Developmental Markers of Time and Associated Moderators

by

Christie Yao
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in the Department of Psychology

Supervisory Committee

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Co-Supervisor

Dr. Esther Strauss, (Department of Psychology)
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Dr. David Hultsch, (Department of Psychology)
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Abstract

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Background: The selection of a developmental time metric is useful in understanding causal processes that underlie cognitive change, and for the identification of potential moderators of cognitive decline. We examined various conceptualizations of developmental time (e.g., chronological age, measurement occasion, time-in-study, and time-to-attrition), and moderators of cognitive decline that are associated with CNS functioning (e.g., intraindividual variability and chronic health conditions).
Methods: Participants were 304 community-dwelling Caucasian older adults (208 women and 96 men), aged 64 to 92 ($\underline{M}$ = 74.02, $\underline{SD}$ = 5.95) in a longitudinal study. HLM models were fit to examine patterns and moderators of cognitive change.
Results: Time-to-attrition was associated with significant cognitive decline. Greater intraindividual variability, a behavioural indicator of CNS deficits, was associated with impaired performance on executive functioning and episodic memory measures.
Conclusions: Our findings underscore the importance of selecting an appropriate time metric in order to address the possible causal mechanisms underlying the association between cognitive loss and selective attrition (i.e., CNS integrity).

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Dedication

This thesis is dedicated to the memory of Dr. Esther Strauss.

Introduction

The aging Canadian population has given rise to an increased research emphasis on understanding heterogeneity in the rate of cognitive change among older adults (Wilson et al., 2002). The main objective is to understand and explain individual differences in cognitive decline associated with aging through the identification of causal processes that contribute to cognitive loss. When describing cognitive change in aging, Baltes and Nesselroade (1979) presented the distinction between non-normative and normative developmental influences, whereby age-related changes in cognition can be attributed to disease processes versus the effects of normative chronological age that affect most individuals. Non-normative developmental influences do not affect all individuals and their influence can be quite diverse depending on the nature, timing and sequence of their occurrence. Thus, the capacity to identify and differentiate between normative and pathological influences on cognitive change is, in part, a function of how developmental time is indexed. If normative age-graded influences are highly associated with chronological age, then conventional longitudinal models for age-based change can effectively capture those influences. However, if pathological influences are present (e.g., dementia, cardiovascular disease) and produce a developmental progression that is different from age-graded trajectories, then age-based models of change will not allow for the accurate description of intraindividual change (e.g., accelerated cognitive decline preceding dementia diagnosis). Thus, the examination of various conceptualizations of developmental time will be useful in understanding causal processes underlying cognitive change, and for the identification of potential moderators of cognitive decline. This thesis focuses on: a) the comparison of indices of developmental time (e.g., chronological

age, time in study, and time to attrition), with time to attrition hypothesized to provide the best fit to data from the multi-wave Project MIND longitudinal study and; b) the subsequent identification of select factors that further moderate cognitive decline.

Common markers of developmental time

Chronological age and occasion of measurement (e.g., baseline assessment, 1st follow-up, 2nd follow-up) are common variables used to specify time in longitudinal studies. Historically, however, development has been indexed according to alternative definitions of time including biological age, functional age, and social age (Schroots & Birren, 1992). Biological age indexes an individual's place relative to his or her lifespan and may provide a better description of individual's physiological capability as it reflects both genetic and lifestyle factors. Social age refers to social norms and roles relevant to a society or a culture, which may be useful in the description of life stages and benchmarks. Lastly, functional age defines individuals based on their performance on a number of tasks and can be useful in a job-related or a task-oriented context. In circumstances where there is great variability among individuals of the same chronological age or at the same occasion of measurement, it becomes evident that alternative specifications of developmental time are needed to more accurately index individual differences. For the present investigation, four developmental time metrics will be contrasted: chronological age, measurement occasion, time in study, and time to event.

Chronological Age. Birren (1959) proposed that chronological age or the time elapsed since birth (e.g., 53.7 years, 55.9 years, etc.) may be the single most important variable in describing an individual's level of functioning. This view implies that many ontogenetic

processes are intrinsically linked to the age continuum. However, Wohlwill (1970) argued that although age differences account for some change in behaviour, how that behaviour changes over time is not well elucidated by chronological age. Chronological age may reflect accumulated biological and environmental influences but itself is not a causal influence; rather it represents a dimension along which causal factors can operate. Thus, representing cognitive performance as a function of chronological age can obscure identification and modeling of important causes of cognitive change, particularly pathological influences such as disease processes. Whereas age-based models describe a considerable length of time (e.g., age 64 to 92), measurement occasion, time in study and time to attrition models index shorter time periods. This refinement in time allows for the focus on the sequence of causal mechanisms producing the observed cognitive deficits.

Measurement Occasion. Occasion of measurement is another time metric that is commonly used in longitudinal studies, whereby each wave of data collection is used as a marker of time (e.g., 0 = baseline, 1 = 1^{st} follow-up, 2 = 2^{nd} follow-up, etc). This time specification fails to take into account that, typically, not all participants are retested at the same interval so each period between data collection points can vary in length depending on individual availability for testing.

Time in Study. An alternate method to characterize occasion of measurement is by calculating the exact time spent in study for each individual. Although similar in convention to measurement occasion, this method improves precision by specifically quantifying each individual retest interval in years and months (e.g., individual 1 was tested at baseline, 1.7 years after baseline, 3.2 years after baseline, etc).

Time to Event. Time-to-event metrics may be particularly advantageous for homogeneous populations (e.g., those with a specific disease) or for a clearly-well defined time point (e.g., date of attrition). In event-based time structures, the study of change is centred on an event of interest (e.g., time to attrition, time pre or post disease onset, etc.), regardless of age or time in study. Thus, it provides a useful representation of time to facilitate the description and identification of causal processes that may operate along the age or time in study continuum. Event-based time structures allow for a more nuanced account of within person change than is simply captured by chronological age or time in study (Alwin, Hofer, & McCammon, 2006). For instance, modeling time as a function of years to dementia diagnosis, rather than chronological age, provided a more sensitive index of cognitive decline by describing the period of accelerated decline that precedes the onset of dementia (Laukka et al., 2006; Sliwinski et al., 2003). That is for individuals with dementia, the more relevant index of developmental time is proximity pre- or post-disease onset, rather than chronological age.

The role of attrition in cognitive decline

Selective attrition is an important methodological concern in longitudinal studies. Participants who drop out before study completion often show lower baseline performance than those who are lost to follow-up, which may result in an underestimation of cognitive decline observed in longitudinal studies (Siegler & Botwinick, 1979; Baltes, Schaie, & Nardi, 1971; Hultsch, Hertzog, Small, Donald-Miszczak, & Dixon, 1992). Selective attrition has been associated with decreased estimates of dementia following ischemic stroke (Desmond, Bagiella, Moroney, & Stern, 1998), positively biased results towards individuals with higher cognitive ability in a

healthy sample (Mitrushina & Satz, 1991), and cognitive decline and dementia (Sliwinski, Hofer, Hall, Buschke, & Lipton, 2003). However, little is known about the mechanisms that are measured by attrition and how it operates on cognitive performance in older adults.

The association between cognitive functioning and attrition has also been examined in the context of terminal decline. The terminal decline hypothesis predicts that there is an accelerated trajectory of cognitive deterioration that is directly related to proximity to death, and that individual differences arise because some individuals are in a terminal decline phase (Berg, 1996; Bäckman & MacDonald, 2006). Of note, proximity to death is a better predictor of cognitive decline than chronological age (Thorvaldsson, Hofer, & Johansson, 2006). The effects of selective attrition and terminal decline may be linked by the impaired functioning of the individuals who eventually drop out, which may partly be related to the effects of specific disease processes underlying terminal decline.

Sliwinski et al. (2003) investigated the relationship between time to attrition and time to death with regard to cognition, and found that attrition effects remained after controlling for time to death. Conversely, the effects of proximity to death were completely eliminated by controlling for time to attrition. The results suggest that time to death and time to attrition assessed similar causal processes; however these processes were better assessed using the time to attrition model. The authors hypothesized that time to attrition was superior to time to death as a predictor of cognitive change for several reasons: 1) time to death is affected by medical interventions that may alter the natural relationship between proximity to death and cognitive deterioration; 2) voluntary

withdrawal from the study may be influenced by the subjective awareness of one's cognitive deficits and; 3) deleterious events and pathological changes that have negative influences on cognitive function may underlie participant attrition (e.g., subclinical cardiovascular disease, preclinical dementia). Thus, we hypothesize that time to attrition will operationalize non-normative aging influences on cognition in a community-based sample, given that attrition can capture not only those in the terminal decline phase but also those who are at risk but death is not imminent.

Multilevel models of change

Longitudinal research designs are superior for examining the factors that affect individual differences in the rate of mental decline and provide insight into the mechanisms of cognitive aging. Modern statistical approaches, such as multilevel modeling, are used to analyze longitudinal data sets. The benefits of multilevel modeling relative to other procedures such as repeated measures ANOVA include: a) the examination of all available data, thus maximizing the number of participants for analysis; (b) the relaxed assumptions regarding comparable change across all participants (both mean change as well as variance about this mean are estimated); and (c) the simultaneous assessment of individual differences at baseline and change over time (Chu et al., 2007).

Multilevel models consist of two levels of analysis examining change over multiple occasions within the individual (Level 1) and change over multiple occasions between individuals (Level 2). Level 1 or the within-person level can be described by the following equation:

$$\text{Cognitive performance}_{it} = \beta_{0i} + \beta_{1i}*(\text{time metric}_{it}) + r_{it} \quad (1)$$

Performance on a cognitive measure for a given individual (*i*) at a given time (*t*) is modeled as a function of how developmental time is specified (e.g., age, time in study, or time to attrition) for the individual at baseline (the intercept), plus the average individual rate of change over developmental time (the slope), plus a residual (*r*). The level 1 equation is the measurement or descriptive model of intraindividual change (Singer & Willet, 2003). The selection of an appropriate Level 1 time index for the data based on relative best fit is essential before Level 2 moderators can be examined.

Level 2 or the between-person level is represented by the following equations:

$$\beta_{0i} = \gamma_0 + U_{0i} \quad (2)$$
$$\beta_{1i} = \gamma_1 + U_{1i} \quad (3)$$

The above equations reflect a given individual's predicted cognitive performance for the intercept (β_{0i}) and predicted rate of change (β_{1i}) as a function of average cognitive performance at baseline (γ_0) and the average rate of change (γ_1) respectively. The random effect in equation 2 (U_{0i}) estimates the variability around the sample mean (e.g., at baseline assessment) while holding other variables constant, whereas the random effect (U_{1i}) in equation 3 estimates remaining individual differences in intraindividual rates of change. The level 2 model can be viewed as the structural or explanatory model to which the effects of moderating variables on cognitive change, such as health status, can be assessed. An example of a multilevel model including such moderators (e.g., total number of medications) can be represented by the following equations:

$$\text{Level 1: Cognitive performance} = \beta_{0i} + \beta_{1i}*(\text{time in study}_{it}) + r_{it} \quad (4)$$

$$\text{Level 2: } \beta_{0i} = \gamma_{00} + \gamma_{01}*(\text{total \# medications}_i) + U_{0i} \quad (5)$$

$$\beta_{1i} = \gamma_{10} + \gamma_{11}*(\text{total \# medications}_i) + U_{1i} \quad (6)$$

Moderators of cognitive decline

We were interested in the neural mechanisms underlying central nervous system (CNS) integrity that are related to normative and pathological cognitive aging. Thus, we focused on behavioural markers of brain health, such as intraindividual variability, total number of chronic health conditions and total number of medications.

Intraindividual Variability. There are three dimensions along which variability can be considered: persons, measures and occasions. First, between-person or inter-individual differences can be examined on a single task at a single point in time. Second, variability can be measured within a single person on multiple tasks on one occasion. The last type of variability is also measured within a single person, however on a single task and over multiple occasions (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000). Intraindividual variability over the lifespan can be represented by a U-shaped function, with greater variability observed in childhood and later adulthood (Williams, Hultsch, Strauss, Hunter, & Tannock, 2005). Within adulthood, all three types of variability are greater in older compared to younger adults even when group differences in speed were controlled (Hultsch, MacDonald, & Dixon, 2002). Increasing variability that accompanies aging is also associated with concurrent impairment on measures of perceptual speed, working memory, episodic memory and crystallized abilities (Hultsch et al., 2002).

Systematic research suggests that intraindividual variability reflects an important marker of age-related cognitive decline as well as pathological changes in the brain (e.g., neurodegenerative disorders, traumatic brain injury). As an example, patients with mild

dementia showed both increased intraindividual variability and cognitive impairment relative to age-matched healthy controls (Hultsch et al., 2000). In addition, a third group of individuals with arthritis, a non-neurological condition that impacts motor control, did not account for increased intraindividual variability. Thus, increased variability uniquely predicted neurological status independent of mean-level performance, and supports the hypothesis that intraindividual variability is an indicator of deteriorating neural mechanisms and deficits in CNS functioning (Hultsch et al., 2000). In this study, we examined intraindividual variability representing transient within-person fluctuations in cognitive functioning on speed and accuracy that occur across relatively short periods of time (e.g., seconds, minutes, days or weeks), with mean-level differences controlled.

Chronic Conditions. A major contributor to variability in cognitive performance and underlying CNS integrity among older adults may be the presence of comorbid chronic health conditions. Among persons 65 and older, more than 80% have at least one chronic illness, and many individuals have multiple conditions (Bäckman, Small, Wahlin, & Larsson, 2000). Thus, it is likely that some proportion of the variance observed in cognitive performance among the elderly population is related to health factors. Research on health factors have focused on both subjective measures (e.g., self-perceived health status) and more objective measures (e.g., total number of chronic health conditions, total number of medications). Objective measures of health are preferable over subjective measures since self-perceived health may reflect a combination of both subjective and objective factors, which can be difficult to interpret.

The effects of chronic illness on the rate of cognitive decline may act independently of an emerging dementing disease, or the presence of cognitive deficits

may be secondary to pathological aging. Generally, studies that screen for aspects of physical health have demonstrated that health conditions are associated with cognitive performance and decline among nondemented older adults (Bäckman et al., 2000). Specifically, declines in cognitive functioning may be smaller when participants are adequately screened for various health related-factors, underscoring the importance of identifying disease processes in order to implement treatment for the maintenance of cognitive vitality.

Bäckman et al. (2003) found a systematic increase in rate of cognitive decline as a function of number of recent diseases in a group of preclinical dementia cases. The number of recent chronic diseases was associated with the rate of cognitive decline when controlling for the effect of age, whereas the reverse was not true. Thus, the number of recent diseases was the stronger predictor of cognitive decline and mediated the effect of age. A limitation of the study is that only a global measure of cognitive functioning (Mini Mental State Examination; MMSE) was used as the outcome variable, rather than measures assessing specific cognitive domains. Another limitation of the study is that analyses were confined to two measurement occasions, which does not facilitate an accurate description of the rate and trajectory of cognitive change. A final limitation of the study was that comorbidity was characterized broadly in terms of number of diseases. A more informative approach would involve examining the relationship between specific diseases or disease categories and cognitive performance. For instance, cardiovascular-related diseases are common among older adults and represent a major cause of death and disability (Bäckman et al., 2000). Cardiovascular-related diseases include a number of conditions such as hypertension, hypotension, and coronary heart disease. At the most

extreme, circulatory changes influenced by cardiovascular-related diseases can have deleterious effects on the brain, resulting in vascular dementia. Therefore, cardiovascular-related diseases as a classification may be particularly relevant for the study of cognitive change (Fahlander et al., 2000; Scuteri et al., 2007; Brady, Spiro, III, & Gaziano, 2005). Other health conditions such as respiratory disease and cancer, in particular the effects of chemotherapy, have been shown to have adverse consequences on cognition and require further consideration as well (Anstey, Windsor, Jorm, Christensen, & Rodgers, 2004; Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005).

Medications. Another objective measure of health status is the total number of medications that an individual is using. Since aging is associated with increasing health problems, it follows that older adults can be expected to have higher and more frequent use of medications. In addition, specific types of commonly used medications, such as benzodiazepines, can have negative effects on the aging brain and may result in cognitive deficits (Foy et al., 1995).

Overall, these behavioural measures may reflect the functioning of physiological systems and processes that are more closely related to the underlying mechanisms of cognitive change than is the simple of passage of time. Several objective measures of behavioural indicators of CNS functioning will be investigated.

Objectives and hypotheses

Building on the extant evidence just summarized, this study has two primary objectives. The first is the examination of various conceptualizations of developmental time using multilevel models to determine the best time metric that will account for the greatest variance observed in the Project MIND longitudinal cognitive data. Change over

time will be defined as a function of chronological age, measurement occasion, time in study, and time to attrition. Given that deleterious events increase in old age, we hypothesize that an event-based time structure (e.g., time to attrition) will be the most sensitive indicator of cognitive change as it will account for non-normative causal processes.

The second focus of this study is the identification of reliable moderators of cognitive change over a 5-year period. Specifically, we are interested in behavioural indicators of CNS integrity as assessed by intraindividual variability, total number of chronic health conditions and the total number of medications. We hypothesize that over and above known risk factors for cognitive decline (e.g., older age, lower education), the greater number of chronic health conditions and the greater number of medications will account for significant variance in cognitive performance.

Method

Data are derived from the longitudinal Project MIND study at the University of Victoria, Victoria Canada. Project MIND was designed to measure short-term inconsistency that reflects moment-to-moment or day-to-day fluctuations in cognitive performance, as well as long-term change in abilities and skills associated with aging. A complete methodological account of Project MIND has been described elsewhere (Strauss, Bielak, Bunce, Hunter, & Hultsch, 2007) and thus, only sections relevant to this study will be summarized here.

Participants

The sample is comprised of 304 community-dwelling Caucasian older adults (208 women and 96 men), aged 64 to 92 ($\underline{M}$ = 74.02, $\underline{SD}$ = 5.95) who were recruited through advertisements in the local newspaper and radio seeking individuals who were concerned about their cognitive functioning, but not diagnosed with any neurological disorder. Exclusionary criteria included physician-diagnosed dementia or a Mini Mental State Examination (MMSE; Folstein et al., 1975) score less than or equal to 24, a history of significant head injury (e.g., loss of consciousness greater than 5 minutes), other neurological or major medical illnesses (e.g., Parkinson's disease, heart disease, cancer), severe sensory impairment (e.g., difficulty reading newspaper-size print, difficulty hearing a normal conversation), drug or alcohol abuse, current psychiatric diagnosis, psychotropic drug use, and lack of fluency in English. Informed written consent was obtained from each participant and the study was approved by the University of Victoria Human Research Ethics Board.

Measures

Cognitive Tasks

A neuropsychological test battery comprised of paper and pencil tasks was used to measure cognitive performance. These tasks may be ordered along a continuum ranging from indicators of basic information processing resources to more complex acquired products of cognition. Relevant variables assessing cognitive performance and health status are summarized below.

Perceptual Speed. Perceptual speed was measured by Trail Making Tests, Part A and B (Reitan & Wolfson, 1985). In the Trail Making Tests, participants connected 25 encircled numbers randomly arranged on a page, in proper order in Part A and 25 encircled numbers and letters in alternating order in Part B. Time required to complete the task was the outcome measure. Both of these tasks are seen as indicators of perceptual speed, but the Trails B portion of the task presumably places greater demands on executive functioning as well.

Episodic Memory. Episodic memory was measured by word recall. The word recall task consisted of immediate free recall of 30 English words (Hultsch, Hertzog, & Dixon, 1990). The word list consisted of 6 words from each of 5 taxonomic categories (e.g., birds, flowers) typed on a single page in unblocked order. Participants were given 2 min to study each list and 5 min to write their recall. The number of correctly recalled words was used as the outcome measure.

Fluid Reasoning. Inductive reasoning was assessed using the Letter Series test (Thurstone, 1962) and WAIS-III Block Design task (Wechsler, 1997). In the Letter Series test, participants were presented with a string of letters forming a distinct pattern.

The task required inductively deciphering the pattern in the target string and providing the next letter in the string congruent with the pattern presented. The outcome measure used was the total number correct out of 20 patterns.

In the Block Design task, participants arranged coloured blocks according to a presented design. A score out of 68 based on accurate and timely completion of the design was used as the outcome measure.

Semantic Memory. Semantic memory was indexed using two tasks: verbal fluency and vocabulary. Verbal fluency was assessed using the Controlled Associations test from the Educational Testing Service (ETS) kit of factor-referenced cognitive tests (Ekstrom, French, Harman, & Dermen, 1976). The test required the generation of as many synonyms as possible in response to a set of target words. Participants were given 6 minutes to complete the test with the total number of correct synonyms representing the fluency score.

Semantic memory was also measured using a recognition vocabulary test. The 36-item multiple-choice test was composed by concatenating two 18-item tests from the Kit of Factor Referenced Cognitive Tests (Ekstrom et al., 1976)). Participants were given 8 minutes to complete the task. The measure used was the total number of correct items.

Global Cognitive Functioning. The Mini-Mental State Examination (MMSE; (Folstein, Folstein, & McHugh, 1975) was included in the battery as a global assessment of cognitive functioning. Participants answered simple questions related to orientation, recalled a small number of items and followed simple directions. A score out of 30 was the outcome measure.

Chronic conditions. A self-report measure was administered to assess the presence and

severity of chronic illnesses. Participants were asked about a variety of conditions including: visual and hearing disorders, arthritis, osteoporosis, thyroid disease, Parkinson's disease, encephalitis or meningitis, lupus, high blood pressure, heart disease, diabetes, cancer, respiratory problems, stomach or digestive problems, and bowel or urinary problems. Participants indicated the presence or absence of each condition, and if present, they rated the severity as either not serious or serious to very serious. To examine the presence of cardiovascular disease (e.g., atherosclerosis) on cognitive performance, chronic conditions were classified as cardiovascular using the International Classification of Diseases, Injuries, and Causes of Death, Ninth Revision (ICD-9) criteria (World Health Organization, 1975).

Medications. Participants were asked to assemble all medications taken on a regular basis and the total number and classification of each medication was recorded.

Reaction Time (RT) Tasks

A set of computer-based tasks varying in complexity were used to assess reaction time to the nearest millisecond. Participants responded to stimuli presented on a 14" laptop colour screen as quickly and accurately as possible by pressing keys on an external keyboard attached to the computer that was configured specifically for the task. Relevant variables assessing reaction time are summarized below.

Choice reaction time (CRT). For CRT, participants received a warning stimulus consisting of a horizontal row of four plus signs on the screen. The response keyboard had four keys in a horizontal array corresponding to the display on the screen. After a delay of 1000 ms, one of the plus signs changed into a box. The location of the box was randomly equalized across trials. Participants were instructed to press the key

corresponding to the location of the box as quickly as possible. Although the instructions emphasized speed, participants were also instructed to minimize errors. A total of 10 practice trials followed by 52 test trials were administered. The measures used were the latencies and percent correct for the 52 test trials.

Choice reaction time 1-back (CRT-1). This task used the same stimulus display and response keyboard as the basic CRT task. However, in this version of the task, participants were instructed to press the key corresponding to the location of the box on the previous trial as quickly as possible. Although the instructions emphasized speed, participants were also instructed to minimize errors. A total of 10 practice trials and 61 test trials were administered. Because participants made no response on Trial 1, the latencies and percent correct of the remaining 60 test trials were actually used for analysis.

Task switching. The stimuli for this task consisted of geometric figures varying in shape (square, circle) and color (red, green). Stimuli were presented in a white frame in the center of the computer screen. A task cue indicating the currently relevant stimulus dimension (shape or color) was presented above the stimulus at the top of the frame. The response keyboard consisted of two keys. The right-hand key was to be pressed for circles and red objects and the left-hand key was to be pressed for squares and green objects. In the case of an error, the word error appeared for 500 ms at the bottom of the frame. For each trial, the task cue word was presented 600 ms before the geometric figure stimulus. Participants were instructed to press the appropriate key as quickly as possible following presentation of the stimulus. Although the instructions emphasized speed, participants were also instructed to minimize errors. Task cue and the stimulus

object disappeared following the response, but the stimulus frame remained throughout. The task cue for the following trial was presented 50 ms after the previous response. Three blocks of 50 trials were presented, each preceded by 10 practice trials. In the first block, participants were instructed to respond to the shape of the figure. In the second block, participants were instructed to respond to the color of the figure. These single-task blocks were followed by a task-switching block in which the relevant response dimension (shape, color) varied randomly without constraint.

Procedure

A telephone interview was conducted initially to assess for eligibility criteria. Thereafter, eligible participants were asked to come to the University of Victoria and provide written consent to participate in the study. After we obtained informed consent, eligible participants were administered a series of measures providing demographic information (age, years of education), self-reported health information (self-reported chronic conditions), RT measures and several neuropsychological test measures assessing multiple cognitive domains.

Testing occurred in seven sessions (1 group and 6 individual in the Project MIND laboratories for group testing or within the participant's home for individual testing) over approximately 3 months. Participants attended two testing sessions (one group and one individual) during which they provided demographic and health information, and completed the cognitive measures. The RT measures were completed in five subsequent individual testing sessions scheduled approximately every two weeks. During each of these sessions, they performed a battery of reaction time tasks designed to assess short-term fluctuations in response speed. Because we were interested in variability, these five

sessions were distributed across days of the week and times of the day rather than scheduling them at the same time.

Participants underwent annual evaluations of cognitive status and perceived measures of health, as well as completed written consent each year. When dropout from study participation occurred, the reason for withdrawal was noted. Baseline assessments began in 2001, and occurred yearly thereafter. The last complete assessment occurred in 2006-2007.

Statistical Analyses

Longitudinal data were analyzed using multilevel models. This statistical approach allows for assessment of within-person change (Level 1) and between-person differences (Level 2). All data analyses were performed with HLM Version 6.06 using full maximum likelihood for parameter estimation. Analyses of the data occurred in two stages. In the first, we investigated model fit for the various developmental time metrics. The second stage examined the moderators of cognitive decline.

To compare different markers of developmental time, change in performance on neuropsychological domains over time (Level 1) was modeled separately as a function of: 1) chronological age; 2) occasion of measurement; 3) years in study; and 4) years to event (i.e., attrition), and compared to identify the metric that best accounts for patterns of cognitive change in the data, and in accordance with hypotheses discussed earlier. Chronological age was calculated as date of yearly testing assessments subtracted from date of birth for each participant. Time in study was determined by subtracting date of yearly testing assessments from participants' baseline testing date. Because participants were contacted on an annual schedule, attrition was defined as the midpoint between the

last occasion of complete testing and the following testing point at which dropout from study participation occurred. For participants who completed the study, the event was defined as occurring three months after their last testing occasion. For participants who died during the study, their date of death was considered as the date of attrition. The four non-nested models of developmental time were compared for fit using Akaike's Information Criterion (AIC), which is based on log-likelihood estimates that penalizes for the number of parameters in the model. Lower AIC values indicate relatively better fit to the data.

For Level 2 analyses, each potential predictor of neuropsychological test performance was added into the model one by one, beginning with reason for attrition, age and education, which were included to control for cohort effects and because they are known to be associated with cognitive performance (Kempen, Brilman, Ranchor, & Ormel, 1999; Mortensen & Gade, 1993). In accordance with earlier work (e.g., (Hultsch et al., 2002), participants were classified by age into two groups: 1) young-old group aged 64-74 years (n = 170, M = 69.67, SD = 2.74) and 2) old-old group aged 75-92 years (n =134, M = 79.54, SD = 4.02) designed to capture the quantitative differences in performance often observed within the older adult age range. Total years of formal education was coded as a continuous variable. At each step, AIC scores for the nested models were compared to assess whether the model fit was significantly improved. Variables that did not improve model fit were omitted. Because several cognitive tasks were considered, a conservative p-value threshold for significance was chosen at 0.01.

Other predictors of interest included reason for attrition, total number of chronic health conditions, total number of medications, and intraindividual variability measures.

Self-reported reason for attrition was examined by comparing dropout from study due to (a) personal health or memory problems or death versus (b) other external reasons (e.g., family health problems, lack of time or interest, moved away or could no longer be located). This variable was dummy-coded to assess its influence on cognitive decline (see Figure 1). Number of chronic conditions has been shown to be a reliable predictor of cognitive decline (Bäckman, Jones, Small, guero-Torres, & Fratiglioni, 2003), and the utility of further classification of cardiovascular versus non-cardiovascular conditions was examined. Total number of medications as an objective measure of number of chronic conditions was covaried in the model as well. Finally, measures of intraindividual variability were included as additional behavioural indicators of CNS functioning.

Preparation of the RT data and statistical computation of individual standard deviations (ISDs) as a measure of intraindividual variability has been described in detail elsewhere (Strauss et al., 2007). In brief, ISDs were computed as a general index of each participant's performance spread about his or her mean RT across trials, controlling for mean-level differences and practice effects. Greater ISDs may reflect slower response time in older adults compared with their younger counterparts. Practice effects across trials or occasions may result in reduced response times and may have differential effects for different groups. For the purposes of the present study, two composite RT factors determined by principal components analyses (PCA), Basic ISD and Complex ISD, were used to provide the most reliable measures of intraindividual variability. The Basic RT factor was composed of the colour, shape and CRT tasks. The Complex RT factor consisted of the one-back and switch RT tasks.

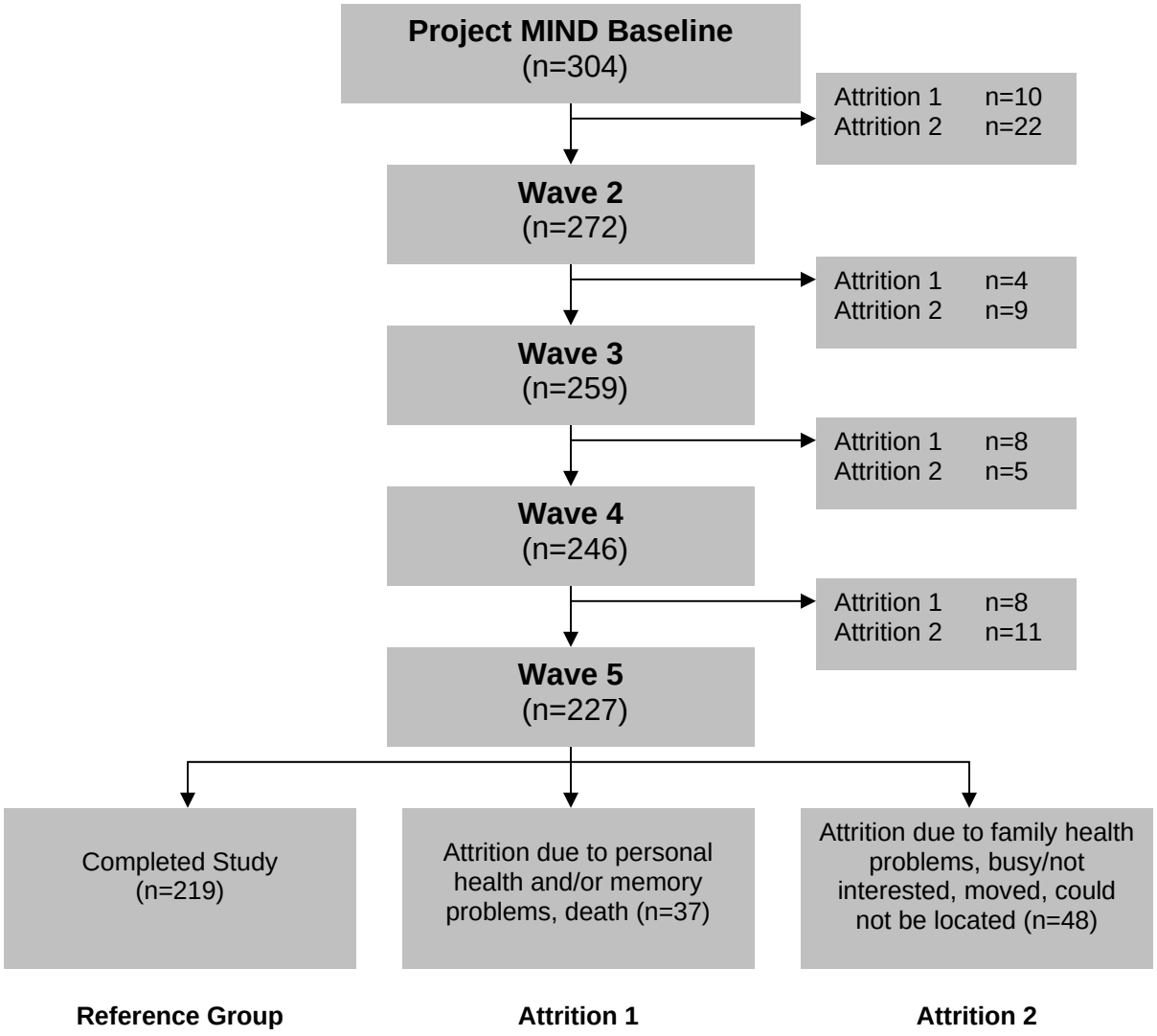

Figure 1 Attrition Status at Wave 5.

Results

Participant Characteristics

Participant characteristics are summarized in Table 1. As expected, our community-dwelling sample in Victoria was generally highly-educated and healthy as compared with their counterparts in the Canadian population (McDowell, Aylesworth, Stewart, Hill, & Lindsay, 2001). Accordingly, our sample had relatively high MMSE scores at baseline and low reported total number of chronic health conditions.

Table 1 Participant characteristics (n=304).

Variable	Mean ± SD (range) and n (%)
Age at baseline, years	74.02 ± 5.95 (64-92)
Age Group	
Young-Old (65 to 74 years)	170 (55.9%)
Old-Old (75+ years)	134 (44.1%)
Education, years	15.15 ± 3.14 (7-24)
MMSE at baseline	28.74 ± 1.23 (24-30)
Basic ISD	7.70 ± 1.88 (3.77-13.31)
Complex ISD	7.61 ± 2.58 (2.11-15.08)
Total number of chronic health conditions	2.92 ± 1.91 (0-10)
History of vascular disease, yes	153 (50.3%)
History of cancer, yes	47 (15.5%)
History of respiratory disease, yes	38 (12.5%)
Total number of medications	5.85 ± 3.56 (0-20)
Attrition Status	
Completed study	219 (72.0%)
Refused to return (health/memory)	37 (12.2%)
Refused to return (family health/busy/not interested/could not locate/deceased)	48 (15.8%)

Comparison of Alternative Time Metrics

A comparison of the initial multilevel models of the four time metrics: 1) chronological age; 2) occasion of measurement; 3) time in study; and 4) time to attrition for each of the seven cognitive measures are summarized in Tables 2 to 8. A relative comparison of the four time metrics did not yield one single metric that was best fitting for all seven cognitive measures. Of note, time to attrition produced the smallest AIC value only for one task, block design.

For the most part, structuring change as chronological age yielded the largest decline in coefficient per unit increase in time, suggesting that this sample of relatively healthy older adults primarily experienced normative aging that is closely associated with chronological age. However, the occurrence of pathological changes to CNS functioning should not be overlooked and utilization of alternative time metrics that are sensitive to capturing these deleterious effects would be optimal in accurately describing the sample. The time to attrition model would employ theory in describing the data, wherein those individuals who cease participation may reflect the occurrence of pathological disease progression that precedes possible neurodegenerative disorders. Given a priori hypotheses that attrition is associated with memory decline and dementia (Sliwinski et al., 2003), we chose to include time to attrition over chronological age as the time metric that will be most informative and sensitive to the causal processes related to normative and pathological aging.

There was a significant variance component for slope for all the cognitive tasks except letter series, which indicates reliable between-person differences in cognitive change and provides impetus to examine potential moderators of these individual

differences. Although significant, the total variance in cognitive performance associated with individual differences in change ranged from 0.11% to 5.80%, suggesting that the rate of cognitive decline is relatively consistent across participants.

Table 2 Comparison of multilevel models as a function of chronological age, occasion of measurement, time in study and time to attrition with the cognitive outcome as WAIS-R Block Design.

	Rate of Change		
Fixed effects	β1i	t	AIC
Model 1: Chronological Age	-0.31	-4.30**	6953
Model 2: Occasion	0.39	2.86*	6945
Model 3: Time in Study	0.37	2.84*	6943
Model 4: Time to Attrition	0.31	2.54*	6942

Random effects	Variance component	p	% Total variance
Model 3: Time to attrition			
Intercept	91.67	<.001	84.54
Slope	1.46	<.001	1.35
Within-person residual	15.30	-	14.11

β1i = rate of change in cognitive performance per additional unit of time in terms of age, occasion, study years, or years to final wave of testing or attrition; AIC = Akaike's information criterion; *p<.01; **p<.001.

Table 3 Comparison of multilevel models as a function of chronological age, occasion of measurement, time in study and time to attrition with the cognitive outcome as Letter Series.

	Rate of Change		
Fixed effects	β1i	t	AIC
Model 1: Chronological Age	-0.16	-6.58**	6187
Model 2: Occasion	-0.02	-0.42	6230
Model 3: Time in Study	-0.03	-0.96	6229
Model 4: Time to Attrition	-0.04	-1.16	6229

Random effects	Variance component	p	% Total variance
Model 3: Time to attrition			
Intercept	19.43	<.001	84.74
Slope	0.01	0.26	0.04
Within-person residual	3.49	-	15.22

β1i = rate of change in cognitive performance per additional unit of time in terms of age, occasion, study years, or years to final wave of testing or attrition; AIC = Akaike's information criterion; *p<.01; **p<.001.

Table 4 Comparison of multilevel models as a function of chronological age, occasion of measurement, time in study and time to attrition with the cognitive outcome as Similarities.

	Rate of Change		
Fixed effects	β1i	t	AIC
Model 1: Chronological Age	-0.09	-2.63*	7296
Model 2: Occasion	0.04	0.61	7290
Model 3: Time in Study	0.01	0.22	7293
Model 4: Time to Attrition	0.01	0.17	7293

Random effects	Variance component	p	% Total variance
Model 3: Time to attrition			
Intercept	20.20	<.001	68.13
Slope	0.16	0.008	0.54
Within-person residual	9.29	-	31.33

β1i = rate of change in cognitive performance per additional unit of time in terms of age, occasion, study years, or years to final wave of testing or attrition; AIC = Akaike's information criterion; *p<.01; **p<.001.

Table 5 Comparison of multilevel models as a function of chronological age, occasion of measurement, time in study and time to attrition with the cognitive outcome as Word Recall.

	Rate of Change		
Fixed effects	β1i	t	AIC
Model 1: Chronological Age	-0.11	-3.40**	6592
Model 2: Occasion	0.05	0.80	6584
Model 3: Time in Study	0.009	0.18	6588
Model 4: Time to Attrition	0.004	0.09	6586

Random effects	Variance component	p	% Total variance
Model 3: Time to attrition			
Intercept	12.57	<.001	71.22
Slope	0.22	<.001	1.25
Within-person residual	4.86	-	27.54

β1i = rate of change in cognitive performance per additional unit of time in terms of age, occasion, study years, or years to final wave of testing or attrition; AIC = Akaike's information criterion; *p<.01; **p<.001.

Table 6 Comparison of multilevel models as a function of chronological age, occasion of measurement, time in study and time to attrition with the cognitive outcome as Trailmaking Part A.

	Rate of Change		
Fixed effects	β1i	t	AIC
Model 1: Chronological Age	0.77	6.38**	8247
Model 2: Occasion	-0.58	-1.90	8377
Model 3: Time in Study	-0.52	-1.74	8368
Model 4: Time to Attrition	-0.35	-1.17	8320

Random effects	Variance component	p	% Total variance
Model 3: Time to attrition			
Intercept	144.24	<.001	65.04
Slope	12.86	<.001	5.80
Within-person residual	64.68	-	29.16

β1i = rate of change in cognitive performance per additional unit of time in terms of age, occasion, study years, or years to final wave of testing or attrition; AIC = Akaike's information criterion; *p<.01; **p<.001.

Table 7 Comparison of multilevel models as a function of chronological age, occasion of measurement, time in study and time to attrition with the cognitive outcome as Trailmaking Part B.

	Rate of Change		
Fixed effects	β1i	t	AIC
Model 1: Chronological Age	2.59	7.16**	10167
Model 2: Occasion	1.54	2.35	10359
Model 3: Time in Study	1.53	2.38	10354
Model 4: Time to Attrition	1.73	2.59*	10329

Random effects	Variance component	p	% Total variance
Model 3: Time to attrition			
Intercept	891.12	<.001	62.37
Slope	42.82	<.001	3.00
Within-person residual	494.85	-	34.63

β1i = rate of change in cognitive performance per additional unit of time in terms of age, occasion, study years, or years to final wave of testing or attrition; AIC = Akaike's information criterion; *p<.01; **p<.001.

Table 8 Comparison of multilevel models as a function of chronological age, occasion of measurement, time in study and time to attrition with the cognitive outcome as Vocabulary.

	Rate of Change		
Fixed effects	β1i	t	AIC
Model 1: Chronological Age	-0.02	-0.76	5823
Model 2: Occasion	0.03	0.83	5823
Model 3: Time in Study	0.02	0.67	5824
Model 4: Time to Attrition	0.01	0.44	5824

Random effects	Variance component	p	% Total variance
Model 3: Time to attrition			
Intercept	16.47	<.001	87.14
Slope	0.02	0.003	0.11
Within-person residual	2.41	-	12.75

β1i = rate of change in cognitive performance per additional unit of time in terms of age, occasion, study years, or years to final wave of testing or attrition; AIC = Akaike's information criterion; *p<.01; **p<.001.

Moderators of cognitive change

An initial multilevel analysis was run with reason for attrition entered in the model to ascertain if there were significant differences between the attrition due to personal reasons group and attrition due to family reasons group on cognitive performance. Generally, those individuals who dropped out of the study due to personal health problems and memory difficulties performed poorer on cognitive tasks at baseline and exhibited a steeper rate of decline over time in comparison to those individuals who dropped out due to other external reasons (Table 9). Since there were reliable differences between reasons for attrition that accounted for significant variance in the model, the attrition groupings were included in all further analyses.

Table 9 Comparison of Attrition (Personal) and Attrition (Family) group on seven cognitive outcomes.

Coefficient (SE)							
Fixed Effects	Block Design	Word Recall	Letter Series	Similarities	Trails A	Trails B	Vocabulary
Initial Status							
Reference	38.91(.83)**	18.08(.29)**	11.39(.31)**	14.74(.40)**	35.24(.79)**	75.77(2.00)**	30.86(.31)**
Attrition (Personal)	-7.13(1.60)**	-3.11(.84)**	-3.20(.86)**	-3.07(.84)**	7.37(3.60)	26.99(9.94)*	-2.04(.82)*
Attrition (Family)	-4.52(1.38)*	-1.63(.61)*	-1.49(.75)	-2.32(.89)*	1.59(1.93)	6.51(4.97)	-1.18(.69)
Rate of Change							
Reference	0.51(.17)*	0.16(.06)*	-0.004(.04)	0.04(.08)	-0.71(.29)	-1.10(.66)	0.05(.03)
Attrition (Personal)	-0.70(.55)	-0.42(.23)	-0.26(.18)	-0.35(.21)	3.93(2.22)	12.05(4.35)*	-0.36(.18)
Attrition (Family)	0.002(.37)	0.16(.18)	0.08(.16)	0.55(.27)	1.07(.62)	0.95(1.82)	0.10(.11)

*p<.01; **p<.001

At the demographic level, the effects of age and education at baseline were considered. Categorical age at baseline was found to vary significantly between attrition groups and thus, age was included as a covariate in all further analyses. Education as a continuous variable did not systematically vary between attrition groups. Moreover, its inclusion in the model did not yield significant coefficients of change and contribute to better model fit based on AIC values. Therefore, education was not a reliable predictor of change in cognitive performance and excluded from subsequent analyses.

A series of hierarchical linear models were run to examine the unique contributions of total number of chronic health conditions, presence of vascular conditions, respiratory conditions or cancer and total number of medications on cognitive performance, while controlling for age and reason for attrition. These health-related moderators were not reliable predictors of cognitive change (results not shown), likely due to the fairly above average nature of the sample (e.g., high IQ, highly educated, healthy), that maximized the benefits of practice on the same cognitive tasks over 6 years. Moreover, attrition may be a reasonable indicator of imminent morbidity rather than a predictor for individuals at risk of pathological changes in CNS functioning that is reflected in the incidence of chronic health conditions within this sample.

Next, a series of hierarchal linear models were run to identify whether measures of intraindividual variability were reliable predictors of cognitive performance. To increase construct validity, Basic ISD and Complex ISD composite factors were used. The complex RT tasks that comprised the Complex ISD factor inherently included components from the basic RT tasks (e.g., a motor control), as well as additional novel aspects requiring more complex cognition. Thus in order to examine the individual

unique contributions of basic and complex RT tasks, the Basic and Complex ISD factors were grand mean centred and entered in the model separately. The results of these multilevel analyses are presented in Tables 10 to 23 and a summary of the meaningful findings is provided in Table 24.

Greater variability on basic and complex RT tasks, as characterized by higher Basic and Complex ISD scores were associated with poorer cognitive performance on initial status, except on Vocabulary task. Other select Level 2 predictors also reliably differentiated performance on cognitive tasks at intercept. Notably, attrition due to personal reasons when compared with the reference group (i.e., participants who completed the study) reliably predicted performance on Block Design, Word Recall, Letter Series and Similarities with Basic ISD in the model. With Complex ISD in the model, attrition for personal reasons predicted performance on Block Design, Letter Series, Similarities, and Trailmaking Part B.

In terms of rate of change, Word Recall was the only task that was significantly associated with Basic ISD, with greater variability linked with faster decline on this task prior to attrition. When the Complex ISD factor was entered in the model individually and subsequent to the covariates, greater variability was associated with a faster rate of cognitive decline on tasks of Word Recall and Trailmaking Part B prior to attrition. Attrition due to personal reasons emerged as the only reliable Level 2 predictor, with slower performance for Trailmaking Part B for both Basic ISD and Complex ISD models.

Table 10 Multilevel models for moderators of change (Basic ISD) on WAIS-R Block Design as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	37.68	0.88	43.01**
Age Group at baseline	-3.44	1.21	-2.83*
Attrition (Personal)	-4.95	1.64	-3.02*
Attrition (Family)	-4.08	1.40	-2.91*
Basic ISD	-1.43	0.33	-4.34**
Rate of change			
Reference	0.42	0.19	2.19
Age Group at baseline	-0.24	0.28	-0.84
Attrition (Personal)	-0.60	0.55	-1.09
Attrition (Family)	-0.02	0.34	-0.05
Basic ISD	-0.11	0.08	-1.43
Random effects	Variance component	SD	P value
Initial status	69.56	8.34	<.001
Rate of change	1.35	1.16	<.001
Level 1 residual	15.26	3.91	-

Model deviance = 6818.13 with 14 parameters; *p<.01; **p<.001

Table 11 Multilevel models for moderators of change (Basic ISD) on Word Recall as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	17.64	0.30	58.80**
Age Group at baseline	-0.66	0.48	-1.38
Attrition (Personal)	-2.33	0.83	-2.81*
Attrition (Family)	-1.47	0.60	-2.48*
Basic ISD	-0.52	0.14	-3.79**
Rate of change			
Reference	0.08	0.06	1.27
Age Group at baseline	-0.19	0.10	-1.90
Attrition (Personal)	-0.30	0.23	-1.34
Attrition (Family)	0.15	0.17	0.90
Basic ISD	-0.09	0.03	-3.37**
Random effects	Variance component	SD	P value
Initial status	9.94	3.15	<.001
Rate of change	0.17	0.41	<.001
Level 1 residual	4.83	2.20	-

Model deviance = 6472.44 with 14 parameters; *p<.01; **p<.001

Table 12 Multilevel models for moderators of change (Basic ISD) on Letter Series as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	10.71	0.34	31.66**
Age Group at baseline	-2.26	0.55	-4.08**
Attrition (Personal)	-2.01	0.82	-2.47*
Attrition (Family)	-1.26	0.74	-1.71
Basic ISD	-0.80	0.14	-5.57**
Rate of change			
Reference	-0.01	0.04	-0.20
Age Group at baseline	-0.05	0.06	-0.73
Attrition (Personal)	-0.27	0.18	-1.50
Attrition (Family)	-0.08	0.16	-0.53
Basic ISD	-0.01	0.02	-0.38
Random effects	Variance component	SD	P value
Initial status	12.94	3.60	<.001
Rate of change	0.01	0.09	0.26
Level 1 residual	3.48	1.87	-

Model deviance = 6092.63 with 14 parameters; *p<.01; **p<.001

Table 13 Multilevel models for moderators of change (Basic ISD) on Similarities as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	14.25	0.40	35.21**
Age Group at baseline	-0.30	0.65	-0.46
Attrition (Personal)	-2.21	0.84	-2.61*
Attrition (Family)	-2.15	0.89	-2.43
Basic ISD	-0.57	0.19	-3.07*
Rate of change			
Reference	-0.002	0.08	-0.02
Age Group at baseline	-0.05	0.11	-0.41
Attrition (Personal)	-0.30	0.22	-1.41
Attrition (Family)	0.54	0.26	2.11
Basic ISD	-0.05	0.03	-1.60
Random effects	Variance component	SD	P value
Initial status	17.53	4.19	<.001
Rate of change	0.14	0.37	0.01
Level 1 residual	9.23	3.04	-

Model deviance = 7227.39 with 14 parameters; *p<.01; **p<.001

Table 14 Multilevel models for moderators of change (Basic ISD) on Trailmaking Part A as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	37.05	0.91	40.89**
Age Group at baseline	6.34	1.59	3.99**
Attrition (Personal)	4.21	3.45	1.22
Attrition (Family)	0.97	1.79	0.54
Basic ISD	2.12	0.47	4.49**
Rate of change			
Reference	-0.55	0.31	-1.77
Age Group at baseline	-0.50	0.63	-0.79
Attrition (Personal)	3.72	2.13	1.75
Attrition (Family)	1.12	0.62	1.82
Basic ISD	0.19	0.17	1.14
Random effects	Variance component	SD	P value
Initial status	100.04	10.00	<.001
Rate of change	10.87	3.30	<.001
Level 1 residual	65.18	8.07	-

Model deviance = 8185.78 with 14 parameters; *p<.01; **p<.001

Table 15 Multilevel models for moderators of change (Basic ISD) on Trailmaking Part B as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	82.67	2.15	38.54**
Age Group at baseline	12.62	3.57	3.53**
Attrition (Personal)	14.99	7.82	1.92
Attrition (Family)	4.31	4.54	0.95
Basic ISD	8.06	1.32	6.09**
Rate of change			
Reference	-0.65	0.66	-0.98
Age Group at baseline	2.56	1.19	2.16
Attrition (Personal)	11.40	4.29	2.66*
Attrition (Family)	0.92	1.84	0.50
Basic ISD	0.52	0.33	1.57
Random effects	Variance component	SD	P value
Initial status	465.54	21.58	<.001
Rate of change	29.63	5.44	<.001
Level 1 residual	486.87	22.07	-

Model deviance = 1 0153.60 with 14 parameters; *p<.01; **p<.001

Table 16 Multilevel models for moderators of change (Basic ISD) on Vocabulary as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	30.72	0.36	86.22**
Age Group at baseline	-0.50	0.55	-0.92
Attrition (Personal)	-1.80	0.86	-2.08
Attrition (Family)	-1.13	0.70	-1.61
Basic ISD	-0.16	0.14	-1.14
Rate of change			
Reference	0.03	0.03	0.79
Age Group at baseline	-0.04	0.06	-0.70
Attrition (Personal)	-0.33	0.18	-1.88
Attrition (Family)	0.10	0.11	0.87
Basic ISD	0.03	0.02	-1.81
Random effects	Variance component	SD	P value
Initial status	15.53	3.94	<.001
Rate of change	0.01	0.11	0.01
Level 1 residual	2.39	1.55	-

Model deviance = 5773.62 with 14 parameters; *p<.01; **p<.001

Table 17 Multilevel models for moderators of change (Complex ISD) on WAIS-R Block Design as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	37.00	0.86	42.18**
Age Group at baseline	-1.74	1.30	-1.34
Attrition (Personal)	-5.90	1.55	-3.81**
Attrition (Family)	-3.81	1.32	-2.90*
Complex ISD	-1.38	0.23	-5.92**
Rate of change			
Reference	0.39	0.20	2.01
Age Group at baseline	-0.15	0.31	-0.49
Attrition (Personal)	-0.60	0.53	-1.14
Attrition (Family)	-0.12	0.35	-0.35
Complex ISD	-0.09	0.06	-1.46
Random effects	Variance component	SD	P value
Initial status	66.26	8.14	<.001
Rate of change	1.34	1.16	<.001
Level 1 residual	15.27	3.91	-

Model deviance = 6801.86 with 14 parameters; *p<.01; **p<.001

Table 18 Multilevel models for moderators of change (Complex ISD) on Word Recall as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	17.47	0.31	56.86**
Age Group at baseline	-0.21	0.50	-0.41
Attrition (Personal)	-2.73	0.83	-3.30**
Attrition (Family)	-1.39	0.58	-2.40
Complex ISD	-0.44	0.10	-4.44**
Rate of change			
Reference	0.05	0.07	0.80
Age Group at baseline	-0.11	0.11	-0.98
Attrition (Personal)	-0.32	0.23	-1.43
Attrition (Family)	0.11	0.17	0.64
Complex ISD	-0.07	0.02	-3.33**
Random effects	Variance component	SD	P value
Initial status	9.76	3.12	<.001
Rate of change	0.16	0.40	<.001
Level 1 residual	4.83	2.20	-

Model deviance = 6465.91 with 14 parameters; *p<.01; **p<.001

Table 19 Multilevel models for moderators of change (Complex ISD) on Letter Series as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	10.26	0.35	29.38**
Age Group at baseline	-1.16	0.57	-2.03
Attrition (Personal)	-2.46	0.79	-3.10*
Attrition (Family)	-1.11	0.72	-1.55
Complex ISD	-0.82	0.10	-8.16**
Rate of change			
Reference	-0.02	0.04	-0.47
Age Group at baseline	-0.02	0.07	-0.25
Attrition (Personal)	-0.25	0.17	-1.44
Attrition (Family)	-0.11	0.16	-0.68
Complex ISD	-0.01	0.01	-0.91
Random effects	Variance component	SD	P value
Initial status	11.56	3.40	<.001
Rate of change	0.01	0.09	0.27
Level 1 residual	3.48	1.87	-

Model deviance = 6057.43 with 14 parameters; *p<.01; **p<.001

Table 20 Multilevel models for moderators of change (Complex ISD) on Similarities as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	13.87	0.42	33.12**
Age Group at baseline	0.59	0.67	0.88
Attrition (Personal)	-2.51	0.82	-3.06*
Attrition (Family)	-2.01	0.87	-2.33
Complex ISD	-0.63	0.14	-4.55**
Rate of change			
Reference	-0.01	0.08	-0.17
Age Group at baseline	-0.01	0.14	-0.04
Attrition (Personal)	-0.31	0.21	-1.48
Attrition (Family)	0.50	0.27	1.90
Complex ISD	-0.04	0.03	-1.50
Random effects	Variance component	SD	P value
Initial status	16.56	4.07	<.001
Rate of change	0.14	0.37	0.01
Level 1 residual	9.25	3.04	-

Model deviance = 7212.55 with 14 parameters; *p<.01; **p<.001

Table 21 Multilevel models for moderators of change (Complex ISD) on Trailmaking Part A as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	37.27	0.93	39.88**
Age Group at baseline	5.37	1.83	2.93*
Attrition (Personal)	6.07	3.51	1.73
Attrition (Family)	0.84	1.81	0.47
Complex ISD	1.47	0.36	4.07**
Rate of change			
Reference	-0.40	0.39	-1.03
Age Group at baseline	-0.85	0.84	-1.02
Attrition (Personal)	3.68	2.10	1.79
Attrition (Family)	1.26	0.61	2.07
Complex ISD	0.22	0.17	1.31
Random effects	Variance component	SD	P value
Initial status	102.25	10.11	<.001
Rate of change	10.60	3.26	<.001
Level 1 residual	65.30	8.08	-

Model deviance = 8186.63 with 14 parameters; *p<.01; **p<.001

Table 22 Multilevel models for moderators of change (Complex ISD) on Trailmaking Part B as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	83.75	2.24	37.37**
Age Group at baseline	8.46	4.09	2.07
Attrition (Personal)	22.07	8.57	2.58*
Attrition (Family)	3.87	4.52	0.86
Complex ISD	5.79	1.07	5.41**
Rate of change			
Reference	0.20	0.71	0.78
Age Group at baseline	0.69	1.19	0.58
Attrition (Personal)	10.68	4.07	2.63*
Attrition (Family)	1.27	1.79	0.71
Complex ISD	0.90	0.27	3.38**
Random effects	Variance component	SD	P value
Initial status	499.15	22.34	<.001
Rate of change	20.81	4.56	<.001
Level 1 residual	494.18	22.23	-

Model deviance = 1 0148.32 with 14 parameters; *p<.01; **p<.001

Table 23 Multilevel models for moderators of change (Complex ISD) on Vocabulary as a function of time to attrition.

Fixed effects	Coefficient	SE	t
Initial status			
Reference	30.47	0.38	79.75**
Age Group at baseline	0.04	0.56	0.07
Attrition (Personal)	-1.79	0.84	-2.14
Attrition (Family)	-1.03	0.71	-1.47
Complex ISD	-0.28	0.12	-2.42
Rate of change			
Reference	0.02	0.03	0.58
Age Group at baseline	-0.01	0.05	-0.25
Attrition (Personal)	-0.34	0.17	-1.98
Attrition (Family)	0.08	0.11	0.67
Complex ISD	-0.02	0.01	-1.85
Random effects	Variance component	SD	P value
Initial status	15.23	3.90	<.001
Rate of change	0.01	0.12	0.01
Level 1 residual	2.38	1.54	-

Model deviance = 5765.83 with 14 parameters; *p<.01; **p<.001

Table 24 Summary of meaningful findings from Tables 10 to 23.

Table	Meaningful Findings
10	Higher Basic ISD and Attrition (Personal) was significantly associated with lower baseline performance on Block Design.
11	Higher Basic ISD was significantly associated with lower baseline performance and a steeper rate of decline on Word Recall. Attrition (Personal) was significantly associated with lower baseline performance only on Word Recall.
12	Higher Basic ISD and Attrition (Personal) was significantly associated with lower baseline performance on Letter Series.
13	Higher Basic ISD and Attrition (Personal) was significantly associated with lower baseline performance on Similarities.
14	Higher Basic ISD was significantly associated with lower baseline performance on Trails A.
15	Higher Basic ISD was significantly associated with lower baseline performance on Trails B. Attrition (Personal) was associated with steeper rate of decline on performance on Trails B.
16	Both Basic ISD and Attrition (Personal) did not significantly influence initial performance or rate of change on Vocabulary.
17	Higher Complex ISD and Attrition (Personal) was significantly associated with lower baseline performance on Block Design.
18	Higher Complex ISD was significantly associated with lower baseline performance and steeper rate of decline on Word Recall. Attrition (Personal) was significantly associated with lower baseline performance only on Word Recall.
19	Higher Complex ISD and Attrition (Personal) was significantly associated with lower baseline performance on Letter Series.
20	Higher Complex ISD and Attrition (Personal) was significantly associated with lower baseline performance on Similarities.
21	Higher Complex ISD was significantly associated with lower baseline performance on Trails A.
22	Higher Complex ISD and Attrition (Personal) were significantly associated with both lower baseline performance and steeper rate of decline on Trails B.
23	Both Complex ISD and Attrition (Personal) did not significantly influence initial performance or rate of change on Vocabulary.

Discussion

Time-to-Attrition metric

Our comparison of various developmental metrics of chronological age, measurement occasion, time-in-study, and time-to-attrition did not find that one metric consistently provided the best fit of data across seven cognitive tasks. This finding differed from our hypothesis that time-to-attrition would account for cognitive decline better than chronological age, as it indexes both normative and pathological influences on aging. Empirically, time-to-attrition yielded the lowest AIC value for a single task assessing fluid reasoning, Block Design. However, most attrition patterns were in the expected direction and given that standard errors were large, a bigger sample size and less select sample, may have yielded significant results. Overall, there was not much variability between AIC values on many of the cognitive measures, indicating that all four metrics indexed developmental time relatively well. This finding suggests that our sample of relatively healthy individuals were for the most part undergoing normative aging, which is well described by chronological age, measurement occasion, and time in study. Thus, one possibility why time-to-attrition was not the best index of development time is that the healthy status of our sample did not exhibit any pathological effects for time-to-attrition to detect.

Another and more plausible explanation concerns the range of reasons underlying participants' decision to drop out of the study. The Level 1 time-to-attrition model included all reasons for dropout, even those individuals who were relatively healthy themselves but cited family health problems, lack of interest in the study, or were too busy to participate. These individuals are likely to be active and high functioning and

their inclusion may have obscured the effects of those who dropped out due to personal health or memory problems. Thus, reason for attrition was examined as a Level 2 moderator, and found to reliably moderate cognitive performance (discussion follows in the next section). Therefore, time-to-attrition may have proved a better time metric were these individuals not included as they did not represent instances of pathological aging.

Although empirically, time-to-attrition was not consistently the best time metric to describe the data, it was selected based on a priori hypotheses regarding attrition effects. Selective attrition is more likely to occur in individuals at risk for rapid cognitive decline, possibly reflecting less pronounced cognitive impairment or less severe health conditions (e.g., subclinical cardiovascular disease; Sliwinski et al., 2003). Thus, it is important to consider the issue of attrition, particularly in an aging population who as a group are more likely to experience health and memory concerns. Otherwise, an underestimation of observed pathological cognitive change may occur. Moreover, time-to-attrition was selected because it yielded reliable between-person differences in cognitive performance that warranted further investigation of the potential moderators of these individual differences.

Reason for attrition as a moderator

Our findings suggest that reason for attrition is a reliable moderator of cognitive performance. At initial status, those individuals who dropped out citing personal health and memory reasons performed lower on several cognitive measures, when compared to individuals who remained in the study. These measures assessed fluid reasoning (Block Design, Letter Series), verbal fluency (Similarities), executive functioning (Trails B) and episodic memory (Word Recall). This finding is consistent with previous research

indicating that individuals who attrite perform lower at baseline than their counterparts who complete the study (Hultsch et al., 1992). Overall, individuals who dropped out due to family health problems and other external reasons did not differ significantly on cognitive performance from those who completed the study, with the exception on Block Design and Word Recall. Bearing in mind that reason for attrition was self-reported, this latter finding may reflect the reality that this attrition group may not exclusively contain individuals who dropped out for external reasons. Rather, this group is probably in part comprised of individuals who are experiencing health or memory problems but did not want to disclose that information. Or there may be unknown person-specific factors related to individuals who decide to drop out that are inherently different from those who choose to remain in the study.

The effect of attrition due to personal reasons on the rate of cognitive decline was only evident on one cognitive task (Trails B), which suggests that executive functioning is particularly vulnerable to the effects of pathological aging as indexed by attrition. In fact, many studies have reported that impaired performance on tasks of executive functioning in normal individuals can predict progression of Alzheimer's disease (Blacker et al., 2007; Chen et al., 2000). Our findings support the view that less pronounced cognitive impairment and mild health conditions in part underlie attrition effects and thus, attrition moderates cognitive performance on tasks that are sensitive to subsequent diagnoses of neurodegenerative processes. Lastly, as expected there was no effect of attrition due to external reasons on rate of decline observed in this sample.

Intraindividual variability moderators of cognitive decline

Our findings suggest that intraindividual variability measures of Basic and Complex ISD reliably moderate cognitive performance on initial status and on rates of cognitive decline. At initial status, greater Basic and Complex ISD were significantly associated with poorer performance on all cognitive tasks, with the exception of Vocabulary. Although non-significant, performance on vocabulary was along the expected direction of decreased performance over time. This is not an unexpected finding, as vocabulary is considered a crystallized ability (Strauss, Sherman, & Spreen, 2006), which is more resistant to the effects of both normative and pathological aging.

In terms of rate of decline, greater variability on basic RT tasks was associated with poorer episodic memory (Word Recall), whereas greater variability on complex RT tasks was associated with poor performance on both episodic memory (Word Recall) and executive functioning (Trails B) tasks. Although non-significant for the other cognitive tasks, the trend was in the expected direction, with the exception of Vocabulary in the Basic ISD model. Basic ISD reflects tasks that tap into fundamental brain processes (e.g., perceptual and sensorimotor speed), whereas Complex ISD tasks require more involved cognition (e.g., cognitive switching) in addition to the basic mental processes. Thus, decline in Trails B performance was only observed when the RT tasks were more cognitively complex, requiring manipulation of information held briefly in mind (one back task), switch cognitive set or inhibit an automatic response. Because Trails B assesses some of those same components, it follows that there is a relationship with complex RT variability. In addition, performance variability has been observed to

increase with age on tasks requiring executive control (West, Murphy, Armilio, Craik, & Stuss, 2002).

The finding that intraindividual variability moderates rate of decline on tests assessing episodic memory and executive functioning is consistent with the extant literature. Studies have found that greater intraindividual variability is associated with lower general intelligence (Li et al., 2004; Rabbitt, Osman, Moore, & Stollery, 2001) and poorer performance on more specific cognitive domains (Hultsch et al., 2002; West et al., 2002; MacDonald, Hultsch, & Dixon, 2003). Hultsch et al. (2002) demonstrated that greater variability on four different RT measures was associated with poorer performance on tasks of perceptual speed, working memory, episodic memory and crystallized abilities at initial status. MacDonald et al. (2003) demonstrated that increasing variability was associated with declining cognitive performance on tasks measuring perceptual speed, working memory, fluid reasoning, and episodic memory. One possibility as to why our other cognitive outcome measures were not significant concerns the healthy status of the sample. Some of the more basic cognitive tasks (Trails A) did not show deficits possibly because the fundamental brain processes remain in large part unaffected (e.g., basic motor skills required in speeded tasks) in these high functioning individuals.

If intraindividual variability is a behavioural index of CNS integrity, our findings suggest that the cognitive domains of executive functioning and episodic memory are the most vulnerable to deficits in CNS. Evidence from numerous studies examining AD prediction indicate that deficits on neuropsychological test performance, particularly those assessing episodic memory and executive functioning, are predicative of subsequent AD diagnosis (Bäckman, Jones, Berger, Laukka, & Small, 2005; Blacker et

al., 2007; Chen et al., 2000). A meta-analysis examining the size of impairments of various cognitive domains in preclinical AD demonstrated that deficits in episodic memory and executive functioning yielded the largest effect sizes, along with perceptual speed and global cognitive ability (Bäckman et al., 2005).

The link between brain processes and behaviour is needed to establish the view that intraindividual variability may reflect changes in CNS functioning. A recent review of current evidence demonstrates that intraindividual variability likely represents multiple neurobiological factors (MacDonald, Nyberg, & Backman, 2006). In brief, the underpinnings of intraindividual variability include changes in gray and white matter caused by lesions or neurodegeneration (Gogtay et al., 2004; Stuss, Murphy, Binns, & Alexander, 2003), changes in neural functionality (Logan, Sanders, Snyder, Morris, & Buckner, 2002; Cabeza, 2001), and neurotransmitter dysfunction, particularly the dopamine system (Li, Lindenberger, & Sikstrom, 2001; Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006). Focusing on the structural evidence, the U-shaped developmental changes in behavioural intraindividual variability parallel the nonlinear structural changes of the brain over the lifespan. Thus, the increase in intraindividual variability in childhood and older adulthood may reflect systematic changes in brain morphology, particularly in the frontal lobes (Gogtay et al., 2004). Another line of evidence demonstrated that patients with focal frontal brain lesions exhibited increased intraindividual variability on RT tasks, when compared to patients with non-frontal lesions (Stuss et al., 2003). Together, the evidence suggests that intraindividual variability seems to reflect changes in the frontal brain regions, an area that is particularly vulnerable to the effects of aging.

To summarize, our findings are consistent with the view that intraindividual variability is associated with CNS functioning, and may underlie the relationship between time-to-attrition and cognitive performance. It is not clear in the present analyses whether intraindividual variability is an outcome or a cause of developmental change. Future directions would include determining the direction of mediation between intraindividual variability and cognitive measures.

Health-related moderators of cognitive decline

Our results did not find that health-related moderators were reliable predictors of baseline cognitive performance or rate of cognitive change (i.e., total number of chronic health conditions, presence of vascular disease, presence of respiratory disease, presence of cancer and total number of medications), as a function of time-to-attrition. It is important to note the healthy status of our sample that reported relatively low numbers of chronic illnesses. When chronic health conditions were further classified by disease category, the resultant cell sizes were quite low. One possibility for the null findings is that there may be lack of power to detect effects of the various chronic health conditions on cognitive change over time. However, close examination of the data showed that the overall trend was not towards the hypothesized direction, suggesting it is not purely an issue of power. Alternatively, there are several plausible explanations for the null prediction findings. First, selective attrition may be an indirect marker of poor health status (Rabbitt, Lunn, & Wong, 2008; Sliwinski et al., 2003) and thus, time-to-attrition may effectively account for worsening health. The addition of the Level 2 health-related moderators did not account for additional variance over and above the health considerations explained by time-to attrition.

Second, time-to-attrition and time-to-death are posited to measure related effects of health factors associated with terminal decline (Rabbitt et al., 2008; Sliwinski et al., 2003). However, a comparison of the two metrics suggests that time-to-attrition better represented cognitive change than time-to-death (Sliwinski et al., 2003). One possibility for this finding was that the effect of attrition reflected the pathological influences of mild health conditions (e.g., dementia, cardiovascular disease). Given our above average sample, it is plausible that time-to-attrition is a reasonable indicator of morbidity.

Third, health-related moderators were not found to be reliable possibly due to improved performance from repeated testing. These retest effects can result from familiarity with the test material, such as remembering specific test items, general application of strategies, and reduced test-taking anxiety. When participants are repeatedly assessed on the same tasks, retest effects can counteract true rates of change, particularly masking accelerated rates of decline (Rabbitt, Diggle, Holland, & McInnes, 2004; Rabbitt, Diggle, Smith, Holland, & Mc Innes, 2001). Retest effects have been found even when there are large retest intervals of several years (Rabbitt et al., 2001). The factors that contribute to retest effects may also vary between cognitive measures (Wilson, Li, Bienias, & Bennett, 2006), and thus repeated assessments may have differential effects on initial status and rate of cognitive change, depending on the cognitive task. Furthermore, there are complex interaction effects between overall ability level (e.g., fluid intelligence), age, and complexity of the task. Less able and older individuals exhibit greater improvement on simple tasks, whereas the more able and younger show greater and sustained improvement on more complex tasks (Rabbitt, Banerji, & Szymanski, 1989).

The implication from these findings for our above average in ability level sample is that we can expect significant practice effects over time. Although our analysis was non-significant, some trends suggest improved performance over time, which is contrary to our expectations that participants will exhibit some evidence of decline or remain stable over the study period. There are statistical and methodological methods to account for practice effects (Rabbitt et al., 2001; Thorvaldsson, Hofer, Berg, & Johansson, 2006; Ferrer, Salthouse, Stewart, & Schwartz, 2004; Salthouse & Tucker-Drob, 2008; Wilson et al., 2006). However, many of these techniques control for individual variability (e.g., individual response to initial testing), which reduces the individual differences that we seek to explain with hypothesized moderators.

Lastly, there are some methodological issues to consider. The structure of Project MIND was not designed to measure objective health; rather intraindividual variability was the primary focus of the study. Thus the specificity and accuracy of health-related measures were lacking when compared with measures of intraindividual variability. Since there was decreased sensitivity for measures of chronic health conditions, a larger sample size may be needed to examine cognitive change. An additional methodological consideration concerns the length of follow-up periods, such that shorter intervals may be useful in capturing declines in cognition.

A strong point of our investigation on the moderating effects of chronic health conditions on cognition is the inclusion of all individuals in our analyses, including those with chronic illnesses who died or dropped out of the study. Thus the true effects of underlying pathologies were not underestimated. If selective attrition was not considered, our sample may include only those participants whose health conditions were

relatively low in severity. The detection of health status on cognition can only be considered if participants with health conditions of varying severity are all included. One avenue of further research would include examining changes in chronic health status over time in relation to cognition.

Possible Limitations

Although the findings from this study provide unique information regarding cognitive trajectories associated with study attrition and moderators of individual differences of these trajectories, some limitations need to be considered. First, it is important to note the healthy and highly educated status of our sample. This selection bias tends to produce a positive bias in research results, which may underestimate the degree of cognitive impairment and affliction of chronic illnesses experienced by the average older adult. Thus, the ability to generalize our findings to the Canadian population may be limited.

The self-report nature of total number of chronic conditions and reason for attrition may limit the validity of these measures. Self-report of the total number of chronic illnesses is less preferable than medical diagnoses of these conditions, as the presence of illness may not be accurately reported. However, the total number of medications was included as a more objective measure of number of chronic health conditions. Self-report reason for attrition may mask the true reason for withdrawal from the study, such as failing health or memory difficulties that hinder their ability to participate.

In addition to the above discussion on retest effects, retest effects in the intraindividual variability RT tasks were statistically accounted for in the computation of

ISD scores, but not in our cognitive tasks. In general, retest influences have been hypothesized to account for the discrepancy observed between large age-related declines in cognitive ability in cross-sectional study designs compared with smaller declines in longitudinal designs. The extent to which individuals in longitudinal studies differ in their ability to benefit from previous testing experience is not well understood (Wilson et al., 2006). However, recent findings suggest that individual variability in response to testing may not strongly affect research on individual differences in change and person specific predictors of such change (Wilson et al., 2006). Further research is needed to support this view.

In terms of outcome measures, this study examined a range of cognitive abilities that are sensitive to cognitive change, including inductive reasoning (Letter Series), episodic memory (Word Recall), verbal fluency (Similarities), fluid reasoning (Block Design), perceptual speed (Trails A), executive functioning (Trails B), and vocabulary. Data for some measures (e.g., Trails B, Trails A) were only available for a span of four years, while the other measures spanned the full six-year period. It would also be advantageous to utilize several tasks to measure each cognitive domain to improve construct validity, and other domains (e.g., visuospatial ability) require study. A final consideration is that attrition and intraindividual variability are indirect indices of the underlying causal mechanisms that contribute to cognitive change in aging and thus, we must be careful of the inferences we draw.

Conclusions

The aims of the present study were two-fold: 1) to compare and contrast various definitions of developmental time, while considering hypotheses of the effect of attrition

on longitudinal studies, to determine the metric of best fit and; 2) to examine behavioural indicators of CNS functioning (e.g., chronic health conditions, intraindividual variability) that moderate individual differences observed in cognitive decline. This is the first study to our knowledge to investigate intraindividual variability in relation to time-to-attrition. Intraindividual variability on both basic and complex RT tasks moderated performance on tasks of episodic and executive functioning as a function of time-to-attrition. Our findings suggest that deterioration to the CNS is a plausible mechanism underlying the association between cognitive loss and selective attrition.

At a methodological level, our findings support recent views underscoring the importance of selecting an appropriate time metric based on theory and a priori hypotheses (Sliwinski et al., 2003). By choosing chronological age as a metric of time, as often is the convention, the assumption follows that significant variance in cognitive change can be accounted for by chronological age. As a result, important pathological influences that affect subsets of the aging population are neglected as they are not strongly correlated with chronological age, and thus causal factors that explain cognitive decline are overlooked. Given that a typical sample of the aging population will consist of individuals with chronic health conditions, it is important to consider pathological influences. At a theoretical level, our findings address the causal mechanisms, providing further evidence that attrition effects and intraindividual variability underlie CNS dysfunction, supporting the hypothesis that time-to-attrition may better capture instances of pathological aging. Further directions for research include more refined markers of intraindividual variability with a more diverse sample, and further elucidation of the

causal mechanisms of intraindividual variability using direct measures of brain and behaviour.

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