Measuring Delirium in the Face of AD/ADRD

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Richard N. Jones, Sc.D.

Brown University, Department of Psychiatry and Human Behavior

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Outline

1. Why is measuring delirium in dementia an issue?
2. What evidence is there that measurement differs in dementia?
3. Potential strategies and work in progress on measurement of delirium in dementia

My perspective

- Epidemiologist, methodologist, psychometrician
- Not a clinician

Is this interesting?

🧐

This Notice Of Funding Opportunity invites research applications focused on understanding the underlying pathophysiology of cognitive fluctuations in people diagnosed with Alzheimer's Disease- Related Dementias (ADRD).

Cognitive fluctuations are intermittent episodes of decreased alertness, attention, and responsiveness that occur in some patients with dementia. Episodes can last from seconds to days, occur unpredictably (e.g., do not happen only in the evenings, as with "sun-downing"), and tend to resolve on their own, with the patient eventually returning to their baseline state.

Cognitive fluctuations are a core clinical feature of Dementia with Lewy Bodies (DLB) and are estimated to occur in up to 90% of these patients. However, they are not unique to DLB and are believed to be present in 20% of patients with Alzheimer's Disease and 30-50% of patients with [Vascular Contributions to Cognitive Impairment and Dementia (VCID)].

1. Why is measuring delirium in dementia an issue?

Why is measuring delirium in dementia an issue?

1. Delirium and dementia: overlapping signs and symptoms
   - Cognitive impairment
   - Sleep disturbance
   - Emotional / mood disturbance
2. Distinguishing features are hard to assess
   - Timing of onset
   - Cause(s) of symptoms
   - Pattern of cognitive impairments (attention, awareness, vs other domains)

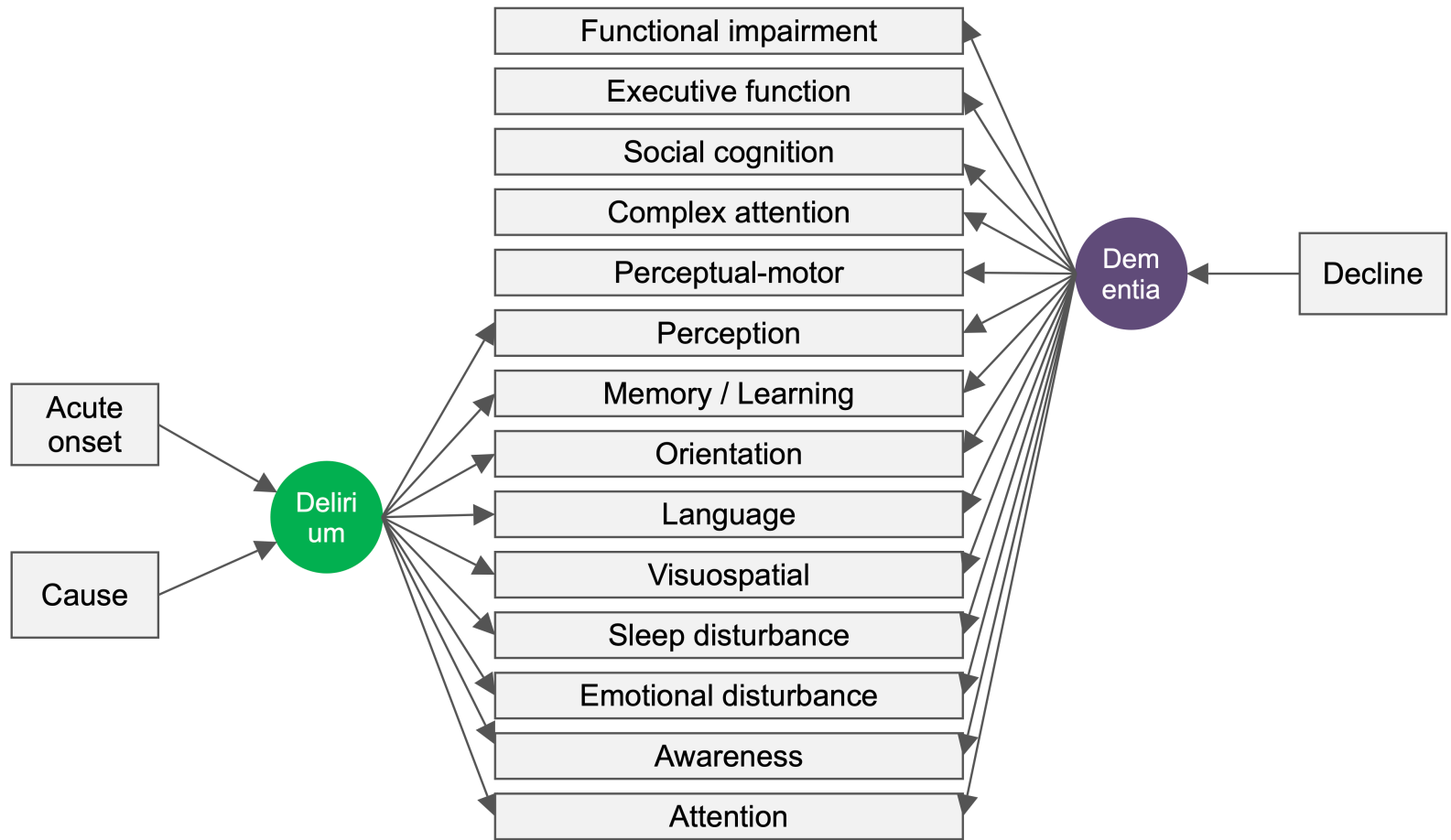**APA Diagnostic and Statistical Manual DSM-5 (2013)**

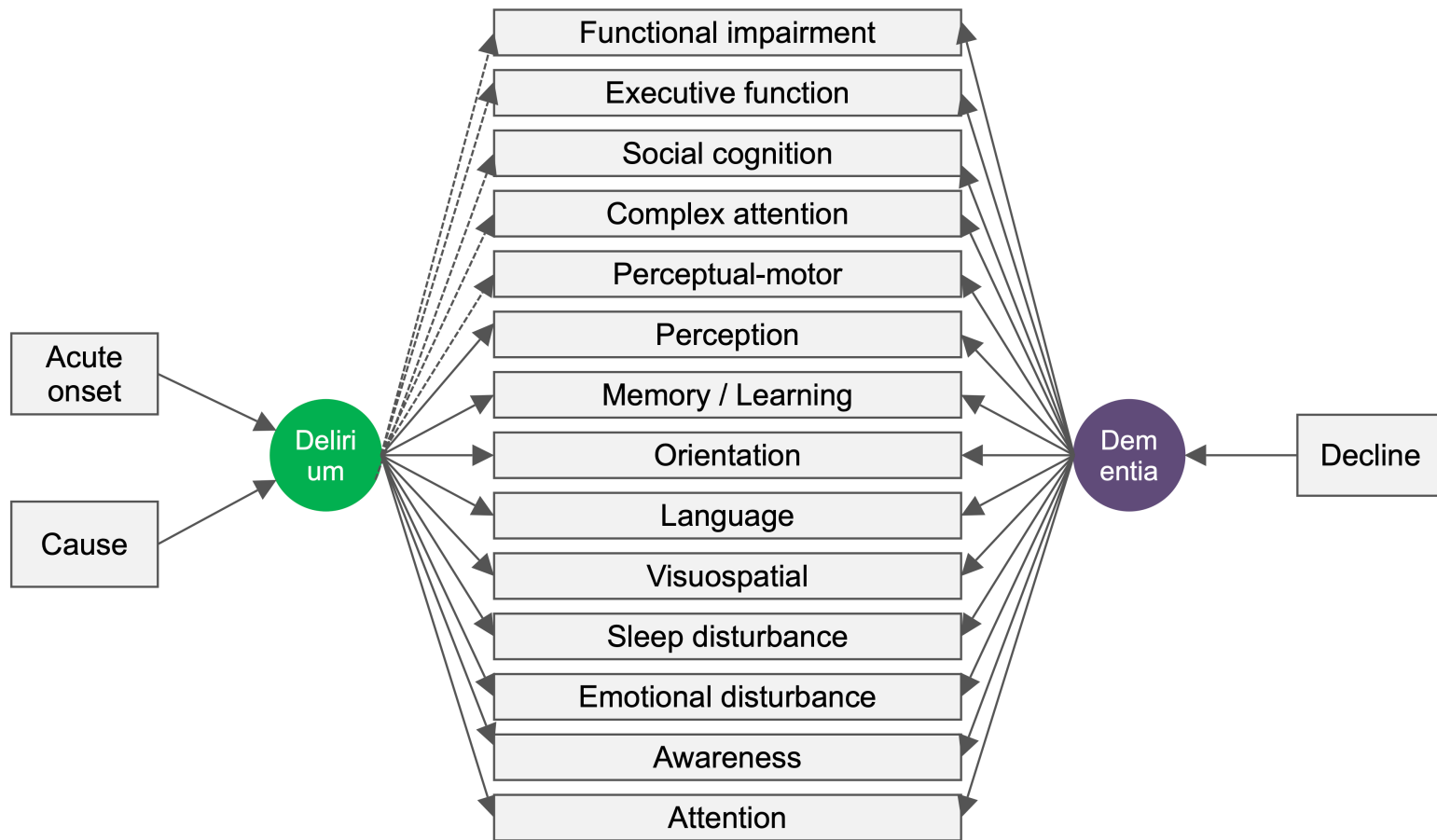|	Delirium	Major Neurocognitive disorder	
Cognitive impairment	**A.** Disturbance in attention† … and awareness		Acute vs decline from previous level
	B. [Acute onset]		
	C. Disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception‡)	**A.** Evidernce of significant decline from a previous level of performance in one or more cognitive dmains (complex attention, executive function, learning and memory, langauge, perceptual motor, or social cognition)	
	D. Criteria A and C are not better explained by … neurocognitive disorder and do not occur in the context of … coma	**C & D.** Cognitive deficits do not occur exclusively in the context of a delirium [and] not better explained by mental disorder	
	E. Evidence … consequence of another medical condition, substance intoxication, or withdrawal…or exposure to a toxin		
		B. Cognitive deficits interfere with independence	
	Associated features:	**Specifiers:**	
Sleep	- Sleep-wake cycle disturbance	- sleep disturbance is a common symptom	
Mood	- emotional disturbances	- mood disturbances … may occur - apathy is common	
	Notes	- psychotic features are common - agitation is common in a wide variety of NCDs	
emphasis on attention, awareness, arrousal	† normal attention / arousal, delirium and coma lie on a continuum…reduced level of arousal…show only minimal responses to verbal stimulation are incapable of engaging with … testing or even interview…this inability to engage should be classified as severe inattention and cognitive change, and hence delirium.		
	‡ perceptual disturbances … include minsinterpretations, illusions, or hallucinations		

Why is measuring delirium in dementia an issue?

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   - Timing of onset
   - Cause(s) of symptoms
   - Pattern of cognitive impairments (attention, awareness, vs other domains)

Limits of the 'Mini-Mental State' as a screening test for dementia and delirium among hospital patients

JAMES C. ANTHONY,[1] LINDA LeRESCHE, UNAIZA NIAZ, MICHAEL R. VON KORFF AND MARSHAL F. FOLSTEIN

·   *From the Department of Mental Hygiene, Johns Hopkins School of Hygiene and Public Health, and the Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, Maryland, USA*

SYNOPSIS   With a psychiatrist's standardized clinical diagnosis as the criterion, the 'Mini-Mental State' Examination (MMSE) was 87% sensitive and 82% specific in detecting dementia and delirium among hospital patients on a general medical ward. The false positive ratio was 39% and the false negative ratio was 5%. All false positives had less than 9 years of education; many were 60 years of age or older. Performance on specific MMSE items was related to education or age. These findings confirm the MMSE's value as a screen instrument for dementia and delirium when later, more intensive diagnostic enquiry is possible; they reinforce earlier suggestions that the MMSE alone cannot yield a diagnosis for these conditions.

2. What evidence is there that measurement of delirium differs in dementia?

Differential sensitivity / specificity for delirium by dementia / no dementia [?]

ORIGINAL ARTICLE

Challenges in diagnosis and management of delirium in Lewy body disease

Sarah Richardson[1] | Rachael A. Lawson[2] | Annabel Price[3,4] | John-Paul Taylor[2]

Methods: A systematic review of published literature on diagnosis and management of delirium in LBD.

Recent studies have evaluated delirium diagnosis methods in delirium superimposed on dementia (DSD); these may, therefore, have utility in LBD. Tests of attention and arousal, including months of the year backwards (MOTYB), letter vigilance tests (SAVEAHEART), spatial span forwards (SSF), Observational Level of Arousal scale (OSLA), performed best in DSD. Validated tools examined in DSD include the CAM, CAM-ICU, DSM-5 criteria and The 4 A's Test (4AT), and the recently developed DSD-4.[8–11] However, the sensitivity and specificity of these measures are generally lower in DSD across studies compared with older adults without dementia.

No cite: is this true?

Richardson, S., Lawson, R. A., Price, A., & Taylor, J. P. (2023). Challenges in diagnosis and management of delirium in Lewy body disease. *Acta Psychiatrica Scandinavica, 147*(5), 475-480.

Review

Recognition of Delirium Superimposed on Dementia: Is There an Ideal Tool?

Priyanka Shrestha [1,*] **and Donna M. Fick** [2]

Diagnostic test accuracy for delirium
According to presence / absence of dementia

Measure and Study	Sensitivity		Specificity	
	Dem	No Dem	Dem	No Dem
3D-CAM (Marcantonio ER et al. Ann Intern Med. 2014:161(8);554) N* = 81	**96**	93	93	**96**
4-AT (Bellelli G et al. Age and ageing. 2014:43(4);496) N* = 101	**94**	83	65	**91**

N* = effective per-group sample size (harmonic mean of N(dementia), N(no dementia))

Only 2 studies in Shrestha & Fick's 2023 review compared, in the same overall sample, the diagnostic test accuracy of a delirium identification tool stratified by the presence or absence of dementia. Both studies find that standard delirium tools (3D-CAM, 4-AT) are *more* sensitive, but also *less* specific, to delirium when dementia is present (versus when dementia is absent).

Shrestha, P., & Fick, D. M. (2023). Recognition of delirium superimposed on dementia: Is there an ideal tool? *Geriatrics*, *8*(1), 22.

2. What evidence is there that measurement of delirium differs in dementia?

Differential sensitivity / specificity for delirium by dementia [maybe not]

What about the measurement of delirium severity?

Is Delirium Different When It Occurs in Dementia? A Study Using the Delirium Rating Scale

Paula T. Trzepacz, M.D.
Benoit H. Mulsant, M.D.
Mary Amanda Dew, Ph.D.
Rona Pasternak, M.D.
Robert A. Sweet, M.D.
George S. Zubenko, M.D., Ph.D.

The authors studied 61 geropsychiatric patients with delirium from a cohort of 843 consecutive admissions to a geriatric clinical research unit. A central study goal was to assess how the presence of dementia affected the presentation of delirium. Eighteen delirious (D) and 43 delirious-demented (D-D) patients were compared on the Delirium Rating Scale (DRS), Mini-Mental State Examination (MMSE), Brief Psychiatric Rating Scale (BPRS), and EEG. D-D patients had lower MMSE scores, but no differences were found in total DRS or BPRS scores or in EEG grade. DRS items were similar in the two groups except that D-D had more cognitive impairment than D. An exploratory principal components analysis of DRS items identified two core factors. The authors conclude that the presentation of delirium in the setting of concurrent dementia is very similar to delirium without dementia, with subtle differences probably attributable to dementia.

Comments on:
Trzepacz, P. T., Mulsant, B. H., Amanda Dew, M., Pasternak, R., Sweet, R. A., & Zubenko, G. S. (1998). Is delirium different when it occurs in dementia? A study using the delirium rating scale. *Journal of Neuropsychiatry and Clinical Neuroscience*, *10*(2), 199-204.

- Authors <u>found no evidence</u> for differences of the presentation of delirium according to whether a patient had dementia
- Sample was small
  - 18 delirious-no-dementia
  - 43 delirious-with-demented
- Only large effects could have been detected (Cohen's d >= 0.8)
- Trzepacz et al (1998) cannot rule out more subtle delirium measurement differences according to dementia

CONCLUSION
2. What evidence is there that measurement of delirium differs in dementia?

- I did not identify a lot of high-quality research on this question
  - o Few studies with both Demented and Non-Demented
  - o Small sample size, esp. for studies of delirium severity
- **No strong evidence of measurement differences**
  - o Remember, sensitivity and specificity are sample statistics and <u>not</u> properties of a test or instrument (Kraemer HC, 1992, Evaluating Medical Tests: Objective Quantitative Guidelines. Sage)

3. Potential strategies and work in progress on measurement of delirium in dementia

Variance decomposition

Royall and Palmer's δ

- For the past dozen years or so, Don Royall and Raymond Palmer have been investigating a variance decomposition approach to modeling dementia progression.

- The variance component, or latent variable, used to quantify dementia severity is labeled δ

- Their models separate covariance in common to neuropsychological performance (g') from covariance common to neuropsychological performance and functional impairment (δ)

- This approach could be applied to delirium (severity) measurement

FIGURE 2. Shared Variance Between the Functional Status Index and Cognitive Performance
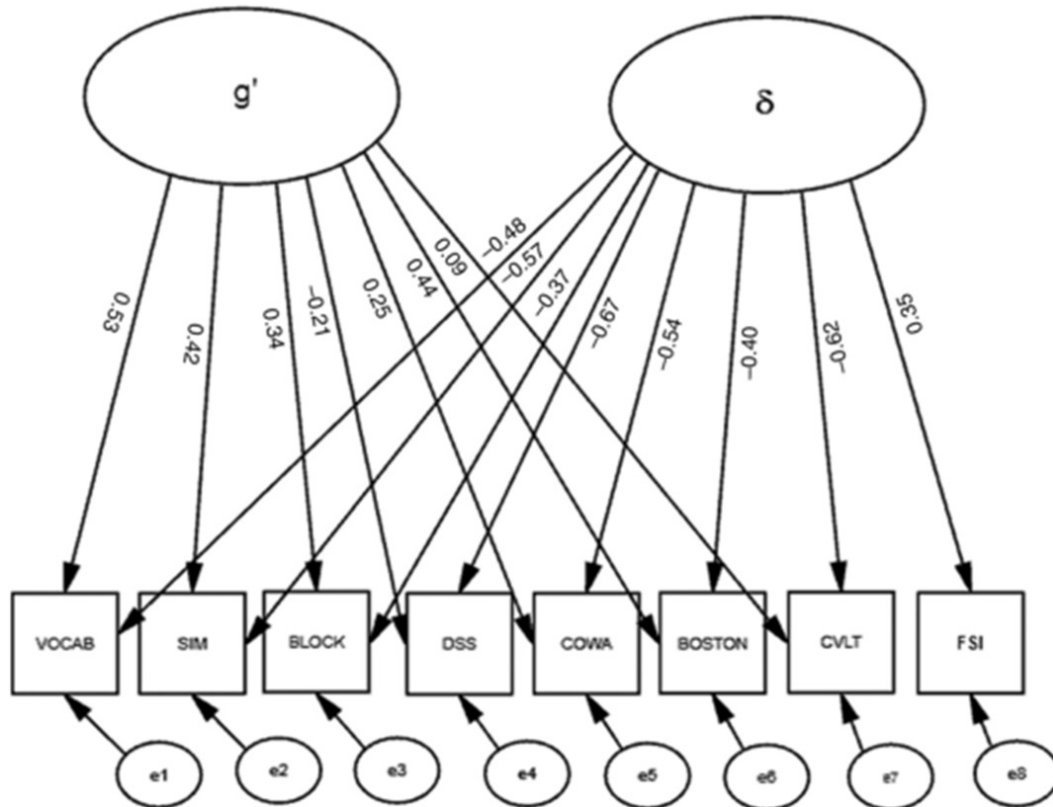
Scales: WAIS–R Vocabulary; WAIS–R Similarities; Block Design; Digit Symbol; Controlled Oral Word-Association; Boston Naming Test; California Verbal Learning Task.

FSI - Functional status index, composed of OARS (Older Adults Resources Scale) ADL and IADL. Higher scores reflect intact functional performance.

Royall, D. R., & Palmer, R. F. (2012). Getting Past "g": Testing a New Model of Dementing Processes in Persons Without Dementia. *The Journal of neuropsychiatry and clinical neurosciences*, *24*(1), 37-46.

Validation of a Latent Variable Representing the Dementing Process

Donald R. Royall[a,b,c,d,*], Raymond F. Palmer[c], Sid E. O'Bryant[e] and for the Texas Alzheimer's Research and Care Consortium
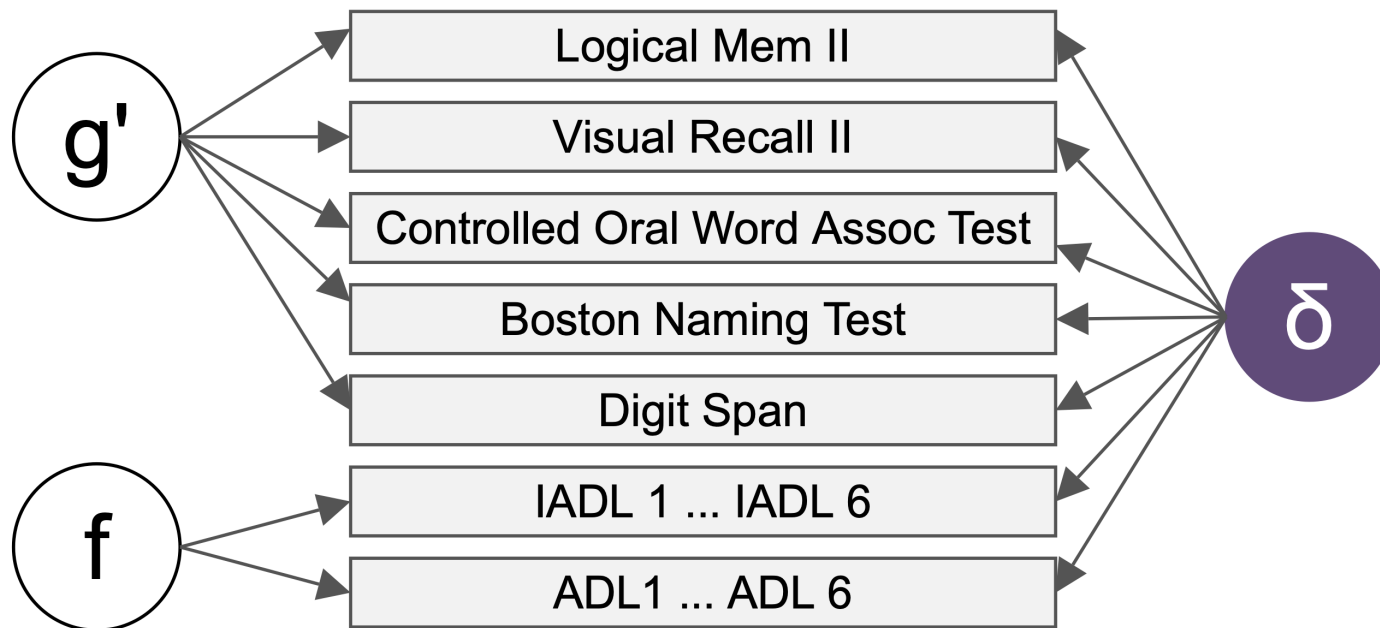
Based on Figure 2: Royall, D. R., Palmer, R. F., & O'Bryant, S. E. (2012). Validation of a latent variable representing the dementing process. *J Alzheimers Dis*, *30*(3), 639-649. https://doi.org/10.3233/JAD-2012-120055
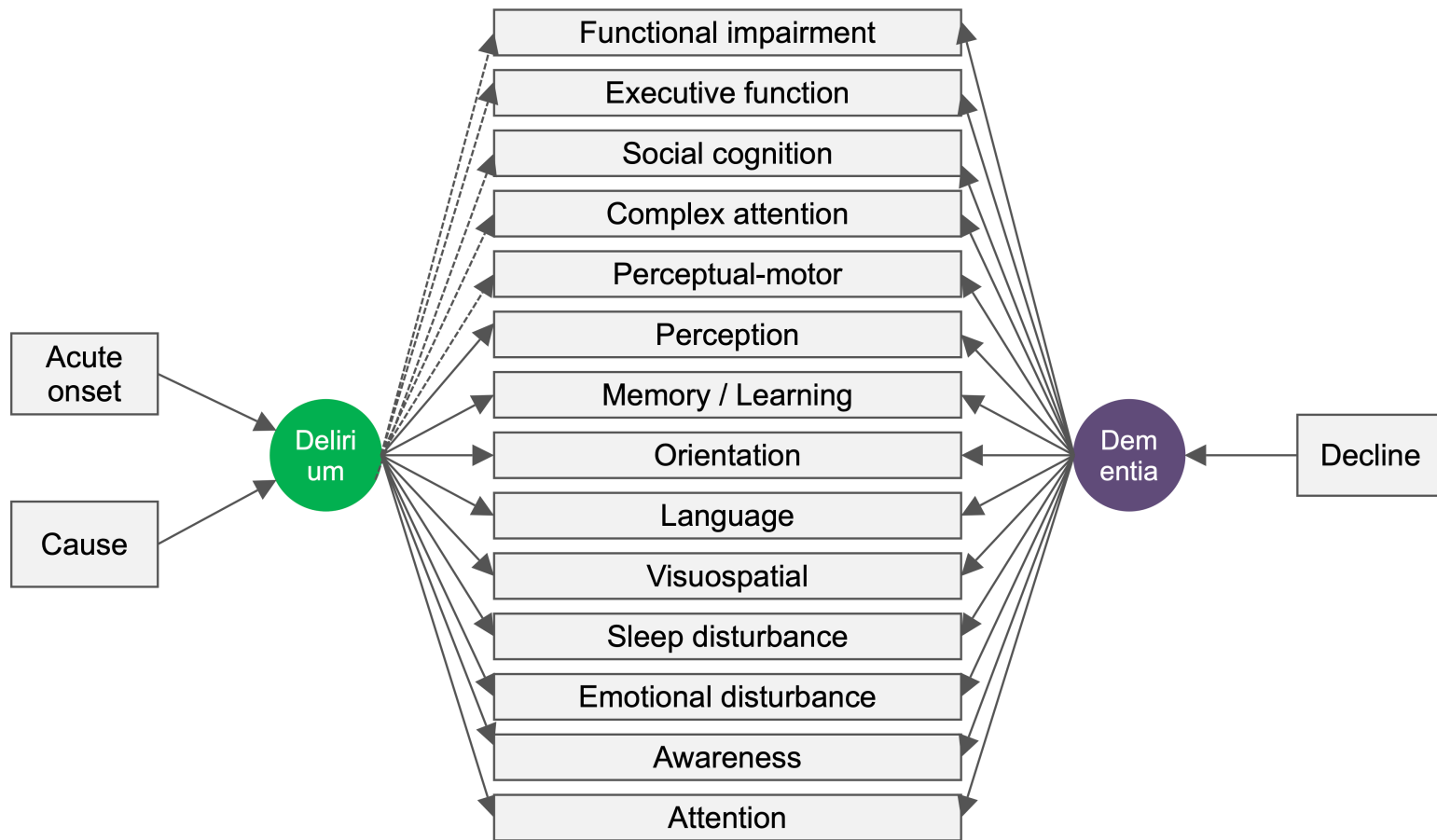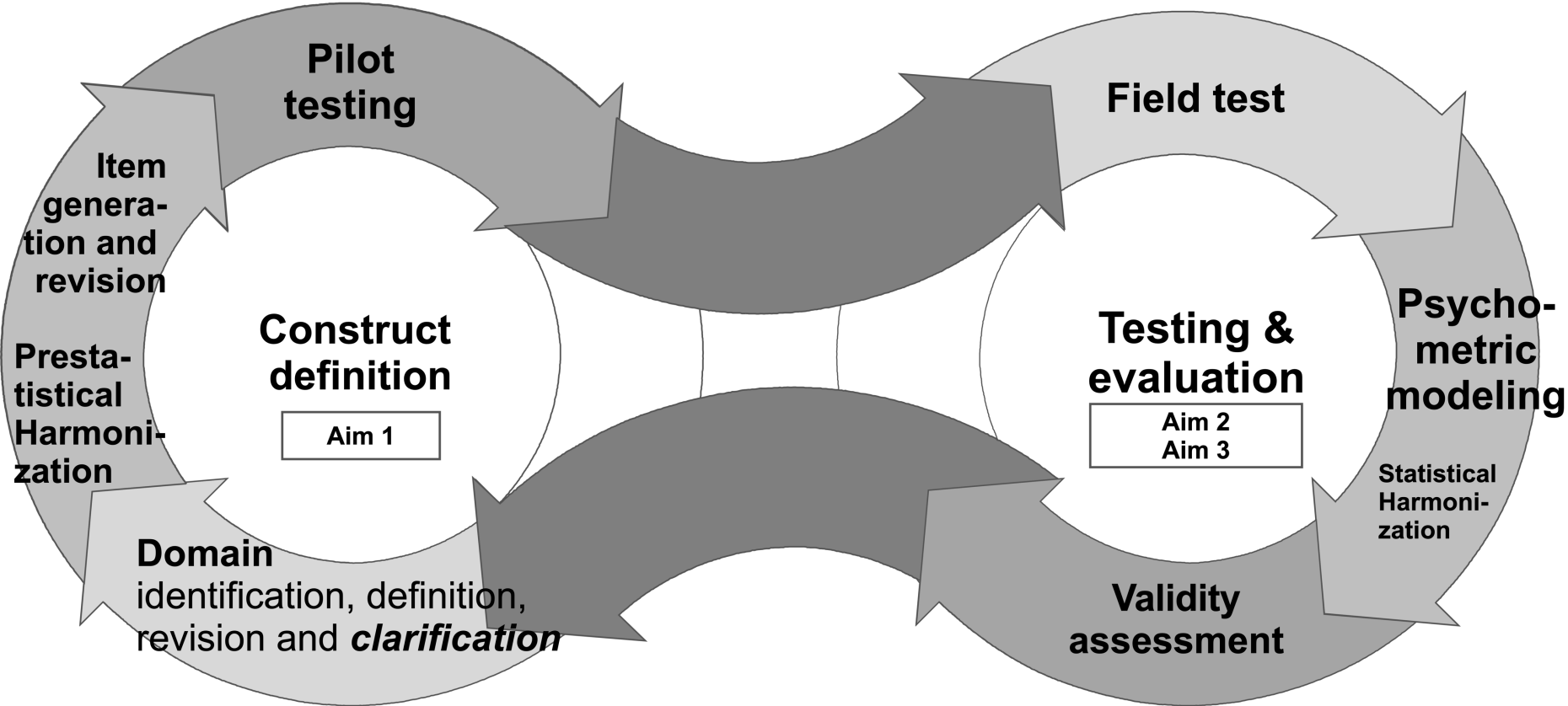
BASIL-II

BASIL - Better Assessment of Illness: Delirium Severity Measures for Persons with and without Dementia

R01-AG044518

Inouye & Jones, MPIs

Background: BASIL-I

Measurement development epicycles

JAMA Internal Medicine | Review

Assessment of Instruments for Measurement of Delirium Severity
A Systematic Review

Richard N. Jones, ScD; Sevdenur Cizginer, MD; Laura Pavlech, DVM, MSLS; Asha Albuquerque, BA;
Lori A. Daiello, PharmD, ScM; Kumar Dharmarajan, MD, MBA; Lauren J. Gleason, MD, MPH;
Benjamin Helfand, MSc; Lauren Massimo, PHD, CRNP; Esther Oh, MD, PhD; Olivia I. Okereke, MD, MS;
Patricia Tabloski, GNP-BC, PhD; Laura A. Rabin, MD; Jirong Yue, MD; Edward R. Marcantonio, MD, SM;
Tamara G. Fong, MD, PhD; Tammy T. Hshieh, MD, MPH; Eran D. Metzger, MD; Kristen Erickson, MPH;
Eva M. Schmitt, PhD; Sharon K. Inouye, MD, MPH; for the Better Assessment of Illness (BASIL) Study Group

Use of an expert panel to identify domains and indicators of delirium severity

Dena Schulman-Green[1] (ID) · Eva M. Schmitt[2] · Tamara G. Fong[2,3,4] · Sarinnapha M. Vasunilashorn[3,4] · Jacqueline Gallagher[4] · Edward R. Marcantonio[3,4] · Charles H. Brown IV[5] · Diane Clark[6] · Joseph H. Flaherty[7] · Anne Gleason[2] · Sharon Gordon[8] · Ann M. Kolanowski[9] · Karin J. Neufeld[5] · Margaret O'Connor[10] · Margaret A. Pisani[11] · Thomas N. Robinson[12] · Joe Verghese[13] · Heidi L. Wald[12] · Richard N. Jones[14] · Sharon K. Inouye[2,3,4] · BASIL Study Group

BMC Medical Research Methodology

RESEARCH ARTICLE

Open Access

CrossMark

Harmonization of delirium severity instruments: a comparison of the DRS-R-98, MDAS, and CAM-S using item response theory

Alden L. Gross[1,2]* , Doug Tommet[3], Madeline D'Aquila[4], Eva Schmitt[4], Edward R. Marcantonio[4,5], Benjamin Helfand[3,6], Sharon K. Inouye[4,5†], Richard N. Jones[3†] and for the BASIL Study Group
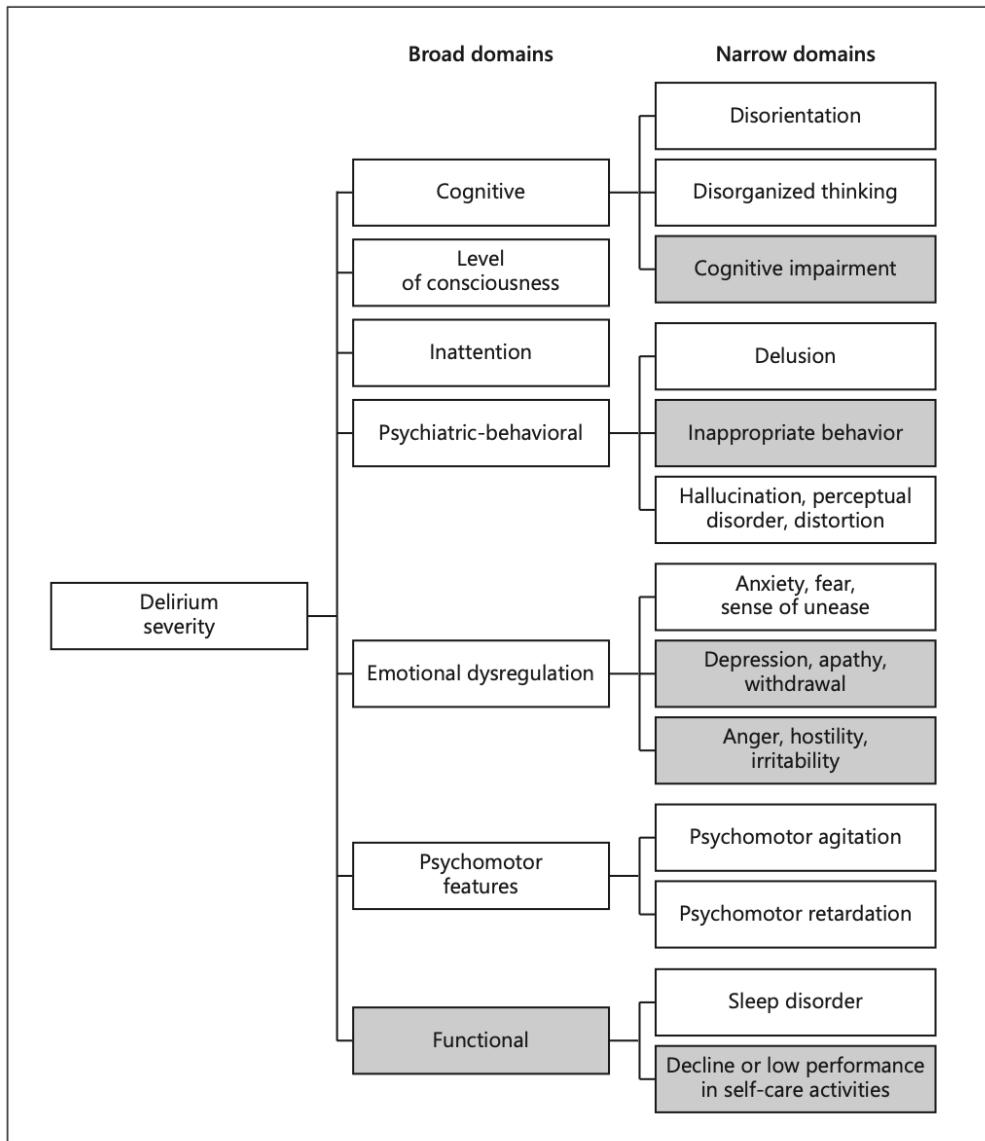
Dementia
and Geriatric
Cognitive Disorders

New Delirium Severity Indicators: Generation and Internal Validation in the Better Assessment of Illness (BASIL) Study

Sarinnapha M. Vasunilashorn[a–c]   Dena Schulman-Green[d]   Douglas Tommet[e]
Tamara G. Fong[a, f, g]   Tammy T. Hshieh[a, h]   Edward R. Marcantonio[a, b, f]
Eran D. Metzger[a, i]   Eva M. Schmitt[f]   Patricia A. Tabloski[j]
Thomas G. Travison[a, f]   Yun Gou[f]   Benjamin Helfand[k]   Sharon K. Inouye[a, b, f]
Richard N. Jones[e, l]   the BASIL Study Team

Vasunilashorn SM et al. Dement Geriatr Cogn Disord. 2020:49(1);77-90 (https://pmid.us/32554974)

Delirium severity assessment: domain framework

Vasunilashorn SM et al. Dement Geriatr Cogn Disord. 2020:49(1);77-90 (https://pmid.us/32554974)

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Table 2. Standardized measurement slopes (factor loadings) for unidimensional and bi-factor measurement models of delirium severity

Domain	Feature	Factor loadings				LF
		f	fb	Sb		
LOC	Consciousness fluctuates	0.74	0.77	0.69	s1	
LOC	Level of consciousness	0.71	0.72	0.62	s1	*
LOC	Exaggerated startle response	0.58	0.62	−0.37	s1	*
INA	Inattentive to conversation	0.87	0.81	0.52	s2	
INA	Difficulty focusing attention	0.81	0.76	0.35	s2	*
INA	Easily distracted	0.70	0.64	0.40	s2	*
DTH	Disorganized thinking evident from speech	0.88	0.92			*
DIS	Disorientation to time or place	0.71	0.74			*
DIS	Self-report feeling confused in the past day	0.67	0.70			*
ANX	Talks about feeling threatened	0.49	0.42	0.79	s3	*
ANX	Acts as if frightened	0.49	0.40	0.79	s3	*
ANX	Asks repeated questions	0.44	0.40	1.00	s3	
PER	Self-report see things not really there	0.72	0.54	1.00	s4	*
PER	Self-report hear things not really there	0.71	0.62	0.42	s4	*
PER	Self-report misperception motion	0.71	0.56	0.52	s4	*
PER	Self-report distortion	0.70	0.61	0.46	s4	*
PER	Beliefs that are not true	0.63	0.64	0.08	s4	*
PER	Self-report misperception sound or object	0.57	0.50	0.40	s4	*
PM	Increased motor activity	0.60	0.62			*
PM	Decreased motor activity	0.44	0.45			*
FUN	Disturbance of sleep-wake cycle	0.46	0.48			
	Omega	0.94	0.93			0.93
	RMSEA	0.04	0.03			−
	CFI	0.92	0.95			−
	SRMR	0.15	0.13			−

Delirium severity assessment: Psychometric modeling and DEL-S instrument development

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Delirium severity assessment: DEL-S Instrument validation

JAMA Network | Open

Sarinnapha M. Vasunilashorn, PhD; Tamara G. Fong, MD, PhD; Benjamin K. I. Helfand, MSc; Tammy T. Hshieh, MD, MPH; Edward R. Marcantonio, MD, SM; Eran D. Metzger, MD; Eva M. Schmitt, PhD; Patricia A. Tabloski, PhD; Thomas G. Travison, PhD; Yun Gou, MA; Richard N. Jones, ScD; Sharon K. Inouye, MD, MPH; for the BASIL Study Team

Delirium Item Bank: Utilization to Evaluate and Create Delirium Instruments

Benjamin K.I. Helfand[a, b, c]   Douglas Tommet[b, c]   Elke Detroyer[d, e]

Koen Milisen[d, e]   Dimitrios Adamis[f, g]   Eran D. Metzger[h, i]

Edward R. Marcantonio[j]   Edwin D. Boudreaux[a]   Sharon K. Inouye[j, k, l]

Richard N. Jones[b, c]   For the BASIL study group

Helfand BKI et al. Dement Geriatr Cogn Disord. 2022:51(2);110-119 (https://pmid.us/35533663)
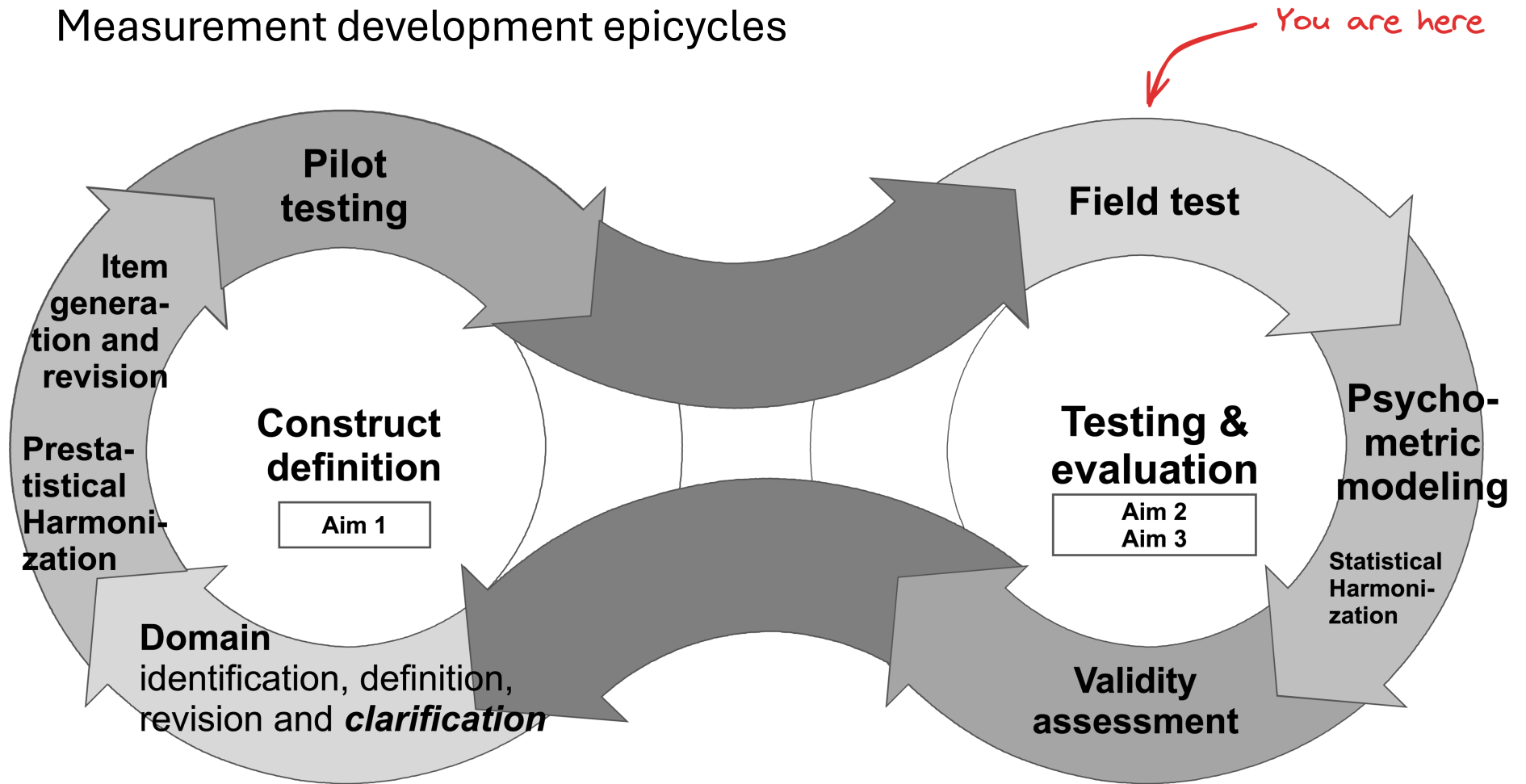
BASIL-II

BASIL - Better Assessment of Illness: Delirium Severity Measures for Persons with and without Dementia

R01-AG044518

Inouye & Jones, MPIs

Measurement development epicycles

You are here

Pilot testing

Item generation and revision

Prestatistical Harmonization

Construct definition

Aim 1

Domain identification, definition, revision and *clarification*

Field test

Psycho-metric modeling

Testing & evaluation

Aim 2
Aim 3

Statistical Harmonization

Validity assessment

Journal of the
American Geriatrics Society

Domains of delirium severity in Alzheimer's disease and related dementias

Dena Schulman-Green PhD[1] | Tammy Hshieh MD, MPH[2,3] | Dimitrios Adamis MD[4,5] |
Michael S. Avidan MBBCh[6] | Dan G. Blazer MD, MPH, PhD[7] |
Donna M. Fick PhD[8] | Esther Oh MD, PhD[9] | Alessandro Morandi MD[10,11] |
Catherine Price PhD[12] | Joe Verghese MB, BS, MS[13] | Eva M. Schmitt PhD[3] |
Richard N. Jones ScD[14] | Sharon K. Inouye MD, MPH[3,15,16] | For the BASIL Study Group

Schulman-Green D et al. J Am Geriatr Soc. 2022:70(5);1495-1503 (https://pmid.us/34951704)
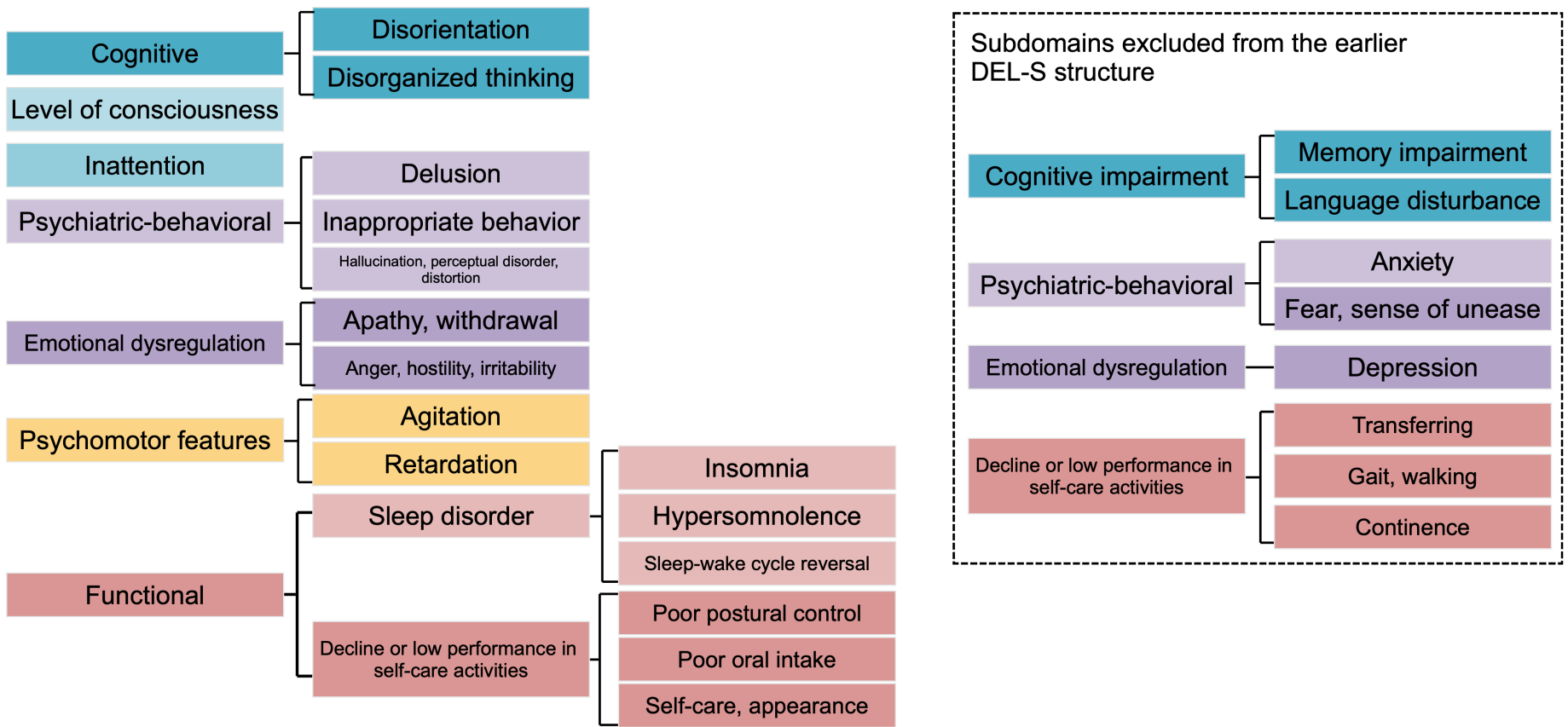
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FIGURE 1 Final DEL-S-AD content domains for delirium severity in Alzheimer's disease and related dementias

Schulman-Green D et al. J Am Geriatr Soc. 2022:70(5);1495-1503 (https://pmid.us/34951704)

BASIL-II Field Study

- Prospective cohort study of older adults (target N=500)

- 3 sites
    1. Hospital inpatients admitted for an acute medical condition (Boston)
    2. Patients scheduled for elective surgery (Florida)
    3. Long-term care or post-acute residents at a skilled nursing facility who experience an acute illness (New York)

- Reference standard rater will conduct a structured interview with participants and their caregivers to assess cognitive function and delirium at pre-illness baseline (except in the acute medical inpatient group) and then in a follow-up evaluation 1-2 days after an acute event or surgical procedure.

- Final diagnoses will be made by an experienced, interdisciplinary gold standard adjudication team.

- Trained research associates administer the DEL-S and DEL-S-AD (as modified given expert panel review) during the follow-up evaluation.

- Psychometric modeling and modification of DEL-S-AD

Conclusion and discussion

- Delirium and dementia share similar presentation, which would seem to make differential assessment difficult, but there is not strong evidence to support that in the literature

- BASIL-II will be large enough to

  1. Detect subtle delirium measurement difference according to dementia status, quantify their effect on (a) case identification and (b) severity measurement

  2. Develop new measures of delirium severity (DEL-S-AD) that are optimized for the rating of delirium severity in the presence of dementia

  3. Harmonize DEL-S and DEL-S-AD scales such that data from the two measures can be combined and compared

Questions