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Psychometric Cognitive Decline (PCD) Precedes the Advent of Subjective Cognitive Decline (SCD) in the Evolution of Alzheimer's Disease

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Abstract

Background: We have been describing the clinical stages of the brain aging and Alzheimer's disease (AD) continuum. In terms of the pre-dementia stages of AD we introduced the terminology, "mild cognitive impairment" (MCI) for the first pre-dementia stage and "subjective

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AUTHOR CONTRIBUTIONS

Barry Reisberg, M.D., conceived of the study, obtained funding for the study and provided oversight and direction for all aspects of the study, including the study analyses and the preparation of this manuscript. Dr. Reisberg worked closely on this study with Dr. Steven Ferris, who died in 2017. Yongzhao Shao, Ph.D, had primary responsibility for the statistical analysis of this study. Mesum Moosavi, M.D., worked closely with Dr. Reisberg on the preparation of the manuscript for this study. Dr. Sunnie Kenowsky worked with Dr. Reisberg on the maintenance of the longitudinal study population for this study. Mr. Alok Vedvyas had primary responsibility for the maintenance of the database for the study, including data checking and associated data analyses including the analyses for the present report. Karyn Marsh, Ph.D., supervised and provided oversight for the study personnel, helping to ensure proper follow-up of subjects and the accuracy of the study data. Ms. Jia Bao performed most of the statistical analyses for this study. Maja Buj, M.D., assisted Dr. Reisberg with the preparation of the manuscript for this study. Carol Torossian, Ph.D, assisted with the statistical analysis of this study. Alan Kluger, Ph.D., who was previously an employee of NYU Langone Health, assisted with the recruitment of subjects for this study. Mr. Gaurav Vedvyas, assisted in the maintenance of the database for this longitudinal study and with the associated analyses. Thet Oo, M.D., assisted with recruitment of the subjects and maintained a follow-up subject schedule for this longitudinal study. Fawad Malik, M.D. and Fauzia Arain, M.D., assisted with the preparation of this report. Arjun V. Masurkar, M.D., who is presently the Director of the Clinical Core of the NYU Alzheimer's Disease Center and Thomas Wisniewski, M.D., who is presently Director of the NYU Alzheimer's Disease Center, assisted in providing oversight for many aspects of the study and in the preparation of this report. All authors approved the final version of this report.

STATEMENT OF ETHICS

The subjects in this study had "no cognitive decline " at baseline and consented to this longitudinal study. All subjects were fully capable of providing consent. This longitudinal study was approved from the time of inception until the present time by the Institutional Review Board (IRB) of NYU Langone Medical Center

DISCLOSURE STATEMENT

Dr. Barry Reisberg, Dr. Yongzhao Shao, Dr. Sunnie Kenowsky, Dr. Karyn Marsh, Ms. Jia Bao, Dr. Carol Torossian, Mr. Alok Vedvyas, Mr. Gaurav Vedvyas, Dr. Thet Oo, Dr. Arjun Masurkar and Dr. Thomas Wisniewski are employees of NYU Langone Health. Dr. Mesum Moosavi, Dr. Maja Buj, and Dr. Fauzia Arain were nontraditional volunteers at NYU Langone Health. Dr. Kluger is presently an employee of Lehman College of the City University of New York and previously had been a full time employee of the NYU School of Medicine. Dr. Fawad Malik is an employee of the Department of Pharmacy of Bellevue Hospital, New York, N.Y.

cognitive decline" (SCD) for the pre-MCI stage. We now report the characteristics of a pre-SCD condition eventuating in likely AD.

Objective: To characterize a pre-SCD condition eventuating in AD.

Method: Sixty healthy persons with "no cognitive decline" (NCD) were recruited and 47 were followed (mean baseline age= 64.1±8.9 years; mean follow-up time, 6.7±3.1 years). Outcome was determined at the final assessment prior to 2002 as "decliner," if SCD or worse, or non-decliner if NCD.

Results: After controlling for age, gender, years of education, and follow-up time, there was a between group difference in the decline rate ($p<0.001$). Also, after controlling for demographic variables and follow-up time, the combinatorial psychometric score was lower at baseline in the future decliners ($p=0.035$). Of the 9 psychometric variables, after controlling for demographic variables and follow-up time, 3 were significantly lower at baseline in future decliners. Since AD is known to be age related, and all subjects in this study were otherwise healthy, we also did an analysis without controlling for age. The combinatorial psychometric score was highly significantly better at baseline in the future non-decliners than in the future decliners ($p=0.008$).

Conclusion: This is ostensibly the first study to link psychometric cognitive decline (PCD) to the subsequent SCD stage of eventual AD.

Keywords

brain aging; psychometric cognition; cognitive decline; cognitive testing; longitudinal studies; psychometric; cognition; Alzheimer's disease

INTRODUCTION

All of the research described below was conducted at the NYU Langone Medical Center and was approved by the NYU Langone Institutional Review Board. Written informed consent to participate in these studies was obtained from the subjects.

In 1982, on the basis of systematic clinical observations over the prior 4 years, we published the Global Deterioration Scale (GDS) which describes 7 major stages in the evolution of brain aging and the dementia of Alzheimer's disease (AD) [1]. The GDS identified a 3rd stage in which, "the earliest clear cut clinical deficits appear…However objective evidence of memory deficit is obtained only through an intensive interview…" In this GDS 3 stage, "Co-workers become aware of the [person's] relatively poor performance." Also, "Difficulties in finding words and names may become evident to intimates." In 1988, we coined the terminology, "mild cognitive impairment," for the 3rd GDS stage [2]. The GDS also identified a stage prior to mild cognitive impairment (MCI) in which older persons have subjective complaints of cognitive decline only (SCD) [1]. This GDS stage 2 was described as a condition in which persons commonly complain of not recalling names and/or where they have placed familiar objects. These persons are otherwise healthy and subsequent studies have shown that GDS stage 2 persons do not perform more poorly on psychometric tests than persons without these memory complaints [2].

In 1986, we hypothesized that SCD was a stage in otherwise healthy older persons and that the duration of this stage was 15 years prior to MCI [3]. In 2006, we published data which supported our temporal estimates [4] as described in an analysis in 2008 [5]. These analyses are summarized below.

Specifically in our 2006 study [4], the non-decliners were followed over a mean of 8.9 ± 1.8 years. If GDS stage 2 is a stage lasting precisely 15 years, as hypothesized in Reisberg's 1986 publication [3], then 6.67% of subjects would be anticipated to decline annually over the 8.9 year mean interval of the 2006 study. Therefore, we would anticipate that 59.36% of subjects would decline to mild cognitive impairment (MCI) or dementia over the 8.9 year mean study interval. The observed finding was that 27 of the 44 baseline subjects declined to MCI or dementia, i.e. 61.36% [5]. Hence, the observed decline rate differed from the hypothesized decline rate by only 2.00% over the 8.9 year mean study interval, or 0.22% per year [5].

Recently, Mitchell et al. conducted a meta-analysis of outcomes of persons with what they termed "subjective memory complaints" and obtained results remarkably congruent with our initial 1986 estimate of the duration of the SCD stage [6, 3]. If the SCD stage lasts precisely 15 years, as estimated in 1986 [3], then we would expect 6.67% of a uniformly distributed population of SCD persons to move towards and convert to MCI per annum. In Mitchell et al.'s analysis of 28 studies, there were 14,714 persons with subjective memory complaints (synonymous with SCD). Eleven of the studies could be analyzed in terms of the annual conversion rate (ACR) of developing MCI. They found that "from 11 studies the ACR of developing MCI was 6.67%," a result precisely in accord with Reisberg's 1986 intial temporal estimate of annual change in GDS stage 2 subjects [3].

With respect to our own studies we believe that the remarkable precision of the above findings are the result in large part of the rigorous inclusion and exclusion criteria applied in our studies. Prior to inclusion, medical, psychiatric, neurologic, and neuroradiologic investigations are completed and subjects with concomitant conditions which might interfere with cognition, or which might progress or recur in a manner which might interfere with cognition, are excluded from our investigations. These exclusions result in robustly homogeneous subject groups.

In 2010, we published another study on the nature and outcome of persons in GDS stage 2, referred to in this 2010 investigation as "subjective cognitive impairment." This study, directly compared outcomes of healthy subjects with and without SCD over a 7 year mean interval [7]. Specifically, we compared outcomes of a consecutive series of subjects at GDS stage 1, i.e., with no subjective or objective declines, with that of subjects at GDS stage 2, i.e., with SCD only. Subject enrollment extended over a 14 year interval. Of 260 subjects comprising the baseline study population, follow-up was completed in 213 subjects (81.9%), 47 with no baseline subjective or objective decline (GDS stage 1), and 166 with SCD only (GDS stage 2). Subject groups followed did not differ in the baseline age or Mini-Mental Status Examination (MMSE) scores. The follow-ups occurred over a mean of 6.8 ± 3.4 years. We observed that 14.9% of GDS stage 1 subjects who, by definition, were free of subjective complaints, or objective evidence of cognitive decline at baseline, declined to a

diagnosis of MCI or dementia. In contrast, 54.2% of GDS stage 2 subjects, by definition, with subjective cognitive deficits at baseline, declined to MCI or dementia. After controlling for baseline demographic variables and follow-up time, a Weibull proportional hazards model revealed increased decline in the baseline GDS stage 2 subjects, with a hazard ratio of 4.5, in comparison with the GDS stage 1 subjects. An accelerated failure time model analysis with an underlying Weibull survival function showed that GDS stage 2 subjects at baseline, declined more rapidly, at 60% of the rate of the GDS stage 1 subjects. Furthermore, mean time to decline was 3.5 years longer for the GDS stage 1 than the GDS stage 2 subjects ($p = 0.0003$).

Largely as a result of the findings from our 7-year follow up study, published in 2010, the scientific community's interest in the SCD entity greatly increased. This resulted in part, in the creation of a Subjective Cognitive Decline Professional Interest Area (PIA) Working Group of the Alzheimer's Association. The PIA has sponsored 2 recent consensus publications on SCD, as well as other recent publications in which we have participated [8–11]. We now report that there is a stage of Psychometric Cognitive Decline (PCD), which precedes the SCD stage in the evolution of the eventual overt dementia of AD.

METHODS

For the present investigation we selected subjects from the prior longitudinal investigation [7], who were GDS stage 1 at baseline. These GDS stage 1 persons were healthy and by definition, free of either subjective or objective evidence of cognitive decline. Since our prior publication [7], describes our selection criteria for the present investigation in detail, we also refer interested readers to our prior publication for this information [7].

Subject Selection and Study Background

Subjects were community residing, over 40 years of age, recruited by public announcement or referral to participate in this longitudinal study on cognition and brain aging. The grant which provided support for this study from 1982 until 2003 was entitled, "Aging and Dementia: Longitudinal Course of Subgroups," (B. Reisberg, Principal Investigator). Additional support was provided by the New York University Alzheimer's Disease Center grant from 1990–2015 (S. Ferris, Principal Investigator, B. Reisberg, Director, Clinical Core, 1990–2014). The objective of these studies was to follow subjects at specified intervals, as long as possible, or until the subject's demise.

At baseline medical, neurological, psychiatric, neuropsychological, clinical laboratory, and neuroradiologic evaluations were conducted to exclude subjects who, in terms of the present investigation, had conditions apart from normal brain aging, without SCD or MCI.

Criteria for exclusion from the present investigation included: (1) the presence of SCD, MCI, or dementia; (2) a history of clinically significant head trauma, seizures, mental retardation, or prior significant neurological disorder; (3) a modified Hachinski Ischemia Score of ≥ 4 [12]; (4) a history of clinically significant cerebral infarction; (5) evidence of cerebral infarction from the brain neuroimaging evaluation (in the great majority of subjects these were magnetic resonance imaging scans, in a small minority of subjects

these were computed tomography scans); (6) a significant history of drug or alcohol abuse; (7) a history of schizophrenia, major affective disorder, or the presence of a Hamilton Depression Scale [13] score of ≥ 16; (8) the presence of cardiac, pulmonary, vascular, metabolic or hematologic conditions of sufficient severity as to effect cognitive functioning; (9) the presence of abnormalities from blood testing which were considered sufficient in magnitude to effect cognition or functioning; the blood testing included: (a) complete blood counts, (b) a comprehensive metabolic panel, (c) serum B12 and folate levels, (d) thyroid function tests, specifically thyroxine [T4], triiodothyronine [T3], and thyroid stimulating hormone [TSH] levels, and (e) screening for syphilis. Additionally, subjects were excluded from participation in this longitudinal study if they were receiving medications that might significantly effect cognitive functioning. If exclusionary factors were uncovered, then potential subjects were referred for treatment by community physicians. Eligible subjects were accepted for entry into our longitudinally followed research population.

Although subjects with complaints of cognitive decline frequently contacted our center for assistance, persons free of subjective or objective cognitive decline were relatively difficult to recruit for the study. Therefore, spouses and other community residing persons were contacted to assist with our recruitment of this cohort.

Subject recruitment occurred from January 1, 1984 until December 31, 1997. During this period, 60 No Cognitive Decline subjects were recruited. These subjects were subsequently followed over approximately 2 year intervals until December 31, 2001. All follow-up evaluations were completed without reference to the prior results.

Assessment measures in the present investigation included demographic variables, MMSE scores [14], Brief Cognitive Rating Scale (BCRS), Axis 1 to 5 scores, and total BCRS axis 1 to 5 scores [15], Hamilton Depression Scale [13], total and item scores, and a psychometric test battery which has been in use at the NYU Alzheimer's Disease Center for several decades [2]. The specific tests used in this test battery are assessments of Paragraph Recall, Initial and Delayed Recall [16], Paired Associates Recall, Initial, and Delayed Recall [16], Memory for Designs [16], Digit Span Recall, Forwards [17], Digit Span Recall, Reverse [17], the Digit Symbol Substitution Test [17], and the WAIS-R Vocabulary subtest [17].

A combinatorial, "Psychometric Deterioration Score" (PDS), was also computed. This was derived from an equal weighing of the 9 tests described above in the test battery. Although, the formula for this computation has been used previously (e.g. see reference 7), the formula appears to not have been published previously. Therefore, we are describing the formula below:

$$\mathrm{PDS} = (8 - (((\mathrm{PARI}) + (\mathrm{PARD}))/45 + ((\mathrm{PRDI}) + (\mathrm{PRDD}))/20 + ((\mathrm{DESN})/10) + ((\mathrm{WASV})/80) + ((\mathrm{DSST})/75) + ((\mathrm{WASDIGF}) + (\mathrm{WASDIGB}))/17) * 1.6)$$

Wherein, "PARI" is Paragraphs Initial Recall, "PARD" is Paragraphs Delayed Recall, "PRDI" is Paired Associates Initial Recall, "PRDD" is Paired Associates Delayed Recall, "DESN" is Design Recall of abstract shapes, "WASV" is the language and vocabulary measure from the WAIS, the "DSST" is the Digit Symbol Substitution Test from the

WAIS, “WASDIGF” is the longest consecutive sequence of numbers recalled correctly, and “WAISDIGB” is the longest number sequence correctly recalled in the reverse order.

RESULTS

As described previously [7], at baseline, there were 60 subjects in the No Cognitive Decline (GDS stage 1) subject group. Forty-seven of the 60 subjects with No Cognitive Decline at baseline were followed. Their mean baseline age was 64.1 ± 8.9 (SD) years; 26 subjects were females and 21 were males. The mean level of education was 16.1± 2.4 years. The mean baseline MMSE score was 29.6 ± 0.8. The subjects’ last GDS staging assessment prior to 2002, was used to determine outcome. On this basis, subjects were divided into 2 groups: (A) decliners, if the final GDS rating was ≥ 2 and (B) non-decliners, if the final GDS rating was stage 1. Thirty-six subjects were found to have declined and 11 subjects were non-decliners.

The future decliners were older at baseline ($p= 0.008$). There were no significant baseline between group differences in gender, education, MMSE scores, BCRS total or individual axis scores, Hamilton Depression Scale total or item scores, or BEHAVE-AD total or item scores [18].

After controlling for age, gender, education, and follow-up time, there was a significant between group difference in decline rate ($p< 0.001$). Also, after controlling for age, gender, years of education, and follow-up time, the combinatorial PDS was significantly lower at baseline in the future decliners ($p= 0.035$). Of the 9 psychometric variables included in the study, after controlling for age, gender, education, and follow-up time, future decliners had significantly lower baseline scores on PARI ($p= 0.036$), from the Guild Memory Scale [16], Digit Span Recall, Forwards ($p=0.016$), and Digit Span Recall, Backwards ($p= 0.049$), from the WAIS [17].

DISCUSSION

This appears to be the first study to directly link Psychometric Cognitive Decline to the subsequent SCD, and by extension, to the MCI, and to the Dementia of the Alzheimer’s Type continuum (see Reisberg, et al., 2017 [19] for a recent discussion of this continuum). A question which immediately arises from our present findings is when in the course of the human lifespan does this continuum of psychometric and subjective cognitive decline begin? At least one publication appears to have recently addressed some aspects of this question [20]. Singh-Manoux, et al. conducted a prospective cohort study in which they investigated 10 year decline in cognitive function from a longitudinal dataset. Subjects were employees of civil service departments in London, U.K. Study participants included 5,198 men and 2,192 women who were aged 45 to 70 at the time of the initiation of cognitive testing. The investigators concluded that, “cognitive decline is already present in middle-age (age 45–49).”

However, a severe limitation of the study of Singh-Manoux et al. is the complete absence of medical, psychiatric, neurologic, neuroradiologic, or clinical laboratory evaluations. Without the exclusion of other conditions, it is unclear how much of Singh-Manoux, et al.’s findings

with respect to cognitive decline and aging should be attributed to Alzheimer's disease. Conversely, the present investigation specifically excluded conditions apart from incipient Alzheimer's disease which could be attributed to the observed changes.

Since Alzheimer's disease is known to be associated with age [21], [22], removing age from the presentation of our findings by "controlling for age" may not be appropriate in terms of conveying the true nature and import of our observations. Accordingly, we are now presenting our data in this discussion without controlling for age.

It should be noted that there were no significant differences between our subject groups in gender, educational background, MMSE scores, BCRS axis 1 to 5 total scores, Hamilton Depression Scale total scores, BEHAVE-AD total scores, follow-up times or follow-up visits.

In terms of the psychometric tests scores, there were very significant differences between the future non-decliner and the future decliner subjects. The combinatorial PDS, in which a lower score signifies better performance, was a mean of 1.13 ± 0.90 (SD) in the future non-decliners and 2.03 ± 0.90 in the future decliners (p= 0.008). Three of the 9 individual scores, in which a higher score signifies better performance, also showed significant differences, all in favor of the future non-decliner subject group. Specifically, on the Paragraph Initial Recall assessments, the subjects in the future non-decliner group scored a mean of 9.77 ± 1.94 at baseline, and the future decliner subjects scored 7.53 ± 2.58 at baseline. This difference was highly significant (p= 0.005). Also, the baseline Digit Symbol Substitution Test score mean in the future non-decliners was 61.36 ± 7.50, which was significantly higher than the scores in the future decliner subject group, i.e. 53.57 ± 11.39 (p = 0.025). Finally, the baseline WAIS Digits Forward assessment was significantly higher in the future non-decliners, i.e., a mean of 7.82 ± 0.98, than in the future decliners, i.e. 6.64 ± 1.45 (p= 0.009).

Hence, we believe this additional analysis, which did not control for age, in these subjects who were selected to be healthy and free of subjective or objective cognitive impairments at baseline, lends further support for a process of cognitive decline for which we suggest the terminology, "Psychometric Cognitive Decline, [PCD]," which antedates the subsequent SCD and MCI stages of the eventual dementia of Alzheimer's Disease.

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