Predicting Alzheimer Disease Using Premorbid Neuropsychological Performance

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Abstract

Individuals with Alzheimer Disease (AD) exhibit deficits across multiple cognitive domains years before clinical diagnosis, when they are in the preclinical stages of the disease. Four studies were conducted to (a) examine the preclinical neuropsychological characteristics of English- and French-speaking Alzheimer Disease (AD) participants from the Canadian Study of Health and Aging (CSHA) and (b) determine the utility of select CSHA neuropsychological and demographic measures in predicting AD over a five-year period. Both English- and French-speaking AD participants demonstrated cognitive changes on episodic memory, verbal fluency, and speeded visuomotor processing tasks five years prior to diagnosis, however declines in performance between initial- and re-assessment were not uniform across these domains for either language group. Advanced age and declines in delayed episodic memory were the most significant indicators of progression to AD over a five-year period for both language groups. A validation study was conducted to investigate how well the predictors of AD prognosticate diagnostic outcome for an independent group of at-risk English-speaking participants. The best predictors of AD for the English-speaking group (age, episodic memory, and speeded visuomotor processing) accurately classified close to 70% of individuals from the at-risk sample. The present findings will contribute to diagnostic decisions regarding AD in older English- and French-speaking Canadian adults.

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In loving memory of my maternal grandmother

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Introduction

As the average life expectancy continues to rise, Alzheimer disease (AD), the most common cause of dementia, will become an increasingly prevalent condition and public health care concern in Canada (Diamond, 2005). AD is a progressive neurodegenerative disorder that is characterized by relentless declines in cognitive abilities that have a devastating impact on an individual's behavioural and social functioning; AD eventually causes death. At the present time, approximately 280 000 Canadians over the age of 65 are living with AD and this level is projected to reach over half a million by the year 2031 (Diamond, 2005). The prevalence of AD is highest in seniors 85 years of age and older (approximately 26%), which is also the fastest growing segment of the population (Canadian Study of Health and Aging Working Group, 1994). In addition, approximately $5.5 billion dollars are being spent on persons with AD and related dementias in Canada each year[1].

The advent of pharmacological, psychoeducational, and behavioural treatments for individuals with AD has led to increasing interest in reliably diagnosing this condition in the earliest stages. Research over the last two decades has revealed that subtle neuropsychological deficits precede diagnostically significant cognitive, behavioural, and social changes by years (Bondi & Monsch, 1998; Small, Mobly, Jonsson Laukka, Jones, & Bäckman, 2003; Tierney, Yao, Kiss, & McDowell, 2005). The term "preclinical phase" has come to represent the period between disease onset and subsequent clinical diagnosis.

The Preclinical Phase of Alzheimer Disease

Alzheimer disease is characterized by intracellular changes that cause formation of neurofibrillary tangles and amyloid-rich plaques as well as neuron degeneration and

[1] Economic cost provided by the Alzheimer's Society of Canada (2006) for the year 2000, based on a projected estimate from Ostbye & Crosse (1994).

synaptic loss that gradually progress to a level that produces clinical symptoms (Bondi & Monsch, 1998; Desai & Grossberg, 2005; Munoz & Feldman, 2000). Katzman and Kawas (1994) presented a chronic disease model of AD in which risk factors such as family history, genetic markers (e.g., Apolipoprotein E or ApoE), head injury, coronary disease, and cerebrovascular conditions ***initiate*** the formation of plaques and tangles diffused throughout the cerebral cortex of potential AD patients. At this "latent stage" (Katzman & Kawas, 1994, p. 119) of the disease, corresponding cognitive and behavioural changes may be extremely subtle. When they experience promoting factors, such as advancing age, individuals in the latent phase may enter the "malignant phase" (Katzman & Kawas, p. 119) of AD, which is typified by chronic and progressive neuropathological changes and corresponding cognitive and functional decline that eventually leads to death. Based on this model, the "preclinical phase" of AD occurs at the transition between latent and malignant phases (Katzman & Kawas, 1994, p. 119).

In recent years, there have been increasing developments in attempts to understand the precise disease manifestations in the preclinical stage of AD (Small, Fratiglioni, & Bäckman, 2001). Researchers have attempted to identify specific cognitive abilities that are affected in preclinical AD as well as determine the precise length of this stage. A growing body of evidence suggests that AD patients demonstrate a subtle or subthreshold level of impairment in various cognitive domains several years or even several decades before they meet clinical diagnosis for the condition (Arnaiz & Almkvist, 2003; Smalll, Mobly, Jonsson Laukka, Jones, & Backman, 2003).

Preclinical Cognitive Deficits

Researchers who have focused on global indicators of cognitive functioning have reported lower performance on measures such as the Mini-mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and the Dementia Rating Scale (DRS; Mattis 1976) among individuals who progress to develop AD, as compared with those

who remain without dementia. For example, Small and his colleagues (2000) found baseline differences in the total score of the Swedish version of the MMSE between incident AD cases and healthy controls almost 7 years before eventual diagnosis. Similarly, in a prospective study, Troster and colleagues (1994) found that the DRS, a dementia staging measure, identified with 93% accuracy those among a group of at-risk individuals who progressed to develop AD over a 4- to 6-year time period.

Studies that have focused on identifying predictors of progression to AD in specific cognitive areas have confirmed preclinical deficits in multiple domains. Tierney and her colleagues (1996) found attention deficits as measured by the Mental Control subset of the Wechsler Memory Scale – Revised (WMS-R; Wechsler 1987) reliably discriminated who among 124 memory-impaired non-demented patients developed AD at 2 year follow-up. In their examination of research on attention and executive functions in AD, Perry and Hodges (1999) reported that attention is the first non-memory domain to be affected in AD. In addition, they reviewed numerous studies indicating that individuals with early AD struggle with everyday as well as neuropsychological tasks that rely on executive functions.

Jacobs and her colleagues (1995) found that language deficits characterized by word-finding and abstract verbal reasoning problems were associated with diagnosis of AD, on average 2.5 years later. Similarly, Flicker, Ferris, and Reisberg (1991) found older adults with clinically identified mild cognitive impairment who developed AD at 2 year follow-up (n=23) demonstrated significantly poorer initial performance on language measures of object identification and object function recognition. In addition, Snowdon and his colleagues (1996), who analyzed the hand written autobiographies of 93 sisters who participated in the renowned Nun Study (Snowdon, Ostwald, & Kane, 1989), found that linguistic ability in early life was a reliable marker of AD in later years. They reported that low idea density and low grammatical complexity in early life autobiographies was

significantly associated with low neuropsychological performance, an average of 58 years later.

Investigations have also revealed preclinical deficits in areas of psychomotor speed and visuo-spatial skills. For example, using a logistic regression model, Masur and her colleagues (1994) found the Digit Symbol subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1987), a task of visuomotor speed, emerged as a significant predictor of progression to dementia. In addition, using cluster analysis, Mitrushina, Uchiyama, and Satz (1995) found visuomotor constructional abilities to be one of the most affected domains of cognitive functioning in groups of individuals with early dementia.

Although, collectively, the studies presented above suggest a lack of specificity in terms of preclinical cognitive deficits, it is noteworthy that a certain degree of memory deficit, in addition to declines in other cognitive areas, was reported for all AD patients. As such, a ubiquitous and pronounced cognitive feature of preclinical AD appears to be memory impairment. Differences in memory performance between AD patients and normal controls are seen in clinical tasks that assess various memory components (e.g., episodic, semantic, prospective, and working memory). In particular, numerous studies have shown that episodic memory deficits for both verbal (Linn et al., 1995; Tierney et al., 1996) and visual information (Small, Herlitz, Fratiglioni, Almkvist, & Bäckman, 1997) are prevalent in preclinical AD. In addition, episodic memory deficits in free recall (Linn et al, 1995; Grober, Lipton, Hall, & Crystal, 2000), cued recall (Bäckman & Small, 1998; Tuokko, Vernon-Wilkinson, Weir, & Beattie, 1991) and recognition (Bäckman, Small, & Fratiglioni, 2001; Fox, Warrington, Seiffer, Agnew, & Rossor, 1998) trials have been reported. In addition, AD patients also have been found to demonstrate compromised semantic memory abilities, characterized by a decline in fund of knowledge (Norton, Bondi, Salmon, & Goodglass, 1997), naming skills (Bayles & Tomoeda, 1983), and

verbal fluency (Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Monsch et al., 1994; Salmon & Chan, 1999). A recent investigation by Spaan and her colleagues (2005) revealed that semantic and implicit memory problems apparent in preclinical dementia may explain some types of episodic memory deficits (e.g., compromised cued recall and recognition abilities) seen at this early stage.

The episodic and semantic memory deficits seen in preclinical AD appears to reflect the underlying neuropathology seen at the earliest stages of the disease. Histopathological, morphological, and neuroimaging studies have revealed that the earliest brain changes in AD occur in the hippocampus and other medial temporal lobe structures. The medial temporal lobe area of the brain has been strongly implicated in episodic and certain semantic memory abilities (Foundas, Leonard, Mahoney, Agee, & Heilman, 1997; Jack et al., 1997; Mega et al., 2002).

Preclinical Episodic Memory Deficits

Episodic memory refers to the ability to learn and retain new information or autobiographical events that have been encoded relatively recently (Craik, 2000). In clinical settings, this type of memory is typically assessed with measures that involve the recall of presented materials such as word lists, stories, number sequences, or pictures. Bäckman and his colleagues (2001) investigated the course of preclinical episodic memory deficits in AD. Using data from the Kungsholmen Project, a Swedish population-based longitudinal study, the researchers compared the episodic and short-term memory performance of people who developed AD (n=15) with individuals who were not demented (n=105) three to six years prior to their diagnosis. Episodic memory (i.e., free recall and recognition) was assessed using two word lists each containing 12 concrete words, and short-term memory was assessed with the Digit Span subtest of the WAIS-R (Wechsler, 1987). Bäckman et al. (2001) found that incident AD cases performed more poorly than their nondemented counterparts both three and six years before diagnosis

on both free recall and recognition measures of episodic memory. In contrast, there were no group differences with respect to short-term memory and there was no evidence of accelerated decline of episodic memory abilities in the incident AD group from six to three years before diagnosis.

Similarly, in a prospective study of asymptomatic individuals at risk of autosomal dominant familial type AD, Fox et al. (1998) found that 10 out of 63 participants progressed to meet full criteria for possible or probable AD over a period of 6 years. When compared to participants who remained healthy, AD patients demonstrated poorer performance on a measure of verbal episodic memory (e.g., recognition test for words) at initial assessment. Fox and colleagues (1998) found no difference in performance between cases and controls on other neuropsychological measures of visual memory, naming, perception, arithmetic, spelling, psychomotor speed, and attention at initial assessment. In addition, for the 10 affected individuals, the mean time from initial assessment to first signs of clinical symptoms was approximately 3 years.

In a prospective community study, Chen and colleagues (2001) found that the delayed recall score of a 10-item word list memory measure best discriminated between individuals who developed AD over a 1 ½ year period from those who remained nondemented. In addition, the authors found that among 16 neuropsychological tests examined, the combination of delayed recall score and Trail Making Test - Part B score, a measure of executive function (Reitan, 1955), had the highest accuracy in identifying individuals at the preclinical phase of AD. Similarly, in a recent study using the CSHA data set, Tierney and her colleagues (2005) found that the short delayed recall score on the Rey Auditory Verbal Learning Test (RAVLT; Taylor, 1959) was the best predictor of incident AD 5 years and 10 years prior to diagnosis. The authors found that it was not until 5 years prior to diagnosis that deficits in other cognitive abilities, including language problems (category fluency) became apparent.

Although the aforementioned and other (see also Linn et al., 1994, Masur, Sliwinski, Lipton, Blau, & Crystal, 1994) studies document episodic memory deficits, they traditionally use memory measures and procedures (e.g., word list recall and recognition paradigms, paired associate learning etc.) that may also be sensitive to deficits in other cognitive systems (e.g., attention, processing capacity, or executive functions). In other words, the deficits reported when using certain memory measures and procedures, may not reflect a pure deficit in the episodic memory system of AD patients. For example, Tuokko and her colleagues (1991) have argued that observed deficits may be attributed solely to memory only when measures that ensure appropriate encoding and processing of the to-be-learned material are used. The Buschke Cued Recall Task (BCRT; Buschke, 1984; modified by Tuokko & Crockett, 1989) is a memory measure that involves a search and selective reminding procedure to control encoding and retrieval. As such, the BCRT ensures reliable processing of information with minimal reliance on other cognitive processes and is deemed to be a relatively "pure" measure of episodic memory processes.

The BCRT appears to be a sensitive measure for the early detection of AD. Using this measure in a prospective study of individuals referred to outpatient diagnostic clinic by community physicians, Tuokko and her colleagues (1991) found that 18 participants who developed AD in the course of 12 to 18 months demonstrated poorer performance on free, cued and delayed recall at initial assessment when compared to 27 participants whose diagnostic status remained unchanged over the same time period. In addition, the authors found that the retrieval score (i.e., total number of items freely recalled over 3 trials) was the best predictor of early AD. Although this study suggests that episodic memory difficulty may be the hallmark of early or possibly preclinical-AD, this finding is based on a relatively small sample of AD patients. The present series of studies aimed to extend this finding to a larger population-based Canadian sample.

Preclinical Semantic Memory Deficits

The term *semantic memory* refers to the memory for general knowledge information or over-learned facts, and principles about objects, people, and events of the world (Farah & Grossman, 2000; Gazzaniga, Ivry, & Mangun, 1998) that are not dependent upon contextual cues for retrieval (Tulving, 1983). Unlike episodic memory, which is temporally specific, semantic memory is not linked to a specific learning event and is based on culturally shared knowledge (Hodges, Salmon, & Butters, 1992). Cognitive models of semantic memory (Collins & Loftus, 1975) assume that semantic knowledge is organized as a complex network of associated concepts. Concepts or objects that share many attributes (e.g., elephant, tiger, and hippopotamus) are more strongly linked within the network than are those that have few attributes in common (e.g., elephant, pencil, and tree). Attributes provide a means of categorizing objects and concepts into superordinate groups, while simultaneously distinguishing among exemplars that constitute a given category. Thus, elephant, tiger, and hippopotamus are all categorized as animals because of their shared attributes (e.g., living things, have four legs, etc.). At the same time, these animals can also be distinguished from each other based on other attributes such as their size, color, and shape (Salmon & Chan, 1999). Semantic memory impairment can result from a lack of access to item-specific knowledge (i.e., retrieval of factual information), or from an actual deterioration of the representational network (Ober, 1999).

Semantic memory is typically studied using clinical measures that assess factual knowledge (e.g., Information subtest of the WAIS-R; Wechsler, 1987), confrontational object naming (Boston Naming Test; Kaplan, Goodglass, & Weintraub, 1983), and verbal fluency. Studies have found that compared to age- and education-matched normal controls, individuals with mild to moderate dementia are impaired in their ability to recall generic factual and conceptual information (Norton et al., 1997; Weingartner,

Kawas, Rawlings, & Shapiro 1983), and in their ability to recognize and name objects (Bayles & Tomoeda, 1983). Lukatela and her colleagues (1998) found that AD patients made more naming errors than vascular dementia patients and healthy normal controls on the Boston Naming Test. These authors found that participants in all three groups tended to make more semantic than phonemic errors. However, qualitatively, AD patients made more superordinate errors (e.g., *animal* instead of *beaver*) compared to patients with vascular dementia.

Another consistent finding in AD is that in the early stages of the disease, AD patients are impaired on verbal fluency tasks that require the time-limited generation of words beginning with a specific letter (e.g., phonemic fluency; Controlled Oral Word Association or FAS test, Spreen & Benton, 1977) or words that are exemplars of a specific semantic category, such as animals or fruit (e.g., category fluency; Animal Naming Test, Rosen 1980). However, studies that have compared the performance of AD patients on phonemic and category fluency measures directly have found that patients are impaired relative to normal controls on the semantic, but not the phonemic, fluency task (Butters et al., 1987; Monsch et al., 1994). Crossley and her colleagues (1997) confirmed this disproportionate reduction in category, as opposed to letter, fluency in a cohort of CSHA participants; mildly to moderately impaired AD patients were found to demonstrate greater impairments on category fluency (i.e., Animal Naming) than phonemic fluency (i.e., FAS test) compared to healthy older adults and other amnestic patients (e.g., Vascular Dementia).

The difference in performance of AD patients between semantic and phonemic fluency tasks has been attributed to the greater demands category fluency places on the hierarchical structure of semantic knowledge (Butters et al., 1987), which is thought to deteriorate during the course of AD. From a neuropsychological perspective, Moscovitch (1995) has proposed that category fluency may be primarily mediated by the mesial

temporal lobe structures (i.e., the same structures that have been implicated in episodic memory), while letter fluency may be carried out by the frontal lobes. In the early stages of the disease, AD is known to affect the mesial temporal lobe structures with relative sparing in the frontal brain areas.

While fluency tasks, and specifically the difference in performance between phonemic and semantic fluency tasks, are considered to be sensitive markers of AD, the use of these measures for detecting the disease is preclinical stages is not well established. There is some preliminary evidence that this specific pattern of semantic memory deficit is apparent in preclinical stages of AD. In a study designed to investigate patterns of cognitive decline over time in pre-symptomatic AD patients, Chen et al. (2001) reported that category fluency appears to be more sensitive to AD than phonemic fluency; the observed effect was small, but significant. As well, in a recent study using the CSHA dataset, Tierney and her colleagues (2005) found category fluency (measured by Animal Naming test; Rosen 1980), in addition to delayed recall on a list learning measure and fund of knowledge to be significant predictors of incident AD over a five year period. In contrast, Fox et al. (1998) did not find differences in naming abilities (using the Graded Naming Test) between asymptomatic individuals at risk of developing familial AD who eventually went on to develop the disease and those who remained healthy. These authors suggest that semantic memory impairment may not be an early feature of familial AD. The present series of studies examine the diagnostic value of category fluency in relation to phonemic fluency at a preclinical stage of AD.

Preclinical Psychomotor Speed Deficits

Generalized decline in the speed of processing information has been suggested as the fundamental mechanism that accounts for age-related differences in cognitive performances (e.g., Salthouse, 1991; 1996). Perceptual speed tasks or simple paper-and-pencil measures that require rapid processing of information (e.g., transcription of

numbers or symbols according to legend, same-different judgments about pairs of digits or symbols etc.) within a specified period of time have been used to study psychomotor speed in clinical and experimental settings. In aging studies, seniors have consistently demonstrated poorer performance on such measures compared to young adult counterparts (Park, 2000).

There is emerging evidence that AD exacerbates the already compromised information processing ability in old age. Storandt and Hill (1989) found the WAIS-R Digit Symbol subtest, a sensitive measure of psychomotor speed, to be among the first tests affected in patients with mild AD. Similarly, using a logistic regression model, Masur and his colleagues (1994) found the WAIS-R Digit Symbol measure to be a significant indicator of progression to dementia. Consequently, the value of the WAIS-R Digit Symbol test in the preclinical detection of was investigated in the present series of studies.

Overview of Present Studies

Collectively, the four studies that constitute this document aim to examine the utility of a select group of neuropsychological measures from the Canadian Study of Health and Aging (CSHA) in distinguishing between individuals who progress to develop AD from those who remain healthy over a five year period. The CSHA, a population-based study of dementia was conducted in three waves (CSHA-1, 1990-1991; CSHA-2,1995-1996; CSHA-3, 2001-2002). The CSHA drew samples from distinct populations; English- or French- speaking Canadians who were assessed in their preferred language as well as individuals who were either residents of the community or institutions. The CSHA is described in detail in Appendix A. Different cohorts of participants from the CSHA were selected for inclusion in the present four investigations.

The major goal in Studies 1 and 2 was to compare performances of AD patients and matched controls on select neuropsychological measures administered both at

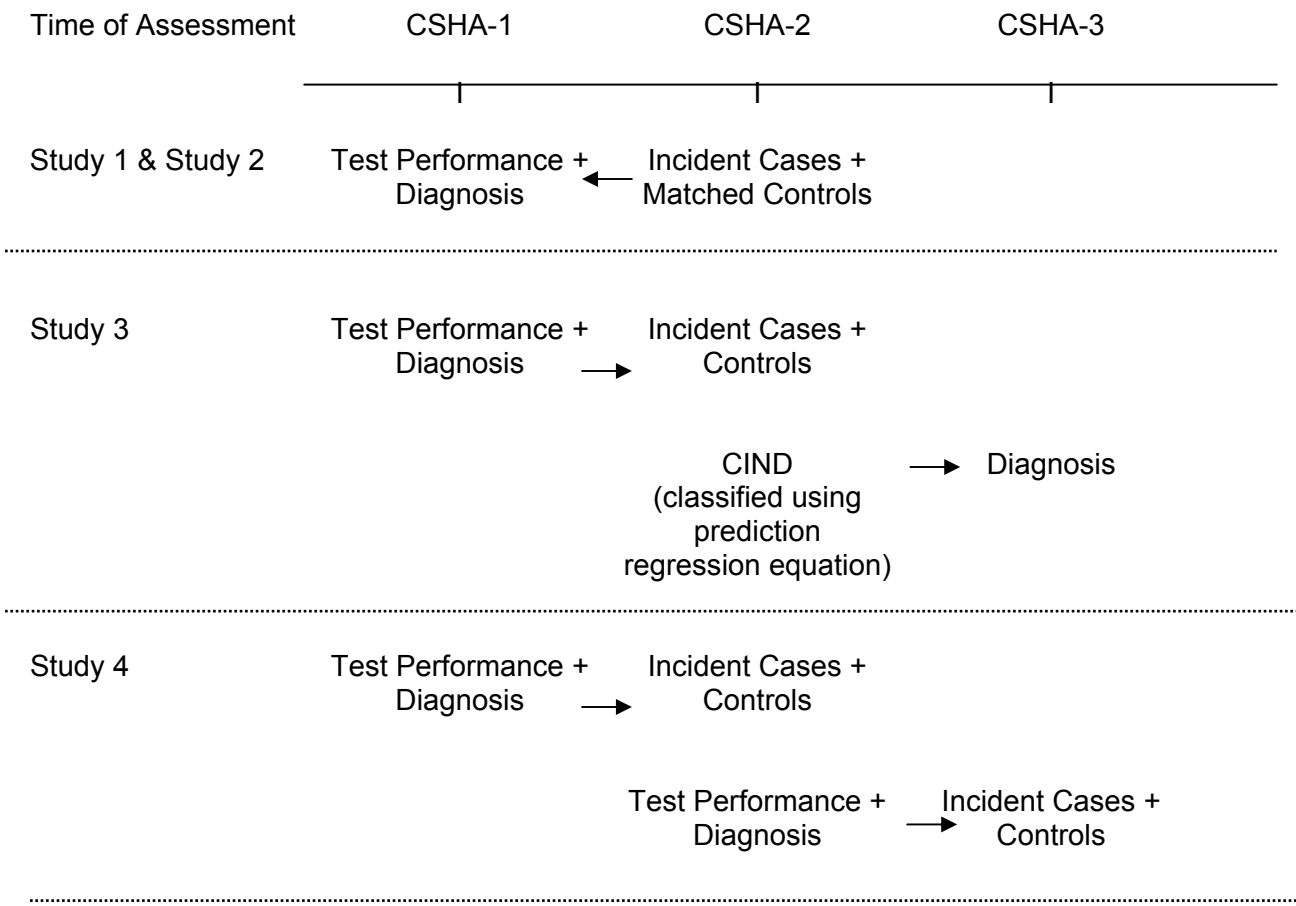
CSHA-1 and CSHA-2. The objective was to investigate neuropsychological performance five years prior to clinical diagnosis. To this end, participants newly diagnosed with AD at CSHA-2 (i.e., incident cases) and a group of normal matched controls were followed retrospectively to CSHA-1; their baseline (CSHA-1) and reassessment (CSHA-2) performances on the neuropsychological measures were described and compared. Study 1 involved an English-speaking CSHA sample and Study 2 involved French-speaking participants.

The decision to focus on English and French-speaking participants separately was based on several factors. First, cultural, language, and educational differences have been recognized as confounding variables in the assessment of older adults of minority groups (Manly, Jacobs, & Mayeux, 1999). In light of this, there was a need to account for the significant differences in educational attainment between English- and French-speaking seniors in the CSHA sample. Second, Tuokko and her colleagues (1995) found significant differences in participation rates and diagnosis of dementia between English- and French-speaking participants. French-speaking participants declined to participate in the assessment at higher rates and were less likely than English-speaking participants to receive a dementia diagnosis. The precise reasons for these discrepancies remain unknown; however, it is possible that individuals at higher risk of dementia diagnosis were also more likely to decline study participation. Rather than attempt to control for sociocultural factors using statistical methods, the decision was made to conduct separate investigations using these distinct populations.

Two main goals were addressed in Study 3, which is presented in a manuscript format within this document. First, this study aimed to examine the predictive value of the neuropsychological measures analyzed in Study 1. Specifically, Study 3 was conducted to determine which neuropsychological measures best distinguish individuals who develop AD from those who remain healthy over a five-year time period using a

larger sample of English-speaking CSHA participants. There was also an interest in determining to what extent demographic variables such as age, gender, and education contribute to the prediction of dementia. Second, Study 3 also aimed to validate how well the best predictors prognosticate clinical outcome in an independent sample of English-speaking participants deemed to be at risk of developing dementia. To date, no other studies have validated how well an established set of predictors can prognosticate who amongst a group of individuals deemed to be at risk of developing dementia will eventually progress to develop the disease in a population-based sample.

The main objective of Study 4 was identical to that of Study 3. Notably, Study 4 was conducted to determine which neuropsychological measures best predict progression to AD. Study 4 involved French-speaking Canadians. Due to a variation in sample selection (see methods section in Study 4), this study did not include an actuarial validation component. A pictorial summary of all four studies is presented in Figure 1.



Note: Cases and controls were selected at the indicated assessment times. Arrows represent direction of comparison/analysis.

Fig. 1: Summary of Study Designs

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Study 1: Preclinical Neuropsychological Performance of English-Speaking Canadians with Alzheimer Disease

Objectives

A major purpose of Study 1 was to examine neuropsychological performance in preclinical AD. Specifically, cognitive performance was compared retrospectively between two groups of initially nondemented, English-speaking CSHA participants: clinical cases who subsequently developed AD and controls who remained nondemented over a five year period (i.e., between CSHA-1 and CSHA-2). The goal was to determine whether or not clinical cases demonstrate significantly lower neuropsychological performance compared to normal controls five years prior to diagnosis, when they are presumably in the preclinical stages of the disease. Specifically, the two groups were compared on a global measure of dementia (i.e., 3MS; Teng & Chui, 1987), an episodic memory task (i.e., BCRT; Buschke 1984 modified by Tuokko & Crockett, 1989), and a psychomotor speed measure (i.e., WAIS-R Digit Symbol; Wechsler, 1987). In addition, phonemic (Controlled Oral Word Fluency Test or FAS test; Spreen & Benton, 1977) and category fluency (Animal Naming; Rosen, 1980) measures were examined to determine if differential performance (i.e., poorer performance on category fluency compared to phonemic fluency) was evident.

Based on previous research, the following hypotheses were made: First, individuals diagnosed with AD will show poorer performance than control participants on all neuropsychological measures at initial assessment (i.e., CSHA-1; five years prior to clinical diagnosis) and reassessment (i.e., CSHA-2; time of diagnosis). Second, the deterioration in performance between the two assessment times will be greater for those diagnosed with AD than healthy controls. Third, those with AD will demonstrate worse performance on the category fluency task relative to the phonemic fluency task, compared to healthy controls, at initial assessment and reassessment.

Methods

Study Design and Participants. See Appendix A for a detailed description of the CSHA. In the present study, the neuropsychological performance of AD participants and healthy older adults who were assessed in English at CSHA-1 and CSHA-2 was analyzed. The CSHA-2 identified 326 (98 males and 228 females) incident cases of AD; twenty-nine individuals from this sample completed neuropsychological assessment in English at both CSHA-1 and CSHA-2. The neuropsychological performance of these 29 individuals (19 with probable AD and 10 with possible AD) was compared to age-, gender-, and education-matched healthy adults. Healthy controls were selected from a group of 181 English-speaking participants who were assessed to be cognitively normal (i.e., no cognitive impairment; NCI) at CSHA-2 and for whom neuropsychological data were available at both CSHA-1 and CSHA-2. The participant matching process involved selecting, from the NCI group, participants who were first of the same gender and who were within 5 years in age and educational level as each of the 29 clinical participants.

Demographic and background characteristics of incident AD cases and healthy controls are presented in Table 1. There were 7 males and 22 females in each group. Univariate analyses indicated that the matching process was successful; there was no significant age- or education- differences between the clinical and control groups (age, $t(56) = -.03$, $p < .98$; education, $t(56) = .52$, $p < .61$). In addition, as expected no participants in the control group were diagnosed with dementia at CSHA-1. In contrast, significantly more participants in the clinical group were classified as having clinical impairment but no dementia (CIND) at CSHA-1 than were individuals in the control group (16 vs 4, respectively, $\chi^2 (1, N = 58) = 10.99$, $p < .01$) suggesting that more individuals in the clinical group had subthreshold levels of cognitive impairment five years prior to clinical diagnosis.

Table 1

Demographic Summary For Clinical and Control Group

	Clinical Group	Control Group
Variable	M (SD)	M (SD)
Age at CSHA-2	86.7 (5.1)	86.7 (5.0)
Education	9.7 (4.2)	10.3 (4.4)
	N	N
Gender		
Male	7	7
Female	22	22
Residence at CSHA-2		
Community	18	25
Institution	11	4
CSHA-1 Diagnosis		
NCI	13	25
CIND	16	4

NCI = No Cognitive Impairment; CIND = Cognitive Impairment No Dementia

Measures. The neuropsychological assessment component of the CSHA included 12 measures designed to assess different domains of cognitive functions including memory, language ability, judgment, abstract thinking, and processing speed From the test battery, a group of neuropsychological measures assessing three domains of cognitive functions (i.e., episodic memory, verbal fluency/semantic memory, and psychomotor speed) were chosen for inclusion in the present analyses. As well, performance on the 3MS, a global indicator of dementia, was investigated. A description of the measures and the specific scores that were examined are presented in Table 2.

The BCRT, FAS, Animal Naming, and Digit Symbol tests were selected for several reasons. First, they were administered in an unmodified manner in all three waves of the CSHA. This was important because collectively the four studies described in this document span all three waves of the CSHA and there was a need to maintain consistency for comparative purposes. Second, the cognitive domains assessed by the selected measures are typically reported to decline in dementia. As such, the interest was to see how participants who develop AD perform on these domains at a preclinical stage. Third, there was a specific interest in investigating performance on the BCRT test, which has previously been described as a relatively “pure” form of memory test than other list learning measures (Tuokko, Vernon-Wilkinson, Weir, & Beattie 1991). As well, there was a specific interest in examining the differential performance on phonemic vs category fluency measures in preclinical AD. It is noteworthy that the Digit Symbol test was added to the analyses, to further understand the neuropsychological markers of AD. Performance on the Digit Symbol, a measure that assesses speeded psychomotor performance, including motor persistence, sustained attention, response speed, and visuomotor coordination, is presumed to be unaffected by memory or learning in healthy older adults.

Table 2

Description of measures and scores used in the analysis

Global Indicator: 3MS A brief screening measure for cognitive impairment consisting of items assessing orientation, attention/concentration, language, constructional ability, and memory	
Score	Total number of item completed accurately (max = 100)
Episodic Memory: Buschke Cued Recall Test (BCRT) Participants are required to identify 12 common items (e.g., bed) presented pictorially; each item's semantic category cue (e.g., furniture) is given. Following a distractor task, participants are asked to freely recall items and are provided with semantic category cues to prompt for missed items. A total of three free and cued recall trials are administered. A final free and cued recall trial is administered after a 15-min time delay.	
Retrieval score	Total number of item recalled freely (i.e., without cuing) over three learning trials (max = 36)
Acquisition score	Total number of items recalled freely and with cuing over three learning trials (max = 36)
Delayed free recall score	Total number of items recalled freely on the delayed recall trial (max = 12)
Retention score	Total number of items recalled freely and with cuing on the delayed recall trial (max = 12)
Verbal Fluency: Phonemic Fluency (FAS Test) Oral generation of words beginning with letters F, A, and S in three 60-sec trials **Category Fluency (Animal Naming)** Oral generation of animal names in one 60-sec trial	
FAS Score	Total number of words generated over three trials
Animal Naming Score	Total number of animal names generated over one trial
Psychomotor Task: Digit Symbol (WAIS-R) Participants are requested to transcribe symbols according to a specified number-symbol legend in a 90-sec trial	
Score	Total number correctly paired number and symbols

Statistical Analysis. The aim of this study was to investigate longitudinal changes in cognitive performance for incident AD cases and healthy controls between initial assessment (CSHA-1) and five year follow-up (CSHA-2). Separate 2(Group: Clinical vs. Control) X 2(Time: CSHA-1 vs. CSHA-2) repeated measures ANOVAs, with group as a between subject variable and time as a within-subject repeated variable, were conducted for each neuropsychological measure. To further understand resultant interaction effects from these ANOVAs, post hoc analyses in the form of separate paired sample t-tests were conducted to examine mean-level differences between clinical and control groups at initial assessment and reassessment. In addition, performance on the phonemic fluency and category fluency measures were directly compared first by converting raw scores to z-scores, expressed in standard deviations from the mean of an independent sample of 105 English-speaking health older adults who had fluency measures data available at both CSHA-1 and CSHA-2. This independent sample comprised of a subgroup of participants from the 181 individuals who were assessed to be cognitively normal at CSHA-2 and who were initially used in the participant matching process, as described above. It is noteworthy that the 29 controls who were matched to clinical participants were excluded from the fluency measures standardization sample to ensure independence of observation (i.e., to ensure that scores will not be counted twice). Phonemic and category fluency tasks were directly compared with a 2 (Group: Clinical vs Control) X 2 (Task: FAS vs Animal Naming) X 2 (Time: CSHA-1 vs CSHA-2) repeated measures ANOVA, with group as a between-subjects variable and task and time as within-subject repeated variables. ANOVA tables for all neuropsychological measures analyses are presented in Appendix B.

Results

Global Indicator of Cognition. The 3MS performance of the participants at CSHA-1 and CSHA-2 are presented in Table 3. A significant main effect of group was found,

Table 3

3MS Performance for Clinical and Control Group Participants at CSHA-1 and CSHA-2

	Clinical Group		Control Group	
	M	SD	M	SD
CSHA-1	77.7	9.8	88.2	7.8
CSHA-2	62.8	9.4	87.1	9.6

with the clinical group performing more poorly than the control group at both initial- and re-assessment, $F(1, 56) = 63.96$, $p < .001$. In addition, there was a significant main effect of time. Both groups of participants evidenced a decline in 3MS performance between CSHA-1 and CSHA-2, $F(1, 56) = 59.14$, $p < .001$. These main effects of group and time were qualified by a significant interaction effect between the variables, with the clinical group showing greater deterioration in performance between the two administrations relative to the control group, $F(1, 56) = 43.61$, $p < .001$. This interaction effect was confirmed by post-hoc analyses; paired sample t-tests revealed a significant change in performance between CSHA-1 and CSHA-2 for the clinical group, but not the control group (clinical group, $t(28) = 6.27$, $p < .001$; control group, $t(28) = 1.08$, $p = .29$).

Episodic Memory Measure (BCRT). Episodic memory performance (i.e., BCRT scores) of clinical and control participants at initial assessment and follow-up is presented in Table 4. Separate repeated measures ANOVAs revealed a significant main effect of diagnostic group for all four BCRT dependent variables, indicating the poorer performance of the clinical group compared to the control group with respect to the retrieval, acquisition, delayed free recall, and retention of BCRT items at both initial- and re-assessment ($F(1,54) = 63.29$, $p < .001$ for retrieval; $F(1,54) = 20.88$, $p < .001$ for acquisition; $F(1,55) = 48.65$, $p < .001$ for delayed free recall; $F(1,55) = 18.81$, $p < .001$ for retention). Although there was a significant main effect of time for all variables ($F(1,54) = 45.25$, $p < .001$ for retrieval; $F(1,54) = 21.87$, $p < .001$ for acquisition; $F(1,55) = 33.86$, $p < .001$ for delayed free recall; $F(1,55) = 22.62$, $p < .001$) for retention, reflecting a decline in performance between CSHA-1 and CSHA-2, this was qualified by significant Group X Time interactions ($F(1,54) = 12.34$, $p < .01$ for retrieval; $F(1,54) = 18.20$, $p < .001$ for acquisition; $F(1,55) = 18.02$, $p < .001$ for delayed free recall; $F(1,55) = 20.34$, $p < .001$ for retention). Post-hoc analyses revealed that the change in performance between initial and reassessment was significantly greater for AD

Table 4

BCRT Performance of Clinical and Control Group Participants at CSHA-1 and CSHA-2

	Clinical Group			Control Group		
BCRT Variable	M	SD	N	M	SD	n
Retrieval						
CSHA-1	19.5	7.0	28	28.2	4.0	28
CSHA-2	11.0	8.6	28	25.5	4.5	28
Acquisition						
CSHA-1	34.0	4.6	28	35.8	0.7	28
CSHA-2	27.8	8.0	28	35.5	1.7	28
Delayed Free Recall						
CSHA-1	7.3	3.0	29	10.4	1.8	28
CSHA-2	3.7	3.6	29	9.8	2.6	28
Retention						
CSHA-1	11.3	1.5	29	11.9	0.3	28
CSHA-2	8.7	3.6	29	11.9	0.6	28

participants than healthy controls for the acquisition (clinical group, $t(27) = 4.61$, $p < .001$; control group, $t(27) = .85$, $p = .40$), delayed free recall (clinical group, $t(28) = 6.03$, $p<.001$; control group, $t(27) = 1.47$ $p = .15$), and retention variables (clinical group, $t(28) = 4.77$, $p < .001$; control group, $t(27) = .81$, $p = .42$). It is noteworthy that although the raw scores indicate that AD participants demonstrated a greater deterioration of performance over time on the BCRT retrieval measure, according to post hoc analyses, the control group also demonstrated significant declines between the two assessment periods. This likely represents the normal-age related decline in episodic memory documented in neuropsychological studies (Craik, 2000).

Verbal Fluency Measures (FAS test and Animal Naming). Table 5 shows the phonemic (FAS) and category (Animal Naming) fluency scores for clinical and control groups at CSHA-1 and CSHA-2. Separate repeated measures ANOVA's revealed significant main effects of diagnostic group and time that were qualified by a significant interaction effect between these variables for both fluency measures. Clinical group participants produced significantly fewer words on FAS and Animal Naming tests compared to control group participants at initial- and re- assessment ($F(1,51) = 14.58$, $p < .001$ for FAS; $F(1,55) = 26.76$, $p < .001$ for Animal Naming). Although a main effect for time suggested that performance of both groups of participants on the two fluency measures declined between assessment periods ($F(1,51) = 17.74$, $p < .001$ for FAS; $F(1,55) = 11.11$, $p < .01$ for Animal Naming), this was qualified by a Diagnostic Group X Time interaction. AD participants demonstrated a greater deterioration of performance over time on the fluency measures compared to healthy older adults ($F(1,51) = 13.71$, $p < .01$ for FAS; $F(1,55) = 9.10$, $p < .01$ for Animal Naming). This pattern of performance was confirmed with post-hoc analyses; paired sample t-tests revealed a significant change in performance between CSHA-1 and CSHA-2 for the clinical group, but not the control group for the phonemic (clinical group, $t(26) = 5.12$, $p <. 001$;

Table 5

Phonemic and Category Fluency Performance of Clinical and Control Group Participants at CSHA-1 and CSHA-2

	Clinical Group			Control Group		
Fluency Measures	M	SD	n	M	SD	n
Phonemic Fluency (FAS test)						
CSHA-1	23.5	13.1	27	31.6	13.2	26
CSHA-2	15.1	9.6	27	31.0	12.2	26
Category Fluency (Animal Naming Test)						
CSHA-1	11.7	3.3	28	14.7	5.0	29
CSHA-2	8.3	3.2	28	14.6	4.0	29

control group, $t(25) = .40$, $p = .70$) and category fluency variables (clinical group, $t(27) = 5.42$, $p < .001$; control group, $t(28) = .20$, $p = .85$).

Letter and category fluency scores were directly compared by converting each participant's score on both measures to standard scores (*z* scores), expressed in standard deviations from the mean of an independent sample of healthy older adults from CSHA-2 (n=150; see Fig 2). A 2 (Group: Clinical vs Control) X 2 (Task: FAS vs Animal Naming) X 2 (Time: CSHA-1 vs CSHA-2) repeated measures AVOVA was performed, with diagnostic group as a between-subjects variable and task and time as within-subject repeated variables. This analysis resulted in a significant main effect of group, $F(1,50) = 23.47$, $p < .001$ and time, $F(1,50) = 21.84$, $p < .001$, which were qualified by a significant interaction effect, $F(1, 50) = 14.75$, $p < .001$. As reported above, AD participants' performance on both the FAS and Animal Naming tests declined significantly over time compared to the control participants. The main effects for task type (FAS vs Animal Naming) and interaction effects among the three factors were not found to be significant.

Psychomotor Performance (WAIS-R Digit Symbol Test). The means and standard deviations for the WAIS-R Digit Symbol test are presented in Table 6. Results were analyzed using a 2 (Group: Clinical vs Control) X 2 (Time: CSHA-1 vs CSHA-2) repeated measures ANOVA, with group as a between-subject variable and time as a within-subject repeated variable. A significant main effect of group was found, suggesting that the participants diagnosed with AD at CSHA-2 performed significantly worse on the WAIS-R Digit Symbol test both at initial- and re-assessment relative to healthy older adults, $F(1,41) = 13.07$, $p < .01$. However, both groups of participants evidenced a decline in performance between initial- and re-assessment as implicated by a significant main effect of time, $F(1, 41) = 28.29$, $p < .001$. There was no significant interaction between the variables.

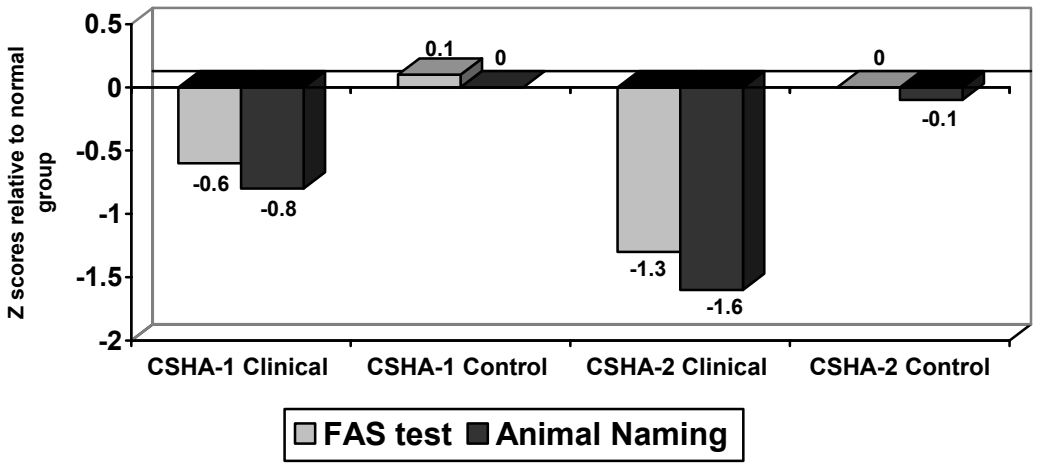

Fig. 2: Standard scores of clinical and control group participants on FAS and Animal Naming tests

Table 6

Digit Symbol Test Performance of Clinical and Control Group Participants at CSHA-1 and CSHA-2

	Clinical Group			Control Group		
	M	SD	n	M	SD	N
Digit Symbol Test						
CSHA-1	21.3	6.5	19	29.9	11.0	24
CSHA-2	14.1	8.2	19	25.5	11.3	24

Discussion

This study investigated the cognitive performance of individuals with incident AD, five years prior to clinical diagnosis. The present results indicate that cognitive changes can be detected when AD participants are at the preclinical phase of the disease, with compromised performance evident on a global indicator of cognition, as well as on measures of episodic memory, verbal fluency, and psychomotor skills. Individuals diagnosed with AD at CSHA-2 demonstrated decline in performance between initial assessment and five year follow-up on all neuropsychological measures. In addition, declines in performance for healthy controls were also evident on the episodic memory free retrieval score and on the psychomotor speed measure, suggesting that these tasks are also sensitive to normal aging processes. The overall results of the present study replicate and expand past findings that the preclinical stage of AD is characterized by cognitive impairment in multiple cognitive domains, including episodic memory, particularly after a long time delay.

An important purpose of the present study was to determine how individuals with preclinical AD perform on the BCRT, an episodic memory measure that controls encoding by means of search and selective reminding procedures and facilitates retrieval with effective categorical cues. Tuokko and her colleages (1991) have previously argued that the rigorous coordination of encoding and retrieval procedures of the BCRT is necessary to ensure that appropriate processing of to-be-remembered material is carried out and that observed deficits are solely attributable to memory capacity and not to attentional or other cognitive factors. Tuokko et al. (1991) also found that 18 out of 45 participants, who were diagnosed with probable or possible AD at 12 to 18 months following initial assessment, performed poorly compared to those who remained nondemented on the BCRT measures of retrieval, acquisition, and retention. The results of the present study confirm this finding with a population-based sample and

a longer reassessment period. The results show that individuals who were diagnosed with probable or possible AD demonstrated poorer performance on all BCRT variables (i.e., retrieval, acquisition, retention, and delayed free recall) at time of diagnosis and five years prior. In addition, clinical participants showed a greater deterioration in performance from initial to follow-up assessment compared to their healthy counterparts on acquisition, retention, and delayed recall. The overall pattern of performance suggests that individuals at the preclinical stage of AD may not benefit from cues, and extensive encoding and retrieval strategies, to the same extent as healthy seniors.

An incidental observation made by Tuokko and her colleages (1991) is that individuals with mild AD and healthy counterparts performed comparably well on the delayed recall trial of the BCRT. The present study did not support this finding. Participants with incident AD at CSHA-2 demonstrated lower performance on the delayed recall trial of the BCRT, compared to their healthy counterparts at time of diagnosis and five years prior. The difference in results between the two studies may be related to methodological variations including the larger community based sample size used in the present investigation. In addition, it is noteworthy that participants in the current study were on average at least 10 to15 years older than the participants involved in Tuokko et al.'s investigation. Given that age is significantly related to episodic memory performance (Craik, 2000), the sample age differences could also account for the discrepancy in results. Alternatively, it is noteworthy that the present results are consistent with other investigations that indicate delayed memory measures have reliably differentiated individuals who progress to develop AD from those who remain healthy at a preclinical stage (Chen et al., 2001; Linn et al., 1995; Saxton et al., 2004).

A second purpose of the present investigation was to determine if differential performance on phonemic vs. category fluency (FAS > Animal Naming) measures is a consistent feature of preclinical AD. Investigations that have compared directly the

performance of AD patients on phonemic and category fluency measures have found that AD patients are impaired relative to normal controls on the category (i.e., semantic), but not the phonemic fluency task (Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Crossley, D'Arcy, & Rawson, 1997; Chen et al., 2001; Monsch et al., 1994; Salmon, Heindel, & Lange, 1999). The present results were inconsistent with these findings. Relative to healthy controls, AD participants in the current sample did not demonstrate poorer performance on the Animal Naming task compared to the FAS test. While there are investigations (see Fox, Warrington, Seiffer, Agnew, & Rossor, 1998) that suggest that semantic memory problems may not be a consistent marker of preclinical AD, in the present case, the relatively small sample size might have limited the ability to detect a statistical difference in performance on the two fluency measures.

The present investigation found that compared to healthy seniors, participants with incident AD demonstrated compromised performance on the WAIS-R Digit symbol measure both at time of diagnosis and five years prior. Interestingly, unlike performance on the episodic and verbal fluency measures, both groups of participants demonstrated a significant decline in performance between the two assessment periods. This finding is consistent with previous studies that have suggested that response slowing or changes in speed of information processing is associated with normal aging (Lezak, 1995; Salthouse, 1996) and is more pronounced in individuals with AD (Crossley, Hiscock, & Foreman, 2004; Storandt & Hill, 1989).

Overall, the results of this study indicate that individuals in the preclinical stages of AD demonstrate compromised performance in several cognitive domains, including episodic memory, verbal fluency, and psychomotor speed. The current study has several advantages. First, the study cohort was selected from a larger population-based sample. This procedure minimizes the selection bias associated with convenience samples, such as senior volunteers or hospital patients, and allows for greater generalizability of

results. In addition, this study accounts for the cognitive changes of normal aging by including a group of demographically matched healthy controls. This study also included the assessment of cognitive functions at two points in time, allowing for longitudinal comparisons, minimizing potential problems associated with a single assessment period.

There are also several limitations to this study. First, because of the specific interest in evaluating performance between CSHA-1 and CSHA-2 on select neuropsychological measures, the study involved a relatively small sample size. This may have led to reduced power in detecting performance differences between clinical and control participants on certain measures (e.g., verbal fluency: FAS vs Animal Naming). To address this potential problem of reduced power, a different sample selection procedure was adopted in a follow-up study, which examined the predictive power of the select neuropsychological measures in distinguishing individuals who progress to develop AD from those who remained healthy over a 5 year period (see Study 3). In addition, the participant sample in the present investigation consisted of relatively older English-speaking Canadians. Consequently, the extent to which the results can be generalized to younger seniors may be limited. In addition, the extent to which the current results can be extended to seniors from diverse populations remains to be determined and was the focus of the next investigation in the current series of studies (see Study 2).

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Study 2: Preclinical Neuropsychological Performance of French-Speaking Canadians with Alzheimer Disease

Introduction

Most research in the area of geriatric neuropsychology has involved seniors of dominant cultural identities who are routinely assessed in English. However, there is increasing evidence that cultural and language differences affect cognitive performance, and consequently diagnostic outcomes. This, in addition to other methodological variations (e.g., definitions of ethnicity, sampling methods, reliability of test translations etc.) between studies, has led to a range of different estimations in the prevalence of dementia across cultural and language groups in North America (Manly, Jacobs, & Mayeux, 1999). However, the finding of age-related increase in the rates of Alzheimer Disease (AD) is ubiquitous. This, coupled with the general population aging trends, suggests that health care professionals are increasingly faced with the challenge of accurately diagnosing dementia in seniors from a variety of cultural and language groups. Therefore, there is a growing need to expand our knowledge of neuropsychological performance in diverse populations.

North American research in the area of cross- and intra-cultural geriatric neuropsychology has mainly focused on Hispanics, African Americans, Asians, and Native Americans residing in the United States. In addition, only a handful of studies involve clinical populations and are conducted in the native language of the participants. Collectively, however, studies have found differences in performances on global screening measures and in specific domains of neuropsychological functions when cultural groups are matched on sociodemographic factors such as age, gender, and levels of education. Bohnstedt and his colleagues (1994) found that the Mini-Mental State Examination (MMSE, Folstein, Folstein, & McHugh, 1975), a global screening measure of dementia, over-diagnosed African American and Hispanic patients

compared to Caucasians when the traditional cut-off score of 23 was used and when the instrument was administered in English, even after adjusting for education between the groups. In another investigation, Marshall and her colleagues (1997) found that only 15 out of the 26 items of the MMSE provide unbiased measurement across groups of English- and Spanish-speaking individuals who were assessed in their native languages, and a separate group of Spanish-speaking individuals assessed in English.

Specific research investigating neuropsychological measures administered in languages other than English has mainly involved Spanish-speaking cultural groups in North America. In their community-based study of non-demented, demographically-matched English- and Spanish-speaking seniors who were assessed in their native language, Jacobs and her colleages (1997) found significant group differences on several neuropsychological measures. Spanish-speaking elders scored significantly lower than their English-speaking counterparts on measures of category fluency (i.e., naming exemplars of animal, food, and clothing), nonverbal abstraction (i.e., identifying similarities and differences from the Dementia Rating Scale, Mattis, 1976), visual recognition memory (i.e., Benton Visual Recognition Test, Benton, 1955), visual perceptual skills (i.e., Benton Visual Recognition Test, matching, Benton, 1955) and auditory comprehension (i.e., Complex Ideation Material subtest from the Boston Diagnostic Aphasia Examination, Goodglass & Kaplan, 1983). Comparable performance between groups was found on the remaining 14 measures of the neuropsychological battery, including those that assessed auditory memory, visual- constructional abilities, and repetition.

Researchers have also found that ethnic differences in neuropsychological performances may be influenced by the inherent differences in linguistic factors of native languages. For example, the fact that the Spanish language consists of less words beginning with the letters “F”, “A”, and “S” compared to the English language has been

cited as the potential reason for the poor performance of Spanish-speaking healthy seniors on the FAS, verbal fluency test (Loewenstein, Arguelles, Arguelles, & Linn-Fuentes, 1994). In the same way, Kempler and his colleagues (1998) found that Vietnemese-speaking individuals generated significantly more animal names on a category fluency task compared to Spanish-speaking individuals of equivalent educational background. The authors attributed this difference to the finding that Vietnamese animal names are mainly monosyllabic while Spanish animal names consist of multiple syllables; the better performance of Vietnamese participants was attributed to the differences in word length of animal names between Vietnamese and Spanish languages, since word length is a parameter that is known to affect word production.

In an intra-cultural investigation using cohorts of Swedish-speaking participants from The Kungsholmen Project, a longitudinal, population-based study of dementia conducted in Sweden, Small and his colleagues (2000) found significant differences between individuals who progressed to develop AD from those who remained healthy over a six year period on the Swedish version of the MMSE. Particularly, AD patients performed more poorly on the orientation to time, and the delayed word recall items of the MMSE. In another investigation of participants from the Kungsholmen Project epidemiological study, Bäckman and his colleagues (2001) found that incident AD cases performed more poorly than their nondemented counterparts both three and six years before diagnosis on both free recall and recognition measures of episodic memory. In contrast, there were no group differences with respect to immediate memory and there was no evidence of accelerated decline of episodic memory abilities in the incident AD group from six to three years before diagnosis.

It is noteworthy that some investigations have indeed failed to find discrepancies in test performance among cultural and language groups after participants were matched on sociodemographic variables. For example, in a recent study, Whyte and her

colleagues (2005) found the CERAD neuropsychological battery (Morris et al., 1989) to be an efficient cognitive screening assessment measure for English-speaking Native Americans. In comparing the performance of 40 Native American seniors and demographically matched Caucasians diagnosed with AD, Whyte et al. (2005) did not find statistically significant differences between the two groups on any of the CERAD measures. Interestingly, when compared to the Caucasian group, Native Americans were found to demonstrate slightly better, albeit not statistically significant, performance on most CERAD measures, with the exception of the constructional praxis test that assessed drawing of geometrical figures. Other investigations have involved comparatively smaller sample groups. For example, Ripich, Carpenter, and Ziol (1997) compared 11 African Americans and 32 Whites with AD and reported no significant ethnic differences on measures of naming, picture vocabulary, verbal abstraction, verbal list learning, and pragmatic language.

The heterogeneity of findings in previous studies suggests that language and cultural differences can impact cognitive performance and not always in the expected direction. Although the source of immigration to Canada has changed over the years, with increasingly more people moving from non-European countries, next to English, French continues to be the most predominant language spoken in households (Statistics Canada, 2002). In addition, with their unique immigration and cultural histories, there is little reason to question the distinct identity of the French-speaking peoples of Canada. As is the case with other cultural groups, the population of French-speaking seniors in Canada is expected to grow exponentially in the future. Given that previous studies have implicated language as a factor that can influence cognitive performance and potentially lead to variable diagnosis of degenerative conditions such as AD and other dementias, there was an interest in understanding the neuropsychological performance of French-speaking Canadians.

The Canadian Study of Health and Aging (CSHA; described in Appendix 1) provided a unique opportunity to examine preclinical and longitudinal cognitive performance of French-speaking Canadians across the country. A total of 1879 participants were administered the neuropsychological battery of measures at the first wave of the study (CSHA-1). Of these individuals, 447 were assessed in their preferred language of French and surviving participants were subsequently followed up at approximately five year intervals for CSHA-2 and CSHA-3. The present investigation examined the preclinical and longitudinal performance of a cohort of French-speaking CSHA participants on select neuropsychological measures.

Conceptually, the goals of the present study are identical to those of Study 1, described above. Specifically, this study compares performance of French-speaking participants diagnosed with AD at CSHA-2 and matched normal controls on 3MS, BCRT, FAS test, Animal Naming, and WAIS-R Digit Symbol measures between CSHA-1 and CSHA-2 to determine if differences are detectable at initial assessment (i.e., five years prior to AD diagnosis). In addition, this study examines if differential performance in phonemic and category fluency measures are evident in a French-speaking population. It is noteworthy that the selected measures were available in French versions and this was one of reasons they were initially included in the CSHA neuropsychological battery (Tuokko, Kristjansson, & Miller, 1995). In addition, it is also notable that, overall, the core battery was equally well tolerated by French- and English-speaking participants (Tuokko et al., 1995).

The rational to study the cognitive performance of English and French-speaking Canadians separately was multifaceted. First and foremost, there was an aspiration to address the growing need for neuropsychological studies with non-English speaking cultural groups, to examine if language-related cognitive differences are evident in a Canadian population. Second, there was a need to consider the demographic and socio-

cultural differences between participants who were administered the CSHA neuropsychological battery in English and in French. Tuokko and her colleagues (1995) found that community-dwelling, French-speaking participants refused to participate in the neuropsychological assessment at higher rates and were less likely than English-speaking participants to receive a diagnosis of dementia. Moreover, there were significant differences in demographic status, including educational attainment between the English- and French-speaking CSHA samples. Tuokko and her colleagues report that French speaking participants who participated in the CSHA neuropsychological assessment component, on average, had about three years less education than their English-speaking counterparts. Interestingly, the assumption that lower education leads to higher rates of dementia diagnosis did not hold true for the French-speaking sample in the CSHA. Rather than attempt to control for sociocultural factors using statistical methods, the decision was made to conduct two separate investigations using these distinct populations.

Methods

Study Design and Participants. Of the 326 (98 males and 228 females) individuals who received an incident diagnosis at CSHA-2, 12 individuals completed neuropsychological assessment battery in French at both CSHA-1 and CSHA-2. The neuropsychological performance of these 12 individuals (7 with probable AD and 5 with possible AD) were compared to 11 age-, gender-, and education-matched healthy adults. Healthy controls were selected from a group of 63 French-speaking participants who were assessed to be cognitively normal (i.e., no cognitive impairment) at CSHA-2 and for whom neuropsychological data were available at both CSHA-1 and CSHA-2. A suitable match for one AD female participant in terms of gender and education was unavailable; consequently, this resulted in the unequal sample size, with one less participant in the control group, as reported above.

Details of demographic and background characteristics of incident AD cases and healthy controls are presented in Table 7. There were 7 males and 5 females in the clinical group and 7 males and 4 females in the control group. Univariate analyses indicated no significant age- or education- differences between the clinical and control groups, $t(21) = -.61$, $p < .55$ for age, and $t(21) = .56$, $p < .57$, for education, which reflected the success of the matching process. As expected, none of the participants in the clinical or control groups were diagnosed with dementia at CSHA-1. However, significantly more participants in the clinical group were classified as having clinical impairment but no dementia (CIND) at CSHA-1 than were individuals in the control group (8 vs 0 respectively, $\chi^2 (1, N = 23) = 11.2$, $p < .01$), suggesting that more individuals in the clinical group had subthreshold levels of cognitive impairment five years prior to clinical diagnosis.

Measures. From the CSHA neuropsychological test battery, measures assessing global cognitive functioning (i.e., 3MS), episodic memory (i.e., BCRT), verbal fluency (i.e., FAS test and Animal Naming), and psychomotor speed (i.e., WAIS-R Digit Symbol Test) were chosen for analyses. To reiterate, these specific measures were selected for inclusion in the present study because they were administered in an unmodified manner in all three waves of the CSHA, and the cognitive domains assessed by the selected measures are typically reported to decline in dementia. In addition, the major goals of this study are identical to those of Study 1, involving English-speaking participants. Specifically, there was an interest in examining how French-speaking preclinical AD patients perform on the BCRT test, which has previously been suggested as an episodic memory test that is not influenced by other cognitive processes, such as impairments in attention and learning strategies. As well, there was a specific interest in examining the differential performance in phonemic vs category fluency measures in preclinical AD. Performance on a non-memory measure was assessed using the WAIS-R Digit Symbol

Table 7

Demographic Summary For Clinical and Control French-speaking Participants

	Clinical Group		Control Group	
Variable	M	SD	M	SD
Age at CSHA-2	82.3	5.4	81.0	4.3
Education	5.8	3.1	6.5	2.7
	N		N	
Gender				
Male	7		7	
Female	5		4	
Residence at CSHA-2				
Community	11		8	
Institution	1		3	
CSHA-1 Diagnosis				
NCI	4		11	
CIND	8		0	

subtest. Please refer to Table 2 in Study 1 for a summary of specific test scores analyzed in the present study.

S*tatistical Analysis.* Longitudinal changes in cognitive performance were examined for incident AD cases and healthy controls between initial assessment (CSHA-1) and five year follow-up (CSHA-2). Separate 2(Group: Clinical vs. Control) X 2(Time: CSHA-1 vs. CSHA-2) repeated measures ANOVAs, with group as a between-subject variable and time as a within-subject repeated measure were conducted for each neuropsychological score. To further understand resultant interaction effects from these ANOVAs, post hoc analyses in the form of matched sample t-tests were conducted to examine mean-level differences between clinical and control groups at initial and reassessment. In addition, performance on the phonemic fluency and category fluency measures were directly compared with a 2(Group: Clinical vs Control) X 2(Task: FAS vs Animal Naming) X 2 (Time: CSHA-1 vs CSHA-2) repeated measures ANOVA, with group as a between-subject variable and task and time as within-subject repeated variables. The FAS and Animal naming scores were converted to z scores for analyses. ANOVA tables for the analyses of neuropsychological measures are presented in Appendix C.

Results

Global Indicator of Cognition. The 3MS performance of the French-speaking participants at CSHA-1 and CSHA-2 are presented in Table 8. There was a significant main effect of group explained by the poorer 3MS performance of the clinical group relative to the control group at CSHA-1 and CSHA-2, $F(1,20) = 32.40$, $p < .001$. There was also a significant main effect of time, $F(1,20) = 6.95$, $p < .05$ that was entirely explained by the participants in the clinical group who demonstrated a greater decline in 3MS performance between CSHA-1 and CSHA-2 assessments compared to their healthy counterparts. This group difference was confirmed by both the significant

Table 8

3MS Performance for Clinical and Control Group Participants at CSHA-1 and CSHA-2 Assessments

	Clinical Group		Control Group	
	M	SD	M	SD
CSHA-1	73.7	9.7	83.7	6.0
CSHA-2	60.5	10.2	85.0	8.3

interaction effect between group and time variables, $F(1,20) = 10.32$, $p < .05$ and by post-hoc analyses using matched sample t-tests which revealed a significant decline between CSHA-1 and CSHA-2 for the clinical group, $t(11) = 3.46$, $p < .01$ but not the normal control group, $t(10) = -1.01$, $p = .33$.

Episodic Memory Measure (BCRT). Episodic memory performance (i.e., BCRT scores) of French-speaking clinical and control participants at initial assessment and follow-up is presented in Table 9. There were significant effects for diagnostic group and time on all four BCRT variables. As expected, participants in the clinical group performed more poorly with regard to retrieval, acquisition, retention, and delayed free recall of BCRT items at initial- and re-assessment compared to participants in the control group, $F(1,19) = 28.43$, $p < .001$ for retrieval, $F(1,19) = 13.36$, $p < .01$ for acquisition, $F(1.21) = 27.0$, $p < .01$ for delayed free recall, $F(1,21) = 13.79$, $p < .001$ for retention. The significant main effect of time, $F(1,19) = 26.62$, $p < .001$ for retrieval, $F(1,19) = 17.07$, $p < .01$ for acquisition, $F(1,21) = 19.2$, $p < .001$ for delayed free recall, $F(1,21) = 21.40$, $p < .001$ for retention, reflecting a decline in performance between CSHA-1 and CSHA-2 was qualified by significant Group X Time interactions for all variables, $F(1,19) = 12.24$, $p < .01$ for retrieval, $F(1,19) = 18.00$, $p < .01$ for acquisition, $F(1,21) = 30.74$, $p < .01$ for delayed free recall, $F(1,21) = 21.40$, $p < .01$ for retention. Post hoc analysis indicated that participants who progressed to develop AD between CSHA-1 and CSHA-2 demonstrated a greater deterioration of performance over the five-year time period on all BCRT variables compared to healthy older adults (clinical group: $t(9) = 4.53$, $p < .01$ for retrieval, $t(9) = 4.08$, $p < .01$ for acquisition, $t(11) = 4.09$, $p < .01$ for delayed free recall, $t(11) = 4.84$, $p < .01$ for retention; control group: $t(10) = 2.10$, $p = .06$ for retrieval, $t(10) = -.27$, $p = .80$ for acquisition, $t(10) = 2.03$, $p = .07$ for delayed free recall; note: t-statistic is not available for retention since control group participants did not exhibit any change in performance between CSHA-1 and CSHA-2. It is noteworthy that post hoc analysis for

Table 9

Neuropsychological Test Performance of Clinical and Control Group Participants at CSHA-1 and CSHA-2

	Clinical Group			Control Group		
Neuropsychological Measure	M	SD	N	M	SD	n
BCRT						
Retrieval						
CSHA-1	22.2	4.6	10	28.1	2.0	11
CSHA-2	13.2	8.6	10	26.4	2.7	11
Acquisition						
CSHA-1	34.8	1.9	10	35.6	0.9	11
CSHA-2	28.0	6.3	10	35.7	0.6	11
Delayed Free Recall						
CSHA-1	8.1	2.1	12	10.3	1.2	11
CSHA-2	4.1	3.3	12	9.5	1.3	11
Retention						
CSHA-1	11.6	0.8	12	12	0.0	11
CSHA-2	9.3	2.2	12	12	0.0	11
Fluency Measures						
FAS						
CSHA-1	13.8	5.4	10	17.1	6.8	9
CSHA-2	8.6	8.7	10	13.6	5.1	9
Animal Naming						
CSHA-1	9.9	2.1	12	13.6	3.9	11
CSHA-2	6.4	2.4	12	12.0	3.4	11
Digit Symbol						
CSHA-1	14.2	7.5	9	23.9	7.1	11
CSHA-2	12.1	4.8	9	19.0	8.4	11

retrieval and delayed free recall performance of control participants all approached significance. This reflects a decline for the control group on these memory variables that is consistent with expected age effects. Limited power related to the small sample size likely hindered the possibility of finding statistical significance.

Verbal Fluency Measures: FAS test and Animal Naming. Table 9 also shows the phonemic (FAS) and category (Animal Naming) fluency scores for French-speaking clinical and control groups at CSHA-1 and CSHA-2. Separate repeated measures ANOVA's revealed a significant effect of time for the FAS variable, suggesting that participants in both the clinical and control groups demonstrated a decline in performance between the two assessment periods, $F(1,17) = 6.05$, $p < .05$. Main effect of group and interaction effect between time and group were not found to be significant for the FAS variable. With respect to the Animal Naming Test, significant effects of group, $F(1,21) = 18.62$, $p < .001$, and time, $F(1,21) = 14.22$, $p < .01$ were found; the interaction between these variables was nonsignificant. Evidently, clinical group participants recalled fewer animal names at initial assessment and at follow-up compared to control group participants and both groups of participants showed a decline in performance, recalling relatively fewer animal names at CSHA-2 and CSHA-1.

Letter and category fluency scores were directly compared by converting each participant's score on both measures to standard scores (z scores), expressed in standard deviations from the mean of an independent sample of healthy older adults (n=51; see Fig. 3). A 2 (Group: Clinical vs Control) X 2 (Task: FAS test vs Animal Naming) X 2 (Time: CSHA-1 vs CSHA-2) repeated measures AVOVA was performed with group as a between-subjects variable and task and time as within-subject repeated variables. A significant main effect of group was found, with the clinical group performing more poorly on both fluency measures at initial and reassessment relative to the control group, $F(1,17) = 10.22$, $p < .01$. As well, a significant main effect of time

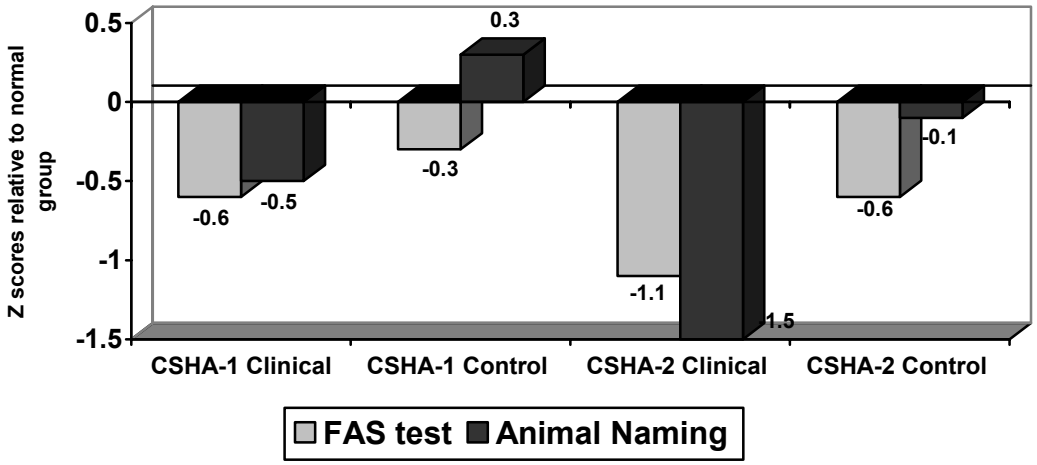

Fig. 3. Standard scores of clinical and control group participants on FAS and Animal Naming tests administered in French.

suggested that the performance of clinical and control participants declined on both fluency measures between initial assessment and follow-up, $F(1,17) = 15.17$, $p < .01$. In addition, a significant interaction effect between task and group suggested that the difference in performance between the two groups is greater for the Animal Naming test than for FAS test at both CSHA-1 and CSHA-2, $F(1,17) = 6.34$, $p < .05$. No other main or interaction effects were observed.

Psychomotor Speed Measure: WAIS-R Digit Symbol. Data for the Digit Symbol test (presented in Table 9) were analyzed using a 2 (Group: Clinical vs Control) X 2 (Time: CSHA-1 vs CSHA-2) repeated measures ANOVA, with group as a between-subject variable and time as a within-subject repeated variable. As with the English sample, significant main effects for group and time were found. Individuals diagnosed with AD at CSHA-2 performed significantly worse on the Digit Symbol test both at initial and reassessment relative to healthy older adults, $F(1,18) = 7.71$, $p < .01$. In addition, both groups of participants evidenced a significant decline in performance between the two assessment periods, $F(1, 18) = 8.82$, $p < .01$. An interaction effect between the time and group variable was not significant.

Discussion

This study investigated the neuropsychological test performance of French-speaking Canadians with incident AD, five years prior to clinical diagnosis. The present results indicate that French-speaking AD participants demonstrated lower performance on several of the neuropsychological measures at time of diagnosis and five years prior, compared to demographically-matched healthy seniors. However, compromised cognitive abilities were not uniform across all domains investigated. French-speaking individuals diagnosed with AD at CSHA-2 performed significantly lower than healthy controls on the global indicator (3MS), the episodic memory (BCRT), the category fluency (Animal Naming), and the psychomotor speed (WAIS-R Digit symbol) measures

at initial assessment (i.e., CSHA-1). In contrast, statistically significant group differences between clinical and control participants were not evident at CSHA-1 on the letter fluency (FAS test) task. In addition, French-speaking participants with AD demonstrated greater decline in performance between the CSHA-1 and CSHA-2 assessments on the 3MS and the BCRT measures, but the decline in performance was comparable for both clinical and control groups on the verbal fluency (Animal Naming and FAS test), and psychomotor speed (WAIS-R Digit Symbol) measures.

The results of the present study confirm the presence of preclinical changes in multiple cognitive domains in French-speaking Canadians, using traditional neuropsychological assessment measures. The finding that French-speaking AD participants demonstrate preclinical deficits in a global indicator of dementia (3MS) is consistent with other investigations that have used such instruments for assessing AD is diverse language groups. Decline in MMSE scores was reported for a Swedish sample three- to six-years before clinical diagnosis in a study by Small and his colleagues (2000). It is noteworthy that the MMSE and the 3MS were found to yield comparable reliability estimates when performance on these measures was directly compared in a study using a sample of English-speaking CSHA participants (Tombaugh, McDowell, Kritjansson, & Hubley, 1996).

Even though English-speaking and French-speaking participants were not directly compared with statistical procedures in the present investigation, the similarities and differences in the performance trends between these groups are worthy of mention and discussion. First, preclinical deficits in the area of episodic memory were consistently noted for both language groups. Given that memory deficit is a principal diagnostic feature of AD, compromised episodic memory performance in the French-speaking sample was confirmatory rather than surprising to find. However, the compromised performance of French-speaking AD participants on all free and cued

recall trials of the BCRT five years prior to diagnosis suggests that language may not mediate the ability of patients to benefit from supported encoding and retrieval. The overall finding of preclinical episodic memory deficit in a group of French-speaking seniors is consistent with other investigations that have sampled non-English speaking individuals (Bäckman et al., 2001; Marcoupulous, McLain, & Giuliano, 1997) and confirms that episodic memory deficit is a instrumental marker of preclinical AD.

With regard to specific BCRT scores, it was discussed in Study 1 that Tuokko and her colleagues (1991) found that individuals with mild AD and healthy counterparts demonstrated comparable performance on the delayed recall trial of the BCRT. The present results do not support this finding. Similar to the English-speaking sample, French-speaking participants with incident AD at CSHA-2 demonstrated lower performance on the delayed recall trial of the BCRT compared to their healthy counterparts at time of diagnosis and five years prior. This finding is consistent with other investigations that have revealed that delayed memory measures are reliable in distinguishing individuals at risk of developing AD at a preclinical stage (Chen et al., 2001; Linn et al., 1995; Saxton et al., 2004).

Different trends in performance on the verbal fluency measures were evident for the English- and French- speaking samples. Compared to their healthy counterparts, English-speaking AD participants demonstrated weaker performance on both phonemic fluency (FAS) and category fluency (Animal Naming) tasks at initial assessment. In addition, they also demonstrated greater decline in performance between CSHA-1 and CSHA-2 on both measures. This was not the case with the French-speaking sample; the difference in performance between AD participants and normal controls was greater on the Animal naming test than the FAS test at both initial and reassessment.

Several factors may have contributed to the above described discrepancies. First, it is noteworthy that performance on these language measures is known to be

significantly affected by educational attainment; individuals with more education tend to demonstrate better performance (Gasquoine, 1999; Kempler, Teng, Dick, Taussig, & Davis, 1998; Wiederholt et al., 1993). Thus, observed changes in performance between two assessment periods can be related to higher baseline ability for the more educated group. Collectively, the English-speaking participants in the current study had approximately 10 years of formal education (M = 9.98; SD = 4.3) compared to the French-speaking group that had approximately 6 years (M = 6.17; SD = 2.9) of formal education. In addition, comparison of raw scores indicates that English speaking participants indeed had higher baseline performance on both the FAS and Animal Naming measures compared to their French-speaking counterparts. It is suspected that the interaction between education and cognitive skills could have played a role in the observed discrepancies in performance on verbal fluency measures between the language groups. Second, issues of word fluency or salience may have contributed to the observed results. For example, the number of words beginning with “F”, “A”, and “S” may be different between the English and French languages and this may have resulted in fewer words being generated by the French-speaking sample.

The present investigation was conducted to determine if differential performance on phonemic vs. category fluency (FAS > Animal Naming) measures is a consistent feature of preclinical AD. Investigators who have compared the performance of AD patients on phonemic and category fluency measures directly have found that patients are impaired relative to normal controls on the semantic, but not the phonemic fluency task (Butters et al., 1987; Monsch et al., 1994; Crossley, D’Arcy, & Rawson, 1997; Saxton et al., 2004). This differential performance was not observed with the English sample. However, in the French sample, AD patients demonstrated significantly poorer performance on Animal Naming compared to the FAS. At face value, this finding suggests that a semantic memory deficit, characterized by compromised performance

on a category fluency measure is a significant feature of preclinical AD in French-speaking Canadians. However, as discussed above, word saliency and educational attainment may have served as confounding variables. In addition, linguistic factors may have also contributed to differences in Animal Naming ability. For example, Kempler et al. (1998) found significant ethnic differences in Animal Naming ability between members of five ethnic groups (African American, White, Chinese, Hispanic, and Vietnamese), assessed in their native language; Vietnamese-speakers produced the highest number and Spanish-speaking participants produced the lowest numbers of animal names in their sample. The authors attributed the exaggerated difference between these two groups to linguistic factors, namely that Vietnamese animal names on average are shorter and mono-syllabic while Spanish animal names are longer, involving 2 to 3 syllables per word than in the other languages involved in the study. It is not known if similar linguistic differences are apparent between the English and French languages. If so, such factors would serve as confounding variables in assessing performance between French- and English-speaking participants on the Animal Naming measures.

Comparable trends in performance were evident between French- and English-speaking participants on the WAIS-R Digit Symbol measure. Mainly, in both samples, compromised performance at a preclinical stage was evident for AD patients, but both clinical and control participants demonstrated a decline in performance between initial and reassessment. This supports previous investigations that have suggested that a decrease in speed of processing is a general mechanism evident in cognitive aging and is generally culturally invariant (Park, Nisbett, & Hedden, 1999).

The advantages and limitations of the current study are similar to those of Study 1. First, the use of a community-based sample allows for generalizability of results to other North Americans of French background. This study also accounts for changes in

normal aging by including healthy normal controls, and investigated change over a five year time period allowing for assessment of the cognitive decline of preclinical AD over time in a French-speaking sample. However, the small sample size was a notable limitation that likely led to limited power to accurately detect “true” cultural differences. For example, with regard to episodic memory performance, low power limited the ability to detect age-related cognitive decline in healthy controls, in turn artificially inflating performance differences between the cultural groups.

The findings of the present study support the growing body of literature suggesting that language differences may play a role in cognitive performance (Gasquoine, 1999; Kempler et al., 1998; Manly, Jacobs, & Mayeux, 1999). Different cognitive performance trends were observed between English- and French-speaking Canadians particularly with regard to language-based verbal fluency measures. These differences should be taken into consideration if diagnostic decisions are made based on such instruments. The results of this study further highlight the importance and the need to study neuropsychological performance in diverse populations.

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Studies 3 and 4: A Brief Introduction

Available treatments for AD appear to be most effective when prescribed at early stages of the disease (Kelly, Harvey, & Cayton, 1997). Consequently, a major goal in the clinical diagnosis of AD is the detection of the condition at the earliest possible stages. Previous investigations have found that AD patients exhibit subtle, isolated impairments in various cognitive domains long before the clinical signs of the condition become apparent (Arnáiz & Almkvist, 2003; Bondi & Monsch, 1998; Small, Mobly, Jonsson Laukka, Jones, & Bäckman; Tierney, Yao, Kiss, & McDowell, 2005). Consistent with these findings, the results of the first two studies in the present series of investigations also indicate that cognitive deficits can be detected at the preclinical stage of AD in samples of English- and French-speaking Canadians. Although some differences in cognitive performance were evident, in general, both English- and French-speaking participants from the CSHA were found to demonstrate compromised performance five years before clinical diagnosis on a global indicator of dementia, as well as on measures of episodic memory, verbal fluency, and psychomotor speed.

The next two investigations were undertaken to examine the predictive value of the selected neuropsychological measures that were examined in Studies 1 and 2. Specifically, the goal was to determine how well the four core neuropsychological measures (i.e., BCRT, FAS test, Animal Naming, and WAIS-R Digit Symbol) distinguish individuals who progressed to develop AD from those who remained healthy over the five year time period between CSHA-2 and CSHA-3. In addition, there was also an interest in determining to what extent demographic variables such as age, gender, and education contribute to the prediction of dementia.

Given that a significant limitation of Studies 1 and 2 was the small sample size, different participant selection and statistical analysis procedures were employed to determine the utility of the neuropsychological measures in predicting dementia. Study 3,

which is presented in manuscript format, involved English-speaking participants. This study also included an validation component. That is, the best predictors were used to determine who amongst an independent group of individuals, deemed to be at risk of developing AD, actually go on to meet criteria for dementia. The final study (i.e., Study 4) in this series was conducted to determine which neuropsychological and demographic predictors best distinguish French-speaking AD participants from those who remain healthy over a five year period.

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Preclinical Neuropsychological Predictors of Alzheimer Disease: How Well Can They Prognosticate Clinical Diagnosis?

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Running Head: Predictors of Alzheimer Disease

Abstract

Objective: To determine the utility of neuropsychological measures and demographic variables included in the Canadian Study of Health and Aging (CSHA) in predicting dementia over a five-year period.

Background: Alzheimer disease (AD) patients exhibit deficits across multiple cognitive domains years before clinical diagnosis. Studies have not verified the efficacy of an established set of predictors to prognosticate outcome in an at-risk sample.

Methods: The CSHA, a population-based study of dementia, was conducted in three waves (CSHA-1, 1990-1991; CSHA-2, 1996-1997; CSHA-3, 2000-2001). Different cohorts of English-speaking community residents who completed neuropsychological testing were included in prediction and validation analyses. First, CSHA-2 incident AD cases (n=78) and normal controls (n=147) were followed retrospectively to CSHA-1 to identify the neuropsychological and demographic variables that best discriminate these two groups. To determine the predictive validity of the significant variables, the variables were used to classify an independent group of CSHA-2 participants deemed to be at risk for AD and for whom diagnostic outcome was recorded at CSHA-3 (n=96).

Results: Age, delayed free recall, and speeded visuomotor processing emerged as three significant predictors from logistic regression in the prediction analyses. The model was significant at χ^2 (3) = 198.2, p<.001 (sensitivity: 88.5%; specificity: 93.9%). The three-variable model was able to accurately classify 68% of individuals from an at risk sample. The overall classification analysis was significant at χ^2 [1] = 12.1 p <.001 (sensitivity: 69%; specificity: 67%).

Conclusions: Age as well as performance on tests of memory and speeded visuomotor processing can identify individuals with high and low probabilities of developing dementia over a five-year time frame.

Introduction

Alzheimer Disease (AD) is characterized by subtle neuropsychological deficits that precede diagnostically significant cognitive, behavioural, and social changes (Bondi & Monsch, 1998; Small et al., 2003). The term “preclinical phase” is often used to describe the period between disease onset and subsequent clinical diagnosis. In recent years, there have been increasing developments in attempts to understand the precise characteristics of individuals in the preclinical phase of AD. Collectively, the studies in this area aim to accurately identify individuals at risk of developing dementia at the earliest possible stage in order to initiate effective treatments.

Previous investigations have revealed numerous neuropsychological predictors of progression to AD (Arnáiz & Almkvist, 2003). Preclinical deficits have been shown in both global indicators of cognition, such as Mini-mental State Examination (Folstein, Folstein, & McHugh, 1975; Small et al., 2000) and in multiple specific domains of cognitive functioning, including attention (Linn et al., 1995; Perry & Hodges, 1999; 2000; Tierney et al., 1996), psychomotor speed (Masur et al., 1994), executive functions (Jacobs et al., 1995; Perry & Hodges, 1999; 2000), language ability (Flicker, Ferris, & Reisberg, 1991; Snowdon et al., 1996), and visuo-spatial skills (Mitrushina, Uchiyama, & Satz, 1995). However, memory deficits appear to be the most pronounced and consistent cognitive feature of preclinical AD. Numerous studies have shown that episodic memory deficits in preclinical AD exist for both verbal (Linn et al., 1995; Tierney et al., 1996) and non-verbal (Small et al., 1997) information, as well as for different retrieval conditions, including free recall (Linn et al., 1995; Grober, Lipton, Hall, & Crystal, 2000), cued recall (Bäckman & Small, 1998; Tuokko et al., 1991), and recognition (Bäckman, Small, & Fratiglioni, 2001; Fox at al, 1998). In addition, a recent investigation by Spaan and her colleagues (2005) revealed that semantic and implicit memory problems are also apparent in preclinical dementia and may explain some types

of episodic memory problems (i.e., compromised cued recall and recognition abilities) seen at this early stage.

To identify preclinical neuropsychological predictors of AD, researchers have traditionally adopted research designs that involve either longitudinal or cross-sectional comparisons. The primary focus has been on determining the strength of the association between an indicator or predictor (i.e., neuropsychological measure or demographic characteristic) and dementia in terms of risk ratios and predictive power. To date, no studies have verified how well an established set of predictors can prognosticate who amongst a group of individuals deemed to be at risk for developing dementia will eventually progress to develop the disease. Validating an established set of predictors is imperative, as such information will aid in making meaningful and accurate prognostic judgments in clinical settings.

The goals of the present study are twofold. First, we aim to determine the predictive value of select neuropsychological measures used in the Canadian Study of Health and Aging (CSHA). Specifically, we are interested in determining which of a select group of neuropsychological measures best distinguish individuals who developed AD from those who remained healthy over a five year time period. We are also interested in determining to what extent demographic variables, such as age, gender, and education contribute to the prediction of AD. These variables have previously been implicated as risk factors for AD. The chances of developing AD increase with age and low educational attainment (Launer et al., 1999; Lindsay et al., 2002). In addition, some investigations have found rates of AD to be higher among women than men (Launer et al., 1999). The second goal of the present study is to examine how well the best neuropsychological and demographic predictors, identified in the first set of analyses, can determine who amongst a second, independent group, of individuals deemed to be at risk of developing dementia, actually go on to meet diagnostic criteria for dementia. The two goals of this

study are addressed in separate sets of analyses, termed “prediction study” and “validation study” as described below.

Background. The Canadian Study of Health and Aging (CSHA) was a population-based, longitudinal study that investigated the prevalence of dementia in Canadians aged 65 years and older. This CSHA was conducted in three waves; the first wave was carried out between 1990 and1991 (CSHA-1) and surviving participants were seen for follow-ups between 1996 and1997 (CSHA-2), and again between 2000 and 2001 (CSHA-3). The longitudinal design of the study presents a unique opportunity to obtain both retrospective (e.g., CSHA-2 vs CSHA-1) and prospective (e.g., CSHA-2 vs CSHA-3) information on the cognitive performance and diagnostic status of older Canadians. Different cohorts of participants (as described below) from the CSHA were identified for the prediction and validation phases of the present investigation.

A representative sample of individuals age 65 and over (n = 10,263) were drawn equally from five geographic Canadian regions (e.g., British Columbia, the Prairies, Ontario, Quebec, and the Atlantic region) and were included in the first wave of the CSHA. All participants were assessed in their preferred language of English or French. The CSHA drew samples from two distinct populations of individuals, residents of the community and residents of institutions. Only community-dwelling residents who were assessed in English were included for analysis in the prediction and validation phases of the present study. The Modified Mini-Mental State Examination (3MS; Teng & Chui, 1987), a screening measure for cognitive impairment, was administered to the CSHA community-dwelling residents to determine who would be included in the clinical assessment component of the study. Individuals who obtained a 3MS score between 50 and 78 out of a possible total score of 100 (i.e., potential cases), and a randomly selected subset of individuals who scored 78 or more out of 100 (i.e., potential healthy controls) were requested to undergo a clinical assessment.

The clinical assessment component of the CSHA was designed to confirm the presence of dementia and to facilitate differential diagnoses. This component included a series of separate evaluations. First, a nurse collected medication information, re-administered the 3MS, and interviewed a caregiver using a semi-structured version of the Cambridge Examination of Mental Disorders in Older Adults (CAMDEX; Roth et al., 1988). Second, a trained psychometrician, blind to the information compiled by the nurse, administered the neuropsychological test battery to all participants who obtained a 3MS score between 50 and 78 on the nurse's administration and to a random sample of those who scored over 78 (i.e., healthy controls). Subsequently, a neuropsychologist evaluated the neuropsychological test results and the CAMDEX data, based on the caregiver interview. Third, a physician performed a physical and neurological examination and made a preliminary diagnosis on the basis of this medical information and the nurse's evaluation. Laboratory bloodwork was conducted for consenting participants suspected of having dementia. Finally, a consensus case conference was held during which the physician and the neuropsychologist reviewed their respective preliminary diagnoses, made a differential diagnosis, and arrived at a final consensus diagnosis based on all historical and currently available clinical information.

For CSHA-1 (data collected 1991-1992), diagnostic criteria for dementia were based on the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (*DSM-III-R*, American Psychiatric Association, 1987). Differential diagnosis for AD, depression, and other subcategories of dementias were based on the DSM-III-R, the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984), and the tenth revision of the International Classification of Disease (ICD-10; World Health Organization, 1992). Diagnostic categories included the following: no cognitive impairment (NCI), cognitive impairment but not dementia

(CIND), Alzheimer's Disease (AD: probable or possible), Vascular Dementia (VD), other specific dementia, or unclassified dementia. It is noteworthy that the diagnoses of CIND was based on clinical impression and was given to individuals who neither met criteria for NCI or dementia (Tuokko et al., 2003)

Surviving participants from CSHA-1 were re-contacted for CSHA-2 five years later, between 1995 and1996, to examine the incidence, clinical progression, and mortality rates associated with dementia in Canada. The same research methodology described for CSHA-1 was used in CSHA-2 to determine participant eligibility for clinical and neuropsychological assessments. The third wave of the CSHA (i.e., CSHA-3) was conducted another five years later, between 2001 and 2002, with minor modifications in research design. CSHA-3 did not involve a nurse's evaluation. Instead, during an initial screening interview a trained interviewer obtained information from a caregiver about the participant's functional, cognitive, and medical status and administered the 3MS to the participant. The neuropsychological battery was abbreviated and administered to all remaining and consenting participants who did not have a diagnosis of dementia at CSHA-2 and who scored between 50 and 89 out of 100 on the 3MS at CSHA-3.

The clinical assessments at CSHA-2 and CSHA-3 used the same diagnostic criteria as in CSHA-1. At CSHA-3, clinicians arrived at a consensus diagnosis in two stages. The first diagnostic decision was made without reference to the CSHA-2 neuropsychological assessment results. Subsequently, all information, including assessment results from CSHA-1 and 2, was reviewed in preparation for a final consensus diagnostic decision.

Overall sample for current studies. As described earlier, only English-speaking, community-dwelling residents were included for analysis in the present studies. The decision to focus on this select sample was based on conclusions drawn from previous investigations that examined the neuropsychological assessment component of the

CSHA. Tuokko and her colleagues (1995) found significant differences in participation rates and diagnosis of dementia between English- and French- speaking participants. French-speaking participants living in the community demonstrated a higher refusal rate and were less likely than English-speaking participants to receive a dementia or a CIND diagnosis. Similarly, Steenhuis and Østbye (1995) found significant differences in neuropsychological performance between CSHA participants residing in the community and those living in institutions. Institutional residents presented with higher rates of cognitive dysfunction and subsequently were more likely to be diagnosed with dementia. Taken together, these investigations highlight the importance of considering language and sociodemographic factors when studying diverse populations of individuals. Rather than attempt to control for these sociocultural factors using statistical methods, we decided to base the current study on the English-speaking community residing participants. Another factor that influenced the selection of our overall participant group was our interest in identifying individuals who are representative of those seen in clinical settings for diagnostic work-up. CSHA participants who were living in the community rather than in institutional care best represent those individuals typically referred to clinical settings for assessment

In the present study, we began by examining the ability of CSHA neuropsychological measures and demographic variables to predict the development of AD over a 5-year period, between CSHA-1 and CSHA-2 in a sample of English-speaking Canadians residing in the community. Since memory impairment is a defining feature of AD, we hypothesized that measures of episodic memory will be sensitive at a preclinical stage to mild impairment in individuals who will progress subsequently to develop AD. Our second goal was to validate the neuropsychological and demographic predictors identified in the first phase of the study. Specifically, we were interested in determining how well these predictors can identify individuals who will progress to develop dementia

from a second sample of community dwelling Canadians from CSHA -2, presumed to be in the preclinical stages of dementia. The two goals of this study are addressed in separate sets of analyses, termed “prediction study” and “validation study” as described below.

Prediction Study

Methods

Study Participants. A number of criteria were used to select participants for inclusion in this retrospective study, the main purpose of which was to determine which neuropsychological and demographic variables from CSHA-1 would best predict a new diagnosis of dementia at CSHA-2. The clinical group was comprised of participants who were first diagnosed with probable or possible AD at CSHA-2 (i.e., incident cases) and who underwent complete neuropsychological assessment at CSHA-1. This resulted in a group of 78 clinical participants; 30 participants in the clinical sample were classified as having NCI at CSHA-1 and the remaining 48 participants were diagnosed with CIND at CSHA-1. The control group was comprised of participants classified as cognitively normal (NCI) at CSHA-2 and with complete neuropsychological assessment data from CSHA-1. This yielded a sample of 147 control participants. It is noteworthy that no participants from the control group were classified as having dementia at CSHA-1. In addition, significantly more participants in the clinical group were classified as having CIND at CSHA-1 then were individuals in the control group (30 vs 16, respectively, χ^2 (1, N = 225) = 64.24, p<.01) suggesting that more individuals in the clinical group had subthreshold levels of cognitive impairment five years prior to clinical.

Measures. The CSHA neuropsychological examination included 12 measures designed to assess different domains of cognitive functions including memory, language ability, judgment, abstract thinking, and processing speed; these tests have been described in detail elsewhere (see Tuokko et al., 1995). From the test battery, candidate

neuropsychological measures assessing three domains of cognitive functioning (i.e., episodic memory, verbal fluency, and visuomotor speed) were chosen for inclusion in the present analyses because their utility as potential predictors of AD has been demonstrated in previous investigations (Crossley, D'Arcy, & Rawson, 1997; Masur et al., 1994; Tuokko et al., 1991). In addition, the chosen neuropsychological measures were administered in an unmodified fashion in all three waves of the CSHA and assessed areas of cognitive functioning typically reported to decline in dementia. Consequently, test scores from the Buschke Cued Recall Test (BCRT; Buschke, 1984; modified by Tuokko & Crockett, 1989) were included in the present analyses as measures of episodic memory, Animal Naming (Rosen, 1980) and the Controlled Oral Word Association Test (COWA, Spreen & Benton, 1977) were included as measures of verbal fluency, and the Digit Symbol subtest of the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981) was included as a measure of speeded visuomotor processing. Gender, age, and education were also entered as predictors to investigate the predictive value of these demographic variables. Please refer to Table 1 for a summary of the demographic and neuropsychological data from the clinical and control groups included in the Prediction Study.

Prediction Study Statistical Methods. First, to examine how well the demographic variables and selected neuropsychological measures completed at CSHA-1 predicted incident AD at CSHA-2, direct logistic regression analysis was conducted. All variables were entered simultaneously (*p* to enter = .05). Next, another logistic regression was conducted with only those variables that significantly entered the forward logistic regression model to determine the predictive accuracy of these variables. Diagnostic category (i.e., AD vs NCI) was used as the outcome variable in all logistic regression analyses. The predictive accuracy of the final model was determined by examining the

Table 1

Description of neuropsychological test scores included in the Prediction Study

Measure/Scores	Description
Episodic Memory	
BCRT	12-words, free and cued recall, selective reminding task with three-learning trials and a 20-min delayed trial
Retrieval score	free recall over three learning trials (max = 36)
Acquisition score	free and cued recall over three learning trials (max = 36)
Delayed free recall	free recall at delayed trial (max = 12)
Retention	free and cued recall at delayed trial (max =12)
Verbal Fluency	
COWA	A *phonemic fluency* task that involves generation words beginning with the specific letters of the alphabet
FAS Score	words generated in three 1-min trials each beginning with letters “F”, “A”, and “S”, respectively
Animal Naming	A *semantic fluency* task that involves generation of animal names in a 1-min trial
Animal naming score	animal names generated in a one-minute trial
Psychomotor Speed of Processing	
WAIS-R Digit Symbol	time-restricted symbol substitution task that involves pairing numbers and symbols according to a legend
Digit Symbol Score	number of correctly paired number and symbols in 90-sec

sensitivity and specificity of the model, as well as the model's positive and negative predictive values. All analyses were conducted using SPSS10 software.

Results

The demographic characteristics and neuropsychological performance for the clinical and control groups at CSHA-1 are summarized in Table 2. There was a significant difference in gender distribution between the groups ($\chi^2(1, N = 225) = 5.5$, $p < .05$); the clinical group had a higher proportion of females than the control group (70 % vs 54%). In addition, participants in the clinical group were significantly older than those in the control group (M = 83.1 vs 75.9 yrs), $t(1,223) = -9.6$, $p < .001$, and had less formal education (M= 9.6 vs 11.4 yrs), t (1,223) = 3.6, p<.001.

The direct regression analysis that incorporated the seven neuropsychological test scores and three demographic variables resulted in a statistically significant model, χ^2 (10) = 204.6, $p < .001$. The results of this logistic regression are presented in the top section of Table 3. Of the candidate variables, age, the BCRT delayed recall score, and the WAIS-R Digit Symbol subtest score significantly contributed to the regression model.

The results of the logistic regression involving only these significant variables are shown in bottom section of Table 3. A goodness-of-fit test revealed that the reduced three-variable model was also acceptable, χ^2 (3) = 198.2, $p < .001$. The odds ratios indicate that age was the strongest indicator of progression to AD; with every one-year increase in age, participants are 1.2 times more likely to develop AD (age OR, 1.2; 95% CI, 1.1 - 1.3). In addition, the odds ratios for the neuropsychological measures indicate that for every unit increase in BCRT delayed recall score, the odds of developing AD are decreased by 49% (BCRT delayed recall OR, .51; 95% CI, .34 - .70), and for every unit increase in WAIS-R Digit Symbol score, the odds of developing AD are decreased by 22% (WAIS-R Digit Symbol OR, .78; 95% CI, .71 - .86). One method of assessing the

Table 2

Demographic Summary For Participants in the Prediction and the Validation Studies

	Prediction Study		Validation Study			
	Clinical Group (incident AD)		Control Group (NCI)		CIND Group	
Number of Participants	78		147		96	
Gender						
Females	55		80		54	
Males	23		67		42	
Mean age at CSHA-1 (SD)	83.1 (5.1)		75.9 (5.5)		75.8 (6.4)	
Mean Education (SD)	9.6 (3.3)		11.4 (3.8)		10.3 (3.6)	
Neuropsychological Measure	M*	SD*	M*	SD*	M**	SD**
BCRT						
Retrieval	18.2	8.1	27.9	3.7	20.1	6.0
Acquisition	33.4	4.9	35.9	.76	34.9	2.3
Delayed Free Recall	6.7	3.5	10.4	1.4	7.3	2.9
Retention	11.2	1.7	12.0	.2	11.6	.89
Fluency Measures						
FAS	21.4	10.9	32.9	12.4	22.4	10.7
Animal Naming	11.2	3.3	16.2	4.3	12.6	3.8
Digit Symbol	18.7	6.6	35.8	10.1	23.7	9.4

* CSHA-1 means and standard deviations; ** CSHA-2 means and standard deviations

Table 3

Results from Logistic Regression Predicting Alzheimer Disease in English-Speaking Canadians at CSHA-2 from Demographic and Neuropsychological Test Variables

Variable	Coefficient	Wald	P Value	OR (95% CL)
All Variables				
Sex	-.32	.26	.61	.73(.22-2.5)
Age at CSHA-1	.20	9.2	.002	1.2 (1.1-1.4)
Education	-.04	.15	.70	.96(.79-1.2)
BCRT retrieve	-.08	.84	.36	.92(.77-1.1)
BCRT acquire	-.17	.20	.66	.84(.39-1.8)
BCRT delayed free recall	-.58	5.0	.03	.56(.34-.93)
BCRT retain	.71	.34	.56	2.0(.19-21.6)
Letter Fluency (FAS)	-.06	2.2	.14	.94(.87-1.0)
Category Fluency (Animal)	-.01	.01	.91	.99(.83-1.2)
WAIS-R Digit Symbol	-.20	13.8	.00	.82(.74-.91)
Constant	-4.5	.16	.69	
Significant Variables				
Age at CSHA-1	.16	9.0	.003	1.2 (1.1-1.3)
BCRT delayed free recall	-.67	17.4	<.001	.51 (.38-.70)
WAIS-R Digit Symbol	-.25	29.0	<.001	.78 (.70-.85)
Constant	-1.2	.002	.97	

overall adequacy of logistic regression models is to examine the classification of cases for purposes of determining predictive properties such as sensitivity and specificity. The classification table that summarizes the fit between the actual and predicted group membership with the three significant variables included in the equation is presented in Table 4. Overall, 92% of the cases were correctly classified. The model was able to correctly identify 69 of 78 participants who developed AD over a five-year period, yielding a sensitivity of 88.5%. In addition, 138 of 147 individuals who remained without dementia over five years were accurately classified, yielding a specificity of 93.9%. Overall, the model yields a positive predictive value of 88.5% in the ability to predict AD and a negative predictive value of 93.9% for the prediction of absence of AD.

Discussion

Our retrospective prediction study tested the ability of selected demographic variables and CSHA neuropsychological test scores to distinguish between seniors who will remain healthy and those who will develop AD during a subsequent five-year period. The results indicate that age, BCRT delayed recall score, and WAIS-R Digit Symbol score may be among the most sensitive early predictors of AD. A regression model comprised of these three predictor variables was able to accurately classify 92% of participants involved in the present investigation. The model was able to accurately predict progression to AD in 88.5% of individuals who actually developed the disease at CSHA-2. In addition, the model was also able to identify 93.9% of participants who remained disease free between CSHA-1 and CSHA-2. In general, these findings support previous investigations suggesting that declines in episodic memory and speeded visuomotor processing may be some of the earliest cognitive indicators of AD. If these findings can be generalized, knowledge of an individual's age and scores on select neuropsychological measures can be used to identify seniors residing in the community

Table 4

Classification Table for Prediction Study

	Predicted Outcomes		
	Clinical	Non-clinical	Total
Observed Outcomes			
Clinical	69	9	78
Non-clinical	9	138	147
Total	78	147	225

who may be at either a very low or a very high risk of developing AD over a five-year period.

The three-variable model identified in this study provides a method of using demographic and cognitive test information to predict probability of future diagnosis. An example of how chronological age as well as BCRT delayed recall and WAIS-R Digit Symbol scores can be used to calculate the probability that an individual will develop AD (or conversely, will not develop AD) within 5 years is described below. The probability of developing AD can be calculated using the following equation:

$$\text{Probability (AD)} = 1/(1+ e^{-Z})$$

where Z = Constant + β(significant variable) + β(significant variable) …

The regression coefficients (i.e., β values) for the model can be found in Table 3. Thus, Z = -1.2 + .16 (age) - .67 (BCRT delayed free recall score) - .25 (WAIS-R digit symbol score) for our model.

The probability of developing AD for an 86 year-old female client whose raw scores on the BCRT delayed free recall trial and on the WAIS-R Digit Symbol subtest were 10 and 31, respectively, will be calculated as follows:

$Z = -1.2 + .16 (86) - .67 (10) - .25 (31) = -1.89$ and Probability (AD) $= 1/(1+ e^{-(-1.89)}) = 0.13$

These operations estimate that this client has a 13% probability of progressing to develop AD in 5 years. Conversely, using the same equation, it can be shown that the probability that a 86 year-old male client who received a score 8 on the BCRT delayed free recall trial and 23 on the WAIS-R digit symbol subtest will progress to develop AD over 5 years is considerably higher at 81%.

Validation Study

The CSHA provided a unique opportunity to conduct an actuarial validation study to examine how well our model could be generalized to predict diagnostic outcome for an independent sample of individuals at the preclinical stage of AD. In each wave of the

CSHA, the term “cognitive impairment but not dementia” (CIND) was adopted to refer to those participants whose cognitive difficulties did not reach the criteria for dementia. Individuals diagnosed with CIND were found to be 5 times more likely than individuals classified as having “no cognitive impairment” (NCI) to develop AD or dementia over a five year period (Tuokko et al., 2003). Conceptually, this suggests that a majority of individuals in the CIND category at any given wave of the CSHA are likely in the preclinical phase of dementia.

Several subcategories of CIND[2] were specified to account for the possibility that a variety of factors, including life-long impairments, fatigue, depression, sensory impairment, or physical disability could lead to identifiable cognitive declines in many areas. In the Validation Study, we examined how well the logistic regression model, based on the three significant predictor variables (i.e., age, BCRT delayed recall score, and WAIS-R digit symbol score), differentiated between a group of English-speaking participants who were diagnosed with CIND at CSHA-2 and who progressed to develop dementia five years later at CSHA-3 from those who remained without the clinical diagnosis.

Methods

Study participants. A number of criteria were used to select participants for inclusion in the validation section of the present study. The population of interest was English-speaking, community-dwelling Canadians who were diagnosed with CIND at CSHA-2 for whom complete neuropsychological data were available at this wave and a final diagnosis was available at five-year follow-up (CSHA-3). Participants diagnosed with multiple sclerosis or epilepsy, and those who were blind or deaf were excluded from this

[2] Subcategories of CIND identified in the CSHA included the following: delirium, alcohol abuse, drug abuse, depression, psychiatric history, age associated memory impairment, mental retardation, cerebral vascular disease, general vascular disease, Parkinson’s disease, brain tumour, Multiple Sclerosis, epilepsy, socio-cultural issues, social isolation, blind/deaf, and other reasons specified by diagnosticians.

study because these neurological and sensory problems were assumed to confound the diagnosis of dementia. These criteria for participant selection resulted in a study sample of 96 participants. Only participants with a CSHA-2 diagnosis of CIND were selected for inclusion in the study because these participants were deemed to be at risk of developing dementia and for purposes of results generalization, were conceptually considered to best represent the types of individuals who may be seen by clinicians for dementia assessment in the community. The demographic characteristics of this sample are summarized in Table 2. As shown in Table 2, participants in this sample, with a mean age of 75.8 years at CSHA-1 and mean education level of 10.3 years, were comparable, demographically, to normal controls in the prediction study.

Measures and Validation Study Statistical Methods. Based on our logistic regression model for the reduced three significant variables (see Table 3), the predicted probability of developing or not developing dementia was calculated for each participant diagnosed with CIND according to the following formula:

$$\text{Probability (AD)} = 1/(1+ e^{-Z})$$

where $Z = -1.2 + .16$ (age) $- .67$ (BCRT delayed free recall score) $- .25$ (WAIS-R Digit Symbol score). All participants with a dementia probability of 50% or greater were assigned to the clinical group. Those with predicted probability of less than 50% were assigned to the nonclinical group. Accuracy of classification based on our model was compared to actual CSHA-3 diagnostic outcome for the participants. Chi-Square tests were conducted to analyze group classification. Likelihood ratios (LRs) were calculated to determine the usefulness of our model for diagnostic decision-making. All analyses were conducted using SPSS-10 statistical software (SPSS Inc. Chicago, ILL).

Results

Of the 96 CSHA-2 participants diagnosed with CIND, 10 (10.4%) were assessed to be “normal” at CSHA-3, 44 (45.8%) individuals remained with CIND, and 42 (43.8%) were diagnosed with dementia. Of the 42 individuals who progressed to develop dementia at CSHA-3, 18 (42.9%) were diagnosed with probable AD and 8 (19%) with possible AD. The remaining 16 (38%) individuals were diagnosed with other forms of dementia (i.e., vascular, or other forms).

The results of the classification analysis are presented in Table 5. The overall classification was significant, χ^2 [1] = 12.1 p <.001. Using the regression equation, 47 of 96 sample participants were predicted to develop dementia at five-year follow-up (i.e., CSHA-3). In actuality, 42 individuals from the sample were diagnosed with dementia using the CSHA-3 protocol.

To assess the overall adequacy of the model, predictive properties of the logistic regression were examined. With the significant predictor variables (i.e., age, BCRT delayed recall score, and WAIS-R Digit Symbol score) included in the equation, 67.7% of the cases were correctly classified. The model was able to correctly identify 29 of 42 participants who developed dementia over a five-year period, yielding a sensitivity of 69.0%. In addition, 36 of 54 individuals who remained without dementia were accurately classified, yielding a specificity of 66.7%. Overall, the model yields a positive predictive value of 61.7% in the ability to predict dementia and a negative predictive value of 73.5% for the prediction of absence of dementia in a sample with documented cognitive impairment.

To examine how well our three-variable regression model classified the individuals in the CIND group who progressed to develop probable or possible AD (n=26), we conducted an additional classification analysis. The model was able to correctly identify 19 of the 26 (73%) individuals who progressed to develop AD

Table 5

Classification Table for Validation Study

	Predicted Outcomes		
	Clinical	Non-clinical	Total
Observed Outcomes			
Clinical	29	13	42
Non-clinical	18	36	54
Total	47	49	96

(χ^2 [1] = 5.5 p=.01). In addition, the model was also able to accurately identify 9 of the 10 individuals who were diagnosed with CIND at CSHA-2, but were classified as "normal" at CSHA-3 (χ^2 [1] = 6.4 p=.01).

In terms of clinical decision-making, the usefulness of a diagnostic measure is determined by the accuracy with which it helps a diagnostician rule-in or rule-out disease in a patient. Likelihood ratios (LRs) are statistical accuracy measures that indicate the extent to which a given diagnostic test result should shift (i.e., raise or lower) a clinician's initial suspicion (i.e., pretest probability) for the presence of disease in a patient after the result of tests are obtained (i.e., posttest probability). Clinicians typically base pretest probabilities on the prevalence of the disease. The "positive likelihood ratio" (LR+) for dementia indicates how much the pretest probability of having dementia increases if the test is positive, while the "negative likelihood ratio" (LR-) indicates how much the pretest probability of dementia decreases if the test is negative. If a test does not appreciably raise or lower the pretest probability, it is not considered diagnostically useful.

Likelihood ratios are defined in terms of sensitivity and specificity: LR+ = sensitivity/(1-specificity) and LR- =(1-sensitivity)/specificity. For our reduced three-variable model, LR+ was 2.07 the LR- was 0.46, for the prediction of dementia. According to the guidelines provided by Jaeschke et al. (1994), these LR values would generate small, but potentially important changes to pretest probabilities regarding the development of dementia over a 5-year period. Assuming that the pretest probability of progression to AD is 50% (1:1 odds), the LR+ value of 2.07 indicates that following a positive test result the posttest probability of developing AD would increase to 67% (2.07/3.07). Conversely, the LR- value of 0.46 indicates that a negative test result would decrease the posttest probability to 31% (0.46/1.46).

Discussion

A little less than half (45.8%) of the individuals diagnosed with CIND who were included in this study progressed to develop dementia over a five-year period. This conversion rate is similar to those found in other investigations with follow-up intervals of 4 to 5 years. For example, in their review of longitudinal studies involving individuals with objective evidence of cognitive impairment that was insufficient to meet criteria for dementia, Tuokko and Frerichs (2000) reported that 48% to 69% of at-risk individuals were found to develop dementia by 5 years.

Overall, the reduced three-variable regression model, consisting of age, BCRT delayed recall score, and WAIS-R Digit Symbol was relatively better at identifying individuals who were diagnosed with probable or possible AD than those who were diagnosed with "dementia", a category, which included AD, vascular dementia, and other dementia (61.7% vs. 73%). This is not surprising given that our original prediction model was based on a sample of individuals who were diagnosed with incident AD at CSHA-2. Although there are no consensus standards for judging sensitivity and specificity, we assume that accuracy rates between 62 and 73% should generally be considered low because more than a quarter of the participants were misclassified. However, it is noteworthy that our model yielded LR values that according to evidence-based practice would provide a small but possibly important change in pretest to postest AD probabilities.

General Discussion

This main purpose of the present study was to examine the efficacy of an established set of demographic and neuropsychological predictors in identifying individuals at risk of developing AD. We present the results of the first actuarial validation study and add to a growing body of literature that aims to characterize the preclinical stage of AD. Using logistic regression procedures, we found advanced age,

declines in episodic memory (measured by BCRT delayed recall score) and speeded visuomotor processing skills (measured by WAIS-R Digit Symbol subtest score) to be the most significant preclinical indicators of progression to AD. In addition, we began the validation process for this particular composite of predictive indicators. The results provide some evidence that a composite equation comprised of age, BCRT delayed recall score, and WAIS-R Digit Symbol score can be used to prognosticate who amongst a group of English-speaking Canadians deemed to be in the preclinical stages of dementia will eventually go on to develop the disease and who will remain without dementia.

Age emerged as the most significant predictor in our model. This is consistent with other investigations that have also suggested that advanced age is a significant demographic predictor of dementia (Small et al., 2000, Tierney et al., 2005). This is not a surprising finding given that the prevalence of dementia is known to increase exponentially with advanced age. Desai and Grossberg (2005) report that 4.5 million United States residents were living with AD in 2000; the prevalence of disease ranged from 5% in people aged 65 to 74 to almost 50% in those 85 years or older. Similarly, in Canada, 252 600 individuals 65 years of age and over were diagnosed with some form of dementia in 1991, with nearly 64% suffering from AD. The prevalence of dementia ranged from 2.4% among seniors aged 65 to 74, to 34.5% among those 85 years or older (Canadian Study of Health and Aging Working Group, 1994).

Interestingly, however, gender did not emerge as a significant predictor of AD in our study. Notably, the distribution of men and women was significantly different in our prediction study samples, with more than twice the number of individuals in our clinical (i.e., incident AD sample) group being woman. Previous investigations have indicated that AD affects a greater proportion of women (Hill et al., 1996). The fact that gender did not emerge as a significant predictor in our study may be a reflection of the fact that

women tend to have a longer life span than men and are more prone to live with dementia into older age; the inclusion of age as a demographic predictor may have diminished the effect of gender in our sample. Given that we used a direct/simultaneous, and not a hierarchical, logistic regression procedure in this study, the possibility that the age variable diminished the effect of gender was not statistically analyzed.

Using the CSHA dataset, Tierney and her colleagues (2005) found education to be an important predictor of AD 10 years before diagnosis. In their study, education did not emerge as a significant predictor at five years before diagnosis. Consistent with these results, education did not add significantly to our prediction model, which was based on a five-year time frame between initial assessment and AD diagnosis. Based on these findings, it is possible that effects of education on the prediction of AD may be related to the length of time between the initial and follow-up assessment periods.

The neuropsychological measures that were significant predictors in our regression model (i.e., BCRT and WAIS-R Digit Symbol subtest) represent distinct cognitive areas that are known to decline in dementia. The BCRT is an episodic memory measure that has been found to be sensitive in the early detection of AD. The presence of early changes in episodic memory in our sample is generally consistent with the findings of several previous longitudinal and cross-sectional studies of dementia. Specifically, several other studies have also suggested that declines in delayed recall on a list-learning task, are among the most reliable measures for distinguishing between AD cases and normal controls (Bäckman et al., 2001; Chen et al., 2000; Masur et al., 1994; Tierney et al., 2005). In addition, using the BCRT in a prospective investigation, Tuokko and her colleagues (1991) found that participants who developed AD in the course of 12 to 18 months evidenced poorer performance on free, cued, and delayed recall at initial assessment when compared to participants whose diagnostic status remained

unchanged over the same time period. Our results suggest that the BCRT delayed recall score is a significant predictor even five years prior to diagnosis.

The episodic memory deficit seen in preclinical AD appears to reflect the underlying neuropathology seen at the earliest stages of the disease. Histopathological and morphological studies have revealed that the earliest brain changes in AD occur in the hippocampus and surrounding neocortex, mesial temporal lobe structures that have been strongly implicated in episodic memory in neuroimaging studies (Foundas et al., 1997; Jack et al., 1997; Mega et al., 2002). In addition, delayed recall appears consistently superior to retrieval procedures such as immediate recall, cued recall, and recognition suggesting that the ability to encode information into long term storage for subsequent free recall is a more useful clinical predictor than other retrieval procedures.

In the current investigation, we also found that the Digit Symbol subtest is a significant predictor of AD, five years prior to diagnosis. The Digit Symbol task is a measure of psychomotor performance, including motor persistence, sustained attention, response speed and visuomotor coordination and is known to be sensitive to response slowing that is associated with normal aging (Lezak, 1995). Storandt and Hill (1991) as well as Masur and his colleagues (1994) found Digit Symbol to be among the first tests to be affected in patients with mild AD. Our results support these previous findings.

Language disturbances, characterized mainly by word-finding deficits, are consistently observed in dementia. A number of studies have demonstrated that AD patients are impaired on a range of language-based tests, including verbal fluency measures. Particularly, performance on category fluency has been found to differentiate AD patients from healthy older adults and other amnesic patients more successfully than performance on letter fluency tasks (Crossley, D'Arcy, & Rawson, 1997; Monsch et al., 1994: Saxton et al., 2004). In addition, several investigators have reported that category

fluency is a significant neuropsychological predictor of progression to AD (Chen et al, 2001; Masur et al., 1994, Tierney et al., 2005).

In the current investigation, category fluency did not add significantly to the regression model. The inconsistency in results between our study and those of other investigators who have found performance on category fluency to be sensitive to early changes in AD may be related to several factors, including differences in diagnostic criteria, variations in length of time between initial and follow-up assessments, and different combinations of neuropsychological measures being included in the assessments. Different domains of cognitive functions have been reported to decline at different rates between the period of disease onset and eventual AD diagnosis. Verbal ability is persumed to decline later in the AD disease process for most affected individuals. Studies that have indicated verbal and category fluency as significant predictors of AD have had typical follow-up assessment periods between 2.5 to 3 years (Arnáiz & Almkvist, 2003). Comparatively, our study attempted to identify cognitive markers 5 years before diagnosis, a time at which language functions may not have been sufficiently affected to emerge as significant indicators of progression to AD.

It is noteworthy that in a recent study using the CSHA dataset, Tierney and her colleagues (2005) found Animal Naming to be among the most significant indicator of progression to AD 5 years prior to diagnosis. The inconsistency in results between our study and that of Tierney et al. (2005) may be related to the fact that our studies involved the analyses of different combinations of neuropsychological measures administered in the CSHA. Consequently, the effects of the category fluency measure may have been diminished in our sample due to the other measures we chose to include in our analyses.

Our prediction model was derived from a community-based cohort selected from a population-based study. This participant selection procedure not only minimized

selection bias typically associated with studying patients and controls in clinical research settings, but also allowed for better generalizability of results. In support of this, a unique and important aspect of our study was that we were able to validate our findings of significant demographic and neuropsychological predictors of AD using an independent sample of individuals known to be at risk of developing dementia and for whom final diagnosis was available five years later. Our reduced three variable model had a positive predictive value of almost 62% and a negative predictive value of 73% in predicting dementia in participants known to be at risk (i.e., participants diagnosed with CIND). In addition, the LRs suggest that our three-variable model would provide a small but potentially important change in diagnostic decision making between pretest and posttest.

The model we propose is not intended to replace a complete neuropsychological assessment. However, our findings can potentially have implications for the diagnosis and care of community dwelling patients who typically are seen in an outpatient clinical setting for diagnostic purposes. Our findings provide a method of using demographic and neuropsychological information to predict future diagnostic outcome, a challenging task that many clinicians face. We have provided information on how to calculate predicted probabilities of dementia based on our three-variable (age, BCRT delayed recall score, and the WAIS-R Digit Symbol subtest score) regression model.

As is common in many population-based studies, our findings are limited to populations similar to our sample: English-speaking seniors who are residing in the community. In addition, the participant sample consisted mainly of individuals between 65 to 85 years of age with slightly less than high-school level education. Our results may not apply to individuals from significantly different sociodemographic and ethnic backgrounds. As well, our validations study, involved participants with a CSHA diagnosis of CIND. Given this, our model will be most useful for individuals who are assessed by clinicians to have subthreshold levels of cognitive impairment and who may be at risk of

developing dementia. Replicating our findings using similar methodologies in other diverse samples is essential to extend the generalizability of results to a broader range of individuals. In addition, it should be noted that more than 25% of participants were misclassified in our validation study. Our results highlight the urgent need to conduct more actuarial validation studies on the efficacy of preclinical AD indicators in predicting outcome.

Overall, the results of this study lend further support to the notion that individuals in the preclinical stage of AD exhibit unique characteristics. Our model demonstrates that performance on tests of memory and speeded visuomotor processing, together with age, can identify individuals with high and low probabilities of developing dementia over a five-year time frame.

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Study 4: Preclinical Neuropsychological Predictors of Alzheimer Disease in a French-Speaking Canadian Cohort

Objectives

A major goal in the clinical diagnosis of Alzheimer Disease (AD) is the detection of the condition in the earliest possible stages. Previous investigations have revealed that individuals with Alzheimer Disease (AD) exhibit subtle neuropsychological deficits years before the clinical signs of the condition become apparent (Bondi & Monsch, 1998; Small et al., 2003); preclinical cognitive deficits have been noted in numerous domains including memory, attention, language abilities, and psychomotor speed. However, decline in memory abilities appear to be the most consistent early predictor of progression to AD (Arnáiz & Almkvist, 2003; Small et al., 2003).

A significant disadvantage of studies that aim to identify preclinical neuropsychological markers of AD is that nearly all investigations have involved English-speaking seniors of dominant cultural identities. There is now substantial evidence that language can affect cognitive functions and subsequent diagnostic decision (Manly, Jacobs, & Mayeux, 1999). Indeed, the results of the first two studies in the present series of investigations suggest that there are differences in cognitive performance between English- and French-speaking seniors who were involved in the CSHA, particularly on language-based neuropsychological measures. In light of such discrepancies, results from the study of English-speaking participants may not be directly generalized to seniors from other linguistic backgrounds particularly for the purposes of making diagnostic decisions. A major objective of this current study is to extend previous work to examine which of a select group of CSHA neuropsychological measures and demographic variables would best predict dementia in French-speaking Canadians over a five-year period.

Methods

Study Participants. See Appendix A for a detailed description of the CSHA. A cohort of community dwelling residents who were assessed in French during all three waves of the CSHA were included for analyses in the present study. Due to the relatively small number of Canadians who completed the neuropsychological assessment in French at all waves of the CSHA, a modified participant selection criteria (from Study 3) was used to select participants for inclusion in this study. Given that the primary purpose was to determine which neuropsychological and demographic variables would predict progression to AD, French-speaking participants who were diagnosed with probable or possible AD for the first time (incident cases) at CSHA-2 or at CSHA-3 who also underwent neuropsychological assessment five years prior to each of these two waves, and for whom no neuropsychological data were missing were included in the clinical group. This resulted in a clinical group of 40 participants. The control group comprised participants who were not diagnosed with dementia (i.e., classified as not clinically impaired) at CSHA-2 and at CSHA-3 and for whom complete neuropsychological assessment data were available five years prior at CSHA-1 and CSHA-2, respectively. This yielded a sample of 101 control participants.

Measures. From the CSHA neuropsychological test battery, a group of candidate neuropsychological measures assessing three domains of cognitive functioning (i.e., episodic memory, verbal fluency, and psychomotor speed) were chosen for inclusion in the present analyses. The measures included the Buschke Cued Recall Test (BCRT; Buschke, 1984, modified by Tuokko & Crockett, 1989), Controlled Oral Word Association Test (COWA, Spreen & Benton, 1977), Animal Naming test (Rosen, 1980), and the WAIS-R Digit Symbol (Wechsler, 1981) subtest. These measures are identical to the ones included in the above mentioned investigation of CSHA English-speaking sample. To reiterate, the neuropsychological variables were chosen for inclusion in the present

analyses because their utility as potential predictors of AD has been demonstrated in previous investigations (Crossley, D'Arcy, & Rawson, 1997; Masur et al., 1994; Tuokko et al., 1991), they were administered in an unmodified manner in all three waves of the CSHA, and they assessed areas of cognitive functions typically reported to decline in dementia. Gender, age, and education were also entered as predictors to investigate the value of these demographic variables in determining clinical outcome for French-speaking Canadians. Previous investigations have found that the risk of developing AD increases with age and low educational attainment (Launer et al., 1999; Lindsay et al., 2002). In addition, studies have also found that women are more likely than men to develop AD (Laurner et al., 1999).

Statistical Methods. Direct regression analysis was conducted to examine how well the demographic variables and selected neuropsychological measures completed by participants at CSHA-1 and CSHA-2 predicted incident AD five years later. All variables were entered simultaneously (p to enter = .05). Next, a second logistic regression was conducted with only those variables that significantly entered the forward logistic regression model to determine the predictive accuracy of these variables. Diagnostic category (i.e., AD vs no cognitive impairment or NCI) was used as the outcome variable in all logistic regression analyses. All analyses were conducted using SPSS 10 software.

Results

The demographic characteristics and neuropsychological performance (five years prior to diagnosis) for the clinical and control samples are summarized in Table 10. There were significant differences in age and education between the two groups (age: $t(1, 139) = -3.1$, $p < .01$; education: $t(1, 139) = 2.6$, $p < .01$). Compared to control group participants, those in the clinical group were significantly older (M = 76.6 vs 73.1 years)

Table 10

Demographic Summary For French-Speaking Clinical and Control Groups

	Clinical Group		Control Group	
Number of Participants	40		101	
Gender				
Females	26		73	
Males	14		28	
Mean age at CSHA-1 (SD)	76.6 (6.1)		73.1 (5.8)	
Mean Education (SD)	6.7 (3.3)		8.6 (4.1)	
Neuropsychological Measure	M	SD	M	SD
BCRT				
Retrieval	20.0	5.8	28.0	4.3
Acquisition	33.1	4.4	35.6	.91
Delayed Free Recall	7.4	2.8	10.6	1.3
Retention	10.9	2.0	11.9	.21
Fluency Measures				
FAS	14.3	8.3	21.5	9.1
Animal Naming	10.1	3.1	14.0	4.0
Digit Symbol	16.5	8.3	27.9	11.5

and had less formal education (*M* = 6.7 vs 8.6 years). Gender distribution between groups was found to be non-significant.

The forward regression analysis that included all seven neuropsychological test scores and three demographic variables resulted in a statistically significant model, χ^2 (10, N = 141) = 84.88, $p < .001$. The results of this logistic regression are presented in the top section of Table 11. Of the candidate variables, sex, age, and the BCRT delayed free recall score significantly contributed to the model. It is noteworthy that the contribution of WAIS-R Digit symbol to the overall model approached significance.

The three significant variables of the full model were entered into a separate logistic regression; the results of this analysis are presented in the bottom section of Table 11. A goodness-of-fit test revealed that the reduced three-variable model was also acceptable, χ^2 (3, N = 141) = 74.2, $p < .001$. However, sex did not emerge as a significant variable in this reduced mode. The odds ratios indicate that age was the strongest indicator of progression to AD in the French-speaking sample; with every year increase in age, participants are 1.2 times more likely to develop AD (age OR, 1.2, 95% CI, 1.1-1.3). Among the neuropsychological measures, only BCRT delayed free recall was found to be a significant predictor. The odds ratio for this measure indicates that for every unit increase in BCRT delayed recall score, the odds of developing AD are decreased by 60% (BCRT delayed recall OR, .40; 95% CI, .28-.58) for French-speaking Canadians.

One method of assessing the overall adequacy of logistic regression models is to examine the classification of cases for purposes of determining predictive properties such as sensitivity and specificity. The classification table that summarizes the fit between the actual and predicted group membership with the initial three significant

Table 11

Results from Logistic Regression Predicting Alzheimer Disease in French-Speaking Canadians from Demographic and Neuropsychological Test Variables

Variable	Coefficient	Wald	P Value	OR (95% CL)
All Variables				
Sex	1.6	4.9	.03*	4.8(1.2-19.5)
Age at preclinical assessment	.16	7.6	.01*	1.2 (1.0-1.3)
Education	-.07	.39	.53	.93(.75-1.2)
BCRT retrieve	-.05	.12	.73	.96(.74-1.2)
BCRT acquire	.13	.17	.68	1.1(.62-2.1)
BCRT delayed free recall	-.67	5.1	.02*	.52(.29-.92)
BCRT retain	-1.2	1.1	.29	.32(.04-2.6)
Letter Fluency (FAS)	.04	.55	.46	1.0(.94-1.1)
Category Fluency (Animal)	-.11	.93	.34	.89(.71-1.1)
WAIS-R Digit Symbol	-.09	3.3	.07	.91(.83-1.0)
Constant	5.8	.50	.48	
Significant Variables				
Sex	.81	2.2	.14	2.3 (.77-6.7)
Age at preclinical assessment	.14	9.7	<.01*	1.2 (1.1-1.3)
BCRT delayed free recall	-.91	24.6	<.001*	.40 (.28-.58)
Constant	-4.0	1.1	.30	

variables included in the equation is presented in Table 12. Overall, 84.4% of the cases were correctly classified. The model was able to correctly identify 24 of the 40 participants who developed AD over a five-year period, yielding a sensitivity of 60%. In addition, 95 of the 101 individuals who remained without AD over five years were accurately classified, yielding a specificity of 94.1%. Overall, the model had a positive predictive value of 80% in the ability to predict AD and a negative predictive value of 85.6% for the prediction of absence of AD.

Discussion

The present retrospective prediction study was concerned with determining which of a select group of CSHA neuropsychological and demographic variables best distinguish between French-speaking Canadians who develop AD over a five-year period from those who remain healthy during the same time period. The results indicate that advanced age and compromised delayed episodic memory (i.e., BCRT delayed recall score) may be among the most sensitive early predictors of AD for French-speaking Canadians. It is noteworthy that sex emerged as a significant predictor in the initial logistic regression analysis that included all seven selected CSHA neuropsychological and three demographic variables. However, sex did not significantly contribute to the reduced regression model when it was considered along with the other two significant variables, namely age and BCRT delayed recall score.

The reduced regression model comprised of age and BCRT delayed recall score was able to accurately classify 84.4% of French-speaking participants involved in the present investigation. 80% of the individuals whom the model predicted would progress to AD actually developed the disease over five years. In addition, 85.6% of the participants who were predicted by the model to remain disease free were healthy at reassessment.

Table 12

Classification Table Prediction of AD in French-speaking participants

	Predicted Outcomes		
	Clinical	Non-clinical	Total
Observed Outcomes			
Clinical	24	16	40
Non-clinical	6	95	101
Total	30	111	141

Age emerged as the most significant predictor of AD in French-speaking Canadians. This is consistent both with previous investigations as well as the above presented study involving English-speaking CSHA participants (Small et al., 2000; Tierney et al., 2005). Advanced age is a well-known risk factor for AD, regardless of an individual's cultural background. Given this, the fact that age emerged as a significant predictor of AD in French-speaking Canadians is confirmatory rather than surprising. Although there are different prevalence estimates for individuals of various cultural backgrounds (Manly, Jacobs, & Mayeux,1999), the incidence of dementia is known to increase exponentially with advanced age in any given cultural group (Canadian Study of Health and Aging Working Group, 1994; Desai & Goldberg, 2005).

As was the case with English-speaking Canadians, gender and education did not emerge as significant predictors of AD for French-speaking seniors. The present finding is inconsistent with previous investigations that have found females as well as individuals with low educational attainment to have higher risks of developing AD (Hill et al., 1996; Launer et al., 1999). However, it is noteworthy that the effects of gender and education on AD do not appear to be unequivocal. Indeed, other investigators have not found sex and education to be significant predictors of incident AD (Cobb et al., 1995; Yoshitake et al., 1995). In addition, using the CSHA database, Lindsay and her colleagues (2002) found advanced age and lower educational attainment to be significant risk factors for AD. In contrast, gender was not associated with higher AD risk. Methodological differences, including sample size, selection and diagnosis criteria, and duration of follow-up may account for the discrepancies between studies.

The present results also suggest that the BCRT is sensitive to the early detection of AD in a French-speaking sample. The delayed recall score of this measure emerged as a significant predictor of progression to AD. This is consistent with previous findings that have suggested that decline in delayed recall on list-learning measures, reliably

distinguish between AD cases and normal controls. Bäckman and his colleagues (2001) also found this to be the case in their population-based study that aimed to predict dementia in a cohort of Swedish (i.e., non-English) speaking seniors.

The episodic memory deficit in preclinical AD is consistent with the underlying neuropathlogical changes seen at the earliest stages of the disease. Investigations have revealed that the earliest changes in the brains of AD patients occur in the hippocampus, a temporal lobe structure that has been strongly implicated in episodic memory (Foundas et al., 1997; Mega et al., 2002). Delayed free recall appears to be superior to other retrieval procedures, such as immediate recall, cued recall, and recognition in predicting AD, regardless of native languages. This finding suggests that the ability to encode information into long term storage for subsequent free recall may be a more useful clinical predictor than other retrieval procedures.

As with the English-speaking sample, verbal fluency measures did not emerge as significant predictors in the present study. This result is inconsistent with previous investigations that have found performance on category fluency to be more sensitive than performance on phonemic fluency in distinguishing between preclinical AD patients and healthy older adults (Chen et al., 2001; Masur et al., 1994; Tierney et al., 2005). Methodological differences, including differences in diagnostic criteria, variations in length of time between initial and follow-up assessments, and different combinations of neuropsychological measures in test batteries may account for these discrepancies. In addition, different domains of cognitive functions have been reported to decline at different rates between the period of disease onset and eventual AD diagnosis. For example, verbal ability is known to decline later in the AD disease process. Studies that have indicated verbal and category fluency as significant predictors of AD have had typical follow-up assessment periods between 2.5 to 3 years (Arnáiz & Almkvist, 2003). Comparatively, the present study attempted to identify cognitive markers 5 years before

diagnosis; a time at which language functions may not have been sufficiently affected to emerge as significant indicators of progression to AD.

Furthermore, there may be several confounding factors in attempting to predict AD in non-English groups using language-based measures. For example, performance on verbal fluency may be influenced by aspects of the language of administration. As discussed in Study 2, word fluency or salience (e.g., the number of words beginning with “F”, “A”, and “S”) may be different between English and other languages and this may moderate performance, leading to discrepancies in total number of words generated between members of diverse language groups. Thus, even if verbal fluency measures emerge as significant predictors of progression to AD in English- and French-speaking seniors, the generalizability of such results to different language groups must be done with caution.

The prediction model in the present study was derived from a community-based cohort selected from a population-based study. This participant selection procedure not only minimizes selection bias typically associated with studying patients and controls in clinical research settings, but also allows for better generalizability of results. In addition, the consistencies in findings between the present study involving French-speaking participants and the above-reported investigation using English-speaking CSHA participants suggest that advanced age and delayed episodic memory are significant risk factors for AD regardless of individual’s language of origin.

The model proposed in this investigation is not intended to replace a complete neuropsychological assessment. However, the findings can potentially have implications for the diagnosis of AD and the care of community dwelling, French-speaking Canadians. The findings provide a method of using demographic and neuropsychological information to predict future diagnostic outcome in this population; a challenging task faced by many clinicians.

There are several limitations to the present study. The current findings are limited to French-speaking seniors who are residing in the community. In addition, the participant sample consisted mainly of individuals in their mid-70s with slightly less than high-school level education. These results may not apply to individuals from significantly different sociodemographic backgrounds. In addition, it will be important to verify the results of the present investigation with a cross-validation sample of French-speaking individuals to determine the true efficacy of preclinical AD markers in predicting outcome.

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General Discussion

Collectively, the four studies that constitute this dissertation examine the preclinical neuropsychological characteristics of English- and French-speaking AD participants from the Canadian Study of Health and Aging (CSHA). First, separate investigations, each involving English- and French-speaking participants, were conducted to compare neuropsychological performance between AD participants and demographic-matched healthy seniors at the time of diagnosis and five years prior. Second, studies were completed to determine which of a select group of CSHA neuropsychological and demographic variables best distinguish between seniors who progressed to develop AD from those who remained healthy over a five year period. An actuarial validation study was also conducted with a cohort of English-speaking participants; the main aim was to determine how well the best predictors of AD in this language sample prognosticate clinical outcome in an independent group of participants deemed to be at risk of developing dementia.

At the onset, it is important to highlight two significant methodological features of the present investigations. First, English- and French-speaking Canadians were studied separately. Second, only a select group of neuropsychological measures from the CSHA neuropsychological battery was included for analyses. The rational to study the cognitive performance of English- and French-speaking Canadians independently was multifaceted. In light of previous investigations that have found language differences to affect cognitive performance (Manly, Jacobs, & Mayeux, 1999), there was an interest in determining if language-related cognitive trends are evident in a Canadian population. In addition, there was an interest in considering the impact educational differences, between the English- and French- speaking CSHA participants, have on cognitive performance, without the use of statistical procedures. French-speaking participants were significantly less educated than their English-speaking counterparts in the CSHA.

However, statistical procedures that equate diverse groups on years of education before assessing cognitive performance do not necessarily guarantee that the quality of education received is comparable (Manly, Jacobs, & Mayeux, 1999). Thus, the decision was made to study the two language groups independently.

All four studies presented above involved a select group of neuropsychological measures (i.e., the BCRT, FAS test, Animal Naming, and WAIS-R Digit Symbol) that were chosen from the CSHA neuropsychological assessment battery. These measures were selected for several reasons. First, they were administered in an unmodified fashion in all three waves of the CSHA. Second, they represent cognitive domains that have been found to be affected in early AD (Arnaiz & Almkvist, 2003; Small et al., 2003; Tuokko et al., 1991). Third, there was a specific interest in investigating performance on the BCRT, a measure that controls encoding and retrieval, and thus, is deemed to be a better estimate of episodic memory than other list-learning tasks (Tuokko & Crockett, 1989). Finally, there was an interest in investigating the diagnostic value of verbal fluency measures; previous investigations have found that individuals with AD demonstrate disproportionate declines in category fluency (e.g., Animal Naming) as opposed to phonemic fluency (e.g., FAS test; Butters et al., 1987; Crossley et al., 1997; Monsch et al., 1994). The present studies aimed to determine if this pattern was observable at the preclinical stage in the CSHA. It is noteworthy that the measures selection procedure used in this study did not allow for the evaluation of other cognitive domains, such as confrontational naming and visuo-spatial abilities that have been implicated to decline in AD (Arnáiz & Almkvist, 2003; Small et al., 2000).

Overall, the present results indicate that both English- and French-speaking AD participants demonstrate cognitive changes in multiple domains at the preclinical stage. For the English-speaking sample, compromised performance was evident on a global indicator of cognition (i.e., 3MS), as well as on measures of episodic memory (i.e.,

BCRT), phonemic fluency (i.e., FAS test), category fluency (i.e., Animal Naming), and speeded psychomotor skills (i.e., WAIS-R Digit Symbol) five years prior to diagnosis. In addition, English-speaking AD participants demonstrated significant decline in performance between initial and reassessment on all neuropsychological measures compared to their healthy counterparts. Advanced age, as well as declines in episodic memory (measured by BCRT delayed recall score) and psychomotor skills (measured by WAIS-R Digit Symbol score), were found to be the most significant indicators of progress to AD in the English-speaking sample.

Results for the French-speaking sample indicate that the AD participants performed significantly worse than healthy controls on a global indicator of dementia as well as on measures of episodic memory, category fluency, and psychomotor speed five years prior to diagnosis. However, unlike their English-speaking counterparts, significant differences in performance between clinical and control participants were not evident on the phonemic fluency task at initial assessment for French-speaking participants. In addition, French-speaking AD participants demonstrated greater decline in performance between CSHA-1 and CSHA-2 assessments on the 3MS and the BCRT measures. In contrast, decline in performance was comparable for both clinical and control groups on the Animal Naming, FAS, and WAIS-R Digit Symbol measures. In the French-speaking sample, advanced age and decline in delayed episodic memory (i.e., BCRT delayed recall score) were found to be the most significant indicators of progression to AD over a five year period.

Preclinical and longitudinal declines in episodic memory were consistent findings in the English- and French-speaking samples. Moreover, next to advanced age, which is noted to be a ubiquitous risk factor for dementia in various cultural and language groups (Lindsay et al., 2002; Manly, Jacobs, & Mayeux, 1999), compromised delayed episodic memory was the next best predictor of progression to dementia for both language

groups in the present investigations. The presence of early changes in episodic memory in the current studies is generally consistent with findings of several previous longitudinal and cross-sectional studies of dementia. Other investigators have found that declines during delayed recall trials on list-learning tasks are among the most reliable measures for distinguishing between AD cases and normal controls (Bäckman et al., 2001; Chen et al., 2001; Masur et al., 1994; Tierney et al., 2005).

Given that memory deficit is a principal diagnostic feature of AD, the overall finding of preclinical changes in this area is not surprising. However, the use of the BCRT to assess episodic memory is a unique feature of the present study. As mentioned previously, the BCRT is considered a better memory measure compared to other list-learning tasks because performance on this task is less influenced by deficits in other cognitive domains (e.g., attention and executive functions). Using the BCRT in a prospective study, Tuokko and her colleagues (1991) found that participants who developed AD in the course of 12 to 18 months evidenced poorer performance on free and cued recall at initial assessment when compared to participants whose diagnostic status remained unchanged over the same time period. The present results indicate that compromised performance on the BCRT is present even five years prior to diagnosis regardless of language of administration. In addition, the findings that French-speaking AD participants also demonstrated compromised performance on all free and cued recall trials at a preclinical stage suggests that language may not mediate the ability of participants to benefit from supported encoding and retrieval procedures.

It is noteworthy that an incidental observation in Tuokko et al.'s (1991) study was that performance on the delayed free recall trial of the BCRT was comparable between individuals with mild AD and their healthy counterparts. In contrast, in the present series of investigations, delayed free recall performance emerged as the most significant predictors of progression to AD in both the English- and French-speaking samples. The

difference in results between the two investigations may be related to methodological variations such as differences in sample selection, duration of follow-up assessments, and diagnostic procedures; the present series of investigations involved a larger community based sample with participants who were assessed at five-year intervals. In addition, the diagnosis of dementia was given following a multi-step assessment process that involved clinical and neuropsychological assessments as well as laboratory investigations and corroborative information from caregivers.

The episodic memory deficit seen in preclinical AD reflects the underlying neuropathology seen at the earliest stages of the disease. Histopathological and neuroimaging studies have revealed that the earliest brain changes in AD occur in the hippocampus, a temporal lobe structure that has been strongly implicated in episodic memory (Foundas et al., 1997; Jack et al., 1997; Mega et al., 2002). In addition, given that the delayed recall appears to differentiate between participants subsequently diagnosed with AD and normal controls better than other recall procedures, such as immediate recall, cued recall, and recognition, suggests that the ability to encode information into long term storage for subsequent free recall may be a more useful clinical predictor than other retrieval procedures, regardless of language of test administration.

The main differences in preclinical cognitive performance between the English- and French-speaking samples were found on language-based verbal fluency measures. As mentioned previously, a major goal of the present series of investigations was to determine if semantic memory deficits (assessed by performance on a category fluency task) is a reliable marker of preclinical AD. Previous investigations have found AD patients demonstrate poorer performance on category fluency tasks compared to phonemic fluency tasks at an early stage of the disease (Butters et al., 1987; Monsch et al., 1994; Crossley et al., 1997; Saxton et al., 2004). In addition, several investigators

have reported that category fluency is a significant neuropsychological predictor of progression to AD (Chen et al., 2001; Masur et al., 1994). The present studies found that for French-speaking participants, the difference in performance between the clinical and control groups was greater on the Animal Naming task than for the FAS measure at both time of diagnosis and five years prior. This pattern of performance was not observed with the English-speaking cohort, where participants demonstrated significant decline in performance on both fluency measures between initial and reassessment compared to their healthy counterparts. In addition, neither the category nor phonemic fluency measure emerged as a significant predictor of AD for either language group.

Conceptually, it is not overly surprising that the most significant differences in cognitive trends between the English- and French-speaking samples occurred on language-based measures. Several factors including differences in educational level and word saliency could have contributed to the discrepancies in results between the two language groups. In addition, the inconsistency in results between the current investigations and those of other researchers who have found performance on category fluency to be sensitive to early changes in AD may be related to several factors, including differences in diagnostic criteria, variations in length of time between initial and follow-up assessments, and different combinations of neuropsychological measures being included in the assessments and regression models. Different domains of cognitive functions have been reported to decline at different rates between the period of disease onset and eventual AD diagnosis. Verbal ability has been found to decline later in the AD process. Studies that have indicated verbal fluency measures as significant predictors of AD have generally had longitudinal assessment follow-up periods between 2.5 to 3 years (Arnaiz & Almkvist, 2003). Comparatively, the current studies attempted to identify cognitive markers 5 years prior to diagnosis; at a time when language and

consequently semantic memory functions may not have been sufficiently affected to emerge as significant indicators of progression to AD.

It is noteworthy that in a recent study using the CSHA dataset, Tierney and her colleagues (2005) found Animal Naming to be among the most significant indicators of progression to AD 5 years prior to diagnosis. The inconsistency in results between the current investigations and that of Tierney et al. (2005) may be related to the fact that the present studies involved the analyses of different combinations of neuropsychological measures administered in the CSHA. Consequently, the effects of the category fluency measure may have been diminished in the present samples due to the other measures included in the analyses.

Performance on the WAIS-R Digit Symbol task was investigated to assess functioning in a non-memory domain. As mentioned above, both English- and French-speaking participants demonstrated compromised performance at a preclinical stage, but this speeded psychomotor task emerged as a significant predictor of AD in the English-speaking sample. The former finding supports previous investigations showing that a decrease in speed of processing is a general mechanism evident in cognitive aging and is generally culturally invariant (Park, Nisbett, & Hedden, 1999). It is noteworthy that the WAIS-R Digit Symbol measure approached significance in the prediction of AD in the French-sample; the comparably smaller sample may have accounted for the discrepancy in results.

The CSHA provided a unique opportunity to conduct an validation study to examine how well the emergent predictors of AD can be generalized to predict diagnostic outcome for an independent sample of individuals at the preclinical stage of AD. Results from the regression analysis of English-speaking participants was used to classify an independent group of participants who were diagnosed with CIND at CSHA-2 and for whom diagnostic outcome was known five years later at CSHA-3. The reduced

three-variable model for English-speaking participants, consisting of age, BCRT delayed recall score, and WAIS-R Digit Symbol score had a positive predictive value of almost 62% and a negative predictive value of 73% in predicting dementia in participants known to be at risk (i.e., participants diagnosed with CIND). In addition, the LRs suggest that the three-variable model would provide a small but potentially important change in diagnostic decision making between pretest and posttest.

There are several advantages to the current series of investigations. First, the studies involved community-based cohorts selected from a larger population-based study. The participant selection procedure minimized the selection bias typically associated with studying patients and volunteers in clinical research settings and allowed for better generalization of results. Second, the longitudinal assessment of cognitive change over a five year time period allowed for assessment of cognitive decline over time, minimizing the potential confounds encountered in the study of one-time cognitive performance. Third, the studies accounted for the cognitive changes of normal aging by including healthy English- and French-speaking seniors. Unique aspects of the present investigations were that English- and French-speaking participants were studied individually and attempts were made to validate findings of significant predictors of AD using an independent sample of English-speaking individuals known to be at risk of developing dementia.

Ultimately, advanced age and delayed episodic memory emerged as significant predictors of AD in both the English- and French-speaking samples. The regression models proposed for each of these language groups are not intended to replace complete neuropsychological assessments. However, the present findings can have implications for the diagnosis AD and care of community dwelling older individuals of English and French backgrounds in Canada. Future diagnoses of illness is a challenging task faced by many clinicians; the present results provide clues about domains of

cognitive functions or what measures are significant in predicting outcome in both English- and French-speaking populations. Increased vigilance and referral for an extensive medical and neuropsychological assessment should be considered, if the proposed regression models from the present studies are used to predict risk of developing AD in clinical practice.

As is common in many population-based studies, the present findings are limited to English- and French-speaking seniors who are residing in the community. In addition, participants from the two language groups were mainly individuals between the ages of 65 to 85 with less than high-school level education. Moreover, it is noteworthy, that the French-speaking participants had significantly less formal education than their English-speaking counterparts. Overall, results may not apply to individuals from significantly different sociodemographic or ethnic backgrounds. In addition, dementia patients were not followed until death in the CSHA. As such, the diagnosis of dementia was solely based on clinical judgment and was not confirmed with autopsy procedures.

The results of the present series of investigations lend further support to the notion that individuals in the preclinical stage of AD exhibit unique cognitive characteristics. Advanced age as well as performance on tests of episodic memory can identify English- and French-speaking individuals who develop AD with reasonable accuracy over a five-year period.

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Appendix A

A Description of the Canadian Study of Health and Aging

The Canadian Study of Health and Aging (CSHA) was a population-based, longitudinal study that investigated the prevalence of dementia in Canadians aged 65 years and older. This CSHA was conducted in three waves; the first wave was carried out between 1990 and1991 (CSHA-1) and surviving participants were seen for follow-ups between 1996 and1997 (CSHA-2), and again between 2000 and 2001 (CSHA-3). A representative sample of individuals aged 65 and over (n = 10 263), were drawn equally from five geographic Canadian regions (e.g., British Columbia, the Prairies, Ontario, Quebec, and the Atlantic region) and included in the first wave of the CSHA. All participants were either residents of the community or residents of institutions, and were assessed in their preferred language of English or French.

The Modified Mini-Mental State Examination (3MS; Teng & Chui, 1987), a screening measure for cognitive impairment, was administered to the CSHA community-dwelling residents to determine who would be included in the clinical assessment component of the study. Individuals who obtained a 3MS score between 50 and 78 out of a possible total score of 100 (i.e., potential cases), and a randomly selected subset of individuals who scored 78 or more out of 100 (i.e., potential healthy controls) were requested to undergo a clinical assessment.

The clinical assessment component of the CSHA was designed to confirm the presence of dementia and to facilitate differential diagnoses. This component included a series of separate evaluations. First, a nurse collected medication information, re-administered the 3MS, and interviewed a caregiver using a semi-structured version of the Cambridge Examination of Mental Disorders in Older Adults (CAMDEX; Roth et al., 1988). Second, a trained psychometrician, blind to the information compiled by the nurse, administered the neuropsychological test battery to all participants who obtained

a 3MS score between 50 and 78 on the nurse's administration and to a random sample of those who scored over 78 (i.e., healthy controls). Subsequently, a neuropsychologist evaluated the neuropsychological test results and the CAMDEX data, based on the caregiver interview. Third, a physician performed a physical and neurological examination and made a preliminary diagnosis on the basis of this medical information and the nurse's evaluation. Laboratory bloodwork was conducted for consenting participants suspected of having dementia or delirium. Finally, a consensus case conference was held during which the physician and the neuropsychologist reviewed their respective preliminary diagnoses, made a differential diagnosis, and arrived at a final consensus diagnosis based on all historical and currently available clinical information.

For CSHA-1 (data collected 1991-1992), participants were classified as cognitively normal (i.e., no cognitive impairment; NCI), cognitively impaired by not meeting criteria for dementia (i.e., cognitively impaired but no dementia; CIND) or demented (i.e., according to the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition; *DSM-III-R*, American Psychiatric Association, 1987). It is noteworthy that the diagnoses of CIND was based on clinical impression and provided to individuals who neither met criteria for NCI or dementia (Tuokko et al., 1993). In addition, those with Alzheimer Disease (AD) were subclassifed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984) criteria. A diagnosis of *probable* AD was given to individuals: with dementia established by clinical examination, documented by the Mini-mental State Examination, and other neuropsychological testing; deficits in two or more areas of cognition, progressive worsening of memory or other cognitive functions; no disturbance of consciousness, onset between the ages of 40 and 90, but most often after 65; and the absence of

systemic disorders or other brain diseases that independently could account for the progressive deficits in memory and cognition. A diagnosis of *possible* AD was given to individuals who met the criteria for probable AD, but also displayed/had one or more of the following: an atypical presentation/course (e.g., major aphasia, apraxia); a history of vascular problems (e.g., stroke or hypertension), Parkinsonism extrapyramidal signs, or had a coexisting disease. The tenth revision of the International Classification of Disease (ICD-10; World Health Organization, 1992) criteria were used to define vascular and other specific types of dementia. These criteria will not be discussed further as they are irrelevant to the present studies.

Surviving participants from CSHA-1 were re-contacted for CSHA-2 five years later, between 1995 and1996, to examine the incidence, clinical progression, and mortality rates associated with dementia in Canada. The same research methodology described for CSHA-1 was used in CSHA-2 to determine participant eligibility for clinical and neuropsychological assessments. Following the clinical assessment, two separate diagnosis were made. First, an *incidence diagnosis* was made using the same diagnostic criteria as in CSHA-1. Second, a *new-criteria* diagnosis was made using the *DSM-IV* (American Psychiatric Association, 1994) criteria for AD and new criteria for vascular dementia (Roman, Tatemichi, Erkinjuntti, et al., 1993) were applied.

The third wave of the CSHA (i.e., CSHA-3) was conducted another five years later, between 2001 and 2002, with minor modifications in research design. CSHA-3 did not involve a nurse's evaluation. Instead, during an initial screening interview a trained interviewer obtained information from a caregiver about the participant's functional, cognitive, and medical status and administered the 3MS to the participant. The neuropsychological battery was abbreviated and administered to all remaining and consenting participants who did not have a diagnosis of dementia at CSHA-2 and to those who scored between 50 and 89 out of 100 on the 3MS at CSHA-3.

At CSHA-3, an initial or incidence consensus diagnosis was made using the diagnostic criteria used in CSHA-1. As in CSHA-2, a new criteria diagnosis was made using *DSM-IV* and NINCDS-ADRDA criteria for AD. In addition, CIND was diagnosed using a revised version of *DSM-III-R* criteria for mild cognitive impairment (MCI). This revision allowed for identification of cognitive impairment other than memory in individuals who did not meet full criteria for dementia. At CSHA-3, clinicians arrived at a consensus diagnosis in two stages. The first diagnostic decision was made without reference to the CSHA-2 neuropsychological assessment results. Subsequently, all information, including assessment results from CSHA-1 and 2, was reviewed in preparation for a final consensus diagnostic decision. It is imperative to note that only the incidence diagnoses (i.e., diagnoses that was based on the CSHA-1 criteria) were considered in all four of the present investigations. This was done to ensure diagnostic consistency, given that the four studies involved all three waves of the CSHA.

Appendix B

ANOVA Summary Tables for Neuropsychological Measures (Study 1)

Table B1

Analysis of Variance for 3MS

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	63.96*	.53	.000
G within-group				
Error	56	(137.77)		
		Within subjects		
Time (T)	1	59.14*	.51	.000
T X G	1	43.61*	.44	.000
T within-				
Group error	56	(31.79)		

Note. Values enclosed in parentheses represent mean square errors. *p<.001.

Table B2

Analysis of Variance for Retrieval BCRT Variable

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	63.29**	.54	.000
G within-group				
Error	54	(59.87)		
		Within subjects		
Time (T)	1	45.25**	.46	.000
T X G	1	12.34*	.19	.001
T within-				
Group error	54	(19.45)		

Note. Values enclosed in parentheses represent mean square errors. *p <.01 **p<.001.

Table B3

Analysis of Variance for Acquisition BCRT Variable

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	20.88*	.28	.000
G within-group				
Error	54	(30.26)		
		Within subjects		
Time (T)	1	21.87*	.29	.000
T X G	1	18.20*	.25	.000
T within-				
Group error	54	(13.52)		

Note. Values enclosed in parentheses represent mean square errors. *p <.001.

Table B4

Analysis of Variance for Retention BCRT Variable

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	18.81*	.26	.000
G within-group				
Error	55	(5.43)		
		Within subjects		
Time (T)	1	22.62*	.29	.000
T X G	1	20.34*	.27	.000
T within-				
Group error	55	(2.40)		

Note. Values enclosed in parentheses represent mean square errors. *p <.001.

Table B5

Analysis of Variance for Letter Fluency Measure (FAS Test)

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	14.58**	.22	.000
G within-group				
Error	51	(262.22)		
		Within subjects		
Time (T)	1	17.74**	.26	.000
T X G	1	13.71*	.21	.001
T within-				
Group error	51	(29.64)		

Note. Values enclosed in parentheses represent mean square errors. *p <.01. **p<.001.

Table B6

Analysis of Variance for Category Fluency Measure (Animal Naming Test)

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	26.76**	.33	.000
G within-group				
Error	55	(23.08)		
		Within subjects		
Time (T)	1	11.11*	.17	.002
T X G	1	9.10*	.14	.004
T within-				
Group error	55	(8.48)		

Note. Values enclosed in parentheses represent mean square errors. *p <.01. **p<.001.

Table B7

Analysis of Variance for Comparison of Standardized Letter and Category Fluency Measures (FAS Test vs Animal Naming Test)

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	23.47*	.32	.000
G within-group				
Error	50	(2.35)		
		Within subjects		
Time (T)	1	21.84*	.30	.000
Task (K)	1	2.15	.04	.149
T X G	1	14.75*	.23	.000
K X G	1	0.39	.01	.536
T X K	1	0.21	.00	.647
T X K X G	1	0.01	.00	.927
T X K within-				
Group error	50	(0.28)		

Note. Values enclosed in parentheses represent mean square errors. *p <.001.

Table B8

Analysis of Variance for Digit Symbol Test

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	13.07*	.24	.000
G within-group				
Error	41	(161.54)		
		Within subjects		
Time (T)	1	28.29*	.41	.000
T X G	1	1.70	.04	.200
T within-				
Group error	41	(25.16)		

Note. Values enclosed in parentheses represent mean square errors. *p <.001.

Appendix C

ANOVA Summary Tables for Neuropsychological Measures (Study 2)

Table C1

Analysis of Variance for 3MS

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	32.40***	.62	.000
G within-group Error	20	(100.39)		
		Within subjects		
Time (T)	1	6.95*	.26	.016
T X G	1	10.32**	.34	.004
T within-group error	20	(55.29)		

Note. Values enclosed in parentheses represent mean square errors. *p<.05. **p<.01. ***p<.001.

Table C2

Analysis of Variance for Retrieval BCRT Variable

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	28.43**	.60	.000
G within-group error	19	(33.45)		
		Within subjects		
Time (T)	1	26.62**	.58	.000
T X G	1	12.24*	.39	.002
T within-group error	19	(11.32)		

Note. Values enclosed in parentheses represent mean square errors. *p <.01 **p<.001.

Table C3

Analysis of Variance for Acquisition BCRT Variable

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	13.36*	..41	.002
G within-group error	19	(14.36)		
		Within subjects		
Time (T)	1	17.07*	.47	.001
T X G	1	18.00**	.49	.000
T within-group error	19	(6.91)		

Note. Values enclosed in parentheses represent mean square errors. *p <.01. **p>.001.

Table C4

Analysis of Variance for Retention BCRT Variable

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	13.79*	.40	.001
G within-group error	21	(2.09)		
		Within subjects		
Time (T)	1	21.40**	.29	.000
T X G	1	21.40**	.27	.000
T within-group error	21	(0.73)		

Note. Values enclosed in parentheses represent mean square errors. *p<.01. **p <.001.

Table C5

Analysis of Variance for Letter Fluency Measure (FAS Test)

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	2.74	.14	.116
G within-group error	17	(59.13)		
		Within subjects		
Time (T)	1	6.05*	.26	.025
T X G	1	0.21	.21	.650
T within-group error	17	(30.00)		

Note. Values enclosed in parentheses represent mean square errors. *p <.05.

Table C6

Analysis of Variance for Category Fluency Measure (Animal Naming Test)

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	18.62**	.47	.000
G within-group error	21	(13.08)		
		Within subjects		
Time (T)	1	14.22*	.40	.001
T X G	1	2.13	.09	.159
T within-group error	21	(5.14)		

Note. Values enclosed in parentheses represent mean square errors. *p <.01. **p<.001.

Table C7

Analysis of Variance for Comparison of Standardized Letter and Category Fluency Measures (FAS Test vs Animal Naming Test)

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	10.22**	.38	.005
G within-group error	17	(1.02)		
		Within subjects		
Time (T)	1	15.17**	.47	.001
Task (K)	1	1.96	.10	.180
T X G	1	1.79	.10	.199
K X G	1	6.34*	.27	.022
T X K	1	1.23	.07	.284
T X K X G	1	0.91	.05	.354
T X K within-group error	17	(.239)		

Note. Values enclosed in parentheses represent mean square errors. *p <.05.

**p<.01.

Table C8

Analysis of Variance for Digit Symbol Test

Source	*df*	F	Eta^2	*p*
		Between subjects		
Group (G)	1	7.71*	.24	.012
G within-group error	18	(88.25)		
		Within subjects		
Time (T)	1	8.82**	.33	.008
T X G	1	1.40	.07	.252
T within-group error	18	(13.83)		

Note. Values enclosed in parentheses represent mean square errors. * p<.05.

**p <.01