnosis of AD (or any other neurological disease for which neuropathological criteria are available).

Particularly because no study has compared the relative contributions of lexical retrieval in confrontation naming, verbal fluency and written discourse, we ask here about their relative sensitivity in predicting AD early in the course of the disease. The written CTP is a more challenging task than the standard lexical-retrieval tasks, as lexical retrieval in discourse requires simultaneous integration of numerous skills and occurs at multiple processing levels. Thus, we predicted more lexical retrieval problems would be evident in the writing task in those who were eventually neuropathologically diagnosed with AD.

Method

Study sample

The FHS is a longitudinal population-based cohort study of 5209 subjects established in 1948. Since 1976, participants deemed to be dementia-free have been followed for development of incident dementia (see Seshadri et al., 2006, for details). In 1997, FHS established a brain donation program that included regular administration of a neuropsychological test protocol to all enrollees. Data were obtained under a protocol approved by the Human Subjects Institutional

Review Board of the Boston University School of Medicine. Written informed consent was obtained from all participants.

Seventy-nine participants were identified as fluent speakers of English who had been administered three or more neuropsychological test batteries and had come to autopsy. All of these participants had been clinically diagnosed based on consensus review that included at minimum one neurologist and one neuropsychologist. Thirty-two participants clinically diagnosed with probable vascular dementia, primary diagnoses of Lewy body disease, or primary or contributing diagnoses of frontotemporal dementia or clinical stroke were excluded (diagnostic procedures are described elsewhere; see Seshadri et al., 2006). The resulting 47 participants comprise our study sample.

Pathological diagnosis of AD

To obtain the definite diagnosis of AD, all participants had undergone autopsy. All pathological examinations were performed by a single neuropathologist (AM) who was completely blinded to participants' clinical status. Details of the neuropathological procedures are described in McKee et al. (2006). Briefly, one cerebral and one cerebellar hemisphere were snap frozen at $-80\,^{\circ}C$, while the remaining tissue was fixed in 4% periodate-lysine-paraformaldehyde (PLP) at $4\,^{\circ}C$ for at least 4 weeks. Ten micron paraffin-embedded sections were evaluated with luxol fast blue, hematoxylin and eosin (LHE), Bielschowsky and Gallyas silver methods, and immunocytochemistry for phosphorylated tau protein and Aß protein were conducted on frozen sections.

A semi-quantitative analysis of neurofibrillary tangles (NFT), Braak stage, and diffuse and neuritic SP density was then performed and categorized into six NFT stages using the criteria delineated by Braak, Braak, and Bohl (1993). Senile plaque density was evaluated according to the procedure for scoring plaque density outlined by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Mirra et al., 1991).

Two study groups were defined using the Braak staging criteria for neurofibrillary damage in AD (Braak & Braak, 1991, 1996). The AD group ($n = 23$) was defined as those with Braak scores of IV–VI, and the comparison group (C; $n = 24$) was defined as those with Braak scores of 0–III (Table 1). Two of the participants in the comparison group had a clinical diagnosis of AD but were not diagnosed with definite AD neuropathologically. None of the participants were recruited for this study because of their cognitive status. At the first testing, 2 of the 23 in the AD group were already clinically diagnosed with dementia, and another 3 did not have a specific date of diagnosis. The remaining 18 had not been diagnosed with dementia before the time of their first testing but were clinically diagnosed at that time or later. Among those 18, the range of time was

Table 1. Demographic characteristics of participants with Alzheimer's disease (AD) and the comparison group (C).

	Overall	AD[a]	C[a]
N	47	23	24
Age at the first NP exam	71 ± 10 [51, 92]	72 ± 11 [51, 92]	70 ± 10 [57, 90]
Years between first NP and death	16 ± 10 [0.3, 29.8]	16 ± 9 [3.7, 28.6]	15 ± 12 [0.3, 29.8]
Age at death	87 ± 10 [59, 105]	88 ± 8 [59, 100]	85 ± 11 [61, 105]
Male, *n* (%)	21 (44.7%)	11 (47.8%)	10 (41.7%)
Education, *n* (%)			
Some high school	7 (14.9)	3 (13.0%)	4 (16.7%)
High school graduate	15 (31.9%)	6 (26.1%)	9 (37.5%)
Some college or more	25 (53.2%)	14 (60.9%)	11 (45.8%)

[a]There is no statistically significant difference between the AD and C groups; all p values are > 0.27.

0–25 years from first testing to diagnosis, with a mean and standard deviation of 12 and 9 years, respectively.

Language tests

The Neuropsychological Test Battery included three lexical access tasks that measured distinct patterns of lexical retrieval evolution. Verbal fluency was assessed using the Controlled Word Association Test (i.e. FAS), with the letters serving as the prompt for lexical access (Benton & Hamsher, 1976). Lexical retrieval via confrontation naming was examined using a 10-item version of the Boston Naming Test (BNT; Kaplan et al., 1983). Language discourse was measured by the written description of the CTP of the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983). All tests were administered using standard administration procedures by trained examiners.

FAS

Two measures were scored from the FAS test: total number of correct responses per letter and total number of correct responses per letter produced within the first 15 second interval. The first 15 seconds were analyzed independently of the total score because they have been reported to be the most productive phase of lexical retrieval in the task (Crowe, 1998; Lomen-Hoerth et al., 2003; Rosen, 1980). Proper nouns, repetitions, neologisms and words beginning with a different letter were excluded. Also words that were the same word with different inflectional endings and/or common derivational endings (such as ''y,'' ''ly,'' ''er'') were excluded. Given the directions originally presented to the subjects and the restricted scope of the examples, irregular verbs (such as ''ran'' following ''run'') were scored as acceptable responses. In addition, credit was given when possible homophones were produced (i.e. ''sea'' followed by ''see''). To insure accuracy of scoring, the first two authors (SP, DW) independently scored a randomly chosen sample of 20% of the administered tests. Inter-rater reliability was 99.87%.

BNT

A modified 10-item BNT included the following 10 pictured stimuli: tree, comb, saw, hanger, bench, faucet, telescope, funnel, stethoscope and accordion. All responses to each item were recorded, and the time that it took the participant to provide each final answer was recorded in seconds.

For purposes of this study, we only looked at correct or incorrect spontaneous responses, without examiner cuing, within 10 seconds. Items were scored either 0 if incorrect or produced in more than 10 seconds or 1 if produced phonologically correctly without any cues. The total number of correct words was computed. To insure accuracy of scoring, the first two authors of this paper independently scored a randomly chosen sample, 20% of the administered tests. Inter-rater reliability was 97.26%.

CTP

An investigator (DW) transcribed the hand-written responses into typed documents. To insure accuracy of transcription, a second investigator (SP) independently transcribed and then compared

a randomly selected sample of 10% of the responses. Five minor spelling discrepancies were resolved through discussion.

Each written description was analyzed for total number of words, total number of target words (target words core), total number of additional words and total time (min:sec).The lists of target words core and target words full (target words core plus additional words) were obtained by examining a random sample of 48 CTP descriptions produced by the participants in the comparison group and calculating and ranking the frequency of nouns and verbs produced. The category Target Words Core consisted of the 22 words these participants produced 10 or more times: mother, girl, sister, boy, child(ren), cookie(s), cookie jar/jar, stool/footstool, dish(es), sink, water, window, floor, wash(es/ing/ed), do(es/ing)/did, dry(ing)/dries/dried, wipe(s/d)/wiping, overflow(s/ing/ed)/flow(s/ing/ed), run(s)/running/ran, steal(s/ing)/stole, tip(s)/tipping/tipped and fall(s/ing)/fell. The category Target Words Full consisted of the words listed above, plus additional words produced between 2 and 9 times by the comparison group: lady, woman, plate(s), reach(es/ing/ed), get(s)/getting/got and stand(s/ing)/stood.

In summary, for each CTP description, the time of response (min:sec) was recorded when available, and the total number of words, target words core and target words full were tallied. If a word was misspelled, it was included if it was recognizable. Inter-rater reliability of scoring between the first two authors of this paper, performed on 20% of the narratives, was 99.98% for CTP words, 98.86% for CTP target words full, and 95.45% for the CTP target words core.

Statistical analysis

A repeated-measures analysis was first conducted with PROC MIXED in SAS using all the available data, 162 testing points (77 AD, 85 C) collected across a 30-year-timespan (1976–2006) on the sample of 47 participants. To determine whether differences between the two groups changed over time, we tested for group by time interactions. For these tests of interaction, in order to highlight patterns of interest, we used a liberal threshold for statistical significance of $p < 0.10$; all other analyses used a significance cut-off of $p < 0.05$.

In order to show how the lexical profiles changed over time, cross-sectional analyses were conducted at three discrete testing points selected to include data from the greatest number of participants irrespective of time of clinical diagnosis in the FHS: The first testing, Time 1, at 8 ± 1 years prior to death (total $n = 15$; 9 AD, 6 C); Time 2 at 5 ± 1 years prior to death (total $n = 29$, 15 AD, 14 C); and the last testing, Time 3, at 3 ± 1 years prior to death (total $n = 30$, 11 AD, 19 C; Table 2).

Results

The participants of this study were 23 individuals with neuropathologically determined AD and a comparison group of 24 individuals who did not meet neuropathologic criteria for AD. The study groups did not differ statistically in age, gender or education (Table 1). Similarly, there were no significant differences in any demographic variables between either of the two participant groups at any discrete testing points (Time 1–3) in the cross-sectional analyses (Table 2). The analyses were adjusted for age, gender and education.

As presented in Table 3, the main effect for group was statistically significant for all lexical measures except for FAS and CTP time, with the AD group performing worse than the comparison group. The main effect for time was statistically significant for CTP Time per Word ($p = 0.016$), and CTP Target Words Full ($p = 0.006$), which demonstrates a significant deterioration of performance across both groups. The interaction between group and time was significant for FAS

Table 2. Demographic characteristics of participants with Alzheimer's disease (AD) and the comparison group (C) at the three testing points (Time 1, Time 2 and Time 3).

	AD[a]	C[a]
Time 1		
N	9	6
Age at the first NP exam	76 ± 12 [51, 92]	75 ± 12 [61, 90]
Years between first NP and death	13 ± 7 [6, 27]	17 ± 12 [6, 29]
Age at death	89 ± 12 [59, 100]	92 ± 3 [88, 97]
Male, *n* (%)	5 (55.6%)	3 (50.0%)
Education, *n* (%)		
Some high school	2 (22.2%)	2 (33.3%)
High school graduate	3 (33.3%)	2 (33.3%)
Some college or more	4 (44.4%)	2 (33.3%)
Time 2		
N	15	14
Age at the first NP exam	75 ± 11 [51, 92]	69 ± 11 [57, 90]
Years between first NP and death	13 ± 9 [4, 29]	17 ± 11 [3, 30]
Age at death	88 ± 10 [59, 100]	86 ± 11 [83, 105]
Male, *n* (%)	10 (66.7%)	5 (35.7%)
Education, *n* (%)		
Some high school	3 (20.0%)	2 (14.2%)
High school graduate	5 (33.3%)	6 (42.9%)
Some college or more	7 (46.7%)	6 (42.9%)
Time 3		
N	11	19
Age at the first NP exam	76 ± 9 [64, 92]	71 ± 9 [58, 90]
Years between first NP and death	15 ± 10 [4, 28]	14 ± 11 [0.32, 29]
Age at death	91 ± 5 [82, 98]	85 ± 11 [61, 105]
Male, *n* (%)	6 (54.5%)	10 (52.6%)
Education, *n* (%)		
Some high school	3 (27.3%)	3 (15.8%)
High school graduate	3 (27.3%)	8 (42.1%)
Some college or more	5 (45.4%)	8 (42.1%)

All results are mean ± SD [min, max] unless otherwise stated.
[a]There is no statistically significant difference between any AD and C groups at any time point; all p values are > 0.05.

Table 3. Lexical Measure Scores: Repeated measures analysis with interaction between participant groups and time to death, adjusted for age, gender and education.

	Interaction (Time × Diagnostic Status)	Time	Diagnostic Status AD versus C
FAS	$F(1,73) = 8.47$, $p = 0.005$	$F(1,32) = 3.66$, $p = 0.065$	$F(1,73) = 3.65$, $p = 0.060$
FAS15	$F(1,73) = 13.52$, $p < 0.001$	$F(1,32) = 3.74$, $p = 0.062$	$F(1,73) = 6.61$, $p = 0.012$
BNT(log)	$F(1,56) = 2.71$, $p = 0.106$	$F(1,34) = 1.16$, $p = 0.289$	$F(1,56) = 4.42$, $p = 0.040$
CTP Words (log)	$F(1,40) = 2.65$, $p = 0.111$	$F(1,27) = 2.67$, $p = 0.114$	$F(1,40) = 5.37$, $p = 0.026$
CTP Time (log)	$F(1,37) = 0.51$, $p = 0.478$	$F(1,27) = 0.38$, $p = 0.542$	$F(1,37) = 0.00$, $p = 0.995$
CTP Target Words Core (log)	$F(1,39) = 3.51$, $p = 0.069$	$F(1,27) = 2.58$, $p = 0.120$	$F(1,39) = 7.29$, $p = 0.010$
CTP Time per Word (log)	$F(1,37) = 1.97$, $p = 0.168$	$F(1,27) = 6.65$, $p = 0.016$	$F(1,37) = 5.22$, $p = 0.028$
CTP Target Words Full	$F(1,40) = 10.43$, $p = 0.003$	$F(1,27) = 8.75$, $p = 0.006$	$F(1,40) = 15.78$, $p < 0.001$

Time: time from the first neuropsychological testing to death; AD: participants with Alzheimer's disease; C: comparison group; FAS: Total number of correct words; FAS15: Number of correct words in 15 seconds; BNT: Total number of correct words; CTP Words: Total number of words for the Cookie Theft Picture; CTP Time: Time in Seconds for the CTP; CTP Target Words Core: Number of Target words for the CTP; CTP Time per Word: Time by number of Target words; CTP Target Words Full: Number of Target Words plus additional words.

total number of correct words ($p = 0.005$), FAS number of correct words in first 15 seconds ($p < 0.001$), CTP Target Words Core ($p = 0.069$), and CTP Target Words Full ($p = 0.003$). For each of these measures, the AD group showed progressively worsening performance relative to the comparison group as they approached death.

In order to better understand the significant interactions of time × diagnosis group, we performed time-specific analyses between the groups at three testing points (Time 1–3). Table 4 displays the mean performance for all tests by the subgroups of participant at each testing point. Time-specific analyses (Table 5) indicate that for FAS and FAS15, the AD group performed significantly more poorly than the comparison group at Time 3 only. For CTP Target Words Core, the interaction stems from worse performance by the AD group at Time 1, whereas for CTP Target Words Full, the AD group did worse than the comparison group at both Time 1 and Time 2. While the interaction of time × group did not reach statistical significance for BNT or CTP Words, it appears the AD group scored significantly worse than the comparison group at Time 3.

Discussion

The purpose of this longitudinal study was to compare the trajectory of lexical-access deficits in individuals with and without neuropathologically determined AD in three different conditions: a discourse task, a confrontation naming task and a verbal fluency task. Our findings indicated that individuals with neuropathologically determined AD did show differences in their lexical retrieval skills over time compared to those who did not meet the pathological criterion for AD, as evidenced by significant main effects for group on CTP Words, CTP Time per Word and BNT. The significant interaction between time prior to death and group indicated divergent performance on two of our lexical measures, the written discourse task (CTP) and the letter verbal fluency task (FAS).

Table 4. Lexical measure scores (mean, SD) of the participants with Alzheimer's disease (AD) and the comparison group (C) at Time 1, Time 2 and Time 3.

	Time 1		Time 2		Time 3	
	AD	C	AD	C	AD	C
N[a]	9	6	15	14	11	19
FAS	27.13 ± 10.03	24.67 ± 5.68	23.14 ± 13.59	23.33 ± 9.35	14.30 ± 14.97	26.82 ± 11.96
FAS15	11.38 ± 3.54	12.17 ± 2.93	9.57 ± 5.47	11.25 ± 2.83	6.90 ± 5.86	11.76 ± 4.74
BNT	8.89 ± 1.36	9.33 ± 1.03	8.40 ± 2.03	9.07 ± 1.27	7.20 ± 2.62	9.00 ± 1.02
CTP Words	33.14 ± 20.43	42.60 ± 22.79	31.08 ± 25.50	45.36 ± 28.29	23.86 ± 24.63	40.85 ± 20.76
CTP Time	187.86 ± 124.70	171.00 ± 103.54	218.50 ± 116.21	193.00 ± 87.69	161.43 ± 138.58	176.15 ± 57.52
CTP Target Words Core	8.43 ± 3.82	11.40 ± 0.89	7.67 ± 4.64	10.45 ± 2.38	8.14 ± 3.18	10.46 ± 2.40
CTP Time per Word	5.61 ± 2.74	3.99 ± 0.88	26.79 ± 65.48	4.73 ± 2.15	8.13 ± 4.50	5.21 ± 2.91
CTP Target Words Full	9.29 ± 3.90	13.00 ± 1.73	8.42 ± 5.04	12.09 ± 3.18	8.71 ± 3.59	11.62 ± 2.66

FAS: Total number of correct words; FAS15: Number of correct words in 15 seconds; BNT: total number of correct words; CTP Words: total number of words for the Cookie Theft Picture; CTP Time: time in Seconds for the CTP; CTP Target Words Core: Number of Target words for the CTP; CTP Time per Word: Time by number of Target words; CTP Target Words Full: Number of Target Words plus additional words.

[a]The *N* for each time differs because if data from one test were missing, a person's entire data set for that time period was not included.

Table 5. Cross-sectional analyses[a] (based on NP Exam at 8 ± 1 (Time 1), 5 ± 1 (Time 2) and 3 ± 1 (Time 3) years prior to death).

	Time 1	Time 2	Time 3
N [AD, C]	15 [9, 6]	29 [15, 14]	30 [11, 19]
FAS	0.63 ± 5.34	−0.33 ± 5.02	−13.25 ± 6.12*
FAS15	−2.02 ± 1.58	−1.32 ± 1.89	−6.19 ± 2.41*
BNT	0.36 ± 0.35	0.35 ± 0.26	0.94 ± 0.23***
CTP Words	−0.31 ± 0.29	−0.60 ± 0.39	−1.06 ± 0.38*
CTP Time	−0.04 ± 0.38	0.003 ± 0.25	−0.59 ± 0.31
CTP Target Words Core	0.62 ± 0.15**	0.21 ± 0.15	0.32 ± 0.19
CTP Time per Word	0.26 ± 0.24	0.66 ± 0.45	0.47 ± 0.30
CTP Target Words Full	−4.70 ± 0.79**	−3.41 ± 1.58*	−3.22 ± 1.81

AD: participants with Alzheimer's disease; C: comparison group; FAS: total number of correct words; FAS15: number of correct words in 15 seconds; BNT: total number of correct words; CTP words: total number of words for the Cookie Theft Picture; CTP Time: time in seconds for the CTP; CTP Target Words Core: number of Target words for the CTP; CTP Time per Word: time by number of Target words; CTP Target Words Full: number of Target words plus additional words.

[a]Adjusted for age, gender and education.

*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

When looking at the lexical access performance of a subgroup of participants at three different points in time, our findings revealed varying sensitivity of our test measures. The written discourse task showed lexical access symptoms in AD as early as 7–9 years prior to death, whereas the confrontation naming task (BNT) and the letter fluency task (FAS), tasks which assessed retrieval of individual lexemes, also showed changes in AD, but only at 2–4 years prior to death.

The finding that the written discourse task revealed lexical-access symptoms close to a decade prior to death in individuals with AD is consistent with the cross-sectional study of Forbes et al. (2004) who reported that even individuals at the early stage of AD could be distinguished from healthy elderly controls on such measures as the content and pictorial themes on the written CTP task. Our study indicated that there was a significant difference in the use of words selected for production in the CTP task between the two groups, involving not only the less frequently occurring words in the overall corpus from this study (e.g. ''reach'', ''stand'', ''get''), but also those words that were produced frequently in this study (e.g. ''mother'', ''cookies'', ''children'').

Even though production of written discourse affords a participant additional time for word choice or revision, the CTP task proved to be more sensitive in detecting changes in lexical access in AD than both the BNT and FAS. We propose that this differentiated sensitivity is due to the complex skills required for written discourse. Unlike tasks like BNT or FAS, discourse requires simultaneous syntactic and semantic processes, spelling, working memory, and graphomotor abilities (Ardila & Surloff, 2006; Groves-Wright et al., 2004; Harnish & Neils-Strunjas, 2008; Roeltgen, 2003) that are likely to be affected in early AD due to attentional and perceptual deficits and difficulties monitoring errors (Forbes et al., 2004). The increase in time to produce written discourse at Time 1 and Time 2 among the individuals with AD can reflect the increased demand in processing and the decline of linguistic skills when performing the task relative to tasks involving retrieval of single words. Forbes et al. (2004) and Groves-Wright et al. (2004) postulate that a shorter written sample and the written errors produced by individuals with AD suggest a semantic impairment that results from damage to temporo-parietal areas. Damage to these areas is usually found very early in AD, even in its preclinical phase (e.g. Adlam et al., 2006; Mickes et al., 2007). Consequently, impaired written discourse samples may be an earlier marker of AD than other lexical measures.

Our findings that individuals with AD performed significantly worse on the BNT and FAS than the comparison group at 2–4 years prior to death are not consistent with earlier reports of a decline in lexical retrieval 2–3 years before clinical diagnosis of AD (for BNT, Mickes et al., 2007; for FAS, Grober et al., 2008). The inconsistency between the studies cannot be due to education levels, as the mean years of education in those studies are 16.9 and 16.5, respectively. Rather, it may be due to the fact that the participants recruited for the earlier studies included individuals who did not have AD, which can only be determined definitively from post-mortem examination. Alternatively, the discrepancy may arise from the limited 10-item version of the BNT used in this study, which may have not been sensitive enough to show word retrieval impairment in AD in the way longer versions have (Saxton et al., 2004). We note that earlier studies using a 15-item version (Chen et al., 2001) and a 30-item version (Mickes et al., 2007) of BNT have indicated a significant difference in the word retrieval performance between individuals with preclinical AD and non-AD controls.

In future research, a longer version of the BNT should be utilized. The 10-item version used in this study showed a decline at only 2–4 years prior to death for the participants with AD, and it may have been too short and/or easy to indicate potential earlier changes in lexical retrieval. In fact, the FHS currently utilizes a 30-item version of the test to offset this issue. It is also possible that multiple exposures to the lexical retrieval tasks used in this study may have resulted in a practice effect (e.g. Chen et al., 2001; Salthouse, 2010). Nevertheless, one can assume that a practice effect is less of an issue for people with progressive memory decline, especially as no participant was tested more frequently than once a year. In fact, Harnish & Neils-Strunjas (2008) have argued that using the same test battery over time provides the most accurate picture of the nature and rate of semantic decline in AD.

In addition, future research should include an oral description task to supplement the written CTP, as different modalities could reveal different aspects of impairment in semantic processing and functional communication in AD (Groves-Wright et al., 2004). Furthermore, qualitative analysis of test performance is needed, as analyzing lexical access in more detail may help find early indicators of progressive pathological conditions, such as AD. For example, analyzing errors produced in a task can reveal error patterns specific to different stages of AD (e.g. Bayles, Tomoeda, & Kaszniak, 1985; Forbes et al., 2004; Pekkala, Albert, Spiro, & Erkinjuntti, 2008). Moreover, investigation of other linguistic measures, such as information content and sentential structure, that have been examined in written (e.g. Croisile et al., 1996; Forbes et al., 2004) and oral (e.g. Chapman et al., 2002; Duong, Giroux, Tardif, & Ska, 2005; Hier, Hagenlocker, & Shindler, 1985; Ulatowska & Chapman, 1995) picture description tasks, can potentially reveal even earlier changes in written language production in individuals developing AD than does investigation of retrieval of single words.

Finally, future study would include a larger and more diverse group of participants, as the number of participants in this study is relatively small and the sample consisted of relatively highly-educated Caucasian individuals who may also have been in better health than average prior to their death. The limited number of participants also did not make it possible to differentiate those who had MCI from those who were cognitively intact. Furthermore, the fact that the participant groups at each of the testing times did not contain the exact same individuals limits interpretation of the cross-testing comparisons. Future research will be needed to confirm these exploratory and largely descriptive findings in a larger study.

Clearly, strengths of this study include the fact that it was a longitudinal study of a participant population in which there was neuropathological confirmation of AD pathology. Because AD diagnosis of a number of our participants took place on or before the initial neuropsychological testing, we cannot conclude that poor performance on a written discourse task is a preclinical marker of AD. However, our study revealed that changes in lexical access reflected in written

discourse may be a useful early marker of AD. While the tasks assessing retrieval of individual lexemes only clearly distinguished individuals with AD who were approaching death at 2–4 years before death, the task of lexical access in written discourse effectively discriminated between the groups at 7–9 years prior to death. We suggest that a simple analysis of lexical-target use in a written picture-description task is a sensitive early indicator of AD.

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Declaration of interest

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