Thesis title: Predicting trajectory of cognitive change in patients with Mild Cognitive Impairment

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## ABSTRACT

Mild cognitive impairment (MCI) represents a state of high risk for dementia but is heterogeneous in its course. To date, the trajectories reflecting distinct developmental courses of cognition among patients with MCI, and their association with readily available clinical information, have not been well defined. Study 1 sought to identify the developmental trajectory of groups with distinct cognitive change patterns among a cohort of MCI patients. Study 2 was conducted to identify individual items/subtests of the Mini-Mental State Examination (MMSE) and demographic variables *at baseline* that predicted the identified trajectories of cognitive change from Study 1. One hundred and eighty-seven MCI patients were evaluated serially with the MMSE for up to 3.5 years. Five trajectories were identified and labeled based on their baseline MMSE score and course: *29-stable* (6.4%); *27-stable* (53.9%); *25-slow-decline* (23.8%); *24-slow-decline* (11.6%); *25-rapid-decline* (4.2%). In multivariate logistic regression analysis, a model was established to dissociate patients with stable vs. declining trajectories. An equation derived from this model that included age, delayed recall, constructional praxis, attention, and orientation to time and floor predicted future cognitive decline with good accuracy (79.9%) and specificity (86.4%), and moderate sensitivity (67.2%). The identification of varying trajectories of cognitive change and predictors of cognitive decline from easily obtained baseline clinical information can help target at-risk groups for early interventions aimed at delaying the onset of dementia.

# ABRÉGÉ

Les déficits cognitifs légers représentent un risque élevé pour le développement de la démence, mais le parcours vers cet état est hétérogène. À ce jour, les trajectoires reflétant des parcours distincts de développement de la cognition chez les individus avec un déficit cognitif léger et leur association avec des informations cliniques facilement accessibles ne sont pas bien définies. La première étude visait à identifier la trajectoire développementale de groupes avec des parcours distincts de changements cognitifs parmi une cohorte de personnes ayant un déficit cognitif léger. La deuxième étude visait à identifier des items/sous-tests du Mini-Mental State Exam (MMSE) et des variables démographiques mesurées au point de départ et qui prédisaient les trajectoires de changements cognitifs identifiées à la première étude. 187 patients avec des déficits cognitifs légers ont été évalués à plusieurs reprises avec le MMSE sur une période de 3,5 années. Cinq trajectoires ont été identifiées et nommées sur la base de leur score au MMSE au point de départ et le parcours : *29-stable* (6.4%); *27-stable* (53.9%); *25-déclin lent* (23.8%); *24- déclin lent* (11.6%); *25- déclin rapide* (4.2%). Avec la régression logistique, un modèle a été établi afin de distinguer les patients ayant une trajectoire stable de ceux ayant une trajectoire déclinante. Une équation dérivée à partir de ce modèle et qui incluait l'âge, le rappel différé, la praxis, l'attention, l'orientation dans le temps et l'étage prédisait le déclin cognitif avec une justesse (79.9%), sensibilité (67.2%) et spécificité (86.4%). L'identification des différentes trajectoires de changements cognitifs et des variables explicatives du déclin cognitif à partir des informations cliniques facilement accessibles peut aider à identifier les groupes de personnes qui ont

un risque élevé afin qu'ils reçoivent des interventions rapides qui ont pour but de retarder l'apparition de la démence.

# TABLE OF CONTENTS

## Index of tables

*Chapter 2*



*Chapter 3*



## Index of figures

## Index of appendix

## PREFACE

Dementia is the most prevalent neurodegenerative disease and one of the major concerns in older persons. The prevalence of dementia has increased over the past few decades. It is estimated that 13.5 million people in developed countries suffered from dementia in 2000. The number of cases of dementia will rise to 21.2 million in 2025, and 36.7 million in 2050 [1].

. With the incidence and prevalence of dementia escalating and limited resources for management of the disorder, there is an increasing need to identify at-risk groups for early intervention. Mild cognitive impairment (MCI) has been regarded as a state in which a person is at increased risk for dementia, yet some patients do not seem to progress to dementia. Therefore, MCI patents are heterogeneous in the their developmental course of cognition. To date, the trajectories reflecting the distinct developmental course of cognition among MCI have not been well defined. Moreover, easy-to-use and reliable approaches to identifying patients with MCI who will follow a declining trajectory are needed, so that appropriate interventions may be offered.

The following is a manuscript-based thesis with two central themes: 1) the identification of distinct trajectories of cognitive change during up to 3.5 years among a cohort of MCI patients; 2) the identification of individual items of the Mini-Mental State Examination (MMSE) and demographic variables at baseline that predict membership in each trajectory group. Chapter 1 consists of the literature on the concept and prevalence of MCI, the heterogeneous evolution of MCI, current approaches for predicting risk of conversion to dementia among individuals with MCI, as well as the principle of group-based trajectory modeling applied in the current project. Chapters 2 and 3 are two

logically connected manuscripts with objectives encompassing the two central themes mentioned above. The first manuscript was published in the journal *Dementia and Geriatric Cognitive Disorders*, and the second manuscript was submitted to the journal *Dementia and Geriatric Cognitive Disorders* in March. Chapter 4 presents a general discussion of the entire project.

*Contributions of Authors*

The manuscripts in this thesis were co-authored with my supervisor, Dr. Lisa Koski, who supervised all stages of this research work, including study design, data analysis and interpretation of data, and who contributed to the critical revision of manuscripts. Dr. Nancy Mayo, one of my thesis committee members, provided recommendations for the research design, technical support for statistical analyses and comments on the manuscripts. Under my supervisor's and Dr. Nancy Mayo's guidance, I developed the conception and design of this work, acquired the data, analyzed and interpreted the data and wrote the initial and subsequent drafts of the manuscripts.

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Many people have contributed to the completion of the present project with support of many kinds: practical help, suggestions for study design, data collection, statistical analyses and revisions to drafts.

I want to thank first my supervisor, Dr. Lisa Koski. This thesis would not have been possible without her valuable guidance, encouragement and support. Her guidance kept me moving in the right direction during the two years of the study. Her encouragement and support allowed me to overcome challenges and develop skills in research reasoning and critical appraisal of evidence. Her illuminating instructions, insightful criticism, frequent feedback and patience were indispensable to the completion of this thesis.

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Chapter 1

# INTRODUCTION

## Mild cognitive impairment

Mild Cognitive Impairment (MCI) is defined as a transitional state between normal aging and dementia [2]. It is a syndrome characterized by cognitive performance that is below the expected level for age and education, but that does not significantly affect activities of daily life. Memory problems are the most common disorder of MCI, but the disorder can affect other domains of cognition, such as language, attention, and executive function [2].

### *The evolution of the MCI concept and diagnostic criterion*

Evidence from neuropathology and neuroimaging has demonstrated that biological changes occur preceding the onset of dementia [3-4]. These changes can be detected by neuropsychological assessments and indicate that cognitive impairment occurs at the prodromal stage of dementia [3-4]. Several concepts, such as age-associated memory impairment (AAMI) [5], aging-associated cognitive decline (AACD) [6], cognitive impairment, no dementia (CIND) [7] or mild cognitive impairment (MCI) [2], have been proposed to define and characterize the population sample with mild impairment in cognition at the stage between normal aging and dementia. Among these concepts, MCI has become widely accepted and used in clinical and research settings in recent years.

The concept of MCI was originally introduced by Peterson in 1999 at the Mayo clinic with these criteria (*Mayo amnestic criteria*): an individual who exhibits subjective and objective memory loss but with remaining activities of daily living still intact and who is not diagnosed as having Alzheimer's disease (AD) [2]. Although this concept was recognized and influential, there was still concern regarding its limitation, as it only emphasized memory loss, while other cognitive inefficiencies were neglected. By taking into account the heterogeneity of MCI in terms of clinical characteristics, etiology, and prognosis, this concept was later revised by Petersen et al. in 2004 [8] as follows: subjective cognitive problems, objective memory impairment and/or impairment in other cognitive domains, intact activities of daily living and absence of dementia. This revised definition is known as the *revised Mayo criteria* and has to date been well accepted.

With the establishment of the concept and diagnostic criteria, numerous epidemiological studies have investigated the incidence of MCI and its evolution in cognition and prognostic approaches in order to evaluate the need for secondary prevention and to develop preventive strategies for dementia. These topics will be discussed in the following sections.

*Prevalence of MCI*

MCI is highly prevalent in elderly populations, notwithstanding inconsistent prevalence rates obtained across studies that studied different age ranges or adopted different definitional criteria for MCI. First, prevalence rates differ when comparing the Mayo amnestic criteria and the revised Mayo criteria. A study reported, in a general elderly population aged 75-95, that the occurrence of MCI per 100 non-demented persons

is 2.1% using the Mayo amnestic criteria, whereas the rate increases to 7.2% using the revised criteria [9]. Second, the prevalence rate increases by age regardless independently of the different criteria applied [10-11]. For instance, in the Cardiovascular Health Study (CHS) Cognition Study, with the revised Mayo criteria, the prevalent of MCI increase with age ranging from 19% under age 75 to 29% over age 85 [11].

*Cognitive change among MCI patients*

Numerous longitudinal studies have investigated the evolutionary nature of cognition among individuals with MCI. These studies mainly focused on two methods of evaluating cognitive outcome: 1. rate of progression to dementia, stability and improvement; 2. rate of change in global cognitive ability.

Rates of progression to dementia

Individuals with MCI are at increased risk of Alzheimer's disease or other types of dementia [2], yet some patients do not seem to progress to dementia [12-13]. Indeed, cognitive change among MCI patients has been investigated by many epidemiological studies and has been shown to be heterogeneous in nature [14], that is, MCI patients may develop dementia, remain stable for many years, or even improve in cognitive ability. The rate of progression to dementia from MCI varies widely depending on such factors as the sample source and the MCI criteria applied. For instance, the conversion rate was higher in clinical-based samples in comparison to community-based samples [12-13]. According to Bruscoli's review, the annual conversion rate is 10.9-31.1% for clinical-based samples and 4.0%-23.1 for community-dwelling

population[13]. Mitchell's meta-analysis of 41 robust studies showed that the relative risk of progression to dementia is 15.9 with Mayo criteria and 9.5 with the non-Mayo riteria[12]. In addition, Mitchell and colleagues also indicated that, across all 41 studies, the overall annual rate of conversion for dementia is 6.7%, which is lower than previous estimates [12]. Despite the fact that the annual progression rate for dementia varied across studies, it is much higher in clinical samples compared with the rates of 1% to 2.5% obtained among the healthy elderly population [8, 15].

Does MCI inevitably progress to dementia? Although MCI has been regarded as a condition with an increased risk of dementia, an improvement or stability in cognitive functioning was observed in a substantial number of MCI patients. Wahlund and colleagues reported, in a clinic-based sample after 3 years follow up, that 11% of MCI patients showed cognitive improvement, 53% were stable, and 35% were diagnosed as demented [14]. Further, Palmer summarized a number of longitudinal studies on the heterogeneous progression of MCI as follows: the rate varies from 15% to 34% for improved MCI patients, 11% to 76% for stable MCI and 9% to 80% for conversion to dementia [16]. These widely varied rates may be explained in part by the duration of follow up. Lower conversion rates were reported in studies with longer durations of follow up. To date, two studies had mean periods of 10 years to observe the evolution of MCI patients. One enrolled 145 MCI patients aged 40-85 years at a memory disorder clinic and found that less than half of MCI patients converted to dementia within five years [17]. Twelve percent of patients progressed to dementia at the 2-year follow up, 21% at the 5-year follow up and 30% at the 10-year follow up. The annual conversion rate was 4.8%. The other community-based study followed 40 MCI patients over 10

years and reported that 55.6% MCI patients had reverted to normal, 20% had developed dementia and others became worse but not demented [18].

Rates of change in global cognitive ability

Complementary to these investigations on the rate of progression to dementia among MCI patients, a few studies have estimated the rate of decline in cognitive function over time. Most of these studies examined global cognitive function measured serially by the Mini-Mental State Examination (MMSE) over a period of time. The rate of cognitive decline varied widely depending on differences in study sample selection. Three clinic-based studies reported the rate of cognitive decline in MCI as follows: Petersen reported that the annual rate of decline on the MMSE was approximately two points per year among 76 MCI patients over 4 years [2]. Another study estimated that, in a cohort of 78 amnesic MCI patients who were followed an average of 13 months, the average annual loss of the MMSE total score is 1.3 point. [19]. A similar result was reported by Hodges [20]. Some limitations in these studies should be acknowledged. The three clinical-based studies estimated the rate of change without controlling for demographic variables such as age and education. One study had a very small sample size (10 subjects) [20]. In addition, the criteria for defining MCI varied across studies. In community-based samples, two studies found that the annual loss of the MMSE was 0.04 and 0.07 [21-22], respectively, a lower rate of cognitive decline than that observed in clinic-based studies.

Limitations of previous studies on cognitive change in MCI

The studies reviewed above present a number of limitations. Firstly, most involved two-point observations with varied follow-up intervals, where the outcome was treated as a change in diagnostic status, i.e., whether or not individuals with MCI convert to dementia over a period of time. Based on this determinative rule, a cohort of MCI patients was simply categorized into two subgroups: MCI-converters vs. MCI-nonconverters. Consequently, the underlying developmental course of MCI is not fully understood. Secondly, although a few studies [19-22] investigated the developmental course of MCI by estimating the rate of change in cognition with multiple observations, samples in these studies were not stratified on baseline cognitive function and the variation of cognitive course has not yet been well defined. Cognitive ability may be expected to decline across time among people with MCI, yet within this population there may be some individuals who decline more, some who decline less and others who show almost no decline over time. Thus, defining cognitive course by the mean rate of change does not adequately represent all individuals in such a heterogeneous population with varied cognitive outcome across time. In short, these limitations oversimplify the complex heterogeneity behind the trajectory of cognitive change of MCI and obscure the full spectrum of developmental course in cognition.

*Current approaches to predicting the evolution of MCI*

As numerous studies have demonstrated the increased risk of dementia in patients with MCI, researchers have been endeavouring to identify reliable and valid predictors to address the question: *who with MCI is more likely to show cognitive decline?* Indeed, a vast variety of approaches have been proposed and shown the possibility of predicting

cognitive change among MCI patients via the use not only of demographic, health-related and lifestyle factors, but also of more sophisticated techniques for measuring brain and cognitive function (neuropsychological assessments, ApoE genotyping, and brain imaging using FDG-PET, SPECT, structural and functional MRI, and Pib-B[3, 23]. A summary of this literature follows.

Some neuropsychological variables, such as delayed recall of word lists [24], category fluency [25], and attention [26], were found to predict the onset of dementia in older persons with MCI, but a majority of these studies showed insufficient predictive power, with both sensitivity and specificity less than 80%.

Increasing interest has been given to investigating structural and functional neuroimaging techniques to predict conversion to dementia from MCI. A number of studies identified the following baseline predictors associated with developing dementia: hippocampal and entorhinal cortex atrophy detected by MRI [27-29], reductions of regional cerebral blood flow shown in SPECT [30], and decreased baseline glucose metabolism in temporoparietal region as measured by PET [31]. The predictive accuracy differed across studies with a sensitivity of 70-90% and a specificity of 65-100% [3, 23]. In addition, recent studies suggest that magnetic resonance spectroscopy (MRS) may be a useful tool to discriminate future dementia. Decrease of N-acetyl-aspartate (NAA) and increased Myo-inositol (mI) were consistently detected by MRS and found to have high predictive accuracy [3, 32].

A combination of neuroimaging and neuropsychological assessments or other biochemical markers significantly improves the predictive power to distinguish those future demented persons from MCI patients [3, 23]. For instance, a study including 67

amenestic MCI patients followed up for one year showed that regional cerebral hypometabolism in PET and memory impairment as assessed by the California Verbal Learning Test—Long Delay Free Recall were predictors of conversion to dementia with a sensitivity of 85% and specificity of 97% [33].

Although the techniques described above showed promising predictive value, these approaches are not recommended for routine use to predict or longitudinally track cognitive change, given their restricted availability, their high cost and the lack of standardized procedures in operation [3, 34].

Thus, a few studies have turned to exploring the prognostic value of some commonly used questionnaires for predicting dementia. Isella and colleagues reported that the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) yielded an accuracy of 81% for predicting the progression to dementia in a cohort of 45 MCI outpatients, of whom 24 converted to dementia over 17 months [35]. In one study, 123 subjects with questionable AD were recruited from a general population [36]. Twenty-three out of 123 subjects were diagnosed with dementia after 3 years. The Clinical Dementia Rating (CDR) scale, in combination with 8 selected questions from an interview, was reported to have an accuracy of 88.6% for predicting dementia in this study. Tierney followed over 2 years 165 CIND patients referred through family physicians [37]. Twenty-nine patients converted to dementia. In this study, a 6-item model that included 4 items of informant and patient subjective ratings from the Cambridge Mental Disorders Examination (CAMDEX) and the MMSE's delayed recall and orientation to day of the week items successfully predicted conversion to dementia with a high accuracy of 90% sensitivity and 94% specificity. The predictive accuracy

could be better for some of these studies, given the low rate of conversion to dementia (29/165) [37] (23/123) [36] and small sample size (45) [35], which might have only allowed for identifying strong predictors. Additional variables that actually possess significant prognostic value might be missing. On the other hand, some features of these studies may limit their application in clinical settings. Tierney et al.'s results may not be generalizable to either clinic patients or the general population, because subjects were recruited only through family physician referrals [37]. In addition, the informant questionnaires used in these studies depend not only on the availability of informants, but also on their suitability for measuring cognitive change in patients. Informants should be caregivers who live closely with patients, so as to provide reliable ratings. Occasionally, the lack of suitable informants may lead to biased reports. Further, informants' ratings on the cognitive ability of patients with cognitive impairment are influenced by the nature of the relationship between patient and informant [38].

Given the limitations described above, an easy-to-use and readily available approach has not yet been made available to distinguish patients at higher risk of developing dementia among MCI patients. Indeed, a recent Canadian consensus report on mild cognitive impairment identified the following knowledge gap: "*We lack easy, reliable and useful tools for predicting which people with Mild Cognitive Impairment will go on to have dementia*" [39]. We hypothesized that individual items from the MMSE may be a potential candidate to fill this gap, as it is a simple examination and readily available in clinical and research settings.

**The Mini-Mental State Examination**

The MMSE, originally developed by Folstein (1975), is the most widely used tool to assess global cognitive function in clinical and research settings. The MMSE is a brief performance-based test, measuring a broad set of cognitive domains: orientation, immediate recall, short-term verbal memory, attention, calculation, language and visuospatial construction. It consists of 10 questions on orientation to time and place, as well as questions on the ability of naming objects, repeating and recalling three words, spelling "world" backward or calculating "serial 7's," following commands, copying a design and writing a sentence. The total score is the sum of correct responses to all questions, and the maximum score is 30 points—the higher the score the better the cognitive function. Administration of the MMSE takes 5-10 minutes.

The MMSE is designed to quantitatively assess the severity of cognitive impairment and is also commonly used as a screening test for dementia, with a cut-off score of 23 or less indicating the presence of cognitive impairment [40].

In addition, the MMSE is often used to serially document cognitive changes occurring over time [41-43]. Cognitive change has been measured using the MMSE for several populations, including patients with different types of dementia [44], community-based elderly [41, 45], and patients with neurological disease. Eslinger et al. identified a decline of three or more points as signifying an important change in health and cognition in a 6-year follow-up study of 287 community-dwelling older persons adults.

Independent from its use as a tool for assessing global cognitive function, the MMSE total score or its individual item scores have been included as prognostic

variables in models designed to predict the onset of dementia over a period of time. First, the MMSE score alone can predict the conversion of MCI with a sensitivity of 69%-82% and a specificity of 62%-78% [37, 46-47]. With the modified MMSE(3MS) score, when combined with age and an informant's report of the presence of memory problems, one study reported a sensitivity of 79% and a specificity of 56% for predicting dementia among a cohort of 861 CIND patients [48]. MMSE 3-word recall alone predicted decline in patients with questionable dementia with 67% sensitivity and 71% specificity [49]. Similar results were reported in Tierney's study, where 3-words recall and orientation to place were identified as predictors for future conversion to dementia after years with a high a specificity of 94% but a low sensitivity of 41% [50]. With such a low sensitivity, it is only useful in predicting individuals who will not develop dementia. Other studies reported that the items evaluating orientation to time, constructional praxis, and attention were associated with conversion to dementia [51-53], but these studies did not evaluate the predictive accuracy.

The MMSE is not yet recognized or recommended as a clinical tool for predicting dementia because the use of the MMSE total score alone, or its individual items alone, yielded disparate results and insufficient predictive utility for identifying those MCI patients who will go on to develop dementia. We noted the availability of a newer and more sophisticated statistical approach to longitudinal data analysis that we hypothesized would be well suited for detecting and modeling the heterogeneity of cognitive change over time. This approach may potentially improve our current ability to accurately predict cognitive decline among MCI patients. Known as group-based trajectory modeling, this approach will be described in the following section.

**Group-based trajectory modeling (GBTM)**

Group-based trajectory modeling, as developed by Nagin [54], is an application of finite mixture modeling. In recent years, this approach has been increasingly recognized and extensively used in longitudinal health research. It is a semi-parametric statistical approach and most useful for longitudinal data with multiple data points. As a general rule, it assumes that a heterogeneous population is composed of a mixture of distinctive groups. Each group of individuals follows a similar developmental trajectory over time for the behavior or outcome of interest. In the context of this principle, the latent trajectory groups can be identified by means of a series of modeling procedures.

Apart from the identification of trajectory groups with similar developmental courses, another important extended use of the GBTM is that it allows for linking covariates, such as the baseline characteristic of individuals, to the probability of trajectory group membership. Therefore, it is useful in addressing the question of whether these individual-level characteristics would predict or distinguish the probability of trajectory group membership. Detailed features and the technique of GBTM in identifying latent trajectory groups are presented in Appendices Ⅱ and Ⅲ.

**Summary and Rationale**

To date, the evolution of MCI in terms of changes in cognitive ability over time is poorly understood. This is because our current knowledge about cognitive change over time among MCI patients has only focused on an end-point outcome (conversion to dementia), or the mean trend in rate of cognitive decline. Yet numerous epidemiological

studies have provided evidence that MCI populations are heterogonous: some remain cognitively stable, some improve, and some decline toward dementia. Moreover, cognition can decline without necessarily resulting in a dementia diagnosis within a specified follow-up period for a study. Thus we would primarily wish to develop intervention strategies for the decline even at this early stage, before the person manifests overt dementia. A need therefore arises to advance our current understanding of the cognitive course of MCI, particularly, to investigate in-depth the variation of cognitive course among those MCI patients at high-risk of developing toward dementia. This would be of great importance to early identify individuals at risk of dementia, so as to propose appropriate and individualized strategies for secondary prevention of the onset of, or for slowing the progression to dementia.

A variety of approaches have been developed and shown potential predictive value to identify of individuals of MCI who will go on developing dementia. However, according to the literature review described above, there exits many limitations that have hampered the use of these approaches in daily clinical practice. In short, our perspective regarding these limitations is consistent with that in a recent review including robust studies involved early identification of dementia: 1) the predictive accuracy of the existing models is poor or uncertain; 2) there is a lack of economic and reliable tools for early identification of individuals at risk of dementia; 3) no model to date has been develop to associate the risk factors and the speed (fast or slow decline) of progression to dementia [55]. Many of the approaches using neuroimaging and other biomarkers for early identification of at-risk case of dementia did not show a high level of accuracy. Although some of studies reported excellent predictive accuracy, these approaches have

not yet been well established for broad clinical practice due to the lack of standardized operational procedure and high-cost. These conclusions point to the need for an easy-to-use and readily available tool, and suggest the potential utility of employing optimal study designs and methodological approaches to predict outcome decline rather than conversion to dementia. Identifying those at greater risk of decline earlier on in the evaluation process could assist clinicians to focus resources on these vulnerable persons.

**Research question**

In the present project, we applied group-based trajectory modeling to characterize the evolution of MCI and to identify predictors of cognitive decline over 3.5 years among patients with MCI.

Two specific objectives were proposed in the current project.

Objective 1

*To identify the developmental trajectory of groups with distinct cognitive change patterns among a cohort of MCI patients, using group-based trajectory modeling (GBTM).*

Hypotheses: Several trajectory groups (cognitive stable vs. decline or stable, slow decline, fast decline) will be identified by GBTM.

Objective 2

*To identify individual items of the MMSE and demographic variables at baseline that predict membership in each trajectory group up to 3.5 years.*

Hypotheses: Success or failure on specific test items has prognostic significance beyond that provided by the total score on a screening test.

Chapter 2

**Identifying and characterizing trajectories of cognitive change in older persons with mild cognitive impairment**

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KEYWORDS

Trajectories, mild cognitive impairment, dementia, aging, cognitive decline, MMSE

## Abstract

***Background:*** Mild cognitive impairment (MCI) represents a state of high risk for dementia but is heterogeneous in its course. To date, the trajectories reflecting distinct developmental courses of cognition among patients with MCI have not been well defined. ***Aim:*** To identify the developmental trajectory of groups with distinct cognitive change patterns among a cohort of MCI patients. ***Methods:*** 187 MCI patients from two geriatric outpatient clinics were evaluated serially with the Mini-Mental State Examination (MMSE) for up to 3.5 years. Group-based trajectory analysis was applied to identify distinct trajectories. Estimates of decline for each group were compared with the mean rate of decline obtained from mixed modeling of the entire sample ***Results:*** Five trajectories were identified and labeled based on their baseline MMSE score and course:

*29-stable* (6.5%); *27-stable* (53.9%); *25-slow-decline* (23.8%); *24-slow-decline* (11.6%); *25-rapid-decline* (4.2%). Annual rate of change in the MMSE score for these five groups was 0.09, -0.43, -1.23, -1.84, and -4.6 points, respectively. None corresponded to the mean rate of -0.82 points estimated for the group as a whole. A majority of MCI patients (60.4%) follow stable cognitive trajectories over time. Within the three groups with declining trajectories, cognitive decline occurs slowly in a vast majority of MCI patients (98.5%). ***Conclusions:*** Results provide direct evidence for the heterogeneous course of cognitive decline that has been suggested by the variable prognosis for patients with MCI.

## Introduction

With the incidence and prevalence of dementia escalating and limited resources for management, there is increasing need to identify those who are at risk of developing dementia so that early interventions may be initiated[56-57]. Progression to dementia can be measured as a change in diagnostic status or as a deterioration in cognitive ability as indicated by a test score.

People with mild cognitive impairment (MCI) are considered at increased risk [2] for progression to dementia, yet estimates of the proportion who will progress vary widely [12-13]. Numerous longitudinal studies [6 - 11] have documented heterogeneous outcomes among people with MCI with some people reverting to normal status (15% to 34%), some staying stable for many years (11% to 76%), and others converting to dementia (9% to 80%)[7]. In a recent meta-analysis of 41 robust inception cohort studies with 3 or more years of follow-up, the annual rate of progression to dementia was found to range from 5-10%. Higher rates of progression were reported from specialist clinic settings than from community samples. Additionally, people diagnosed with MCI according to the Mayo criteria, i.e., with subjective memory complaints showed higher conversion rates than in people diagnosed by non-Mayo defined criteria[12]. The heterogeneous nature of MCI was emphasized in this review.

When scores on cognitive tests are analyzed and used to estimate change, most commonly a mean change over a defined time period of one year, is reported[8-11]. For example, Teipel and colleagues [11] estimated the average annual change on the Mini-Mental State Examination (MMSE) total score among people with MCI at -1.3

points (SD: 0.69). The mean hides the observation that the range of deterioration was large ranging from -0.01, essentially stable, to -2.9 points, putting a person into a range indicative of dementia within 2 years [19]. In other words, the different cognitive trajectories that people with MCI experience cannot be appreciated by presenting the single value of average change with its variance.

Thus, the underlying developmental course of MCI is poorly understood due to substantial variation in prevalence of conversion to dementia and in the rate of cognitive decline. Average rates of cognitive decline contribute little to our understanding of actual cognitive trajectories in such a heterogeneous population as MCI. In fact, very few people may actually show the average decline. Variation in the developmental course of cognition across individuals with MCI poses a challenge to management.

A longitudinal statistical approach developed by Nagin [58-60], group-based trajectory modeling, provides a solution to this problem. As applied to an MCI cohort, this approach assumes that the sample is composed of a mixture of distinct groups. Each distinct group of individuals follows a similar developmental trajectory in terms of the evolution of cognitive impairment over time. This method was developed for applications in the social sciences and has only recently been applied in the health field [61-63]. Wilkosz and colleagues have used this approach in a sample of persons with a dementia diagnosis [63]. It has not been used to characterize change in people with MCI. The primary objective of this study was to identify trajectories of cognitive change within a cohort of people with MCI. A secondary objective was to compare the interpretation of change between the trajectory approach and the average change approach.

## Methods

*Setting and database*

Data was obtained from the geriatric outpatient clinics at two sites within the McGill University Health Centre (MUHC): the Royal Victoria Hospital (RVH) and the Montreal General Hospital (MGH). Older persons in need of cognitive or comprehensive geriatric assessment were referred to these clinics from a variety of sources, including general practitioners, specialists and social services. All outpatients underwent cognitive screening at their first clinic visit, with the MMSE administered by geriatric nurses or physicians. Follow-up visits were scheduled at 3-12 month intervals as clinically indicated and often included re-evaluation with the MMSE.

A computerized database was constructed from a detailed review of the clinic charts for all persons screened for cognitive impairment at the geriatric outpatient clinics from 1999 to present. Information migrated to the database included age, gender, years of education, first language, clinical diagnoses, itemized responses to cognitive screening tests, language version of the test, values on measures of functional capacity, and results of neuropsychological assessments. The use of this anonymized clinical data for this study was approved by the McGill University Health Centre (MUHC) Research Ethics Board (BMB-06-002).

*Inclusion/exclusion criteria*

This study included all patients diagnosed with MCI who had been administered the MMSE at their initial visit to the clinic and at least once more over a period of up to 3.5

years. MCI patients who were not administered the MMSE at initial visit or who were only administered the MMSE once during the observed period were described in terms of their demographic and clinical characteristics at baseline for comparison with the main study cohort, but were excluded from the subsequent trajectory analyses.

*Description of study cohort*

In the clinical database, we identified 311 MCI patients who were evaluated at the clinics from April 1999 to June 2009. MCI had been clinically diagnosed according to Petersen's criteria[2, 8]: a) subjective cognitive complaints, evaluated via a detailed patient history and informant interview; b) objective verification of cognitive impairment; c) normal general cognitive function; d) intact or only mildly impaired activities of daily living; and e) absence of dementia based on DSM-IV criteria [64]. Diagnosis was based on history and clinical examination, clinical interview with the patient and an informant when available, results of screening tests for cognitive impairment and assessment of functional status with respect to basic and instrumental activities of daily living. For people in whom dementia was suspected, CT images were also obtained.

All MCI patients underwent cognitive screening with the MMSE and/or Montreal Cognitive Assessment (MoCA) at their initial visit. Of 311 MCI patients, a total of 187 MCI patients with two or more examinations with the MMSE were included in the analysis of trajectories. Of the 124 excluded MCI patients, 112 patients had one examination of the MMSE and one clinic visit; five patients had one clinic visit and one examination of the MoCA; one patient was administered the MoCA at two clinic visits;

and six patients had one MMSE examination and one MoCA examination over two clinic visits.

**Data analysis**

Characteristics of included and excluded subjects at first assessment were compared using t-tests and Chi-square tests.

Group-based trajectory analysis [60] was applied to identify different trajectories of cognitive impairment as reflected in the MMSE total score over time. Conceptually, this approach identifies latent subgroups with distinct developmental trajectories for the outcome measured over time. Time can vary by person. The proportion of the population that follows each trajectory is estimated. Individuals are assigned to specific groups, based on the largest posterior probability of group membership.

Based on substantive considerations, models with 2 to 6 trajectories were evaluated. Among these, the optimal number of groups was determined by selecting the best-fitting model as defined by the largest Bayesian Information Criterion (BIC) value. The final model provides descriptive information on the identified trajectory groups, including (a) posterior probability of an individual belonging to a specific trajectory group; (b) the proportion of each group following the same trajectory; and (c) the regression parameters to define the shape of the trajectories (constant, linear, quadratic, or cubic). The fixed covariates of age at study entry, sex, and educational level were examined as univariate predictors of trajectory group membership.

To test the robustness of the trajectory groups we conducted 20 analyses removing a random sample of 20 persons each time (approximately 10% sample). All analyses were carried out using the SAS procedure Proc TRAJ.

Next, the results of trajectory analysis were compared with those obtained by estimating average change per year in the whole cohort using mixed-effects models [65]. Time was modeled as a linear and a quadratic function (with time centered on the mean) and the better fitting model selected. The impact of age, gender, educational level, testing language, and first language, on average change in MMSE, was examined by including each variable one at a time into the mixed effects model. Mixed effects modeling permits the testing for variability in the initial MMSE score and in the developmental course of cognition.

## Results

### *Description of the Sample*

Table 1 presents the characteristics of persons with MCI included (n=187) and excluded (n=124) from the analysis. Excluded patients had fewer than 2 MMSE examinations. Both groups were comprised of slightly more women than men and the mean age was 80 years for both groups. To test whether exclusion of patients with fewer than 2 MMSEs resulted in a biased sample, we compared the baseline characteristics for these two groups. No statistically significant differences were found for age, gender, education, language, or baseline MMSE score.

Also shown in Table 1 is that, for the 187 patients included, the average number of

MMSE administrations is 4 (±1.7), with a range from 2 to 9: 20% of patients had two examinations, 30% of patients had three examinations, and 50% of patients had 4 or more examinations. In total, 709 observations on the MMSE were obtained for the trajectory modeling in the 187 patients. The average duration of follow-up was 23.6 months, ranging from 1.8 to 42.8 months.

**Table 1. Characteristics at study entry of persons included and excluded from the analysis**

| | Included (n=187) | Excluded (n=124) |
|---|---|---|
| Women/Men (%) | 54/46 | 57/43 |
| Education (%) | | |
| ≤ 12 years | 30 | 39 |
| >12 years | 43 | 42 |
| Missing | 27 | 19 |
| Language (%) | | |
| English | 72 | 73 |
| French | 22 | 22 |
| Other languages | 6 | 5 |
| Age in years: mean (SD) | 80 (6.0) | 80 (7.2) |
| MMSE total score: mean (SD) | 26.6 (2.0) | 26.2 (2.8) |
| Number of examinations | | |
| 0/1/2/3/>3 | 0/0/40/49/98 | 8/116/0/0/0 |
| Average | 4 (1.7) | n.a. |
| Range | 2-9 | n.a. |
| Months of follow-up: mean (SD) | 23.6 (11.3) | n.a. |
| Range | 1.8-42.8 | n.a. |

*Groups identified by group-based trajectory analysis*

The analysis proceeded to test how many distinct trajectory groups best fit the data available from this sample. Models were fit for 1 to 6 groups. The 5-group model produced the highest Bayesian Information Criterion (BIC) values indicating best fit: -1683 when total number of participants was considered and -1694 considering total number of observations.

**Figure 1. Trajectories of cognitive change on the MMSE score**

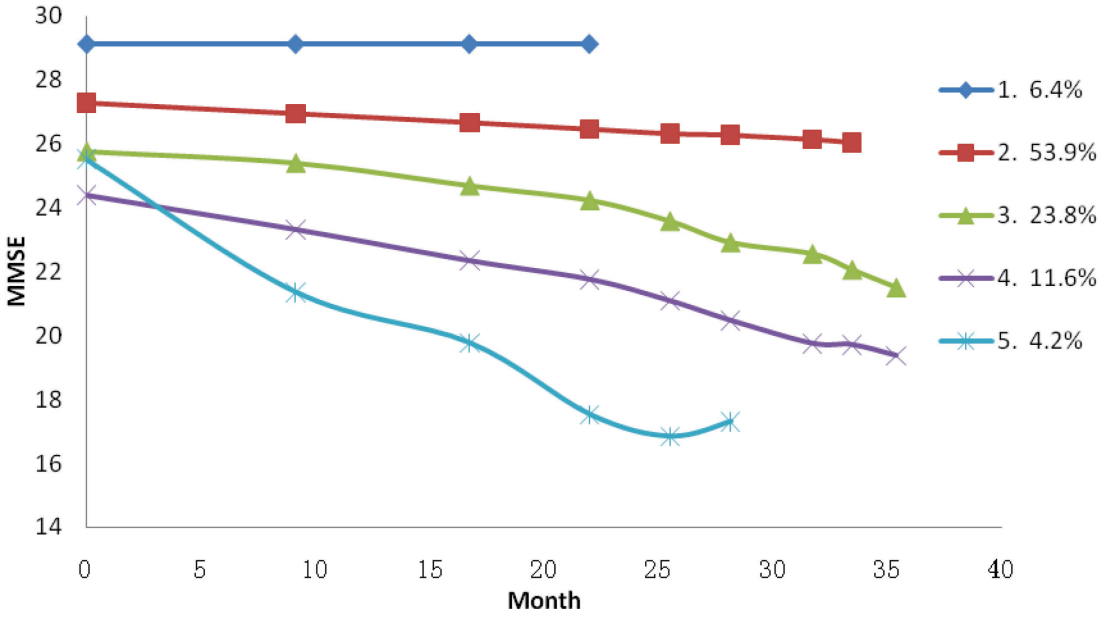



Figure 1 shows these 5 groups. The trajectories were labeled based on their estimated starting MMSE value and shape of the change. Table 2 presents characteristics of the 5 trajectory groups. The *29-stable* group represented only 6.4% of the sample (n=12). They remained stable over approximately two years and received no further clinical follow-up. Each trajectory group is described by the shape of the longitudinal change. The 29-stable group described above showed no change, two groups showed linear decline and 2 groups showed curvilinear change as indicated by the presence of a

quadratic term to the linear model. Also shown is the mean and range of posterior probability of group membership for the full sample. In all five groups, the average posterior probability is greater than 0.7, which is considered acceptable model fitting [59]. For sensitivity analyses, also shown in Table 2, when a 10% random sample was removed, the 5 trajectories remained significant and visually present over all 20 iterations. For one group, 25-slow decline, the quadratic term lost significance in 8 of the 20 iterations (40%). Across the 20 sensitivity analyses, the group-specific mean posterior probabilities were very similar to the full group. All met Nagin's[59] "rule of thumb" that the minimum average posterior probability is 0.70.

Analyses were done to identify variables that influenced group membership and none of the tested variables, age, gender, or education, was significant.

**Table 2. Description of trajectories**

| Assigned group (Label*) | % | N | Trajectory polynomials | Posterior probability (%) | |
|---|---|---|---|---|---|
| | | | | Full Group | Sensitivity analyses (20 data sets) |
| | | | | Mean(SD)[ min] | Mean (SDM) |
| 1 (29-Stable) | 6.4 | 12 | Constant | 76.3 (19)[51] | 80.1 (0.04) |
| 2 (27-Stable) | 53.9 | 108 | Linear | 86.3 (13)[50] | 86.3 (0.02) |
| 3 (25-Slow decline) | 23.8 | 41 | Quadratic | 75.6 (19)[40] | 75.1 (0.02) |
| 4 (24- Slow decline) | 11.6 | 20 | Linear | 82.2 (18) [50] | 82.1 (0.03) |
| 5 (25-Rapid decline) | 4.2 | 6 | Quadratic | 98.8 (1) [98] | 94.9 (0.04) |

* Label is based on the modeled MMSE starting value and shape of the change

Min – minimum value for an individual, maximum was always 100

Sensitivity analyses: values are means of the 20 mean posterior probabilities

SDM is standard deviation of these means

*Profiling the Trajectory Groups and Comparison to Mixed Models*

**Table 3. Characteristics of the persons assigned to each trajectory group**

| Group | 29-stable | 27-stable | 25-slow-decline | 24-slow-decline | 25-rapid-decline |
|---|---|---|---|---|---|
| Theoretical % | 6.5 | 53.9 | 23.8 | 11.6 | 4.2 |
| Linear slope (points/year)* | 0.09 | -0.43 | -1.23 | -1.84 | -4.60 |
| 95% CI | -0.62, 0.80 | -0.64, -0.23 | -1.59, -0.88 | -2.37, -1.30 | -6.60, -2.60 |
| Deterministic % (n) | 6.4 (12) | 57.8 (108) | 21.9 (41) | 10.7 (20) | 3.2 (6) |
| Age in years: mean (SD) | 78(9.5) | 79 (5.6) | 81 (5.6) | 82 (5.4) | 83 (4.6) |
| Education (n with data) | 11 | 72 | 34 | 15 | 5 |
| ≤ % 12 years | 27 | 51 | 62 | 80 | 100 |
| Women/Men % | 67/33 | 52/48 | 49/51 | 60/40 | 83/17 |
| Test language | | | | | |
| English | 64 | 77 | 68 | 63 | 67 |
| French | 36 | 19 | 24 | 32 | 17 |
| Others | 0 | 5 | 7 | 5 | 17 |
| First language | | | | | |
| English | 50 | 50 | 51 | 33 | 50 |
| French | 33 | 33 | 26 | 40 | 50 |
| Others | 17 | 17 | 23 | 27 | 0 |

* Slopes estimated using linear term only in trajectory model (without quadratic)

Table 3 presents the characteristics of the people who were assigned deterministically to a trajectory group based on the highest posterior probability. For comparison purposes we have reproduced the theoretical proportions of group assignment. As can be seen, the proportions assigned deterministically were very similar to the theoretical proportions from the trajectory modeling, an indicator of good fit. Also shown for comparison to the mixed model approach are the linear estimates of slope for each trajectory group

along with 95% CI. The linear slopes across groups were 0.09, -0.43, -1.23, -1.84, -4.60.

The average age across groups at study entry ranged from 78 to 83 years. People in the *25-rapid-decline* group were the oldest at 83 years. The proportion of people with high vs. low education appears to differ across groups but education did not significantly affect the posterior probability of group assignment derived from the trajectory model.

*Mixed effects modeling*

The model with time as a linear function yielded better fit than the model with time as a quadratic function. The random effect for slope was significant ($p<0.0001$), confirming the presence of significant variability in the developmental course of cognition and in the initial MMSE score. The average change over time was 0.-0.82 MMSE units per year (95% CI: -0.62 to -1.02). This estimate does not match the estimate of linear change obtained for any of the trajectory groups, although it falls between the estimates of the two largest groups. Older age significantly predicted higher rate of cognitive decline for all MCI patients ($\beta$=-0.042 MMSE per year, SE 0.017, $p$=0.0147). Controlling for age, the linear mean rate of decline in MMSE score was -0.85 points/year (SE 0.10, $p<0.0001$). Gender did not affect the rate of cognitive decline, nor did education although this was assessed only in the sample with this information (n=137).

## Discussion

The developmental course of cognitive change over 3.5 years was examined in a cohort of MCI patients using group-based trajectory modeling. The cohort was found to be comprised of five distinct groups that differed significantly in their initial cognitive status and trajectory of cognitive change over time. The results confirm the hypothesis that MCI is a heterogeneous entity, as suggested by epidemiologic studies demonstrating widely disparate outcomes for patients with MCI [14, 16]. This observation in people with MCI is consistent with that in a recent study of people with late-onset Alzheimer's disease, in which subgroups of patients with comparable MMSE scores showed significantly different trajectories of cognitive decline over a 4-year period [63].

The *29-stable* and the *27-stable* groups accounted for the majority (60%) of the sample. The trajectory group with a starting value of 27 was labelled as "stable" because cognitive decline in this group, while statistically significant, was not clinically significant in the sense that even three years from the initial visit the MMSE score would not be in a range clearly indicative of dementia in this age group. The results of this study support the argument of some researchers that MCI should not be regarded simply as a transition stage preceding dementia. A large proportion of patients with MCI do not seem to decline in cognition or to develop dementia[16, 66]. In fact, a recent meta-analysis of 41 robust longitudinal studies revealed that the cumulative proportion of conversion to dementia in specialist centers is 39.2% over approximately 5 years. This figure is lower than that suggested by others [66] but completely consistent with the observation that only 40% of our sample showed an important decline in MMSE score.

The three groups that followed declining trajectories began at a lower cognitive level (MMSE <26) in comparison with the two stable groups. The rate of progression was slow in the vast majority of those patients who exhibited decline (98.5%). Patients in the *24-slow-decline* group had the lowest MMSE score among the groups (mean 24.2, SD1.8), but they declined at a rate similar to that of the *25-slow-decline* group. This indicates that, although some MCI patients initially have poorer performance in cognitive tests, they are not necessarily destined to progress more rapidly to dementia. In contrast, a small proportion of MCI patients (4.2%) began with a MMSE score of 25 yet declined dramatically to reach a level of cognitive impairment that would be consistent with a diagnosis of dementia.

Our results also provided evidence of temporal variation in the rate of cognitive decline in people with MCI. Several previous studies [21, 67-68] showed nonlinear accelerating rates of cognitive decline in older persons with cognitive impairment. Some have documented the existence of a changing point, at which acceleration in the slope of cognitive decline occurs [67-69]. In the present study the *25-slow-decline* group showed an accelerating rate of decline; however the *25-rapid-decline* group showed a decelerating rate of decline and the other groups showed trajectories that were best fit with a linear slope. These differences in the shape of the cognitive trajectory could be seen to reflect the different stages of impairment at which the people in our sample first presented to a specialty clinic. Cognitive ability was sampled over a specific window of time in the developmental trajectory of each patient and we cannot rule out the possibility that trajectories of more similar shape might be detected if cognitive ability were measured over a much longer time frame. Nevertheless, the observation that cognitive

decline can occur at different rates as well as a different shape over the same window of time highlights the likelihood that different pathological processes may account for the impairment seen in people who share the diagnosis of MCI.

The early steep drop in cognitive ability displayed by the *25-rapid-decline* group suggests a link with the recently introduced phenomenon of Rapid Cognitive Decline (RCD) described in patients with dementia [70-73]. A patient is considered to have RCD when "experiencing a significant deterioration on specified dementia assessment scales, with a greater than average or expected loss, within a short period of time [71]." Patients with RCD are associated with worse prognoses, such as reduced mobility, loss of autonomy, and shorter life span [73]. In recognition of the importance of RCD in medical practice, a consensus definition of RCD was proposed as the loss of 3 or more points in MMSE during six months [73]. The annual drop in MMSE score was 5.1 points in our small proportion of patients with rapid decline. This finding has important implications for clinical practice, such as the identification of these patients *a priori* for the purpose of rapid implementation of aggressive intervention strategies.

The linear rate of decline derived from mixed modeling of the whole MCI sample was -0.82 points per year, which is slightly lower than the estimate of -1.3 obtained previously for clinic-based samples [19, 74]. This could be explained by differences in diagnostic criteria as those studies were conducted in people with objective mild impairment and subjective memory complaints whereas our sample included people without subjective memory complaints. We note that the overall rate of decline we obtained from mixed modeling did not correspond to the linear rate of decline observed

in any of the trajectory groups although it fell within the 95% confidence limits of the estimate for the largest group (27-stable).

The results presented here illustrate the advantage of visualizing the data in advance of choosing a model that best describes the data. Nagin[59] points out that there are a large number of situations where a common pattern of change over time cannot be assumed. Group-based trajectory modeling could be used early on in the descriptive stage of the data analysis to visualize the changes that can be discriminated from the data. This view will aid in the choice of further modeling strategy and in interpretation of the results.

*Limitations*

The *25-fast-decline* group consisted of only 6 persons with 25 observations on the MMSE. This may have resulted in an inadequate description of the pattern of the trajectory. However, there is no doubt of the existence of this group, which has been well established by the empirical procedures, including very high posterior possibilities of group membership. Increasing sample size would add information to better characterize this group regarding the developmental course of cognition, such as by providing a more precise shape of the trajectory.

Reliance on existing clinical data always entails certain limitations due to variable frequencies and durations of follow-up. For analyses using group-based trajectory modeling, time may vary by person. A balanced study design would have allowed us to calculate rates of conversion to dementia for each trajectory group; however, we could not accurately estimate conversion rates in this study due to variable rates of loss to

follow-up across the five trajectory groups. Two years after study entry, the 29-stable group were no longer followed up with MMSE examinations. Would this group have declined during the remainder of the 3.5 year time window for this study, thus resulting in a different trajectory than the one identified here? This outcome is unlikely as individuals with near-normal cognitive ability may discontinue follow-up at our clinic if there is no decline overr two years, but they are encouraged to return if they experience any significant changes. A patient who declined within the next year and a half would have re-entered the study sample and been included in the trajectory analysis. Thus a stable cognitive trajectory over 3.5 years is likely a valid interpretation for the 29-stable group.

Our analysis of the effect of education on the rate of cognitive decline was conducted on a subset of the sample due to missing data on this variable in 27% of the sample, which limited the power to detect an effect if present. However, our conclusion of a non-significant education effect is supported by the results of many previous studies [21, 69, 75]

The amnestic subtype of MCI has been viewed as an early stage of Alzheimer's disease, whereas the cause and outcome of cognitive impairment in non-amnestic MCI may be more heterogeneous[76]. Here, the diagnosis of MCI was made without subdivision into amnestic vs. non-amnestic types because the data were collected in the course of regular clinical care. Memory must be impaired for age and education for specification of amnestic MCI and access to neuropsychological assessment was likmited to a subset of patients. A more homogeneous set of trajectories might exist within subtypes of MCI patients; however, tools for rapid identification of these subtypes are

lacking at present and standard clinical variables including MMSE total score are insufficient to predict conversion to dementia even *within* the amnestic subtype of MCI [77]. Therefore, our results likely represent the heterogeneity among patients with MCI as it is diagnosed in many clinic settings.

Finally, we cannot rule out the possibility of misdiagnosis at baseline, a potential limitation of all studies in which clinical criteria, rather than a definitive test, are used to diagnose. The rapidly declining group may have included patients with a dementing illness that could not be detected at baseline. Future studies aimed at identifying baseline variables that predict membership in the rapidly declining trajectory group could ultimately improve our current methods for discriminating MCI from dementia.

*Conclusions*

This study is the first to demonstrate heterogeneous trajectories of cognitive decline among people with MCI, and is by far the largest study to date to examine change in the MMSE score longitudinally in a clinic sample. The identification of five distinct cognitive trajectories provides direct empirical evidence that an individual patient with MCI may follow any one of a variety of clinical courses, from stable cognition to slow cognitive decline or, rarely, rapid cognitive decline. This knowledge may instigate further exploration of the underlying etiology or predictive factors associated with different cognitive courses among people with MCI.

Chapter 3

**Prognostic predictors of the trajectory of cognitive decline from a cognitive screening test in patients with mild cognitive impairment at geriatric clinics**

Haiqun Xie  Nancy Mayo  Lisa Koski

KEYWORDS

Group-based trajectory analysis, dementia, aging, cognitive decline, MMSE, clinical prediction, sensitivity,

## Abstract

This study sought first to identify individual items of the Mini-Mental State Exam (MMSE) and demographic variables *at baseline* that predicted the trajectories of cognitive change among patients with Mild Cognitive Impairment (MCI), and second to quantify the risk of cognitive decline in such patients based on their pattern of failure of MMSE items. 187 MCI patients were evaluated serially with the MMSE for up to 3.5 years. Patients who followed a declining cognitive trajectory differed from the stable reference group in their baseline profile of MMSE test performance. Patient age and performance on delayed recall, constructional praxis, attention, and orientation to time and floor predicted future cognitive decline with good accuracy (79.9%) and specificity (86.4%), and

moderate sensitivity (67.2%). These results are presented in the form of a simple clinical tool for quantifying risk of future cognitive decline in MCI.

## Introduction

Mild Cognitive Impairment (MCI) has been defined as a transitional state between normal aging and dementia [2]. Given its high prevalence in the elderly and increased risk for the development of dementia [9-13, 16, 47, 78-80], considerable attention has been given to investigating the possibility of predicting diagnostic outcome in individual patients with MCI. Combining information from neuropsychological assessment, neuroimaging, and genotyping with clinical and demographic variables yields high accuracy for predicting who will progress to dementia [3, 23]; however, these approaches are expensive, restricted in availability, and thus not recommended for routine use to predict cognitive decline [34]. More widespread utility could be obtained by developing approaches to the prediction of conversion to dementia that are based on available clinical data.

Several investigators have evaluated the predictive utility of individual questions or subtests from the Mini-Mental State Examination (MMSE), which is widely used and readily available in clinical and research settings [40, 81]. A study of 168 community-based elderly persons showed that the total MMSE score predicts the risk of conversion to dementia within 5 years among people with MCI, with a sensitivity of 82% but a specificity of only 62% [46]. In contrast, the MMSE suffers from low sensitivity to dementia conversion in studies conducted in clinical samples. Among 75 memory clinic patients with questionable dementia, the score

on 3-word recall from the MMSE was the best predictor of conversion to dementia, with a sensitivity of 67% and a specificity of 71% [49]. In 165 non-demented patients referred for memory or other cognitive complaints, 3-word recall and orientation to time were specific (98%) but not sensitive (41%) predictors of conversion to dementia within 2 years [50]. Others demonstrated an association between performance on the attention item (serial 7s subtraction) of the MMSE and conversion from MCI to Alzheimer's disease (AD), although predictive accuracy was not reported in that study [51].

Interestingly, prediction based on the MMSE improves to a sensitivity of 90% and specificity of 94% when adding information from self- and informant-ratings [37]. Alternatively, combining clinician rating scales and patient-reported symptoms can predict conversion to dementia over 3 years with an accuracy of 89% in 123 community-dwelling elderly people who had questionable dementia at baseline[36]. Data from an informant questionnaire predicted conversion from MCI to dementia with 84% sensitivity and 75% specificity in a small group of 45 people from a neuropsychology outpatient clinic [35]. Unfortunately, 13% of volunteers for this study had to be excluded due to lack of an informant, suggesting that a more widely applicable approach might be to rely exclusively on patient-reported and/or performance-based predictors.

A commonality shared by the studies summarized above was the use of conversion to dementia as the primary outcome of interest. A potentially useful alternative is to examine baseline predictors of future decline in cognitive functioning as indicated by performance on the MMSE. A decline in MMSE performance is linked to the development of dementia but has the advantage of being an objective, measurable outcome. The concept of conversion to dementia over a specific time period may have heuristic value but it implies a defined transitional cut-point that holds little validity in the context of a progressive neuropathological process. Moreover, a person may decline in cognitive performance over time but still not meet criteria for dementia. The identification of such persons is arguably as important as identifying those who will convert to dementia over a specified period of time, to the extent that continued decline may be expected beyond the follow-up period of a study. Demographic variables such as older age have been associated with a greater rate of decline in MMSE score among people with MCI [82]; however, little is known about clinical predictors of change in cognitive ability. In a study of 505 elderly nursing home residents, orientation to time was found to predict subsequent decline in the total MMSE score [53]. Lower rates of decline were observed in people who scored high on delayed recall plus one of either attention or orientation to place. Of note, the sample for that study was not stratified by cognitive ability at baseline and

included people with MMSE scores ranging from 10–25 out of 30 points. Furthermore, the accuracy of prediction for identifying individuals at risk of greater decline was not reported.

Considering the limited evidence for clinical predictors of cognitive decline in people with MCI, the current study aimed to identify MMSE items and demographic variables that, alone or in combination, predicted future trajectories of cognitive decline. It is well established that MCI is a heterogeneous condition that may result in outcomes ranging from "conversion to normal" to dementia [12-13]. Therefore, longitudinal models of cognitive decline that are based on the concept of "average" change may be misguided. In our previous work using a group-based trajectory modeling approach [59-60], we provided empirical evidence for the existence of five distinct trajectories of cognitive change as measured by the MMSE total score, among a clinic sample of people with MCI who were followed for up to 3.5 years (see Figure 1) [82]. The first objective of the present study was to identify items of the MMSE for which failure at the first clinic visit was significantly predictive of the probability of membership in each of these trajectory groups. The second objective was to develop a model based on these identified baseline variables that would optimize accuracy for predicting which patients with MCI will progress to a declining trajectory vs. those who remain cognitively stable.

## Methods

*Setting and sample*

This is a longitudinal study based on historic data collected for clinical purposes, with repeated measurements of the MMSE over 3.5 years, to identify baseline individual items of the MMSE and demographic variables that predict the trajectories of cognitive change. Data were obtained from a clinical database at the Geriatric Cognitive Disorders Clinic of the McGill University Health Centre (MUHC). Clinic patients had been referred for evaluation cognitive impairment and the MMSE was administered at their initial visits by geriatric nurses or physicians, using the serial 7s subtraction variant for the attention item. A geriatrician diagnosed MCI according to Petersen's criteria [2, 8] based on a clinical evaluation that included a full chart review, history, physical exam, assessment of basic and instrumental activities of daily living, blood tests, brain CT, as well as the results of the cognitive screening tests. Follow-up visits were scheduled at 3–12 month intervals with re-evaluation using the MMSE as clinically indicated.

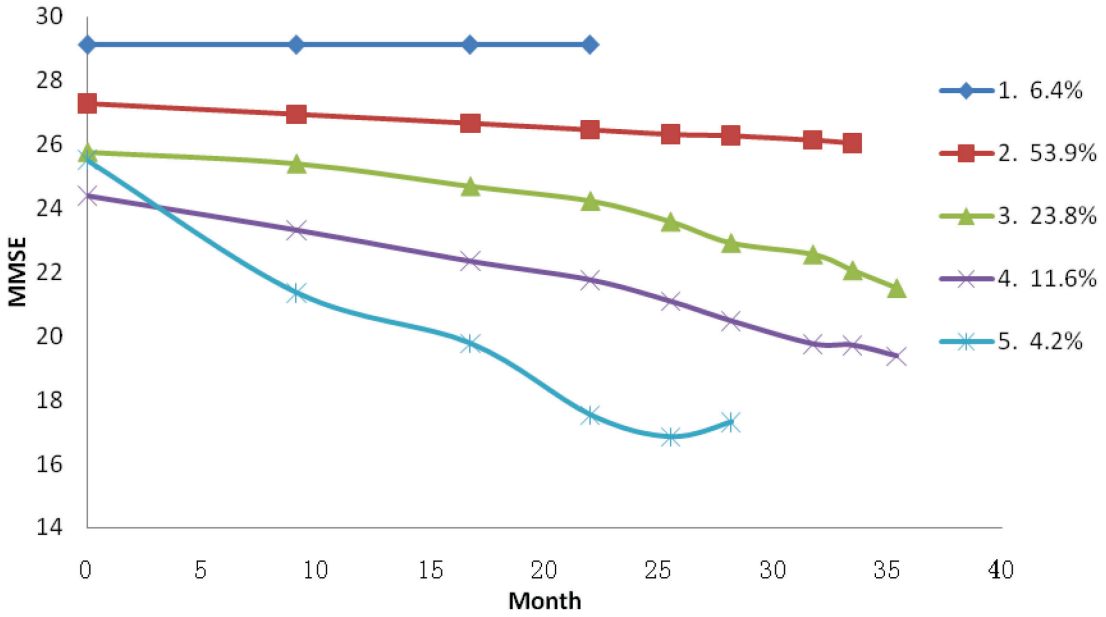
The sample for this study was identical to that examined in our previous study for which trajectories of cognitive change were identified [82]. Of 311 MCI patients, a total of 187 patients who had been administered the MMSE at their

initial visit to the clinic and at least once more over a period of up to 3.5 years were included. This subgroup did not differ by age, sex, education, language, or baseline MMSE score from the 124 who were not administered the MMSE at their initial visit or who had the MMSE only once [82]. The average number of MMSE administrations for included patients was 4 (±1.7; range 2–9). The time elapsed between consecutive assessments was 1.8 to 42.8 months (average 23.6 months). The MUHC Research Ethics Board approved this use of de-identified clinical data for research purposes (BMB-06-002).

*Data analysis*

The proportion of people who failed items on the MMSE according to trajectory group was calculated. The 5 trajectory groups identified in our previous study are depicted in Figure 1 and named with reference to the initial MMSE score and the shape of the trajectory of cognitive changes, as follows: *29-stable* (n=12), *27-stable* (n=108), *25-slow-decline* (n=41), *24-slow-decline* (n=20), and *25-rapid-decline* (n=6).

Figure 1. Trajectories of cognitive change on the MMSE score




A two-stage analysis was performed to identify baseline variables that related to different trajectories of cognitive decline, using the 27-stable group as a reference. In the first stage, the univariate effect of individual baseline predictors on the probability of membership in each trajectory group (relative to the 27-stable group) was examined via conditional group-based trajectory analysis. This extension of the basic group-based trajectory analysis allows for introducing time-independent covariates into the model and examining their association with the probability of group membership [59-60].

Variables evaluated for their predictive utility were baseline MMSE items/subtests, age, sex, years of education (low: <13 years vs. high: 13+ years), first language, and test language. The total MMSE score could not be included in the analyses because it was not independent of the outcome variable. Correlations

between individual items and the total MMSE score were examined and only 3 exceeded 0.4 with a single item reaching a correlation of 0.56 (3 word recall). The degree to which a variable altered the probability of group membership is expressed as an odds ratio (OR) with 95% confidence intervals (95% CI).

Variables that were predictive of group membership from this first phase were then evaluated in a second stage of analysis to develop a multivariate model. It would have been ideal to contrast the stable group to the three different decline groups but the two slow decline groups were very similar and the rapid decline group comprised only 6 subjects. For all further analyses all the decline trajectories were combined into one decline group for contrast with the stable group using multivariate logistic regression. For this analysis individuals were assigned to trajectory groups deterministically based on highest posterior probability. The characteristics of these two groups were contrasted using Chi-square tests.

To identify the best predictive model for cognitive decline, forward stepwise logistic regression was used including the predictors identified in stage 1. Sensitivity, specificity, and positive and negative predictive (PPV, NPV) of competing models were estimated as well as C-statistics representing the area-under-the-receiver operating characteristic curve (AUC) as a measure of predictive accuracy.

To illustrate a clinical application of the predictive model, an index was created based on the strength of the prediction of each item. For this the beta coefficients for the MMSE items from the logistic model were used as weights with beta 0.5 to 0.9 set to 1; 1.0 to 1.5 set at 2; 1.5 to 1.9 set at 3; 2.0 to 2.4 set at 4. A weight was derived for whether the person recalled none, 1, 2 or all of the words in word recall item. The maximum value of the index is 15. The predicted probability of belonging to a declining trajectory over the subsequent 3.5 years was calculated based on the index and age.

**Results**

Table 1 presents proportion of failure in items/subtests of the MMSE at baseline according to the trajectory group membership. Delayed recall, constructional praxis and orientation to time were the most commonly failed items among all groups. The 25-slow-decline group appears to show a slightly disproportionate tendency to make more errors in attention and writing a sentence when compared with the 24-slow-decline group: 51% made one or more errors on the attention item vs. 40% in the 24-slow-decline group, and 13% failed writing a sentence vs. none in the 24-slow-decline group. The proportion of patients in the 25-rapid-decline group who failed at carrying out a complex command was higher than for the other groups.

**Table 1.** Proportion of patients who failed individual items/subtests of the MMSE at baseline within each trajectory group

| Group | 29-stable (n=12) | 27-stable (n=108) | 25-slow-decline (n=41) | 24-slow-decline (n=20) | 25-rapid-decline (n=6) |
|---|---|---|---|---|---|
| Year | 0.0 | 0.0 | 2.5 | 40.0 | 0.0 |
| Season | 0.0 | 4.7 | 5.0 | 15.0 | 0.0 |
| Month | 8.3 | 3.8 | 5.0 | 15.0 | 0.0 |
| Date | 16.7 | 17.0 | 35.0 | 40.0 | 66.7 |
| Day of the Week | 8.3 | 9.4 | 15.0 | 35.0 | 33.3 |
| Country | 0.0 | 0.0 | 0.0 | 5.0 | 0.0 |
| Province | 0.0 | 0.0 | 2.5 | 0.0 | 0.0 |
| City | 0.0 | 0.0 | 2.5 | 0.0 | 0.0 |
| Hospital | 0.0 | 1.9 | 2.5 | 5.0 | 0.0 |
| Floor | 0.0 | 6.6 | 20 | 15.0 | 16.7 |
| Watch | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Pencil | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Repeating sentence | 0.0 | 10.4 | 15.0 | 26.3 | 33.3 |
| Eyes | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Constructional praxis | 16.7 | 31.1 | 47.5 | 50.0 | 50.0 |
| Writing | 8.3 | 3.8 | 12.8 | 0.0 | 0.0 |
| Delayed recall=0 | 0.0 | 15.1 | 32.5 | 45.0 | 16.7 |
| Delayed recall≤1 | 8.3 | 39.6 | 52.5 | 65.0 | 33.3 |
| Delayed recall≤2 | 58.3 | 77.4 | 85.0 | 90.0 | 66.7 |
| Attention≤3 | 0.0 | 8.5 | 25.6 | 25.0 | 0.0 |
| Attention≤4 | 0.0 | 17.0 | 51.3 | 40.0 | 20.0 |
| Commands≤2 | 0.0 | 20.0 | 17.5 | 10.0 | 50.0 |
| Orientation to time≤2 | 0.0 | 1.9 | 5.0 | 15.0 | 0.0 |
| Orientation to time≤3 | 8.3 | 4.7 | 15 | 55.0 | 33.3 |
| Orientation to time≤4 | 25.0 | 28.3 | 42.5 | 70.0 | 66.7 |

The univariate effects of single MMSE items/subtests were examined with conditional group-based trajectory analysis are shown in Table 2. The 29-stable group could not be discriminated from the 27-stable reference group. Patients who failed orientation to date were 4 times more likely to be in a slowly declining group, and 11 times more likely to be in the 25-rapid decline group, than in the 27-stable reference group. Failing constructional praxis, attention, and orientation to floor was associated with higher risk of being in the *25-slow-decline group* than in the 27-stable reference group. Failing attention, delayed recall, and Orientation to time, especially day of the week, was associated with higher risk of being in the *24-slow-decline* group than in the 27-stable reference group. Failing Repeat a sentence and obtaining ≤ 3 points on the orientation to time subtest was associated with increased risk of being in the *25-rapid-decline* group rather than the 27-stable reference group. Age, educational level, test language and first language were not significantly associated with the probability of group assignment.

**Table 2.** Univariate effect of MMSE items for which failure significantly predicted probability of trajectory group membership relative to the 27-stable reference group

| | 29-stable | | | 25-slow-decline | | | 24-slow-decline | | | 25-rapid-decline | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | *β* | SE | OR | *β* | SE | OR | *β* | SE | OR | *β* | SE |
| Date | - | - | - | 4.57 | 1.52 | 0.63* | 4.10 | 1.41 | 0.67* | 11.1 | 2.41 | 0.94* |
| Day of the week | - | - | - | - | - | - | 5.26 | 1.66 | 0.66* | - | - | - |
| Floor | - | - | - | 10.5 | 2.35 | 1.10* | - | - | - | - | - | - |
| Repeating sentence | - | - | - | - | - | - | - | - | - | 6.05 | 1.80 | 0.9* |
| Constructional praxis | - | - | - | 2.94 | 1.08 | 0.54* | - | - | - | - | - | - |
| Delayed recall=0 | - | - | - | - | - | - | 4.48 | 1.5 | 0.64* | - | - | - |
| Attention≤3 | - | - | - | 7.17 | 1.97 | 0.75** | 5.21 | 1.65 | 0.75* | - | - | - |
| Attention≤4 | - | - | - | 8.94 | 2.19 | 0.64*** | - | - | - | - | - | - |
| Orientation to time≤2 | - | - | - | - | - | - | 11.9 | 2.48 | 1.13* | - | - | - |
| Orientation to time≤3 | - | - | - | - | - | - | 25.3 | 3.23 | 0.76*** | 10.7 | 2.37 | 1.06* |
| Orientation to time≤4 | - | - | - | - | - | - | 6.69 | 1.9 | 0.68** | - | - | - |

OR: Odds ratio *$p$<0.05;**$p$<0.01;***$p$<0.001

Group differences in demographic and clinical variables were examined after assigning patients to groups based on posterior probabilities and then combining the two stable groups (29-stable, 27-stable) and the three declining groups (25-slow-decline, 24-slow-decline, 25-rapid-decline). Table 3 contrasts age,

educational level, sex, test language, and first language for the groups characterized as Stable and Declining. Patients in a declining trajectory were older and less educated, but did not differ by sex, test language or first language.

**Table 3.** Comparison of baseline characteristics of the Stable vs. Declining groups

| Group | Stable N = 120 | Declining N = 67 |
|---|---|---|
| Age in years: mean (SD) | 78.8 (6.1) | 81.3(5.4) |
| Education (n with data) | 83 | 54 |
| % ≤ 12 years | 48.2 | 70.4* |
| % Female | 53.3 | 55.2 |
| Test language | | |
| % English | 75.4 | 66.7 |
| % French | 20.4 | 25.7 |
| % Others | 4.2 | 7.6 |
| First language | | |
| % English | 50.0 | 46.3 |
| % French | 30.3 | 31.5 |
| % Others | 16.7 | 22.2 |

* $p<0.05$ compared with Stable group by t-test (Age) or Chi-square test (all others)

In the next step, combinations of different baseline characteristics and MMSE items were used to build a model with the best accuracy for predicting cognitive decline. Table 4 shows the best fitting model for predicting cognitive decline vs. stable cognition identified with stepwise regression. Each additional year of age increased by 10% the odds of cognitive decline within the next 3.5 years. Increased risk of cognitive decline was also predicted among those who

failed constructional praxis or orientation to floor, and among those who lost at least 2 points on orientation to time, 1 point on attention, or 3 points on delayed recall. For example, in an MCI patient who obtains ≤3 points on the attention item, the odds of cognitive decline within the next 3.5 years are 8.3 times greater than that of a patient who obtains >3 points on attention.

Sex was not significantly associated with cognitive decline. When sex was forced in the model, it did not improve model fitting and resulted in reduced predictive ability of the model, so that it was not included in the final model.

**Table 4.** Best-fitting model for predicting increased risk for membership in a declining cognitive trajectory as identified with multivariate logistic regression

| Variables | Estimated beta | Odds Ratio | 95% Wald Confidence Limits | | Pr > Chi-Sq |
|---|---|---|---|---|---|
| Attention≤4 | 2.0 | 7.7 | 3.2 | 18.3 | <.0001 |
| Orientation to time≤3 | 2.1 | 8.3 | 2.6 | 27.1 | 0.0004 |
| Delayed recall=0 | 1.6 | 5.0 | 1.5 | 16.7 | 0.0089 |
| Orientation to floor=0 | 1.3 | 3.6 | 1.1 | 11.3 | 0.0304 |
| Constructional praxis | 1.0 | 2.7 | 1.2 | 5.9 | 0.0128 |
| Age | 0.1 | 1.1 | 1.0 | 1.2 | 0.0025 |

Probability modeled is all declining group (c=0.830, R-Square 0.3102, Max-rescaled R-Square 0.4269)

Table 5 compares the AUC values for predicting cognitive decline based on the different models tested. The best-fitting model had an AUC value of 0.83. The model showed 67.2% sensitivity and 86.4% specificity for cognitive decline. The

accuracy of classification into declining vs. stable groups was 79.7%. The positive and negative predictive values of the model were 72.9% and 82.9%, respectively.

**Table 5.** Comparison of the accuracy (AUC values) of different models for predicting cognitive decline

| Variables in the base model | Base model | Variables added to the base model | | | | |
|---|---|---|---|---|---|---|
| | | +Attention | +Orientation to time | +Delayed recall | +Attention +orientation to time | +Attention +orientation to time +delayed recall |
| Age | 0.605 | 0.710 | 0.691 | 0.668 | 0.782 | 0.807 |
| Age +Orientation to floor | 0.647 | 0.741 | 0.710 | 0.701 | 0.792 | 0.815 |
| Age +Constructional praxis | 0.653 | 0.736 | 0.730 | 0.710 | 0.799 | 0.823 |

Columns 1 and 2 refer to the variables included in the base model, and their AUC values, respectively. Columns 3–7 presents the AUC values obtained when adding different predictor variables to the base model.

To facilitate the use of these findings in clinical practice, Table 6 shows the age-specific probability of cognitive decline over 3.5 years as a function of failing particular MMSE items at first interview. The weights for each item are shown on the left side of the table. The total score derived from summing these weights is represented by the rows with the columns indicating the age group of the patient.

**Table 6.** Individual risk of cognitive decline over 3.5 years as predicted by baseline characteristics and MMSE item failure

| MMSE items | Yes | No | Total Score | AGE RANGE (years) 60-63 | 64-67 | 68-71 | 72-75 | 76-79 | 80-83 | 84-87 | 88+ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Orientation to timeŠ3 | 4 | 0 | <4 | <50 | <50 | <50 | <50 | <50 | <50 | <50 | <50 |
| Orientation to floor=0 | 2 | 0 | 4 | <50 | <50 | <50 | <50 | <50 | <50 | 30-57 | 40-65 |
| AttentionnŠ4 | 4 | 0 | 5 | <50 | <50 | <50 | <50 | <50 | <50 | 55-71 | 66-78 |
| Delayed recall=0 | 3 | 0 | 6 | <50 | <50 | <50 | <50 | 34-61 | 45-72 | 56-78 | 71-85 |
| Delayed recall=1 | 2 | 0 | 7 | <50 | <50 | <50 | 47-62 | 56-72 | 67-81 | 76-87 | 84-90 |
| Delayed recall=2 | 1 | 0 | 8 | <50 | <50 | 41-63 | 46-73 | 58-81 | 69-87 | 82-92 | 88-94 |
| Delayed recall=3 | 0 | 0 | 9 | 37-55 | 49-66 | 60-76 | 71-83 | 80-89 | 86-93 | 90+ | 90+ |
| Constructional praxis=0 | 2 | 0 | 10 | 46-65 | 55-75 | 69-83 | 75-88 | 83-92 | 90+ | 90+ | 90+ |
| **Total score** | | | 11 | 65-77 | 72-84 | 82-89 | 87-93 | 90+ | 90+ | 90+ | 90+ |
| | | | 12 | 70-83 | 79-89 | 86-93 | 90+ | 90+ | 90+ | 90+ | 90+ |
| | | | 13 | 83-90 | 90+ | 90+ | 90+ | 90+ | 90+ | 90+ | 90+ |
| | | | 14 | 90+ | 90+ | 90+ | 90+ | 90+ | 90+ | 90+ | 90+ |
| | | | 14+ | 90+ | 90+ | 90+ | 90+ | 90+ | 90+ | 90+ | 90+ |

The risk score (Total Score) is calculated based on performance on specific MMSE items using the legend on the left. The % risk of cognitive decline is determined by the cell corresponding to the patient's age range and risk score.

## Discussion

The first objective of this study was to identify individual items/subtests of the MMSE that were significantly predictive of future cognitive trajectories amongst people with mild cognitive impairment. In our previous work, we identified 5 cognitive trajectories that could be characterized by different starting points in terms of their baseline MMSE score and by different patterns of longitudinal cognitive change [82]. Here, we demonstrate that each group that followed a declining cognitive trajectory could be distinguished from the 27-stable reference group by a slightly different baseline profile of MMSE test performance. The 24-slow-decline group failed orientation to time, delayed recall, and attention subtests; the 25-slow-decline group failed orientation to date and floor,

constructional praxis, and attention subtests; and the 25-rapid-decline group failed orientation to time and repeating a sentence.

MMSE items that emerged as significant predictors of membership in a declining trajectory were similar to those identified in previous studies on predictors of risk for cognitive decline [51-53]. However, previous studies analyzed all participants with MCI as if they constituted a homogeneous group, despite ample evidence that they are not [12-13]. Potentially informative predictors of future cognitive status may fail to be identified by analysis of the correlation with "average" cognitive decline. The present study is unique in that it sought to identify predictors of membership in specific cognitive trajectory groups, identified through group-based trajectory modeling as being comprised of patients who follow a similar cognitive course.

In the current approach, we conducted separate analyses of the distinct longitudinal relationship between baseline predictors and each cognitive trajectory group. A consequence is that we were able to discover differences in baseline cognitive profiles, as determined by failure of specific MMSE items, amongst people with a similar MMSE total score, and to associate these failure profiles with a particular cognitive outcome. Items predictive of membership in the *24-slow-decline* group, orientation to time and delayed recall, have been associated with episodic memory ability [83], hippocampal dysfunction caused by

beta-amyloid deposition [84], and possession of the APOE-4 genetic variant [85-86]. In contrast, items failed by the *25-slow-decline* group, namely attention and constructional praxis, are known to correlate with performance on neuropsychological tests of working memory [81, 87]. Deficits in working memory have been associated with small vessel cerebrovascular disease, visualized as white matter hyperintensities on neruoimaging [88], and commonly seen in the frontal lobe [89]. Thus, heterogeneous pathological processes may exist in MCI patients, who then experience different cognitive dysfunction patterns. Different cognitive profiles are also associated with different prognoses, with episodic memory impairment regarded as a predictor of development of AD [86, 90-91], whilst working memory impairment is more strongly associated with the onset of other types of dementia, such as Vascular dementia and Lewy body dementia [92-96].

The small size of the *25-rapid-decline* group limited the statistical power to detect baseline variables that distinguished patients in this group from those in other trajectory groups. Regardless of this limitation, orientation to time and repeating a sentence were found to have predictive value in this group when compared with the 27-stable group. Although orientation to time was failed by a majority of MCI patients who followed a declining trajectory, language impairment appeared to be of greater importance in patients in the

*25-rapid-decline* group. This suggests that language impairment, which is usually a late symptom in patients with dementia, occurred relatively early in the course of disease for patients in this group.

The second objective of this study was to develop a model for specifying the risk of following a declining trajectory over the next 3.5 years in a person with a new diagnosis of MCI. The final model was selected to maximize accuracy of prediction in the clinic (80%). The best-fitting prediction model included the variables age, failure of constructional praxis, failure of orientation to floor, losing 2 or more points on orientation to time, losing 1 or more points on the attention item, and losing all 3 points for delayed recall. The specificity of the model was 86%, which is slightly lower than the value obtained when using delayed recall and orientation to time to predict conversion to dementia (98%) [50], but the sensitivity is better (67% vs. 41%).

Age has been identified previously as a significant predictor of cognitive decline or of conversion to dementia [97-101]. In the present study, the odds ratio was 1.1 per year of age and the predictive accuracy of age alone was 0.61. The effect of education on cognitive trajectory could not be fully resolved in the present study due to missing data in 27% of the sample. In the subsample of 136 patients with complete data, education was a significant predictor of risk of cognitive decline; however, the partial effect of education was not significant after

controlling for other covariates. Others have also reported that level of educational achievement, although associated with cognitive performance [102-103], was not associated with the developmental course of cognition in people with MCI [35, 37, 41, 48, 104-105]. Therefore, in this study, we developed the model for predicting cognitive decline without controlling for education, in order to avoid sacrificing sample size and statistical power.

A limitation of this study is the small sample size in some of the cognitive trajectory groups. This had an impact on the choice of statistics used to analyze multiple covariates simultaneously. The conditional group-based trajectory approach allows for introducing multiple covariates into the model, a process through which the joint effect of multiple variables is linked to the probability of trajectory of group membership. Due to limited sample size in some trajectory groups, a convergence problem occurred when we attempted to fit the model with more than three covariates. Thus, although group membership is not definitely determined for individuals, we chose to classify patients into trajectory groups based on the maximum posterior probability and then to collapse some of the groups before modeling multiple predictors using conventional multiple logistic regression techniques. As Roeder indicated, this approach may overestimate the effect of covariates [106].

In conclusion, our results suggest that a simple screening test can provide

indications of domain-specific cognitive impairment that are early clues as to the risk and etiology of later cognitive decline. Furthermore, performance on specific items of the MMSE provided showed good accuracy in predicting those patients with MCI who went on to show cognitive decline. Our results were obtained in a clinic setting, so the results may not generalize to community-based populations. However, the model can be applied easily for prognostic purposes in a geriatric clinic setting. For example, the baseline risk of belonging to a declining cognitive trajectory is 40% in our sample [82]. Table 6 shows how this estimate must be revised upward or downward depending on failure of specific MMSE items and on a patient's age. The risk index presented here was developed using the same methods as the widely used Charlson Index of prognostic comorbidity [107]. In clinical settings without access to sophisticated neuroimaging, neuropsychological, or biochemical techniques, a simple screening test may serve as a useful tool for identifying MCI patients at higher risk of cognitive decline, and may help target at-risk groups for early interventions aimed at delaying the onset of dementia.

Chapter 4

# GENERAL DISCUSSION

The principal objective in the present work was to identify individual items of the MMSE and demographic variables at baseline that predict distinct trajectories of cognitive change among MCI patients. In the first study, we identified five trajectories, as serially measured by the MMSE over 3.5 years among a cohort of 187 MCI patients (Chapter 2). The identified trajectory groups exhibited variations in initial global cognitive ability as well as cognitive course across time, with some remaining stable, some declining slowly and rare cases that declined rapidly. Over the first 3.5 years after diagnosis, 60.3% of MCI patients remained cognitive stable. In groups following a declining course, a majority of MCI patients declined slowly with annual loss of around 1.5 points on the MMSE. The second study revealed the association between each distinct trajectory group and risk factors as suggested by baseline performance on the MMSE (Chapter 3). A model with combined significant baseline factors including age, delayed recall, constructional praxis, attention, and orientation to time and floor achieved good accuracy for predicting individuals who would further decline in cognition.

Our finding is generally in support of current knowledge on the heterogeneity of cognitive outcome among patients with MCI. Most importantly, these results have advanced understanding of the evolutionary nature of MCI, with evidence of the specific courses of cognitive change experienced by different subgroups of individuals with MCI. It has been well recognized that MCI patients are at risk of developing dementia. Yet it is unclear the variation of declining course in global cognitive ability among those MCI patients who progress to dementia. In other words, do MCI patients who are at risk of dementia follow the same pattern of cognitive decline over time? Only one study has addressed a similar question in a cohort of 205 patients with Alzheimer's disease. In this study, six trajectories were identified and showed significant difference in the rate of cognitive decline measured by the MMSE up to 13.5 years [63]. Although our sample is MCI patients, we reached the same conclusion that the trajectory of cognitive decline varied substantially across individuals with cognitive impairment.

These distinct developmental patterns of cognitive change overtime were identified using the group-based trajectory approach, and could not have been detected by observing exclusively conversion to dementia. This approach allowed for better and more reliable prediction of at risk individuals who will further decline in cognition. Previous risk models for predicting dementia relied on

diagnostic outcome at a specified time frame, assuming *a priori* the existence of dichotomous outcome. This traditional determinative rule to subdivide individuals based on the diagnosis of dementia is inevitably subjective, given that it does not account for the uncertainty about the diagnosis of dementia for some cases. A diagnosis of AD cannot be determined by definitive tests. No clear threshold exists to determine which patients belong to a category of MCI or AD. Thus diagnosis criteria emerged for "probable" Alzheimer's disease [108]. More specifically, specifying the point in time at which a person "transitions" from MCI to Alzheimer's disease is meaningless given that cognitive decline and its underlying neuropathology may be continuous in such patients. Due to this limitation in determining diagnostic outcome, group assignment (converters vs. non-converters) is not guaranteed with 100% accuracy for a cohort of MCI patients. Overall, previous studies aiming to predict disease progression have followed a classify-analysis procedure that assigns individuals to categories and treats these classifications without error. This can lead to bias for causal inference [106]. The present work used a group-based trajectory approach that identified a mixture of groups with distinct developmental course in cognition. This approach avoided the uncertainty of group assignment and thus provided an empirical foundation for developing a predictive model. Further, it allowed for detecting atypical but important developmental patterns, as evidenced by the identified

25-rapid-decline group in our data set, which was not identifiable by a determinative rule with dementia diagnosis as the outcome.

This work yields an important contribution to the early identification of groups with risk of cognitive decline toward dementia. First, the model developed in the present study for predicting overall cognitive decline achieved good predictive accuracy of 79.9%. With a proposed table presenting the probability of cognitive decline based on the performance of the MMSE and demographic variables, this model can be easily applied in clinical practice. Second, the results revealed the association between baseline cognitive dysfunction and a declining cognitive course. More specifically, whether or not cognitive function will decline slowly or rapidly can be predicted by baseline performance on the MMSE. Third, the risk model for predicting at-risk groups of cognitive decline was empirically derived from a taxonomical approach by means of group-based trajectory modeling. Our work therefore provides evidence and a new pathway to further explore and validate the prognostic value of previously proposed methods, such as neuropsychological assessments, biochemical markers, neuroimaging techniques. Indeed, a recent published review advocated a need for new strategies to develop risk predictive models for dementia, given that the predictive accuracy of most of these dementia risk model for the MCI population are poor and uncertain[55].

The decision to select potential predictors from amongst the MMSE items

and demographic variables examined here was not optimal for predicting overall cognitive decline with accuracy >80%. Impairment in episodic memory has been observed in preclinical AD [109-110]. However, delayed recall and other items in the MMSE was not sufficiently sensitive to detect subtle deficit in episodic memory due to a ceiling effect [83]. Moreover, it has been established that the MMSE is not well suited for assessing cognitive domains such as working memory [87, 111-112], which may be present in some subtypes of MCI[113-114]. Finally, the effect of education on cognitive decline remains to be confirmed, given that education was not included in the analysis because of missing data, as mentioned previously. A recently proposed concept of "cognitive reserve" suggests that, in patients with cognitive impairment, who had higher level of education, faster rate of cognitive decline occurred once they reached the stage of the clinical manifestations of the disease, [115-120]. However, most of previous studies confirmed this notion in patients with AD[115-118, 120]. Only one study explored MCI population and found no association between cognitive reserve with rate of cognitive decline [121].

In spite of these limitations, our results may influence future developments in the prediction of progressive decline in cognition. The results of our model using variables from the MMSE and demographic factors are promising, and may potentially offer an opportunity to develop a model with enhanced predictive

accuracy by incorporating other approaches. Previously successful approaches focused on neuropsychological assessments, neuroimaging technique, biomarkers, and other clinical information such as the presence of vascular risk factors. However, if the goal is to establish a prognostic multifactor model for daily clinical practice, potential predictors should be easy and cost-effective to obtain. An example of such a model was developed by Kivipelto and colleagues. This model, comprised of age, education, sex, systolic blood pressure, body mass index, and total cholesterol level, reached a predictive accuracy of 78% to predict incident dementia in a total of 1409 middle age people who were followed 20 years [122]. One more candidate is the MoCA, a brief screening test that assesses multiple cognitive domains and detects MCI with higher sensitivity (90%) and specificity (87%) compared with 18% and 100% respectively for the MMSE[123].

Neuropsychological tests that target episodic memory impairment could be of help to improve the predictive accuracy on the basis of our proposed model. Firstly, the use of domain-specific tasks rather than the administration of a whole battery of neuropsychological tests could be a cost-effective approach for developing risk models. Secondly, a growing body of evidence has suggested that a prominent episodic memory deficit is observed in the preclinical stage of AD [124-126]. Thus, among variables from neuropsychological tests, tasks that

measure episodic memory have been consistently found to be important predictive variables for future dementia [127-128]. In our study, although the episodic memory items of orientation to time and delayed recall were of prognostic value, previous work indicates that the association between these items and Free and Cued Selective Reminding Test (FCSRT), a validated test of episodic memory, was not strong [83].

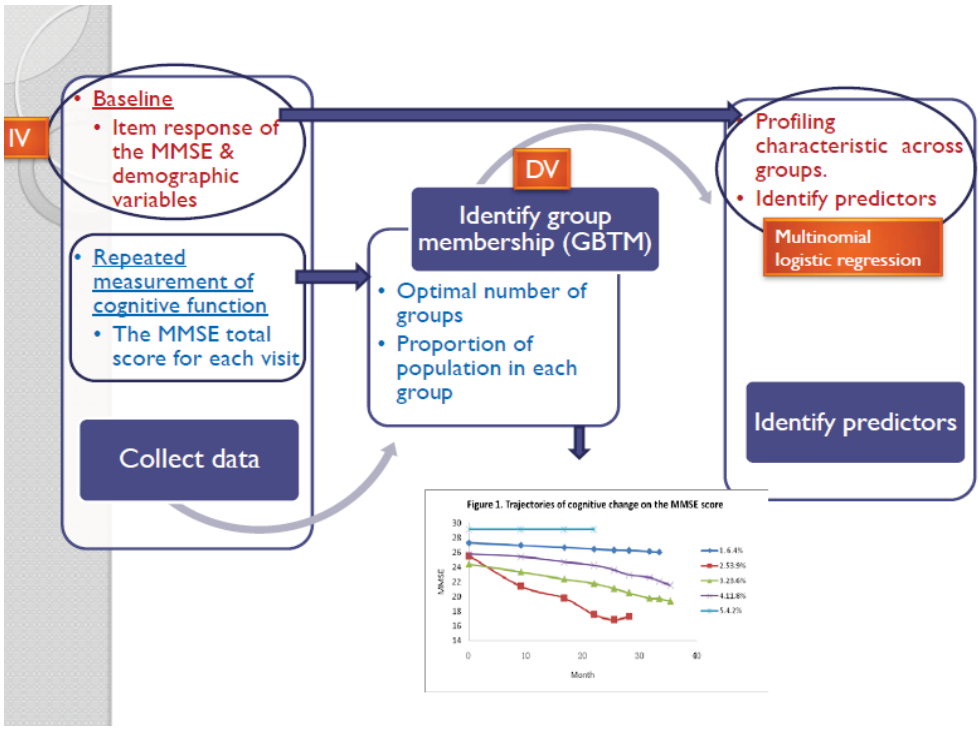
Neurodegenerative changes, largely, amyloid plaques and neurofibrillary tangles in the brain, occur before the onset of AD [129]. Some drugs have been developed and are near marketplace for modifying the neuropathological change by reducing amyloid accumulation, for instance. With this new advance in the treatment of AD, early and accurate identification of at-risk patients in preclinical stage of dementia become crucial, so that this group can benefit from effective intervention long before the onset of frank dementia. In this context, our finding yields important contributions to this task. The MMSE, as an easy-to-use, cost-effective screening test that, together with age, can serve as a useful tool for not only dissociating patients remaining stable vs. declining, but could also be used in future work stratifying at-risk cases with different patterns of cognitive impairment that may associate with different etiologies and patterns of cognitive outcome. This will facilitate proposing appropriate and individualized strategies for MCI patients. For those at risk of further cognitive decline, it may be

necessary to offer further evaluation with restricted approaches such as comprehensive neuropsychological tests and neuroimaging, etc, risk factors manipulation, and more frequent re-evaluation. For those with high risk of rapid decline, early intervention should be initiated at the very early stage of disease aimed at slowing the deterioration of cognition and delay the onset of disease. Given that the current study did not firmly establish the ability to identify individuals who will show rapid decline due to a small size of this group, further investigations should include a larger sample size in order to more accurately characterize the trajectory of rapid cognitive decline.

In conclusion, the results of our two studies not only provides further support but also new insights into the heterogeneous evolution of cognitive impairment in individuals with MCI. The various cognitive courses, particularly the likelihood of progressive cognitive decline can be captured by means of domain-specific cognitive dysfunction as suggested by the performance of the MMSE at baseline. Since our sample is derived from clinical settings, the results are not generalizable to other MCI populations. Thus further investigation of the prognostic value of the MMSE in other populations, such as community-based MCI patients, is warranted.

# APPENDICES

## Appendix Ⅰ: Study design




## Appendix Ⅱ: Basic features of the GBTM

Before describing the analysis procedure of GBTM, we briefly introduce the principle of this approach and the estimated parameter derived from the analysis. The basic feature of the GBTM is as follows: (1) it identifies latent subgroup with distinct developmental trajectories over time for the outcome measured. This can

be achieved based on the model selection procedure and an objective group assignment rule, by which individuals are assigned into a group that best matches their developmental course for the behavior or outcome interested. As a result, it is considered that the developmental trajectory for these individuals within the same group is relatively homogeneous; (2) the model developed by the GBTM provides descriptive information of the identified trajectory groups. Included are (a) posterior probability of group membership; (b) the proportion of each group following the same trajectory; (c) the shape of the trajectories as defined by polynomial function.

The *posterior probability* of group membership is the probability of an individual belonging to a specific trajectory group. It is referred as *posterior* probability because it derives from post hoc calculation based on the estimation coefficients of the best-fitting model, which estimates an individual's probability belonging to each identified trajectory group. The *posterior probability* is a key parameter used for assigning an individual to a specific group, for which he or she holds the largest posterior probability. This is known as the maximum probability assignment rule, as described by Nagin [59]. On the basis of this rule, *average posterior probability* of group membership can be calculated for each trajectory group by averaging the maximum posterior probability for all individuals in the same group.

**Appendix Ⅲ: Data analysis via GBTM to identify distinct trajectory groups**

In this part of analysis, we conducted model fitting for collected data by means of SAS procedure (Proc TRAJ) [60] to identify trajectory groups with similar developmental course in cognition measured by the MMSE. Firstly, the model fitting procedure was defined as a censored normal model that handles psychometric scale or continuous data. Next, to select the best fitting model, we proceeded with a two-stage modeling strategy, that is, determine 1) the optimal number of trajectory group and 2) the shape of the trajectory for each identified groups.

1) Determine the optimal number of trajectory group

In this part, the optimal number of trajectory group was determined by an iterative modeling fitting procedure with respect to the MMSE score over time. This can be achieved by selecting a model that best describes the heterogeneity of our sample according to the objective statistical criteria, rather than assuming the existence of the number of groups and the developmental pattern of cognitive change a priori. Among several of these criteria for selecting the best model, Bayesian Information Criterion (BIC) is the most consensual and widely used criteria for model selection. The larger BIC value, the better is the model fitting. In SAS proj traj, the BIC is given as a negative value. Therefore, the least

negative of the BIC indicates the best-fitting for a model with the optimal number of trajectory group. As noted above, the modeling fitting is iterative. Upon the determination of a priori maximum number of groups based on our common sense, clinical interest and sample size, the model was repeatedly fitted from 2 to 6 trajectory groups. Firstly, we began with fitting a two-group model and then the one with three groups. The more complex model (with a larger number of trajectory) is compared with the null model (with a smaller number of trajectory) by the log form of Bayes Factors ($B_{10}$), which is used to determine which model is better:

$$2\log_e(B_{10}) \approx 2(\Delta BIC)$$

$$\Delta BIC = BIC_{complex} - BIC_{null}.$$

If the log form of Bayes Factors ($\approx 2\Delta BIC$ ) between two models is approximately greater than 10, a better-fitting model with a larger number of groups is favored[60]. This procedure was repeated to compare two groups with an increasing number for up to six groups until the least BIC value was obtained and there was no evidence of improvement for model fitting.

2) Determine the shape or the pattern of trajectory group.

After identifying the optimal number of trajectory group, the next step was choosing an appropriate degree of polynomial that determines the shape of each group's trajectory over time. SAS proc allows up to four polynomial

trajectories: constant, linear, quadratic, cubic. As a general rule, a more appropriate order for the shape of the trajectory was selected when it's polynomial function is statistical significant ($p<0.05$) [59].

Finally, following the selection of the best model, the *posterior probability* of group membership for individuals belong to the identified trajectories were produced by the model. These probabilities were subsequently used to assign individuals to the trajectory group for which he or she has the highest posterior probability.

**Appendix Ⅳ: MMSE**

## Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

***Instructions:*** ***Ask the questions in the order listed. Score one point for each correct response within each question or activity.***

| Maximum Score | Patient's Score | Questions |
|---|---|---|
| 5 | | "What is the year? Season? Date? Day of the week? Month?" |
| 5 | | "Where are we now: State? County? Town/city? Hospital? Floor?" |
| 3 | | The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____ |
| 5 | | "I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Stop after five answers.<br>Alternative: "Spell WORLD backwards." (D-L-R-O-W) |
| 3 | | "Earlier I told you the names of three things. Can you tell me what those were?" |
| 2 | | Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them. |
| 1 | | "Repeat the phrase: 'No ifs, ands, or buts.'" |
| 3 | | "Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.) |
| 1 | | "Please read this and do what it says." (Written instruction is "Close your eyes.") |
| 1 | | "Make up and write a sentence about anything." (This sentence must contain a noun and a verb.) |
| 1 | | "Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)<br>  |
| 30 | | TOTAL |

***Instructions for administration and scoring of the MMSE***

*Orientation (10 points):*

- Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?"). One point for each correct answer.
- Ask in turn, "Can you tell me the name of this hospital (town, county, etc.)?" One point for each correct answer.

*Registration (3 points):*

- Say the names of three unrelated objects clearly and slowly, allowing approximately one second for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0-3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials. Record the number of trials it takes for the patient to learn the words. If the patient does not eventually learn all three, recall cannot be meaningfully tested.
- After completing this task, tell the patient, "Try to remember the words, as I will ask for them in a little while."

*Attention and Calculation (5 points):*

- Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.
- If the patient cannot or will not perform the subtraction task, ask the patient to spell the word "world" backwards. The score is the number of letters in correct order (e.g., dlrow=5, dlorw=3).

*Recall (3 points):*

- Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score the total number of correct answers (0-3).

*Language and Praxis (9 points):*

- Naming: Show the patient a wrist watch and ask the patient what it is. Repeat with a pencil. Score one point for each correct naming (0-2).
- Repetition: Ask the patient to repeat the sentence after you ("No ifs, ands, or buts."). Allow only one trial. Score 0 or 1.
- 3-Stage Command: Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." Score one point for each part of the command correctly executed.
- Reading: On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the sentence and do what it says. Score one point only if the patient actually closes his or her eyes. This is not a test of memory, so you may prompt the patient to "do what it says" after the patient reads the sentence.
- Writing: Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary.
- Copying: Show the patient the picture of two intersecting pentagons and ask the patient to copy the figure exactly as it is. All ten angles must be present and two must intersect to score one point. Ignore tremor and rotation.

(Folstein, Folstein & McHugh, 1975)

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