

Screening properties of the German IQCODE with a two-year time frame in MCI and early Alzheimer's disease

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ABSTRACT

Background: The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is a widely used screening tool for dementia. We aimed to determine the ability of the German version of the 16-item IQCODE with a two-year time frame to discriminate healthy mature control participants (NC) from mild cognitive impairment (MCI) and probable early Alzheimer's disease (AD) patients (all with Mini-mental State Examination (MMSE) scores $\geq 24/30$) and to optimize diagnostic discriminability by shortening the IQCODE.

Methods: 453 NC (49.7% women, age = 69.5 years \pm 8.2, education = 12.2 \pm 2.9), 172 MCI patients (41.9% women, age = 71.5 years \pm 8.8, education = 12.3 \pm 3.1) and 208 AD patients (59.1% women, age = 76.0 years \pm 6.4, education = 11.4 \pm 2.9) participated. Stepwise binary logistic regression analyses (LR) were used to shorten the test. Receiver operating characteristic curves (ROC) determined sensitivities, specificities, and correct classification rates (CCRs) for (a) NC vs. all patients; (b) NC vs. MCI; and (c) NC vs. AD patients.

Results: The mean IQCODE was 3.00 for NC, 3.35 for MCI, and 3.73 for AD. CCRs were 85.5% (NC-patient group), 79.9% (NC-MCI), and 90.7% (NC-AD), respectively. The diagnostic discriminability of the shortened 7-item IQCODE (i.e. items 1, 2, 3, 5, 7, 10, 14) was comparable with the longer version (i.e. 7-item CCRs: NC-patient group: 85.3%; NC-MCI: 80.1%, NC-AD: 90.5%).

Conclusions: The German 16-item IQCODE with two-year time frame showed excellent screening properties for MCI and early AD patients. An abbreviated 7-item version demonstrated equally high diagnostic discriminability, thus allowing for more economical screening.

Key words: informant report, dementia screening, cognition, cognitive decline

Introduction

A diagnostic criterion for dementia is evidence that cognitive functioning has declined from a previous, higher level. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is a well-established and widely used informant-based screening tool designed to estimate cognitive decline from a previous level of functioning (Jorm *et al.*, 1989; Jorm, 2004). Its administration is recommended to supplement the patient's clinical findings and especially in cases where direct patient

testing is difficult (e.g. comprehension difficulties) and for patients with very low levels of education (Fuh *et al.*, 1995; Senanarong *et al.*, 2001; Perroco *et al.*, 2009). The IQCODE exists in two forms – a longer 26-item and a shorter 16-item version – and requires the informant to rate the patient's cognitive decline from a previous level over the last 10 years on a five-point scale from “much improved” (1) to “much worse” (5), where a score of 3 represents a “no change” judgment. Its validity has been established in longitudinal studies where mean IQCODE scores were significantly correlated with cognitive performance on a number of different neuropsychological tasks (for an overview, see Jorm, 2004). Since its inception, the IQCODE has become one of the most frequently used and best-studied informant-based screening tools and has been translated into several different languages including Dutch, French, Spanish, Italian, Thai

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and Chinese (de Jonghe *et al.*, 1997; Law and Wolfson, 1995; Del-Ser *et al.*, 1997; Isella *et al.*, 2002; Senanarong *et al.*, 2001; Fuh *et al.*, 1995, respectively).

IQCODE informants are typically required to base their judgments of changes in the patient's functioning on a 10-year time interval, although a five-year (Barba *et al.*, 2000; Pisani *et al.*, 2003) or variable (Patel *et al.*, 1993) time interval has been used to address different questions. However, in dementia screening, judgments of changes in a patient's functioning over a 10-year time interval are often confounded by multiple changes associated with retirement (Calero-Garcia *et al.*, 2007). Additionally, it may be difficult for informants to remember patients' cognitive performance over this long time period (Coughlin, 1990). Given these potential confounds, and advancements in the early detection and treatment of dementia, a shorter time-frame for informant judgments appears more appropriate for the screening of dementia symptoms with the IQCODE.

The goals of the present study were to determine the diagnostic discriminability of the German 16-item version of the IQCODE with a two-year observation interval to discriminate between healthy older individuals and those with cognitive changes impacting on daily functioning, i.e. mild cognitive impairment (MCI) or a probable Alzheimer's disease (AD) patients. A two-year-observation interval was selected for the reasons outlined above, and corresponded to the test-retest interval of the healthy participants in the present study, all of whom were members of the longitudinal BASEL study (Basel Study on the ELderly; Monsch *et al.*, 2000; see also Shultz *et al.*, 1998). Since, to our knowledge, no normative data on the German IQCODE exist, we collected IQCODE data from informants of healthy older participants. These normative data allowed us to quantify the judgments of significant others (spouses, carers, etc) regarding changes in healthy older individuals' cognitive functioning and thus provided us with a baseline for interpreting rated changes in MCI and AD patients' cognitive functioning. To ensure that the earliest possible stages of cognitive changes were studied, we only included individuals with MMSE (Minimal Status Examination; Folstein *et al.*, 1975) scores $\geq 24/30$. We aimed to determine optimal cut-off scores to discriminate healthy individuals from both patient groups, and to determine which cut-off scores best differentiated MCI and AD patients from the healthy older individuals. Finally, we also explored whether it was possible to significantly reduce the number of IQCODE items while retaining its diagnostic discriminability in an attempt to develop a more economical dementia screening tool.

Methods

Participants and procedures

HEALTHY AGED PARTICIPANTS

As part of the BASEL study (Basel Study on the ELderly; Monsch *et al.*, 2000), a longitudinal study assessing cognitive performance in older individuals, a large number of healthy individuals (NC) were neuropsychologically tested with the Consortium to Establish a Registry on Alzheimer's Disease Neuropsychological Assessment Battery (CERAD-NAB; Morris *et al.*, 1988; 1989; Welsh *et al.*, 1994) and were assessed with a detailed medical history questionnaire. While collecting the informant anamnesis, the accompanying significant other of 453 NC study participants (see Table 1) filled out the German 16-item IQCODE with a two-year time frame. All NC participants fulfilled the following inclusion criteria: they spoke German as their first language; obtained z-scores ≤ -1.96 (2.5th percentile) in no more than one of the 11 CERAD-NAB variables; and were in good general health, i.e. had no current systemic illnesses, no psychiatric problems, no diseases interfering with the administration of neuropsychological tests (e.g. severe hearing or visual deficits), no diseases of the central nervous system (CNS), no diseases or events during life which could have negatively impacted CNS activity; and did not suffer from depression according to the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994) as assessed with a standardized questionnaire (Kühner, 1997). See Table 1 for demographic characteristics of the NC sample.

The project was approved by the local Ethics Committee, and written informed consent was obtained from all participants.

PATIENTS WITH MCI AND VERY MILD TO MILD DEMENTIA

Data from two groups of patients from the Memory Clinic of the University Hospital Basel were available for analysis: 215 individuals with a diagnosis of MCI according to the Winblad *et al.* criteria (2004) and 267 patients with a diagnosis of probable AD according to the criteria outlined by the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann *et al.*, 1984) and DSM-IV criteria for AD (American Psychiatric Association, 1994). MCI and AD patients had undergone extensive standardized neuropsychological testing and medical examinations including neurological, neuroimaging and laboratory tests as part of their routine clinical workup (Monsch *et al.*, 1995). To

Table 1. Demographic characteristics of healthy mature individuals (NC), patients with mild cognitive impairment (MCI), and patients with probable Alzheimer's disease (AD)

	NC (N = 453)	MCI (N = 172)	AD (N = 208)	DIFFERENCES WITH $p < 0.05$ †
Age (years) \pm SD	69.5 \pm 8.2	71.5 \pm 8.8	76.0 \pm 6.4	NC < MCI < AD
Gender (% male)	50.3	58.1	40.9	MCI > AD
Education (years) \pm SD	12.2 \pm 2.9	12.3 \pm 3.1	11.4 \pm 2.9	NC, MCI > AD
MMSE \pm SD	28.9 \pm 1.2	27.9 \pm 1.7	26.0 \pm 1.6	NC > MCI > AD
min-max	24-30	24-30	24-30	
IQCODE-mean \pm SD	3.00 \pm 0.26	3.35 \pm 0.36	3.73 \pm 0.46	NC < MCI < AD
Source of information				Differences with $p < 0.05$ †
Spouse, n (%)	330 (72.8)	121 (70.3)	119 (57.2)	NC, MCI > AD
Child, n (%)	41 (9.1)	29 (16.9)	62 (29.8)	NC < MCI < AD
Friend, n (%)	40 (8.8)	7 (4.1)	11 (5.3)	NC > MCI
Other, n (%)	42 (9.3)	15 (8.7)	16 (7.7)	

MMSE = Mini-mental State Examination (Folstein *et al.*, 1975)

† Comparisons using t test (continuous variables) or χ^2 (discrete variables).

determine the ability of the IQCODE to correctly classify cognitively impaired individuals in the early stage of the disease process, we only included data from patients with MMSE scores $\geq 24/30$, i.e. in the same range as the NC participants. The IQCODE (16 items, two-year observation period) was completed by the informants while the respective patient was neuropsychologically tested. Since the NC questionnaires had no missing items, only the IQCODE data from 172 MCI and 208 AD patients with completely filled in questionnaires were included in the analyses.

A comparison of complete vs. incomplete IQCODEs in the MCI group revealed that only Item 1 received a lower mean score in individuals with complete compared to incomplete questionnaires (3.78 vs. 3.87; t [209] = -2.492, $p = .013$ (two-tailed)). In the AD group, there was a difference in overall mean IQCODE score (3.73 vs. 3.92; t [265] = -2.73, $p = 0.007$) as well as lower mean scores on items 1 (3.78 vs. 4.05; t [263] = -2.539, $p = 0.012$), 2 (4.10 vs. 4.33; t [263] = -2.017, $p = 0.045$), 5 (3.64 vs. 3.91; t [263] = -2.696, $p = 0.007$), 6 (3.82 vs. 4.07; t [263] = -2.273, $p = 0.024$), 7 (4.06 vs. 4.36; t [261] = -2.755, $p = 0.006$), and 12 (3.61 vs. 3.93; t [262] = -2.919, $p = 0.039$) for patients with complete compared to incomplete questionnaires. The IQCODE mean was calculated according to standard procedures by dividing the sum of all items by the number of completed items (cf. Jorm 2004). Thus, the estimated cognitive decline was greater for patients with missing items on the IQCODE in both patient groups. Importantly, the

demographic status of patients with complete vs. incomplete questionnaires did not differ in both groups. Because of our goal to detect cognitive decline as early as possible, we included only complete questionnaires in our study.

The demographic characteristics and information regarding the informants of the final patient groups are listed in Table 1. Of note are the mean education levels of the final participant groups: NC sample = 12.2 (2.9) years; MCI sample = 12.3 (3.1); AD sample = 11.4 (2.9).

Statistical analyses

Following the descriptive statistics on the mean IQCODE score, we calculated binary logistic regressions and receiver operating characteristic (ROC) curves to determine the ability of the IQCODE to discriminate between (a) the NC and entire patient group (i.e. MCI and AD); (b) the NC and MCI groups; and (c) the NC and AD groups. The cut-off values in the logistic regression were determined by the proportions of the respective group sizes and were 0.46 (NC vs. all patients), 0.28 (NC vs. MCI), and 0.32 (NC vs. AD). The confidence intervals for sensitivities and specificities were calculated following the exact method described in Clopper and Pearson (1934).

The most common and practical IQCODE scoring method in the clinical setting is the simple mean score. We aimed to determine how well the simple average of IQCODE items discriminated healthy controls from patients in the earliest stages of a degenerative illness compared to a

statistically more sophisticated scoring system in which IQCODE items were weighted according to their diagnostic relevance. We therefore performed a binary logistic regression analysis of all 16 items and compared the diagnostic discriminability of this model with that of the simple mean. Finally, a binary logistic regression model (backward stepwise elimination using the WALD statistic, exclusion criterion: $p = 0.10$; inclusion criterion: $p = 0.05$) was used to identify a subset of items which optimally differentiated NC individuals from patients. Thus, this final model included only significant predictors.

The areas under the ROC curves of the 16-item and shorter IQCODE versions were compared using Hanley and McNeil's (1983) method to test for differences in the correct classification of individuals. We computed 1000 bootstrap replicates (Efron, 1979) to estimate the variability of the cut-off scores.

All statistical analyses were conducted with SPSS 15.0 (SPSS Inc., Chicago, IL) and the freely available software package R (www.cran.r-project.org).

Results

Using the German 16-item version of the IQCODE, significant others rated NC participants on average as having displayed no changes in cognitive functioning over the two-year observation period (IQCODE: mean 3.00, SD 0.26). The mean IQCODE scores were 3.56 (SD 0.46) for both patient groups combined, 3.35 (SD 0.36) for the MCI group and 3.73 (SD 0.46) for the AD patients. Thus, overall, cognitive changes in the preceding two years were rated as more negative in the MCI group than the NC group ($t [240.12] = -11.81$, $p < 0.0001$ (two-tailed) and more negative in the AD than the MCI patients ($t [376.47] = -8.89$, $p < 0.0001$ (two-tailed)). Interestingly, 68% of NC participants were rated as having exhibited no changes or an improvement in functioning (IQCODE mean ≤ 3.00) compared to only 15% of MCI and 2.4% of AD patients.

The results of the binary logistic regression analyses aiming to discriminate NC from patient groups are shown in Table 2(a-c). This table also lists values for the areas under the ROC curves constructed using mean IQCODE scores, and the corresponding optimal cut-off scores. The correct classification rates (CCRs) of the mean 16-item IQCODE were 85.5% for the discrimination of NC from all patients, 79.9% for the discrimination of NC and MCI, and 90.7% for NC vs. AD. An analysis of the areas under the ROC curves following Hanley and McNeil (1983) demonstrated

that the mean IQCODE (16 items) was superior to the MMSE in its ability to discriminate NC from all patients ($z = 5.82$; $p < 0.0001$), NC from MCI ($z = 5.36$; $p < 0.0001$) and NC from AD patients ($z = 3.48$, $p < 0.001$). Thus, based on the predetermined equal weighting of sensitivity and specificity, bootstrap resampling generated an optimal cut-off score of 3.19 to differentiate NC from all patients. This cut-off score was reached by 67% of the bootstrap samples, whereas 33% resulted in the next higher cut-off score of 3.25.

The cut-off score of 3.19 also optimally differentiated NC from MCI individuals (88% of bootstrap samples), whereas 10% of bootstrap samples resulted in the next higher cut off score of 3.25, and 2% resulted in the next smaller cut-off score of 3.13. In the differentiation of NC from AD, 44% of bootstrap samples resulted in an optimal cut-off score of 3.25, while 31% of bootstrap samples generated the next higher score (3.31), 21% the next lower score (3.19) and 3% the score of 3.38. A comparison of the areas under the ROC curves demonstrated that the linear combination of 16 items differentiated groups as well as the mean of the 16 items (NC vs. all patients: $z = 0.10$, $p = 0.92$; NC vs. MCI: $z = 0.43$, $p = 0.67$; NC vs. AD: $z = 0.36$, $p = 0.72$).

To explore the possibility of generating a shorter version of the IQCODE with high diagnostic discriminability, we performed a binary logistic regression with backward stepwise elimination. This analysis resulted in an 8-item version (IQCODE items 1, 2, 3, 4, 5, 7, 10 and 14) which optimally distinguished NC individuals from all patients. Since the negative weighting of Item 4 in the regression equation resulted in a rating of "worsening" adding positively to the mean, this item was also eliminated, such that only items 1, 2, 3, 5, 7, 10 and 14 remained in the final model (see Table 3). The following equation best discriminated the groups of NC and all patients: $-20.051 + (1.135 \cdot IQ1) + (0.682 \cdot IQ2) + (1.143 \cdot IQ3) + (0.694 \cdot IQ5) + (0.713 \cdot IQ7) + (0.616 \cdot IQ10) + (1.085 \cdot IQ14)$ (where $IQ_x = IQCODE\text{-item Nr. } x$). The following equation describes the optimal differentiation of NC from MCI with these items: $-18.589 + (1.175 \cdot IQ1) + (0.829 \cdot IQ2) + (0.828 \cdot IQ3) + (0.432 \cdot IQ5) + (0.822 \cdot IQ7) + (0.398 \cdot IQ10) + (0.999 \cdot IQ14)$. Finally, the optimal differentiation of NC from AD was achieved with the following equation: $-26.809 + (1.16 \cdot IQ1) + (0.398 \cdot IQ2) + (1.766 \cdot IQ3) + (1.65 \cdot IQ5) + (0.418 \cdot IQ7) + (1.063 \cdot IQ10) + (1.393 \cdot IQ14)$. By applying these formulae to participants' data, CCRs of 86.4% (NC vs. all patients), 80.2% (NC vs. MCI) and 92.0% (NC vs. AD) were reached (see Table 2). Significantly, comparisons of AUCs

Table 2. Diagnostic discriminability of the Mini-mental State Examination, 16-item and 7-item IQCODE as estimated by the results of a binary logistic regression analysis (sensitivity, specificity, correct classification rate), areas under receiver operating characteristic curves, as well as corresponding cut-off-scores

	SENSITIVITY (95% CI)	SPECIFICITY (95% CI)	ROC (AUC) CCR (95% CI)	CUT-OFF
(a) differentiation of healthy mature individuals and all patients (i.e. MCI and probable AD)				
MMSE	60.8 (55.7–65.7)	88.7 (85.5–91.5)	74.8 0.806 (0.776 – 0.836)	27.5
16 item IQCODE linear combination score	80.8 (76.5–84.6)	91.2 (88.2–93.6)	86.0 0.912 (0.890 – 0.934)	
Mean 16-item IQCODE	78.4 (73.9–82.5)	92.5 (89.7–94.8)	85.5 0.911 (0.889 – 0.933)	3.19
7-item IQCODE linear combination score	82.6 (78.4–86.3)	90.1 (86.9–92.7)	86.4 0.906 (0.883–0.929)	
Mean 7-item IQCODE	76.1 (71.4–80.3)	94.5 (92.0–96.4)	85.3 0.907 (0.884 – 0.929)	3.43
(b) Differentiation of healthy mature individuals and patients with MCI				
MMSE	57.6 (49.8 – 65.1)	70.4 (66.0–74.6)	64.0 0.677 (0.628–0.726)	28.5
16-item IQCODE linear combination score	75.0 (67.8–81.3)	89.0 (85.7–91.7)	82.0 0.854 (0.814–0.894)	
Mean 16-item IQCODE	72.1 (64.8–78.7)	87.6 (84.3–90.5)	79.9 0.848 (0.808–0.888)	3.19
7-item IQCODE linear combination score	75.0 (67.8–81.3)	85.4 (81.8–88.6)	80.2 0.840 (0.798–0.883)	
Mean 7-item IQCODE	75.0 (67.8–81.3)	85.2 (81.6–88.4)	80.1 0.842 (0.801–0.883)	3.29
(c) Differentiation of healthy mature individuals and patients with probable AD				
MMSE	81.7 (75.8–86.7)	88.7 (85.5–91.5)	85.2 0.912 (0.889–0.936)	27.5
16-item IQCODE linear combination score	87.5 (82.2–91.7)	94.5 (92.0–96.4)	91.0 0.966 (0.949–0.983)	
Mean 16-item IQCODE	88.9 (83.9–92.9)	92.5 (89.7–94.8)	90.7 0.964 (0.946–0.981)	3.25
7-item IQCODE linear combination score	89.4 (84.4–93.3)	94.5 (92.0–96.4)	92.0 0.960 (0.942–0.978)	
Mean 7-item IQCODE	86.5 (81.1–90.9)	94.5 (92.0–96.4)	90.5 0.960 (0.942–0.978)	3.43

IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; MCI = mild cognitive impairment; AD = Alzheimer's disease; CI = Confidence interval; CCR = correct classification rate; ROC = receiver operating characteristic; AUC = area under curve; MMSE = Mini-mental State Examination

Table 3. The 7-item IQCODE questions whose diagnostic discriminability equals that of the longer 16-item version

1	Remembering things about family and friends, e.g. occupations, birthdays, addresses
2	Remembering things that have happened recently
3	Recalling conversations a few days later
5	Remembering what day and month it is
7	Remembering where to find things which have been put in a different place from usual
10	Learning new things in general
14	Handling financial matters, e.g. the pension, dealing with the bank

of the 16-item and 7-item linear combination IQCODE scores demonstrated that both solutions discriminated participant groups equally well (NC vs. all patients: $z = 0.82$, $p = 0.41$; NC vs. MCI: $z = 0.57$, $p = 0.57$; NC vs. AD: $z = 0.42$, $p = 0.67$).

The CCR of the mean 7-item version were 85.3% (NC vs. all patients), 80.1% (NC vs. MCI) and 90.5% (NC vs. AD) (see Table 2). Thus, no change or an improvement in cognitive functioning (IQCODE mean ≤ 3.00) was apparent in 70% of NCs compared to 18% of MCI and 2.4% of AD patients. The quality of these classifications – as judged by an AUC comparison – was comparable to that of the mean 16-item version (NC vs. all patients: $z = 0.60$, $p = 0.55$; NC vs. MCI: $z = 0.43$; $p = 0.67$; NC vs. AD: $z = 0.53$; $p = 0.60$)

as well as the linear combination of the 7 IQCODE items (NC vs. all patients: $z = 0.06$, $p = 0.99$; NC vs. MCI: $z = 0.18$; $p = 0.86$; NC vs. AD: $z = 0.72$; $p = 0.47$). The mean of the 7-item IQCODE was also superior to the MMSE in discriminating NC from all patients ($z = 5.47$; $p < 0.0001$), NC from MCI ($z = 5.13$, $p < 0.001$) and NC from AD ($z = 2.59$; $p < 0.01$).

The internal consistencies of both versions of the IQCODE were high (Cronbach's α : IQCODE 16 item = 0.913; IQCODE 7 item = 0.818).

The ideal cut-off scores of the mean 7-item IQCODE version were 3.43 (NC vs. all patients; 61% of bootstrap samples; 39% resulted in the next smaller cut-off of 3.29), 3.29 (NC vs. MCI; 93% of bootstrap samples; 7% resulted in the next higher

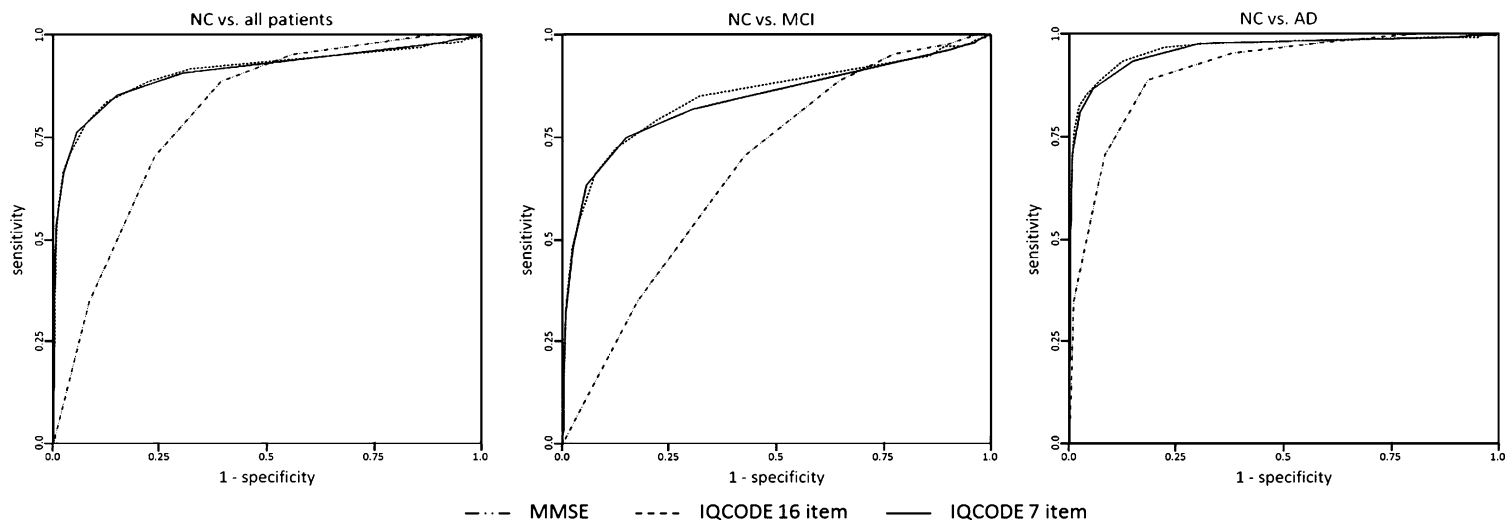


Figure 1. Comparison of receiver operating characteristic (ROC) curves of MMSE, mean 16-item IQCODE, and mean 7-item IQCODE comparing (a) healthy mature individuals (NC) vs. all patients (MCI and AD); (b) NC vs. MCI; and (c) NC vs. AD.

cut-off of 3.43) and 3.43 (NC vs. AD; 98% of bootstrap samples; 1.7% resulted in the next smaller cut-off of 3.29, 0.3% resulted in the next higher cut-off of 3.57).

Figure 1 shows the ROC curves of MMSE and mean 16-item and 7-item IQCODE scores.

Discussion

The goal of our study was to determine the diagnostic discriminability of the German short 16-item IQCODE version with a two-year time frame in patients with MCI and probable early AD. We also explored whether the number of IQCODE items could be significantly reduced without compromising its diagnostic discriminability. In general, the IQCODE consistently correctly classified individuals more effectively than the MMSE, although the MMSE demonstrated a surprisingly good performance, especially in the discrimination of NC from early stage AD with its correct classification rate of 85%. However, the present findings demonstrate that the short IQCODE with a two-year time frame has excellent screening properties. Importantly, a logistic regression analysis produced a very short 7-item IQCODE with a diagnostic accuracy as high as the longer version. Interestingly, all of these seven items are also part of the Brazilian 15-item short form of the IQCODE, recently developed by Perroco *et al.* (2009) in a study of NC and AD groups (mean MMSE = 27.9 and 19.8, respectively) with low levels of education (mean education level = 5.4 and 4.8, respectively). Moreover, five of our seven items are also represented in the group of the eight best discriminating items of the Brazilian short form. These consistencies suggest that educational level, culture and ethnicity do not necessarily determine the selection of optimally discriminating IQCODE items. However, Senanarong *et al.* (2001) found that three IQCODE items significantly discriminated samples of NC and AD Thai participants with four or less years of education. This difference, which is unlikely to be the result of a single factor, supports our view that absolute cross-cultural compatibility of diagnostic instruments may not be an attainable goal.

Clearly, it will be necessary to replicate the diagnostic performance of the 7-item version when only these items are presented for ratings. For both the short and very short versions, mean IQCODE scores correctly classified individuals as well as linear combinations of individual IQCODE items. This impressive finding signifies that the easily calculated IQCODE mean score need not be replaced by a more complicated scoring system in the clinical setting. Taken together, these results

show that compared to NC participants, patients with MCI and an early stage of probable AD appear to show cognitive decline in daily life to such an extent that ratings for all three participant groups significantly differed from one another.

Since the purpose of dementia screening is to detect pathologic cognitive functioning as early as possible, the more stringent cut-off scores which discriminate NC from MCI patients appear appropriate for both versions of the IQCODE. This corresponds to a score of 3.19 for the mean 16-item IQCODE version, and 3.29 for the mean 7-item version. Higher cut-off scores for the discrimination of NC from AD patients have been reported for the 16-item IQCODE version (e.g. Jorm *et al.*, 1996; Del-Ser *et al.*, 1997; Perroco *et al.*, 2009). This difference is most likely due to the inclusion in these previous studies of patients in more advanced stages of the disease process and to longer IQCODE judgment intervals. Because of the increased sensitivity of its combination of items, the cut-off scores for the 7-item version are slightly higher than those for the 16-item version. Thus, further diagnostic examinations are indicated when at least three of the 16 items, and at least two of the seven items, are judged as "a bit worse".

The version of the IQCODE used in the present study instructed informants to rate target participants' changes in cognitive functioning over the preceding two years. For dementia screening with the IQCODE, longer observation periods (e.g. 10 years) are typically used (e.g. de Jonghe *et al.*, 1997; Del-Ser *et al.*, 1997; Lim *et al.*, 2003). However, since individuals in their early seventies are typically referred to a memory clinic (Rosness *et al.*, 2009; Frisoni *et al.*, 2009), and since retirement usually takes place around the age of 65 in German-speaking countries, the common 10-year time frame requires informants to compare patients' current cognitive performance during retirement with cognitive performance during the last few years of occupational activity. These different phases of life have different cognitive demands (Powell, 1994; Calero-Garcia *et al.*, 2007) which may confound IQCODE ratings, despite its focus on non-occupational aspects of daily life. Moreover, informants may have difficulty remembering patients' performance over the relatively long observation period of 10 years (see, for example, Coughlin, 1990). The present choice of a two-year time frame circumvents both of these potential confounders without diminishing the IQCODE's diagnostic discriminability compared to versions with longer observation periods mentioned above.

Other potential confounders of IQCODE ratings exist. For example, it may be necessary to

correct IQCODE scores for the influence of a patient's demographic status, as is commonly done for many neuropsychological tests (Berres *et al.*, 2008). Without going into the details of the results, we conducted a thorough set of such analyses for the mean 16-item IQCODE and found that demographically adjusted mean IQCODE scores did not perform significantly better in correct classification than the unadjusted measures presented above. Fuh *et al.* (1995) and Isella *et al.* (2006) also found no effect of education in their studies. Moreover, in his review of the variables influencing IQCODE results, Jorm (2004) concluded that the effect of education was "negligible". Thus, it is unlikely that the older age of the MCI and AD patients compared to the NC group significantly influenced our results. These negative findings may reflect the informants' unconscious subjective adjustment of their expectations concerning the cognitive abilities of the patient, e.g. their assumption that "it is normal to get slower when getting older". Thus, the use of raw IQCODE scores represents a simple and still very reliable scoring method in the clinical setting. While patient's demographic characteristics were not associated with IQCODE ratings, future studies will determine whether factors related to the informant should be used to adjust IQCODE scores. For example, informant anxiety or depression may influence judgments (Jorm *et al.*, 1996), while the influence of social considerations on IQCODE ratings – for example, whether the informant's goal is to obtain more caregiver support – remain inconclusive (Del-Ser *et al.*, 1997; Lim *et al.*, 2003). Other informant-related factors appear less important, as reviewed by Jorm (2004): "IQCODE-scores are not influenced by length or type of relationship (Fuh *et al.*, 1995) or by age and education of the informant (Jorm *et al.*, 1996)" (p. 286). Thus, the potential influence of informant-associated factors on IQCODE judgments requires further investigation.

To date, one major focus of studies using the IQCODE has been differentiating healthy individuals from those with a possible dementia syndrome. The present study shows that the IQCODE also effectively differentiates MCI from healthy performance, consistent with previous reports (Isella *et al.*, 2002; 2006). While the present NC-MCI cut-off scores require confirmation in a longitudinal study comparing the baseline performance of NC and MCI patients who convert to AD, they suggest that the IQCODE is an effective screening tool for individuals in the very early stages of the disease process. Such screening allows for further diagnostic examinations and implementation of therapies early in the course of

the disease, when they are expected to have their maximal benefit. Considering the pressing need for new AD therapies, the earliest possible diagnosis of this syndrome in the MCI stage is of central importance as it identifies individuals for testing new therapeutic interventions.

One caveat of the present study is the inclusion criterion that patients' IQCODES were completely filled in, and thus, strictly speaking, the reported results can only be applied to complete questionnaires. Upon comparing complete and incomplete questionnaires, we found that negative cognitive changes were rated as more pronounced in some items in patients (especially those with AD) with incomplete IQCODES. Since our goal was to detect cognitive change as early as possible, we decided to use only complete cases in the search for a subset of best differentiating items. Nevertheless, we performed an additional set of analyses comparing models of complete with combined complete and incomplete data, where missing values were estimated with multiple imputation methods (which assume that missing data can be modeled as random, an assumption not met in our data). These models produced essentially the same results as those based on complete questionnaires. We recognize that complete questionnaires may be difficult to obtain in clinical practice. The common method of calculating the IQCODE mean by dividing the item sum by the number of completed items (Fuh *et al.*, 1995; Perroco *et al.*, 2009), although clinically useful, may underestimate a patient's deterioration in cognitive functioning. Given these problems associated with missing items, it is advisable to ask significant others to fill in the missing items to the best of their knowledge. It remains to be determined whether the short version of the IQCODE is also able to detect early cognitive changes associated with depression and other non-AD causes of dementia such as vascular dementia, Parkinson's disease dementia, and frontotemporal lobar degeneration.

The collection of informant information is necessary whenever factors such as sensory disturbances, severe somatic diseases and reduced compliance (e.g. based on diminished insight) minimize or prohibit the ability to collect direct information while working with the patient (cf. Jorm, 2004). These judgments of changes eliminate the need for a premorbid evaluation and avoid the special challenges inherent in interpreting longitudinal findings which are influenced by learning effects and "test sophistication" (Anastasi, 1981) during repeated testing. Moreover, the informant-based questionnaire of change circumvents difficulties associated with detecting changes in the test performance of high functioning individuals whose

subtle changes can be overlooked when they result in still normal test performance.

Ideally, screening instruments should be sensitive, specific, socially acceptable, inexpensive and brief (Parker and Philp, 2004). In particular, the time expended on data acquisition is becoming an increasingly important factor in many health systems. Primarily because previous informant-based questionnaires on cognitive changes were deemed too time-consuming, Galvin *et al.* (2005) developed the 8-item AD8, a brief informant interview to detect dementia. Here we demonstrate that the IQCODE can be reduced from 16 to 7 items with no loss in diagnostic accuracy, thereby obviating the concern expressed by Galvin *et al.* regarding the length of the IQCODE. Thus, the short 7-item version of the IQCODE with its high diagnostic discriminability provides clinicians with an excellent tool for screening for AD and its MCI prodrome.

Conflict of interest

None.

Description of authors' roles

M. M. Ehrensperger and A. U. Monsch designed the study. M. M. Ehrensperger collected the data, carried out the statistical analyses and was primarily responsible for writing the paper. M. Berres assisted in preparing the statistical design and supervised the statistical analyses. All authors discussed the results and conclusions. K. I. Taylor translated the manuscript.

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