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Editorial

Welcome Back to Your Future: The Assessment of Dementia by the Latent Variable "δ"

Donald R. Royall[a,b,*]
[a]*Departments of Psychiatry, Medicine, Family and Community Medicine, The University of Texas Health Science Center, San Antonio, TX, USA*
[b]*South Texas Veterans' Health System Audie L. Murphy Division GRECC, San Antonio, TX, USA*

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Abstract. The latent variable "δ" (for "dementia") has been proposed as a phenotype for all cause dementia. δ is extracted from cognitive batteries by a specific confirmatory factor analysis in a structural equation modeling framework. δ appears to be uniquely responsible for cognition's association with functional status. Because it is extracted from Spearman's general intelligence factor "*g*", this has broad implications for dementia's assessment and pathophysiology. This issue of the *Journal of Alzheimer's Disease* brings together several demonstrations of δ's psychometric properties by investigative groups from three continents. In their aggregate, they suggest that δ homologs may have far ranging applications in dementia's clinical assessment and biomarker selection.

Keywords: Alzheimer's disease, dementia, intelligence, latent variable, longitudinal

In this issue of the *Journal of Alzheimer's Disease*, several articles addressing the latent variable "δ" (for "dementia") are assembled. δ is a *latent* variable, meaning that it cannot be measured directly. Instead, δ is derived from a theory-driven confirmatory factor analysis in a structural equation model framework.

Our approach 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 the functional disability; and 3) The disability must be related to the cognitive impairment(s) that are observed.

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

This implies that the essential features of any dementia can be resolved to the cognitive correlates of functional status. δ embodies those correlates, making them amenable to empirical description.

The use of latent variables for dementia assessment has several potential advantages over observed test scores. First, when compared to observed scores, latent variables are relatively free of measurement error, which has challenged the psychometric enterprise since its inception. The structural equation model shows how it can be inaccurate to attribute observed scores solely to the domain a test purports to measure. Some variance in observed scores is always attributable to measurement bias (e.g., educational, linguistic or cultural).

Moreover, there is even more information buried in observed cognitive performance. All cognitive measures are also informed by intelligence. This was first

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demonstrated by Spearman at the dawn of neuropsychology [2]. Spearman actually invented factor analysis to demonstrate his general intelligence factor, "*g*".

However, Spearman labored long before the advent of computing. Despite his demonstration of *g*, clinicians have persisted in a domain-specific way of thinking about dementia, i.e., as a disorder of memory, executive function, etc. [3]. δ demonstrates that memory tests measure more than memory, and that only δ's fraction, which is a subset of *g*'s, is relevant to Instrumental Activities of Daily Living, and therefore to dementia. Where has *g* been in our recent thinking on dementia? Might *g* explain dementia's "global" effects, observed across multiple cognitive domains? How would that finding constrain dementia's biomarkers? These are the questions addressed in this issue.

δ's strong and specific association with clinical dementia has been demonstrated repeatedly by receiver operating curves and by its strong correlation with dementia severity, as measured for example by the Clinical Dementia Rating Scale (CDR) [4]) (e.g., [5–7]). As a lucky happenstance, δ's derivation from *g* also ensures that it can be abstracted from almost any psychometric battery, provided that it also includes a measure of Instrumental Activities of Daily Living. We have explored this claim down to item level-data [8]. Thus, it appears that δ might be constructed *post hoc* from literally *any* existing dataset, or prospectively from variables selected for other agendas (e.g., brevity, cost, low administrative burden, or availability in translation). Because there are so many possible batteries from which to construct δ, we refer to each specific embodiment as a δ "homolog."

Furthermore, a latent variable's factor weights can be used to create a composite score by using them to weight the observed indicator scores, and summing those products. Thus, δ can be output as a "d-score". While δ's "reification" as a composite score potentially introduces new biases, 1) these are not the familiar cultural or linguistic biases that plague the cross-cultural interpretation of observed measures, and 2) the composites' diagnostic accuracy remains impressive, as evidenced by these and many prior analyses.

The strength of δ is primarily the result of its unique bifactor derivation, not its behavior as a latent variable, *per se*. For the purposes of dementia case finding, the entire variance of *g*' is irrelevant, as is evidenced by its poor receiver operating curve, and therefore constitutes another form of "measurement error" from which all δ homologs are immune.

The d-score provides a continuous measure of dementia severity, a dementia phenotype. This phenotype can be interrogated for its biomarkers [9–11]. The current articles add new information on the psychometric properties and biomarkers of δ. Three of the analyses were recently presented as a symposium at the 43rd Annual Meeting of the International Neuropsychological Society in Denver, Colorado. Previously, Gavett et al. [7] demonstrated a strong correlation between longitudinal changes in δ and change in the CDR, using the National Alzheimer's Coordinating Center (NACC)'s Uniform Dataset (UDS) ($n = 26{,}606$). Gavett et al. performed that analysis by computing d-scores over serial assessments and using those as "observed" indicators of a latent growth curve (LGC).

However, there is more than one way to approach this problem. Palmer & Royall [12] have replicated Gavett's findings by constructing δ entirely from latent indicators, themselves latent slope estimates derived from LGCs of longitudinally observed cognitive performance. This maximizes the latent variable approach's relative freedom from measurement error. Incidentally, it also confirms Gavett et al.'s demonstration of δ's strong longitudinal association with the CDR in a second and ethnically diverse cohort with a different psychometric battery and functional status measure.

Gavett et al. [13] extend their earlier work with δ to a consideration of its biomarkers. One caveat to δ is that it appears to be agnostic to dementia's etiology. In their earlier work, Gavett et al. showed that δ can achieve an area under the receiver operating curve of 0.96 for the discrimination between all cause dementia versus normal controls + mild cognitive impairment [7]. However, the NACC UDS contains many cases of frontotemporal dementia, vascular dementia, and Lewy body disease, in addition to Alzheimer's disease (AD). Thus, d-scores appear to address the dementing aspect of a disease's cognitive impairments, independent of their etiology(ies).

This has important implications. First, δ may allow us to detect and thus redress the disabling (i.e., "dementing") aspects of any condition. The list may include many non-neurodegenerative disorders. If they affect d-scores, they are dementing too. Second, change in d-scores will reflect clinically salient cognitive change, *by definition*. Any improvement in cognitive performance unrelated to δ may be functionally trivial. This has implications for the utility of clinical interventions and the assessment of outcomes in clinical trials.

One potential disadvantage of this property is that biomarkers of δ, although indicative of a dementing process, might vary as a function of the sample under

study. They can be interpreted as "AD" biomarkers only if the sample is highly selected for that condition. In their current article, Gavett et al. limit their analysis to autopsy-proven AD cases. Several AD-related risk factors are shown to be associated with δ. As might be expected, those associations are entirely mediated by AD neuropathology in autopsy-proven AD cases. However, although the ε4 allelic burden is also significantly related to ischemic pathology, that pathology is not related to δ. This unexpected finding may shed light on δ's (and therefore dementia's) nature. Where exactly would one place an ischemic lesion such that it could affect performance on every cognitive measure via Spearman's intelligence factor *g* (or its derivative δ)?

Alternatively, since δ has been associated with the default mode network (DMN) [14, 15], dementia may necessarily require an insult of that network's structure or function [16, 17]. The latter findings undermine the notion that dementia results from the aggregate burden of neuropathology [18], and further suggest that so-called "vascular dementia" may not be due to ischemic lesions (at least outside of very specific strategic locations).

Recent studies help reconcile these alternatives. Crossley et al. have drawn attention to certain "rich club" networks as targets of major mental illness [19]. These regions are highly connected, with each other, and with less highly connected structures. Connectivity is a potential biomarker of *g*/δ. The "rich club" includes the DMN, but also the thalamus and basal ganglia. Crossley et al. examined the connectivity of regions affected by AD-related neuropathology. The DMN may be AD's most highly connected target. The basal ganglia and thalamus are even more richly endowed, which could explain their involvement as a dementia defining vascular pathology. In contrast, most of the neocortex is less highly connected. Thus, connectivity of an affected structure might inform the relative contribution of its pathology to the dementia phenotype (i.e., δ), and reconcile δ's association with the DMN (in an AD cohort) to *g*'s protean effects on cognitive performance.

Finally, Koppara et al. [20] take advantage of δ's "indifference to its indicators" to construct three δ homologs in a German cohort, the Dementia Competence Network, a well-characterized multicenter memory-clinic cohort. The first was derived from the item-set of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [21]. The second was constructed from the item set of the Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-Cog) [22]. The third was constructed from both measures.

Although the relevance of functional outcome measures to dementia case-finding is increasingly recognized [23], multi-scale composites are often advocated as outcomes rather than latent variables. This approach potentially compounds measurement error instead of reducing it. In contrast, δ is necessarily "greater than the sum of its parts" [8, 24] and is actually improved by the incorporation of additional indicators. Koppara et al. demonstrate that δ homologs are superior both to the scales from which they are derived and to composites that combine them with functional status measures [20].

Another finding to note in Koppara's analysis is that although δ homologs were generally superior to the CERAD, ADAS-cog, and Mini-Mental Status Exam [25] 1) for the prediction of incident mild cognitive impairment conversion, and 2) for the prediction of an AD-specific cerebrospinal fluid biomarker panel, the area under the receiver operating curves achieved were far weaker than δ's discrimination between demented and non-demented cases (e.g., 5, 7, 13). This reiterates δ's claim to be a dementia phenotype, and exposes how short AD-specific biomarkers fall from predicting that condition. It is increasingly clear that AD pathology can arise years if not decades before the onset of dementia and that many affected persons never reach that state. Biomarkers of δ, on the other hand, will inherently reflect clinically salient processes and could suggest opportunities for the prevention, stabilization or reversal of dementing illness, regardless of its cause(s).

Despite the promising findings in this issue, this approach has several potential limitations that will need to be addressed before it can be made use of clinically. Chief among these is the problem of "factor score indeterminacy" [26]. An essential limitation of the common factor model is that an infinite number of unique factor score composites can be derived from any factor. While they all might be consistent with the factor's loadings, some composites may be orthogonal to others, or even inversely related, potentially resulting in wildly discrepant subject rankings, depending on the composite selected.

However, these can be divided into "determinant" and "indeterminant" fractions [27]. Fortunately, many common factor score estimates are highly intercorrelated and yield an identical reproduced covariance matrix [28]. Several statistical methods are available to test a factor's determinacy. We have tested δ in TARCC [5] by Grice's "Refined Factor Score Evaluation

Program (Equation 5)" [26], and found its determinacy to be adequate (i.e., having a Total Item Squared Multiple Correlation = 0.84). This method maximizes composite validity and is recommended when the factor composite scores are to be used as "observed" variables in subsequent analyses (e.g., as predictors). However, factor determinacy may need to be tested for each individual δ homolog or ortholog before it can be validated as a clinical phenotype.

There is also a potential for tautology in a δ homolog's validation, especially when the severity or diagnosis of dementia are rated with knowledge of δ's indicators. However, several observations militate against this. First, δ is a latent variable, indirectly related to observed performance. Raw test scores generally share <50% of their variance with δ. Therefore, knowledge of observed test scores is not knowledge of δ. Second, *g*' and the observed indicators themselves are vulnerable to the same criticism, and yet δ improves upon the diagnostic accuracy of both. Third, d-scores also predict biomarkers and future clinical outcomes better than observed test scores (e.g., [20]). Neither outcome is known to clinicians at the time indicators of δ are obtained. Finally, recent studies from Japan confirm the validity of δ, even when its indicators are obtained blind to the CDR [8, 24, 29].

δ may also be constrained by the population(s) in which its homologs are validated and/or applied. δ homologs are usually validated in convenience samples of well-characterized subjects. However, they might also be developed in less well-characterized population-based samples. In theory, cross-sample differences in dementia's prevalence or in the distributions of δ's indicators might affect the psychometric properties of the resulting composites. In practice, this has not been a troublesome issue. In this issue of the *Journal of Alzheimer's Disease*, analyses involving at least seven δ homologs developed in four cohorts on three continents, and in at least three languages are included. All appear to exhibit similar psychometric characteristics.

In short, dementia assessment by the latent variable δ offers many practical advantages over traditional psychometrics. Moreover, δ may be the principal psychometric determinant of dementia status. That insight would constrain our conceptualization of dementia to a disturbance of general intelligence, as operationalized by Spearman's *g*. *g* seems to have been overlooked as a potential determinant of dementia-related cognitive decline, yet is compatible with dementia's protean cognitive-performance decrements. δ's necessary contribution would constrain dementia's pathophysiology, and might open new opportunities for the prevention, diagnosis, and remediation of dementia.

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The author's disclosure is available online (http://j-alz.com/manuscript-disclosures/15-0249r3).

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