Research Domain Criteria (RDoC): Toward Future Psychiatric Diagnosis

Norwegian Psychiatric Association

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NIH National Institute of Mental Health

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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).***

Toward the Future

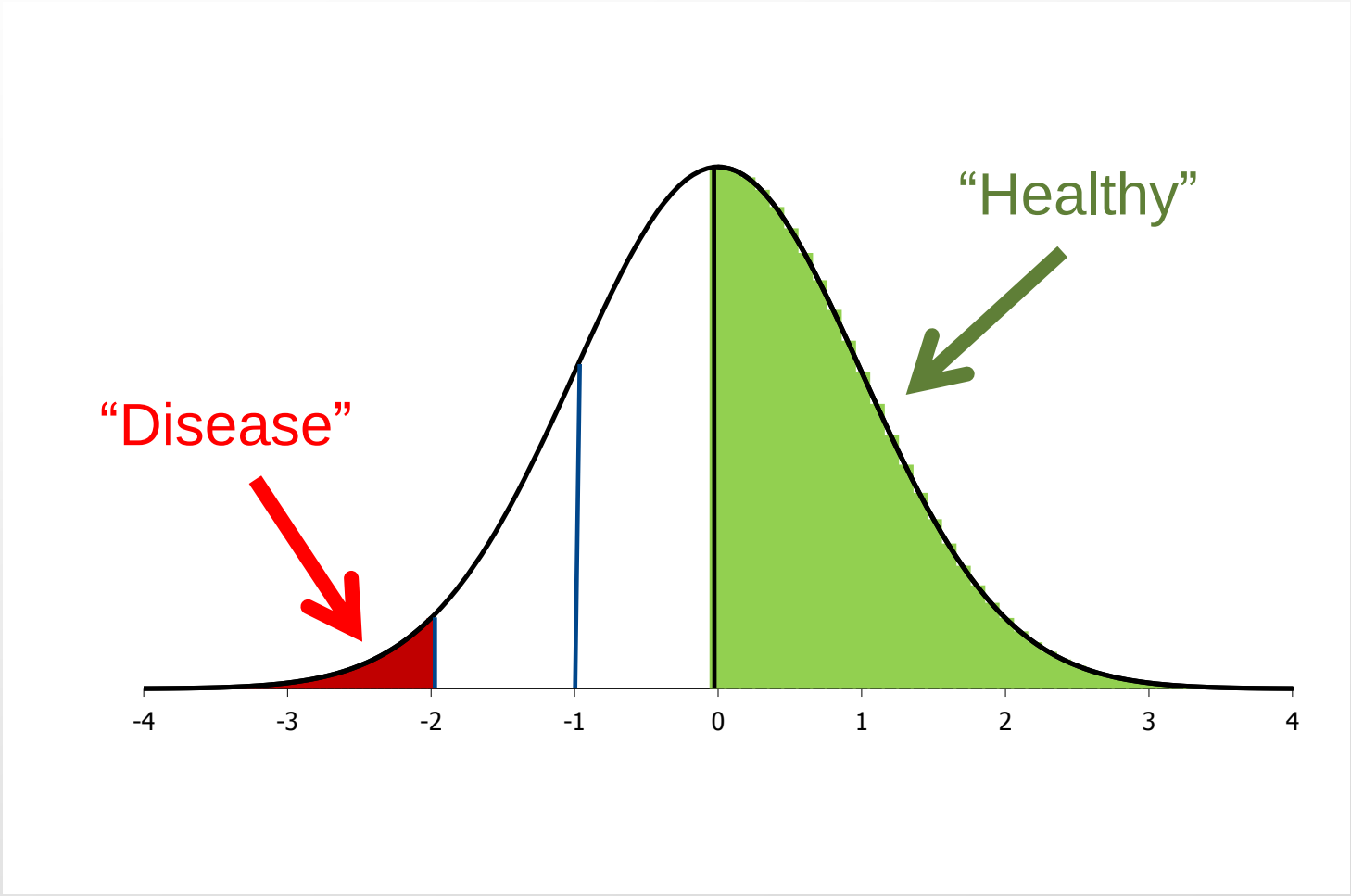
- Changing viewpoints based on the concepts of modern research — neural, cognitive, and behavioral science.
- Shift the discovery paradigm from diagnostic constructs based purely on symptoms, to those based upon the relationships among neural systems, behavior/cognition, and symptoms.
- Experimental designs: studies based upon dimensions of functional systems rather than disease categories.

The Overarching Goals of RDoC

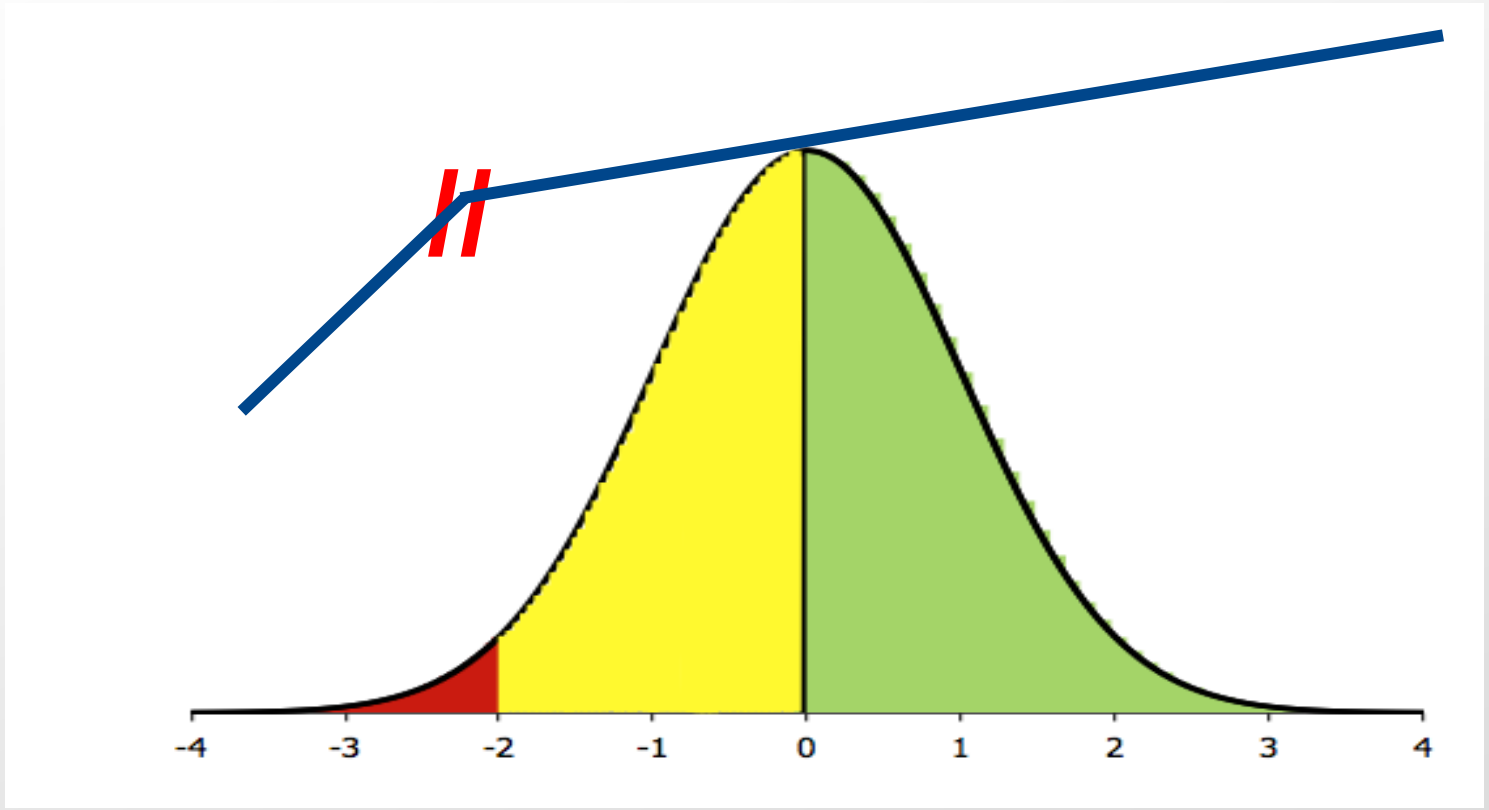
Develop a **framework** for studying psychopathology based on dimensions of observable behavior and neurobiological measures.

- Posit fundamental components that may span multiple disorders (e.g., executive function, affect regulation)
- Determine the full range of variation, from normal to abnormal
- Integrate genetic, neurobiological, behavioral, environmental, and experiential components
- Develop reliable and valid measures of these fundamental components for use in basic and clinical studies

Dimensional Psychiatry: Shift from (categorical) infectious disease model to …

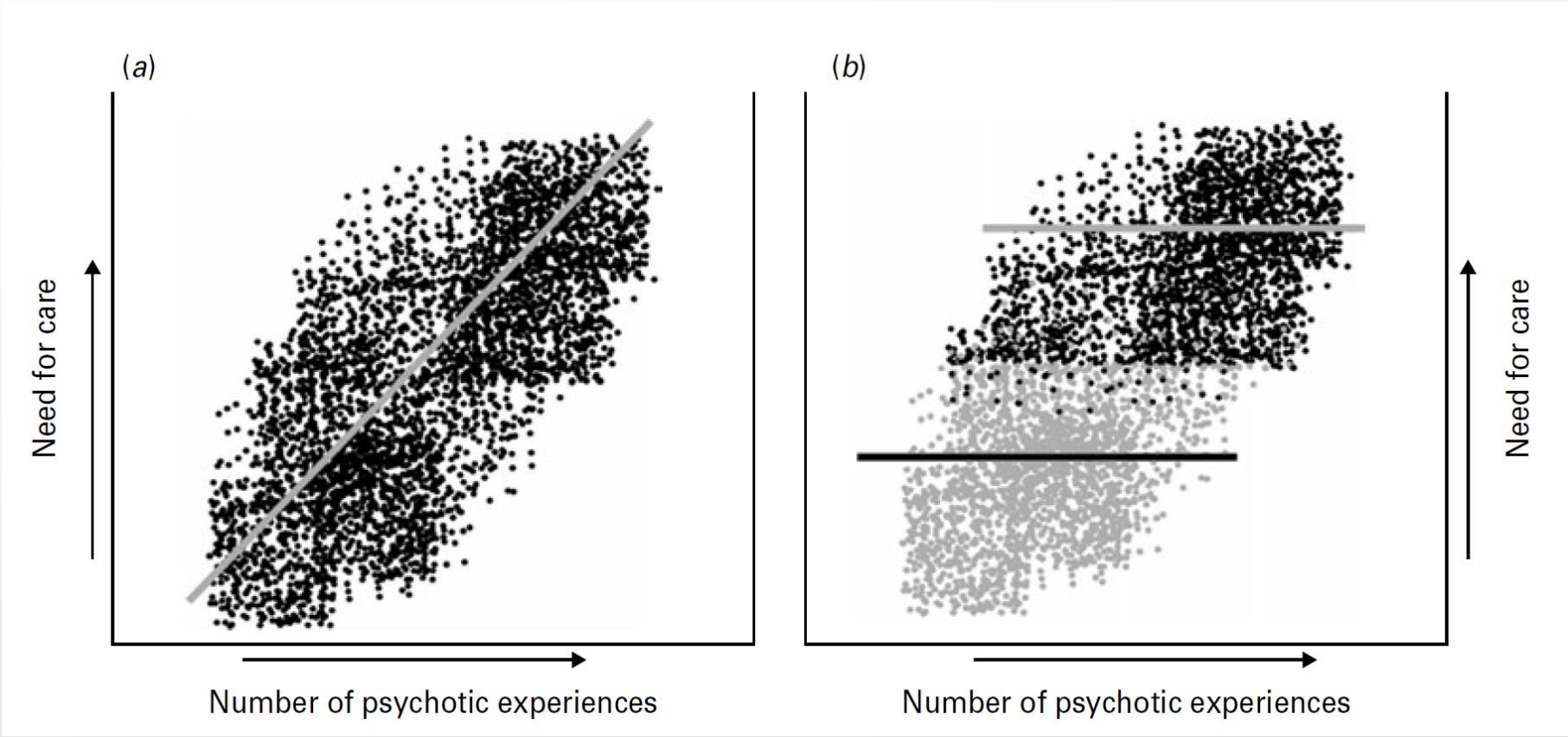


Complex Trait Model (full distribution)



Empirically-based cutpoints for (e.g.) mild, moderate, severe levels of dysfunction

Dimensional Psychosis Phenotype

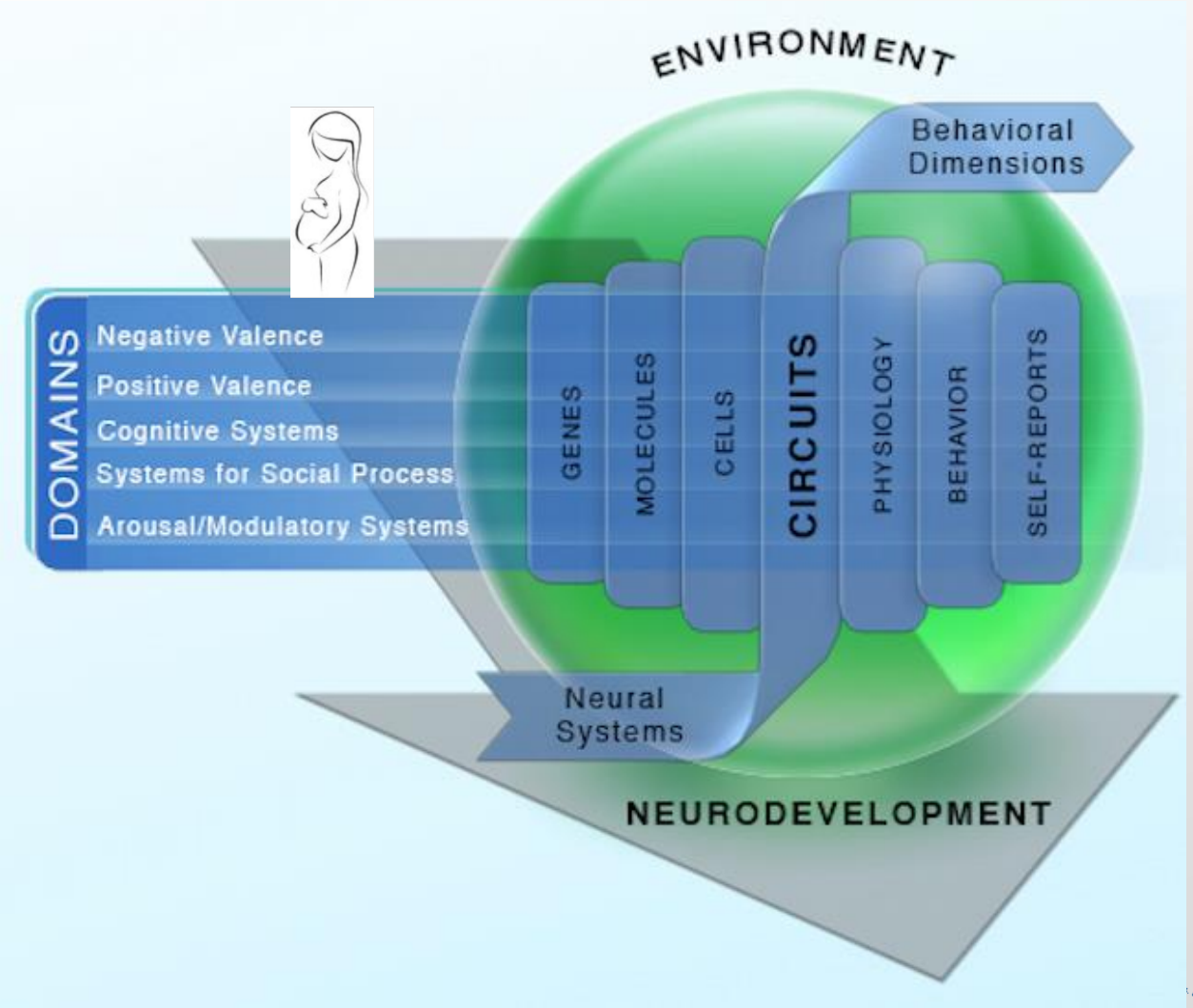


Kaymaz and van Os, *Psychological Medicine*, 2010

Exactly what *does* RDoC involve?

- Focused research initiative moving "toward a new classification system": study and validate trans-diagnostic, dimensional constructs
- 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								
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								

[Symptoms]

- Altered Stress Reactivity
- Emotion regulation problems
- Lack of pleasure in usual activities
- Lack of energy for productive tasks
- Language delays
- Executive function problems
- Social withdrawal
- Poor relationships
- Problems with arousal-modulating systems
- Sleep problems

Dynamic: Always “Under Construction”

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Potential New RDoC Constructs/Domains

- Motor construct or domain
- Resting state/default network (function?)
- Neuroimmune factors: Construct (row) or Unit of Analysis (column)?
- Overlaps between impulsivity and executive function?

Misunderstandings: RDoC Myths (1)

- “NIMH does not accept DSM/ICD applications”
- A: Over half our clinical applications are DSM/ICD.
- “RDoC ignores the environment and development”
- A: Wrong. About half our RDoC grants involve children.
- “The RDoC matrix blocks my research because the construct that I want to study is not listed”
- A: We encourage the study of new constructs – they are needed to grow the matrix.

Misunderstandings: RDoC Myths (2)

- “I can’t study interactions among the constructs”
- A: We encourage studies among 2 or more constructs.
- “RDoC is reductionistic and ignores psychology and/or experiential factors”
- RDoC is integrative, not reductionistic.
- “You must study multiple DSM/ICD disorders to do RDoC”
- A: Wrong. We encourage transdiagnostic studies, but accept those using a single DSM/ICD diagnosis.

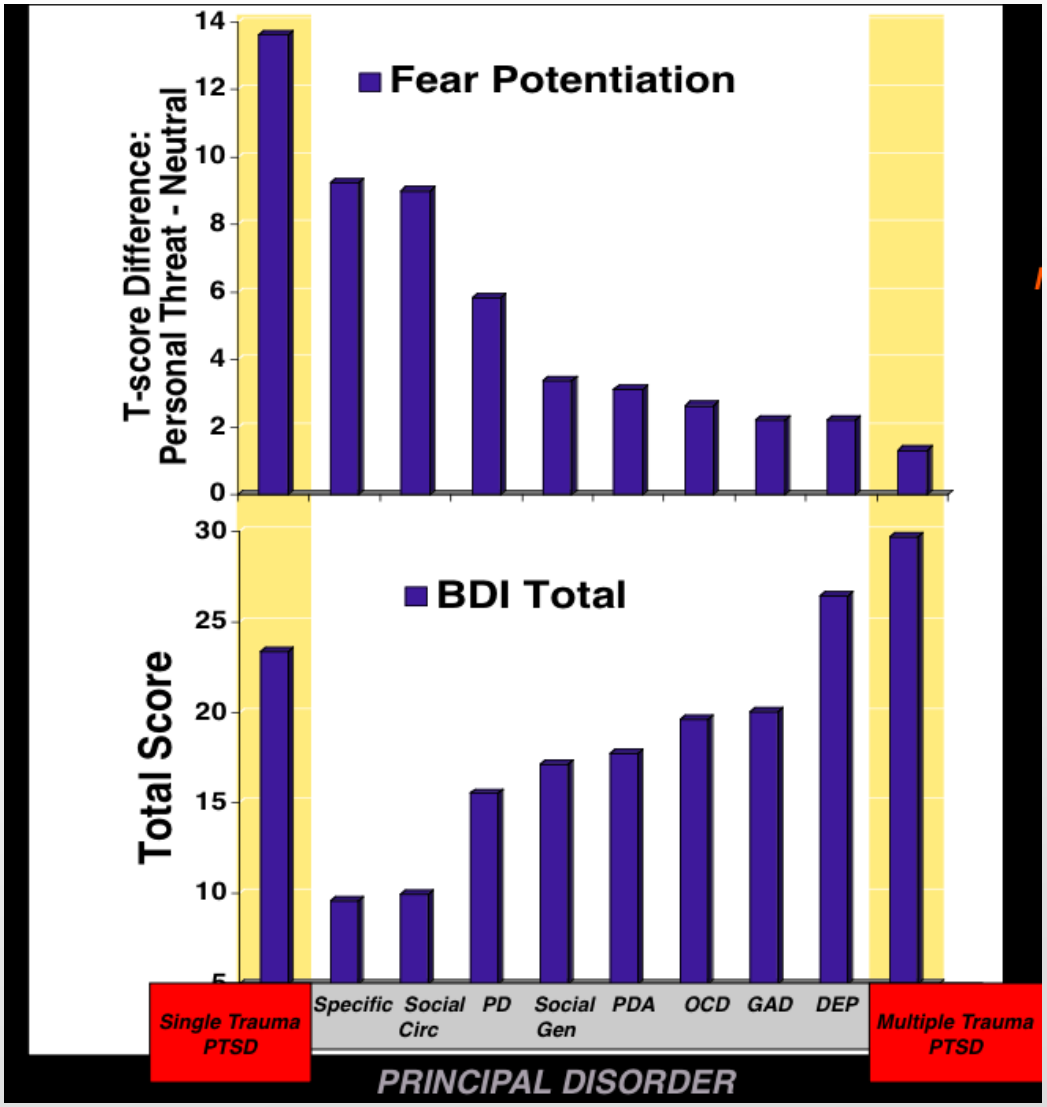
Substantive Hazards/Challenges

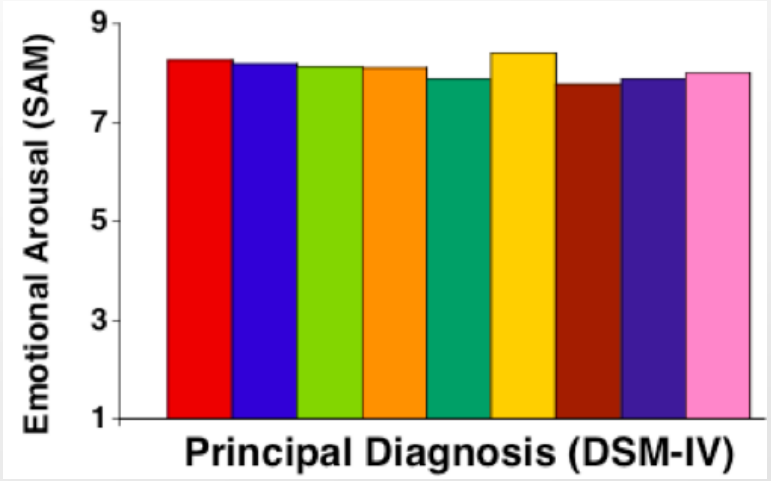
- “Grain size”: e.g., cognition vs executive function vs working memory
- Measurement: new instruments, techniques
- Relating lab/task measures to clinical symptoms, outcomes
- Assessing symptoms versus functioning
- Determining cut points for continuous phenomena

Examples of RDoC-compatible data

- (1) Anxiety disorders
- (2) Psychotic disorders
- (Neither incorporate normal-to-abnormal dimension)

Anxiety: Divergence among response measures

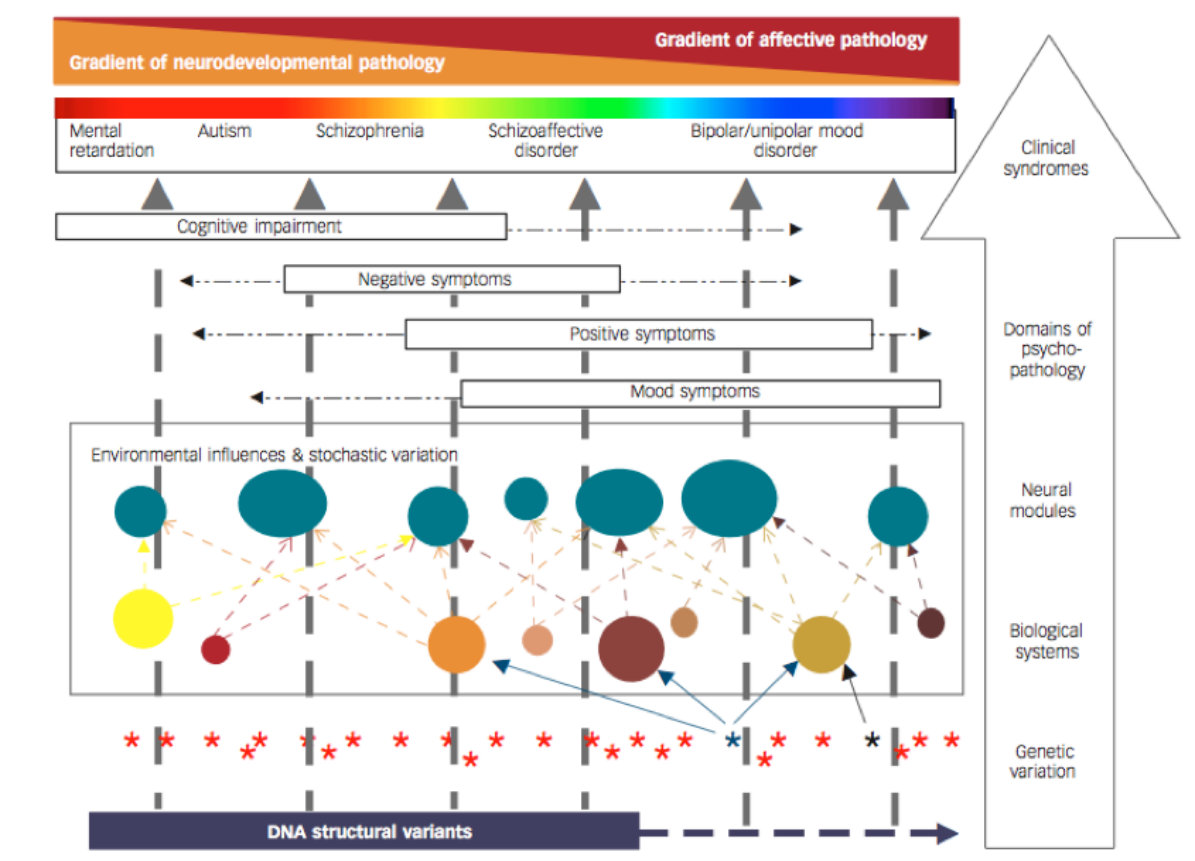




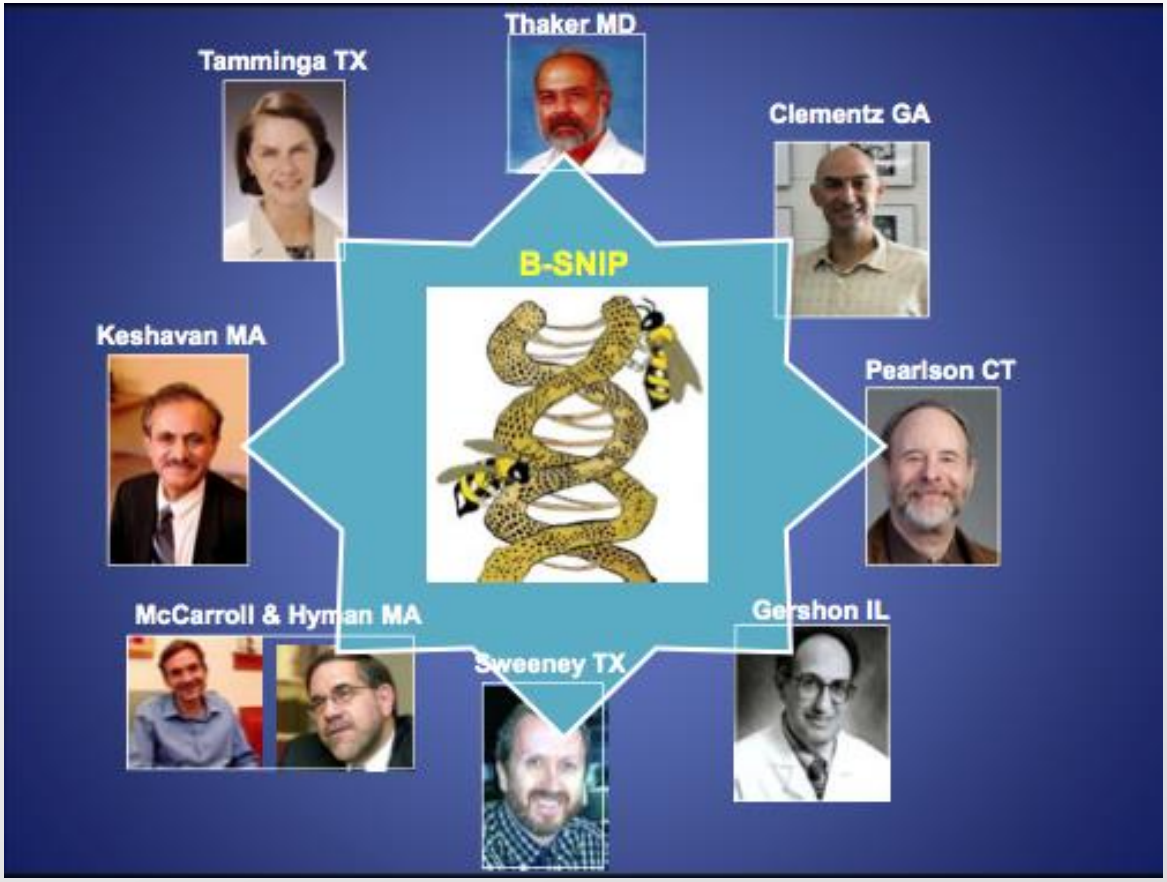
McTeague & Lang, Int'l Society for Traumatic Stress Studies, 2013

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)



Example: BSNIP*, parsing the schizophrenia-bipolar spectrum



* Bipolar-Schizophrenia Network on Intermediate Phenotypes

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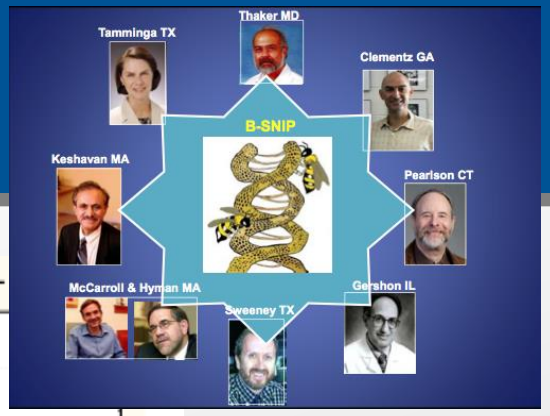
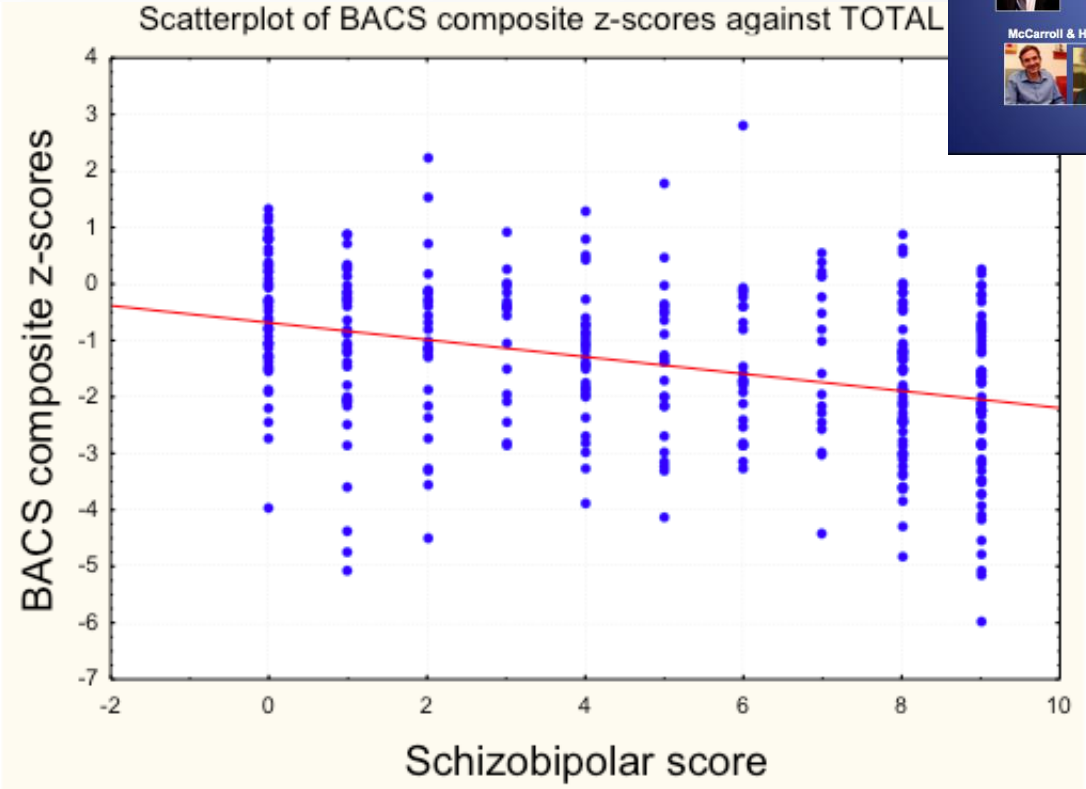


Composite cognitive score



Schizobipolar scores strongly inversely correlated with BACS composite scores r= .35; p= <.0000

Sweeney et al., SOBP Symposium, 2012

BP-like

Sz-like

* Bipolar-Schizophrenia Network on Intermediate Phenotypes

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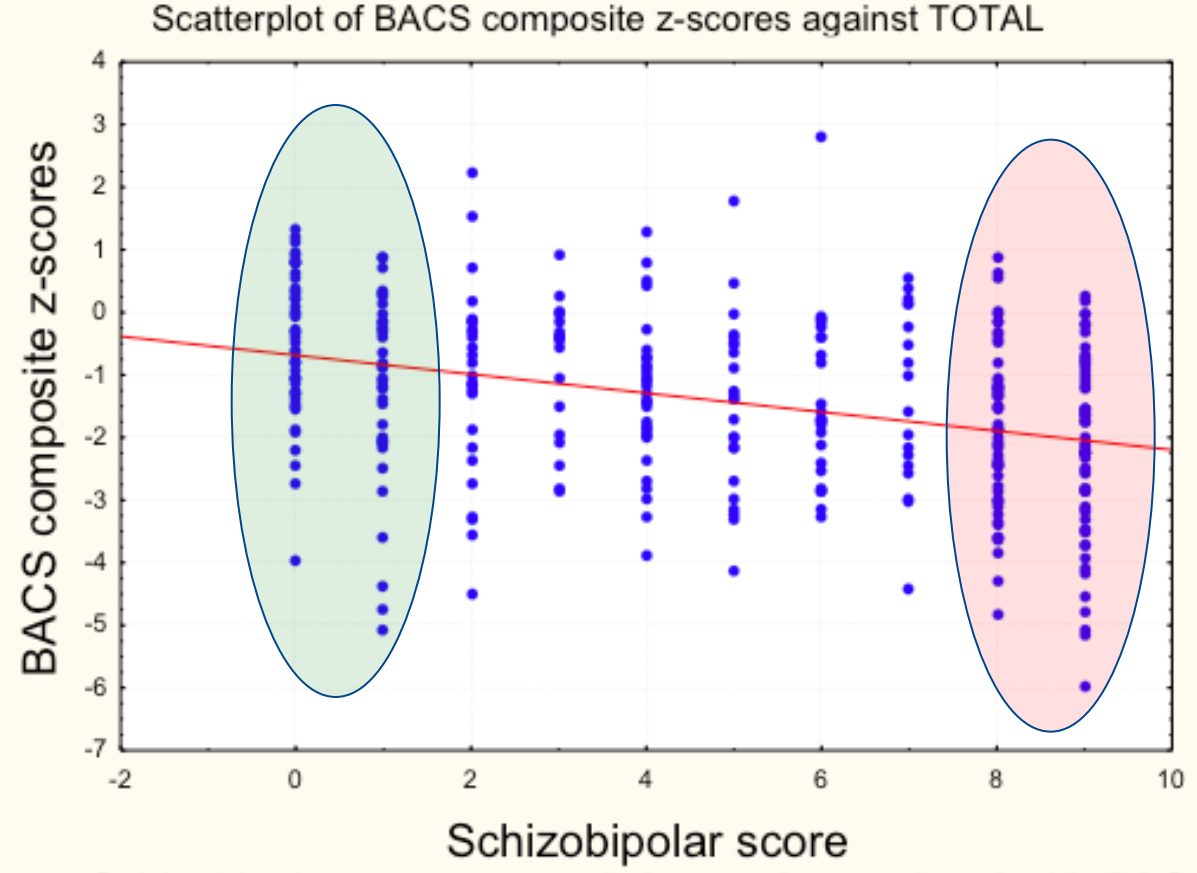
BSNIP: Sz-bipolar spectrum (DSM analysis)

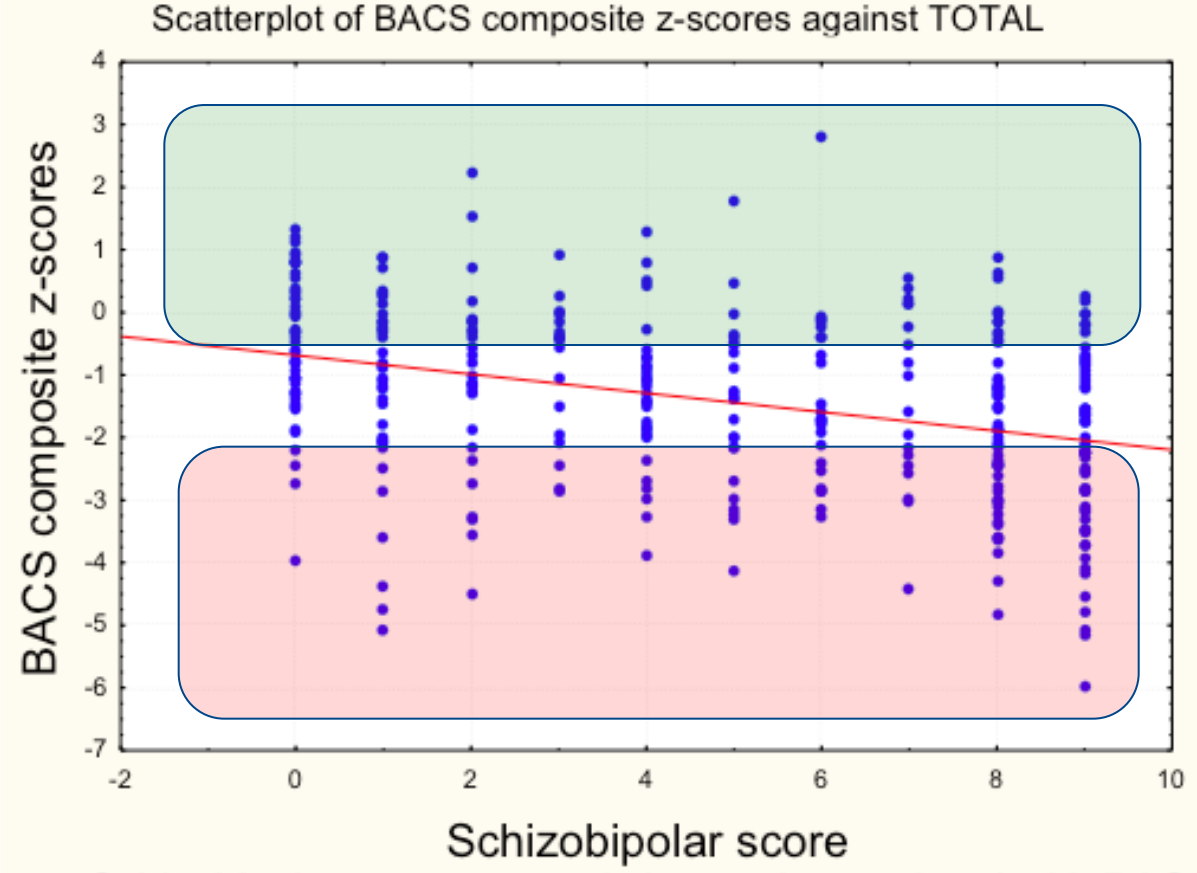


Schizobipolar scores strongly inversely correlated with BACS composite scores r= .35; p= <.0000

Sweeney et al., 2012

A significant DSM effect does not indicate meaningful differences at the individual level!

BSNIP: Sz-bipolar spectrum (RDoC approach)



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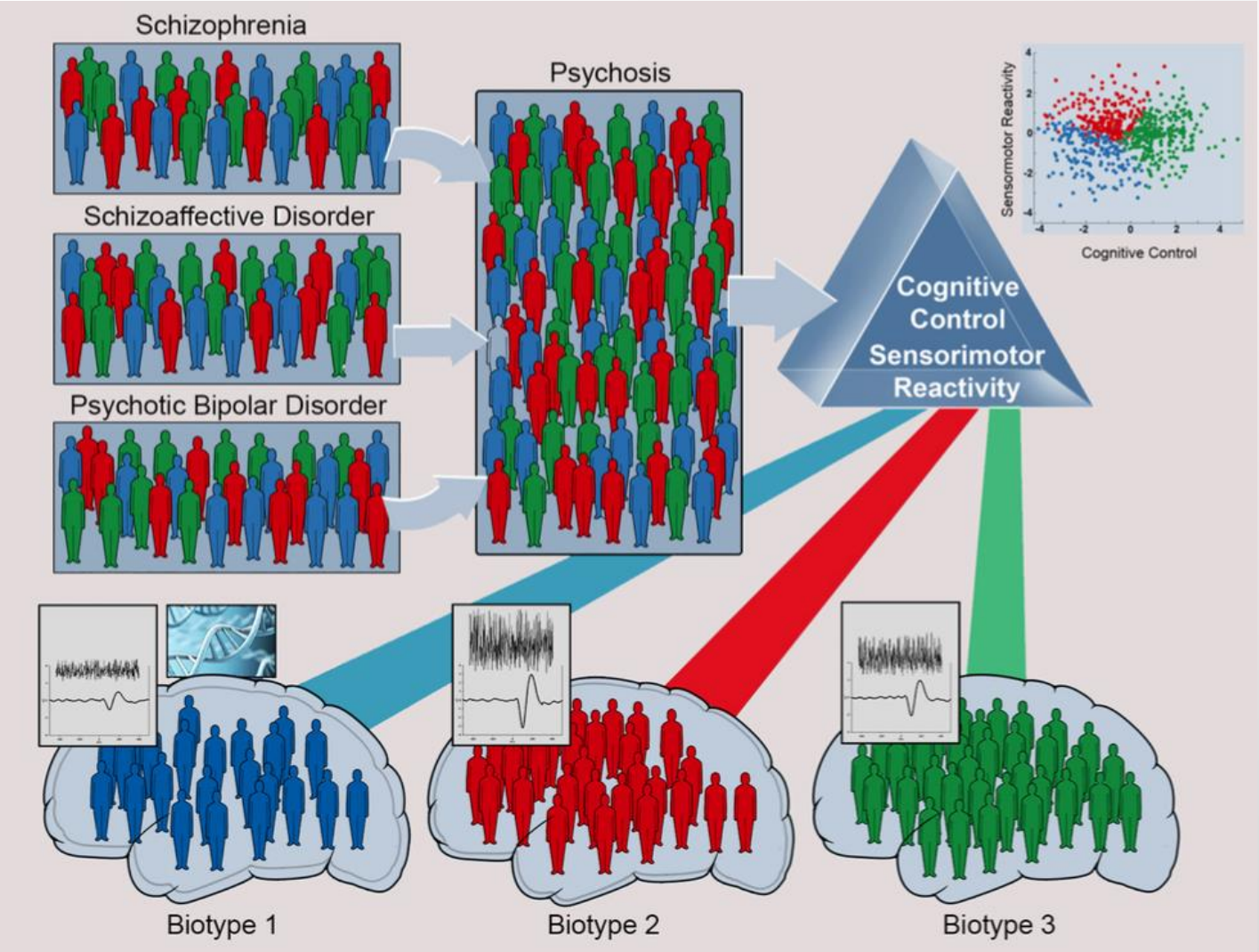
Sweeney et al., 2012

BSNIP "Biotypes: (1) Cognitive Control, (2) Sensorimotor Reactivity



Clementz, …. & Tamminga, *Am J Psychiatry*, in press

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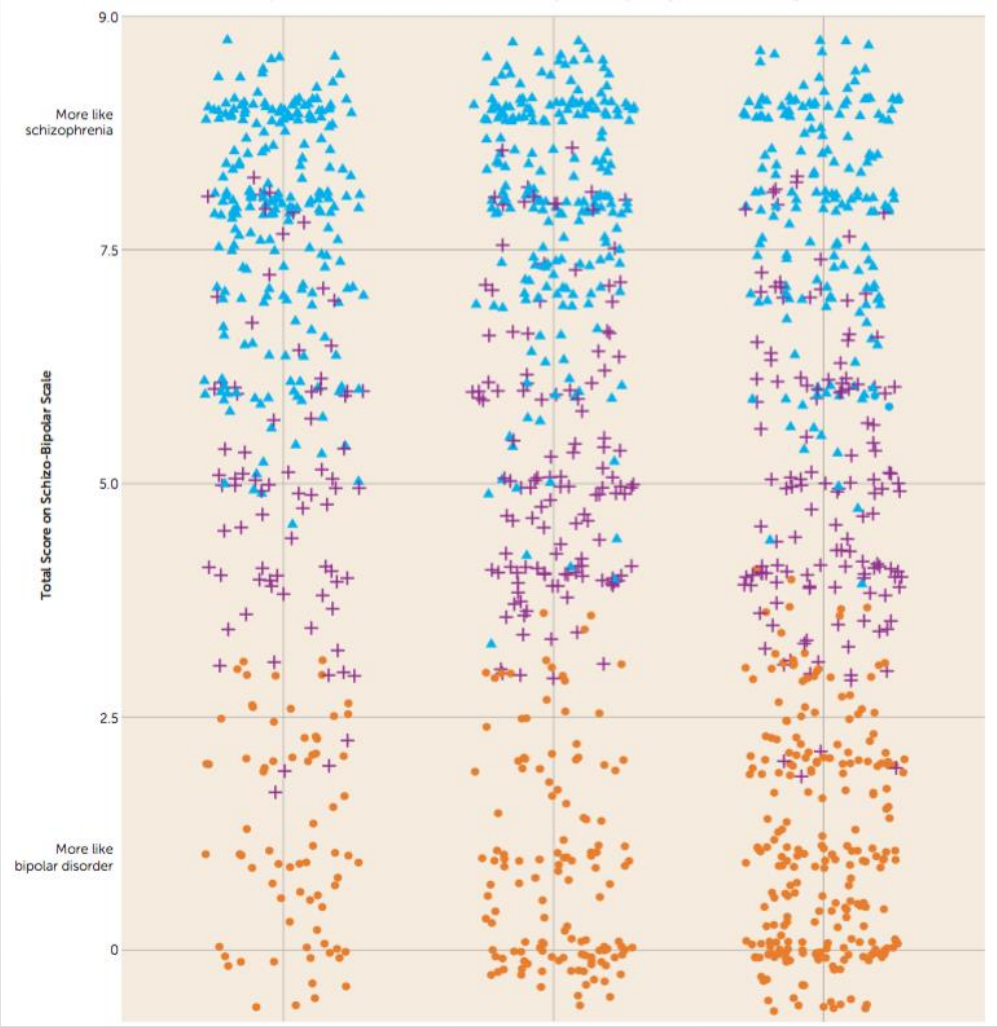
Schizo-bipolar scores by Biotype and Diagnosis

Bio 1 Bio 2 Bio 3

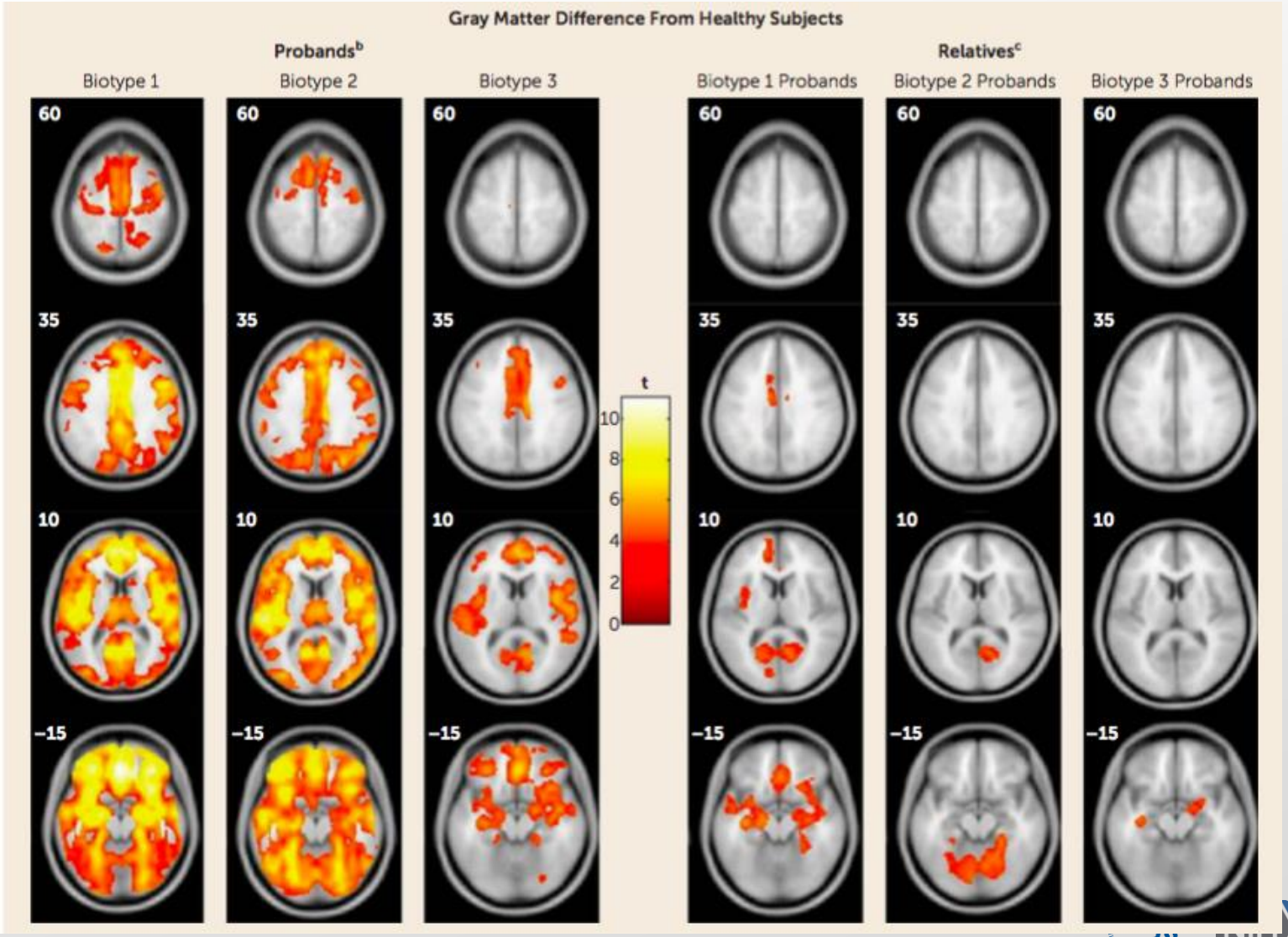
More Sz-like



More Bipolar-like

Clementz, …. & Tamminga, *Am J Psychiatry*, in press

BSNIP: Gray Matter Loss by Biotype: Probands and Relatives

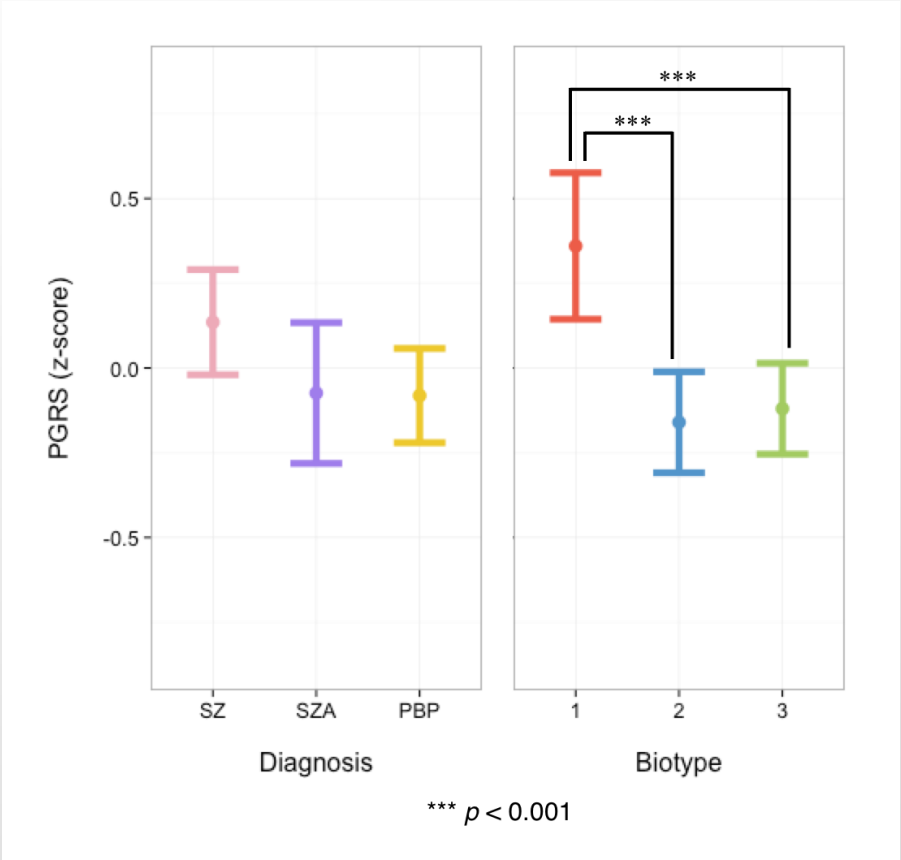


Clementz, …. & Tamminga, *Am J Psychiatry*, in press

National Institute of Mental Health

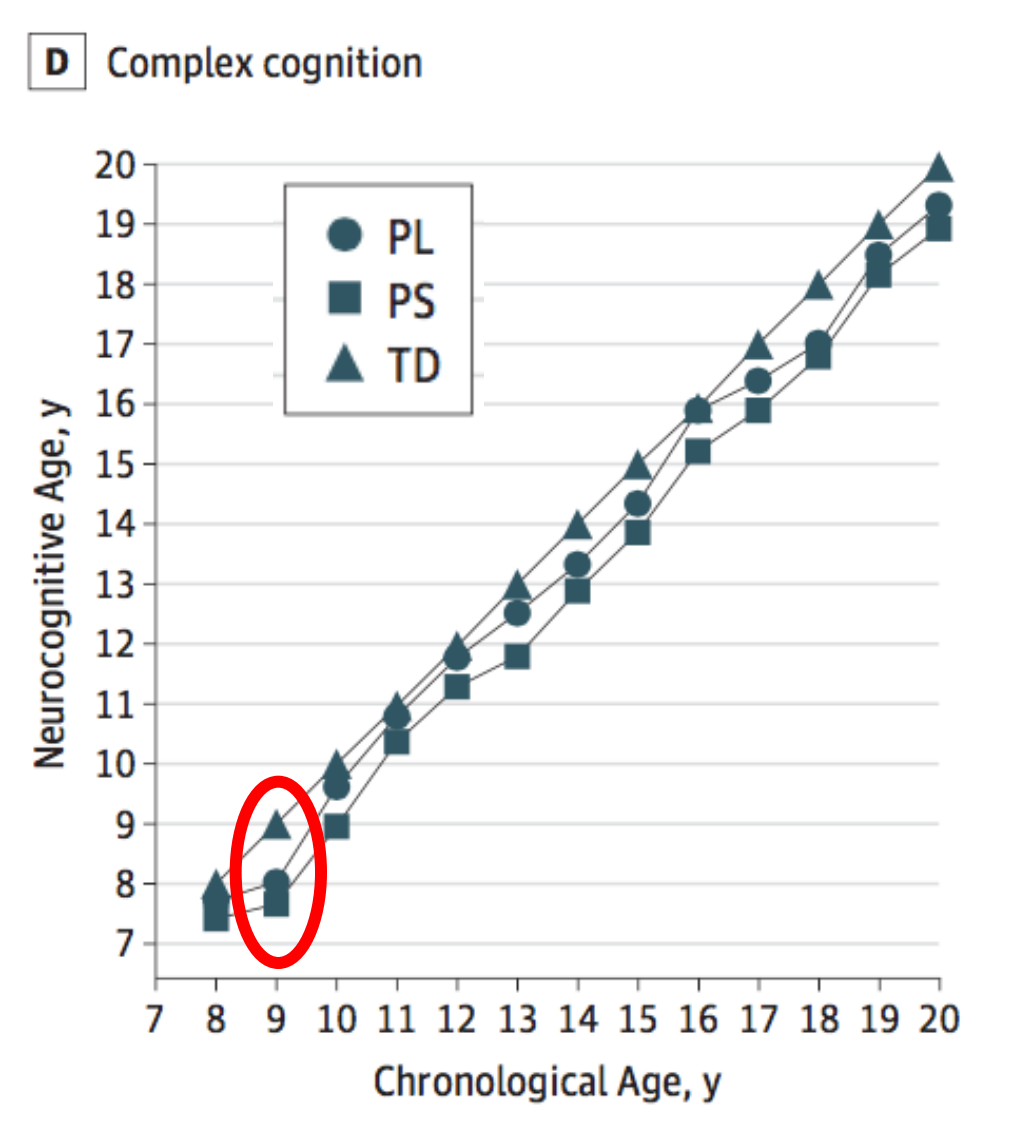
BSNIP biotypes, but not DSM, predict schizophrenia (Sz) polygene risk

Sz Polygene score (Sz workgroup of PGC, *Nature* 2014)



Clementz, Keshavan, Pearlson, Sweeney, & Tamminga, ICOSR, 2013, shared by permission

Toward Indicated Prevention: Early (pre-clinical) signs of psychosis risk



Pennsylvania Neurodevelopmental Cohort (N = 4,642): Gur et al., *JAMA Psychiatry*, 2014

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Ongoing RDoC Activities

- Curation and development of tasks & instruments
- RDoCdb (database): common data elements, data sharing
- Data mining: discovering relationships in large cohorts
- RDoC Forum for online discussions
- Regulatory agencies: (FDA/EMA)

Summary: Contemporary Directions for Mental Disorders

- Need to move from symptom management toward cure, pre-emption, and prevention
- RDoC: Flexible, dimensional research **framework** that includes neurodevelopment, environment
- Dimensional approach to mental disorders
- Big data, common data elements, different sampling frames
- Computational neuroscience: Identify new dimensions/subgroups rather than seeking correlates of current disorders
- The future: toward precision treatment and prevention for CNS disorders, consistent with other areas of medicine

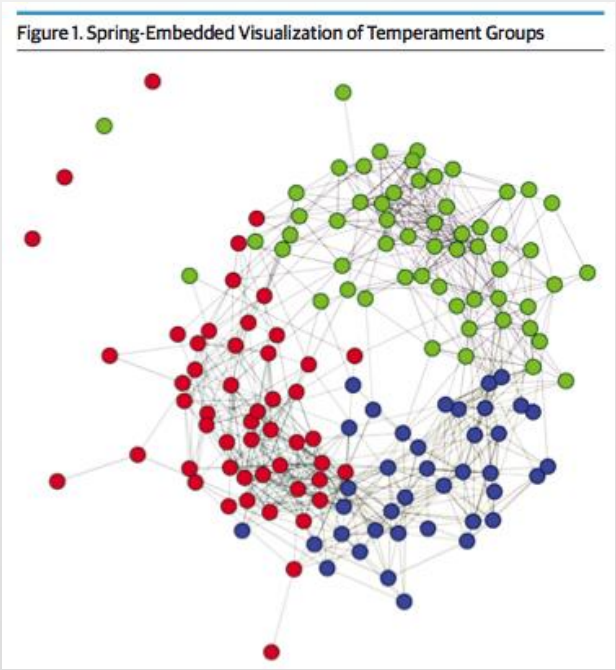
How might impulsivity be conceived in RDoC? Karalunas, … & Nigg, *JAMA Psychiatry* 2014

Nigg et al.: Attention-Deficit Hyperactivity disorder

ADHD deconstructed in terms of temperament traits:

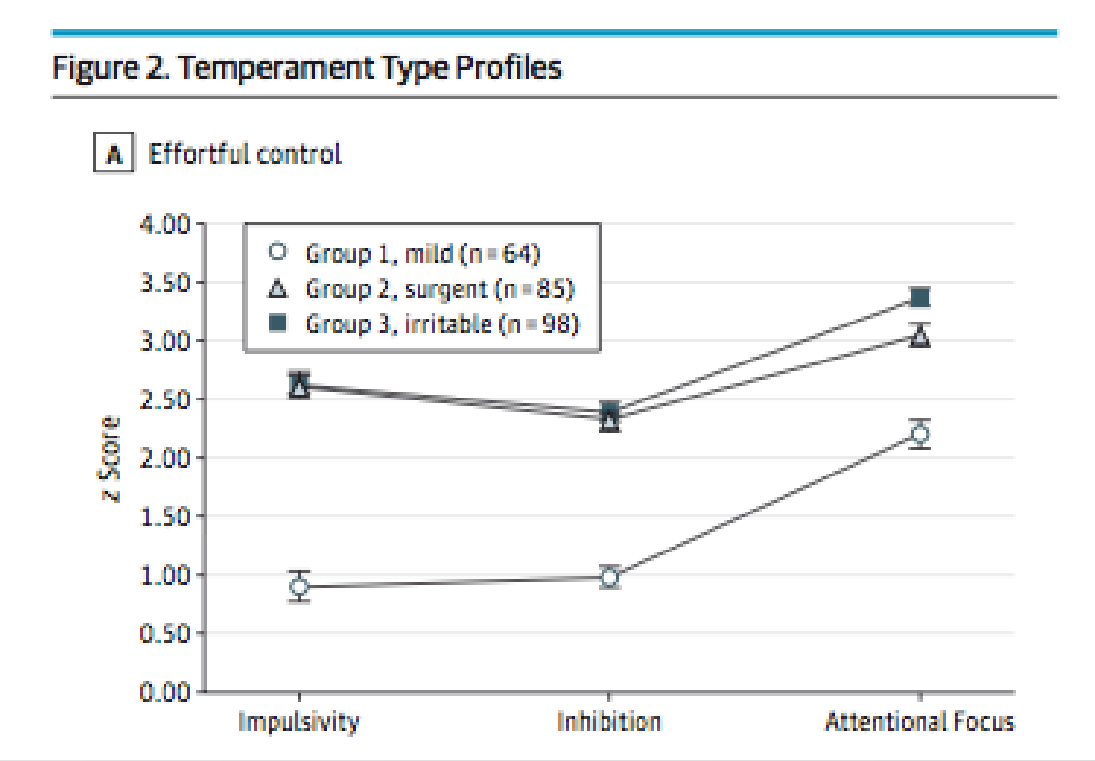
1) Negative valence systems (fear, anxiety, stress)
2) Positive valence systems (reward, approach)
3) Cognitive/effortful control (cognition)

"To better parse heterogeneity … [look] beyond existing symptom lists toward phenotypic measures that can be represented dimensionally and have well-theorized relationships with neurobiological systems. …. Phenotypic measures that retain clinical applicability are desirable."



Type 1: “Mild” ADHD (but meet DSM criteria)

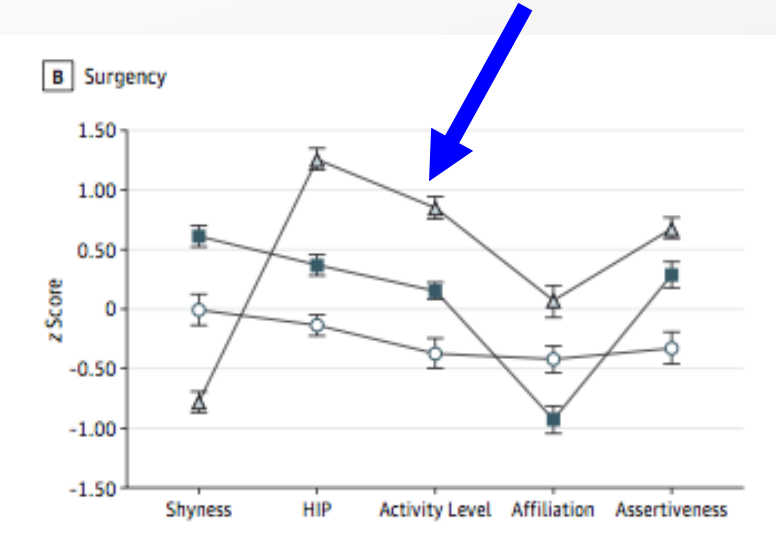
“Effortful Control” (impulsivity) scores)
[more impulsive is upward on the graph]



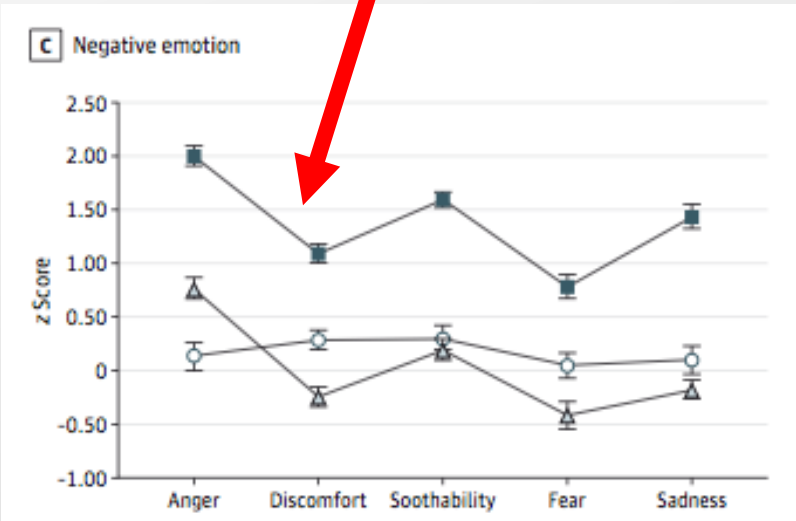
Karalunas, … & Nigg, *JAMA Psychiatry* 2014

Types 2 and 3: Temperament Differentiation

Type 2: “Surgent” (assertive, pleasure-seeking, activity)



Type 3: “Negative emotion”: (anger, discomfort, fear, sadness)



“ … revising the nosologic criteria in the case of ADHD is tractable and will be biologically meaningful.”

Karalunas, … & Nigg, *JAMA Psychiatry* 2014