Biomarker-based Best Practice

Majid Barekatain, M.D.,

Professor of neuropsychiatry

ICSS

11/12/1403
01/03/2025

MAZUMS Webinar CME

https://live.mazums.ac.ir/ch/amozesh

- *“I like to say that developing a new antidepressant with the diagnostic system we have today would be like developing a new antibiotic for someone with a fever when you don’t know if it’s caused by a bacterial or viral illness,”*
  Thomas Roland Insel, former chief of NIMH. 2008
- **"Best practice"** refers to the most efficient and effective methods, processes, or techniques for achieving optimal outcomes in an organization or within a specific project.
- These practices are based on empirical evidence, research, and experience, and they aim to improve productivity, quality, and overall performance.

Key aspects of best practice

- **Evidence-Based:** Best practices are grounded in scientific research and data, ensuring that the methods used have been tested and proven to be effective.

- **Efficiency and Effectiveness:** They focus on achieving the best possible results with the least waste of resources - whether that be time, money, or materials - leading to higher productivity.

- **Standardization:** Best practices often involve establishing standardized procedures that can be replicated across various areas of an organization, ensuring consistency in outcomes.

Key aspects of best practice

- **Continuous Improvement:** They promote an ongoing process of refinement and enhancement based on feedback and changing conditions, adapting to new evidence, technologies, or methodologies.

- **Benchmarking:** Organizations often compare their practices against those of industry leaders or competitors to identify gaps and opportunities for improvement.

Biomarkers

- **Biological material:** This can be blood, urine, tissue samples, any biological fluid, or any kind of signals from organs or systems.
- **Function of marker:**
  - Diagnostic: Identify the presence of a disease.
  - Prognostic: Indicate the likely course and outcome of a disease.
  - Predictive: Help assess the response to a specific treatment.
- **Validation:** Markers must be validated through research studies to confirm their clinical relevance.

Biomarkers

- **Sensitivity and specificity:** Sensitivity refers to the biomarker's ability to correctly identify individuals with a disease (true positive rate), while specificity is its ability to correctly identify individuals without the disease (true negative rate).
- **Feasible assay methods:** Techniques used to measure biomarkers, must be standardized for consistency, non-invasive, societal acceptant, and cost-effective.
- **Reproducibility:** The results should be consistent across different populations, settings, and measurement techniques.
- **Clinical utility:** The practicality of using the biomarker in clinical settings, including its impact on diagnosis, treatment, and patient management.

Chemical biomarkers

- Metabolites (like glucose or cholesterol)
- Proteins (such as hormones, enzymes or antibodies)
- Genetic markers (like specific DNA mutations)
- Microelements
- Tissue staining

Physical biomarkers:

- Biometric measurements (such as BP,HR, BMI, or blood counts)
- EKG (simple or stress-exercise EKG)
- EEG (like surface, QEEG, or ERP)
- Imaging results (like X-ray, sonography, CT scan, PET, or SPECT)
- Magnetic investigations (MRI, MRS, MEG, or TMS)
- NIRS and fNIRS
- Optokinekitcs

Data-driven Behavioral Research

- It refers to the systematic analysis of large-scale behavioral data to uncover patterns, predict outcomes, and enhance theoretical models of human behavior, cognition, and social interactions.
- This approach leverages massive, high-dimensional datasets with:
  1. High-Volume and High-Velocity Data
  2. Computational and Machine Learning Models
  3. Predictive and Prescriptive Analytics
  4. Multimodal and Cross-Disciplinary Integration
  5. Scalability and Generalizability
  6. Ethical and Privacy Considerations

Data-driven approach

- **Data Collection:** Gathering relevant data from various sources, such as clinical data, psychometrics, biomarkers, or environmental and social data (quantitative or qualitative data).
- **Data Analysis:** Utilizing statistical methods, algorithms, and tools (like machine learning or data mining) to extract meaningful insights, identify patterns, correlations, and anomalies.
- **Data Interpretation:** Understanding the results of the analysis in the context of the specific objectives. This involves translating the data findings into actionable insights. For example, if we find that suicide rate are increasing, it must explore possible causes and implications.

Data-driven approach

- **Informed Decision-Making:** Using the insights gained from data analysis to make informed decisions. This leads to backing strategies, policies, or actions with evidence, which can result in more effective and efficient outcomes.
- **Continuous Monitoring and Iteration:** A data-driven approach recognizes that data is not static. Continuous monitoring of data trends and outcomes allows organizations to adapt their strategies over time. This iterative process helps refine decisions and improves responses based on new data.

The RDoC Matrix: From Its Inception to Its Current Form

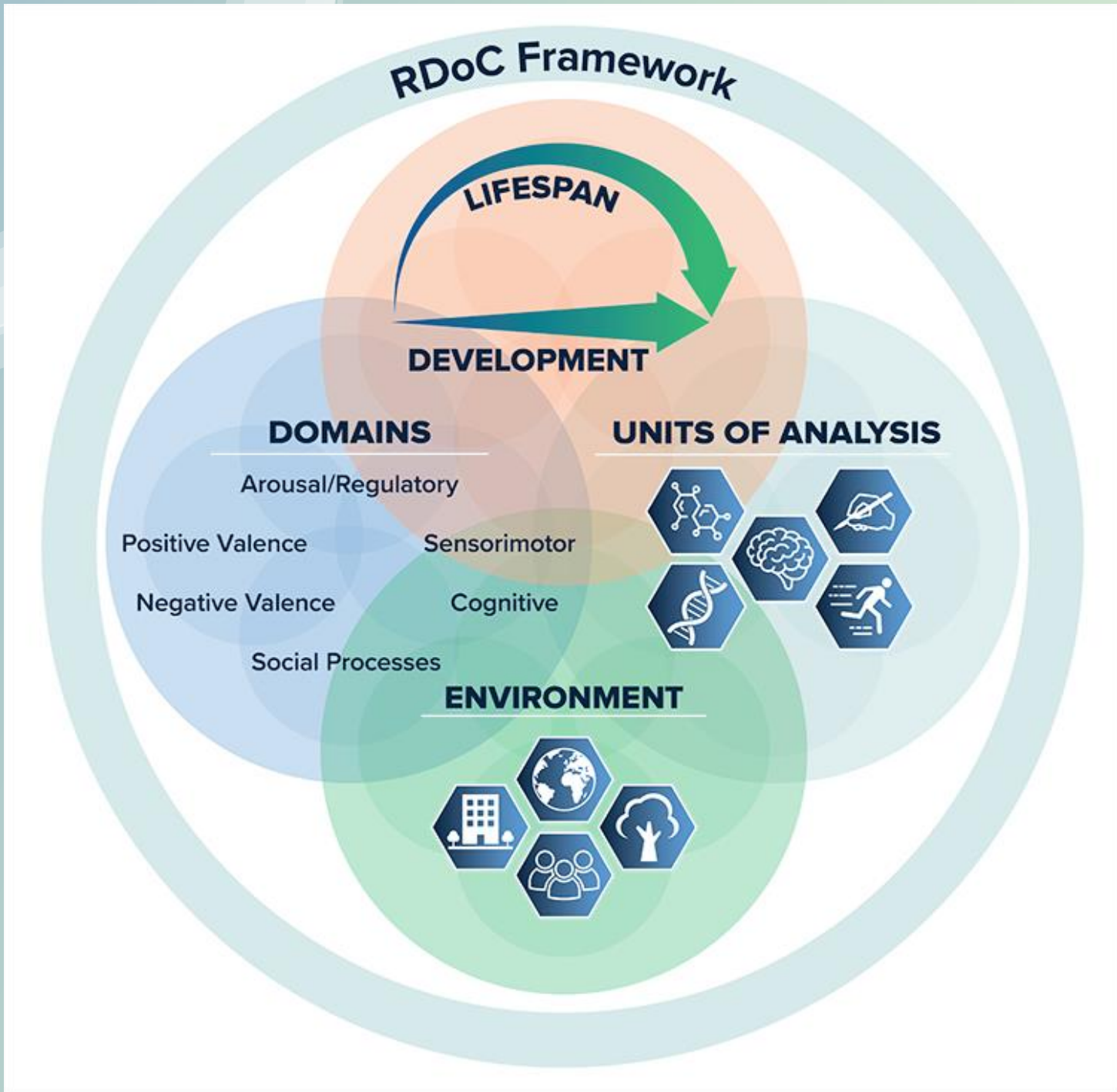
- In 2008, Dr. Thomas Insel, then director of NIMH, questioned the validity of existing diagnostic frameworks.
- He argued that psychiatry needed a scientifically-grounded framework that prioritized the biological, psychological, and behavioral mechanisms of mental illness.
- Insel called for a research agenda focused on identifying biomarkers and bridging the gap between neuroscience and psychiatry.
- It then was named “Research Domain Criteria” or RDoC matrix.

The RDoC Matrix: From Its Inception to Its Current Form

- RDoC integrates neurobiological mechanisms, behavioral phenotypes (e.g., emotional regulation, cognitive processes) and environmental influences to move beyond symptom-based diagnoses.
- It focuses on fundamental dimensions of behavior and brain function and cross-cutting phenomena across disorders (e.g., anxiety across PTSD, OCD, and GAD).
- It accepted dimensional approach that considered mental illnesses as extremes on a spectrum of normal functioning rather than discrete categories.

The RDoC Matrix: From Its Inception to Its Current Form

- Multilevel integration of RDoC incorporated data from genes, molecules, cells, circuits, behavior, and self-reports.
- It would evolve iterative development over time, incorporating new scientific discoveries.
- RDoC was initially organized into domains of functioning, each representing a major system involved in mental health.
- These domains were further divided into constructs, which are measurable units of behavior or function.
- Constructs were mapped across different units of analysis.

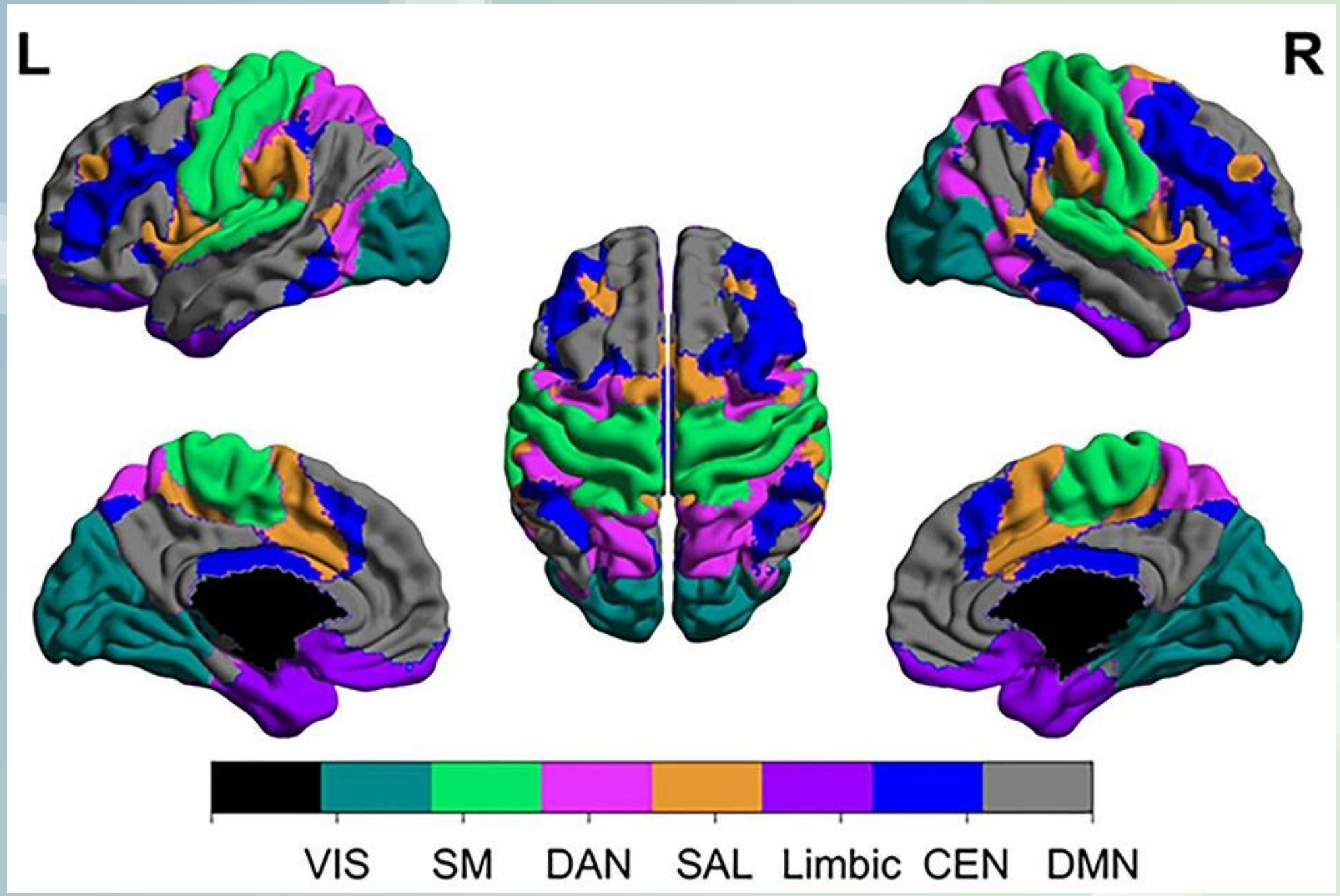

RDoC Framework
LIFESPAN
DEVELOPMENT
DOMAINS
Arousal/Regulatory
Positive Valence
Sensorimotor
Negative Valence
Cognitive
Social Processes
UNITS OF ANALYSIS
ENVIRONMENT

Larg-scale brain networks

- In the 19th century, early neuroscientists, such as Paul Broca and Carl Wernicke, identified specific brain regions associated with language and motor functions, initiating the idea of localized brain functions by lesion studies.
- Despite limitations of technology, Donald Hebb in the 1940s introduced the concept of "cell assemblies," suggesting that groups of neurons form networks to represent experiences. Karl Pribram proposed the holographic theory of memory, which emphasized the distributed nature of brain processes.
- The development of fMRI, PET), and ERP in the 1980s and 1990s allowed scientists to study brain activity in real time. Resting-state fMRI, pioneered by Biswal et al.

Larg-scale brain networks

- In 1995, revealed the Default Mode Network (DMN) as a distinct pattern of brain activity. The DMN discovery sparked interest in the brain's intrinsic activity and the idea of large-scale functional networks.
- Networks such as the DMN, Salience Network (SN), and Central Executive Network (CEN) were identified, challenging the view of the brain as a purely modular system.
- Marcus Raichle, Michael Greicius, and others mapped systematically large-scale networks using resting-state fMRI.
- Studies demonstrated that networks like the Dorsal Attention Network (DAN) and Ventral Attention Network (VAN) coordinate to regulate attention and cognition.


L
R
VIS
SM
DAN
SAL
Limbic
CEN
DMN

Larg-scale brain networks

- **DMN** involved in self-referential thinking, memory, and internal states.
- **SN** detects and prioritizes relevant stimuli, linking sensory input with emotional responses.
- **CEN** supports goal-directed behavior, problem-solving, and working memory.
- **DAN** facilitates focused attention and task engagement.
- **VAN** governs attentional shifts and orientation to unexpected stimuli.
- **SMN** coordinates sensory input and motor output.

The Human Connectome Project

- Launched in 2009, the Human Connectome Project (HCP) aimed to create a detailed map of human brain connectivity.
- The project integrated structural and functional imaging data to map brain networks at unprecedented resolution.
- Large-scale networks are not static; their interactions vary depending on cognitive demands, emotional states, and individual differences.
- The field moved toward dynamic functional connectivity, capturing changes in network activity over time.

The Human Connectome Project

- Integration of Multimodal Data by combining fMRI with other methods like EEG, MEG, and invasive recordings allowed for a more complete understanding of networks across spatial and temporal scales.
- The concept of large-scale brain networks has shifted neuroscience from a focus on isolated brain regions to a holistic view of the brain as an integrated system.
- Future research aims to map networks at the cellular level with technologies like optogenetics and advanced microscopy.
- Integration of brain and body networks (e.g., gut-brain axis and leveraging network science to develop new therapies for mental and neurological disorders are in the process.

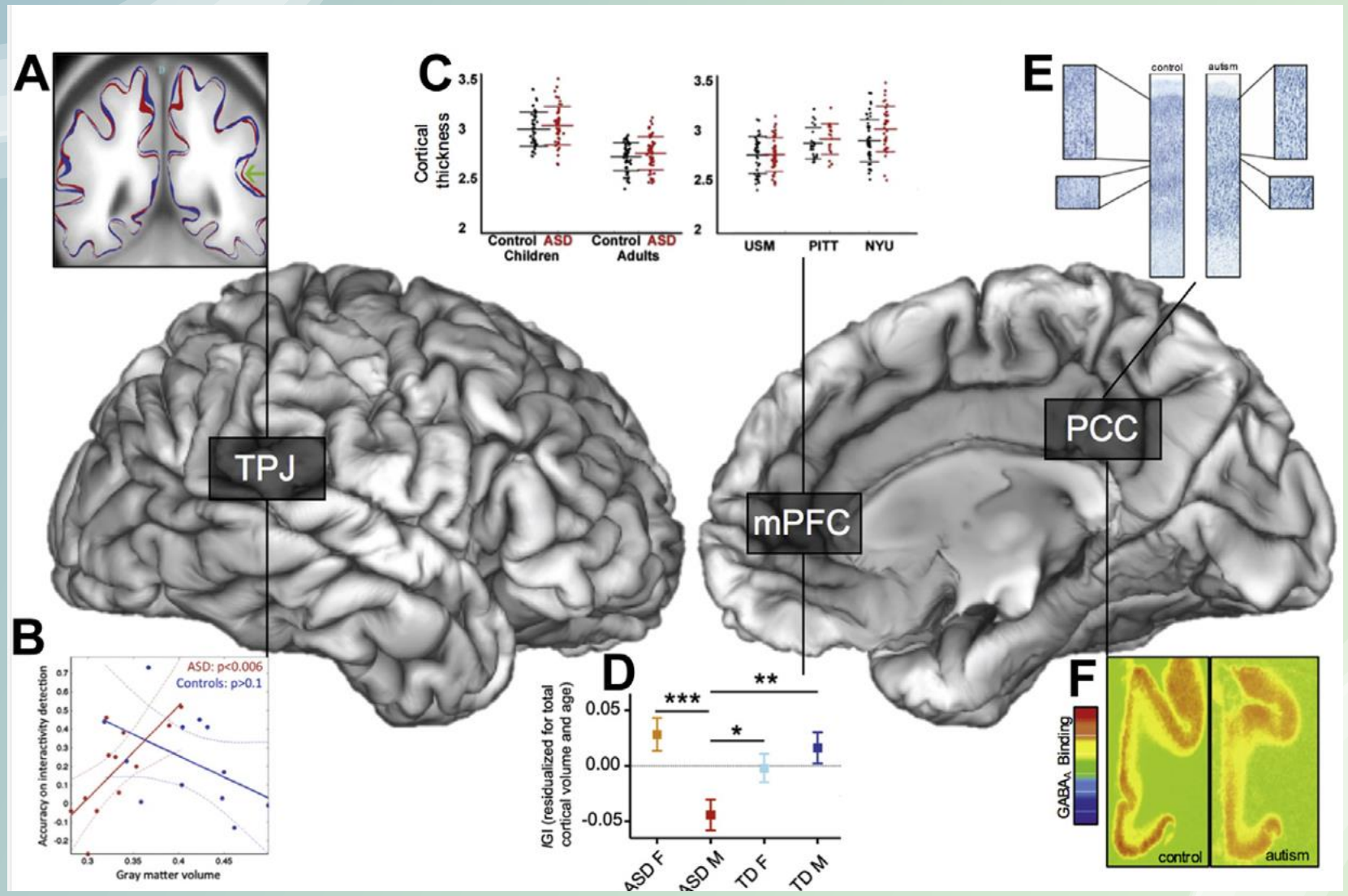
Mapping Large-Scale Brain Networks to RDoC Domains

- Negative Valence Systems Relevance: Fear and anxiety are linked to the overactivity of the amygdala, hyperconnectivity within the DMN, and disrupted Salience Network (SN) function.
- SN: Prioritizes threat-related stimuli and initiates stress responses.
- DMN: Sustained activation can contribute to rumination in anxiety and depression.
- In PTSD, abnormal SN activity contributes to hypervigilance, while disrupted DMN-SN interactions impair emotion regulation.
- The unique connectivity markers was found for subtyping robust functional connectivity signatures that may serve as targets for PTSD/DID treatment engagement.

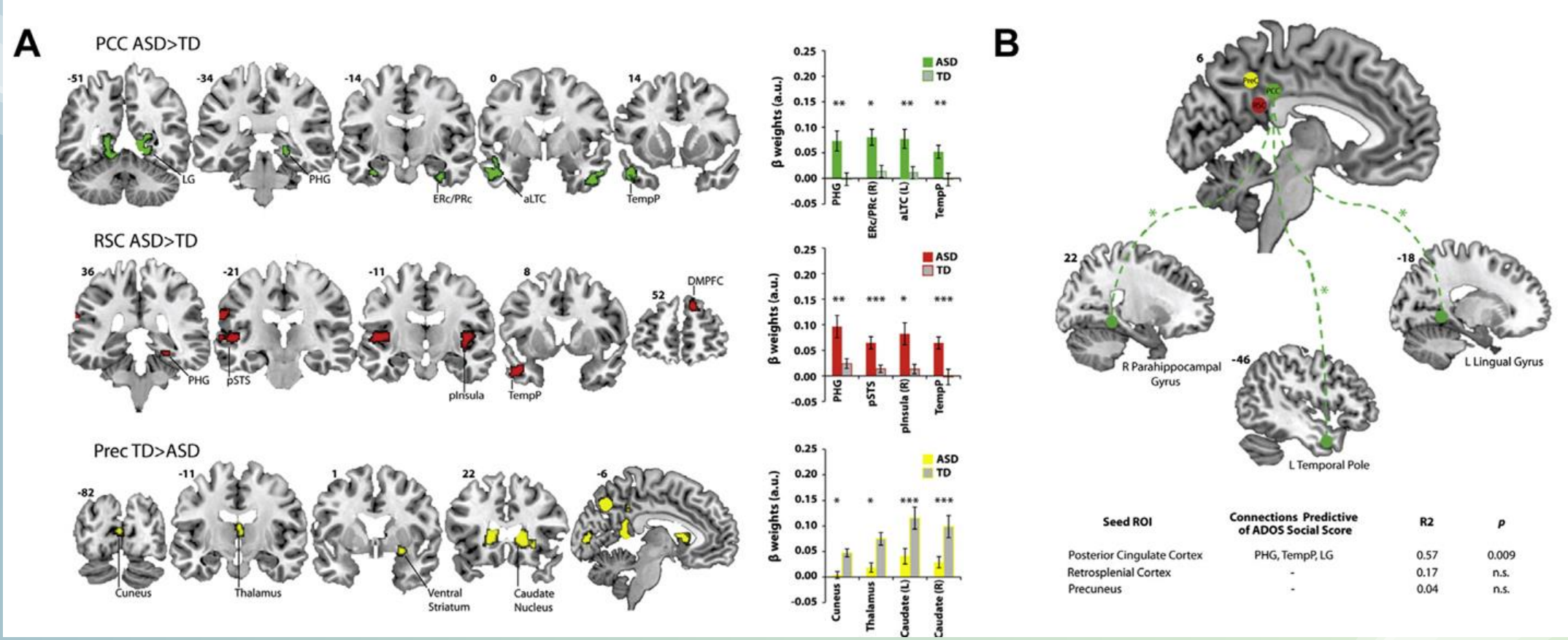
The Default Mode Network in Autism

- Altered functional and structural organization of the DMN and its atypical developmental trajectory are prominent neurobiological features of ASD.
- Atypical cytoarchitectonic organization and imbalance in excitatory-inhibitory circuits, which alter local and global brain signaling, to scrutinize putative mechanisms underlying DMN dysfunction in ASD.
- Aberrancies in key nodes of the DMN and their dynamic functional interactions contribute to atypical integration of information about the self in relation to “other” as well as to impairments in the ability to flexibly attend to socially relevant stimuli.

The Default Mode Network in Autism



The Default Mode Network in Autism

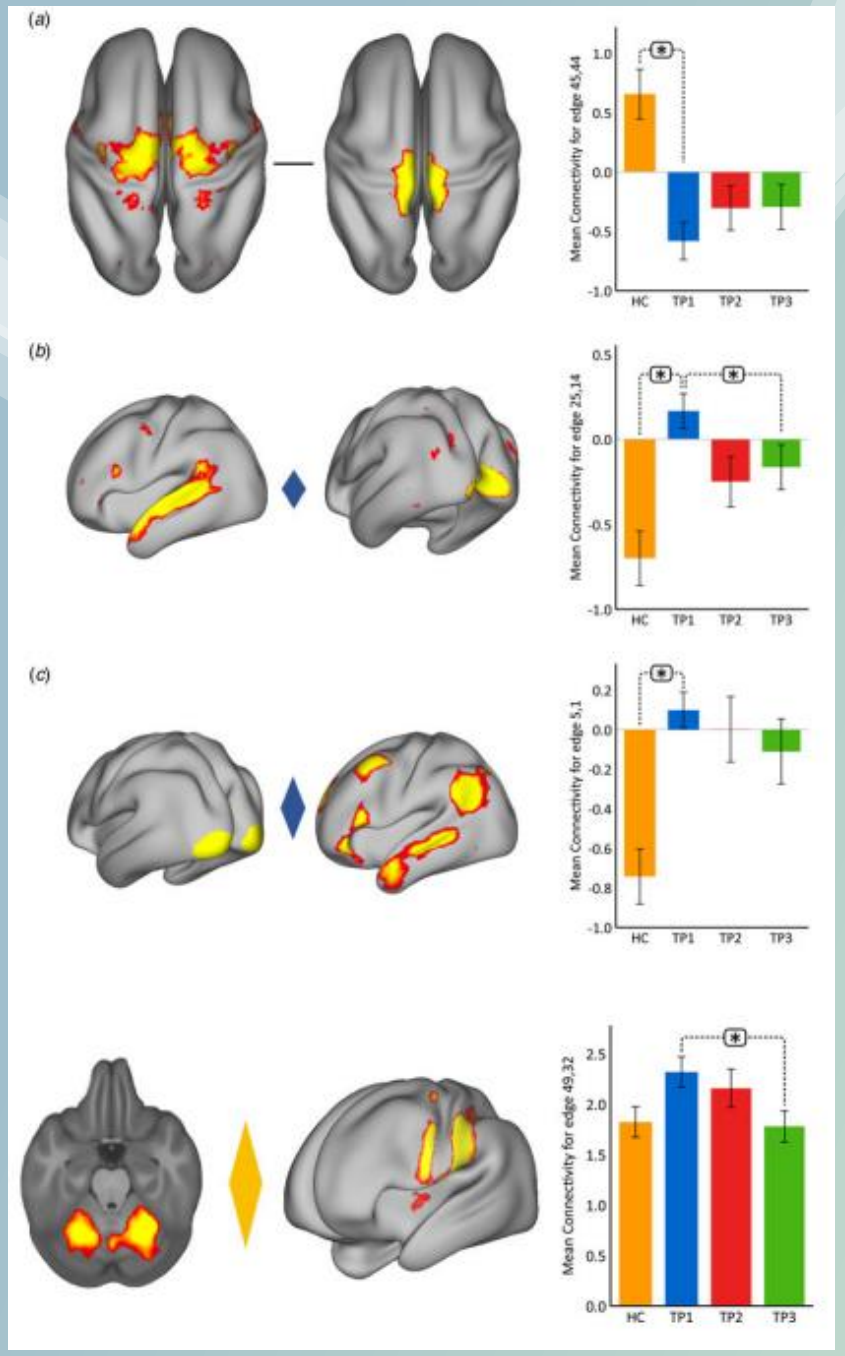


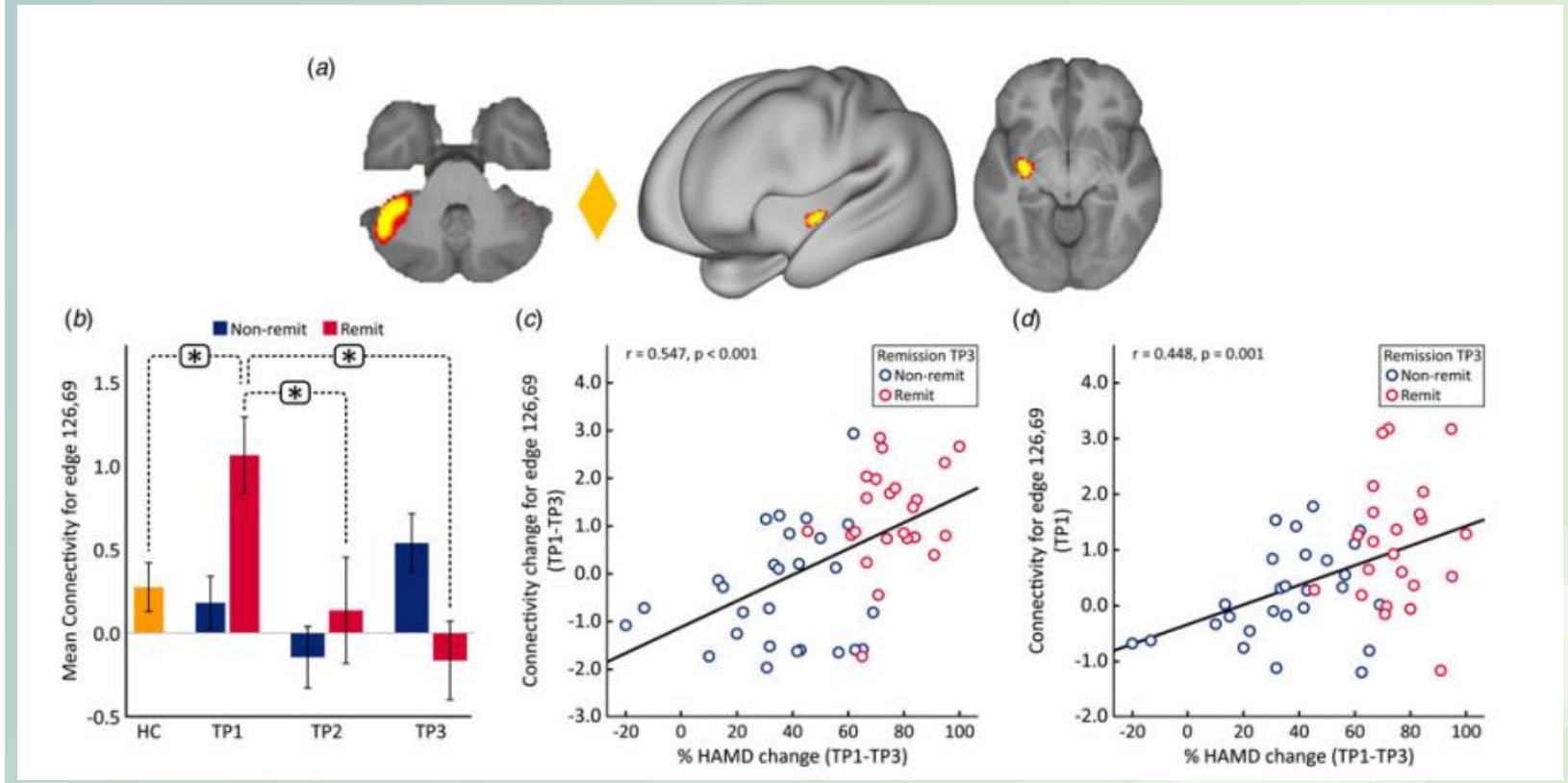
Seed ROI	Connections Predictive of ADOS Social Score	R2	p
Posterior Cingulate Cortex	PHG, TempP, LG	0.57	0.009
Retrosplenial Cortex	-	0.17	n.s.
Precuneus	-	0.04	n.s.

Hyperconnectivity with the posterior cingulate cortex (PCC) predicts social communication deficits in children with autism spectrum disorder

Modulation of the functional connectome in MDD by ketamine therapy

- Patients with MDD revealed significant differences at baseline in the somatomotor network and between association and default mode networks.
- These disruptions in FC in MDD patients trended toward control patterns with ketamine treatment.
- Ketamine treatment leads to neurofunctional plasticity between distinct neural networks that are shown as disrupted in MDD patients.
- Cortico-striatal-cerebellar loops that encompass the SN could be a potential biomarker for ketamine treatment.


(a)
Mean Connectivity for edge 45,44
HC
TP1
TP2
TP3
(b)
Mean Connectivity for edge 25,14
(c)
Mean Connectivity for edge 5,1
Mean Connectivity for edge 49,32


(a)
(b)
Non-remit
Remit
Mean Connectivity for edge 126,69
HC
TP1
TP2
TP3
(c)
r = 0.547, p < 0.001
Remission TP3
Non-remit
Remit
Connectivity change for edge 126,69 (TP1-TP3)
% HAMD change (TP1-TP3)
(d)
r = 0.448, p = 0.001
Connectivity for edge 126,69 (TP1)

Digital phenotyping

"During my last year (2015) as director of the National Institute of Mental Health (NIMH), I was in Oregon, giving a presentation to a roomful of mental-health advocates, mostly family members of young people with a serious mental illness. During my tenure as the "nation's psychiatrist," the nickname for my role, I oversaw more than $20 billion for mental-health research, and I was eager to share evidence of the agency's scientific success. While I could see heads nodding in the front row, a tall, bearded man in the back of the room wearing a flannel shirt appeared more and more agitated. When the Q&A period began, he jumped to the microphone. "You really don't get it," he said. "My 23-year-old son has schizophrenia. He has been hospitalized five times, made three suicide attempts, and now he is homeless. Our house is on fire, and you are talking about the chemistry of the paint." As I stood there somewhat dumbstruck, he asked, "What are you doing to put out this fire?"

- Digital phenotyping is a concept that involves using smartphone data and other digital tools to gather information about an individual's behaviors, experiences, and well-being in real time.
- This approach aims to supplement traditional methods of psychiatric assessment and provide a more nuanced understanding of mental health.

Key Aspects of Digital Phenotyping

- **Data Collection:** It relies on data collected through wearable devices, mobile apps, and sensors. This can include factors like location, physical activity, social interaction, and communication patterns.
- **Real-Time Monitoring:** By continuously monitoring these data points, researchers and clinicians can gain insights into changes in mood, behavior, and mental health status, often noticing trends that might not be evident in episodic clinical visits.
- **Personalized Medicine:** The ultimate goal of digital phenotyping is to enable more personalized approaches to mental health treatment, where interventions can be tailored to the unique patterns and needs of each individual.

Key Aspects of Digital Phenotyping

- **Intervention Development:** Insights from digital phenotyping can help in the development of targeted interventions, potentially leading to more effective treatments by identifying triggers or protective factors in a person's environment or lifestyle.
- **Challenges and Considerations:** Privacy Concerns, integration with Clinical Practice, equity in Access:

Digital Phenotyping