Journal of Alzheimer's Disease 67 (2019) 67–79
DOI 10.3233/JAD-171053
IOS Press

A δ Homolog for Dementia Case Finding with Replication in the Alzheimer's Disease Neuroimaging Initiative

Donald R. Royall[a,b,c,d,*], Raymond F. Palmer[c] and the Alzheimer's Disease Neuroimaging Initiative[1]
[a]*Department of Psychiatry, The University of Texas Health Science Center, San Antonio, TX, USA*
[b]*Department of Medicine, The University of Texas Health Science Center, San Antonio, TX, USA*
[c]*Department of Family and Community Medicine, The University of Texas Health Science Center, San Antonio, TX, USA*
[d]*South Texas Veterans' Health System Audie L. Murphy Division GRECC, San Antonio, TX, USA*

Accepted 29 August 2018

Abstract. Dementia can be empirically described by the latent dementia phenotype "δ" and its various composite "homologs". We have explored δ's blood-based protein biomarkers in the Texas Alzheimer's Research and Care Consortium (TARCC) study. However, it would be convenient to replicate those associations in the Alzheimer's Disease Neuroimaging Initiative (ADNI). To this end, we have engineered a δ homolog from observed cognitive performance measures common to both projects. Our findings were replicated in randomly selected 50% splits of TARCC data (Group 1, N = 1,747; Group 2, N = 1,755), and then independently in ADNI (N = 1,737). The new δ homolog, i.e., "dT2A" (d-TARCC to ADNI), fit the data of both studies well, and was strongly correlated with dementia severity, as rated by the Clinical Dementia Rating Scale "sum of boxes" (TARCC: $r = 0.99$, $p < 0.001$; ADNI: $r = 0.96$, $p < 0.001$). dT2A achieved an area under the receiver operating characteristic curve of 0.981 (0.976–0.985) for the discrimination of Alzheimer's disease from normal controls in TARCC, and 0.988 (0.983–0.993) in ADNI. dT2A is the 12th δ homolog published to date, and opens the door to independent replications across these and similar studies.

Keywords: Aging, Alzheimer Disease Neuroimaging Initiative, cognition, dementia, *g*, intelligence, TARCC

INTRODUCTION

We have pioneered a novel approach to the assessment of dementia. It is conceptually simple. While cognitive impairment is widely held to be the hallmark of dementia, three conditions are necessary to that diagnosis [1]: 1) there must be acquired cognitive impairment(s); 2) there must be functional disability; and 3) the disability must be related to the cognitive impairment(s) that are observed.

This formulation implies that the essential feature(s) of dementing processes can be resolved to the cognitive correlates of functional status. Explicitly measuring that construct can open a way to the

[1]Some data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). ADNI had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. However, ADNI investigators contributed to the design and implementation of ADNI and/or provided data. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

*Correspondence to: Donald R. Royall, MD, Department of Psychiatry, The University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900, USA. Tel.: +1 210 567 1255; Fax: +1 210 567 1269; E-mail: royall@uthscsa.edu.

completely empirical assessment and diagnosis of dementia.

Surprisingly, the association between many observed cognitive measures/domains and functional status is statistically weak [2]. However, an empirical definition of the "cognitive correlates of functional status" can be approached by confirmatory factor analysis in a structural equation model (SEM) framework. We have found that functional status is linked to cognitive performance through Spearman's General Intelligence factor "*g*" rather than through domain-specific cognitive abilities [3, 4]. Our bifactor SEM model parses *g* into two orthogonal (unrelated) fractions: 1) δ, i.e., "the psychometric correlates of functional status", and 2) g', i.e., residual variance in *g* that is empirically unrelated to Instrumental Activities of Daily Living (IADL). Cognitive variance empirically unrelated to IADL cannot contribute to dementia by our definition. Thus, our method divorces functionally salient cognitive impairment from cognitive impairment *per se*.

The latent variable δ can be "reified" as a composite "d-score" and applied to individuals as an omnibus dementia severity metric, i.e., a dementia-specific phenotype. Because *g* is thought to contribute to all cognitive measures, it has proven feasible to construct δ from a wide range of measures, batteries, and samples. δ can be constructed from a comprehensive battery of formal measures, from small batteries of formal measures, from brief batteries of "bedside" measures, and even from the items of a single measure.

We refer to each embodiment as a δ "homolog". In genetics, a homolog is a gene descended from an ancestral gene in the same species and preserving the original's function. Similarly, and regardless of their cognitive indicators, all δ homologs (twelve published to date) share the bifactor construction of δ, target a measure of IADL, exhibit strong associations with dementia severity (e.g., as measured by the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) [5] and achieve high areas under the receiver operating characteristic curve (AUC/ROC) for the discrimination of various dementias from normal controls (NC).

Furthermore, it appears that δ is agnostic to the etiology of dementia [6, 7]. This observation suggests that variance in cognitive performance can be divided into fractions that are necessary to dementia (i.e., δ) and irrelevant to it (i.e., disease-specific variance). To the extent that disease-specific cognitive changes (and domain-specific ones, by definition) and their biomarkers are orthogonal (unrelated) to δ [7], they may be incapable of explaining functionally salient effects. In contrast, the biomarkers of δ (regardless of their disease specificity) may be functionally salient, and intervention on them should produce functionally salient outcomes.

We have been studying δ homologs and their biomarkers in the Texas Alzheimer's Research and Care Consortium (TARCC) study. TARCC is a large ($N \cong 3{,}500$), well-characterized, ethnically diverse [$n \cong 1{,}200$ Mexican-American (MA)] convenience sample with annual longitudinal follow-up [8].

We have associated δ with a large number of serum proteins, including pro- and anti-inflammatory cytokines [9, 10]. Many of these associations appear to have profound ethnicity effects in TARCC [11, 12]. We have also published the serum protein mediators of specific dementia risks (including age, depressive symptoms, and the apolipoprotein (APOE) $\varepsilon 4$ allele) [12–16].

All these associations have been replicated in random subsets of TARCC's large sample. Regardless, TARCC has its limitations. No imaging is available and its protein biomarkers have been obtained in serum. Biomarker associations have been notoriously difficult to replicate and may be impacted by the biofluid in which they are measured [17].

The Alzheimer's Disease Neuroimaging Initiative (ADNI) offers an opportunity to replicate our TARCC findings [18]. Its cognitive battery overlaps substantially with that of TARCC, and both deployed similar blood-based biomarker panels processed by a common vendor [i.e., Rules Based Medicine (RBM) of Austin, Texas]. If we can validate a common δ homolog across both studies, we might be able to confirm blood-based biomarkers of δ across those studies and integrate ADNI's neuroimaging into the growing literature of δ.

MATERIALS AND METHODS

Subjects

The present study is a secondary analysis of data collected by TARCC and ADNI. Informed consent was obtained from all participants (or their legally authorized proxies) before data collection, and both studies are approved by their respective Institutional Review Boards (IRB).

TARCC

Subjects included 3,502 TARCC participants. TARCC is a longitudinally followed convenience sample of elderly persons with Alzheimer's disease (AD) ($n = 1,275$), mild cognitive impairment (MCI) ($n = 732$), or normal cognition (NC) ($n = 1,445$) (and 58 "others") recruited from five Texas medical schools. Each participant underwent a standardized annual examination that included a medical evaluation, neuropsychological testing, and clinical interview. Categorical clinical diagnoses of AD, MCI, and NC were established through consensus. The diagnosis of AD was based on National Institute for Neurological Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [19]. The diagnosis of MCI was based on site-specific consensus-based clinical diagnoses derived from all available information but without reliance on specific neurocognitive tests and/or cut-scores. "All available information" included the results of TARCC's entire neuropsychological battery, clinical evaluations, informant interviews, and any available outside medical records. We could not easily use cut-scores because MA norms are not available for many measures.

ADNI

ADNI data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

ADNI is a well-characterized longitudinal convenience sample developed to validate the magnetic resonance, positron emission tomography, cerebrospinal fluid, and genetic biomarkers of AD. The initial 5-year study, ADNI-1, enrolled NC, MCI, and AD subjects, and subsequent studies (ADNI-GO and ADNI-2) added early- and late-MCI cohorts. ADNI has provided a framework for similar initiatives worldwide, including TARCC. In ADNI's combined sample (N = 1738), N = 342 were diagnosed with AD, N = 978 with MCI, and N = 417 as NC. For this analysis, all MCI subtypes were combined, including ADNI-GO participants with subjective cognitive impairment.

Clinical variables

dT2A, a δ homolog for ADNI

Since *g* manifests in all cognitive performance measures, it does not seem to matter which are employed to estimate δ, provided that they survey a broad range of cognitive domains. While TARCC and ADNI have similar batteries, we decided to limit dT2A to observed cognitive measures that are common to both studies, including the Boston Naming Test (BNT) [20], Category Fluency (Animals) [21], Logical Memory I (LMI) and II (LMII) [22], the Mini-Mental State Examination (MMSE) [23], and Trail-Making Part B (TrailsB) [24]. All are available in TARCC in Spanish translation.

Boston Naming Test [20]: The BNT is a confrontation naming test that requires the subject to verbally name line drawings of objects associated with words of increasingly lower frequency in the target language. TARCC uses 30 item BNT. ADNI uses 60 item BNT.

Categorical Fluency (Animals) [21]: This test of verbal fluency asks subjects to verbally generate as many animal names as they are able in one minute.

Logical Memory II [22]: Immediately (LMI), and following a 30 min delay (LMII), the subject recalls two paragraphs read aloud.

Mini-Mental State Examination: The MMSE [323] is a well-known and widely used test for screening cognitive impairment.

Trail Making Part B (Trails B) [24]: Trails B is a timed test of attention, speed, and mental flexibility that requires the subject to alternately connect between numbers and letters. TARCC reports Trails B as scaled scores.

Target indicators of dT2A

In TARCC, we used informant-rated IADL as a target indicator of dT2A. Unfortunately, IADL is not available in the ADNI, and so the Functional Assessment Questionnaire (FAQ) [25] was used instead. The FAQ has been successfully incorporated into δ homologs by other investigators [6, 7].

Instrumental Activities of Daily Living: IADL is assessed using the Older Adults Resources Scale (OARS) [26]. The OARS is a structured clinical interview that provides informant-reported information on

7 IADLs. Each item is scored on a four-point Likert scale with zero signifying "no impairment".

The Functional Activities Questionnaire [25]: The FAQ is an informant-rated measure of a participant's ability to perform IADLs. The FAQ is commonly used in dementia evaluations [27, 28].

Observed clinical measures

Observed clinical measures are often used as covariates or to provide external validation. The following measures are available in both TARCC and ADNI.

Self (informant)-reported age, education, and gender are self-explanatory. Ethnicity is coded dichotomously according to self-reported Hispanic affiliation. TARCC has a substantial number of MA participants. MA ethnicity has pronounced effects on serum protein biomarkers in TARCC [11–13, 29]. There are no racial distinctions in TARCC, and no reported racial effects on plasma protein biomarkers in ADNI.

The Clinical Dementia Rating Scale Sum of Boxes [5]: The CDR is used to evaluate dementia severity. The rating assesses the patient's cognitive ability to function in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Information is collected during an interview with the patient and their caregiver (15 min).

Geriatric Depression Scale (GDS): Depressive symptoms were assessed in both studies by the Geriatric Depression Scale (GDS) [30, 31]. GDS scores range from zero-30. Higher scores are worse. The GDS is valid in demented persons [32].

Statistical analyses

Construction of dT2A: These analyses were conducted in TARCC's most recent dataset (N = 3,502) and in a combined sample of ADNI-1, ADNI-2, and ADNI-GO data (N = 1,737).

The analysis was performed using Analysis of Moment Structures (AMOS) software [33]. The maximum likelihood estimator was chosen for these models. All observed indicators were adjusted for age, education, ethnicity, gender, and GDS. Covariances between the residuals were allowed to be estimated if they were significant and improved model fit.

The observed variables were fit to a linear confirmatory bifactor measurement model specified in [1]. Measurement errors are assumed uncorrelated and the latent variables means and variances were fixed to 0 and 1 respectively allowing all loadings to be freely estimated.

Missing data

We used Full Information Maximum Likelihood (FIML) methods to address missing data. FIML uses the entire observed data matrix to estimate parameters with missing data. In contrast to listwise or pairwise deletion, FIML yields unbiased parameter estimates and preserves the overall power of the analysis [34, 35].

Fit indices

The validity of structural models was assessed using two common test statistics. A non-significant chi-square signifies that the data are consistent with the model [36]. However, the ratio of the chi-square to the degrees of freedom in the model is also of interest. A CMIN/DF ratio <5.0 suggests an adequate fit to the data [37]. The comparative fit index (CFI), with values ranging from between 0 and 1, compares the specified model with a model of no change [38]. CFI values below 0.95 suggest model misspecification. Values of 0.95 or greater indicate adequate to excellent fit. A root mean square error of approximation (RMSEA) of 0.05 or less indicates a close fit to the data, with models below 0.05 considered "good" fit, and up to 0.08 as "acceptable" [39]. All three fit statistics should be simultaneously considered to assess the adequacy of the models to the data.

Factor determinacy

One potential limitation to the common factor model is that an infinite number of unique factor score composites can be derived from any factor. These can be divided into "determinant" and "indeterminant" fractions [40]. Several statistical methods are available to test determinacy. We used Grice's "Refined Factor Score Evaluation Program (equation 5)" [41]. This method maximizes composite validity and is recommended when the factor composite scores are to be used as "observed" variables in subsequent analyses (i.e., as LGC indicators). We report three indices from this program's output: R-Squared (RSQR), the Multiple R (MultiR), and a minimum correlation (MC). Acceptable values should be $\geq$0.50.

Factor equivalence

The factor equivalence of dT2A was tested across two random 50% subsets of TARCC's participants (i.e., Group 1, N = 1,747; Group 2, N = 1,755). The indicators' loadings on dT2A were constrained to be equal across groups and χ^2 fit was compared in constrained versus unconstrained models.

RESULTS

Descriptive statistics are presented by group in Table 1, and by diagnoses in Tables 2 (TARCC) and 3 (ADNI). Cohen's d and t tests of significance are reported in Table 1, where estimable, for TARCC (total sample) versus ADNI. These samples differed significantly on all measures. There were no significant differences across the TARCC random splits on any variable. Both splits differed from ADNI on all measures. ADNI appears to have a relatively high fraction of MCI cases, which were recruited explicitly into ADNI-2 and ADNI-GO. TARCC has a much higher prevalence of MA participants.

dT2A's unadjusted and constrained TARCC models had excellent fit [$\chi^2 = 73.6$ (20), $p < 0.001$; CFI = 0.996; RMSEA = 0.028]. All the observed cognitive performance measures loaded significantly on dT2A, ranging from BNT ($r = -0.31$) to LMII ($r = -0.84$; all $p < 0.001$). dT2A exhibited excellent factor determinacy (Table 2). dT2A's factor weights all replicated in a random split of TARCC's sample [ΔCHI SQ = 11.8 (6), $p > 0.05$]. The constrained unadjusted model correlated $r = 0.99$ with CDR-SB ($p < 0.001$). For comparison, IADL correlated $r = 0.86$ ($p < 0.001$) with CDR-SB across TARCC's entire sample.

The dT2A composite achieved an AUC = 0.981 (0.976–0.985) for the discrimination between AD and NC. IADL alone achieved an AUC = 0.936 (0.927–0.945) for the same discrimination. This was statistically inferior to dT2A's by DeLong et al.'s method ($p < 0.001$). dT2A's IADL adjusted bivariate AUC was 0.983. Both dT2A ($p < 001$) and IADL ($p < 0.001$) made significant contributions. The fully adjusted constrained dT2A correlated $r = 0.86$ ($p < 001$) with CDR-SB (Fig. 1).

In ADNI, dT2A's model had excellent fit [$\chi^2 = 12.464$ (7), $p < 0.001$; CFI = 0.999; RMSEA = 0.019]. All the observed cognitive performance measures loaded significantly on dT2A, ranging from BNT ($r = -0.53$) to MMSE ($r = 0.86$; all $p < 0.001$). The unadjusted dT2A exhibited excellent factor determinacy, and correlated $r = 0.96$ with CDR-SB ($p < 0.001$). For comparison, the FAQ correlated $r = 0.83$ ($p < 0.001$) with CDR-SB. dT2A's composite achieved an AUC = 1.0 (0.995–1.00) for the discrimination of AD from NC (Table 2). The FAQ alone achieved an AUC = 0.985 (0.974–0.993) for the same discrimination. This was statistically inferior to dT2A's by DeLong et al.'s method ($p = 0.001$). dT2A's FAQ adjusted bivariate AUC was 0.9997. However, only dT2A made a significant contribution ($p < 0.001$). The FAQ did not enter ($p = 0.08$). The fully adjusted ADNI dT2A correlated $r = 0.96$ ($p < 001$) with CDR-SB (Fig. 2).

In TARCC, dT2A contributed to 5-year prospective AD conversion risk independently of other demographic risks (Table 5). dT2A's effect attenuated all the unadjusted risks, and fully attenuated the effect of depressive symptoms (Table 6).

DISCUSSION

We have employed SEM to construct a latent dementia-specific phenotype engineered to allow direct comparisons between TARCC and the ADNI. dT2A fits well in either dataset, is strongly associated with CDR-SB in both, and has a high AUC for discrimination of AD from controls in both. Thus, it may now be feasible to replicate TARCC's proteomic findings in ADNI.

Replications across these studies would be highly desirable because ADNI offers access to multimodality neuroimaging and AD-specific cerebrospinal fluid biomarkers while TARCC does not. ADNI's biomarkers could be used to test the relevance of TARCC's proteomic findings to AD-specific biomarkers and explore the neuroimaging mediators of their associations with cognitive performance. TARCC has the advantage of a larger and more ethnically diverse sample. Moreover, a third well-characterized cohort, i.e., the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL), also has RBM proteomic data. Like TARCC, its cognitive battery is based on ADNI's. Like ADNI, it measures proteomic data in plasma. It should be possible to construct dT2A in the ABIL dataset and provide yet other opportunities for the independent replication of TARCC's and ADNI's findings.

However, obstacles remain to these goals. First, while TARCC and ADNI share dT2A's indicators, those are but a fraction of the measures available

Table 1
Descriptive statistics by sample (raw scores except where indicated)

	TARCC Total N = 3502	TARCC Group 1 N = 1747	TARCC Group 2 N = 1755	ADNI N = 1738
AD cases	1275 (37.0%)	613 (35.6%)	662 (38.3%)	342 (19.7%)
MCI cases	723 (21.0%)	371 (21.6%)	352 (20.4%)	978 (56.3%)
NC	1445 (41.9%)	734 (42.7%)	711 (41.2%)	417 (24.8%)
Gender (%♀)	61.6	60.0	63.1	55.1
Ethnicity (%MA)	35.7	36.7	34.7	3.4
	Mean (SD)	Mean (SD)	Mean (SD /d2)	Mean (SD /d1, d2, d3)
Age	70.8 (9.6)	70.6 (9.7)	71.0 (9.5/ 0.04†)	73.8 (7.2 / 0.35‡, 0.37, 0.33)
Education	13.3 (4.3)	13.3 (4.3)	13.3 (4.3/ 0.00†)	15.9 (2.9 / 0.71‡, 0.71, 0.71)
MMSE	25.6 (4.7)	25.8 (4.6)	25.4 (4.9/ 0.08†)	27.2 (2.7 / 0.42‡, 0.37, 0.45)
Animals	14.9 (5.5)	15.0 (5.5)	14.9 (5.6/ 0.02†)	17.2 (5.9 / 0.39‡, 0.38, 0.40)
BNT*	7.9 (4.3)	8.0 (4.3)	7.9 (4.2/ 0.02†)	26.1 (4.51 / **)
CDR-SB	2.4 (3.3)	2.3 (3.2)	2.5 (3.4/ 0.06†)	1.6 (1.8 / 0.28‡, 0.27, 0.33)
GDS30	5.6 (5.2)	5.6 (5.3)	5.6 (5.1/ 0.00†)	1.4 (1.4 / 1.09‡, 1.08, 1.12)
LMI	7. 9 (4.2)	7.9 (4.2)	7.8 (4.2/ 0.02†)	9.3 (4.8 / 0.30‡, 0.31, 0.33)
LMII	8.2 (4.6)	8.3 (4.5)	8.2 (4.6/ 0.02†)	7.1 (5.3 / 0.22‡, 0.24, 0.22)
Trails B (s)	144.24 (84.05)	8.0 (3.8)	8.0 (3.9/ 0.00†)	122.2 (75.8 / 0.27‡,-,-)

d1 = Cohen's d versus TARCC's entire sample. d2 = Cohen's d versus TARCC Group 1. d3 = Cohen's d versus TARCC Group 2. *Scaled scores. **TARCC uses 30 item BNT, ADNI uses 60 item BNT. † $p > 0.05$; ‡ $p < 0.001$. ADNI, Alzheimer's Disease Neuroimaging Initiative; Animals, Animal Naming; BNT, Boston Naming Test; CDR-SB, Clinical Dementia Rating scale "Sum of Boxes"; GDS, 30 item Geriatric Depression Scale; LMI, Wechsler Logical Memory immediate recall; LMII, Wechsler Logical Memory delayed recall; MA, Mexican-American; MMSE, Mini-Mental State Examination; SD, standard deviation; TARCC, Texas Alzheimer's Research and Care Consortium; Trails B, Trail Making Test Part B. *Scaled scores.

Table 2
Descriptive statistics by diagnosis (TARCC)

	TARCC Total Sample N = 3502 Mean (SD)	TARCC AD N = 1275 Mean (SD)	TARCC MCI N = 732 Mean (SD)	TARCC Controls N = 1445 Mean (SD)
Gender (%♀)	61.6	56.2	58.0	68.3
Ethnicity (%MA)	36.0	13.7	45.4	50.3
Age	70.79 (9.56)	75.44 (8.41)	71.34 (8.54)	66.42 (8.99)
Education	13.30 (4.28)	14.04 (3.71)	12.73 (4.31)	12.92 (4.63)
MMSE	25.57 (4.73)	21.49 (4.91)	26.81 (2.82)	28.55 (1.91)
Animals	14.92 (5.53)	10.88 (4.66)	14.85 (4.99)	17.45 (4.85)
BNT*	7.92 (4.27)	6.59 (3.58)	7.84 (4.03)	9.11 (4.58)
CDR-SB	2.39 (3.32)	5.76 (3.29)	1.24 (0.88)	0.01 (0.06)
GDS30	5.58 (5.23)	6.06 (5.12)	6.93 (5.76)	4.52 (4.80)
LMI	7.86 (4.22)	4.23 (2.53)	7.67 (3.28)	10.74 (3.39)
LMII	8.22 (4.56)	3.75 (2.39)	8.13 (3.42)	11.69 (3.06)
Trails B (sec)	144.24 (84.05)	210.21 (84.60)	146.85 (77.30)	100.62 (46.31)

*TARCC uses 30 item BNT. Animals, Animal Naming; BNT, Boston Naming Test; CDR-SB, Clinical Dementia Rating scale "Sum of Boxes"; GDS, 30 item Geriatric Depression Scale; LMI, Wechsler Logical Memory immediate recall; LMII, Wechsler Logical Memory delayed recall; MA, Mexican-American; MMSE, Mini-Mental State Examination; SD, standard deviation; TARCC, Texas Alzheimer's Research and Care Consortium; Trails B, Trail Making Test Part B.

in either study. Second, TARCC and ADNI are convenience samples with differing case-mixes and demographic profiles. Third, although they share a common proteomic profile, TARCC and ADNI's blood-based biomarkers have been measured in two different biofluids (i.e., serum and plasma).

dT2A's indicators are but a fraction of the measures available in TARCC and ADNI. We have observed that the diagnostic accuracy of a δ homolog can be affected by its indicators. In general, accuracy improves with larger and more comprehensive batteries. Such batteries are less likely to be compromised by domain-specific variance, and more likely to attain Spearman's *g*. Had there been a greater direct correspondence across these studies, we might have engineered a better homolog.

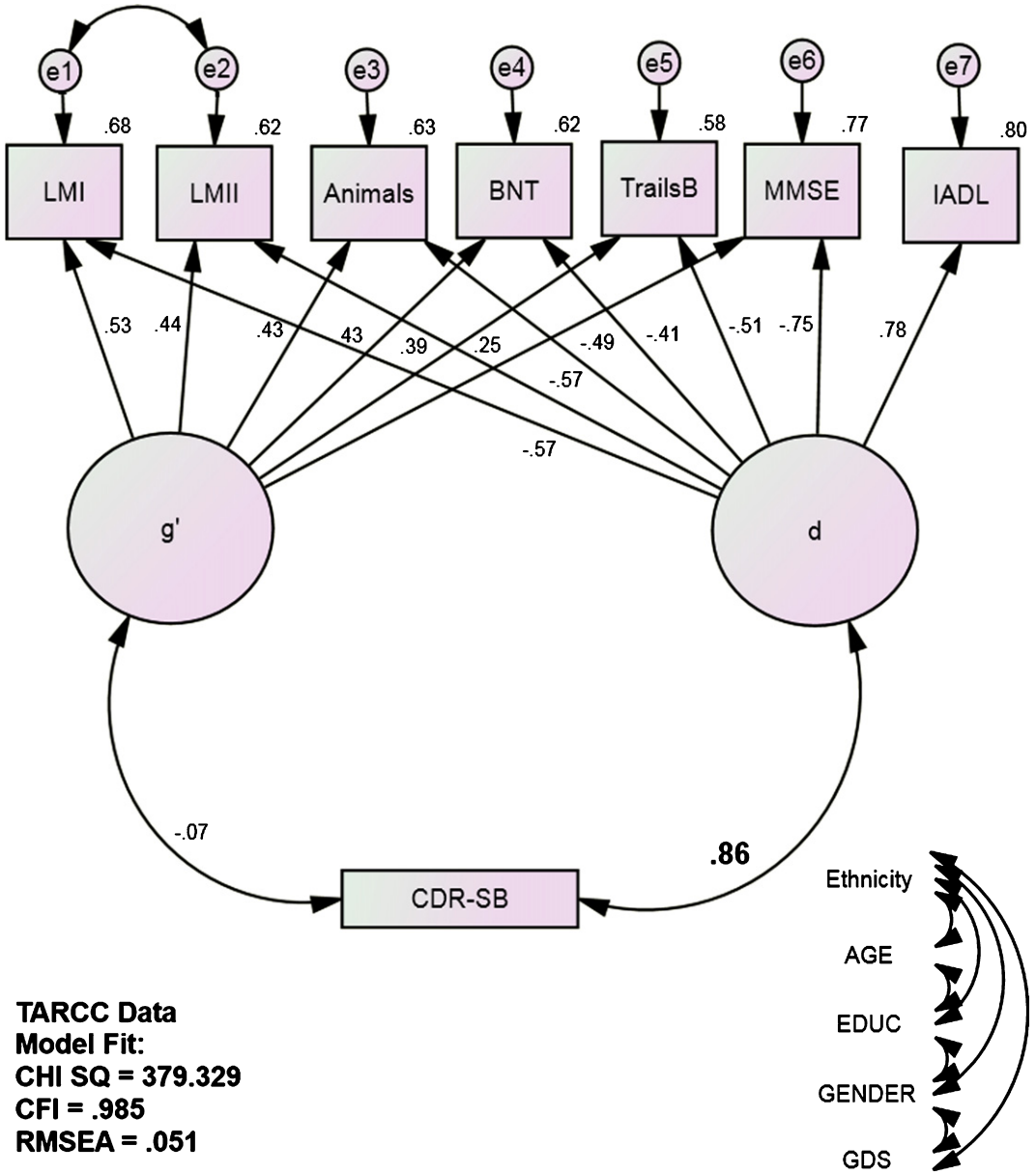

Fig. 1. Fully Adjusted dT2A Homolog and its Association with CDR-SB in TARCC*. *dT2A bifactor δ homolog model in random 50% splits of TARCC's sample and with parameters constrained across splits. All observed indicators are adjusted for age, education, ethnicity, GDS scores, and gender (paths not shown for clarity). Animals, Animal Naming; BNT, Boston Naming Test; CHI QS, Chi Square; CFI, Comparative Fit Index; EDUC, Education (years); GDS, 30 item Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; LMI, Wechsler Logical Memory immediate recall; LMII, Wechsler Logical Memory delayed recall; MMSE, Mini-Mental State Exam; RMSEA, Root Mean Square Evaluative Assessment; TARCC, Texas Alzheimer's Research and Care Consortium; Trails B, Trail-Making Test part B.

Regardless, δ homologs seem to be robustly "indifferent" to their indicators. The current homolog still exhibits a high degree of diagnostic accuracy. The same feature is widely acknowledged to be a property of *g*, and is a notable feature of "intelligence" as measured by these constructs. This property explains one major advantage of our approach. δ homologs can be engineered to accommodate a wide range of agendas. δ can be constructed as easily from bedside assessments as from formal psychometrics [1, 6, 42, 43]. The resulting loss of diagnostic accuracy may be justified by lesser administrative burdens and an

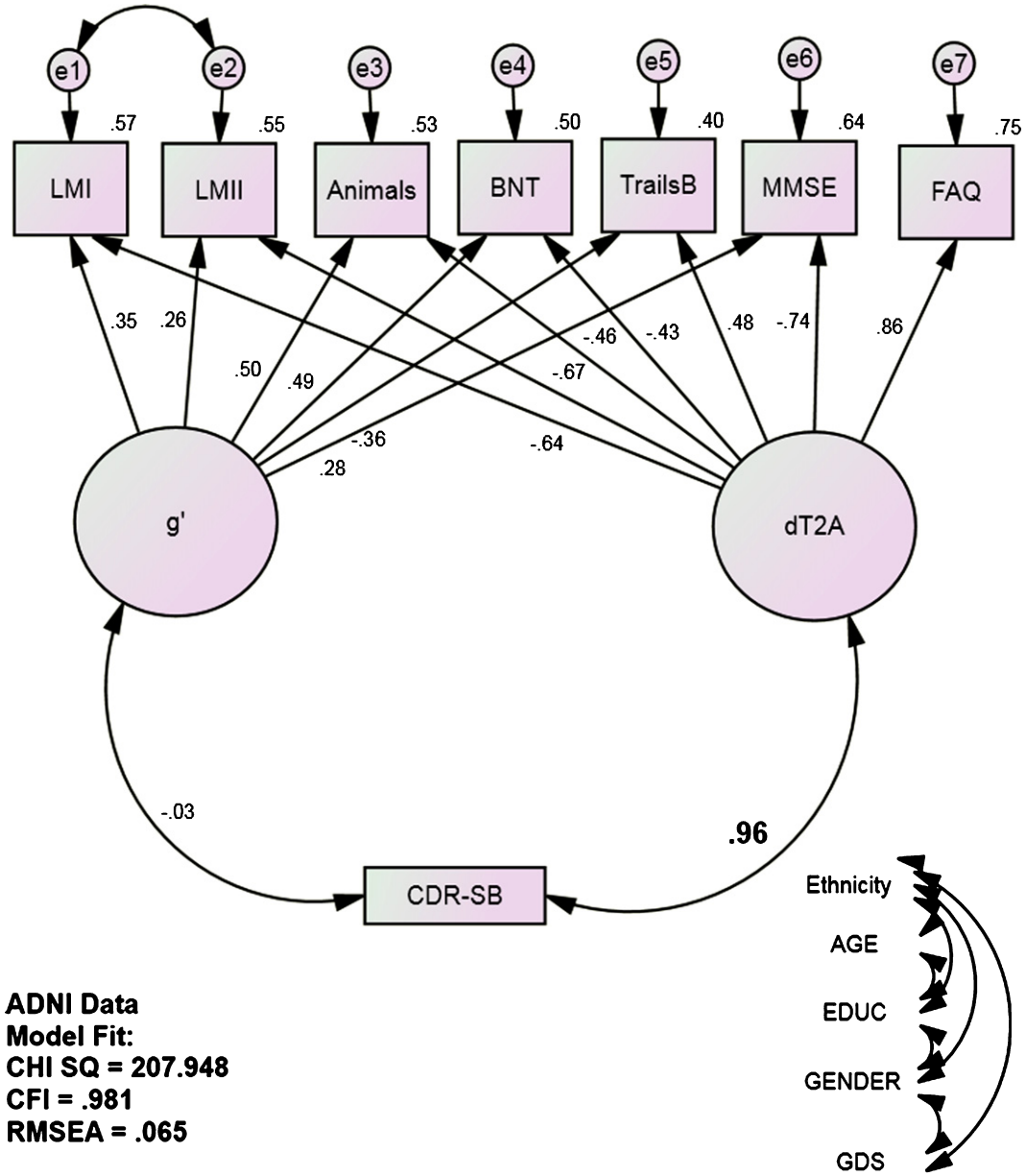

Fig. 2. Fully Adjusted dT2A Homolog and its Association with CDR-SB in ADNI*. *All observed indicators are adjusted for age, education, ethnicity, GDS scores, and gender (paths not shown for clarity). ADNI, Alzheimer's Disease Neuroimaging Initiative; Animals, Animal Naming; BNT, Boston Naming Test; CHI QS, Chi Square; CFI, Comparative Fit Index; EDUC, Education (years); FAQ, Functional Abilities Questionnaire; GDS, 30 item Geriatric Depression Scale; LMI, Wechsler Logical Memory immediate recall; LMII, Wechsler Logical Memory delayed recall; MMSE, Mini-Mental State Exam; RMSEA, Root Mean Square Evaluative Assessment; Trails B, Trail-Making Test part B.

increase in the number and availability of qualified administrators.

δ can be even be constructed from the items sets of individual cognitive measures [44] or from verbal batteries, i.e., in anticipation of telephone administration [45]. However, the loss of diagnostic accuracy may be consequently greater, presumably due to contamination by domain-specific variance, which would be orthogonal to *g* (and δ) when derived from a more comprehensive battery.

Another potential obstacle is that TARCC and ADNI are convenience samples with differing case-mixes and demographic profiles. However, the latent variable approach minimizes non-systematic

Table 3
Descriptive statistics by diagnosis (ADNI)

	ADNI Total Sample N = 1738 Mean (SD)	ADNI AD N = 342 Mean (SD)	ADNI MCI* N = 978 Mean (SD)	ADNI Controls N = 417 Mean (SD)
Gender (%♀)	55.1	44.7	42.8	49.9
Ethnicity (%MA)	3.4	3.5	3.3	3.4
Age	73.8 (7.19)	75.03 (7.79)	72.91 (7.42)	74.76 (5.73)
Education	15.91 (2.86)	15.18 (2.99)	16.00 (2.82)	16.28 (2.73)
MMSE	27.17(2.67)	23.22 (2.07)	27.75 (1.81)	29.07 (1.12)
Animals	17.15 (5.93)	12.25 (4.98)	17.39 (5.22)	20.60 (5.50)
BNT**	25.97 (4.51)	22.24 (6.05)	26.43 (3.68)	27.94 (2.66)
CDR-SB	1.64 (1.79)	4.39 (1.67)	1.36 (0.95	0.03 (0.13)
GDS30	1.42 (1.40)	1.65 (1.44)	1.63 (1.41)	0.75 (1.12)
LMI	9.28 (4.83)	4.08 (2.80)	9.10 (3.91)	13.98 (3.25)
LMII	7.07 (5.33)	1.37 (1.89)	6.46 (4.10)	13.18 (3.33)
Trails B (s)	122.23 (75.78)	191.46 (89.69)	113.61 (65.42)	85.68 (43.18)

*Includes all subtypes and subjective cognitive impairment (SCI). **ADNI uses 60 item BNT. ADNI, Alzheimer's Disease Neuroimaging Initiative; Animals, Animal Naming; BNT, Boston Naming Test; CDR-SB, Clinical Dementia Rating scale "Sum of Boxes"; GDS, 30 item Geriatric Depression Scale; LMI, Wechsler Logical Memory immediate recall; LMII, Wechsler Logical Memory delayed recall; MA, Mexican-American; MMSE, Mini-Mental State Examination; SD, standard deviation; Trails B, Trail Making Test Part B.

Table 4
Validation of dT2A's Properties in TARCC versus ADNI

Comparison	TARCC (N = 3503)*	ADNI (N = 1737)
DT2A Model Fit: CHISQ (df); CFI; RMSEA	73.6(20); 0.996; 0.028	12.464(7); 0.999; 0.019
DT2A's Factor Determinacy [71] (MultR; RSQR; MinCor)	0.999, 0.997; 0.994	0.999; 0.999; 0.999
AUC for AD v NC (95% CI)	0.981 (0.976–0.985)	1.0 (0.995–1.00)
Correlation with CDR-SB	$r = 0.99$, $p < 0.001$	$r = 0.96$, $p < 0.001$

*Constrained across random 50% splits.

Table 5
Logistic regression of dT2A's significant association with 5-year prospective AD conversion from non-demented states [normals and mild cognitive impairment (TARCC data)]

Parameter	Estimate	SE	χ^2	p
Intercept	–1.266	0.183	47.939	<0.001
Age >80 y	0.770	0.215	12.853	<0.001
Ethnicity	–1.132	0.205	30.504	<0.001
GDS_{30} >10	–0.009	0.238	0.001	0.970
APOE ε4	0.692	0.185	14.058	<0.001
dT2A	–2.623	0.213	152.073	<0.001

measurement bias, including cultural and linguistic bias. TARCC has a relatively high prevalence of Hispanic participants, many of whom were tested in Spanish, and with significantly lower educational attainment. Regardless, δ's factor loadings, obtained from data collected in TARCC, have been exported to Japanese data without loss of diagnostic accuracy [47], and δ homologs perform similarly in well-characterized European [43] and Asian [48] samples.

Table 6
Odds ratios (OR)

Risk Factor	Unadjusted OR (95% CI)	dT2A Adjusted OR (95% CI)
Age >80 y	2.977 (2.02–4.38)	2.160 (1.41–3.29)
Ethnicity	0.540 (0.38–0.77)	0.323 (0.21–0.48)
GDS30 >10	1.656 (1.09–2.53)	0.991 (0.62–1.58)*
APOE ε4	2.350 (1.69–3.28)	1.998 (1.39–2.87)
dT2A		0.073 (0.05–0.11)

*Non-significant.

Therefore, we did not attempt to demonstrate factor equivalence across these samples. We reasoned instead that the effects of study-specific demographic differences would be pushed up into δ's residuals, potentially changing its indicator loadings, but without necessarily compromising its performance. This seems to be validated by δ's similar performance across cohorts.

TARCC and ADNI also differ in their case-mixes. Since d-scores are standardized to each study's distribution, the optimal diagnostic threshold may not replicate across samples. However, we have reported that factor weights derived *post hoc* (as in this application) in poorly-characterized epidemiological samples can be exported into well-characterized samples for validation and the resulting thresholds exported back to the original sample without performance compromise [46].

Moreover, there may be cross-sample variation with regard to the within diagnosis prevalence of AD-specific biomarkers. Even though both the current samples are likely to be highly enriched with AD cases, no AD-specific biomarkers are available in TARCC, while a clinical diagnosis of "AD" is not confirmed by amyloid imaging in a substantial fraction of cases [49, 50]. We cannot be sure that a clinical diagnosis of "AD" is bioequivalent across these cohorts.

Regardless, δ appears to be "agnostic" to dementia's etiology [6, 7]. Just as δ distinguishes functionally-salient cognitive variance from cognitive impairment *per se*, its biomarkers (including any disease-specific ones) should distinguish dementia-salient biological processes from non-dementing ones, e.g., the disease-specific cognitive changes recently shown to orthogonal to δ [7]. Thus, the distinction between δ and disease-specific cognitive changes may allow for the identification of functionally-salient dementia-specific biomarkers.

Moreover, clinical dementia in either cohort is likely to be "overdetermined" by multiple contributors to δ's variance [51]. Age, the APOE ε4 allele, and depressive symptoms contribute variance to δ independently of each other [12]. Each of their effects is mediated by largely non-overlapping sets of serum proteins [13–16]. Cross-study differences in the prevalence of these risks could alter δ's biomarker associations.

dT2A attenuates multiple prospective "AD risks" in TARCC, and fully explains the nearly twofold conversion risk associated with depressive symptoms. However, to the extent that dT2A failed to fully attenuate the other risks, they can be said to contribute to conversion *independently of disabling cognitive decline*. That insight implies demographic bias in clinicians' estimates of cognitive status. Second, AD-specific neurodegeneration may not mediate either age's or depression's effects on δ [43, 52]. Moreover, without either autopsy or AD-specific cerebrospinal fluid or neuroimaging biomarkers, it remains unclear from TARCC data whether AD-specific neurodegeneration is involved in any of these dementing processes.

We have associated an ethnicity equivalent δ homolog (i.e., "dEQ") with multiple serum proteins in TARCC [13]. Similarly, O'Bryant et al. have identified yet another set of proteins related to clinical "AD" [53]. The latter have not yet been tested for their relationship to δ, but it seems very likely that they will be related, given their relatively high AUC for the discrimination of AD from controls in TARCC [54] and other cohorts [55, 56]. The relationship of these biomarkers to those we have associated with δ [11] is yet untested, but there is little overlap across the two sets. O'Bryant et al. find evidence for their panel's association with dementia in Hispanics [57], while we do not for ours [11, 12].

Finally, TARCC and ADNI's blood-based biomarkers have been measured in two different biofluids (i.e., serum and plasma). Some observers opine that blood biomarker studies are plagued by failure to replicate findings. Regardless, none have employed our (latent variable) SEM methods. Those can be applied equally to biomarkers as to cognitive batteries. Moreover, few studies have employed samples as large as TARCC's, which is twice as large as ADNI's. We remain optimistic that this approach will finally allow for biomarker replications cross-cohort and across biofluids.

ACKNOWLEDGMENTS

This project was supported in part by funding provided to the Texas Alzheimer's Research and Care Consortium by the Darrell K Royal Texas Alzheimer's Initiative, directed by the Texas Council on Alzheimer's Disease and Related Disorders and by the Julia and Van Buren Parr endowment for the study of Alzheimer's disease. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Texas Alzheimer's Research and Care Consortium List of Investigators

Baylor College of Medicine: Valory Pavlik PhD, Paul Massman PhD, Eveleen Darby MA/MS, Monica Rodriguear MA, Aisha Khaleeq Ansari MD; Texas Tech University Health Sciences Center: John C. DeToledo MD, Hemachandra Reddy PhD, Henrick Wilms MD, PhD, Kim Johnson PhD, Victoria Perez; University of North Texas Health Science Center: Thomas Fairchild PhD, Janice Knebl DO, Sid E. O'Bryant PhD, James R. Hall PhD, Leigh Johnson PhD, Robert C. Barber PhD, Douglas Mains DrPH, Lisa Alvarez; University of Texas Southwestern Medical Center: Munro Cullum PhD, Roger Rosenberg MD, Benjamin Williams MD, PhD, Mary Quiceno MD, Joan Reisch PhD, Linda S. Hynan PhD, Ryan Huebinger PhD, Janet Smith, Trung Nguyen MD, PhD; University of Texas Health Science Center – San Antonio: Donald Royall MD, Raymond

Palmer PhD, Marsha Polk; Texas A&M University Health Science Center: Alan Stevens PhD, Marcia Ory PhD/MPH; University of Texas at Austin/Dell Medical School: David Paydarfar MD, John Bertelson MD, Martin Woon PhD, Gayle Ayres DO; Alyssa Aguirre LCSW; University of North Carolina: Kirk C. Wilhelmsen MD, PhD, Jeffrey L. Tilson PhD.

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/17-1053r4).

REFERENCES

[1] Royall DR, Palmer RF, O'Bryant SE (2012) Validation of a latent variable representing the dementing process. *J Alzheimers Dis* **30**, 639-649.

[2] Royall DR, Lauterbach EC, Kaufer DI, Malloy P, Coburn KL, Black KJ; Committee on Research of the American Neuropsychiatric Association (2007) The cognitive correlates of functional status: A review from the Committee on Research of the American Neuropsychiatric Association. *J Neuropsychiatry Clin Neurosci* **19**, 249-265.

[3] Spearman C (1904) General intelligence, objectively determined and measured. *Am J Psychol* **15**, 201-293.

[4] Royall DR, Palmer RF (2014) "Executive functions" cannot be distinguished from general intelligence: Two variations on a single theme within a symphony of latent variance. *Frontiers Behav Neurosci* **8**, 369.

[5] Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL (1982) A new clinical scale for the staging of dementia. *Br J Psychiatry* **140**, 566-572.

[6] Gavett BE, Vudy V, Jeffrey M, John SE, Gurnani A, Adams J (2015) The δ latent dementia phenotype in the NACC UDS: Cross-validation and extension. *Neuropsychology* **29**, 344-352.

[7] John SE, Gurnani AS, Bussell C, Saurman JL, Griffin JW, Gavett BE (2016) The effectiveness and unique contribution of neuropsychological tests and the δ latent phenotype in the differential diagnosis of dementia in the Uniform Data Set. *Neuropsychology* **30**, 946-960.

[8] Waring S, O'Bryant SE, Reisch JS, Diaz-Arrastia R, Knebl J, Doody R; for the Texas Alzheimer's Research Consortium (2008) The Texas Alzheimer's Research Consortium longitudinal research cohort: Study design and baseline characteristics. *Texas Public Health J* **60**, 9-13.

[9] Bishnoi R, Palmer RF, Royall DR (2015) IL-15 as a serum biomarker of Alzheimer disease. *PLoS One* **10**, e0117282.

[10] Bishnoi R, Palmer RF, Royall DR (2015) Vitamin D binding protein as a serum biomarker of Alzheimer disease. *J Alzheimers Dis* **43**, 37-45.

[11] Royall DR, Palmer RF (2015) Ethnicity moderates dementia's biomarkers. *J Alzheimers Dis* **43**, 275-287.

[12] Royall DR, Palmer RF (2016) Thrombopoeitin is associated with δ's intercept, and only in Non-Hispanic Whites. *Alzheimers Dement (Amst)* **3**, 35-42.

[13] Royall DR, Al-Rubaye S, Bishnoi R, Palmer RF (2016) Serum protein mediators of dementia and Aging Proper. *Aging* **8**, 3241-3254.

[14] Royall DR, Al-Rubaye S, Bishnoi R, Palmer RF (2016) Serum protein biomarkers of δ fully mediate multiple AD conversion risks and offer targets for intervention [abstract]. *J Prevention Alzheimers Dis* **3**, 283.

[15] Royall DR, Al-Rubaye S, Bishnoi R, Palmer RF (2017) Few serum proteins mediate APOE's association with dementia. *PLoS One* **12**, e0172268.

[16] Royall DR, Al-Rubaye S, Bishnoi R, Palmer RF (2017) Serum protein mediators of depression's association with dementia. *PLoS One* **12**, e0175790.

[17] O'Bryant SE, Lista S, Rissman RA, Edwards M, Zhang F, Hall J, Zetterberg H, Lovestone S, Gupta V, Graff-Radford N, Martins R, Jeromin A, Waring S, Oh E, Kling M, Baker LD, Hampel H (2015) Comparing biological markers of Alzheimer's disease across blood fraction and platforms: Comparing apples to oranges. *Alzheimers Dement (Amst)* **3**, 27-34.

[18] Weiner MW, Veitch DP (2015) Introduction to special issue: Overview of Alzheimer's Disease Neuroimaging Initiative. *Alzheimers Dement* **11**, 730-733.

[19] McKhann D, Drockman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group. *Neurology* **34**, 939-944.

[20] Kaplan EF, Goodglass H, Weintraub S (1983) *The Boston Naming Test*. Experimental edition. Kaplan & Goodglass. 2nd ed., Boston, Lea & Febiger, Philadelphia.

[21] Morris JC, Heyman A, Mohs RC, Hughes JP, vanBelle G, Fullenbaum G, Heyman A (1989) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* **39**, 1159-1165.

[22] Wechsler D (1997) *Wechsler Memory Scale – Third Edition*. The Psychological Corporation, San Antonio, TX.

[23] Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatry Res* **12**, 189-198.

[24] Reitan RM (1958) Validity of the Trail Making test as an indicator of organic brain damage. *Perceptual Motor Skills* **8**, 271-276.

[25] Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM, Filos S (1982) Measurement of functional activities in older adults in the community. *J Gerontol* **37**, 323-329.

[26] Lawton MP, Brody EM (1969) Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179-186.

[27] Juva K, Mäkelä M, Erkinjuntti T, Sulkava R, Yukoski R, Valvanne J, Tilvis R (1997) Functional assessment scales in detecting dementia. *Age Ageing* **26**, 393-400.

[28] Teng E, Becker BW, Woo E, Cummings JL, Lu PH (2010) Subtle deficits in instrumental activities of daily living in subtypes of mild cognitive impairment. *Dement Geriatr Cogn Disord* **30**, 189-197.

[29] O'Bryant SE, Xiao G, Edwards M, Devous M, Gupta VB, Martins R, Zhang F, Barber R; Texas Alzheimer's Research and Care Consortium (TARCC) (2013) Biomarkers of Alzheimer's disease among Mexican Americans. *J Alzheimers Dis* **34**, 841-849.

[30] Sheikh JI, Yesavage JA (1986) Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clin Gerontologist* **5**, 165-173.

[31] Maixner SM, Burke WJ, Roccaforte WH, Wengel SP, Potter JF (1995) A comparison of two depression scales in a geriatric assessment clinic. *Am J Geriatr Psychiatr* **3**, 60-67.

[32] Burke WJ, Houston MJ, Boust SC, Roccaforte WH (1989) Use of the Geriatric Depression Scale in dementia of the Alzheimer type. *J Am Geriatr Soc* **37**, 856-860.

[33] Arbuckle JL (2006) *Analysis of Moment Structures-AMOS* (Version 7.0) [Computer Program], SPSS, Chicago.

[34] Schafer JL, Graham JW (2002) Missing data: Our view of the state of the art. *Psychol Methods* **7**, 147-177.

[35] Graham JW (2009) Missing data analysis: Making it work in the real world. *Ann Rev Psychology* **6**, 549-576.

[36] Bollen KA, Long JS (1993) *Testing Structural Equation Models*. Sage Publications, Thousand Oaks, CA.

[37] Wheaton B, Muthén B, Alwin DF, Summer GF (1977) Assessing reliability and stability in panel models. In *Sociology Methodology*, Heise DR, ed. Jossey-bass, San Francisco, CA.

[38] Bentler PM (1990) Comparative fit indexes in structural models. *Psychol Bull* **107**, 238-246.

[39] Browne M, Cudeck R (1993) Alternative ways of assessing model fit. In *Testing structural equation models*, Bollen KA, Long JS, eds. Sage Publications, Thousand Oaks, CA, pp. 136-162.

[40] McDonald RP, Bolt DM (1998) The determinacy of variables in structural equation models. *Multivariate Behav Res* **33**, 385-401.

[41] Grice JW (2001) Computing and evaluation factor scores. *Psychol Methods* **6**, 430-450.

[42] Royall DR, Matsuoka T, Palmer RF, Kato Y, Taniguchi S, Ogawa M, Fujimoto H, Okamura A, Shibata K, Nakamura K, Nakaaki S, Koumi H, Mimura M, Fukui K, Narumoto J (2015) Greater than the sum of its parts: δ Improves upon a battery's diagnostic performance. *Neuropsychology* **29**, 683-692.

[43] Koppara A, Wolfsgruber S, Kleineidam L, Schmidtke K, Frölich L, Kurz A, Schulz S, Hampel H, Heuser I, Peters O, Reischies FM, Jahn H, Luckhaus C, Hüll M, Gertz H-J, Schröder J, Pantel J, Rienhoff O, Rüther E, Henn F, Wiltfang J, Maier W, Jessen F, Kornhuber J, Wagner M (2016) The latent dementia phenotype δ is associated with CSF biomarkers of Alzheimer disease and predicts conversion to AD dementia in subjects with MCI. *J Alzheimers Dis* **49**, 547-560.

[44] Royall DR, Palmer RF, Matsuoka T, Kato Y, Taniguchi S, Ogawa M, Fujimoto H, Okamura A, Shibata K, Nakamura K, Nakaaki S, Koumi H, Mimura M, Fukui K, Narumoto J (2016) Greater than the sum of its parts: δ can be constructed from item level data. *J Alzheimers Dis* **49**, 571-579.

[45] Royall DR, Palmer RF (2018) Construction of a potential telephone assessment of dementia prevalence and severity. *J Neuropsychiatry Clin Neurosci* **30**, 202-207.

[46] Royall DR, Palmer RF, Markides KS (2017) Exportation and validation of latent constructs for dementia case finding in a Mexican American population-based cohort. *J Gerontol B Psychol Sci Social Sci* **72**, 947-955.

[47] Royall DR, Palmer RF, Matsuoka T, Kato Y, Taniguchi S, Ogawa M, Fujimoto H, Okamura A, Shibata K, Nakamura K, Nakaaki S, Koumi H, Mimura M, Fukui K, Narumoto J (2016) Greater than the sum of its parts: δ scores are exportable across cultural and linguistic boundaries. *J Alzheimers Dis* **49**, 561-570.

[48] Peh CX, Abdin E, Vaingankar JA, Verma S, Chua BY, Sagayadevan V, Seow E, Zhang Y, Shahwan S, Ng LL, Prince M, Chong SA, Subramaniam M (2016) Validation of a latent construct for dementia in a population-wide dataset from Singapore. *J Alzheimers Dis* **55**, 823-833.

[49] Witte MM, Trzepacz P, Case M, Yu P, Hochstetler H, Quinlivan M, Sundell K, Henley D (2014) Association between clinical measures and florbetapir F18 PET neuroimaging in mild or moderate Alzheimer's disease dementia. *J Neuropsychiatry Clin Neurosci* **26**, 214-220.

[50] Degenhardt EK, Witte MM, Case MG, Yu P, Henley DB, Hochstetler HM, D'Souza DN, Trzepacz PT (2016) Florbetapir F18 PET amyloid neuroimaging and characteristics in patients with mild and moderate Alzheimer dementia. *Psychosomatics* **57**, 208-216.

[51] White LR, Edland SD, Hemmy LS, Montine KS, Zarow C, Sonnen JA, Uyehara-Lock JH, Gelber RP, Ross GW, Petrovitch H, Masaki KH, Lim KO, Launer LJ, Montine TJ (2016) Neuropathologic comorbidity and cognitive impairment in the Nun and Honolulu-Asia Aging Studies. *Neurology* **86**, 1000-1008.

[52] Royall DR, Palmer RF (2013) Alzheimer's disease pathology does not mediate the association between depressive symptoms and subsequent cognitive decline. *Alzheimers Dement* **9**, 318-325.

[53] O'Bryant SE, Xiao G, Zhang F, Edwards M, German DC, Yin X, Como T, Reisch J, Huebinger RM, Graff-Radford N, Dickson D, Barber R, Hall J, O'Suilleabhain P, Grammas P (2014) Validation of a serum screen for Alzheimer's disease across assay platforms, species, and tissues. *J Alzheimers Dis* **42**, 1325-1335.

[54] O'Bryant SE, Xiao G, Barber R, Reisch J, Hall J, Cullum CM, Doody R, Fairchild T, Adams P, Wilhelmsen K, Diaz-Arrastia R; Texas Alzheimer's Research and Care Consortium (2011) A blood-based algorithm for the detection of Alzheimer's disease. *Dement Geriatr Cogn Disord* **32**, 55-62.

[55] O'Bryant SE, Xiao G, Barber R, Huebinger R, Wilhelmsen K, Edwards M, Graff-Radford N, Doody R, Diaz-Arrastia R; Texas Alzheimer's Research & Care Consortium; Alzheimer's Disease Neuroimaging Initiative (2011) A blood-based screening tool for Alzheimer's disease that spans serum and plasma: Findings from TARC and ADNI. *PLoS One* **6**, e28092.

[56] O'Bryant SE, Edwards M, Johnson L, Hall J, Villarreal AE, Britton GB, Quiceno M, Cullum CM, Graff-Radford NR (2016) A blood screening test for Alzheimer's disease. *Alzheimers Dement (Amst)* **3**, 83-90.

[57] Villarreal AE, O'Bryant SE, Edwards M, Grajales S, Britton GB; Panama Aging Research Initiative (2016) Serum-based protein profiles of Alzheimer's disease and mild cognitive impairment in elderly Hispanics. *Neurodegener Dis Manag* **6**, 203-213.