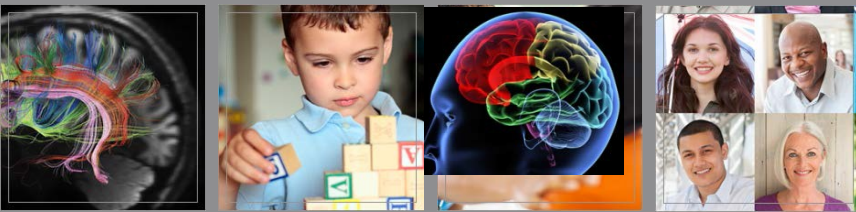


Research Domain Criteria (RDoC): An Overview



IACC

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Why RDoC?

- Unremitting public health burden of mental disorders
- Current practices in clinical diagnosis (DSM, ICD) are no longer optimal for contemporary research.
- Diagnosis remains restricted to symptoms and signs, disorders are broad syndromes.
- Symptom-based approach hampers prevention.
- ***Problem: While sufficient for current clinical use, DSM/ICD categories also drive the entire research system (research grants, journals, trials, regulatory).***

The three traditional autism factors

- Alterations in social cognition, social behavior
- Communication impairment
- Repetitive interests, behaviors, and activities
- Factors correlate weakly (for a given symptom, only 20-40% have two symptoms; London, *Trends in Neurosciences*, 2014)

The experts weigh in

- Gillberg: “ESSENCE” (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations)
- London: need for alternative diagnoses in ASD, e.g., “developmental brain disorder” (London, *Trends in Neurosci*, 2014)
- Hyman: “makes sense to lump neurodevelopmental disorders for now,... to give researchers a chance to start over again, free of the bias created by current unwarranted splits.” (spectrumnews.org)
- Lai, ... Baron-Cohen, 2013: “autism is not homogeneous, and defining it using the umbrella term ASD risks whitewashing the evident heterogeneity, which has a substantial impact for research into this condition.” (*PLoS Biology*, 2013)

Waterhouse & Gillberg: “Taking Autism Apart”

- (1) “Relinquish the belief that a single defining ASD brain dysfunction exists” (ignores individual variation)
- (2) Reduce the noise caused by thorny brain-symptom inference problems (“exploring very narrowly partitioned subgroups”)
- “Conduct analyses of individual variation in brain measures” (e.g. Campbell et al 2013; three distinct genomic groups: disrupted neuron development, impaired nitric oxide signaling, impaired skeletal development pathways)

Toward the Future

- Scientific research: study appropriate groups, dimensions
- What if our groups are not correct; what do we do then?
- Shift from diagnostic approaches based purely on broad syndromes, to those based upon other classifiers: genetics, behavior, neural systems activity, specific symptoms
- Important: must examine the **relationships** among these different aspects
- What is the right way to do this?
- Einstein: “If we knew what we were doing, we wouldn’t call it research!”

Example: Grouping by genetics

A Genotype-First Approach to Defining the Subtypes of a Complex Disease

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Medical genetics typically entails the detailed characterization of a patient's phenotypes followed by genotyping to discover the responsible gene or mutation. Here, we propose that the systematic discovery of genetic variants associated with complex diseases such as autism are progressing to a point where a reverse strategy may be fruitful in assigning the pathogenic effects of many different genes and in determining whether particular genotypes manifest as clinically recognizable phenotypes. This "genotype-first" approach for complex disease necessitates the development of large, highly integrated networks of researchers, clinicians, and patient families, with the promise of improved therapies for subsets of patients.

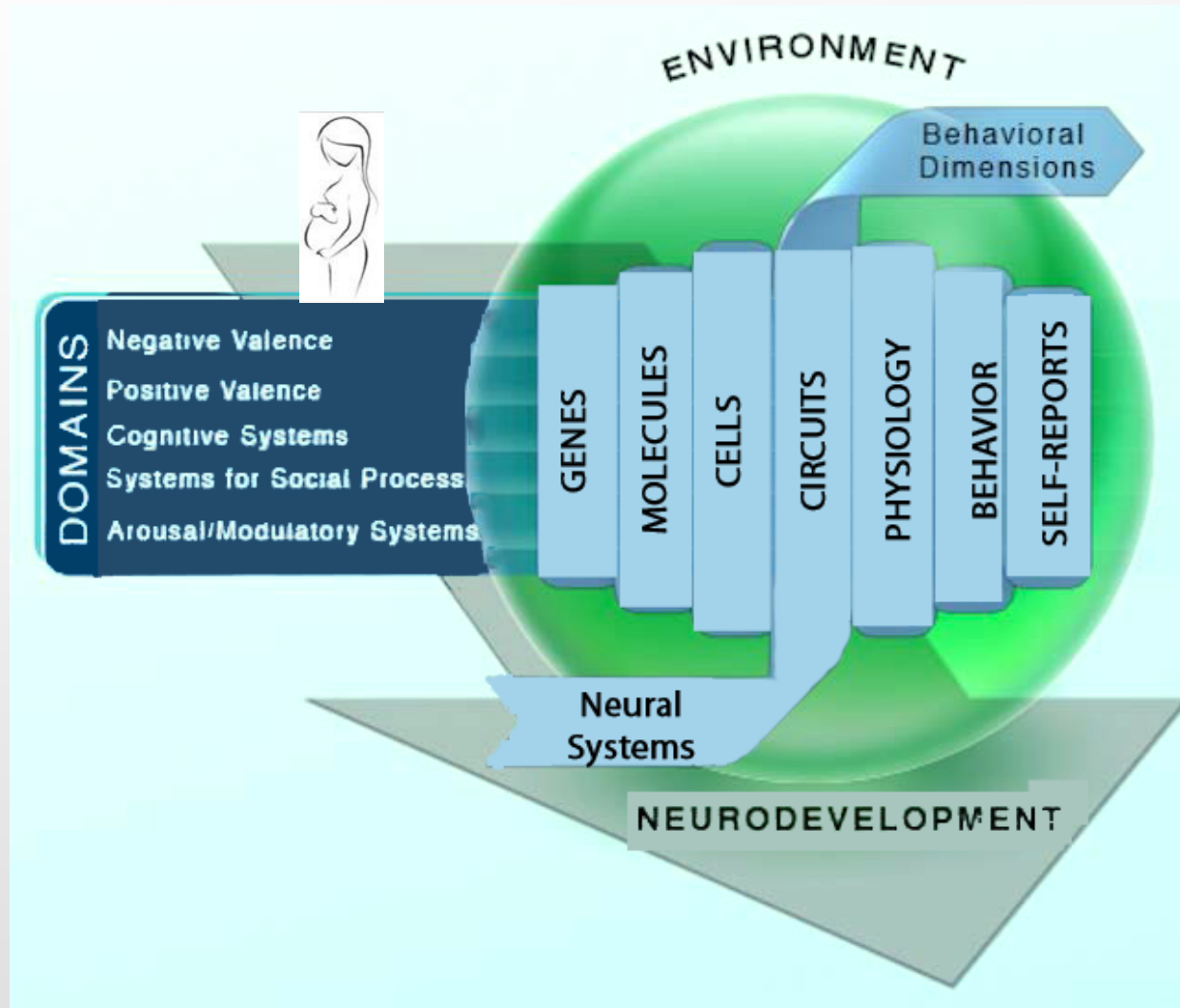
872 Cell 156, February 27, 2014 ©2014 Elsevier Inc.



How does RDoC fit in?

- Focused research initiative moving “toward a new classification system”:
- Start with dimensional constructs related both to behavior and to brain systems (and that may cut across current diagnoses)
- Concept:
 - 1) Deeper understanding of psychological & biological systems related to mental illness →
 - 2) New biomarkers & biosignatures →
 - 3) More homogeneous groupings for psychopathology/pathophysiology →
 - 4) new intervention development

The RDoC Framework: Four dimensions



RDoC Matrix: Integrative Framework (Workshops July 2010 – June 2012)

v. 5.1, 07/15/2012		RESEARCH DOMAIN CRITERIA MATRIX						
		----- UNITS OF ANALYSIS -----						
DOMAINS/CONSTRUCTS	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Negative Valence Systems							[Symptoms]	
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
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/attachment								
Social Communication								
Perception/Understanding of Self								
Perception/Understanding of Others								
Arousal/Modulatory Systems								
Arousal								
Biological rhythms								
Sleep-wake								

- Altered Stress Reactivity
- Emotion regulation problems

- Lack of pleasure in usual activities
- Lack of energy for productive tasks

- Communication problems
- Executive function problems

- Social functioning impairments
- Poor relationships

- Problems with arousal-modulating systems
- Sleep problems

Dynamic: Always “Under Construction”

v. 5.1, 07/15/2012	RESEARCH DOMAIN CRITERIA MATRIX							
	----- UNITS OF ANALYSIS -----							
DOMAINS/CONSTRUCTS	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
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Potential threat (“anxiety”)								
Sustained threat								
Loss								
Frustrative nonreward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Revised version								
Hal								
Cog								
Att								
Per								
Wo								
Dei								
Lar								
Cor								
Sys								
Affl								
Sol								
Per								
Per								
Aro								
Arousal								
Biological rhythms								
Sleep-wake								



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Updating the research domain criteria: the utility of a motor dimension

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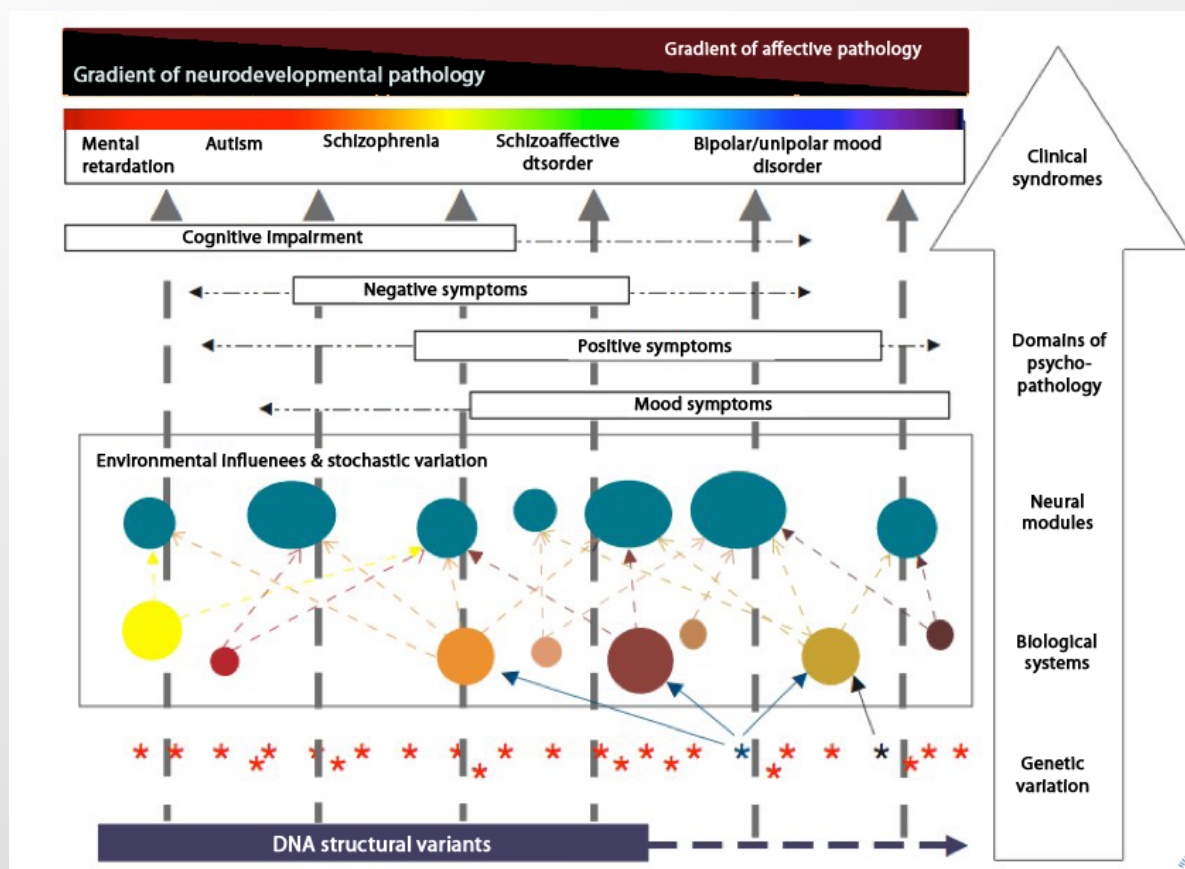
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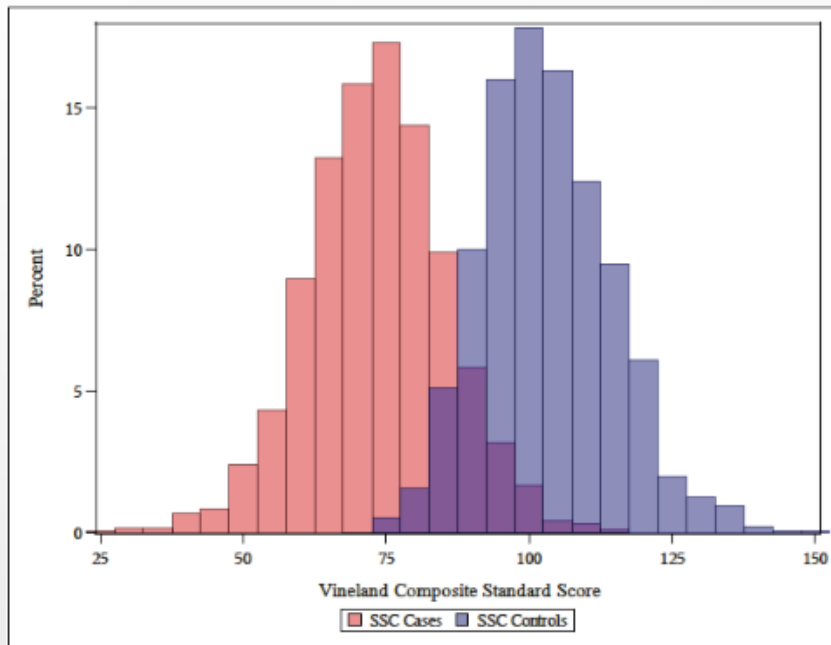
Contemporaneous Dimensional Approaches to Diagnosis

“Psychiatry will need to move from using traditional descriptive diagnoses to clinical entities (categories and/or dimensions) that relate more closely to the underlying workings of the brain.” Craddock & Owen, *Br J Psych* (2010)



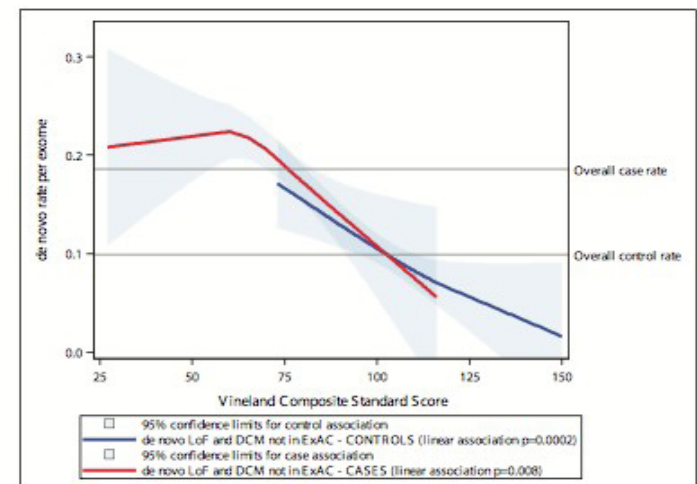
Continuity between neurotypical and ASD

Figure 2a. The distribution of Vineland scores overlaps between SSC cases and controls



Note: SSC=Simond Simplex Collection. The Vinekand Composite Standard Score is normed, across ages, at mean 100, atandard deviation 15 in general population

Figure 2b *De novo* variation influences a continuum of functional outcomes in ASD cases and controls



Robinson et al., bioRxiv preprint, [dx.doi.org/10.1101.027771](https://doi.org/10.1101.027771)

Ongoing RDoC Activities



- Develop tasks & instruments
- Common data elements
- NIMH data archives (NDAR)
- Data mining: seek more homogeneous dimensions, “microgroups” in large cohorts
- Regulatory agencies
- Goal: how do we best parse and understand the heterogeneity, to develop better treatment and preventive interventions?
- Precision medicine for ASD