REFINING A LATENT DEMENTIA INDICATOR FOR A MULTI-STUDY CONSORTIUM

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I. Introduction

- A variety of dementia indicators have been proposed when clinical diagnoses are unavailable, ranging from cutoff scores on a cognitive screening measure such as MMSE to weighted combinations of cognitive test scores.
- Latent variable dementia indicators, "delta" (δ), are reliable predictors of dementia risk (Gavett et al., Peh et al., Royall & Palmer). δ reflects variance in a set of cognitive and functional ability indicators beyond variance accounted for by a general intelligence factor (g') solely indicated by cognitive scores. δ is a continuous measure of liability to dementia.
- We built on this δ approach utilizing samples from the Interplay of Genes and Environment in Multiple Studies (IGEMS) consortium. Instead of creating a separate latent construct of g', we correlated the residuals of cognitive items that are indicative of cognitive ability. We also included memory and functional ability as indicators of δ.
- We first examined samples where clinical diagnoses were available to test the validity of δ. We then applied this approach with a sample where clinical diagnoses were not available.

II. Goals

- Goal 1: Assign δ scores in IGEMS studies where cognitive, memory, and functional ability assessments and dementia diagnoses were available
- Goal 2: Estimate sensitivity, specificity, and accuracy against clinical diagnosis of dementia
- Goal 3: Assign δ scores and dementia status to participants in studies where cognitive and/or functional assessments were available but no clinical diagnosis was available
- Goal 4: Use the twin sample to estimate heritability of δ and heritability of clinical diagnoses.

III. Method: IGEMS Studies

- Within IGEMS, we examined 5 studies, selecting most recent assessment wave with cognitive, memory, and/or functional ability scores (*n*s reported are analytic sample):
- Swedish Twin Registry (STR): Including Harmony (impaired twins and their co-twins), SATSA (Swedish Adoption/Twin Study of Aging; same-sex pairs), Gender (opposite-sex pairs)
- Older Australian Twins Study (OATS)
- Carolina African American Twin Study of Aging (CAATSA)

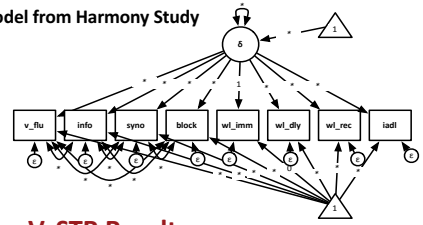
Table 1. Study Demographics

Study	N	% Female	# of Twin Type			Mean Age (SD)	% Demented (method)
			MZ	DZ-ss	DZ-os		
Harmony	1,381	56%	391	611	349	81.0 (7.41)	41% (clinical)
SATSA	548	60%	197	348	0	77.8 (8.92)	12% (clinical)
GENDER	479	50%	0	0	479	80.0 (3.96)	17% (clinical)
OATS	599	65%	332	162	88	74.9 (5.70)	4% (clinical)
CAATSA	675	41%	241	261	166	49.2 (14.5)	21% (TICS<27)

IV. δ Analytic Procedure

Fig 1. Example of δ Model from Harmony Study

- Confirmatory Factor Analysis (1-factor model)
- Multigroup modeling in Swedish studies
- Single group models for OATS and CAATSA
- Manifest items scaled to % correct and age adjusted
- δ means & variances scaled by immediate recall (word list or logical memory)

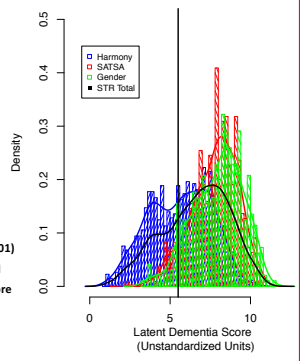


V. STR Results

Table 2. δ Loadings, Means, & Variances

Raw Results	Harmony (*n*=1381)	SATSA (*n*=548)	Gender (*n*=479)
LOADINGS	δ	δ	δ
Verbal Fluency	0.43		
Block Design	0.60	0.71	0.55
Synonyms		0.65	0.72
Symbol Digit	0.48	0.53	0.47
Information	0.73	0.83	
Digits_Forward		0.29	
Digits_Backward		0.60	
Analogies		0.68	
Rotation A		0.66	0.39
Figure Identification_A		0.65	0.39
List Immediate Sum	1.00=	1.00=	1.00=
List Delayed Recall	1.12	1.39	1.52
List Recognition	1.17	0.82	0.58
Thurstone		0.84	0.76
Logical Memory			
IADL (functional abilities)	-0.80	-0.25	-0.35
Delta	M=5.53 Var=4.31	M=7.68 Var=2.51	M=7.85 Var=2.84

Fig 2. δ Scores



- δ correlation with clinical diagnosis = .72 , MMSE = .37 (*p*s <. 001)
- Means and variances of δ differed across 3 studies as expected
- Sensitivity, specificity, and accuracy were good with 5.5 cut score

Table 3. Tests of δ Validity

False +	Sensitivity	Specificity	PPV	NPV	Accuracy	Disease Prevalence
165 (6.9%)	82.9	90.3	78.0	92.7	88.1	29.5

VI. Other Study Results

Table 4. δ in OATS

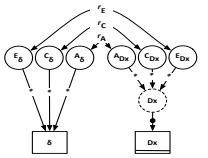
N=599	δ FACTOR LOADINGS
Trails A	0.10
Digit Symbol	0.34
Naming	0.37
Semantic Fluency	0.27
Block Design	0.55
Verbal Fluency	0.19
Trails B	0.12
Digits Forward	0.18
Digits Backward	0.37
Similarities	0.61
Logical Memory Delayed	0.80
List Immediate Sum	1.00=
List Immediate Recall	1.56
List Delayed Recall	1.65
Visual Memory	0.33
Logical Memory Immediate	0.69
IADL (functional abilities)	-0.13
Delta	M=7.24 Var=1.86

Table 5. δ in CAATSA

N=675	δ FACTOR LOADINGS
Digits Forward	0.32
Digits Backward	0.44
Digit Symbol	0.48
List Immediate	0.48
Logical Memory Immediate	1.00=
Logical Memory Delayed	0.80
Alpha Span	0.52
IADL (functional abilities)	-0.09
Delta	M=2.48 Var=1.40

- OATS δ correlation with MMSE = .53 (*p* <. 001)
- CAATSA δ correlation with TICS (removing List Immediate included in δ) = .48 (*p* <. 001)

VII. Heritability Analytic Procedure & Results



Note. A = additive genetic component; C = shared environmental component; E = nonshared environmental component. δ = latent dementia scores; Dx = clinical diagnosis of dementia; rA = genetic correlation; rC = shared environmental correlation; rE = nonshared environmental correlation; * indicate estimated factor loadings; the dashed circle indicates that the binary variable (rectangle with single horizontal line) is transformed into a continuous latent variable using a probit link function (solid dot) based on the thresholds.

Table 6. Model Estimates in All Studies

	STR		OATS		CAATSA
	Delta	Clinical Dx	Delta	Clinical Dx	Delta
Model					
A	.43 (.16 - .56)	.37 (.12 - .53)	.60 (.45- .69)	.67 (.00 - .12)	.68 (.34 - .77)
C	.04 (.00 - .24)	.02 (.00 - .21)	.00 (.00 - .12)	.19 (.00 - .63)	.01 (.00 - .32)
E	.53 (.44 - .64)	.61 (.47 - .75)	.40 (.31 - .51)	.14 (.03 - .37)	.31 (.23 - .41)
Correlations					
rA	-1.00 (-1.00, -.94)		-.94 (-1.0, -.72)		
rC	-.94 (-.96, -.91)		-.83 (-.91, -.72)		
rE	-.90 (-.95, -.83)		-1.0 (-1.0, -.60)		

VIII. Conclusions

- Results support validity of a latent dementia model in differentiating residual cognitive ability from δ as a construct that strongly overlaps with dementia risk.
- The same genetic sources of variance strongly contribute to both δ and clinical diagnosis, indicating that δ is a genetically-informative phenotype.

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