Optimizing Measurement of Very Early AD: Increasing Power in the Presence of Ceiling Effects

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Disclosure: President and CEO of Pentara Corporation through which I am a paid consultant for several public, private and non-profit organizations

Quantitative Composites

- Prevention Instruments – cognitive composites
  - APCC
  - Pre-MCI composite for Columbian Cohort
  - PACC
- MCI composites – cognitive, global+cog, function+cog
  - ADCOMS (Logovinsky)
  - Roche composite (Morrison)
  - RBANS composite (Ropacki)
  - J & J Composites (Raghavan)
  - PROADAS- AZ (Hannesdottir)
  - Lilly composites (Wessels)

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Why Use a Composite?

- It can't perform worse than the worst component in the composite
- It often performs better than the best component in the composite
- We're already using composites!
- Do we believe that all points are equivalent? Are they all on the Disease trajectory?
- Patients may change more on Visual Cognition than Verbal Cognition or vice versa – Composite allows both changes to be relevant.

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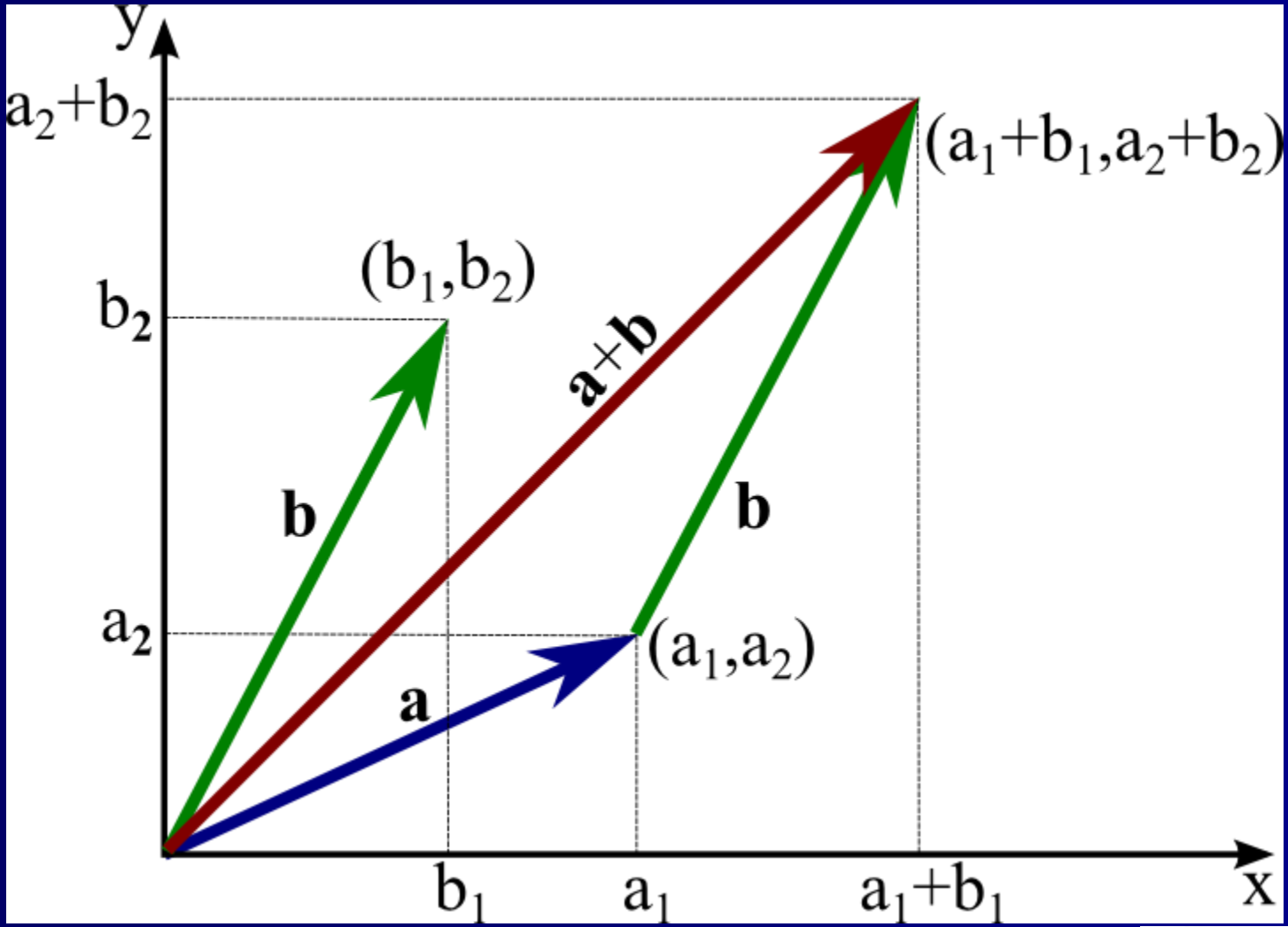
A Composite is a Summed Vector



http://mathinsight.org/vectors_cartesian_coordinates_2d_3d

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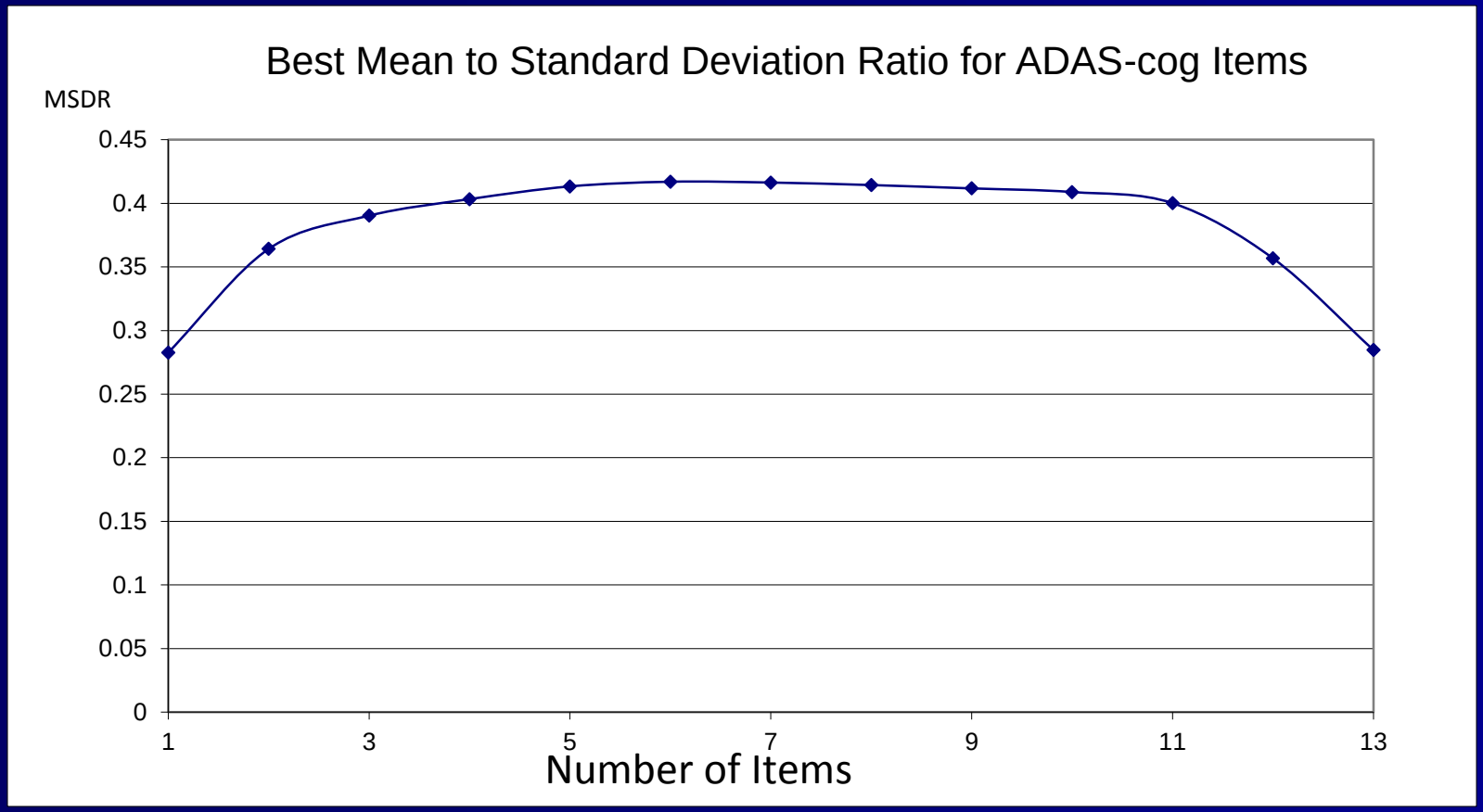
Signal to Noise Improves with Fewer Items, Then Worsens with Too Many



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Data-Based Composites Increase Power /Reduce Sample Sizes

	Popu-lation	ADAS-13	Composite (adj)	% improve ment	% patients wasted	% patients used	Multiple of patients
ADAS8 MCI	MCI	0.285	0.381	34%	44.0%	56.0%	1.79
ADAS6+MMSE1	MCI	0.285	0.466	63%	62.5%	37.5%	2.67
ADAS6+MMSE1+ NTB2	MCI	0.285	0.489	71%	66.0%	34.0%	2.94
ADCOMS	MCI	0.285	0.427	50%	55.5%	44.5%	2.25
ADAS13 vs RBANS Optimized	MCI	0.285	0.589	107%	76.6%	23.4%	4.27
		Logical Memory II					
Best Single Item vs APCC	pre-MCI	0.13	0.156	20%	30.9%	69.1%	1.45

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Items That Change in Early Cognitive

- Based on Rush ROS data
- Confirmed in other data sets
  - NACC
  - ADNI
  - Columbian Cohort
  - Arizona Cohort
  - Etc.
- Replacement Items – still effective

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Items Included in APCC

Cognitive assessment	Domain	Unadjusted MSDR	Adjusted MSDR
Boston Naming Test (15 item)	Semantic memory	0.072	0.061
Category fluency – Fruits/Vegetables	Semantic memory	0.165	0.122
East Boston Naming Test, Immediate recall (Memory I)	Episodic memory	0.088	0.097
Logical Memory IIa (Delayed)	Episodic memory	0.091	0.128
MMSE – Orientation to Time	Orientation	0.111	0.093
Ravens Progressive Matrices Subset – 9 items	Visuospatial / working memory	0.100	0.086
Symbol Digit Modalities	Perceptual speed	0.142	0.077
PACC			**0.1928**

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Cognitive assessment	Domain	Unadjusted MSDR	Adjusted MSDR
Category fluency – Animals	Semantic memory	0.129	0.088
CERAD Word list recall (Immediate)	Episodic memory	0.109	0.102
CERAD Word list memory (Delayed recall)	Episodic memory	0.127	0.104
CERAD Word List Recognition	Episodic memory	0.083	0.080
Complex Ideational Material	Auditory comprehension	0.060	0.057
Digit Ordering	Working memory	0.078	0.048
Digit Span - forward	Working memory	0.070	0.035
Digit Span - backward	Working memory	0.084	0.035
East Boston Naming Test, Delayed recall	Episodic memory	0.108	0.087
Judgment of Line Orientation	Visuospatial	0.075	0.059
Logical Memory Ia (Immediate)	Episodic memory	0.081	0.110
Mini-Mental Status Examination (MMSE) - Total	General / Global Cognition	0.133	0.109
MMSE – Orientation to Place	Orientation	0.093	0.088
MMSE – Registration	Working memory	0.040	0.029
MMSE – Attention and Concentration	Attention and Concentration	0.045	0.037
MMSE – Recall	Episodic memory	0.029	0.022
MMSE – Language	Language	0.034	0.008
National Adult Reading Test (NART) – 10 items	Semantic memory	0.031	0.034
Number Comparison Test	Perceptual speed	0.112	0.071
Ravens Progressive Matrices – 16 items	Visuospatial / working memory	0.108	0.077
Wide Range Achievement Test (WRAT) 15 items	Semantic memory	0.034	0.024

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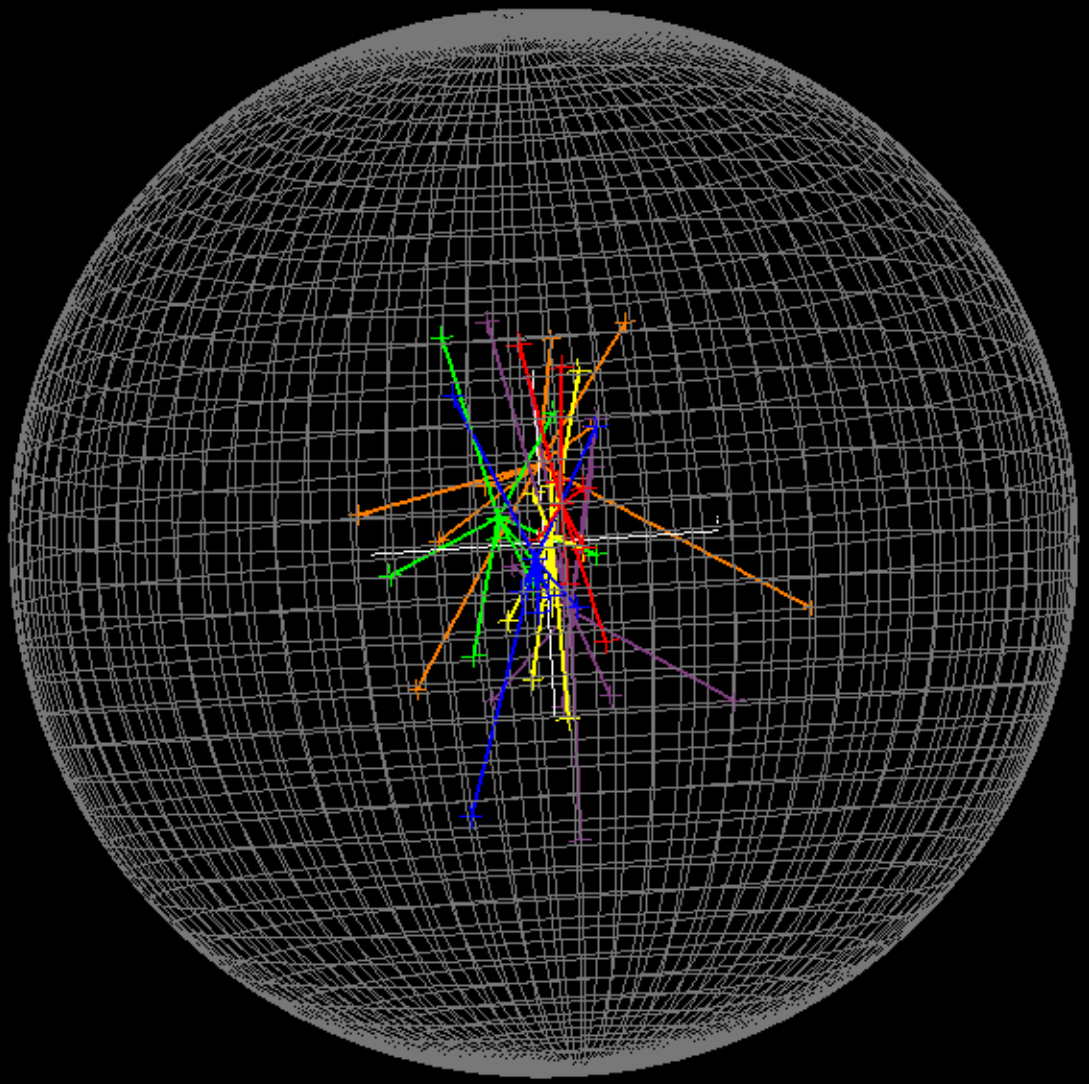

Comments

- AD is nearly unidimensional (axis 1) = progression path
- Learning Effects and Normal Aging are opposite ends of the next dimension (axis 2)
- Composites are identifying a latent variable associated with dimension 1 – Progression of Alzheimer's Disease
  - Factor Analysis does not achieve this same goal.
- Cognition represents the Core Disease Symptoms – it is not a biomarker(!)

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Historical Topics

- Items that show early, disease related decline
  - Requires “Normal aging/ learning effects” adjustment
- Improved power over single outcome measure
  - Weighted combinations
  - “Unweighted” combinations
- Items that show early, disease related decline
- Improved power over single outcome measure

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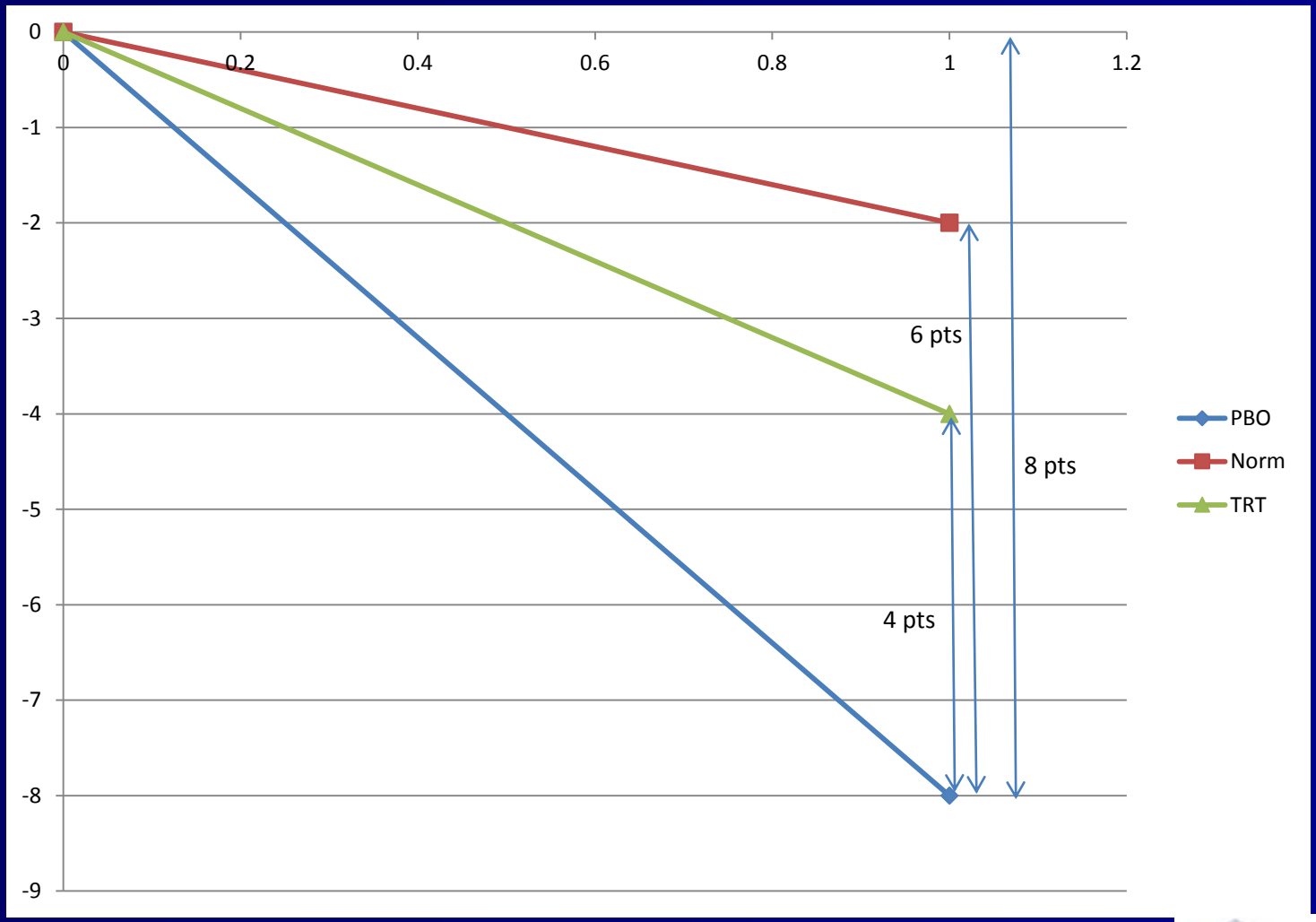
Normal Aging Correction



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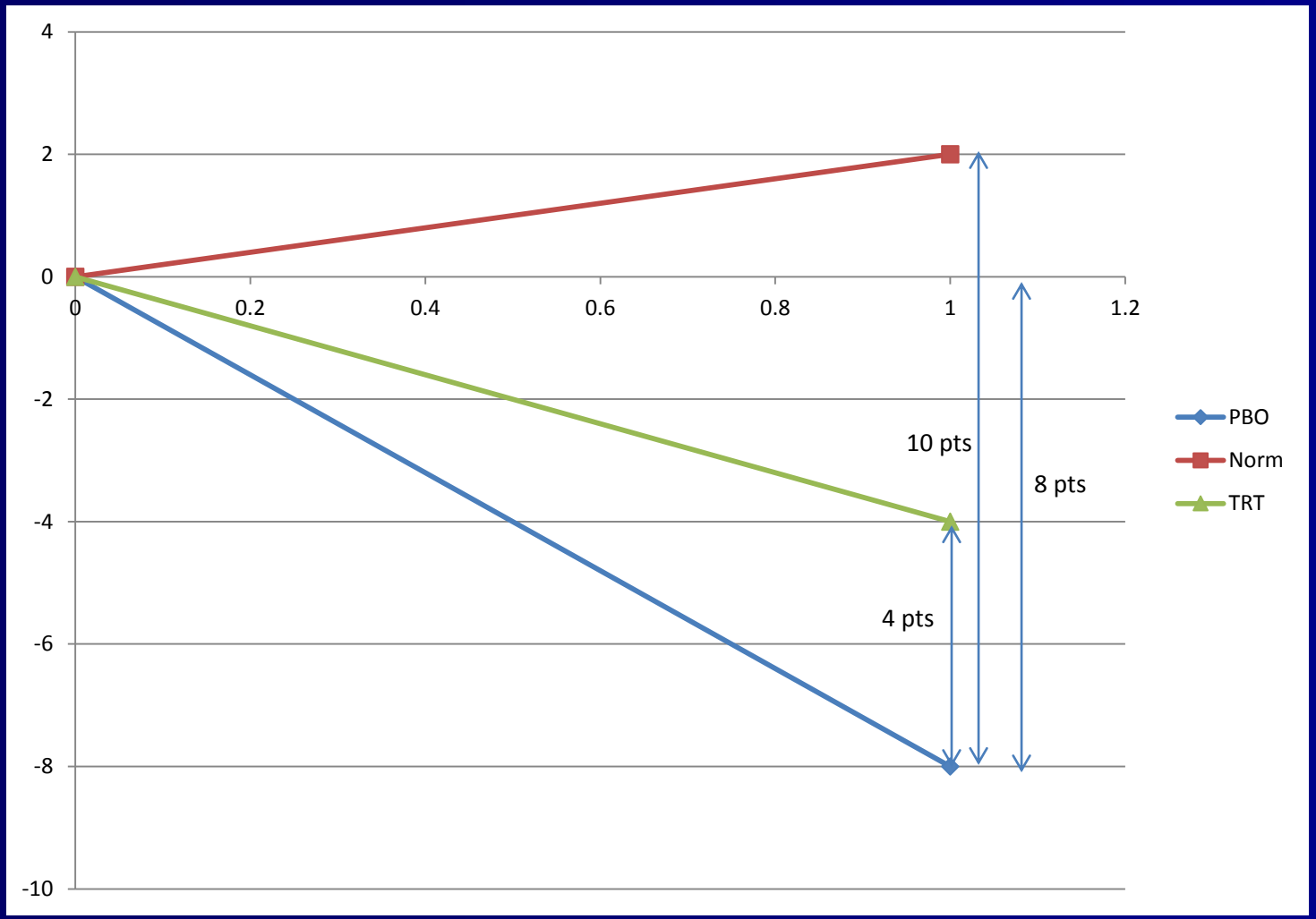
Learning Effects Correction



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Current Issues for Composites in Very Early AD

- Concept of “slowing” of disease trajectory, curvature at very early stages
- Comparing power for event based outcomes to clinical decline outcomes
- RBANS versus other cognitive tests

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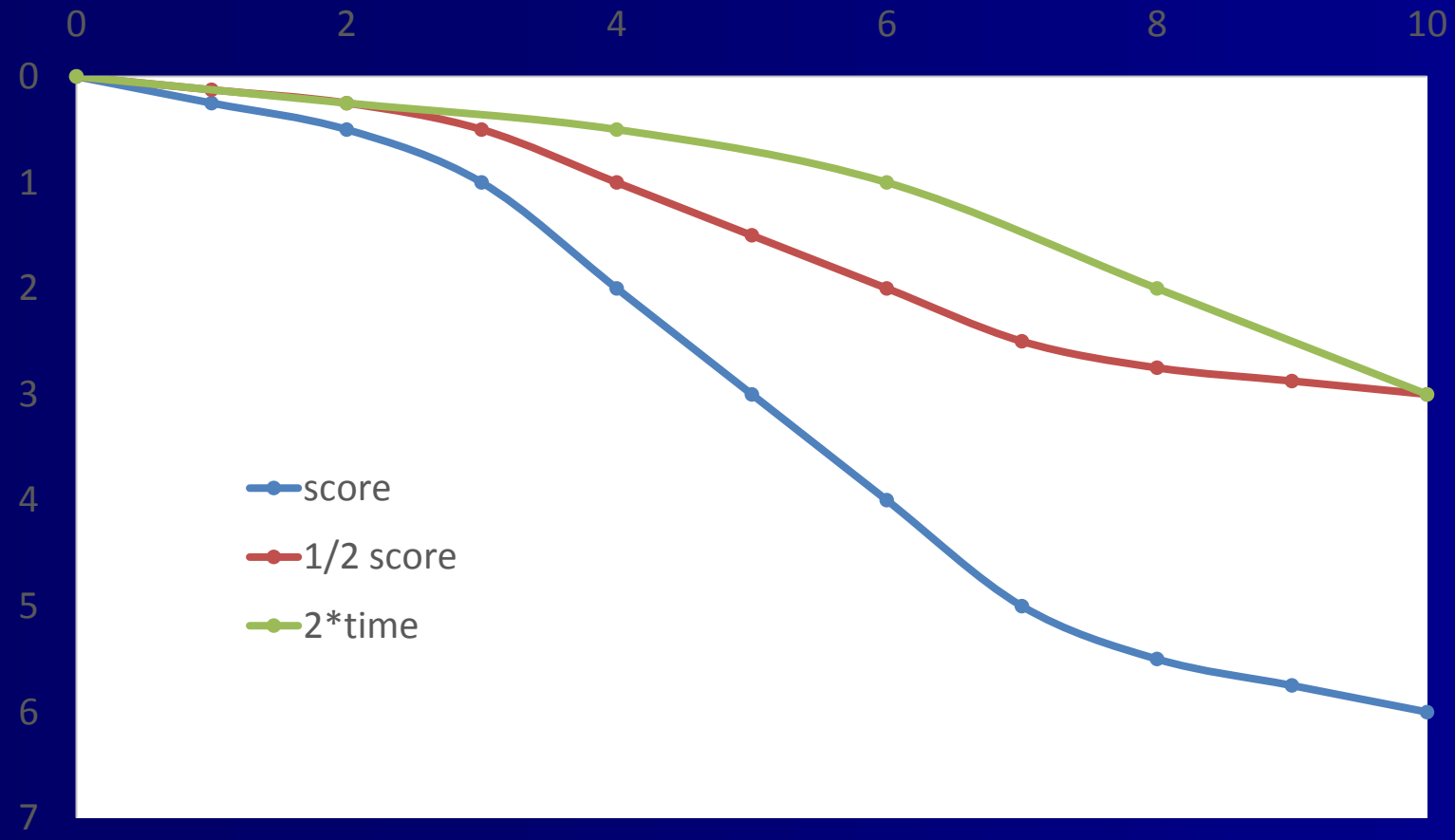
Curvature, Proportional Treatment Effect, “Expanded Time” Effect



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Conclusions

- Cognitive composites help a lot
- Curvature is important to consider in both development and analysis
  - Particularly in very early AD
  - Affects power calculation (decline rate)
  - Affects treatment effect (proportional vs. non-proportional)
- Power calculations are often not optimal

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Disclosures and Thanks

- Rush ROS, ADCS and ADNI for data
- Eisai and API for the first composite projects
- Stephanie Stanworth, Noel Ellison and Leah Garriott (Pentara)
- Bruce Brown (BYU) – Data mining tools

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