Wrangling the Matrix:
Lessons from the RDoC Working Memory Domain

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Philosophical Issues in Psychiatry V: The Problems of Multiple Levels, Explanatory Pluralism, Reduction and Emergence

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Organized by Professor Josef Parnas (University of Copenhagen), Professor Kenneth S. Kendler (Virginia Commonwealth University), Professor Peter Zachar (Auburn University at Montgomery), the Mental Health Centre Glostrup and the Center for Subjectivity Research, University of Copenhagen

Topics for this talk

- Overview of the NIMH Research Domains Criteria (RDoC) initiative and the ”matrix”
  - How does NIMH define RDoC?
  - How does RDoC represent “levels” as units of analysis?
  - How are the entities in the RDoC matrix defined?
  - How are relations among the entities in the matrix defined?
  - “Working Memory” as an example
- Examine prevailing approaches to spanning levels
  - Effect model (reflective) vs causal model (formative)
  - Missing link between cellular and network systems to behavior (body-mind)
  - Finding the “right” units of analysis and methods for traversal

NIMH RDoC Initiative: Why?

- RDoC is a research framework for new approaches to investigating mental disorders. **It integrates many levels of information** (from genomics and circuits to behavior and self-reports) in order to **explore basic dimensions of functioning** that **span the full range of human behavior from normal to abnormal**. RDoC is not meant to serve as a diagnostic guide, nor is it intended to replace current diagnostic systems. The goal is to understand the nature of mental health and illness in terms of varying **degrees of dysfunctions in general psychological/biological systems**.

NIMH RDoC Initiative: How?

- Workgroups centered on dimensional **psychological constructs (or concepts)** that are relevant to human behavior and mental disorders, as measured using multiple methodologies and as studied within the essential contexts of developmental trajectories and environmental influences. Constructs are in turn grouped into higher-level **domains of human behavior and functioning** that reflect contemporary knowledge about major systems of emotion, cognition, motivation, and social behavior. **Methods** used to investigate and understand constructs (termed "**units of analysis**") can include molecular, genetic, neurocircuit and behavioral assessments.

NIMH RDoC Initiative: What?

- 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

Matrix = Constructs X Units of Analysis

- Genes
- Molecules
- Cells
- Circuits
- Physiology
- Behaviors
- Self-Reports
- Paradigms

The matrix **columns specify Units of Analysis** used to study the Constructs, and include genes, molecules, cells, circuits, physiology, behavior, and self-reports. The matrix also has a separate column to specify well-validated **paradigms** used in studying each Construct. These paradigms may be relevant for more than one unit of analysis and rather than list them in separate columns, they are included under the Paradigms heading. In the body of the matrix are specific elements which are empirically associated with the construct and are grouped under the appropriate unit of analysis.

National Institute of Mental Health

	Units of Analysis							
	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
Negative Valence Systems								
Active Threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative non-reward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Affiliation and attachment								
Social communication								
Perception and understanding of self								
Perception and understanding of others								
Arousal/Regulatory Systems								
Default mode network								
Sleep/Wakefulness								
Biological rhythms								
Arousal								

Fig. 1. The draft Research Domain Criteria matrix.

Cognitive Systems

Construct/Subconstruct		Genes Notice	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
Attention			Elements	Elements	Elements	Elements	Elements		Elements
Perception	Visual Perception		Elements	Elements	Elements	Elements	Elements	Elements	Elements
	Auditory Perception		Elements	Elements	Elements	Elements	Elements	Elements	Elements
	Olfactory/Somatosensory/Multimodal/Perception								Elements
Declarative Memory			Elements	Elements	Elements	Elements	Elements	Elements	Elements
Language					Elements	Elements	Elements	Elements	Elements
Cognitive Control	Goal Selection; Updating, Representation, and Maintenance ⇒ Focus 1 of 2 ⇒ Goal Selection				Elements			Elements	Elements
	Goal Selection; Updating, Representation, and Maintenance ⇒ Focus 2 of 2 ⇒ Updating, Representation, and Maintenance		Elements	Elements	Elements	Elements	Elements	Elements	Elements
	Response Selection; Inhibition/Suppression ⇒ Focus 1 of 2 ⇒ Response Selection		Elements	Elements	Elements	Elements	Elements	Elements	Elements
	Response Selection; Inhibition/Suppression ⇒ Focus 2 of 2 ⇒ Inhibition/Suppression		Elements	Elements	Elements	Elements	Elements	Elements	Elements
	Performance Monitoring		Elements		Elements	Elements	Elements	Elements	Elements
Working Memory	Active Maintenance		Elements	Elements	Elements	Elements			Elements
	Flexible Updating		Elements	Elements	Elements	Elements			Elements
	Limited Capacity		Elements		Elements	Elements			Elements
	Interference Control		Elements	Elements	Elements	Elements			Elements

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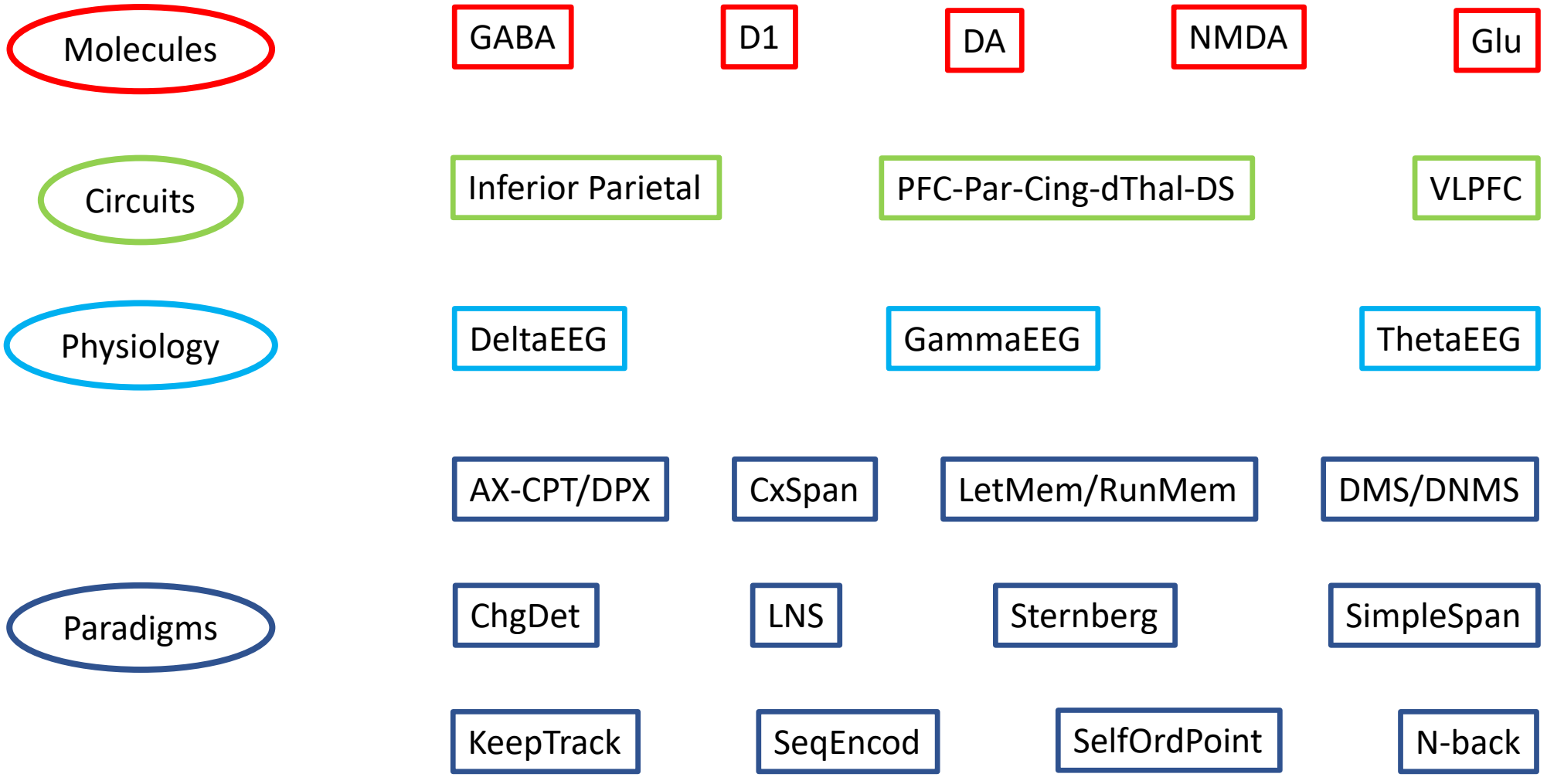
Unit of Analysis		Active Maintenance	Flexible Updating	Limited Capacity	Interference Control
Genes	NRG1/Neuregulin				
	DISC1				
	DTNBP1/Dysbindin				
	BDNF				
	COMT				
	DRD2				
	DAT1				
Molecules	Dopamine	X	X	X	X
	D1	X	X	X (gain)	X
	D2	X	X	?	X
	Glutamate	X	X	X	X
	NMDA	X			
	AMPA ?				
	GABA	X	?	X	X
	A ?				
	B ?				
Cells	Pyramidal	X			
	Distinct Types of Inhibitory Neurons	X			X
	Parvalbumin				X
	Calbindin				X
	Calretinin				
	Medium Spiny Neurons (Basal Ganglia)		X		
Circuits	Key Circuit: PFC-Parietal-Cingulate-Dorsal Thalamus-Dorsal Striatum				
	DLPFC		X	X	
	VLPFC	X		X	
	Dorsal Striatum		X		
	Dorsal Parietal			X	
	Inferior Parietal		X		X
	MD & VA Thalamus (by virtue of their role in circuit)		X	?	

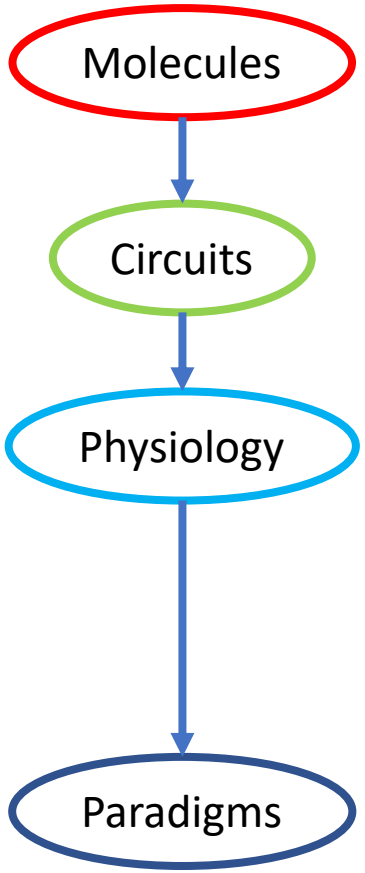
Unit of Analysis		Active Maintenance	Flexible Updating	Limited Capacity	Interference Control
Behavior and Paradigms	**N-Back**	X	X (?)	X	X (if you include non-target lures)
	Delayed Match to Sample	X	---	X	X (if you use repeated items, or delay period interference)
	Delayed Match to Non-Sample	X	---	X	X (if you use repeated items, or delay period interference)
	Sequence Encoding and Reproduction	X	---	X	---
	Sternberg Item Recognition (including recent negative variations)	X	X (recent negative task increases demand on updating)	X	X (if you use repeated items, recent negative variation)
	Complex Span Tasks	X	X	X	X
	Letter Memory/Running Memory	X	X (?)	X	X (?)
	Letter Number Sequencing	X	X	X	X
	Simple Span Tasks (may be more appropriate for developmental populations, in adults may not capture all key elements of WM)	X	---	X	X (if you use concurrent interference, as in Digit Span Distraction)
	Change Detection Tasks	X	---	X	---
	Keep Track Task	X	X	X	X
	AX-CPT/DPX	X	X	X	---
	Self-Ordered Pointing	X	X (?)	X	X

RDoC Matrix is a Graph Without Edges: WM example



RDoC Matrix: Implied Edges (Reductionistic)

Is everything connected to everything else down here? Directionality?



GABA D1 DA NMDA Glu

Inferior Parietal PFC-Par-Cing-dThal-DS VLPFC

DeltaEEG GammaEEG ThetaEEG

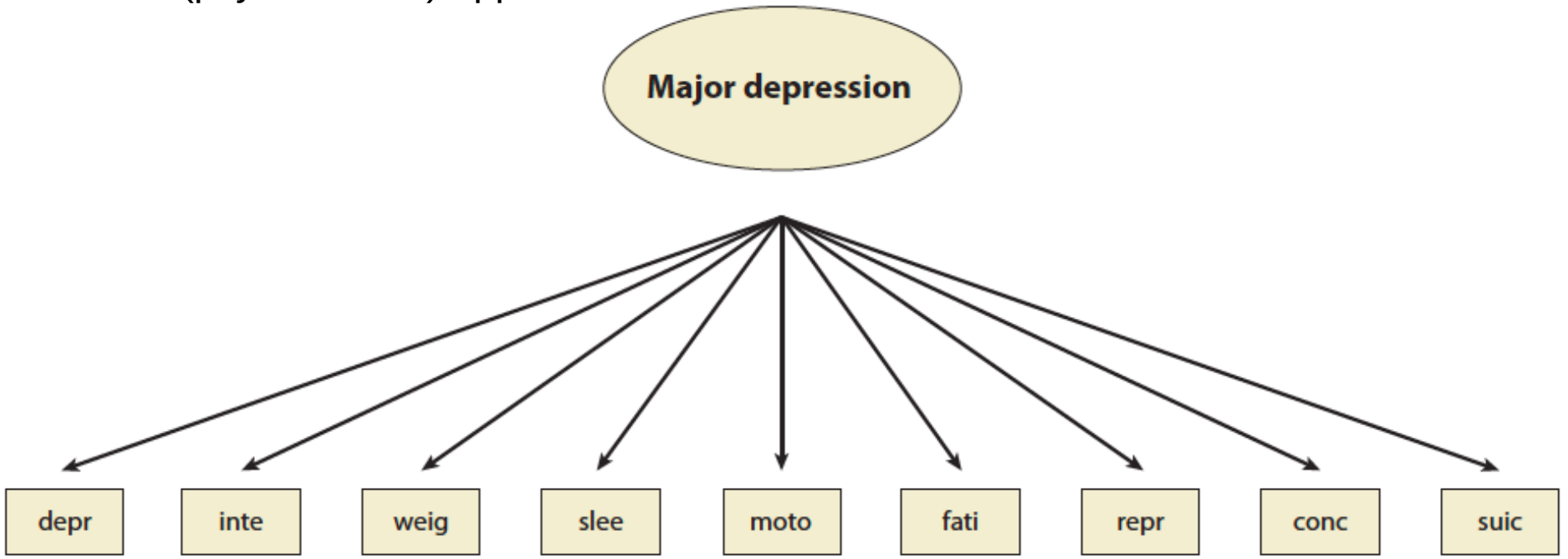
AX-CPT/DPX CxSpan LetMem/RunMem DMS/DNMS

ChgDet LNS Sternberg SimpleSpan

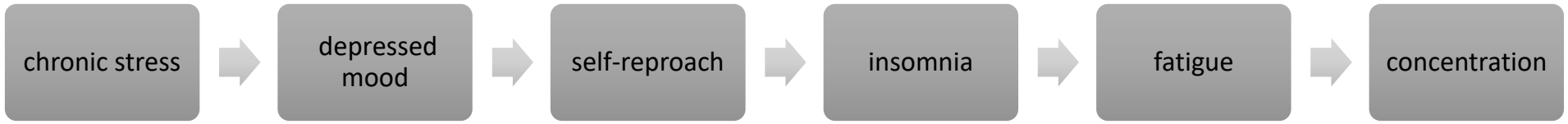
KeepTrack SeqEncod SelfOrdPoint N-back

Is there a better way?

Classic (psychometric) approach



Network (causal modeling) approach



Borsboom & Cramer 2013 Annual Rev Psychology

“In sum, not only do we not know that symptoms are caused by mental disorders, but it is in fact extremely unlikely that they are. As a result, the hypothesis that such disorders are the proper entities to steer the organization of research, diagnosis, and treatment is, at best, awaiting scientific justification.”

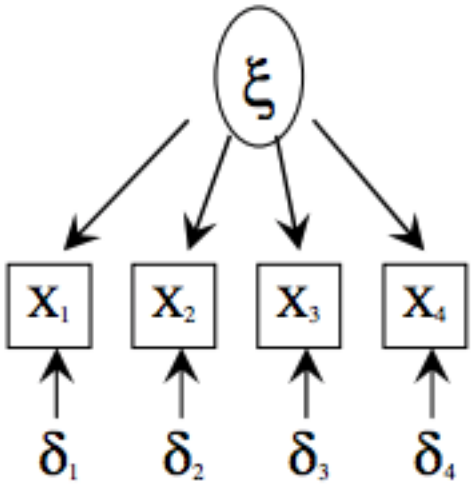
Borsboom & Cramer 2013 Annual Rev Psychology

What are the proper entities?

What are the proper relations among these entities?

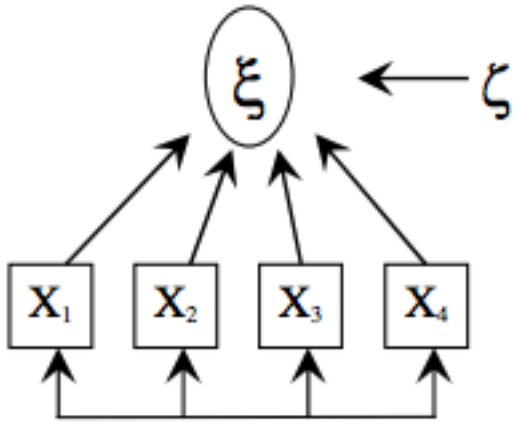
Figure 1: Reflective and Formative Measures

Effect Model (Reflective indicators)



$$X_1 = \lambda_1\xi + \delta_1$$
$$X_2 = \lambda_2\xi + \delta_2$$
$$X_3 = \lambda_3\xi + \delta_3$$
$$X_4 = \lambda_4\xi + \delta_4$$

Causal Model (Formative indicators)



$$\xi = \gamma_1X_1 + \gamma_2X_2 + \gamma_3X_3 + \gamma_4X_4 + \zeta$$

Coltman, T, Devinney, TM, Midgley, DF & Veniak, S, Formative versus reflective measurement models: Two applications of formative measurement, Journal of Business Research, 61(12), 2008, 1250-1262.

THE ATTACK OF THE PSYCHOMETRICIANS

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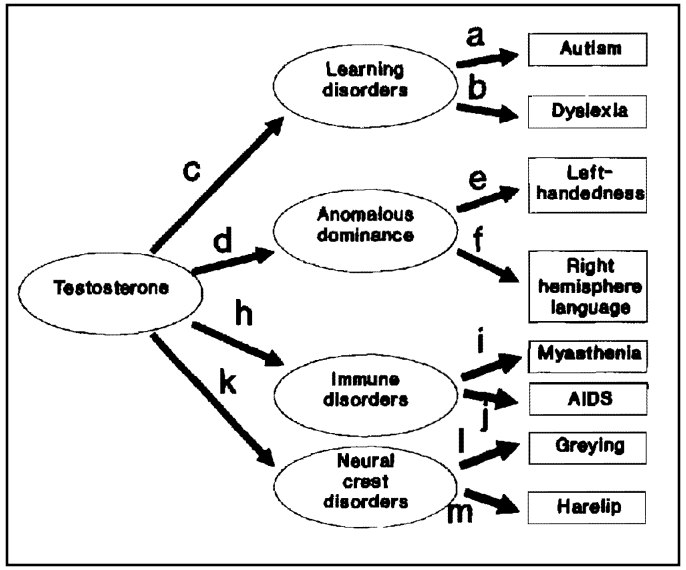
This may be the central problem of psychometrics: psychological theory does not motivate specific psychometric models. It does not say how theoretical attributes are structured, how observables are related to them, or what the functional form of that relation is. It is often silent even on whether that relation is directional and, if so, what its direction is. It only says that certain attributes and certain observables have something to do with each other. But that is simply not enough to build a measurement model.

PSYCHOMETRIKA—VOL. 71, NO. 3, 425–440
SEPTEMBER 2006
DOI: 10.1007/s11336-006-1447-6

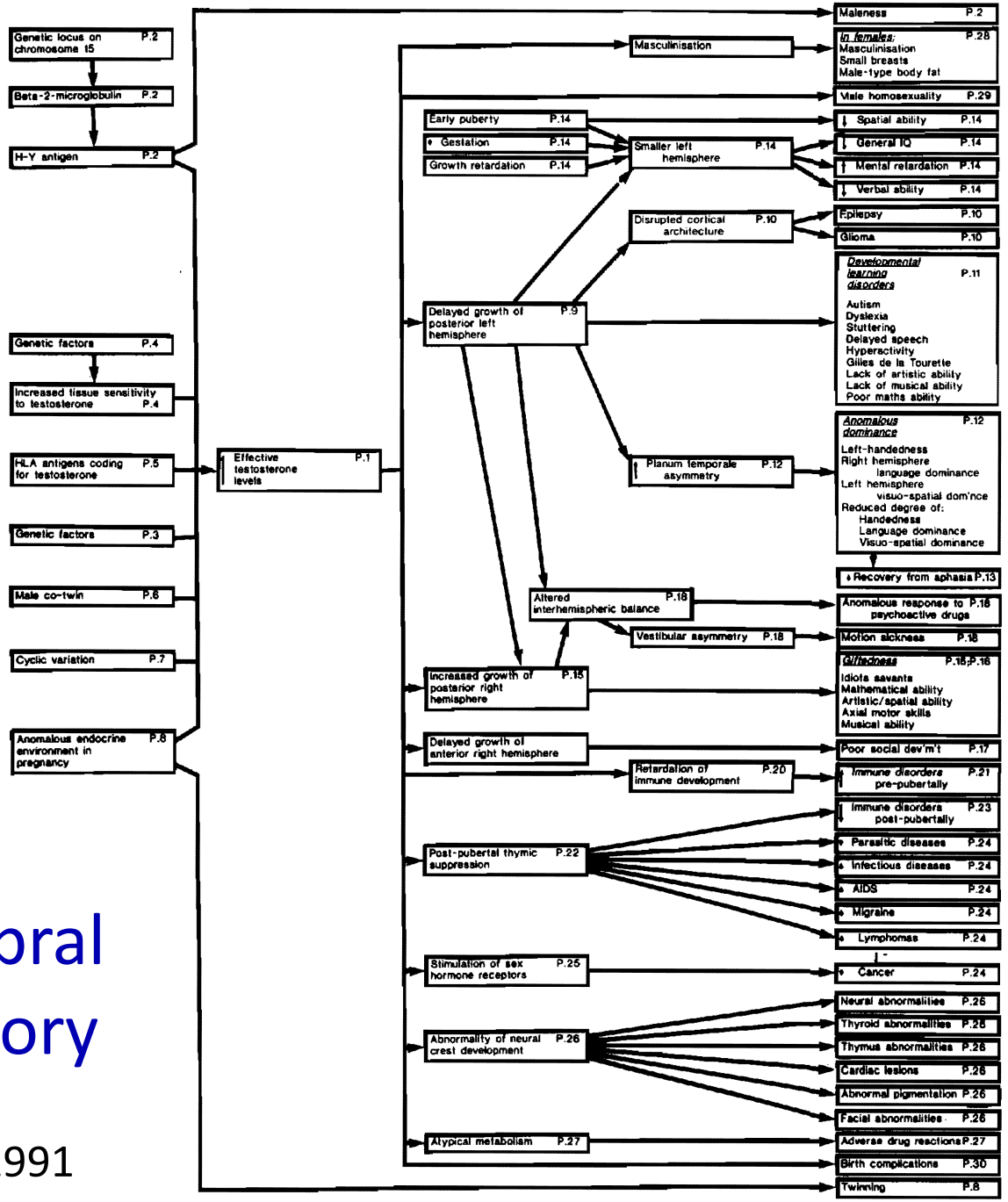
Hypothesis:

fetal testosterone levels are key to development of the left brain, and also of the immune system



Geschwind's Cerebral Lateralization Theory

McManus & Bryden, 1991



frontiers in
NEUROINFORMATICS

ORIGINAL RESEARCH ARTICLE
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The cognitive atlas: toward a knowledge foundation for cognitive neuroscience

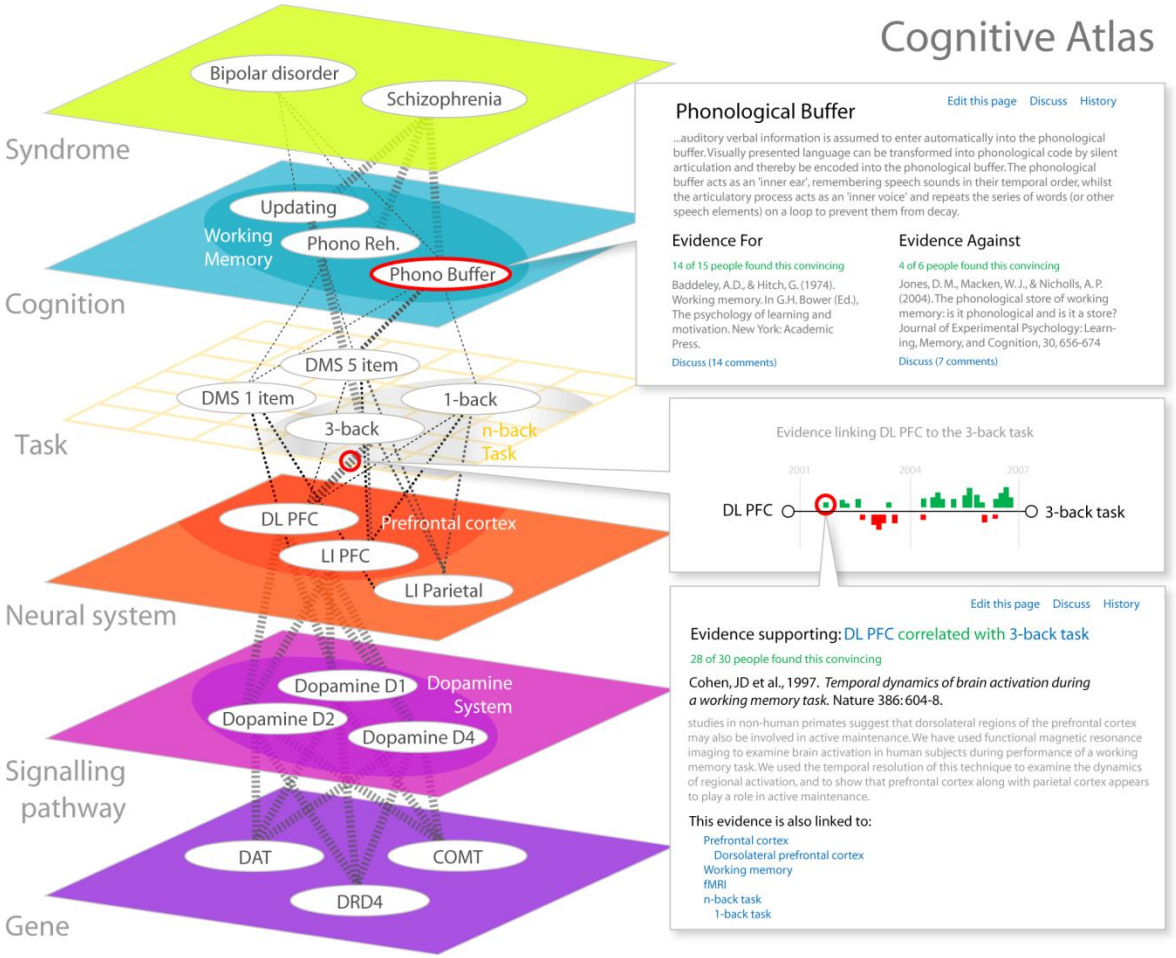
Russell A. Poldrack[1], Aniket Kittur[2], Donald Kalar[3], Eric Miller[4], Christian Seppa[4], Yolanda Gil[5], D. Stott Parker[6], Fred W. Sabb[7] and Robert M. Bilder[7]*

Cognitive neuroscience aims to map mental processes onto brain function, which begs the question of what "mental processes" exist and how they relate to the tasks that are used to manipulate and measure them. This topic has been addressed informally in prior work, but we propose that cumulative progress in cognitive neuroscience requires a more systematic approach to representing the mental entities that are being mapped to brain function and the tasks used to manipulate and measure mental processes. We describe a new open collaborative project that aims to provide a knowledge base for cognitive neuroscience, called the *Cognitive Atlas* (accessible online at http://www.cognitiveatlas.org), and outline how this project has the potential to drive novel discoveries about both mind and brain.

NIH Roadmap for Medical Research

RO1MH082795, and Consortium for Neuropsychiatric Phenomics (UL1DE019580, PL1MH083271, RL1LM009833)

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

NIH Roadmap for Medical Research

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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

Bilder, Howe & Sabb, 2013, Journal of Abnormal Psychology

Cross-level traversals

- Cognitive to Syndromal levels: operationalized by Chinese menu rules using symptoms and occasionally cognitive measures
  - Mostly all reflective models
  - All statistical estimations with validity ceilings in the .7 to .9 range
- Genomic to Cellular levels: increasingly specified by Gene Ontologies and other bioinformatics resources and cell models
  - Mostly causal models
  - Mechanistic models, but complexity is daunting (local validity ~.99, but practically much lower; consider genotype to mRNA to quarternary protein
- Missing link: from cellular function to cognitive/functional layer
  - The “hard” problem?

Journal of Abnormal Psychology
2013, Vol. 122, No. 3, 917–927

0021-843X/13/$12.00 DOI: 10.1037/a0032263

Multilevel Models From Biology to Psychology: Mission Impossible?

Robert M. Bilder, Andrew G. Howe, and Fred w. Sabb
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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)

NIH Roadmap for Medical Research

Consortium for Neuropsychiatric Phenomics (UL1DE019580, PL1MH083271, RL1LM009833)

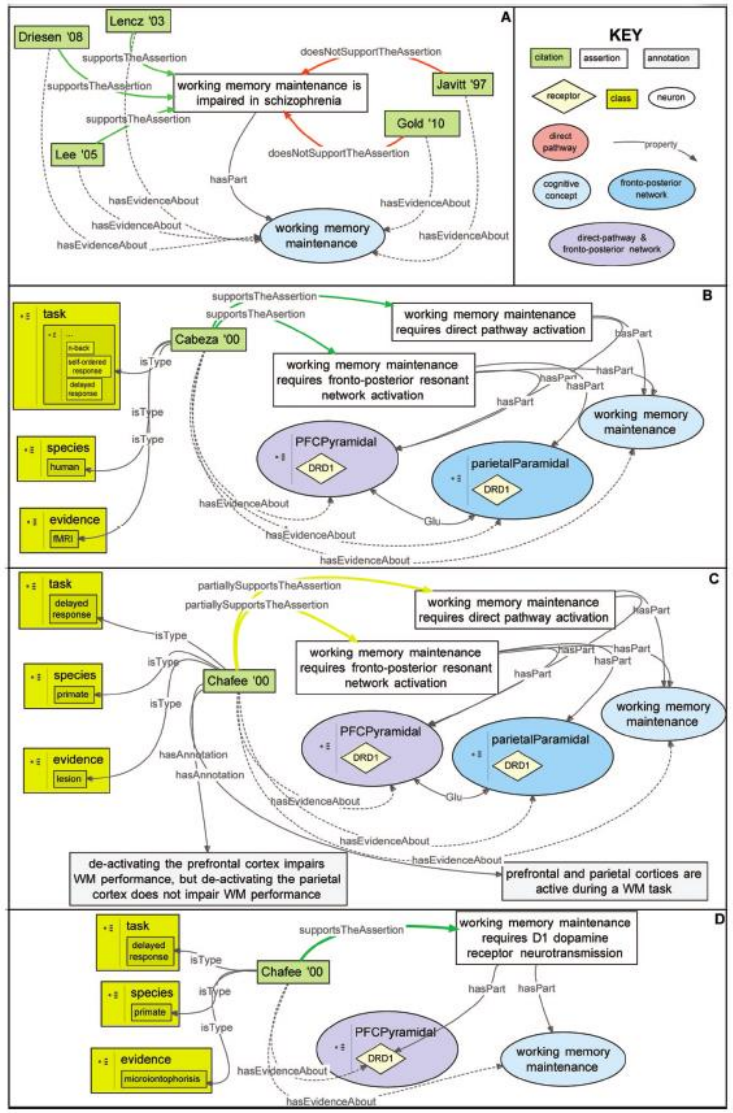
Approximations to modeling mind from brain

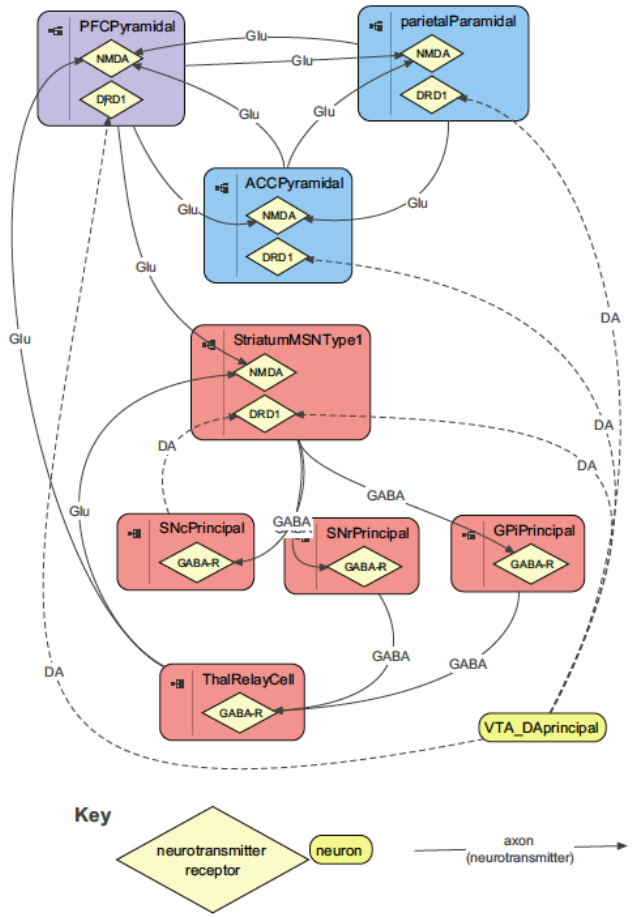
- High: modeling effects of paradigms, manipulations on predicated fMRI activation effects (e.g., The Virtual Brain; “ignition” [Deco])
  - Network activity = f (paradigm manipulation, architecture)
- Intermediate: simulated neural circuits with elements of neural network function (back propagation)(Frank, O’Reilly, Grossberg)
  - Network activity = f (circuit inputs, goals, architecture)
- Low: simulating neural circuits using biophysically detailed models of cell membranes and intracellular assemblies (BlueBrain, Edelman, Durstewitz, Seamans)

Challenges for network strategies

- Nodes in fMRI graphs are not neurons
- “Inputs” to and ”outputs” from regions are not unidimensional
- Not clear nodes and/or edges in network models are performing “computations”; computations describe network behavior
- If “computations” are performed these are at levels lower than network “nodes”; membrane potentials or intracellular molecular reactions that trigger other biological activities
- A comprehensive model yielding brain-like network function based on biophysically accurate cell models is so far lacking, but seems plausible; at least two approaches are plausible: assertion maps, and formal biological models

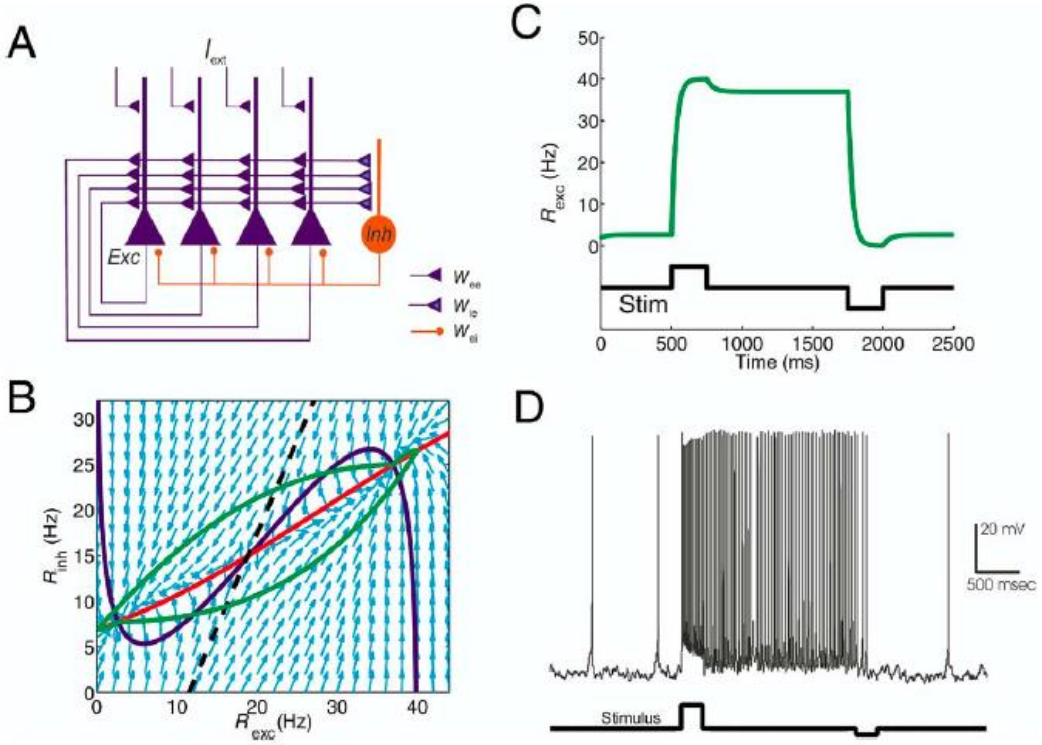
Managing assertions about brain-behavior relations using a neural circuit description framework: canonical cell types = unit of analysis

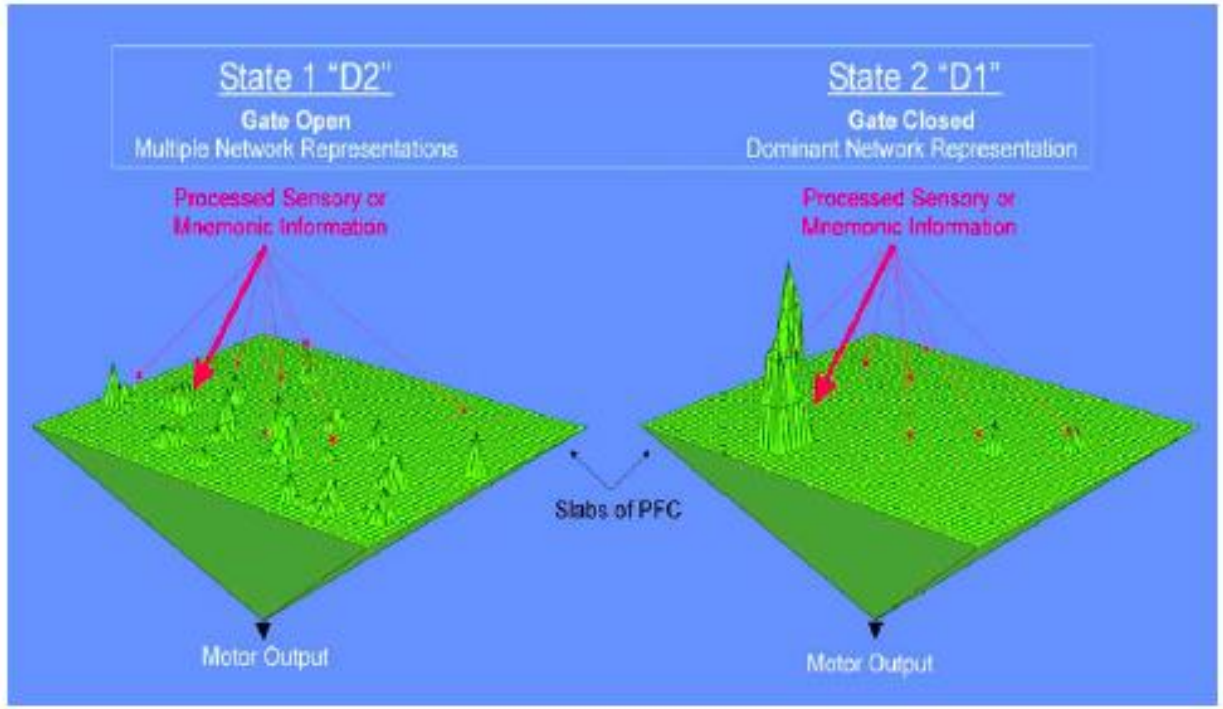




Bilder, Howe & Sabb, 2013
Journal of Abnormal Psychology

Forging the missing link: from cellular processes to network activity





RDoC: Is the matrix worth wrangling?

- Current RDoC “matrix” is a BFG of nodes with edges only implied
- RDoC relaxes assumptions about the traversal from biological processes to syndromes (probably a good thing?)
- Current research on WM illustrates reasonable descriptive models at higher levels, but without real traversal of levels
- Low-level biological mechanisms are better fleshed out and growing
- Current efforts to traverse neural to functional levels are largely non-mechanistic so far but soon mechanisms may simulate reality
- WHAT THEN? What would it mean to build a thing that thinks?

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Tennenbaum Center for the Biology of Creativity

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http://www.semel.ucla.edu/creativity

http://healthy.ucla.edu