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Sound Measurement of Neurological Disorders

Satyendra Nath Chakrabartty[1*]

[1]Indian Statistical Institute, Indian Maritime University, Indian Ports Association.

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Corresponding Author: Satyendra Nath Chakrabartty, Indian Statistical Institute, Indian Maritime University, Indian Ports Association, Flat 4B, Cleopetra, Dc 258, Street No. 350, AA-1, New Town, Kolkata 700156, India. Mobile No: 919831597909, ORCID: 0000-0002-7687-5044

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Abstract

Background

Dementia has emerged as a public health priority for elderly people worldwide. Quality of life (QOL) of people with dementia (PWD) is a desired outcome due to the chronic progressive nature and absence of cure. Planning of QOL improvement interventions can be best done by constructing a methodologically sound index of QOL and an index of overall dementia status.

Method

The paper suggests the transformation of scores of biomarkers, items of different questionnaires, to follow Normal distributions with different parameters for meaningful aggregation to get a normally distributed index ($I_{Dementia}$) reflecting overall disease status and another index of Quality of life ($I_{\mathbb{QOL}}$), satisfying desired properties, including quantification of changes by one or a sample of patients over time.

Results

The indices can be tested across time and space and facilitate the prediction of dementia status using QOL and vice versa. Each index can be computed separately for each socio-economic-demographic factor. $I_{Dementia}$ can be broken into $I_{Dementia_{Pathological\ Markers}}$ for emphasizing clinical diagnosis and $I_{Dementia_{NT}}$ for neurological tests.

Conclusion

Combination of ordinal data and ratio level data, like biomarkers, by a simple method, is a novelty. It contributes to comparisons of the biomarkers across the AD continuum. The index $I_{Dementia}$Based on cognitive dysfunctions, along with plasma biomarkers, may help to assess changes in biomarkers in cross-sectional and longitudinal data along the AD continuum across gender, age, and types of dementia.

Keywords: Amyloid plaque, Dementia, Mild cognitive impairment, Neurological tests, Normal distribution, Quality of Life.

Introduction

Neurodegenerative diseases like dementia contribute significantly to the disability among aged persons in terms of cognitive impairment (CI), low speed of information processing, progressive memory loss, etc. **[1]**. Dementia is defined as an aggregation of deficits in various cognitive domains, and an increase in such deficits causes the severity of dementia. The increasing prevalence of neurodegenerative diseases with high mortality rates, significant cost of care affecting society are challenging. Aging is taken as an important factor that adversely affects cognition **[2]**. For elderly persons, empirical finding includes high correlation between processing speed and cognitive decline **[3]**; slow reaction times reflecting early signs of Alzheimer's disease (AD) **[4]**; selection of a few stimuli at the expense of others **[5]**; compromising inhibitory control **[6]**, etc. However, the mechanism of age-related deficits contributing to impairment of working memory is not clear **[7]**. Dementia with different types is a global health priority **[8]**.

Assessment of disease status and evaluation of the effect of treatment, and prognosis are extremely important for better planning and intervention **[9]**. Counts of the total number of plaques (diffuse or neuritic), dense neurofibrillary tangles (NFTs) in tissue samples from several brain regions are important pathological markers to confirm the clinical diagnosis of AD. Other neuropathological markers are there like the presence of amyloid plaques, deposition of Aβ42, etc. Computational model was developed by **[10]** to predict brain β-amyloid (Aβ) pathology based on Aβ42, Aβ40, T-tau, P-tau181, NfL with APOE genotypes (categorized into different groups according to their Aβ risks (41): (a) ε2/ε2 or ε2/ε3; (b) ε3/ε3; (c) ε2/ε4 or ε3/ε4; (d) ε4/ε4) and scores of translated cognitive tests like Mini-Mental State Examination (MMSE) **[11]**, Montreal Cognitive Assessment (MoCA) **[12]**, Activities of Daily Living (ADL) **[13]** and different cognitive domains and key demographic variables. However, empirical verifications of the complex models in a cohort of the AD Neuroimaging Initiative resulted in different levels of accuracies and stabilities. Limitations of the approach include consideration of variables in ratio scale, ordinal scale, and categorical data with different distributions, which are unknown and lack sample size requirement (minimum 415). Other sophisticated quantitative approaches

like support vector machine, logistic regression, Bayes classifier, random forest, decision tree algorithms, etc. **[14 - 16]** also suffer from methodological limitations. Neuropathological count data like plaques and tangles may be skewed toward the lower end of possible score ranges. Natural logarithmic transformations to homocysteine and C-reactive protein data in a sample of MCI and AD patients **[17]** do not ensure normality.

Approaches to treat dementia have changed from drug treatment to non-pharmacological therapies (NPTs) for improving cognitive functions in patients with dementia. Among the NPTs like photobiomodulation (PBM), enriched environment (EE), exercise therapy (ET), computerized cognitive training (CCT), and cognitive stimulation therapy (CST), PBM performed best **[18]**. PBM or low-level laser therapy (LLLT) is being used in the treatment of AD/dementia and other debilitating diseases for the reduction of pain, inflammation, and adverse effects of various brain disorders **[19]**. Use of Photons with specific wavelengths (660 nm. and 905 nm) in PBM for 4 - 6 minutes per day for about 28 days illuminates the mitochondria which improves cellular health, regional blood flow and supply of oxygen to brain parenchyma **[20]**, Anti-inflammatory effects caused by changing the phenotype of the brain microglia from pro-inflammatory M1 to anti-inflammatory M2 could reduce beta-amyloid plaque in the brains of AD patients by shifting amyloid precursor protein (APP) and improve cognitive functions **[21]**. However, standardizing parameters of PBM for the treatment of Alzheimer's disease is needed for higher consistency and treatment reliability **[22]**.

Different interventions address neuropathological markers, cognitive, functional, and behavioural state for better quality of life (QOL). The effectiveness of these interventions is evaluated by one or more neuropsychological tests (NTs) and is included in the guidelines of the model, consisting of 35 Dementia Observatory (GDO) indicators to track progress of the Global dementia action plan **[23]**. However, the NTs with different objectives differ with respect to areas (domains) covered, number of activities, items, and formats, scoring methods, score ranges, etc., and are not comparable. Summative scores assuming interchangeability of the items suffer from methodological limitations. Most neuropsychological evaluations are influenced by gender (two levels), age (10 – 15 levels), education (5 - 6 levels), etc. Different number of levels for different demographic factors results in different cell sizes and may bias the results. Testing statistically significant differences between matching factors like gender, age, and educational level for the Control Group (healthy persons) and dementia patients using *t*-test, paired *t*-test, ANOVA, etc., requires normally distributed data. NT scores not following normal distribution violate the assumptions of the techniques and may distort results.

QOL among the people with dementia (PWD) has been emphasized primarily due to the chronic progressive nature of dementia and to minimize the impact on morbidity and socio-economic status of the PWD **[24]**. The relationship between QOL and the severity of cognitive impairment among PWD showed mixed evidences **[25]** due to various factors, including non-overlapping domains of multidimensional QOL and NTs and methodological limitations. For example, $\bar{X} > \bar{Y}$ is meaningless for ordinal scores generated by QOL tools, which fail to satisfy the equidistant property **[26]**.

Self-reported QOL questionnaire contains a number of domains, and each domain contains binary items and/or *k*-point items, giving rise to ordinal scores. For example, the 36-Item Short Form Health Survey questionnaire (SF-36) has seven binary items, 3-point items (10), 5-point items (8), 6-point items (10), and another item regarding health transition over the last year. Mean, SD, and distribution are different for Yes-No type, 3-point, 5-point, and 6-point items. A single score of SF-36 is not computed as per the Manual (http://www.webcitation.org/6cfeefPkf), due to several independent dimensions being measured by the scale. For a given sample, different QOL instruments may result in different conclusions, and thus, such instruments are not comparable.

Dementia–specific QOL instruments are DEMQOL (4-point, 28 items in 4 domains: daily activities, memory, negative emotion, and positive emotion) for mild-to-moderate stages of dementia and DEMQOL-Proxy (4-point, 31 items in two domains: functioning and emotion) for severe dementia **[27]**. While $28 \leq$ DEMQOL score ≤ 112, the same for DEMQOL-Proxy is **[31,124]**, where higher scores imply better QOL. Increasing cognitive impairment may not cause poorer QOL across time, and non-AD patients have a worse prognosis in QOL **[25]**.

The paper suggests transformation of scores of biomarkers, items of different NTs, to follow Normal distributions with different parameters for meaningful aggregation to get a normally distributed index ($I_{Dementia}$) reflecting overall disease status and another index of Quality of life ($I_{\mathbb{QOL}}$), satisfying desired properties including quantification of changes by one or a sample of patients over time, statistical inferences, and better evaluation of psychometric properties.

Literature Survey

NT Scales in Use

Illustrative NT tools are given in Table 1.

Table 1

Illustrative Neuropsychological Tests

Tool/Uses	Features	Measurement Issues	Observations
MMSE Screening tool for CI among older, community-dwelling, hospitalized, and institutionalized adults.	Measures five areas of cognitive function: orientation (2 items, Max. score 10), registration (1 item, Max. score 3), attention and calculation (1 item, Max score 5), recall (1 item, Max score 3), language (6 items, Max score 9). A score	-Areas differ w.r.t. number of items and score range. Scale score $=\sum Item\ scores$ suffers from the substitution effect. A low score in an area is compensated by a high score in other dimensions.	Not sensitive to MCI **[28]** with limited sensitivity to change. Biased towards a high level of education. MMSE scores may be high, even showing clinical signs of dementia **[29]**. Individuals with

	≤ 23 (out of 30) indicates CI. MMSE takes 5-10 minutes to administer.	-Unknown distributions of items/dimensions may not make the addition meaningful.	MMSE>24 are classified as *normal, mild* (19–23), *Moderate* (10-18), *Severe* (score≤ 9), without indication of the efficiency of such classification. Not suitable for diagnosis as the only means **[30]**.
MoCA Screening tool	Cognition domains assessed are: auditory memory, attention, orientation, language, executive functions, computational and spatial skills, and abstraction. $0 \leq Scale\ score \leq 30$. Scores below 26 indicate CI	Each cognition area is assessed with a single exercise, giving two possible scores. Distorted results of confirmatory factor analysis (CFA) and exploratory factor analysis (EFA) indicate mapping of individual tests and the cognitive domains is not robust **[31]**.	Validity is found as $r_{\mathrm{MoCA,MMSE}}$ despite MoCA being more sensitive than MMSE. Less accurate for people with lower education. The factor structure of MoCA was different in different studies **[32]** Consideration of executive function makes it useful for patients with vascular Impairment and vascular dementia. Cut-off score is too high **[33]**.
Short Portable Mental Status Questionnaire (SPMSQ) **[34]** Screening test/interview	10 10-item questionnaire to detect the degree of CI in older adults. A poor SPMSQ score is highly correlated with cognitive disorders.	Scoring: Normal mental functioning (0-2 errors), cognitive impairment: mild(3-4 errors), moderate (5-7 errors), severe (≥8 errors)	Problems with false-positives and false-negatives (particularly in patients with MCI) are disadvantages of SPMSQ. High SPMSQ error scores indicate the need for further medical and/or psychiatric evaluation.
Milan Overall Dementia Assessment (MODA) **[35]**. Detects and measures the severity of Alzheimer 's-like cognitive decline	The autonomy *scale* considers walking, dressing, personal hygiene, control of sphincters, and eating. *Orientation enquiry* has Temporal, Spatial, Personal & Family orientations. The NT section features tests drawn from standardized NTs.	Total score ∈ [0, 100]. Autonomy (15 points), orientation (35 points), and NTs (50 points). The rate of progress or decline is given by 1st-2nd MODA score ÷ time interval (in months) between the two administrations.	More effective than the DSM-III-R for discriminating patients with CI from normal subjects. However, MODA/DSM-III-R inconsistency exists. MODA has very high sensitivity and performs better than MMSE as a screening tool. $r_{MODA,MMSE}$ in controls < same for AD patients.
Short Neuropsychological Examination - 2 (ENB-2) **[36]**. Screening tool containing 16 tasks	A battery of 14 tests covering *cognitive domains* (trail making test A (TMT-A) and B (TMT-B)); *Memory* (digit span, Babcock story recall test (BSRT) and interference memory), plus *attention*, *executive functions*, and *perceptive* (spontaneous drawing and copy drawing tests) *and praxis abilities*.	A wide ranges of cognitive domains help to detect different types of MCI. For each ENB-2 test, the following are computed: Mean, SD= $\sqrt{Variance}$ plus global normative value as weighted average of normative scores in the 7-levels of age-education.	Normative data may be based on samples of small size or have limited validity or reliable data.
ADL and Instrumental activities of daily living (IADL) **[37]**	ADL covers basic actions required to care for oneself and body, including personal care, mobility, and eating. Domains of IADLs include cooking, cleaning, laundry, transportation, and managing finances.	Each of the six criteria of ADL is graded as (1 if independent, 0 if dependent). The domains of IADL are 5 for men and 8 for women. IADL score ranges from 0	Each instrument of IADL considers a different definition of IADL disability. Thus, results differ depending on the instrument used.

		(low function, dependent) to 8–5 (high function, independent).	
Alzheimer's Disease Assessment Scale (ADAS) **[38]**. Assessment tool.	The cognitive section of ADAS(ADAS-Cog) provides a detailed cognitive assessment for dementia. Different versions like 3-, 5-, 11-, and 13-item ADAS-Cog perform differently	Covers cognitive and behavioral domains prone to be affected by AD. Executive functions are not captured by ADAS-Cog 11. Assess cognitive changes in drug trials in dementia	Testing requires 45 to 60 minutes. It is less influenced by educational level and language competencies. Routinely being used by AD researchers, especially those involved in pharmaceutical trials, for monitoring and measuring the effects of medication.
Clinical Dementia Rating Scale (CDR) **[39]**	5-point ratings scale where 0 stands for healthy people, 0.5 for questionable dementia, and 1, 2, and 3 for mild, moderate, and severe dementia, respectively	CDR-Sum of Boxes (CDR-SB) Score is the primary outcome, ranging from 0: normal cognition to 16 – 18: severe neurocognitive disorders. Used to determine stages of dementia and evaluate interventions.	CDR measures cognition and functional autonomy like judgment skills & problem solving, in addition to actions of everyday life. Thus, CDR is more comprehensive. Low correspondence between classification by MMSE and CDR in the earlier stage.
Mini International Neuropsychiatric Interview (MINI) **[40]**	Diagnostic assessment of both ICD-10 MH and DSM-IV/V categories.	10 items, each of a 4-point scale from 0 (do not agree at all) to 3 (agree fully) and a Visual Analog scale (VAS, 0 to 100).	Some questions are problematic, and a few are seen as extreme. Results could be biased by interpretation and the extent of guessing. It can be used as the first step in outcome tracking in clinical settings.

Observations

Most of the tools use the sum of scores of items or tasks/subtasks without considering their distributions to get scale scores following an unknown distribution, and suffer from the following limitations:

Combination of ordinal scores generated by questionnaires and count data like number of errors (Seashore Rhythm Test of HRB), ratio scale data like Time taken to complete tasks (Tactual Performance Test of HRB) and biomarkers like number of plaques and tangles, Plasma amyloid beta (Aβ)1-42/Aβ1-40 ratio, phosphorylated-tau181 (p-tau181), glial fibrillary acidic protein (GFAP), etc. have inherent problems.

Directions of the scales are different. While a low score in MMSE, MoCA indicates severity, the reverse is true for ADL. Studies involving several NTs need to ensure uniform direction (low score $\Longrightarrow$ severity) by reverse scoring or by subtracting observed score from the maximum possible score for scales like ADL to support a strong negative association between dementia and QOL.

For two items/tasks $X + Y = Z$ is not meaningful where X and Y follow different distributions and does not enable computation of $P(Z = t) = P$ (X= x, Y= t - x) for the discrete case and $P(Z \leq t) = P\ (X + Y \leq t) = \int_{-\infty}^{\infty}(\int_{-\infty}^{z} f_{X,Y}(x, t-x)dt)\ dx$ for the continuous case. From the angle of probability distribution, meaningful arithmetic aggregation demands a similar distribution of X and Y, enabling finding the distribution of Z by, say, convolution. One solution is to convert each item/task score to a normally distributed score, irrespective of the number of levels of the tasks/items.

Non-uniform importance given to the tasks results in different contributions of sections to the total score. For example, in MMSE, out of a total score of 30, 10 points are given to orientation, against only 1 point for constructional apraxia. Similarly, in MoCA, the Visuospatial/Executive section has 6 points and only 3 points for the Naming section. Orientation in MoCA, with 6 points, contributes more to the total test score.

Psychometric properties of the multidimensional NTs are routinely computed, ignoring the definition of reliability or without checking assumptions of Cronbach's alpha, like a single construct (unidimensionality), the same true score variances for all items, and the same relationship to the measured construct (equal factor loadings). However, alpha has been reported despite several independent factors emerging from Principal Component Analysis (PCA) or Factor Analysis (FA). For example, against a two-factor solution (memory factor and visuo-spatial factor) for Repeatable Battery for Assessment of Neuropsychological Status (RBANS) with 12 sub-tests, five index scores, and a total scale score, Cronbach's alpha = 0.92 was found **[41]**. Battery reliability is ≠ Average of sub-test reliabilities. Alpha of the Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV) was 0.98 against reliability of constituent scales, ranging from 0.90 to 0.96 **[42]**. Avoiding the unidimensionality assumption, **[43]** proposed theoretically defined reliability ($r_{tt-Theoritical}$) by dichotomizing a test in two parallel subtests (g-th and h-th) and computing

$$r_{tt-Theoritical} = \frac{S_T^2}{S_X^2} = 1 - \frac{S_E^2}{S_X^2} = 1 - \frac{\frac{1}{N}[\|X_g\|^2 + \|X_h\|^2 - 2\|X_g\|\|X_h\|Cos\theta_{gh}]}{NS_X^2}$$

where N: sample size; $\|X_g\| = \sqrt{\sum_{i=1}^{N} X_{ig}^2}$ is the length of the g-th vector, $\|X_h\|$ is computed accordingly and θ_{gh} is the angle between the g-th and h-th vectors.

Reliability of a battery consisting of K-subscales could be found (without weights) in terms of sub-test reliabilities by $r_{tt\,(Battery)} = \frac{\sum_{i=1}^{K} r_{tt_i} S_{X_i}^2 + \sum_{i=1}^{K} \sum_{i \neq j} \sum_{j-1}^{K} 2\,Cov(X_i, X_j)}{\sum_{i=1}^{K} S_{X_i}^2 + \sum_{i=1}^{K} \sum_{i \neq j} \sum_{j-1}^{K} 2\,Cov(X_i, X_j)}$

Similarly, the validity of Scale-1 as a correlation with Scale-2 indicates the validity of Scale-2 also and raises a question on the factor of the multidimensional scale for which validity is reported. **[44]** found lower test validity if the proportion of high performers is higher in the sample. **[45]** reviewed cognitive screening tests (CSTs) and found poor evidence of validity/reliability; sensitivity/specificity; factorial structures, which often fail to meet statistical standards.

Different cut-off scores are reported for different tests. The question arises whether the cut-off score of 23 in MMSE is equivalent to the cut-off score of 26 in MoCA. In other words, if both MMSE and MoCA were administered to the same sample, whether each normal person would have scored >23 in MMSE and >26 in MoCA? Similar questions may be raised for boundary points of the classification of persons with CI.

Prediction of MMSE by regressing MMSE (Y) on scores of ENB (X_1), ADL (X_2), and IADL (X_3), resulted in R^2 =0.512 but $Y = \alpha + \beta(X_1 + X_2 + X_3)$ gave R^2 =0.207 **[46]**, despite the use of the same items in both regression models. The authors found through Receiver Operating Characteristic (ROC) curve analysis that, global functioning score as a battery combining scores of ENB, ADL, and IADL discriminates the patients better than the component scores taken separately. The apparent contradictory results could be due to the reduction of the number of independent variables in the second case and not checking of leverage points. The point (X_i, Y_i) is a leverage point for the regression equation $Y = \alpha + \beta X$ where X_i is an outlier. If r_i is an outlier in the set of residuals $\{r_1, r_2, \ldots\ldots, r_n\}$ and the corresponding (X_i, Y_i) is a leverage point, then (X_i, Y_i) is a bad leverage point, implying a poor fit of the linear model. The least median of squares estimator can detect bad leverage points of the linear regression equation **[47]**. Another method is to compute the slope (β) as the median of $S_{ij}'s$ where $S_{ij} = \frac{Y_i - Y_j}{X_i - X_j}$ for each $i < j$ and the intercept $\alpha = M_Y - \beta M_X$ where M_Y is the median of $\{Y_1, Y_2, \ldots\ldots, Y_n\}$ and M_X is the median of $\{X_1, X_2, \ldots\ldots, X_n\}$. **[48]** proposed computation of slope and intercept, removing the bad leverage points. **[49]** proposed non-linear transformation $\mathcal{y}$=$\boldsymbol{G}.\|x\|\|y\|.x$ to get $r_{x\mathcal{y}} = 1$ where x and y are deviation scores, $\boldsymbol{G}_{n\times n}$ is the G-inverse of the matrix **A**= $x.x^T$ and $\mathcal{y}$ denotes the transformed scores. The concept can be extended to multiple correlation coefficients $R^2 = C'^T R_{XX}^{-1} C'$ where the original vector $\boldsymbol{C} = (r_{x_1 y}, r_{x_2 y}, \ldots r_{x_n y})^T$ of raw data is replaced by $\boldsymbol{C'} = (r_{x_1 \hat{y}}, r_{x_2 \hat{y}}, \ldots, r_{x_m \hat{y}})^T$ ensuring $C'^T R_{XX}^{-1} C' = 1$.

ROC curve depicts a plot of (1-Specificity) versus Sensitivity. Optimal cut-off is found by minimizing $d^2 = (1 - Sensitivity)^2 + (1 - Specificity)^2$ or by the Youden index. ROC – AUC analysis fails if the assumption of independence is violated. The ROC curve may be improper if data violate the normality assumption or if within-group variations are dissimilar. The cut-off score by Youden index did not agree with the other methods, where score distribution was skewed and diagnostic odds ratio (DOR) failed to produce valid informative cut-points **[50]**.

Suggested Method

Method to transform the ordinal score of i-th item to equidistant scores (E_i) with a fixed zero point was suggested **[51]** using weights ($W_{ij} > 0$) to j-th level of the i-th item satisfying $\sum_{j=1}^{K} W_{ij} = 1$ and $KW_{ik} - (K-1)W_{i(K-1)} =$ Constant $\forall k$ = 2, 3, 4, 5, ……

followed by $Z_i = \frac{E_i - \bar{E}_i}{SD(E_i)} \sim N(0,1)$ and proposed item score $\mathcal{S}_i$ by

$\mathcal{S}_i = (100 - 1)\left[\frac{Z_i - MinZ_i}{MaxZ_i - MinZ_i}\right] + 1 \sim N(\mu_i, \sigma_i)$ where $1 \leq \mathcal{S}_i \leq 100$.

Score of a QOL domain ($\mathbb{QOL}_j$) is taken as $\sum \mathcal{S}_i$ each following a normal distribution with a mean $\sum_i \mu_i$ and SD = $\sqrt{\sum \sigma_i^2 + 2\sum_{i \neq j} Cov(\mathcal{S}_i, \mathcal{S}_j)}$. The index of Quality of Life ($I_{\mathbb{QOL}}$) is defined as the sum of all $\mathbb{QOL}_j$'s.

For the index Ordinal item scores of ADL, CDR, MINI, etc., can be converted to $\mathcal{S}_i$-scores and count data like number of errors (Seashore Rhythm Test of HRB), ratio scale data like Time taken to complete tasks (Tactual Performance Test of HRB), and biomarkers like number of plaques and tangles, Plasma amyloid beta (Aβ)1-42/Aβ1-40 ratio, p-tau181, etc., can be straightaway standardized and transformed to normally distributed item scores $\mathcal{S}_i$. The index $I_{Dementia} = \sum \mathcal{S}_i$ where summation is taken over all $\mathcal{S}_i$'s of ordinal item/task scores and biomarkers, including count data.

Here, each index $I_{Dementia}$ and $I_{\mathbb{QOL}}$ follows normal distribution, and parameters of each such distribution can be found from the data since each is a convolution of normally distributed scores.

For an individual, $I_{Dementia_i}$ reflects his/her overall dementia status, combining pathological markers to confirm clinical diagnosis and NT scores of that individual. Similarly, $\mathbb{QOL}_i$ The value reflects the overall QOL status of the individual.

Properties

$I_{Dementia}$ and $I_{\mathbb{QOL}}$ can be computed by combining pathological markers and several scales, irrespective of their formats and correlations among the scales.

Properties satisfied by the indices are:

- Continuous and monotonically increasing
- Zero value of E-scores corresponds to f_{ij} =0.
- Avoid skew and give unique ranks to the individuals.
- Can be computed separately for each socio-economic-demographic factor.
- $I_{Dementia}$ can be broken into $I_{Dementia_{Pathological\ Markers}}$ for emphasizing clinical diagnosis and $I_{Dementia_{NT}}$ for neurological tests.

Benefits

The domains of $I_{Dementia}$ and $I_{\mathbb{QOL}}$ can be ranked with respect to the relative importance given by $\frac{D_i}{I_{Dementia}} \times 100$ or $\frac{i\text{-}th\ dimension\ of\ \mathbb{QOL}}{I_{\mathbb{QOL}}} \times 100$ respectively.

Progress registered by i-th subject in consecutive time-periods in terms of dementia can be assessed by $\frac{I_{Dementia_{(t)}} - I_{Dementia_{(t-1)}}}{I_{Dementia_{(t-1)}}} \times 100$ which also indicates the effectiveness of adopted interventions (assumed low score $\Longrightarrow$ severity for each variable). Progress of $I_{\mathbb{QOL}}$ can be assessed similarly. For a sample of persons with neurological disorders, $\overline{I_{Dementia_{(t)}}} < \overline{I_{Dementia_{(t-1)}}}$ implies progress. Domain(s) showing deteriorations are critical and require initiation of necessary corrective interventions.

Path of progress/deterioration of $I_{Dementia}$ and $I_{\mathbb{QOL}}$ across time can be compared using longitudinal data. The significance of progress can be tested by H_0: $\frac{I_{Dementia_{(t)}}-I_{Dementia_{(t-1)}}}{I_{Dementia_{(t-1)}}} = 0$ or $\frac{I_{\mathbb{QOL}_{(t)}}-I_{\mathbb{QOL}_{(t-1)}}}{I_{\mathbb{QOL}_{(t-1)}}} = 0$ by χ^2 test.

Normality of $I_{Dementia}$ and $I_{\mathbb{QOL}}$ facilitate:

- Testing equality of the mean and variance of $I_{Dementia}$ or $I_{\mathbb{QOL}}$ for two groups or a single group at different time periods, like $H_0: \mu_1 = \mu_2$ or $H_0: \sigma_1^2 = \sigma_2^2$ using cross-sectional or longitudinal data.
- Finding equivalent scores for NTs by solving $\int_{-\infty}^{x_0} f(x)dx = \int_{-\infty}^{y_0} g(y)dy$, even if scales are of different formats or contain different dimensions, and help to integrate NTs.
- Enables PCA and finding the eigenvalue, which in turn helps finding: (i) factorial validity (FV= $\frac{\lambda_1}{\sum \lambda_i}$) from a single administration of a test reflecting the main factor for which the test was developed **[52]**. However, FV needs to tally with clinical findings. (ii) Max. Cronbach's alpha (α_{PCA}) = $\left(\frac{m}{m-1}\right)\left(1-\frac{1}{\lambda_1}\right)$ **[53]**, (iii) Relationships among psychometric qualities as
  - $\alpha_{PCA} = \left(\frac{m}{m-1}\right)\left(1-\frac{1}{FV.\sum \lambda_i}\right) = \left(\frac{m}{m-1}\right)\left(1-\frac{1}{m.FV_{Z-scores}}\right)$ for a test with m-number of standardized items, $FV_{Z-scores} = \frac{\lambda_1}{m}$. **[51]**. Clearly, higher $FV_{Z-scores}$ increases α_{PCA}
- Correlation between $I_{Dementia}$ and $I_{\mathbb{QOL}}$ indicating an association between them can be used to find the regression equation of $I_{Dementia}$ on different dimensions of QOL, where the coefficient β_i may indicate the relative importance of the *i*-th dimension of QOL in predicting $I_{Dementia}$. Similar regression equation of $I_{\mathbb{QOL}}$ on dimensions of NTs and biomarkers can be fitted.

Discussion

The index $I_{Dementia}$ combines changes in brain and cognitive impairment in a simple way, avoiding complex approaches like support vector machine, logistic regression, Bayes classifier, random forest, decision tree algorithms, etc., each of which is associated with a number of assumptions that need to be verified before application. The sub-indices $I_{Dementia_{Pathological\ Markers}}$ and $I_{Dementia_{NT}}$ help in clinical diagnosis, assessment of disease stages, and evaluation of prognosis, respectively. The two proposed indices contribute to improving the scoring of NT and QOL instruments, avoiding limitations of ordinal/categorical scores and facilitating parametric analysis for meaningful comparisons, classification, and integration of various scales. Proposed scores offer significant benefits, including testing of statistical hypotheses across time and space, and prediction of ND status using QOL and vice versa, along with fluctuation of the association between the two measures across time.

A combination of ordinal data and ratio level data, like biomarkers, by a simple method, is a novelty. It contributes to comparisons of the biomarkers across the AD continuum. The index $I_{Dementia}$based on cognitive dysfunctions along with plasma biomarkers, may help to assess changes in biomarkers in cross-sectional and longitudinal data along the AD continuum across gender, age, and types of dementia.

Conclusions

The relationship between ND and QoL, along with the identification of critical areas, helps to plan medical, social, and economic interventions to mitigate the burden of ND, particularly among vulnerable groups. Planners and researchers can take advantage of the proposed normally distributed scores satisfying desired properties, including the detection of changes by longitudinal data and better evaluating psychometric parameters from a single administration. Future studies with multiple sets involving longitudinal data may be undertaken for (i) generalization of findings along with psychometric properties of the proposed transformation, and to stimulate an approach leading to robust and generalizable empirical findings (ii) studying changes of plasma biomarkers due to various factors and comorbidities. (iii) Predicting brain Aβ pathology from integrated plasma biomarkers and NT scores from a cohort-based investigation.

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Reference

1. Patterson, C. (2018). World Alzheimer Report 2018-The State of the Art of Dementia Research: New Frontiers. Alzheimer's Disease International. 1-48.
2. Jerkins L, Myerson J, Joerding JA, Hale S. (2000). Converging evidence that visuospatial cognition is more age-sensitive than verbal cognition. Psychol Aging. 15(1): 157-175.
3. Wahl H, Schmitt M, Danner D, Coppin A. (2010). Is the emergence of functional ability decline in early old age related to change in speed of cognitive processing and also to change in personality? Journal of Aging and Health. 22(6): 691-712.
4. Triebel K, Martin R, Christianson T, Swenson Dravis D, Pankratz V. (2014). Cognitively normal older adults with preclinical Alzheimer's disease demonstrate slower processing speed on everyday financial tasks. Archives of Clinical Neuropsychology. 29(6): 531-532.
5. Mazzucchi A. (2012). Neuropsychological rehabilitation. Theoretical premises and clinical applications. Elsevier, USA.
6. Hasher L, Zacks R. (1988). Working memory, comprehension, and aging: A review and a new view. Psychology of Learning and Motivation. 22: 193-225.
7. Bopp K, Verhaeghen P. (2018). Aging and n-back performance: A meta-analysis. Journals of Gerontology: Psychological Sciences. 1-12.
8. Long, S, Benoist, C, Weidner, W. (2023). World Alzheimer Report 2023: Reducing dementia risk: never too early, never too late. London, England: Alzheimer's Disease International.
9. Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN & Rubino I. (2021). Diagnosis of Early Alzheimer's Disease: Clinical Practice in 2021. J. Prev. Alzheimers Dis. 8(3): 371–386.
10. Pan, F, Huang, Y, Cai, X. (2023). Integrated algorithm combining plasma biomarkers and cognitive assessments accurately predicts brain β-amyloid pathology. Commun Med .3(1): 65.

11. Folstein MF, Folstein SE, McHugh PR. (1975). "Mini-mental state" A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 12(3): 189-198.

12. Nasreddine ZS, Phillips N, Bédirian V, Charbonneau S, Whitehead V. (2005). The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society. 53(4): 695-699.

13. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. (1963). Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial functions. JAMA. 185: 914–919.

14. Palmqvist, S. Insel PS, Zetterberg H, Blennow K, Brix B, Stomrud E. (2019). Accurate risk estimation of beta-amyloid positivity to identify prodromal Alzheimer's disease: Cross-validation study of practical algorithms. Alzheimers Dement. 15(2): 194-204.

15. Benedet, A.L, Brum, W.S, Hansson, O. (2022). The accuracy and robustness of plasma biomarker models for amyloid PET positivity. Alz Res Therapy. 14(1): 26.

16. Chang, C. H, Lin, C. H. Lane, H. Y. (2021). Machine Learning and Novel Biomarkers for the Diagnosis of Alzheimer's Disease. Int. J. Mol. Sci. 22(5): 2761.

17. Malek-Ahmadi M, Patel A, Sabbagh MN. (2013). KIF6 719Arg carrier status association with homocysteine and c-reactive protein in amnestic mild cognitive impairment and Alzheimer's disease patients. Int J Alzheimers Dis. 2013:242303.

18. Luo G, Zhang J, Song Z, Wang Y, Wang X, Qu H, Wang F, Liu C and Gao F. (2023).
Effectiveness of non-pharmacological therapies on cognitive function in patients with dementia—A network meta-analysis of randomized controlled trials. Front. Aging Neurosci.15:1131744.

19. Hamblin MR and Salehpour F. (2021). Photobiomodulation of the Brain: Shining Light on Alzheimer's and Other Neuropathological Diseases. Journal of Alzheimer's Disease. 83(4): 1395-1397.

20. Ehlis, A.C. and Fallgatter, A.J. (2011). Simulation of Near-Infrared Light Absorption Considering Individual Head and Prefrontal Cortex Anatomy: Implications for Optical Neuroimaging. PLOS ONE. 6(10): 26377.

21. Zhang, Z, Shen, Q, Wu, X, Zhang, D, and Xing, D. (2020). Activation of PKA/SIRT1 signaling pathway by photobiomodulation therapy reduces Aβ levels in Alzheimer's disease models. Aging Cell. 19(1): 13054.

22. Ramanishankar A, S AS, Begum RF, Jayasankar N, Nayeem A, Prajapati BG, Nirenjen S. (2024). Unleashing light's healing power: an overview of photobiomodulation for Alzheimer's treatment. Future Sci OA. 10(1): FSO922.

23. Global Dementia Observatory (GDO). (2021). *Diagnosis,* treatment, and care. Tratto da World Health Organization.

24. Beerens HC, Sutcliffe C, Renom-Guiteras A, Soto ME, Suhonen R. (2014). Quality of life and quality of care for people with dementia receiving long term institutional care or professional home care: the European RightTimePlaceCare study. J Am Med Dir Assoc. 15(1): 54–61.

25. King, D, Farina, N, Burgon, C. (2022). Factors associated with change over time in quality of life of people with dementia: longitudinal analyses from the MODEM cohort study. BMC Geriatr. 22: 469.

26. Jamieson, S. (2004). Likert scales: How to (ab) use them. Medical Education, 38(12): 1212-1218.

27. Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B. (2005). Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. Health Technology Assessment (Winchester, England). 9(10): 1-93.

28. Mitchell AJ. (2009). A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. Journal of Psychiatric Research. 43(4): 411-431.

29. Fritsch T, McClendon MJ, Smyth KA, Lerner AJ, Chen CH. (2001). Effects of educational attainment on the clinical expression of Alzheimer's disease: results from a research registry. American Journal of Alzheimer's Disease and Other Dementias. 16(6): 369-376.

30. Kalish VB, Lerner B. (2016). Mini-mental state examination for the detection of dementia in older patients. American Family Physician. 94: 880-881.+

31. Coen RF, Robertson DA, Kenny RA, King-Kallimanis BL. (2016). Strengths and Limitations of the MoCA for Assessing Cognitive Functioning: Findings From a Large Representative Sample of Irish Older Adults. J Geriatr Psychiatry Neurol. 29(1):18-24.

32. Smith CR, Cavanagh J, Sheridan M, Grosset KA, Cullen B, Grosset DG. (2020). Factor structure of the Montreal Cognitive Assessment in Parkinson disease. Int J Geriatr Psychiatry. 35(2): 188-194.

33. Ihle-Hansen H, Vigen T, Berge T, Einvik G, Aarsland D, Rønning OM, Thommessen B, Røsjø H, Tveit A, Ihle-Hansen H. (2017). Montreal Cognitive Assessment in a 63- to 65-year-old Norwegian Cohort from the General Population: Data from the Akershus Cardiac Examination 1950 Study. Dement Geriatr Cogn Dis Extra. 7(3): 318-327.

34. Julayanont P, Phillips N, Chertkow H, Nasreddine Z. (2017). The Montreal Cognitive Assessment (MoCA): Concept and clinical review. In cognitive screening instruments: A practical approach. 111-152.

35. Brazzelli M, Capitani E, Della SS, Spinnler H, Zuffi M. (1994). A neuropsychological instrument adding to the description of patients with suspected cortical dementia: The Milan overall dementia assessment. Journal of Neurology, Neurosurgery and Psychiatry. 57(12): 1510-1517.

36. Mondini S, Mapelli D, Vestri A, Arcara G, Bisiacchi PS. (2011). Brief Neuropsychological Examination 2 (ENB-2). A battery of tests for neuropsychological screening. Raffaello Cortina Editore.

37. Lawton MP, Brody EM. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 9:179–186.

38. Rosen WG, Mohs RC, Davis KL. (1984). A new rating scale for alzheimer's disease. American Journal of Psychiatry. 141(11): 1356-1364.

39. Morris J. (1993). The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology. 43(11): 2412-2414.

40. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E. (1998). The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 59(20): 22-33.

41. De la Torre GG, Suárez-Llorens A, Caballero FJ, Ramallo MA, Randolph C, Lleó A, Sala I, Sánchez B. (2014). Norms and reliability for the Spanish version of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Form A. J Clin Exp Neuropsychol. 36(10): 1023-1030.

42. Sherman, E, Brooks, BL, Iverson, GL, Slick, DL. and Strauss, E. (2011): Reliability and Validity in Neuropsychology.

43. Chakrabartty, S. N, Kangrui, Wang and Chakrabarty, Dalia. (2024): Reliable Uncertainties of Tests & Surveys - a Data-driven Approach. International Journal of Metrology and Quality Engineering (IJMQE). 15(4): 1-14.

44. Vaughan E D. (1998). Statistics: Tools for understanding data in the behavioral sciences. Upper Saddle River, NJ: Prentice- Hall.

45. Aiello, E. N, Rimoldi, S, Bolognini, N, Appollonio, I, Arcara, G. (2022). Psychometrics and diagnostics of Italian cognitive screening tests: A systematic review. Neurological Sciences. 43(2): 821–845.

46. Palumbo, R, Di Domenico, A, Piras, F. (2020). Measuring global functioning in older adults with cognitive impairments using the Rasch model. BMC Geriatr. 20: 492.

47. Rousseeuw, P. J, van Zomeren, B. C. (1990). Unmasking multivariate outliers and leverage points. Journal of the American Statistical Association. 85(411): 633–639.

48. Wilcox, R. R. (2023). Robust Correlation Coefficients That Deal With Bad Leverage Points. Methodology. 19(4): 348–364.

49. Chakrabartty, SN. (2023). Improving linearity in health science Investigations. Health Science Journal. 17(4): 1010.

50. Hassanzad M, Hajian-Tilaki K. (2024). Methods of determining optimal cut-point of diagnostic biomarkers with application of clinical data in ROC analysis: an update review. BMC Med Res Methodol. 24(1): 84.

51. Chakrabartty, SN. (2024). Association of Index of Cardiovascular risk factors with Socio-economic status index. Journal of Cardiovascular Investigations and Insights. 1(1).

52. Parkerson, HA, Noel, M, Gabrielle MP, Fuss, Samantha, Katz, J, Gordon J.G. Asmundson. (2013). Factorial Validity of the English-Language Version of the Pain Catastrophizing Scale–Child Version, The Journal of Pain. 14(11): 1383-1389.

53. Ten Berge JMF & Hofstee WKB. (1999). Coefficients alpha and reliabilities of unrotated and rotated components. Psychometrika. 64(1): 83– 90.