Precision Medicine: Spanning Levels of Analysis Down to Basic Biology
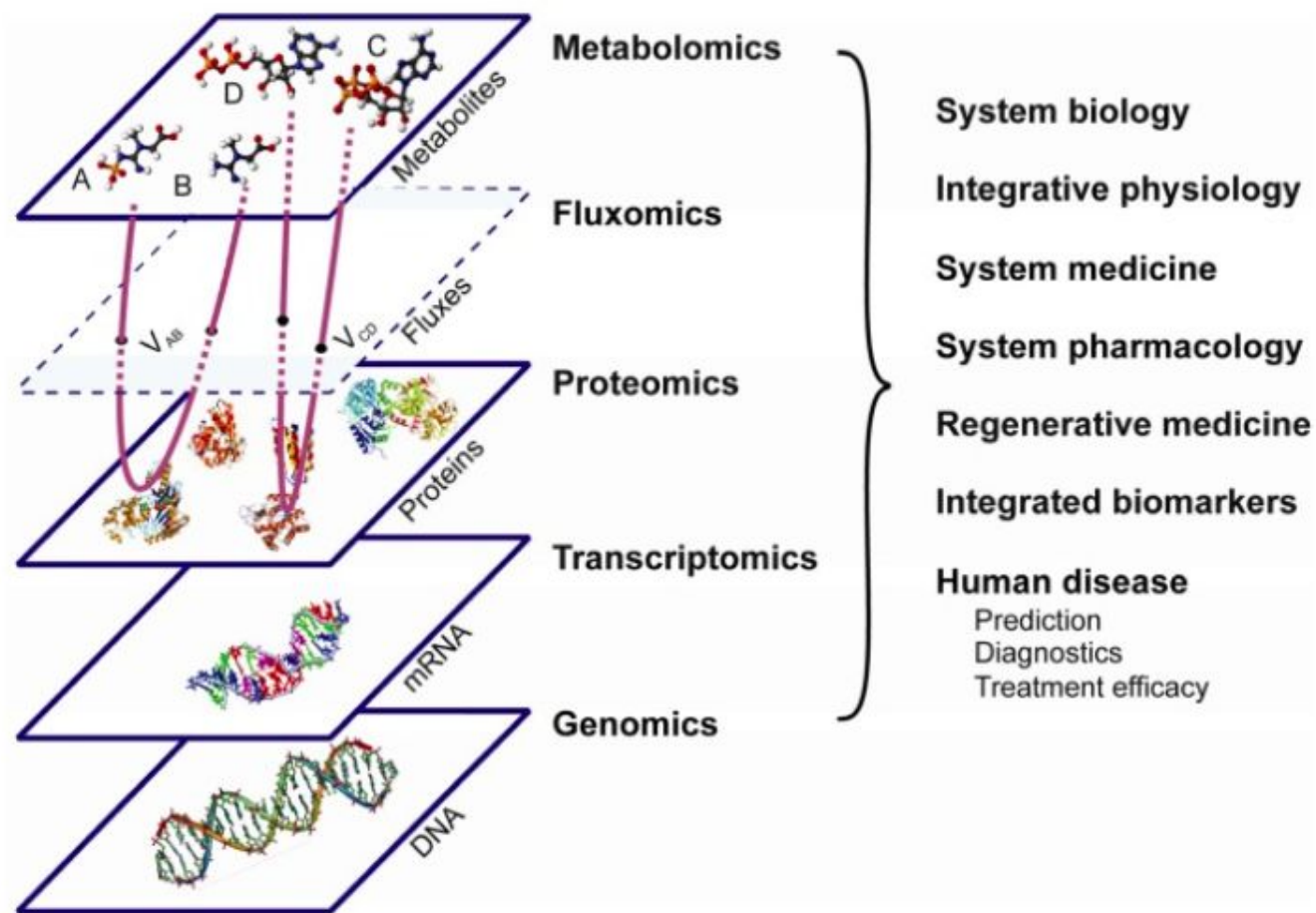
General Issue
Research Paper

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

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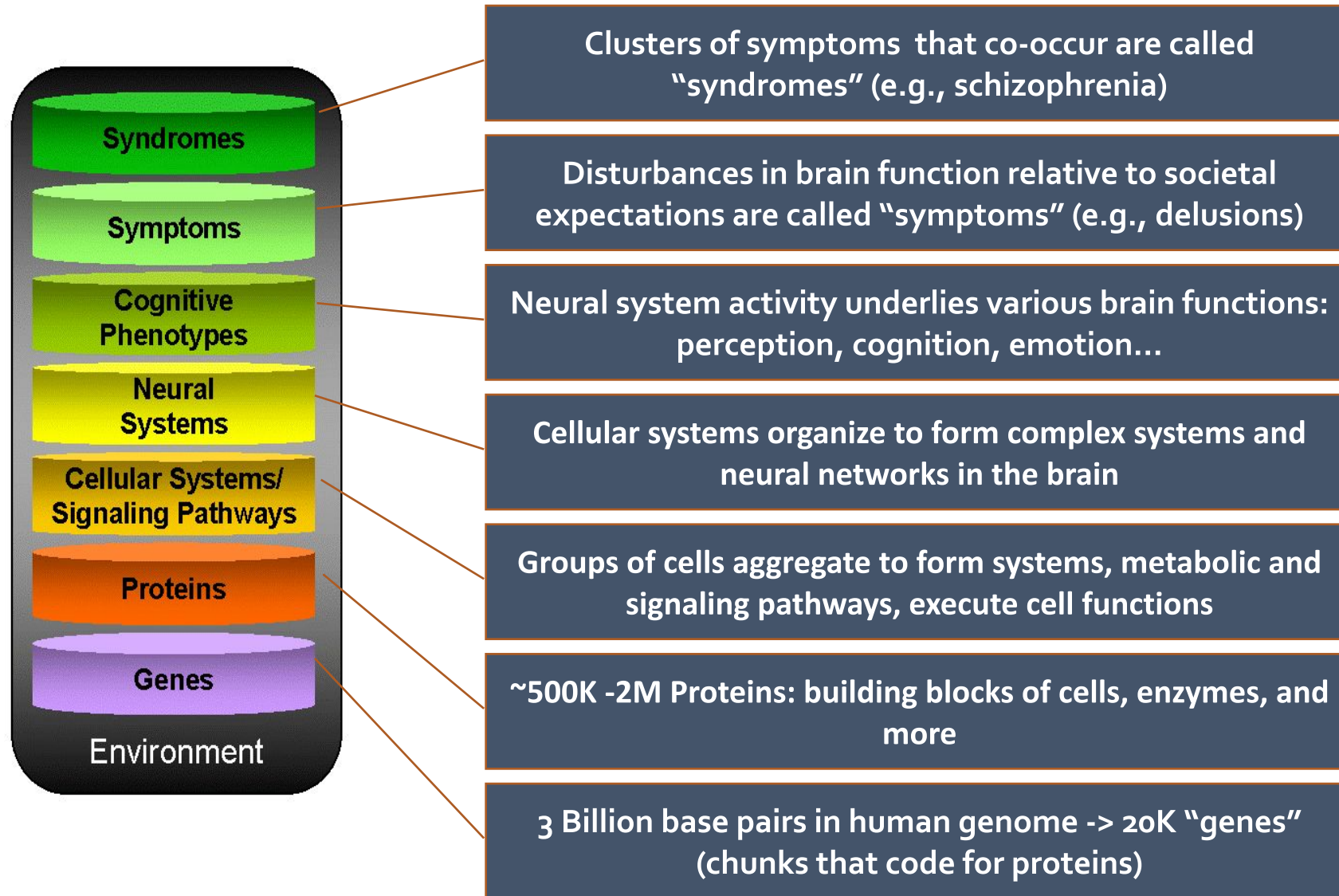
[1]Freimer & Sabatti, *Nat Genet* 2003

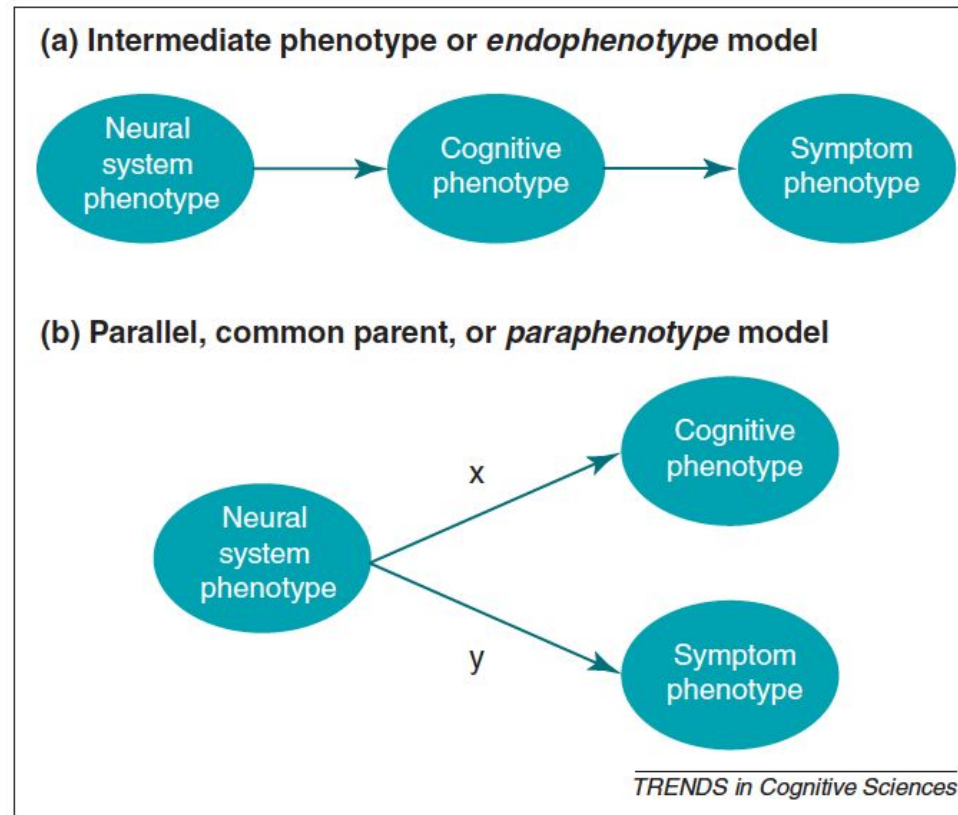# The Human Phenome Project

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From Genome to Syndrome?
Example for Neuropsychology

Syndromes

Symptoms

Cognitive Phenotypes

Neural Systems

Cellular Systems/ Signaling Pathways

Proteins

Genes

Environment

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)
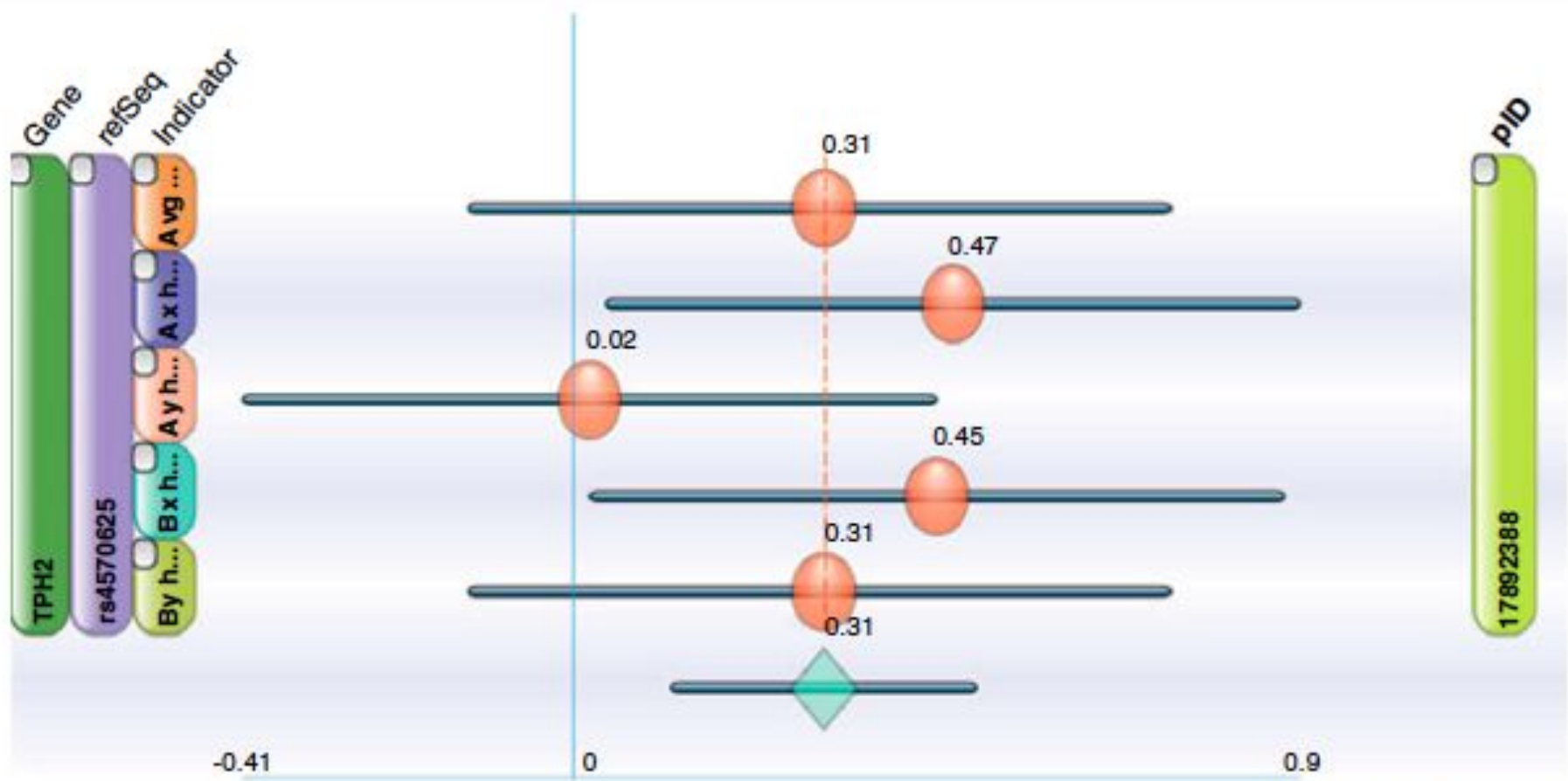
Special Issue: The Genetics of Cognition

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]

(a) Intermediate phenotype or *endophenotype* model

Neural system phenotype → Cognitive phenotype → Symptom phenotype

(b) Parallel, common parent, or *paraphenotype* model

Neural system phenotype → (x) Cognitive phenotype

Neural system phenotype → (y) Symptom phenotype

TRENDS in Cognitive Sciences

Bilder et al 2011

Knowledge Base 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 plants, 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)

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
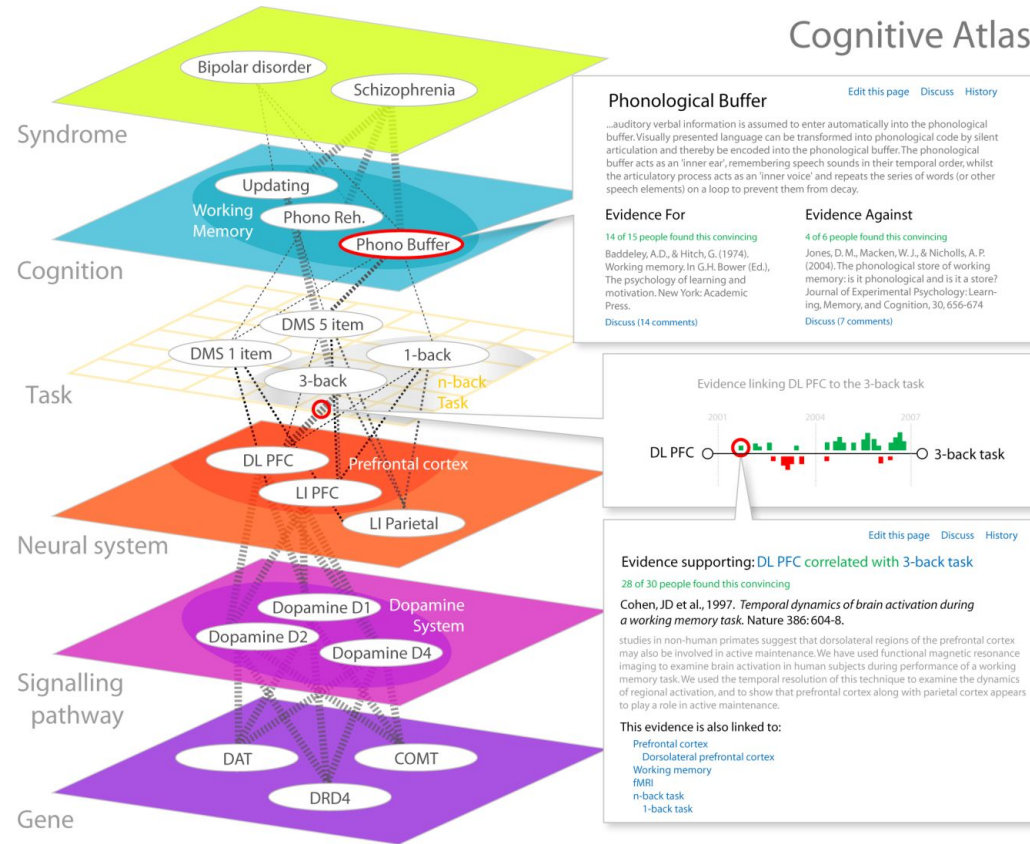[4] Interactive Design, Squishymedia, Portland, OR, USA
[5] Information Sciences Institute, University of Southern California, Marina Del Rey, CA, USA
[6] Department of Computer Science, University of California Los Angeles, Los Angeles, CA, USA
[7] Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA

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- 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

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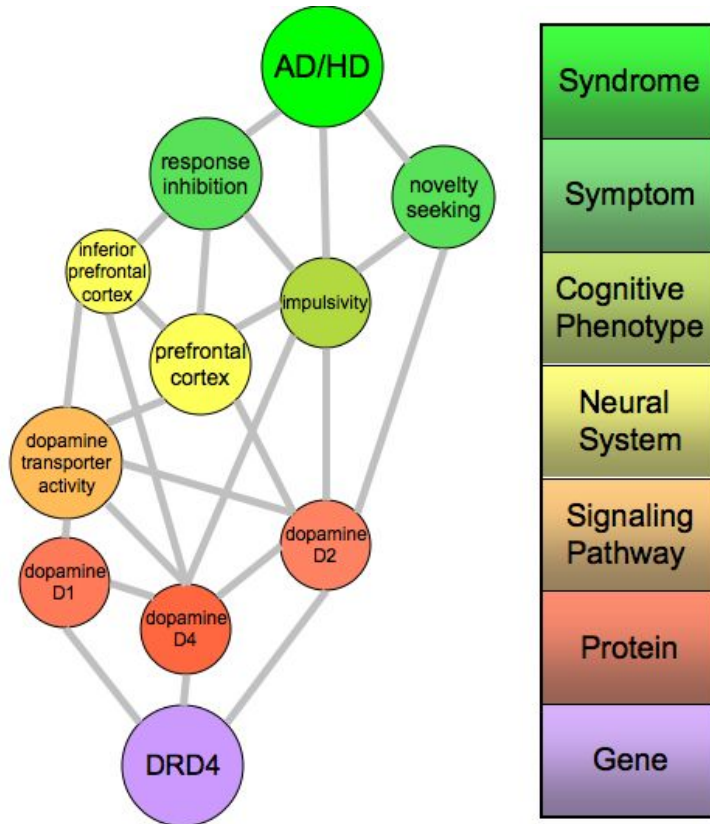
- Hypotheses for complex neuropsychiatric syndromes demand representation at multiple levels and span multiple biological scales
- Plausible mechanistic hypotheses should have representation at all levels
- Strongest hypotheses are those possessing paths with strongest effects
- Causal models can be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

Graph representation of multi-level hypotheses for neuropsychiatry research

Multilevel Models from Biology to Psychology: Mission Impossible?

Bilder RM, Howe AG, Sabb FW

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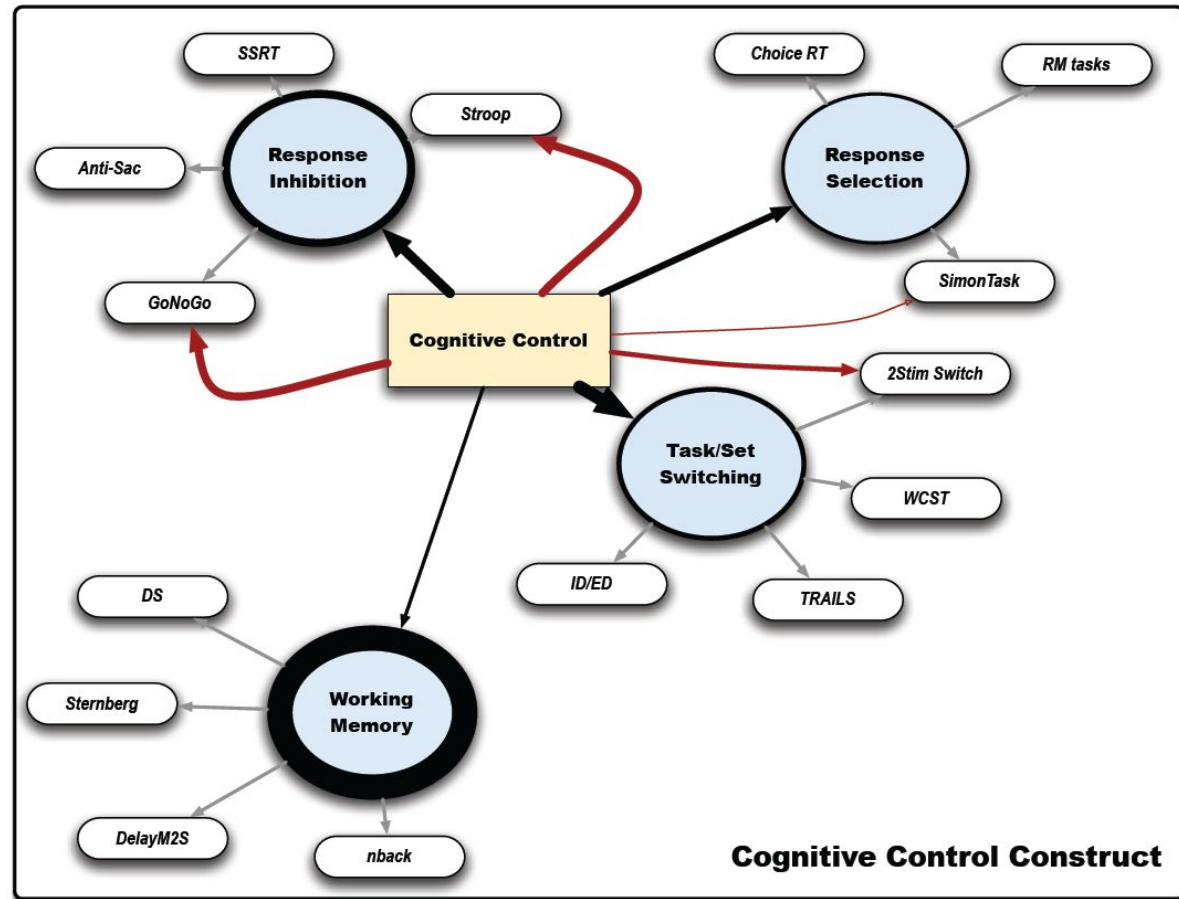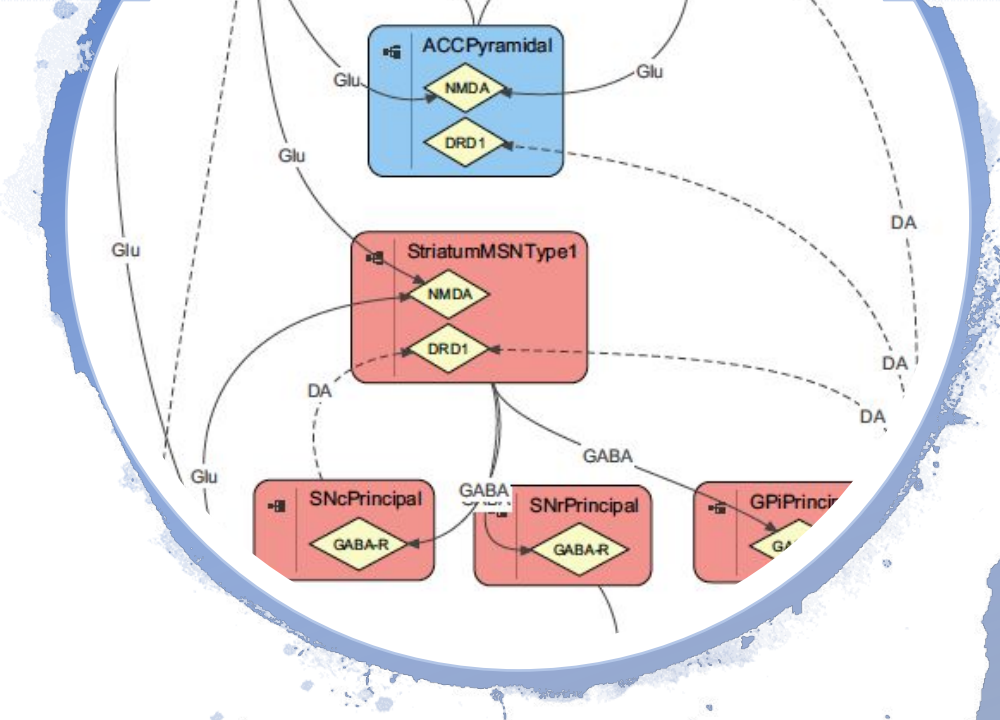   (D. O. Hebb, 1949, p. xi)

Table 1

Examples of Ontologies or Descriptive Systems Used to Represent Concepts and Relations Among Concepts for Levels of Analysis From the Syndrome to the Genome

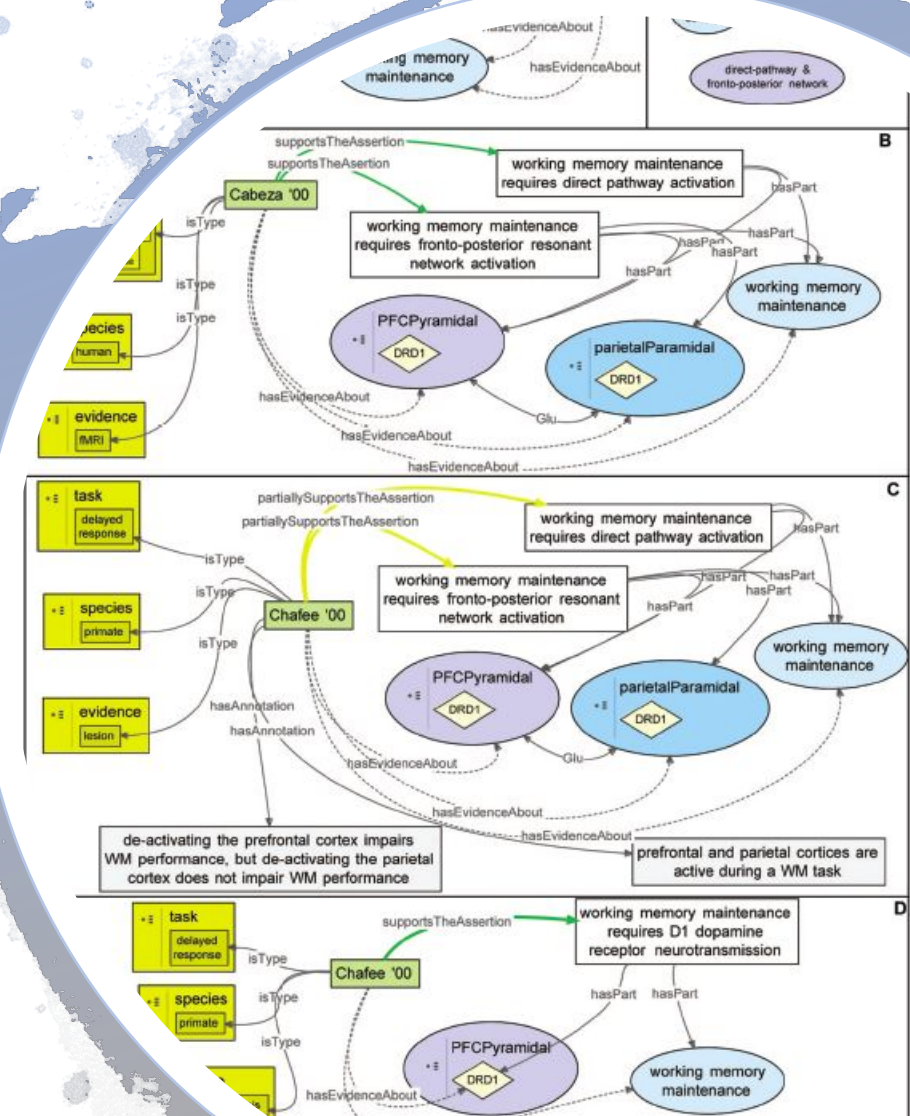| Level of analysis	Example ontologies/descriptive systems
Syndrome	Diagnostic and Statistical Manual of Mental Disorders
Symptom	Measurement models with latent symptom constructs based on rating scales, interview schedules
Cognitive	Measurement models with latent cognitive constructs based on psychometric test scores
Neural system/circuit	NeuroML; CocoMac; Xanat
Cellular systems/ signaling pathways	Ingenuity Pathways Analysis; Gene Ontologies biological processes; KEGG Pathway
Proteins	Entrez Protein; UniProt/SwissProt; NextProt
Genes and gene expression	Gene Ontologies; Entrez Gene, Gene Expression Omnibus

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.

Cognitive Control Construct

Sabb FW, Bearden CE, Glahn DC, Freimer N, Parker DS, Bilder RM. *Molecular Psychiatry*, 2009
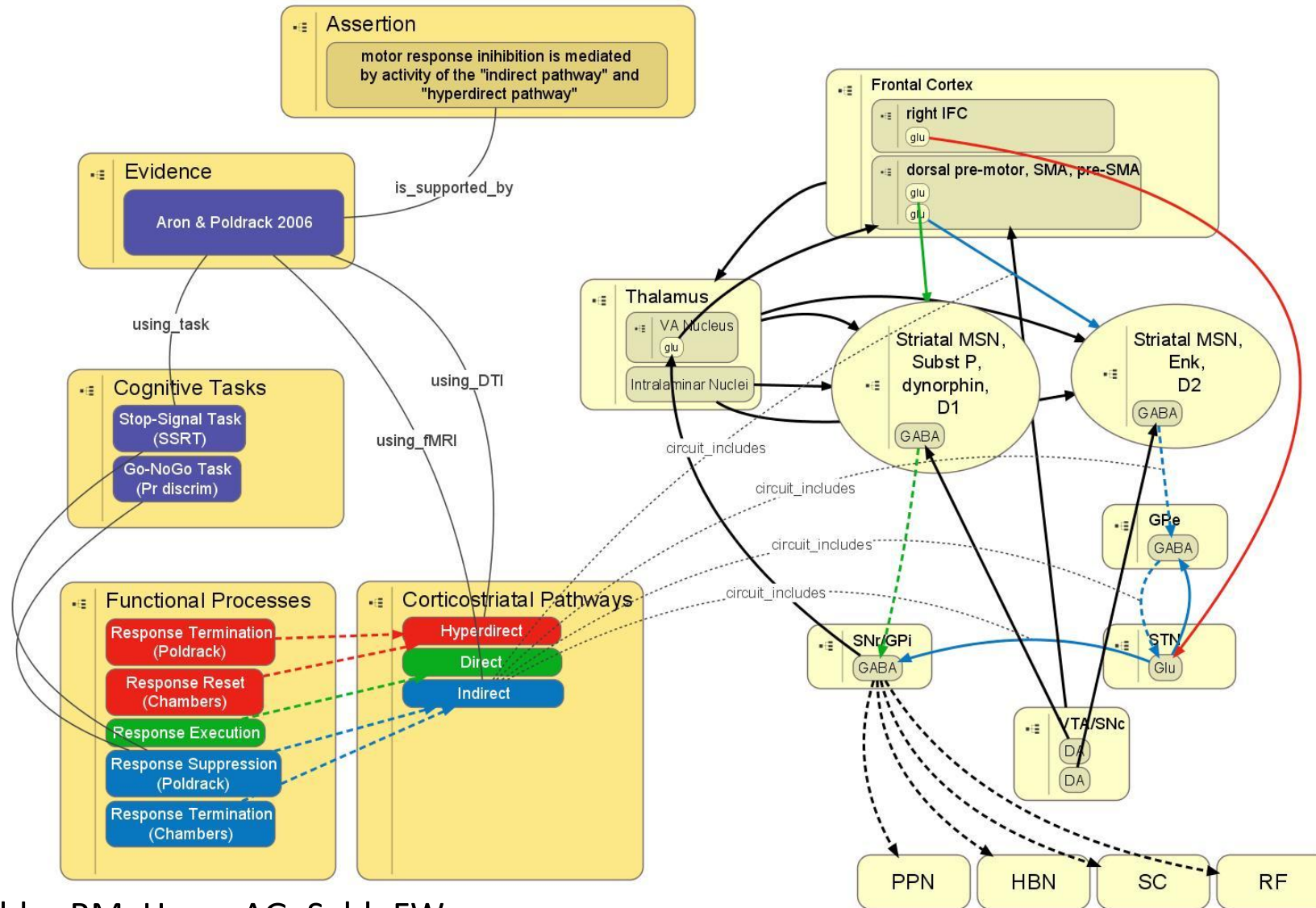
- Managing assertions about brain-behavior relations using a neural circuit description framework
- Enabling machine operations on knowledge elements to test hypotheses and generate new experimental designs

Bilder, Howe & Sabb, 2013

Journal of Abnormal Psychology

Schema for Validation of Hypotheses about Neurocognitive Concepts

Assertion

motor response inihibition is mediated by activity of the "indirect pathway" and "hyperdirect pathway"

is_supported_by

Evidence

Aron & Poldrack 2006

using_task

using_DTI

using_fMRI

Cognitive Tasks

Stop-Signal Task (SSRT)

Go-NoGo Task (Pr discrim)

Functional Processes

Response Termination (Poldrack)

Response Reset (Chambers)

Response Execution

Response Suppression (Poldrack)

Response Termination (Chambers)

Corticostriatal Pathways

Hyperdirect

Direct

Indirect

Frontal Cortex

right IFC — glu

dorsal pre-motor, SMA, pre-SMA — glu — glu

Thalamus

VA Nucleus — glu

Intralaminar Nuclei

Striatal MSN, Subst P, dynorphin, D1 — GABA

Striatal MSN, Enk, D2 — GABA

circuit_includes

circuit_includes

circuit_includes

circuit_includes

GPe — GABA

SNr/GPi — GABA

STN — Glu

VTA/SNc — DA — DA

PPN | HBN | SC | RF

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

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

The Path to Precision Neuropsychology
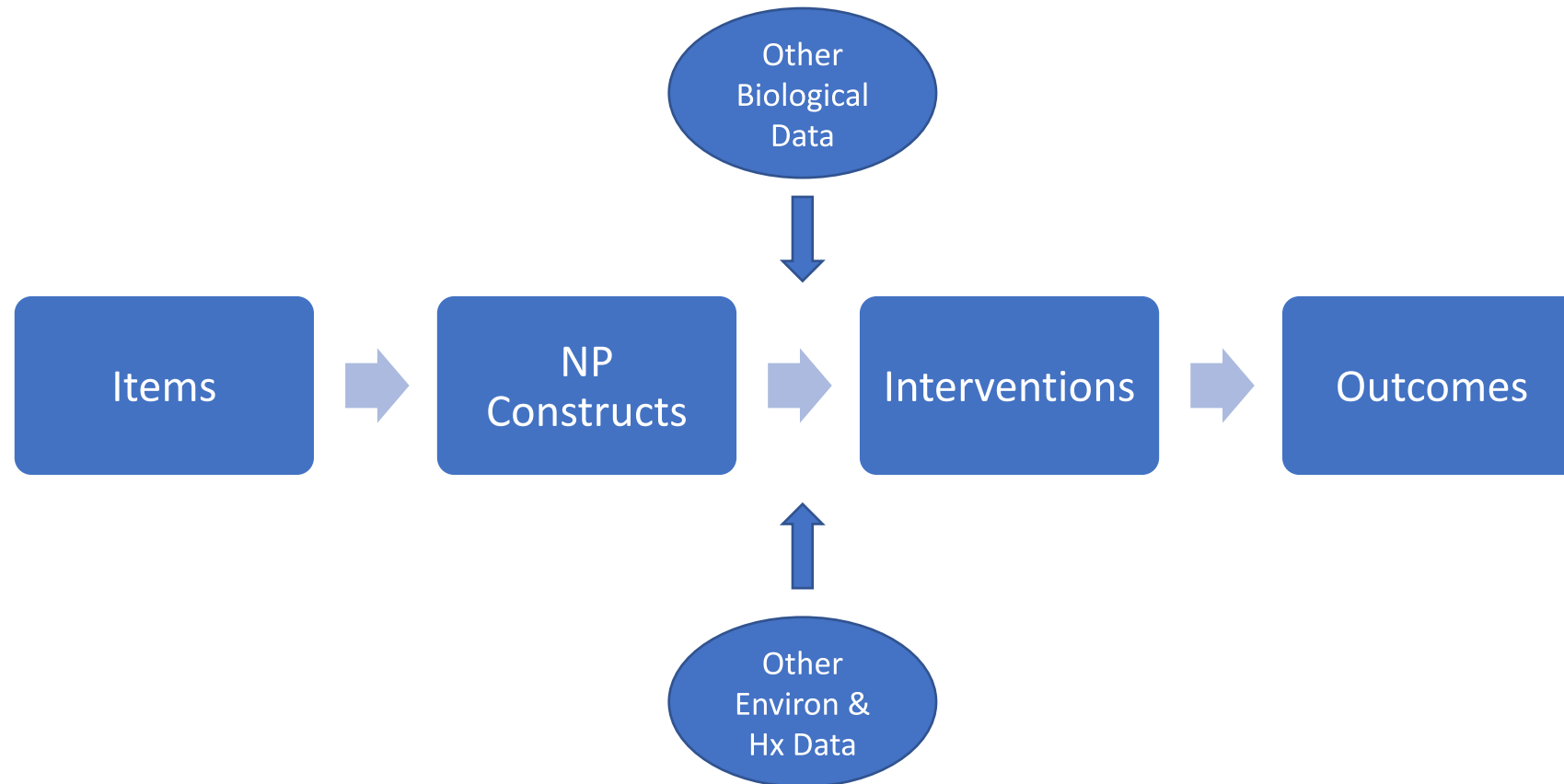
Many thanks!

National Neuropsychology Network (Bauer, Drane, Loring, Umfleet, Cavanagh, Enriquez)
RDoC projects (Rissman, Loo, Lenartowicz, Reise, Sugar, Helleman, Anderson, Mansolf, Truong, Walsh)
Consortium for Neuropsychiatric Phenomics (Parker, Freimer, Poldrack, Bearden, Cannon, London, Sabb, Evans)

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http://healthy.ucla.edu