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Neuropsychological Predictors of Transition From Healthy Cognitive Aging to Mild Cognitive Impairment: The PATH Through Life Study

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Objective: To identify neuropsychological predictors of transition from healthy cognitive aging to mild cognitive impairment (MCI) or any mild cognitive disorder (any-MCD) in a community-based longitudinal study of aging. **Design:** Longitudinal. **Participants:** Two thousand eighty-two individuals, aged 60–64 years and participating in a prospective epidemiologic study of mental health, and aging were assessed at two time points 4 years apart for MCI using the International Consensus Criteria, the clinical dementia rating scale (CDR, 0.5), or any of a suite of criteria sets for MCDs (any-MCD). **Measurements:** Logistic regression was used to assess the neuropsychological predictors of conversion to diagnosis including the Mini-Mental State Examination, immediate and delayed recall (IR and DR), Digit Backward, Spot-the-Word (STW), Symbol Digits Modalities Test (SDMT), simple and choice reaction time, and reaction time variability. **Results:** Of the 2,082 participants with no cognitive impairment in the first wave of data collection, 18 participants were diagnosed with MCI, 32 with CDR 0.5, and 64 participants presented with any-MCD 4 years later. The main neuropsychological predictors of conversion identified in multivariate analyses were measures of IR/DR, STW, Symbol Digit Modalities Task, and reaction time variability. **Conclusions:** Although most measures were significant predictors of conversion to MCI or any-MCD when assessed independently, four tests (IR/DR, STW, SDMT, and simple reaction time variability) accounted for the explained variance in diagnosis when all tests were assessed together. When predictive value, stability across clinical categories, and psychometric characteristics were considered together, the reaction time variability measure was the best predictor of future cognitive disorder. (*Am J Geriatr Psychiatry* 2010; 18:723–733)

Key Words: Mild cognitive impairment, cognition, behavioral variability, screening

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With the promise of early intervention strategies on the horizon, the focus in recent years has moved to the detection of neurocognitive disorders at an early stage. There has consequently been an exponential increase in studies of mild cognitive impairment (MCI). MCI is recognized as a prodromal stage to Alzheimer disease (AD) with 30% of people diagnosed with MCI converting to dementia during 2–5 years.^{2,3} It has been suggested that over longer periods, the conversion rate might be even higher and reach 50%.⁴ MCI status has also been shown to be associated with neuroanatomical changes^{5,6} consistent with those found in the progressive stages of neurodegeneration leading to AD.^{7,8}

Because the pathologic processes involved in the development of AD are already detectable in individuals in their 40s,^{7,8} the focus of investigations should move to middle-aged individuals. It is arguable that by the time individuals receive the diagnosis of MCI, they are likely to already have suffered considerable neurodegenerative change. True primary prevention warrants the identification of at-risk individuals before the development of MCI. To achieve this, information is required from longitudinal studies of cohorts of healthy individuals in midlife or early late life, to enable discovery of the most sensitive early markers of cognitive decline. It is likely that sensitive neuropsychological tests will detect impairment even before the manifestation of mild cognitive symptoms in the clinical setting. Although many studies report on the sensitivity of neuropsychological predictors for conversion to dementia, we have not been able to identify a large population-based study investigating this topic.

A number of cognitive domains are affected quite early in the process of neurodegenerative disorders, and these include memory, lexical decision making, speed of information processing, and intraindividual response variability (trial to trial variability during reaction time tasks). Memory function impairment has been shown to be strongly associated with MCI and dementia and is linked to AD and other pathology affecting particularly the medial temporal lobe in the early stages of the disease. Therefore, memory measures are expected to be strong predictors of cognitive impairment. Lexical decision is thought to be relatively spared until the onset of severe dementia and is not expected to be highly predictive of early cognitive impairment. Progressive slowing in

speed of processing is known to be associated with both normal cognitive aging⁹ and dementia¹⁰ and, therefore although important, may not be the most sensitive predictor of cognitive impairment. Although global measures of cognition such as the Mini-Mental State Examination (MMSE) have been found to have good sensitivity and specificity in screening for dementia,¹¹ their psychometric performance have been lower in screening for MCI.¹² Consequently, MMSE and Symbol Digits Modalities Test (SDMT) measures are not expected to be highly predictive of cognitive impairment.

It has been reported that increased intraindividual variability in response time, which is thought to be due to decreased efficiency of executive prefrontal function, increased neural noise, and impaired cerebral connectivity, may prove more sensitive as a very early marker of cognitive decline. Hultsch et al.¹³ found that intraindividual variability in a number of tasks (including simple and complex reaction time) both within and across testing sessions was a significant predictor of dementia, enabling the accurate categorization of 91% of nondemented and 77% of demented individuals participating in their study. Similar associations were found between intraindividual variability and cognitive decline in a large longitudinal study of 447 older individuals with a 13-year follow-up.¹⁴ Increased intraindividual variability is likely to have multiple pathologic and physiological neurobiological origins. In the context of cognitive decline and dementia, Murtha et al.¹⁵ demonstrated a strong link between intraindividual variability and prefrontal dysfunction, whereas Bunce et al.¹⁶ showed that higher reaction time variability in cognitively healthy 60–64-year olds was associated with increased white matter hyperintensities volume in the prefrontal cortex but not in other brain regions. These findings and others showing an association between intraindividual variability and biomarkers and life style factors such as systolic blood pressure, forced expiratory volume, depression, smoking, and physical activity¹⁷ known to be associated with cognitive decline¹⁸ suggest that intraindividual variability measures might be particularly sensitive to early cognitive changes occurring in MCI.

In this study, we examine the value of a battery of neuropsychological tests to identify healthy individuals who will go on to develop MCI.

METHODS

Study Population

The design of the Personality and Total Health (PATH) through life study has been described elsewhere.¹⁹ Briefly, participants who were residents of the city of Canberra and the adjacent town of Queanbeyan, Australia, were recruited randomly through the electoral roll to participate in a study interested in the risk and protective factors for common mental disorders, normal aging, and dementia. Enrolment to vote is compulsory for Australian citizens. Participants were recruited in three age cohorts 20–24, 40–44, 60–64 years and are to be followed-up every 4 years, over a total period of 20 years. The study was approved by the Australian National University Ethics Committee. Results presented here concern the first- and second-wave interviews with 60–64-year olds, which were conducted in 2001–2002 and 2003–2006, respectively. Of 4,831 people contacted, 2,551 (58.3%) were interviewed in Wave 1. Of these, 2,222 (87.1%) individuals completed Wave 2 assessments. A further 139 participants were excluded from analysis because they were either assessed to have mild neurocognitive deficits at Wave 1 (N = 72) or refused a detailed neuropsychological assessment after screening positive on cognitive impairment measures (N = 64). One participant was excluded due to the loss of Wave 1 measures (Fig. 1).

Clinical Assessment

For each wave, the clinical assessment was conducted in two phases.¹⁹ In Phase 1, all participants were screened for cognitive disorders and were selected for further assessment if they had any of the following: 1) a MMSE score ≤ 25 ; 2) a score below the 5th percentile on immediate or delayed recall (II/DR) of the first trial of the California Verbal Learning Test (immediate or delayed score of <4 and <2 , respectively), or 3) a score below the 5th percentile on either of the following two tests: Symbol-Digit Modalities Test (<33) or Purdue Pegboard with both hands (Wave 1 <8 ; Wave 2 <7) or reaction time (third set of 20 trials) (Wave 1: >310 milliseconds; Wave 2: >378 milliseconds). In the second phase, those who screened positive in Phase 1 and con-

FIGURE 1. Sample Selection

sented to participate in further assessment were given a Structured Clinical Assessment for Dementia by one of two physicians,¹⁹ a neuropsychological assessment and the Clinical Dementia Rating (CDR) Scale.²⁰ It also involved an informant where possible. The neuropsychological assessment included frontal executive function (Trails A and B,²¹ Verbal Fluency,²² and Clock Drawing),²³ language (Boston naming short form),²⁴ constructional praxis of CERAD,²⁵ memory (Rey Auditory Verbal Learning Test with verbal recall and recognition),²⁶ recall of constructional praxis, apraxia, and agnosia.²⁵ Diagnoses were made by consensus clinical judgment according to criteria for diagnosis of MCI,¹ Age-Associated Memory Impairment (AAMI),²⁷ Age-Associated Cognitive Decline (AACD),²⁸ Mild Neurocognitive Disorder (MNC),²⁹ Impairment on the CDR,³⁰ and Other Cognitive Disorder. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria were used to assess dementia.²⁹ Importantly for this study, clinicians were blind to the diagnosis (if any) obtained at Wave 1. In addition, because a previous study³¹ investigating the same cohort has shown that

being classified as suffering from any cognitive disorder (i.e., MNC, Other cognitive disorder, AAMI, MCI, AACD, and impaired on CDR) showed a good stability during a 4-year follow-up (89% versus 29% for MCI), participants were also classified as any-mild cognitive disorder (any-MCD) to assess how predictors for this clinical group differed from those for MCI alone.

Neuropsychological Measures

The Mini-Mental State Examination. The MMSE² is the most widely used screen for dementia, it consists of 30 questions surveying orientation in time and space, IR and DR, attention, language, and praxis.

Immediate and Delayed Recall. Immediate and delayed memory were assessed using the first trial of the California Verbal Learning Test, which requires participants to remember 16 shopping list items and either recall them immediately or after a delay of 20 minutes.

Digits Span Backward. Verbal working memory was assessed with the Digits Span Backward test from the Wechsler Memory Scale, which requires participants to repeat a list three to six words in length backward.

Spot-the-Word. The Spot-the-Word (STW) test is a lexical decision task comprising 60 questions and requiring participants to indicate which of two items is a valid word. It has been shown to be an adequate estimate of premorbid abilities.³³

Symbol Digits Modalities Test. The SDMT requires participants to find in a key the digit corresponding to a specific symbol and to complete a list of 110 symbol-digit pairs. The SDMT has been found to be a significant predictor of conversion from amnesic MCI to AD over 36 months.³⁴

Simple and Choice Reaction Time. Participants performed four blocks of 20 simple reaction trials and two blocks of 20 choice reaction time (CRT) trial. As a measure of RT variability, mean absolute residuals (MARs; in milliseconds) were calculated for each individual by finding the average deviations from the mean RT for the SRT (MARS) and CRT measures. In addition, a measure of reaction time variability independent of mean performance (mean independent variability [MIVs], see Ref. 35 for a detailed description) was computed for SRT (MIV for SRT)

and for CRT using the formula $MIV = MAR(-b/RT)$ where b is the slope of the logarithmic function describing the relationship between MAR and RT.

Statistical Analysis

Descriptive analyses were conducted using χ^2 for categorical data and t tests to compare groups on continuous variables. Logistic regression analysis was used to identify significant predictors of binary group membership (cognitively healthy versus MCI or any-MCD). In the first phase, each neuropsychological measure was assessed in a univariate analysis while controlling for age, sex, and education. In the second phase, multivariate logistic regression analyses were conducted to determine which variables had the highest predictive value of conversion from normal aging to MCI, CDR 0.5, and to any-MCD while controlling for age, sex, and education. For all cognitive measures except for reaction time measures, odds ratios (ORs) were computed for 1 unit change. For mean reaction time and absolute residuals measures, the ORs were computed for a 100-millisecond change, whereas for the MIV measures, ORs were computed for a 1 SD change. The alpha level was set at $p = 0.01$.

RESULTS

Table 1 presents the demographic and neuropsychological measures of the study groups (normal, MCI, CDR 0.5, and any-MCD). Eighteen MCI, 32 CDR, and 64 any-MCD (18 MCI, 24 AAMI, 14 MNC, 3 other cognitive disorder, and 32 impaired on CDR) individuals were identified from the 2,082 participants who did not have a diagnosis at Wave 1 and who were included in the study. Fifteen participants were diagnosed with both MCI and CDR 0.5.

The predictive value of conversion to MCI, CDR, and any-MCD for each test, assessed independently of each other, while controlling for sex, age, and education is presented in Table 2. Table 3 shows the predictive values of conversion to MCI, CDR, and any-MCD for all tests assessed together in multivariate analyses (full and reduced models) while controlling for sex, age, and education. The independent variability SRT and CRT measures (MIV for SRT and

TABLE 1. Demographic, Clinical, and Genetic Characteristics of Normal, MCI, and Any-MCD Subsamples

	Normal at Wave 2 (n = 2,018)	MCI at Wave 2 (n = 18)	CDR 0.5 at Wave 2 (n = 32)	Any-MCD at Wave 2 (n = 64)
Females, n (%)	996 (49.25)	8 (44.44)	14 (43.8)	28 (43.75)
Age at Wave 1, years (SD)	62.53 (1.51)	62.22 (1.77)	62.41 (1.68)	62.53 (1.63)
Education, years (SD)	14.05 (2.67)	13.11 (2.15)	12.50 ^a (2.06)	13.13 ^a (2.36)
White, n (%)	1,850 (96.60)	15 ^b (83.30)	30 (93.75)	60 (93.80)
English-Speaking, n (%)	1,822 (90.29)	12 ^a (66.70)	27 (84.38)	54 (84.40)
MMSE				
At Wave 1 (SD)	29.37 (0.90)	29.11 ^a (0.83)	28.96 ^a (1.00)	28.92 ^a (0.98)
At Wave 2 (SD)	29.33 (0.96)	27.5 ^a (1.65)	27.73 ^a (1.68)	27.94 ^a (1.84)
Immediate Recall (SD)	7.49 (2.08)	6.17 ^a (1.89)	5.94 ^a (1.71)	5.86 ^a (1.53)
Delayed Recall (SD)	6.55 (2.33)	5.11 ^a (2.06)	4.59 ^a (1.92)	4.75 ^a (1.67)
Digits Backward (SD)	5.11 (2.19)	4.11 (2.32)	4.28 ^b (2.16)	4.27 ^a (1.96)
Spot-the-Word (SD)	52.6 (5.19)	46.97 ^a (5.73)	48.39 ^a (6.37)	48.93 ^a (6.84)
SDMT (SD)	51.16 (8.53)	45.00 ^b (10.80)	43.22 ^a (10.47)	44.86 ^a (10.07)
Simple reaction Time, milliseconds (SD)	251.80 (52.77)	291.10 (114.10)	278.10 (83.70)	276.30 ^a (71.43)
Choice reaction Time, milliseconds (SD)	316.90 (42.91)	351.30 (86.37)	344.80 ^b (68.26)	335.90 ^a (55.55)
Mean absolute residuals SRT (SD)	39.00 (20.68)	61.20 (44.85)	57.10 ^a (37.39)	53.90 ^a (31.14)
Mean absolute residuals CRT (SD)	50.70 (16.57)	65.50 ^a (22.87)	60.10 ^a (18.31)	56.00 ^b (16.38)
Mean independent variability SRT (SD)	258.80 (81.70)	315.20 ^a (96.45)	323.00 ^a (107.47)	305.6 ^a (97.47)
Mean independent variability CRT (SD)	157.60 (55.41)	182.90 (35.70)	171.80 (32.53)	162.8 (33.26)

^a *t* test, significantly different from normal sample: ^a*p* < 0.01 and ^b*p* < 0.05.

TABLE 2. Baseline Neuropsychological Predictors (Assessed Individually) of Transition From Normal Aging to MCI and Any-MCD Adjusted for Age, Sex, and Education

Predictors	MCI		CDR 0.5		Any-MCD	
	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p
MMSE at Wave 1	0.82 (0.54–1.26)	0.365	0.78 (0.58–1.05)	0.104	0.72 (0.59–0.82)	0.002
Immediate Recall (1st trial CVLT)	0.71 (0.53–0.93)	0.016	0.67 (0.53–0.83)	0.001	0.63 (0.53–0.73)	0.001
Delayed Recall (1st trial CVLT)	0.74 (0.58–0.95)	0.017	0.65 (0.53–0.79)	0.001	0.67 (0.58–0.77)	0.001
Digits Span Backward	0.81 (0.64–1.03)	0.091	0.87 (0.73–1.04)	0.132	0.85 (0.75–0.96)	0.010
Spot-the-Word	0.89 (0.84–0.94)	0.001	0.91 (0.87–0.96)	0.001	0.91 (0.88–0.95)	0.001
SDMT	0.93 (0.88–0.98)	0.006	0.92 (0.88–0.95)	0.001	0.93 (0.90–0.95)	0.001
SRT	2.20 (1.30–3.69)	0.003	1.85 (1.17–2.91)	0.001	1.83 (1.30–2.57)	0.001
CRT	1.98 (1.19–3.29)	0.008	1.95 (1.27–2.99)	0.002	1.80 (1.27–2.55)	0.001
MARS	9.80 (3.26–29.45)	0.001	7.70 (3.12–18.99)	0.001	6.52 (3.19–13.34)	0.001
MARC	1.63 (0.96–2.77)	0.069	1.62 (0.98–2.67)	0.061	1.45 (0.90–2.32)	0.124
MIVS	1.61 (1.18–2.19)	0.002	1.64 (1.29–2.07)	0.000	1.50 (1.25–1.80)	0.001
MIVC	1.20 (1.01–1.41)	0.034	1.18 (1.00–1.38)	0.046	1.50 (1.25–1.80)	0.001

Notes: For mean RT and mean absolute residuals measures, ORs were computed for 100-millisecond change. For mean independent variability measures, ORs were computed for a 1 standard deviation change. Significance assessed with Wald test, *df* = 1. MARC: mean adjusted residuals for CRT; MIVS: mean independent variability for SRT; MIVC: mean independent variability for CRT adjusted for age, sex, and education ORs computed for 1 unit change for all measures except RT.

MIV for CRT) did not enter the model because these measures were too highly intercorrelated with the nonadjusted SRT and CRT mean residual measures (MARS). For MCI two measures, STW and MARS, were significant predictors, showing that every additional word correctly identified was associated with a 11% decreased risk, whereas every additional 100 milliseconds residual for SRT was associated with a 741% increased risk of conversion to

MCI. For CDR three measures, DR, SDMT, and MARS, were significant predictors, showing that every additional word recalled was associated with a 42% decreased risk, every additional symbol correctly transcribed was associated with a 5% decreased risk, and every additional 100 milliseconds residual for SRT was associated with a 406% increased risk of conversion to MCI. For any-MCD four measures: immediate recall, STW, SDMT, and

TABLE 3. Baseline Neuropsychological Predictors (Multivariate Analyses) of Transition From Normal Aging to MCI, CDR 0.5, and Any-MCD Adjusted for Age, Sex and Education (Full and Reduced Models)

Diagnoses	MCI			CDR 0.5			Any-MCD		
	Full		Reduced	Full		Reduced	Full		Reduced
	Sig.	Odds Ratio	Sig.	Sig.	Odds Ratio	Sig.	Sig.	Odds Ratio	Sig.
MMSE at Wave 1 (SD)	0.415	0.126 (0.73-2.17)		0.561	1.12 (0.76-1.66)		0.817	0.97 (0.75-1.26)	
Immediate Recall (SD)	0.504	0.86 (0.55-1.34)		0.540	0.90 (0.65-1.25)		0.041	0.78 (0.62-0.99)	0.001
Delayed Recall (SD)	0.560	0.89 (0.60-1.32)		0.044	0.74 (0.55-0.99)	0.001	0.083	0.83 (0.67-1.03)	
Digits Span (SD)	0.848	0.97 (0.74-1.27)		0.561	1.06 (0.87-1.29)		0.832	1.02 (0.88-1.17)	
Back (SD)	0.003	0.90 (0.84-0.97)	0.001	0.100	0.94 (0.88-1.01)		0.036	0.95 (0.91-0.99)	0.029
Spot-the-Word (SD)	0.516	0.98 (0.92-1.04)		0.058	0.96 (0.91-1.02)	0.016	0.045	0.97 (0.94-0.99)	0.019
SDMT (SD)	0.635	0.71 (0.17-2.87)		0.140	0.41 (0.13-1.34)		0.207	0.58 (0.25-1.35)	
Simple RT, milliseconds (SD)	0.979	0.98 (0.23-4.18)		0.328	1.74 (0.56-5.25)		0.371	1.46 (0.64-3.38)	
Choice RT, milliseconds (SD)	0.046	9.27 (1.04-82.52)	0.000	0.009	10.85 (1.82-64.39)	0.008	0.003	7.52 (1.96-28.89)	0.003
MARS (SD)	0.801	1.23 (0.25-6.15)		0.534	0.61 (0.13-2.87)		0.279	0.46 (0.11-1.87)	
MARC (SD)									
Model fit ^a	R^2 change, 0.13 ^b	-2 Log likelihood, 176.66	R^2 change, 0.12 ^b	-2 Log likelihood, 178.64	-2 Log likelihood, 275.63	R^2 change, 0.14 ^b	-2 Log likelihood, 280.68	-2 Log likelihood, 489.96	R^2 change, 0.13 ^c

Notes: Wald test is used to assess contribution of individual predictors ($df = 1$), χ^2 test is used to assess model (full: $df = 13$). MARC: mean adjusted residuals for CRT adjusted for age, sex, and education.

^aNagelkerke R^2 change from initial model with covariates.

^b $p < 0.001$.

^c $p < 0.01$.

MARS were significant predictors, showing that every additional word recalled was associated with a 28% decreased risk, every additional word correctly identified was associated with a 5% decreased risk, every additional symbol correctly transcribed was associated with a 4% decreased risk, and every additional 100 milliseconds residuals in the simple reaction time (SRT) task were associated with a 48% increased risk of conversion to MCI.

The previous multivariate analyses were conducted on raw scores for easier interpretations. However, to compare their relative predictive strength, the same analyses were recomputed on standardized scores producing the following ORs for MCI: STW (OR, 0.56; 95% confidence interval [CI]: 0.40–0.77, $p = 0.001$) and MARS (OR, 1.55; 95% CI: 1.21–2.00, $p = 0.001$), for CDR: DR (OR, 0.43; 95% CI: 0.26–0.71, $p = 0.001$), SDMT (OR, 0.63; 95% CI: 0.44–0.92, $p = 0.016$), and MARS (OR, 1.36; 95% CI: 1.08–1.71, $p = 0.008$), and for MCD: Immediate Recall (OR, 0.45; 95% CI: 0.32–0.64, $p = 0.001$), STW (OR, 0.77; 95% CI: 0.61–0.97, $p = 0.029$), SDMT (OR, 0.72; 95% CI: 0.55–0.95), and MARS (OR, 1.32; 95% CI: 1.10–1.58, $p = 0.003$).

Post-Hoc Analyses

The predictive value of MARs for SRT was assessed for each of the four blocks of trials, but none of them produced stronger ORs than their average used in the above analyses.

We ran further analyses on the whole sample of participants for whom neuropsychological tests were available at baseline (irrespective of their baseline diagnosis) and who either were screened as negative or who accepted the full clinical assessment in the second wave of measurement ($N = 2,018$, MCI = 56, CDR = 52, any-MCD = 95). ORs were generally similar for all measures: Immediate Recall (any-MCD: OR, 0.62; 95% CI: 0.55–0.69, $p = 0.001$), IR (CDR: OR, 0.60; 95% CI: 0.51–0.70, $p = 0.001$), similar for STW (MCI: OR, 0.89; 95% CI: 0.85–0.94, $p = 0.001$; any-MCD: OR, 0.95; 95% CI: 0.91–0.98, $p = 0.003$), SDMT (CDR: OR, 0.60; 95% CI: 0.51–0.70, $p = 0.004$; any-MCD: OR 0.96; 95% CI: 0.94–0.99, $p = 0.003$), and response variability on the SRT task (MCI: OR, 6.92; 95% CI: 2.57–18.61, $p = 0.001$; CDR: OR 2.94;

95% CI: 1.15–7.52, $p = 0.024$; any-MCD: OR, 3.05; 95% CI: 1.38–6.72, $p = 0.006$).

Finally, to assess the sensitivity and specificity of the most significant predictors (response variability, IR and DR, and STW), we computed a composite measure (z score average) and conducted sensitivity/specificity analyses. Receiver operating characteristic curves for the different clinical groups are presented in Figure 2. The composite measure performed systematically better than the MMSE. Areas under the curve were composite = 0.767, MMSE = 0.606 for MCI; composite = 0.800, MMSE = 0.633 for CDR 0.5; composite = 0.801, MMSE = 0.643 for any-MCD.

DISCUSSION

The aim of this study was to assess the value of individual neuropsychological tests in predicting conversion during a 4-year period from normal cognition to mild cognitive deficits including MCI, CDR 0.5, and any-MCD. Two main findings were produced. First, the pattern of impairment in neuropsychological tests were remarkably similar across the clinical groups, suggesting that these groups share many similar features. Second, although most tests investigated were significant predictors of all clinical categories, IR/DR, STW, SDMT, and MARs for SRT were particularly sensitive to conversion.

Three clinical categories were investigated: MCI, CDR 0.5, and any-MCD. MCI was assessed based on the criteria proposed by the International Consensus Conference (memory complaints, normal activity of daily living, normal general cognition, abnormal memory for age, and no dementia). The MCI diagnosis has been very useful in identifying individual at higher risk of developing dementia. At least 20%–40% of individuals with MCI will convert to AD within a few years, and MCI and AD are known to share similar risk factors. However, the usefulness of an MCI diagnosis has also been questioned because it has been found not to be always very stable with some studies showing substantial proportions of those diagnosed with MCI and who have not developed dementia reverting to a “normal cognition” status.^{31,36} The CDR scale is popular in clinical settings because it is simple, structured, and relatively short. It relies on the assessment of six domains:

FIGURE 2. Receiver Operating Characteristic Curves for the Composite Cognitive Measure (z-Score Average of Response Variability, Immediate and Delayed Recall, and Spot-the-Word) and for the MMSE for the Different Clinical Categories: MCI (Top), CDR 0.5 (Middle), Any-MCD (Bottom)

Memory, Orientation, Judgment and Problem solving, Community Affairs, Home and Hobbies, and Personal Care. A CDR of 0.5 is thought to be similar to a diagnosis of MCI, but recent studies suggest that CDR 0.5 is a more inclusive category than MCI³⁷ although Quadri et al.³⁸ demonstrated conversion rates from CDR 0.5 to dementia similar to those from MCI. Finally, a clinical category including all those with some MCD diagnosis (any-MCD) including, AAMI, MND, AACD, MCI, and CDR was also investigated because recent studies showed that this category was more stable than MCI with 89% of cases meeting the same criteria in a 4-year follow-up compared with only 29% for MCI, and because MCI and any-MCD were also found to share a large number of health and life style risk factors in the same cohort,³⁹ suggesting some common origin. Thus MCI, CDR 0.5, and any-MCD were seen as overlapping and progressively more inclusive and less specific categories of MCDs, which may carry a shared risk of progression to dementia.

The results of this study bring more support to this view by showing that most cognitive variables assessed here share a common predictive value across the three clinical categories, such that if we examine the most predictive measures, every 100 milliseconds increase in SRT variability was associated with a six to ninefold increased risk of conversion to MCI, CDR 0.5, and any-MCD, whereas every additional word recalled was associated with a 35%–58% decreased risk of conversion, and every additional word correctly identified as word was associated with a 10%–11% decreased risk of conversion to any of these clinical categories. Similar patterns were also found in the other predictors, and although no single measure was sufficiently sensitive to be used as individual predictor of cognitive impairment, a composite measure based on the most predictive variables achieved respectable psychometric properties and was substantially more sensitive than the MMSE.

The major aim of this study was to identify the most sensitive cognitive predictors of transition from healthy cognitive ageing to mild impairment, however, defined. It was found that variability in reaction time for SRT (MARS), IR/DR, STW, and SDMT were the best predictors across all categories. These measures assess different but somewhat overlapping domains (variability in speed of processing, memory, lexical decision, and label identification and substi-

tution). Although their impairment has been demonstrated in dementia, what seems to make them particularly predictive in the present context is their broader scale, which directly affects their sensitivity. SRT variability is a continuous measure, and DIX, STW, and SDMT assess a large number of items (15, 110, and 128, respectively), because these measures cover a broad behavioral range they appear more able to index subtle interindividual variability not easily detected by other measures. For instance, the MMSE, which has proven to be an effective tool in screening individuals already suffering from dementia,¹¹ has proven comparatively insensitive to MCI.¹² This is again supported by the present findings showing that the MMSE has nonsignificant or low predictive values, and it can be easily understood because every 1-point change on the 30-point MMSE scale involves a substantial mistake on an item that may assess a very different domain such as forgetting where one is, the date, or not being able to follow simple instructions. In contrast, changes in variability, word recall, and word recognition are more fine grained and may enable discrimination among small differences in cognitive performance in a single relevant domain. When all measures are considered together across clinical categories and in light of their psychometric characteristics, SRT variability is the most sensitive of all measures.

It is particularly interesting to note that the measure of MARS was a better predictor of cognitive impairment than reaction time or MIV (measures of variability corrected for reaction time). This could suggest that response variability is substantially independent of overall reaction time in young-old populations. However, because a strong correlation is present between reaction time and MARS in this cohort ($r = 0.77$, $p < 0.001$), a more adequate explanation is that MARS integrates information relating to speed of processing and to response variability specifically associated with neuropsychological and neuroanatomical changes associated with MCI and any-MCD.

It should also be noted that the predictors identified in this study were assessed in a sample that had been screened as cognitively normal at baseline only 4 years earlier, consequently it may reasonably be expected that their predictive value would be substantially higher in a random sample not previously screened for cognitive impairment. Post-hoc anal-

yses using the same cohort but without excluding those participants who had a diagnosis or who refused full clinical assessment at baseline (but not in the second wave of data collection) supported this hypothesis because model fit was much improved in these analyses.

Previous studies have suggested that the STW task is a good measure of premorbid intelligence in elderly populations,³³ the present findings suggest this might not always be the case. If performance on the STW task can predict cognitive impairment 4 years later, it is unlikely this task is an unbiased measure of premorbid intelligence. It could be argued that because education is related to cognitive abilities, and because it has been shown to be protective of cognitive impairment and dementia, performance on the STW task predicts cognitive impairment through its association with education.⁴⁰ However, because the effect of education level was controlled for in the present analyses, the STW predictive value described here seems to be independent and having an effect above and beyond that of education. Nevertheless, it is possible that lower STW performance reflects some portion of premorbid intelligence not accounted for by education and that lower intelligence is associated with a higher risk of cognitive impairment.

Another point worthwhile noting is that non-English speaking individuals were overrepresented in the MCI group in this cohort. The reason for this effect is unclear, but it may be mediated by sociodemographic factors and warrants further investigation.

There were a number of limitations to this study. The number of participants who converted to MCI during 4 years was relatively small and may not be representative of the broader MCI population. However, the fact that predictors of any-MCD, a clinical group almost four times as large as the MCI group, were consistent with the predictors of MCI might suggest otherwise. Moreover, the post-hoc analysis assessing predictors in the larger cohort, which included individuals who had a diagnosis at baseline, also suggests that the present findings might be generalizable to other populations. In addition, the use of the neuropsychological tests in the two-stage diagnostic procedure might imply that the predictors were not independent of the diagnosis. However, all participants who screened positive and went on to be diagnosed with an impairment at baseline were excluded from the main analysis. The diagnosis proce-

dures used in the second wave of data collection was blind to performance at baseline, so it can be reasonably assumed that follow-up diagnoses were independent of baseline predictors. It is notable that the absolute residual reaction time measures, which were among the more sensitive predictors, were not used at all in either baseline or follow-up screening or clinical assessments.

This study also had strengths. Its sample was large and sourced from a community-based randomly selected sample; therefore, unlike studies based on memory clinics, it is more likely to provide information relevant to community screening assessment and could be even more sensitive in clinical environments. Because the participants surveyed were comparatively young for a study of this type, it also provides important information to target young populations when prevention of cognitive impairment is the goal.

In conclusion, performance on the DR and STN tasks and reaction time variability in SRT were shown to be important predictors of conversion from

normal cognitive aging to MCI, CDR 0.5, and any-MCD 4 years later in a large community-based sample. This study also provides evidence of shared characteristics between the clinical categories examined and important normative data for comparison in other investigations. Future studies of even longer duration should be conducted to further assess the sensitivity of these tasks in the early detection of cognitive impairment in aging.

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