Cognitive Phenotypes
What are Cognitive Phenotypes?

- The term ‘intermediate phenotype’ has been proposed to describe measures indexing biological risk for a mental illness that are intermediate between gene expression and clinical diagnoses (or symptoms).
  - Meyer-Lindenberg & Weinberger, 2006

- Could be a biomarker, a cognitive index, or a latent behavioral factor
RDoC

- The NIMH recently proposed the Research Domain Criteria (RDoC) strategy
- RDoC encourages new ways of classifying psychopathology by developing biologically valid *dimension based taxonomies*
  - *i.e., intermediate phenotypes*

Cuthbert & Insel 2010; Insel et al., 2010
Spearman’s general intelligence factor:
Spearman C. *Am J Psychol*, 1904

- $g$ is the shared variance across a battery of cognitive performance measures.
- $g$ is “indifferent to its indicators.”
  - $g$ can be demonstrated in all cognitive assessments.
    - Spearman took $g$ down to sensory tasks.
- $g$’s biology is poorly understood.
- $g$ is heritable, but no $g$-related genes have been identified.
- $g$ can be demonstrated in animal cognitive performance.
- $g$’s relationships with Alzheimer’s Disease and neurodegeneration are understudied.
“δ”

- The “cognitive correlates of functional status”
  - AKA “Dementia”
- δ is the *only* variance in a battery related to functional outcomes\(^{11}\)
- Constructed by a unique confirmatory bifactor model in a structural equation model (SEM) framework\(^{8,9}\)
- Can be output as a “d-score”
  - Can be used as a predictor or as an outcome
Can be constructed from any cognitive battery that has a measure of IADL.\textsuperscript{8,9}
  - Even the items of a single measure. \textsuperscript{5,14}
No linguistic or cultural bias.\textsuperscript{13,18}
Can be output as a continuous measure of dementia severity.\textsuperscript{15}
Achieves better ROC / AUC for dementia’s diagnosis than any of its indicators.\textsuperscript{5,12,14}
Future dementia severity is almost entirely explained by baseline $\delta$ ($r = 0.90 \times \text{CDR-SB}$) and $\Delta\delta$ ($r = 0.94 \times \Delta\text{CDR-SB}$).\textsuperscript{2,7}
δ

- Is “agnostic” to dementia etiology.\(^2\)
  - Dementia status becomes the sum of independent δ-related processes.

- δ’s biomarkers are dementia’s biomarkers and offer dementia-specific treatment targets.\(^{10,19}\)

- Correcting ANY might improve dementia severity and/or reduce conversion risk.

- δ could be an “omnibus” clinical outcome.
Recommendations:

- Train OAIC /AD investigators to build *ad hoc* δ homologs from their existing datasets, where possible (R13).

- Construct an acceptable δ homolog (from MoCA items?; $AUC = 0.95$) and insert it into routine data collection streams across multiple OAIC and AD centers.
  - Validate its diagnostic threshold in well characterized AD center cases.

- Use AD Center data to construct “more accurate” δ homologs (and orthologs) and ascertain their biomarkers.
  - $AUC = 0.96$ in 26,000 NACC cases$^2$

- Use δ homologs as outcomes in clinical trials (e.g., targeting δ biomarkers).
References:

7. Palmer RF, Royall DR. Future dementia status is almost entirely explained by the latent variable δ’s intercept and slope. Journal of Alzheimer’s Disease 2016;49:521-529.
15. Royall DR, Palmer RF. Thrombopoietin is associated with δ’s intercept, and only in Non-Hispanic Whites. Alzheimer’s & Dementia: Diagnosis, Assessment & Disease Monitoring, 2016;3:35-42.
16. Royall DR, Palmer RF. Aging is a weak but relentless determinant of dementia severity. Oncotarget (Aging/Gerotarget), 2016. 10.18632/oncotarget.7759.