"Omics" in Neuropsychology: Current State and Future Directions

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American Psychological Association, Chicago, 2019 August

UCLA Semel Institute
Tennenbaum Center for the Biology of Creativity

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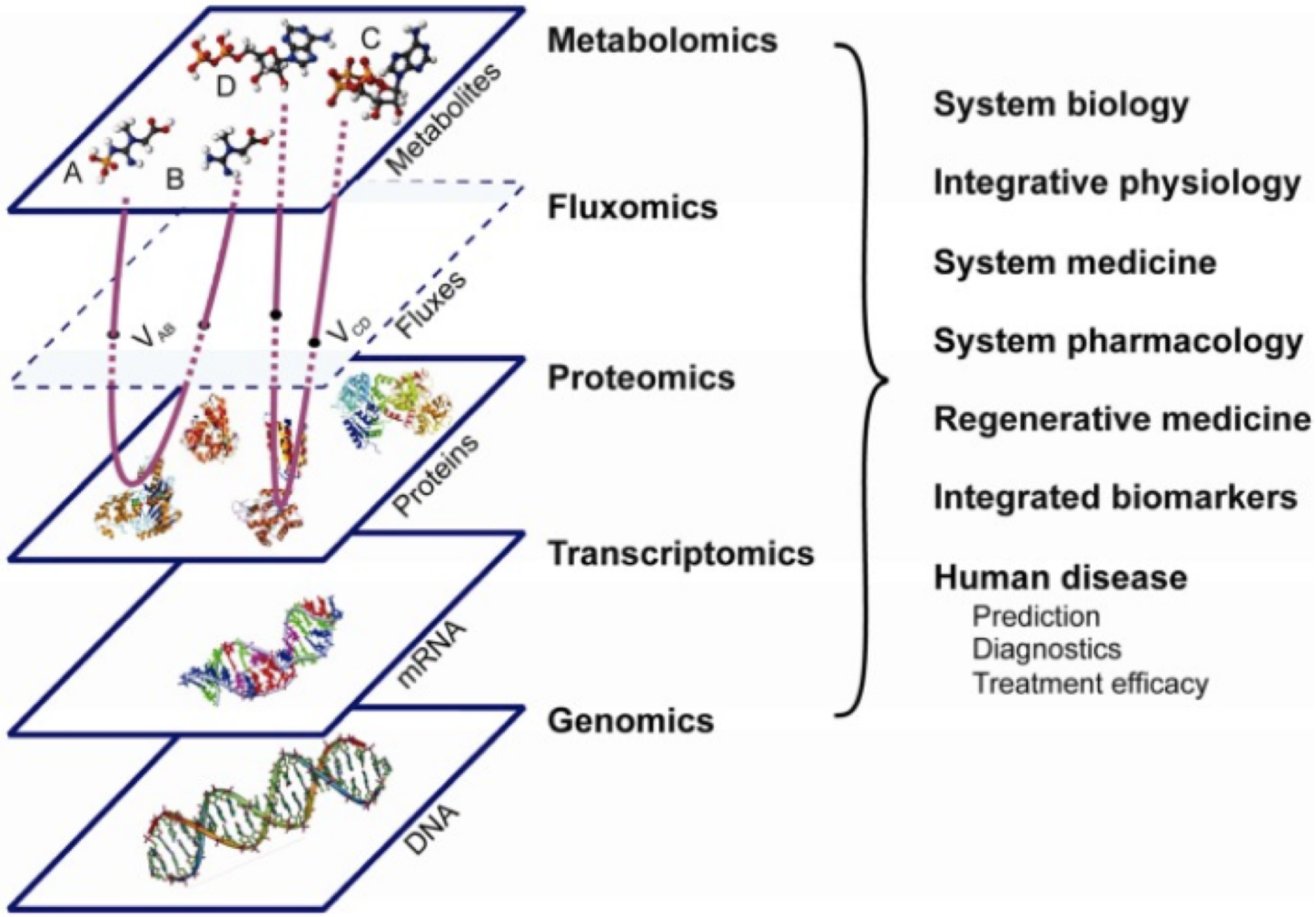
Omics revolution



The Human Phenome Project

ELSEVIER

Neuroscience

Volume 164, Issue 1, 24 November 2009, Pages 30-42

General Issue

Research Paper

Phenomics: the systematic study of phenotypes on a genome-wide scale

R.M. Bilder [a, b, e], F.W. Sabb [a, e], T.D. Cannon [a, b, e], E.D. London [a, c, e], J.D. Jentsch [b, e], D. Stott Parker [d], R.A. Poldrack [b, e], C. Evans [a, e], N.B. Freimer [a, e]

Show more

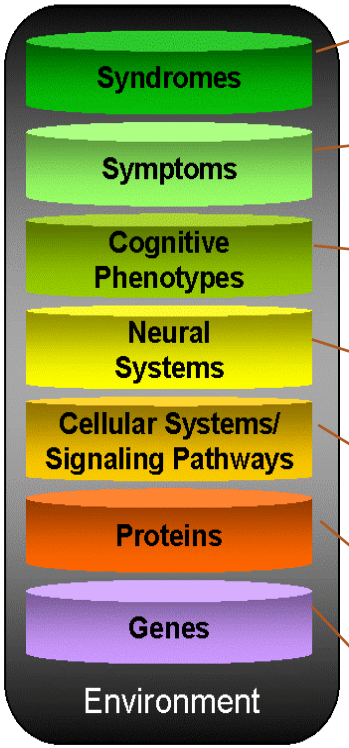
https://doi.org/10.1016/j.neuroscience.2009.01.027

Get rights and content

- Human Genome Project is now "complete"
- Knowledge is rapidly being accumulated to represent gene expression, proteomics (bottom-up approach), but higher levels are not well represented
- "The main hurdle for biomedical science for the next century is the ***Human Phenome Project***[1] – characterizing the manifold human phenotypes from molecule to mind"

[1]Freimer & Sabatti, *Nat Genet* 2003

From Genome to Syndrome?
Example for Neuropsychology



Clusters of symptoms that co-occur are called "syndromes" (e.g., schizophrenia)

Disturbances in brain function relative to societal expectations are called "symptoms" (e.g., delusions)

Neural system activity underlies various brain functions: perception, cognition, emotion…

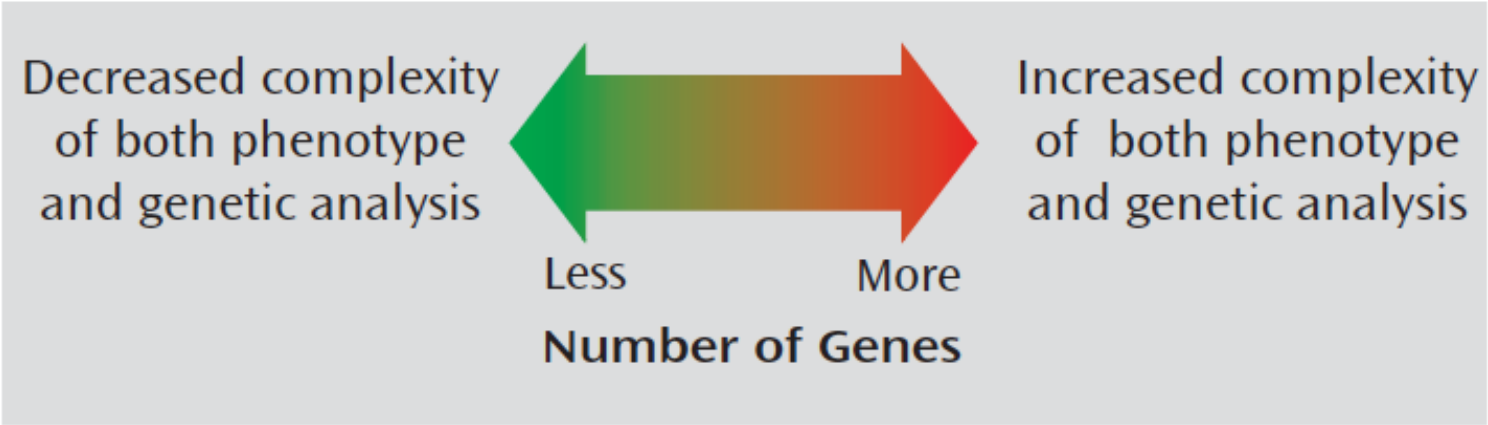
Cellular systems organize to form complex systems and neural networks in the brain

Groups of cells aggregate to form systems, metabolic and signaling pathways, execute cell functions

~500K -2M Proteins: building blocks of cells, enzymes, and more

3 Billion base pairs in human genome -> 20K "genes" (chunks that code for proteins)

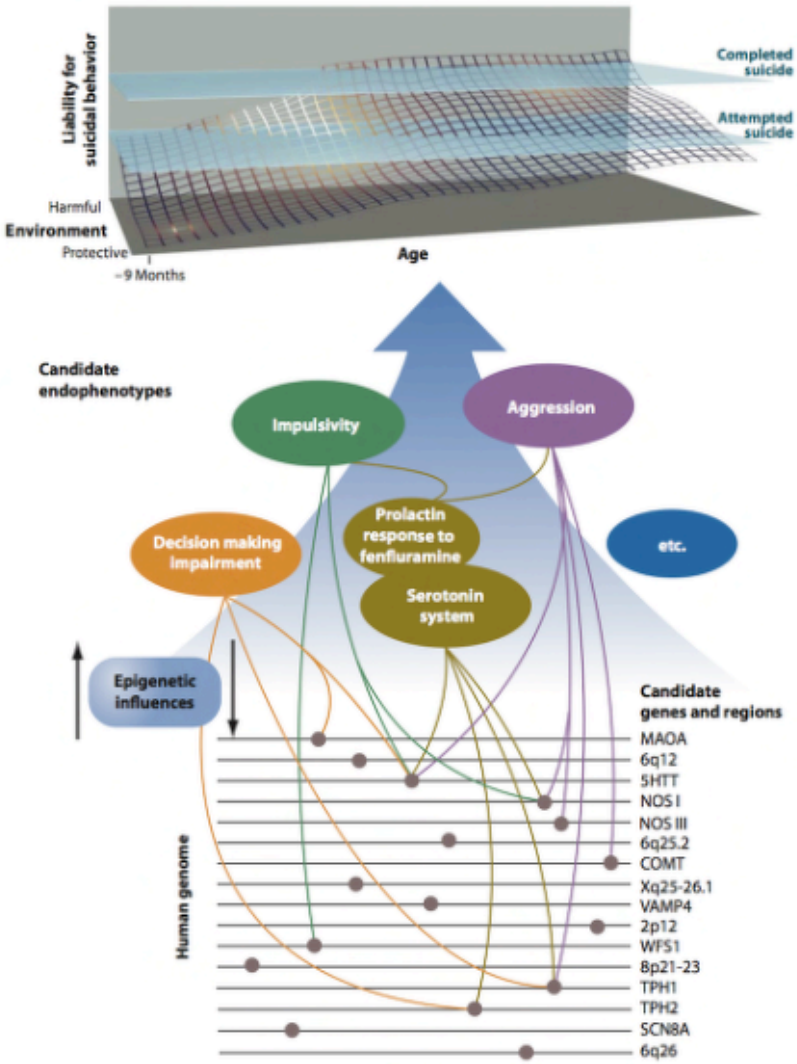
FIGURE 1. Rationale for an Endophenotype Approach to Genetic Analysis of Disorders With Complex Genetics[a]



[a] The number of genes involved in a phenotype is theorized to be directly related to both the complexity of the phenotype and the difficulty of genetic analysis (28–34).

From Gottesman & Gould 2003

Gottesman & McGue – Endophenotype *(2013); Wiley-Blackwell Encyclopedia of Clinical Psychology* Robin L. Cautin & Scott O. Lillienfeld (Eds.)



But complexity rears its ugly head

- The hope that endophenotypes would have a simpler genetic architecture has not been born out
- Flint & Munafo (2007): meta-analysis –
  - A review of the genetic architecture of traits in model organisms … provides no support for the view that the effect sizes of loci contributing to phenotypes closer to the biological basis of disease is any larger than those contributing to disease itself.

Flint & Munafo 2007: What about mice?

- Average effect ~2.2% variance explained across physiological, biochemical, hematological, immunological phenotypes
- Even for *expression*, only about 27% of transcript level is explained by genotype

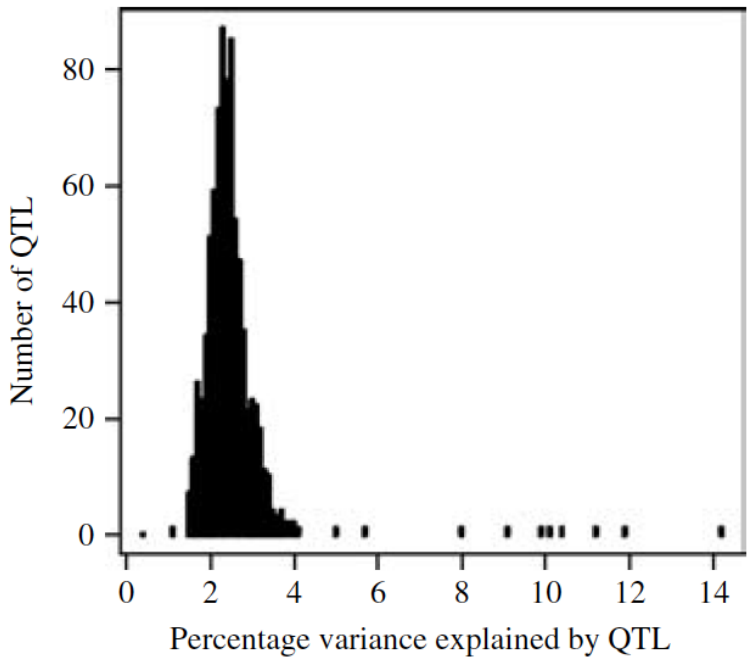


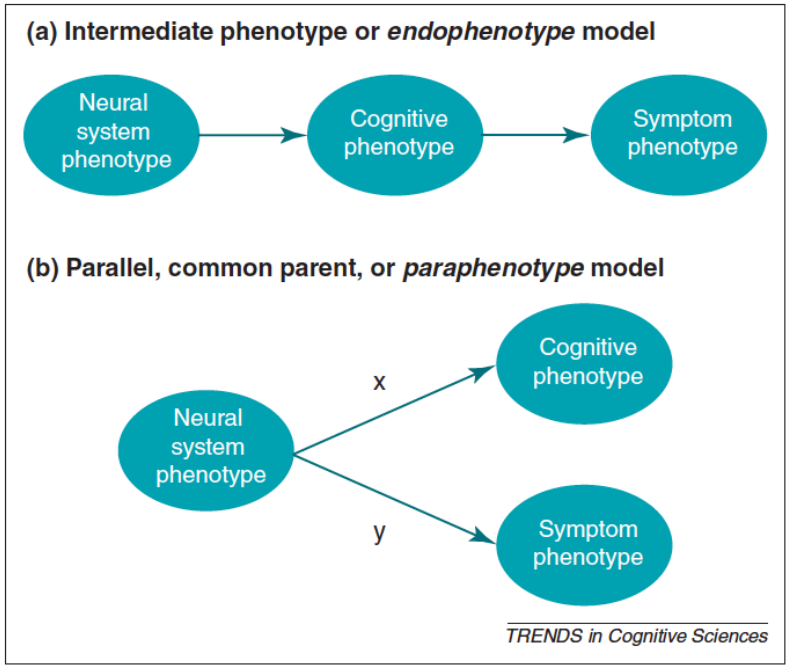
FIG. 4. Distribution of effect sizes of 843 mouse quantitative trait loci (QTL).

Review

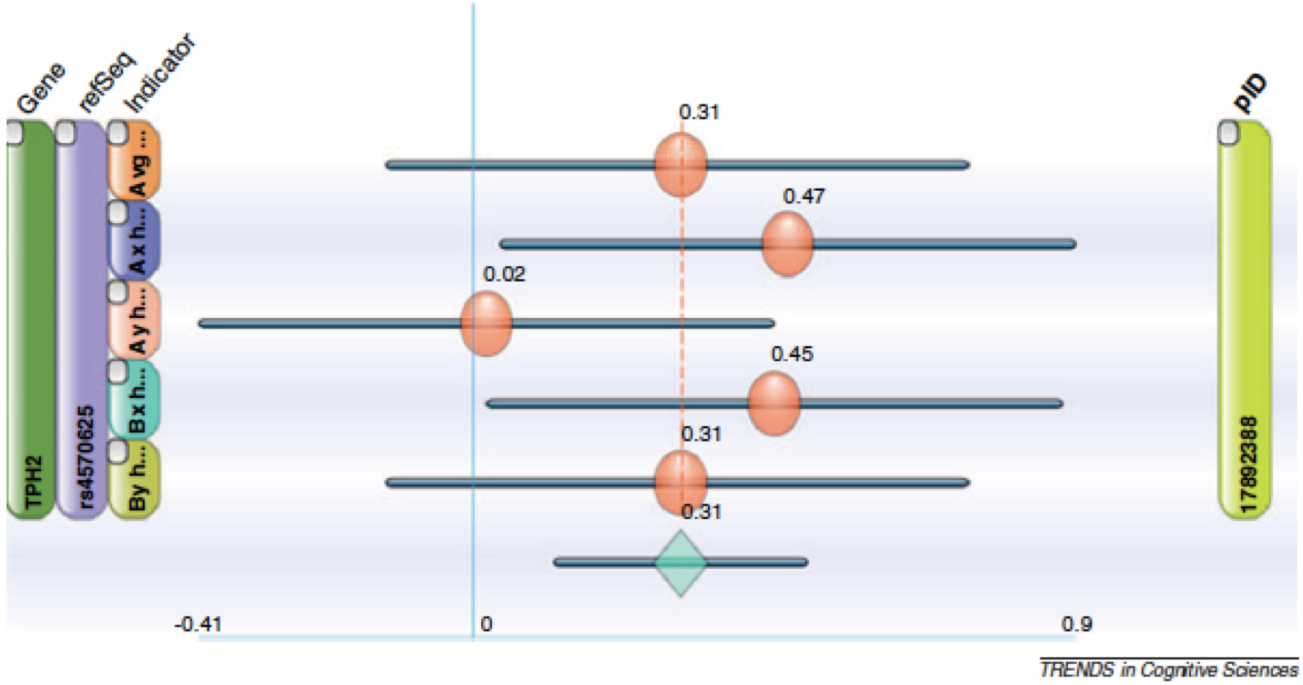
Special Issue: The Genetics of Cognition

The genetics of cognitive impairment in schizophrenia: a phenomic perspective

Robert M. Bilder[1], Andrew Howe[2], Nic Novak[3], Fred W. Sabb[1] and D. Stott Parker[2]



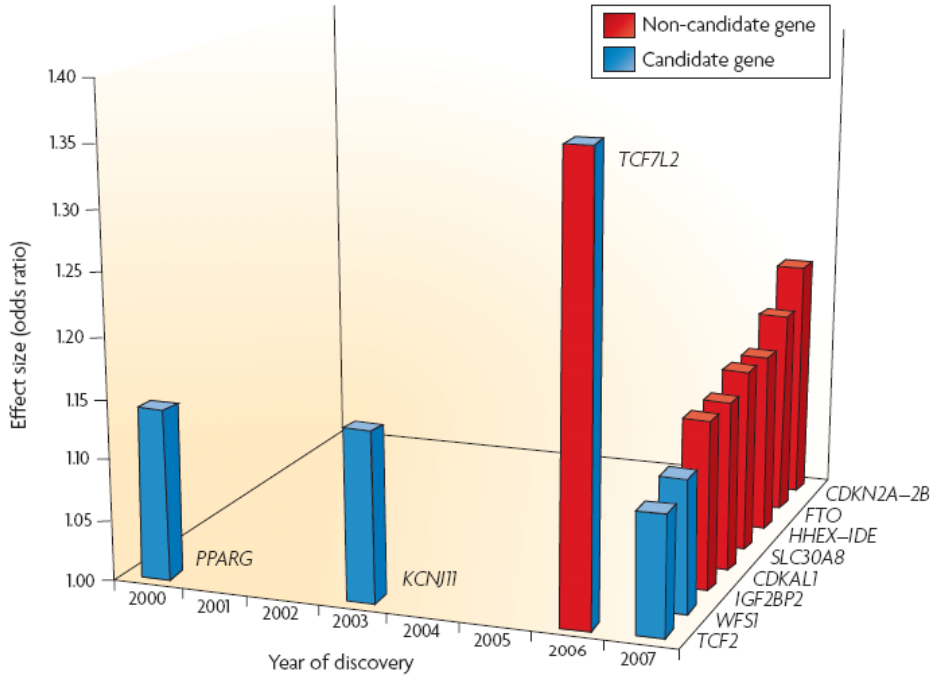
Bilder et al 2011


Gene
refSeq
Indicator
pID
TPH2
rs4570625
By h...
Bxh...
Ayh...
Axh...
Avg ...
17892388
0.31
0.47
0.02
0.45
0.31
0.31
-0.41
0
0.9
TRENDS in Cognitive Sciences

“Candidate genes” being overtaken by GWAS findings: Type 2 diabetes

Note: 4 of 11 established candidates were identified using traditional approaches over the prior decade; the other 7 were identified in previously unsuspected genes during 2006-7.

Frayling (2007) *Nature Genetics*



Hale *et al. BMC Systems Biology* 2012, **6**(Suppl 3):S16
http://www.biomedcentral.com/1752-0509/6/S3/S16

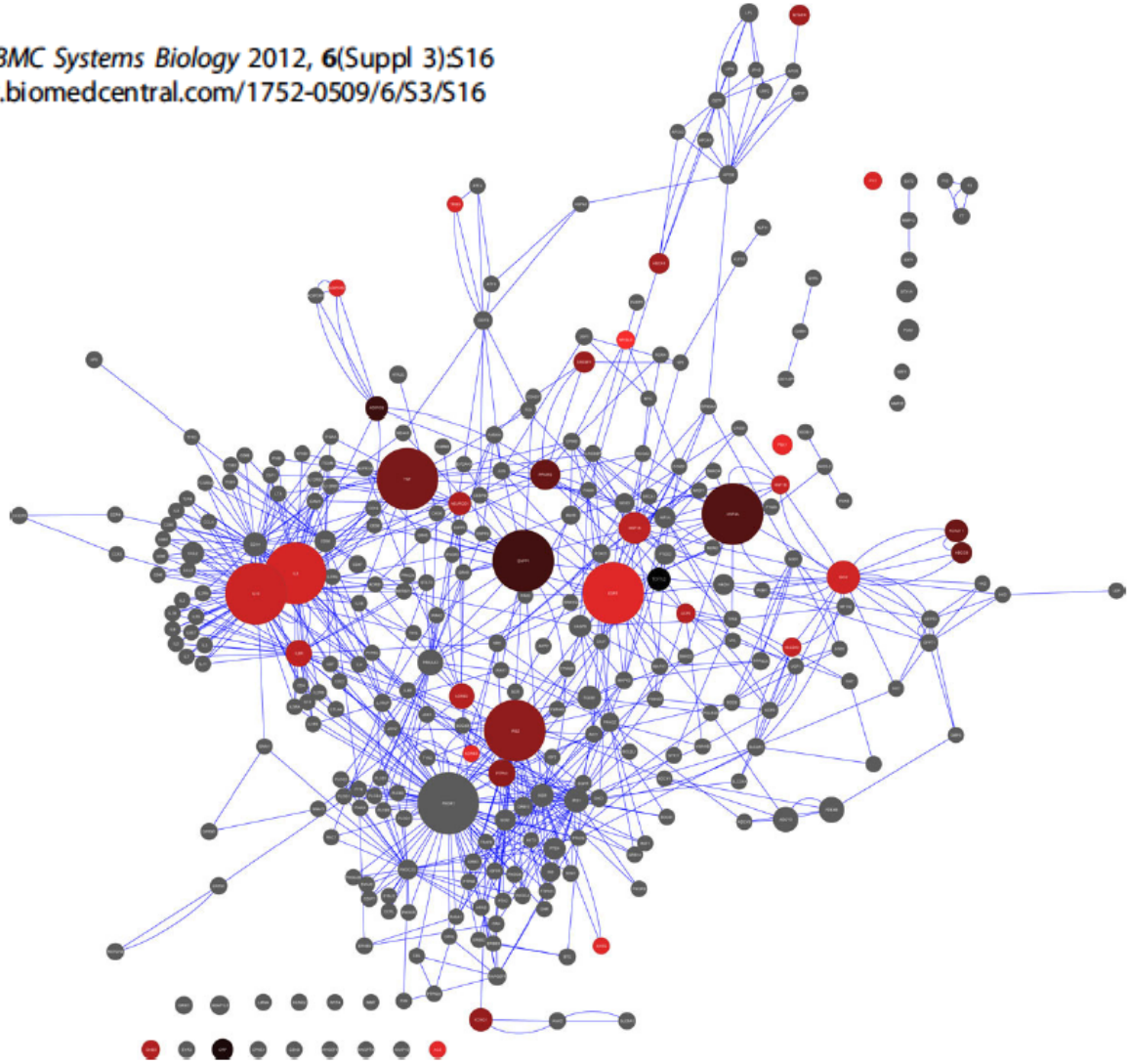


Figure 1 T2D risk gene network. Genes are represented as nodes drawn to the scale of their r_{mod} scores. Higher-risk genes (high average odds ratio) are colored black and lower-risk genes (low average odds ratio) are colored red. Genes without significantly reported risk information are colored grey.

nature COMMUNICATIONS

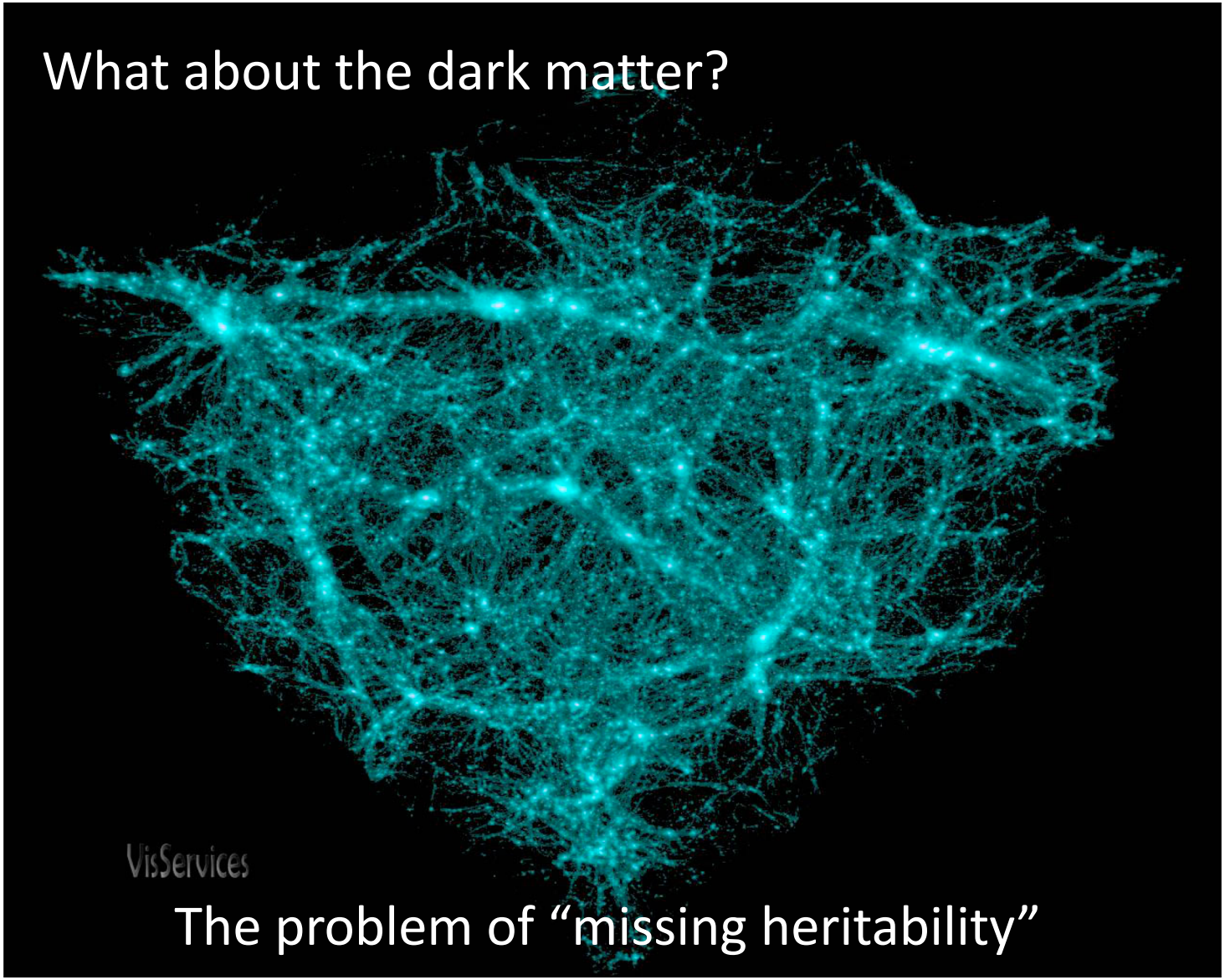
Article | OPEN ACCESS | Published: 29 May 2018

Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function

Gail Davies, Max Lam, [...] Ian J. Deary

… We combine cognitive and genetic data from the CHARGE and COGENT consortia, and UK Biobank (total N = **300,486**; age 16–102) and find **148** genome-wide significant independent loci ($P < 5 \times 10{-}8$) associated with general cognitive function. Within the novel genetic loci are variants associated with neurodegenerative and neurodevelopmental disorders, physical and psychiatric illnesses, and brain structure. Gene-based analyses find **709** genes associated with general cognitive function. Expression levels across the cortex are associated with general cognitive function. Using polygenic scores, up to **4.3%** of variance in general cognitive function is predicted in independent samples. We detect significant genetic overlap between general cognitive function, reaction time, and many health variables including eyesight, hypertension, and longevity. In conclusion we identify novel genetic loci and pathways contributing to the heritability of general cognitive function.

What about the dark matter?



The problem of “missing heritability”

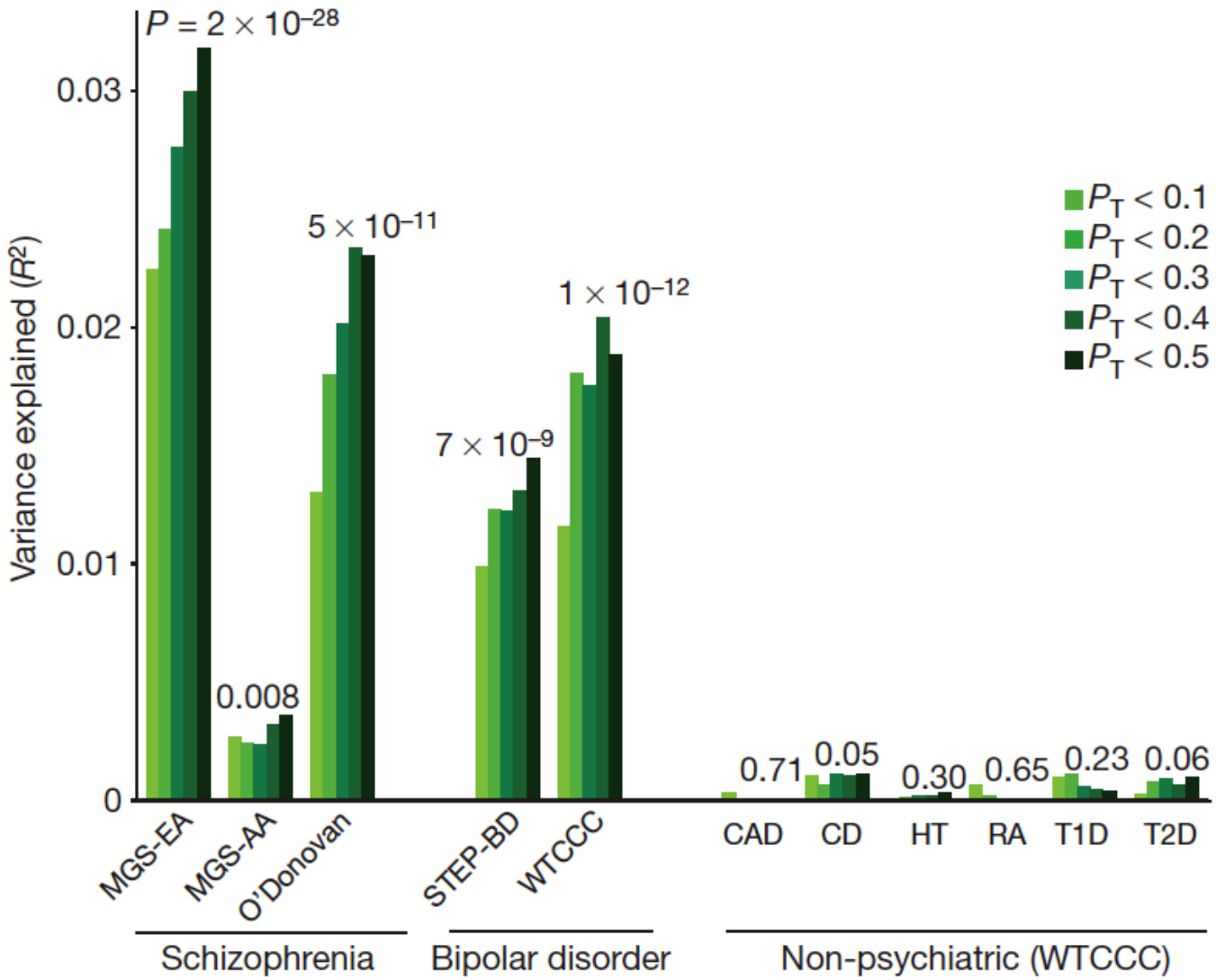
doi:10.1038/nature08185 nature

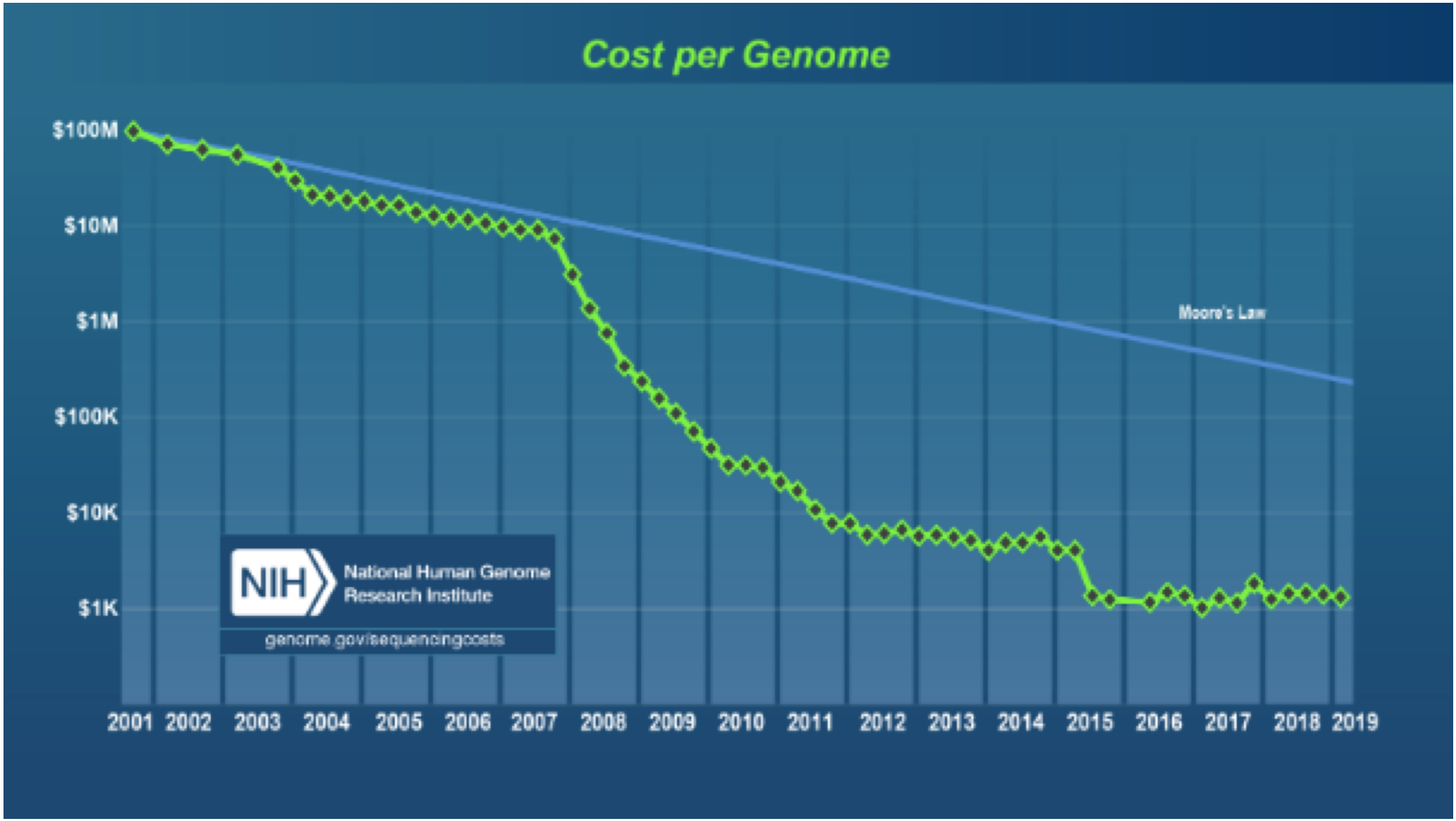
LETTERS

Common polygenic variation contributes to risk of schizophrenia and bipolar disorder

The International Schizophrenia Consortium*

- Schizophrenia: H2 ~80%
- Common SNPs cumulatively explain ~34% of variance in phenotype
- Probably due to thousands, not few or even hundreds of variants
- Substantial overlap of SNPs associated with both schizophrenia and bipolar disorder


P = 2 × 10−28
5 × 10−11
1 × 10−12
7 × 10−9
0.008
0.71
0.05
0.30
0.65
0.23
0.06
Variance explained (R2)
0.03
0.02
0.01
0
PT < 0.1
PT < 0.2
PT < 0.3
PT < 0.4
PT < 0.5
MGS-EA
MGS-AA
O'Donovan
STEP-BD
WTCCC
CAD
CD
HT
RA
T1D
T2D
Schizophrenia
Bipolar disorder
Non-psychiatric (WTCCC)


Cost per Genome
$100M
$10M
$1M
$100K
$10K
$1K
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001
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2016
2017
2018
2019

PLOS | GENETICS

OPINION PIECE

Solving the missing heritability problem

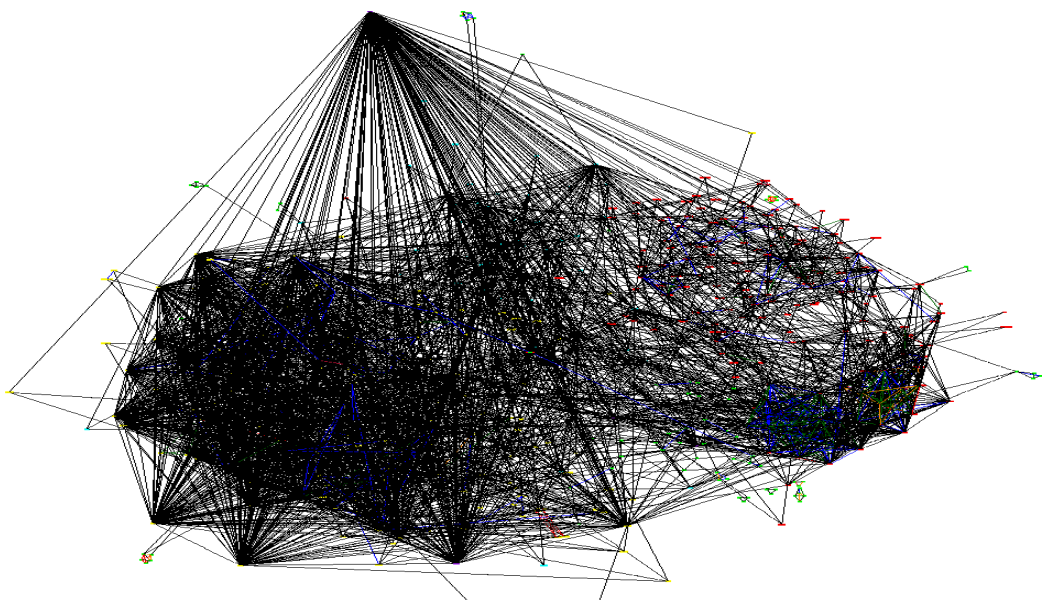
Alexander I. Young *

Big Data Institute, University of Oxford, Oxford, United Kingdom

* alextisyoung@gmail.com

- Might be solved by whole genome sequencing data? … OR …
- Other explanations:
  - complex traits are highly polygenic and affected by many rare variants;
  - twin studies have overestimated heritability.
- Both appear to be partially true, and accurate estimates will likely need large studies including families to account for indirect genetic effects ("genetic nurture") effects associated with parental alleles not carried by offspring

Informatics Simplifies Everything



- Phenomics KB – 2006_02_06 w/ ~600 nodes, 4200 edges
- Diagnoses, Symptoms, Cognitive_phenotypes, Neuroanatomy, Neuroscience_genes

KB Development for Biomedicine

- Genetics, genomics, and proteomics (Entrez GEO, Gene, Protein, OMIM, SNP, …)
- Controlled vocabulary resources: UMLS/MeSH, Metathesaurus, Semantic Web, OntoWorld, "Web 2.0"
- "Phenomics" DBs (mostly mouse so far)
- Comparable developments for cognitive neuroscience and neuropsychology?
- If available, would enable connection of NP findings to other sources of biological knowledge (genetic, proteomic, -omic)

frontiers in
NEUROINFORMATICS

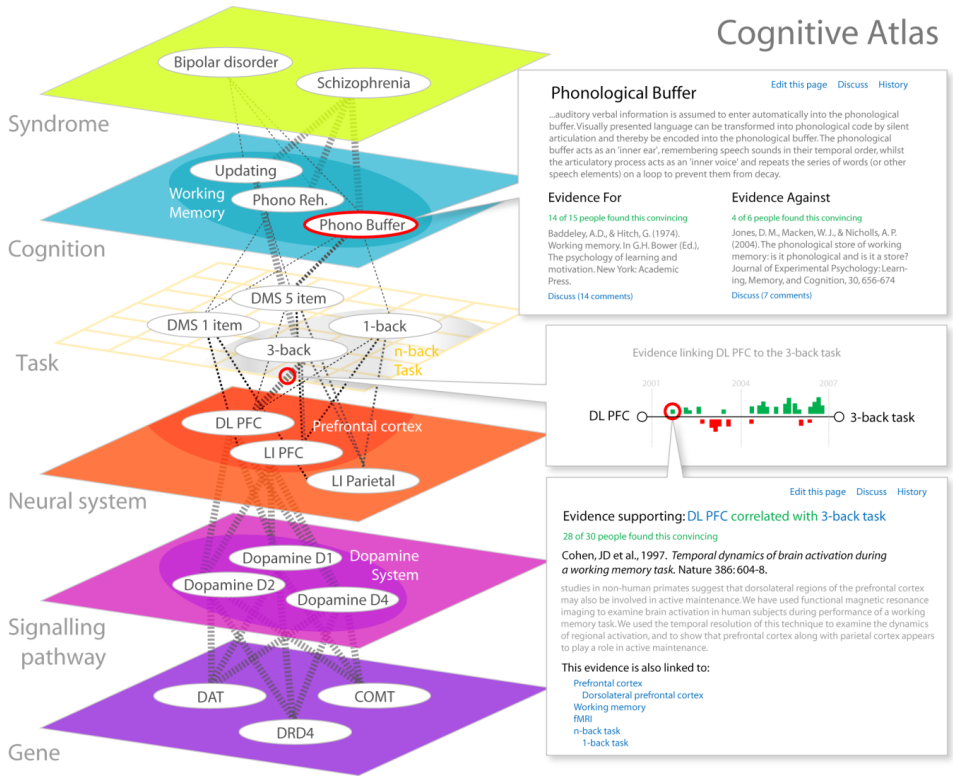
ORIGINAL RESEARCH ARTICLE
published: 06 September 2011
doi: 10.3389/fninf.2011.00017

The cognitive atlas: toward a knowledge foundation for cognitive neuroscience

Russell A. Poldrack[1]*, Aniket Kittur[2], Donald Kalar[3], Eric Miller[4], Christian Seppa[4], Yolanda Gil[5], D. Stott Parker[6], Fred W. Sabb[7] and Robert M. Bilder[7]

[1] Imaging Research Center and Departments of Psychology and Neurobiology, University of Texas, Austin, TX, USA
[2] Human–Computer Interaction Institute, Carnegie Mellon University, Pittsburgh, PA, USA
[3] National Aeronautics and Space Administration, Ames Research Center, Mountain View, CA, USA
[4] Interactive Design, Squishymedia, Portland, OR, USA
[5] Information Sciences Institute, University of Southern California, Marina Del Rey, CA, USA
[6] Department of Computer Science, University of California Los Angeles, Los Angeles, CA, USA
[7] Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA

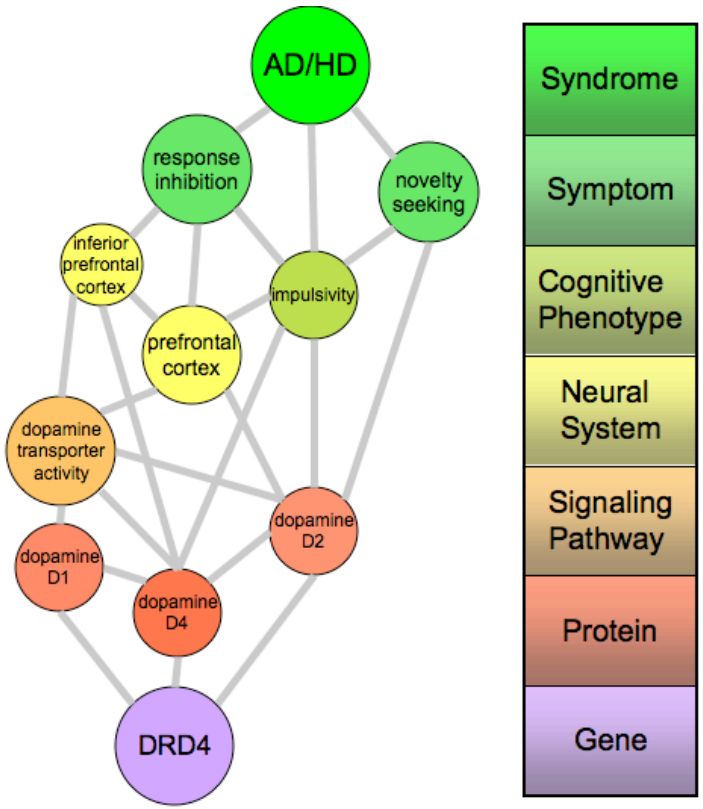
Architectures for cognitive ontology development



The Cognitive Atlas is conceptualized as a related set of maps. A given map may contain sets of related concepts, quantitative models of literature association, annotated effect size statistics, raw data, summaries of voting, and qualitative free-text inputs.

For cognitive concepts (e.g., the "phonological buffer") there are associated cognitive concepts, and a "test" layer comprising objective indicators of the concepts

Graph representation of multi-level hypotheses for neuropsychiatry research



- Hypotheses for complex neuropsychiatric syndromes demand representation at multiple levels and span multiple biological scales
- Plausible mechanistic hypotheses should have representation at all levels
- Strongest hypotheses are those possessing paths with strongest effects
- Causal models can be constructed, compared (goodness of fit); results can rule out dead ends (pruning) or suggest areas where evidence could yield transformation of current knowledge

Multilevel Models from Biology to Psychology: Mission Impossible?

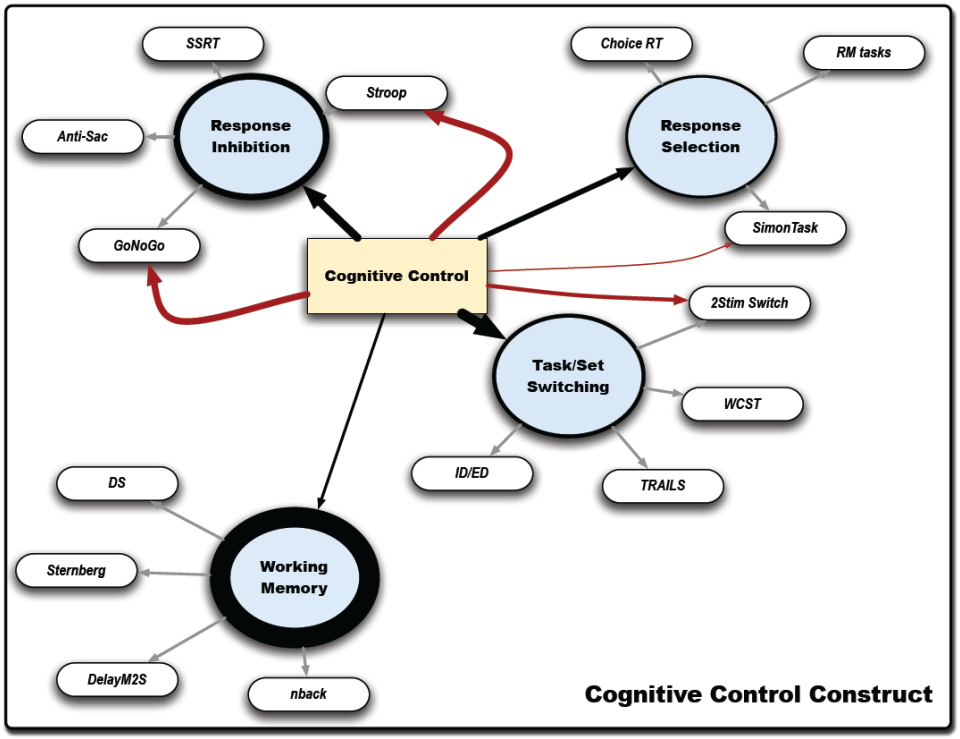
Bilder RM, Howe AG, Sabb FW
Journal of Abnormal Psychology, 2013 Aug;122(3):917-27.

It might be argued that the task of the psychologist, the task of understanding behavior and reducing the vagaries of human thought to a mechanical process of cause and effect, is a more difficult one than that of any other scientist.

(D. O. Hebb, 1949, p. xi)

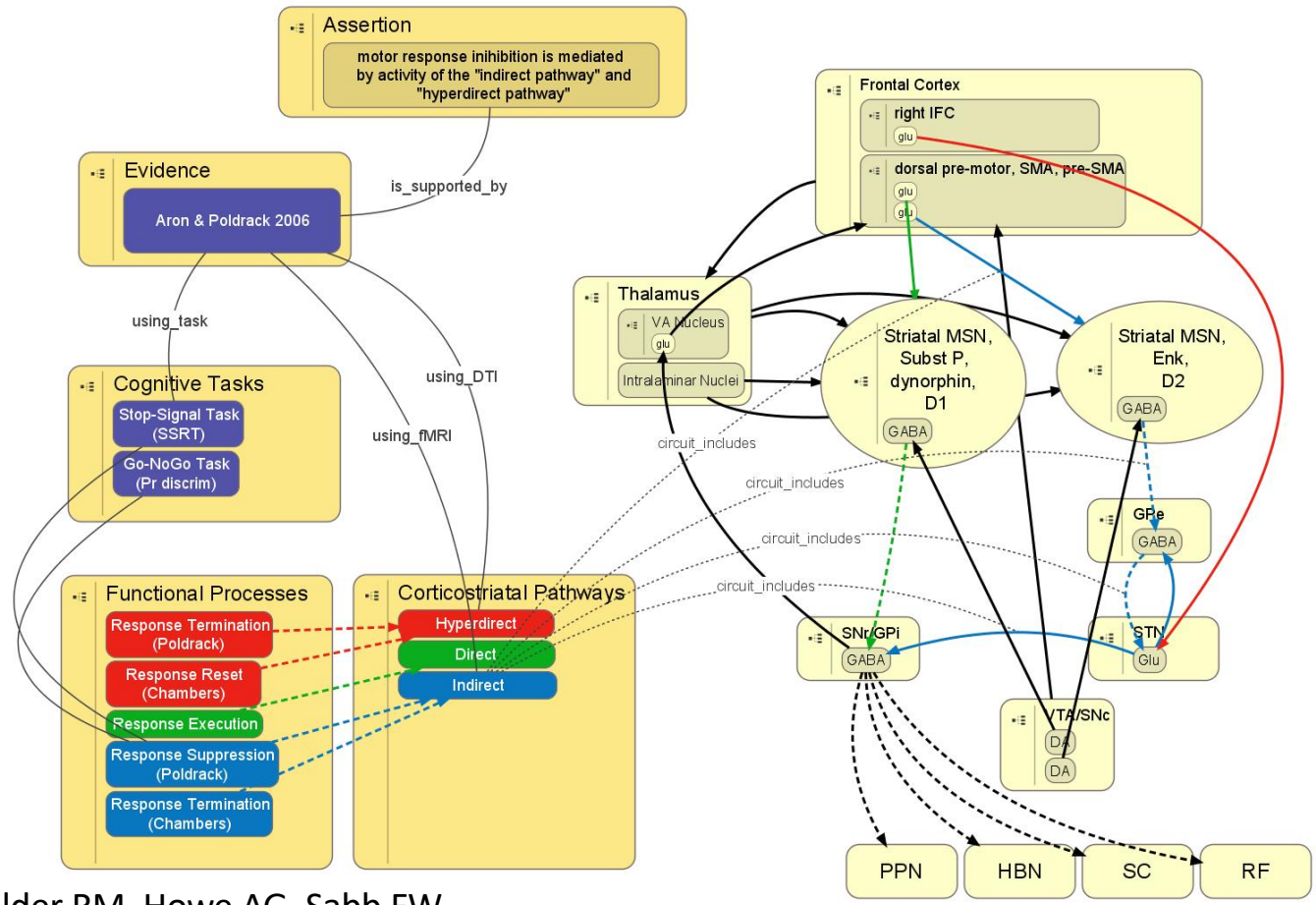
Concept definition via multiple sub-constructs and test indicators

"Cognitive control" has been associated in PubMed literature with RI, RS, TSS and WM. Sampling all 5 concepts (x30 papers) identified the task indicators used to assess these concepts. CC itself was measured using *only* task indicators already used to define RI, RS and TSS.



Sabb FW, Bearden CE, Glahn DC, Freimer N, Parker DS, Bilder RM. *Molecular Psychiatry*, 2009

Schema for Validation of Hypotheses about Neurocognitive Concepts



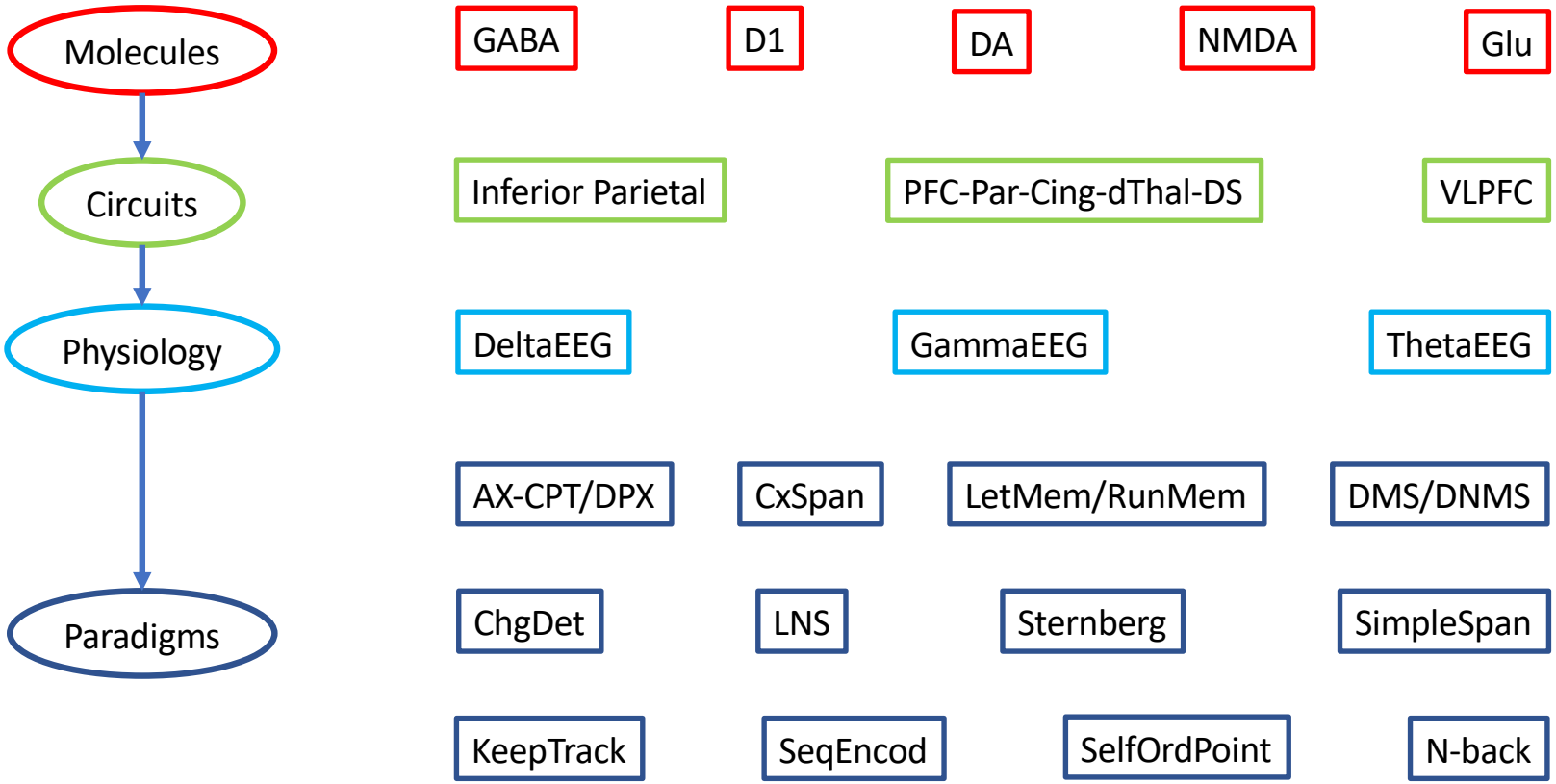
Bilder RM, Howe AG, Sabb FW
Journal of Abnormal Psychology, 2013 Aug;122(3):917-27.

The NIMH Research Domains Criteria (RDoC) Initiative

- The RDoC matrix depicts the constructs, domains, and units of analysis that are currently part of the RDoC framework. These are based on extant research and were vetted by over 200 researchers from relevant fields.
- Presently, there are five Domains in the RDoC matrix, though this will change as research on RDoC accrues and evolves.
  - Negative Valence Systems
  - Positive Valence Systems
  - Cognitive Systems
  - Systems for Social Processes
  - Arousal/Regulatory Systems

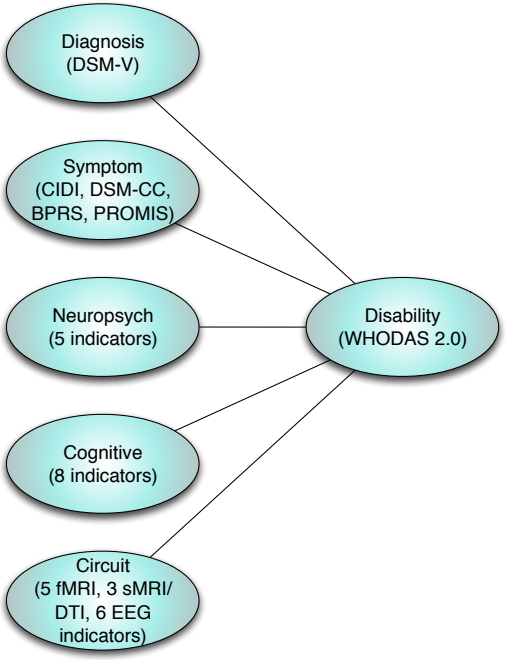
RDoC Matrix: Implied Edges

Is everything connected to everything else down here? What causes what?



Mapping to Functional Status

Do symptoms or diagnosis add useful prediction over basic measures of circuit, cognitive or neuropsychological measures?

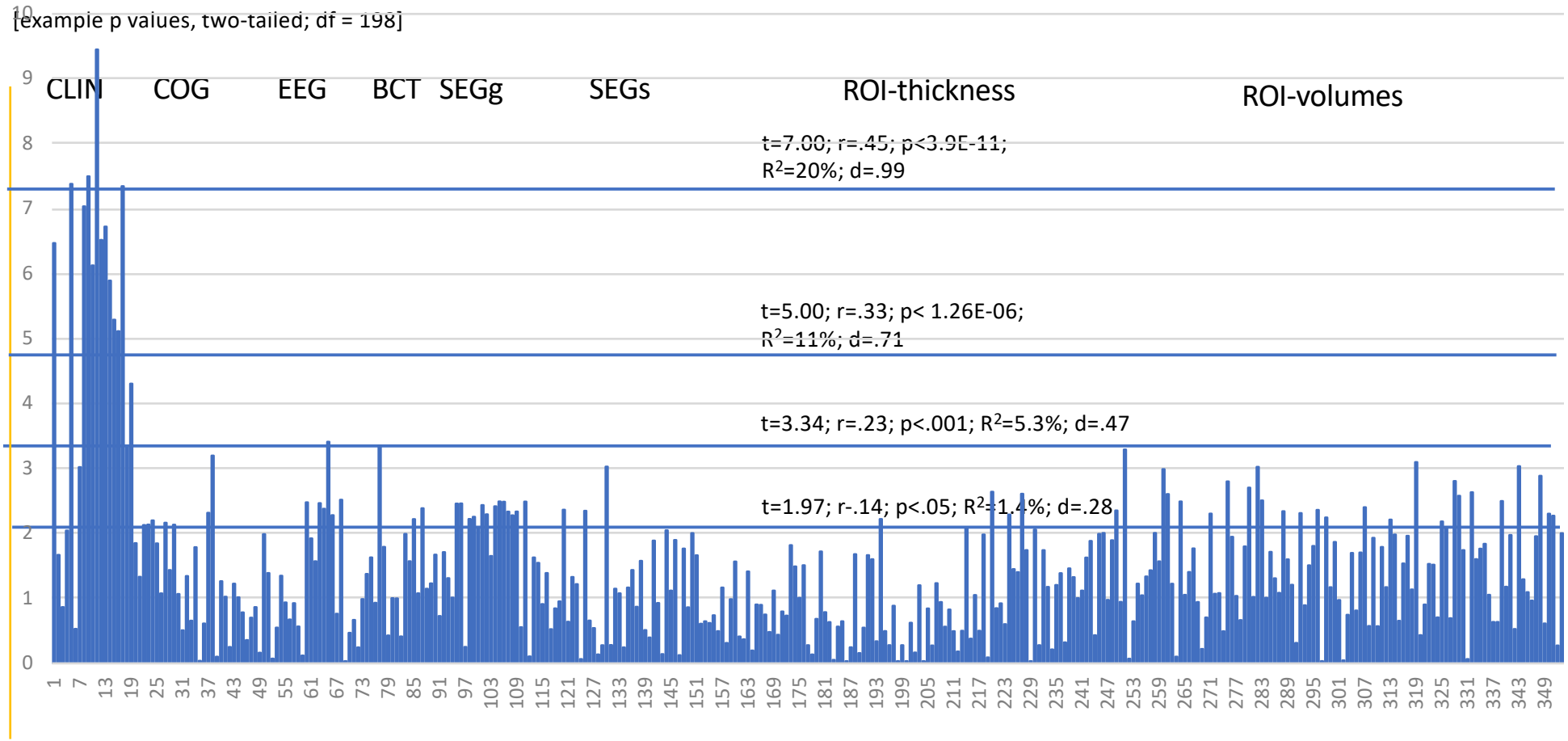


To avoid extreme group bias, sampling strategy is agnostic to diagnosis, and comprises two groups:

- Care-seeking
- Not Care-seeking

Diagnoses assigned *after* enrollment, as one of the dependent variables under study

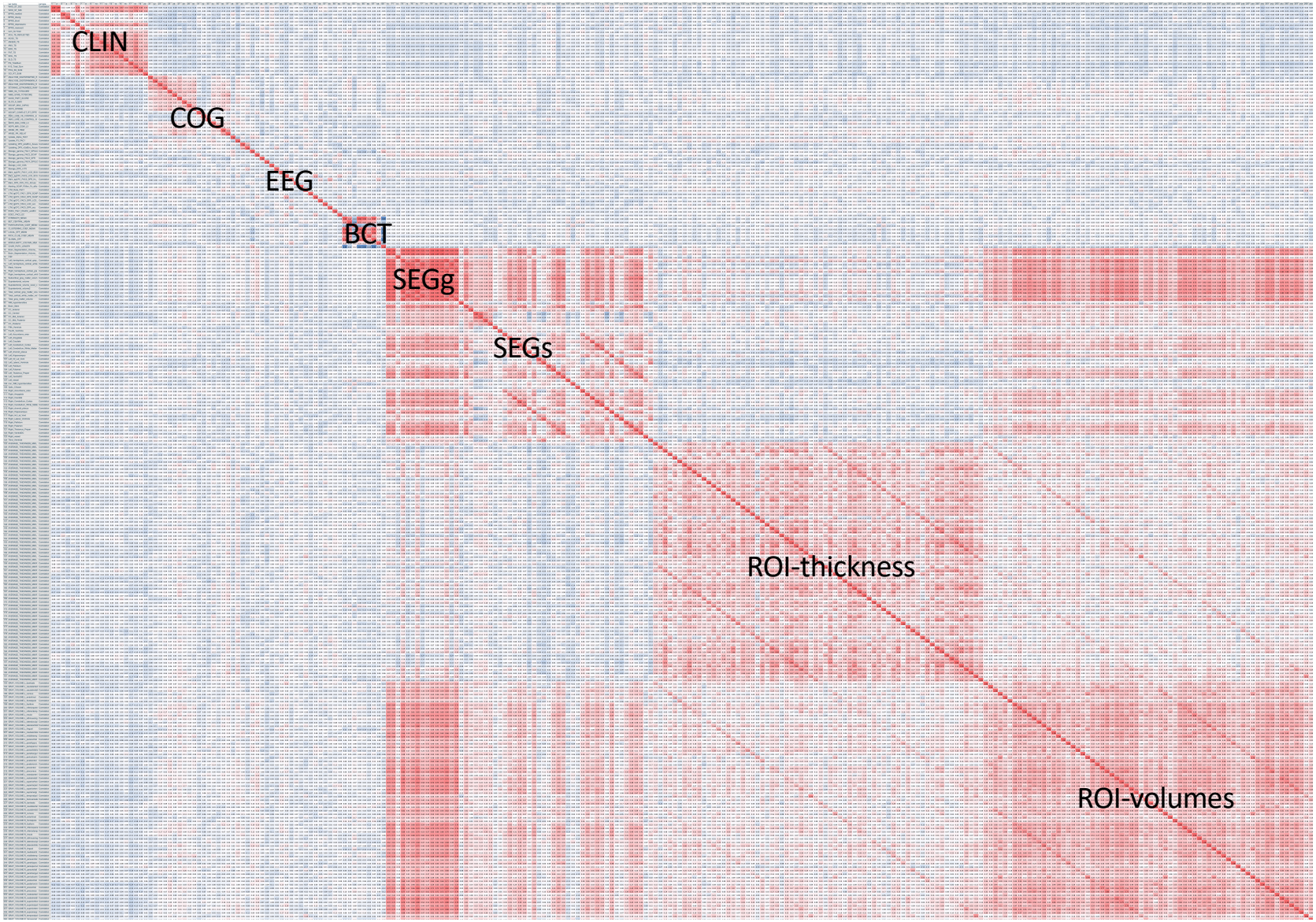
Differences Between Care-Seeking and Non-Care-Seeking Participants on Clinical, Cognitive, EEG, rsfMRI Brain Connectivity Metrics, and sMRI Freesurfer Segmentations (global, specific) and Parcellation ROIs



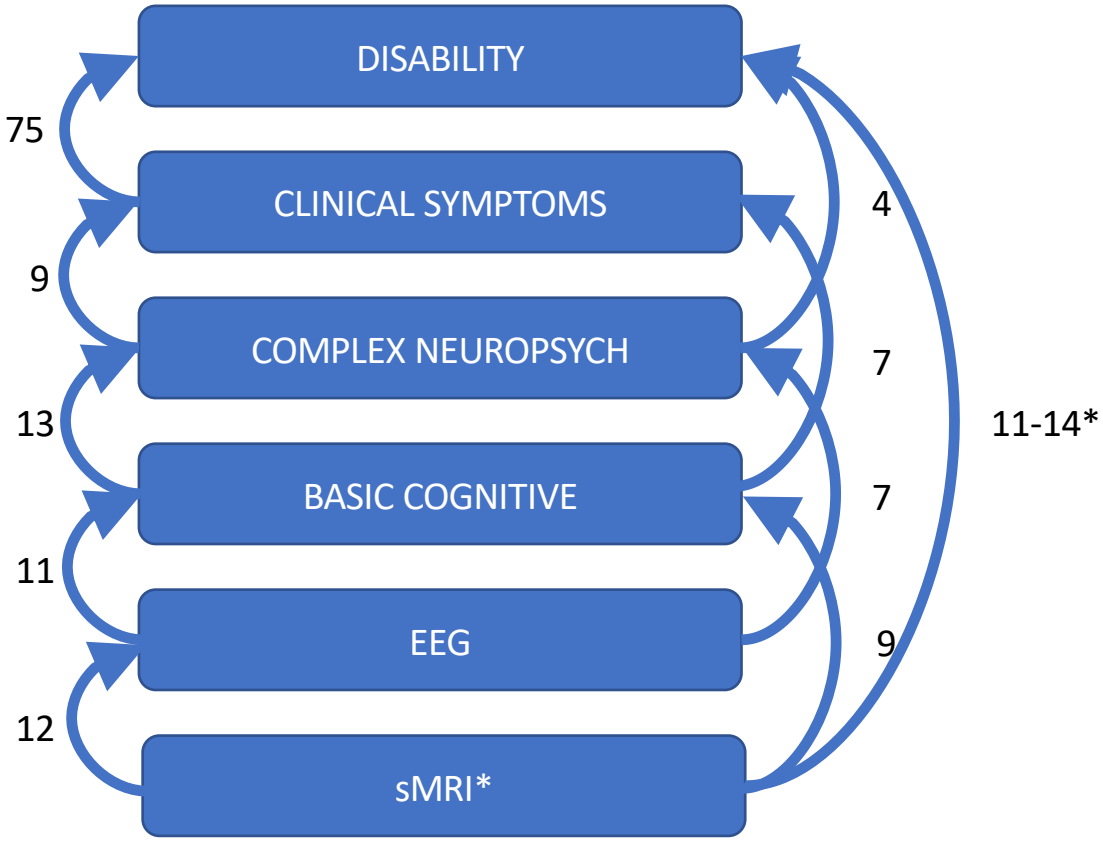
RESULTS

Correlations 260x260= 67,600

Bonferroni-adjusted alpha = 7.39E-7



Shared variance across levels of analysis from sMRI to Disability



*PREDICTORS:

CORTICAL THICKNESS (11%): R_entorhinal, R_caudalmiddlefrontal, L_precuneus, L_lateraloccipital, R_bankssts, R_inferiortemporal, L_inferiortemporal (after entering average thickness, sex, and scanner version)

CORTICAL SURFACE AREA (14%): SCANNER, SEX, L_transversetemporal, R_parahippocampal, R_posteriorcingulate, R_caudalanteriorcingulate (after entering sex, and scanner version)

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Journal of the International Neuropsychological Society (2011), **17**, 7–13.
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SHORT REVIEW

Neuropsychology 3.0: Evidence-Based Science and Practice

Robert M. Bilder[1,2,3]

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[3]Department of Psychology, UCLA College of Letters & Science, Los Angeles, California

(Received August 13, 2010; Final Revision October 16, 2010; Accepted October 18, 2010)

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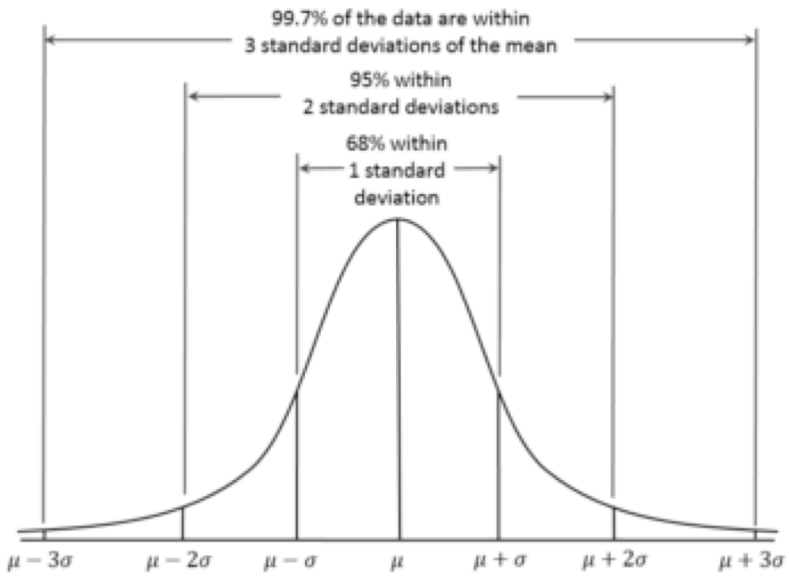
NP 1.0 (1950-1979)

- Term: “Neuropsychology” (Klove, 1963); Founding of INS (1967)
- Effects of discrete brain lesions, use of the “sign” approach and syndrome analysis:
  - Luria
  - Halstead & Reitan
  - Benton and the Iowa school
  - Teuber and the NYC school
  - Kaplan and the Boston school

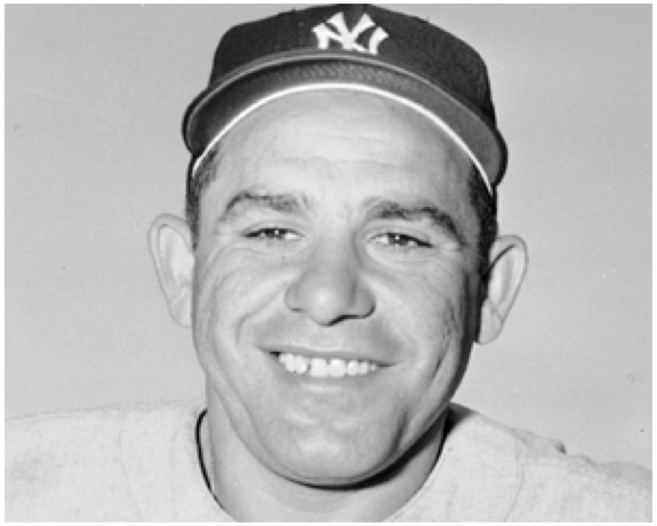
NP 2.0 (1980-present)

- Neuroimaging displaces localization role (mostly)
- Late 70's – training programs
- Board certification (ABPP) 1981
- Houston Conference (1998)
- "Era of classical psychometrics"
- Characterization of strengths and weaknesses: "Profile" analysis



NP 3.0: now… future

- Novel technology-driven assessments (e.g., wearables, passive monitoring devices, and IOT)
- Formal definition of neuropsychological concepts and tasks in cognitive ontologies, enabling creation of collaborative neuropsychological knowledge-bases, modern psychometrics and EB-NP, with dynamic refinement of neuropsychological tests and the constructs these aim to assess
- Development of causal models within brain, and models spanning levels of analysis from genome to syndrome



Prognostication is very difficult – especially when it comes to the future.

Path to Development of Novel NP Paradigms

Ontology Development: formalization of neuropsychological concepts and their relations to measurements, with links to neuroanatomic models and other biomedical knowledge

Collaborative Knowledge Aggregation: Creation of repositories for group- and individual case–level data, generating dynamic reference samples for clinical inference and new test development

Computerized Adaptive Test Development: Parallel development of computerized procedures featuring adaptive designs, trial-by-trial validity checks, and web deployment with links to electronic medical records

THE CLINICAL NEUROPSYCHOLOGIST
2019, VOL. 33, NO. 2, 220–245
https://doi.org/10.1080/13854046.2018.1521993

Routledge
Taylor & Francis Group

Check for updates

Neuropsychological tests of the future: How do we get there from here?

Robert M. Bilder[a,b] and Steven P. Reise[b]

[a]Departments of Psychiatry & Biobehavioral Science, Jane & Terry Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, California, USA; [b]Department of Psychiatry & Biobehavioral Science, Los Angeles, California, USA

Method	Current	Future	Advantage
NP trait models	Unidimensional	Bifactor models, multidimensional IRT models (mIRT)	Each item can provide information about different traits; a single item or test can help specify both general factors and domain scores
Nominal response model	Different kinds of errors are treated identically	Each wrong response has a different meaning	Each item carries more information, enabling greater precision and/or assessing different constructs
Test linking	Total scores are compared in studies that use both tests	Item banks can be drawn from existing tests and new items, and all items calibrated together	Enables direct comparison of different tests and construction of new tests that are back-compatible with the originals
Computerized adaptive testing	Paper-pencil, fixed administration order, minimal branching	Information from each item response selection and speed used to select next most informative item	Efficiency gain of 50-95% in administration time or precision of measurement.
Differential item functioning (DIF)	Effects of group (diagnostic, age, sexual, racial, ethnic, cultural, etc.) determined by comparing total scores	DIF examines group effects for each item	Increased precision in specifying diagnostic and other group differences that may not be apparent in the scores of the whole test
Person fit statistics	Performance validity based on "cutoff" scores, mostly based on accuracy	Performance validity based on the fit of item response characteristics to the examinees overall estimated trait level	Performance validity can be examined within each test; every item response can be useful in detecting anomalies; increase sensitivity to intentional failure
Non-IRT Item-Level Strategies	Most emphasis on summary scores not trial-by-trial analysis	Focus on sequential dependence of responses and meaning of response sequences	Increased efficiency in identifying primary constructs; identification of qualitatively distinct response patterns

Method	Current	Future	Advantage
Evidence-based diagnostic batteries	Batteries with limited flexibility involve redundant testing	Test selection will proceed based on positive predictive power	Testing efficiently focuses time with respect to differential diagnostic questions or recommendations
Computerized testing	Print publishing model; paper-pencil data acquisition and scoring	Computerized tests for stimulus presentation and response acquisition	precision in timing of stimulus presentation and response collection, automatic recording, scoring and database entry of responses, and automatic updating of software to new versions; acquisition of voice, video, motion.
Web-based testing	Testing done in clinic or lab	Testing done at home or wherever convenient for examinee	Scalable assessment at lower cost
Healthcare informatics and bioinformatics	Test results go to file cabinets, report text goes on medical record	Data elements will be part of medical record and integrated with analytics relating these to other health variables	NP data integrated into comprehensive model of patient; implications pushed to all care-team members and hypotheses fed back to NP clinicians for follow-up; "big data" analytics will find new patterns to inform future evidence-based practice
Mobile platforms	Not used; not trusted	Passive monitoring will dramatically increase data flow; experience sampling will augment self reports	Marked increase in longitudinal repeated measures for self-reports and tests; new variables extracted from passive monitoring
Wearables	Not used; not trusted	Passive monitoring of diverse physiological, activity, and experiential data	Data previously available only in cross-sectional lab studies (sleep, EEG, cardiovascular) will be widely available and assessed longitudinally)
Internet of Things (IOT)	Not used; not trusted	Passive monitoring of activities across multiple environments	Ecologically valid assessments will be done in real-world contexts; and environment can "respond" with appropriate cues and assistance

How do we get from here to there?

- Barriers
  - Legacy instruments … have a legacy!
  - Inertia in the NP customer base: validity, familiarity
  - IRT and computerized adaptive test developments require large samples to calibrate items
  - Evaluation of positive predictive power for different exam outcomes requires large samples
  - How can we get enough data to generate modern psychometric approach to the NP exam?

National Neuropsychology Network

- National Data Archives (NDA) now aggregating item-level test data for NIH projects (autism, RDoC, ADNI), n's increasing (RDoC=12k total), BUT…
  - Patient selection follows grant inclusion/exclusion criteria – how representative?
  - Test selection follows grant protocols, usually selected experimental measures, often not tests most widely used in practice
- Meanwhile: ***Clinical NP exams = 500K/year (!)***
- Proposed:
  - National Neuropsychology Network: clinical sites sharing item-level data with NDA for open analysis, generation of back-compatible, efficient assessments, and forward-looking introduction of novel items to expand banks for existing and novel construct measurement

The Towers of London, Hanoi… and Babel… Which instruments should be included?

- Daunting challenge: how to accommodate the broad range of tests used?
- Surprise: despite flexible approaches to NP there is considerable homogeneity of actual tests used
- Rabin et al (2016) survey – 80% of exams covered by:
  - Wechsler Adult Intelligence Scale, 4th Edition (WAIS-IV)
  - Wechsler Memory Scale, 4th Edition (WMS-IV)
  - California Verbal Learning Test, 2nd Edition (CVLT-2)
  - Delis-Kaplan Executive Function System (D-KEFS)
    - Trail Making, Verbal Fluency, Design Fluency, Color Word Interference Test
  - OTHERS: Rey Auditory Verbal Learning Test [RAVLT], Hopkins Verbal Learning Test [HVLT], Rey Osterrieth Complex Figure Test (ROCFT), Wide Range Assessment of Memory & Learning, 2nd edition (WRAML-2), Brief Visuospatial Memory Test, Revised (BVMT-R), Wisconsin Card Sorting Test (WCST); Boston Naming Test; Mini Mental State Exam (MMSE), Montreal Cognitive Assessment (MoCA)

Structured Clinical Protocol/ Common Data Elements

- Clinical measures include structured demographic, diagnostic, and dimensional ratings of key symptoms using instruments proposed as common data elements by the NIMH Research Panel (Barch et al., 2016):
  - Structured History Protocol for Neuropsychology (SHiP-NP)
  - Patient Reported Outcome Measures (Self-Reports)
    - DSM-5 Self-Rated Level 1 Cross-Cutting Symptoms Measure - Adult
    - Patient Reported Outcomes Measurement Information System (PROMIS) Adult Depression Computerized Adaptive Test (CAT)
    - PROMIS Adult Anxiety CAT
    - World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0)
  - DSM-5 Clinician-Rated Dimensions of Psychosis Symptom Severity
  - NINDS CDEs, Neuro-QOL, NIDA Substance Abuse HER Data Elements, NIH Toolbox

R01MH118514 – (3/4/19 to 1/31/24): National Neuropsychology Network

- Sites
  - University of Florida, c/o Russell Bauer, ABPP-CN
  - Medical College of Wisconsin, c/o Laura Umfleet
  - Emory, c/o Daniel Drane, ABPP-CN, David Loring, ABPP-CN
  - UCLA, c/o Robert Bilder, ABPP-CN
- UCLA – coordinating, statistical expertise including:
  - Steve Reise: head of quantitative area, UCLA Psychology
  - Catherine Sugar, head of Semel Institute Biostatistics Core
- Pearson – collaborative deposition of Q-interactive results into NIMH Data Archive for shared use by NP community
  - Dustin Wahlstrom (Director of Portfolio Management and Delivery - Therapeutics) Kristen Getz (Research Director, Digital Products/Platforms, Clinical Assessment)
- Total Budget: ~$4.4M/5 years. Sample size: up to ~10K

Deliverables: Data

- Collect data on 10,000 cases over 4 years and deposit all item-level data in RDoCdb (enrollment targets are 325 cases per site/year, yielding ~1300 cases/year for the network, or ~5200 cases over the 4-year period of data collection).
- Inclusion/Exclusion criteria:
  - Broad: representative of clinical NP services nationally
  - dementia and degenerative conditions, epilepsies (including psychogenic non-epileptic seizures [PNES]), movement disorders, and other complex neuropsychiatric disorders
  - In all these syndromes, depression, anxiety, or psychotic symptoms are either directly part of the differential diagnosis (e.g., “dementia vs depression”) or the psychiatric symptoms may be critical moderators of cognitive impairment

Deliverables: Results

- Evidence-based battery selection – this includes adaptive test selection within batteries of tests, to determine which test in the battery provides the highest predictive power for selected differential diagnostic applications, given prior test results
- Computerized adaptive tests – including adaptive item selection within tests, given prior item results, to provide measurement of specific traits with prescribed levels of precision
- Fixed short-forms of tests that increase efficiency of testing even when adaptive testing is not practical
- Analyses will examine test operating characteristics, sensitivity, specificity, positive and negative predictive power of both original and new measures to aid in differential diagnosis of neurocognitive disorders and major psychiatric syndromes
- Establish a testbed for evidence, enabling future measures to be examined directly for equivalence or superiority

Next steps -- on to the Future

- Expand data elements/tests to include both English & Spanish, over time add other languages
- National NP Network in the USA could serve as model for ex-US development
- Modern psychometric specs critical for alignment with test characteristics in other languages and cultures
  - For this – various methods to identify invariance including DIF, “harmonization” and “phenotype alignment” may help
- Ideal – a global bank of methods to be shared freely, used to expand access to high quality NP services and reduce health disparities, and increase knowledge about human health and disease in the broadest sense

https://www.sistat.ucla.edu/NNNWeb/index.html

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