Neuromodulation CRC

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Digital Psychiatry in the Era of Artificial Intelligence: Focus on Computational Psychiatry

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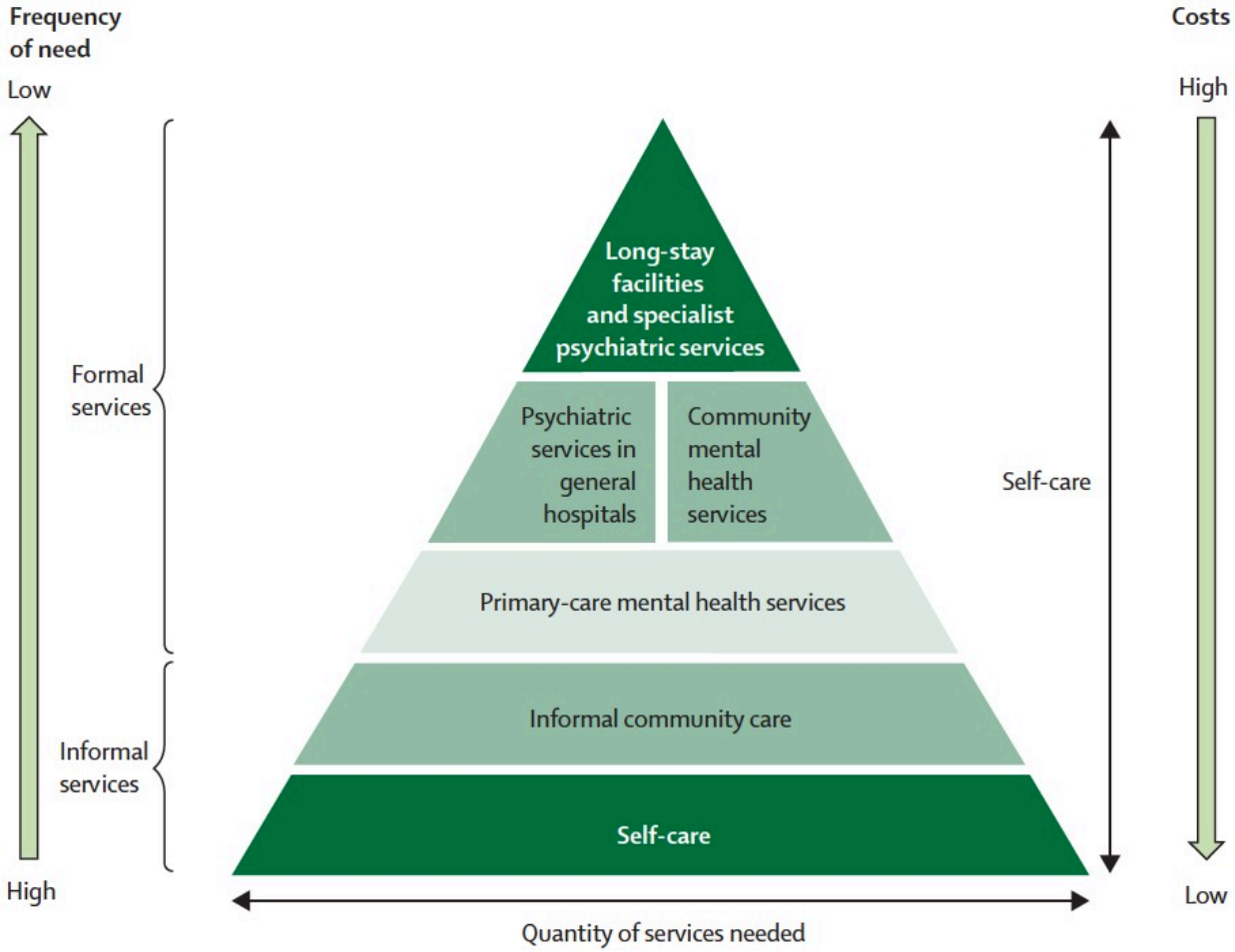
InSTAR
Individualized Schizophrenia Treatment And Reintegration

TRANS PSYCH
Translational Psychiatry Laboratory
Cognitive Neurobiology Division
Neurobiology Research Centre
NIMHANS, India

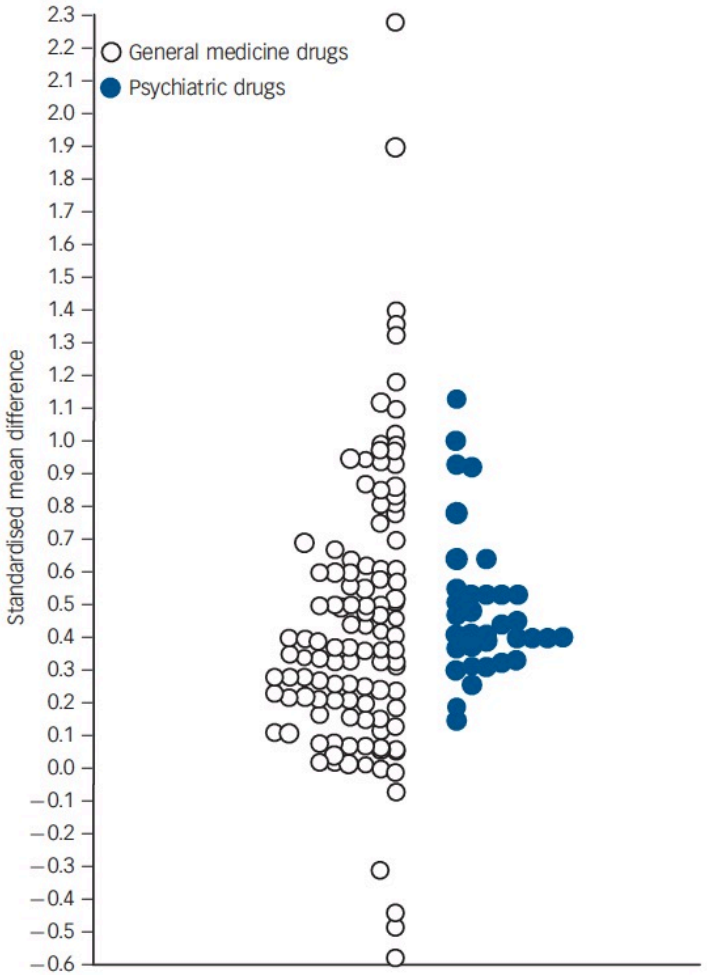
Mental Health: Service Organization Pyramid (WHO)



The most costly services are the least frequently needed,
whereas the most needed services can be provided at a relatively low cost.

Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses

BJPsych



<u>94 meta-analyses</u>
48 drugs in 20 medical diseases,
16 drugs in 8 psychiatric disorders

There were some general medical drugs with clearly higher effect sizes than the psychotropic agents, but the psychiatric drugs were not generally less efficacious than other drugs.

Leucht et al 2012

Psychiatry – Need for Innovations

- One of the holy grails of clinical psychiatry is laboratory tests to assist in diagnostic assessment—a standard component of diagnosis in most other medical specialties.

- Existing definitions of mental disorders are based exclusively on subjective signs and patient reported symptoms that are prone to recall error and misinterpretation.

- Laboratory tests have potential advantages, including being more objective and facilitating the detection of mental disorders in primary care settings, in which the use of laboratory tests is routine

- Unfortunately, although one of the goals of DSM-5 was to make the diagnostic system more based on the underlying pathophysiology of mental disorders than on their symptomatic presentations, no laboratory tests or other biomarkers were deemed to be sufficiently sensitive and specific to warrant their inclusion in the DSM-5 diagnostic criteria sets for any of the mental disorders

The RDoC Project

- The US National Institute of Mental Health (NIMH) has developed the Research Domain Criteria (RDoC) project to promote “research to validate dimensions defined by neurobiology and behavioural measures that cut across current disorder categories and that can inform future revisions of our diagnostic system”

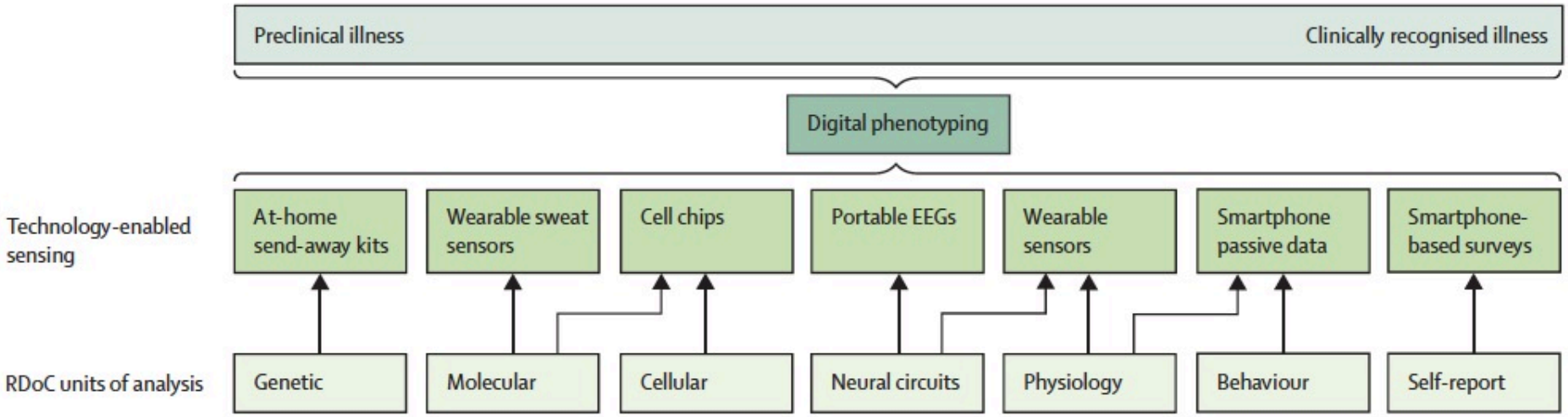
- RDoC-inspired insight into the relationship between biological processes and psychiatric symptoms might allow for the incorporation into psychiatry of clinically useful, diagnostically specific biomarkers over the next decade.

- To facilitate the incorporation of such measures in diagnostic practices, the DSM revision process is moving from one that permits updates only at fixed intervals to one that allows for the incorporation of empirically based changes on a continuous basis.

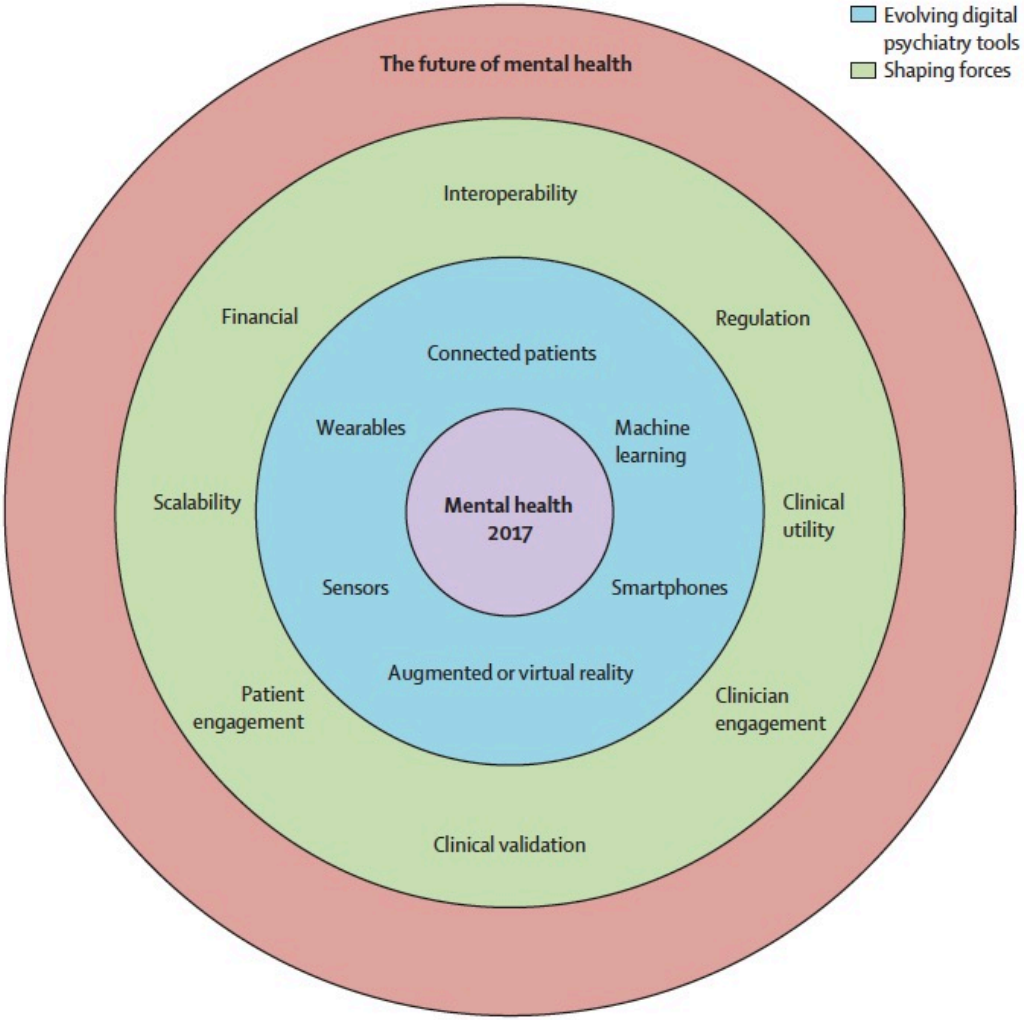
Paradigms in Science

- **Empirical (Millennia)**
  - Describing Observations
- **Theoretical (Centuries)**
  - Models & Concepts to explain the genesis of Observations
- **Computational (Decades)**
  - Simulating Observations
- **Data-Driven (Present time)**
  - Data-Intensive Scientific Computing
  - Synthesis of Observations, Theory, Computation with Statistical Learning

The Potential of Digital Psychiatry



The Future of Psychiatry: Significance of Technology



Biological Psychiatry – A Simple & Compelling Idea!

The idea of biological psychiatry seems simple and compelling:

"**the brain is the organ that generates, sustains and supports mental function, and modern psychiatry seeks the biological basis of mental illnesses**"

This approach has been a primary driver behind the development of generations of anti-psychotic, anti-depressant, and anti-anxiety drugs that enjoy widespread clinical use.

Montague et al. TRENDS in Cognitive Sciences 2012

Biological Psychiatry – The Explanatory Gap!

- Despite this progress, biological psychiatry and neuroscience face an enormous explanatory gap.

- This gap represents a **lack of appropriate intermediate levels of description that bind ideas articulated at the molecular level to those expressed at the level of descriptive clinical entities**, such as schizophrenia, depression and anxiety.

Montague et al. TRENDS in Cognitive Sciences 2012

Biological Psychiatry – The Lacuane!

- There has been insufficient understanding of human cognition (and cognitive phenotypes) to provide a bridge between the molecular and the phenomenological.

- Such lacunae get reflected in questions and concerns regarding the classification of psychiatric diseases themselves which in turn, interferes with developing translational approaches towards treatment

Montague et al. TRENDS in Cognitive Sciences 2012

Computational Psychiatry - Definition

- Computational psychiatry is a heterogeneous field at the intersection of computational neuroscience and psychiatry.
- Incorporating methods from psychiatry, psychology, neuroscience, behavioural economics, and machine learning, computational psychiatry focuses on building mathematical models of neural or cognitive phenomena relevant to psychiatric diseases.
- The models span a wide range – from biologically detailed models of neurons or networks to abstract models describing high-level cognitive abilities of an organism.
- Psychiatric diseases are conceptualized either as an extreme of normal function or as a consequence of alterations in parts of the model.

Computational Psychiatry

Computational psychiatry uses formal models of brain function to characterise the mechanisms of psychopathology, through integrated application of cognitive science, computational neuroscience, statistical learning & data science as well as several other related scientific techniques

Neuromodulatory systems

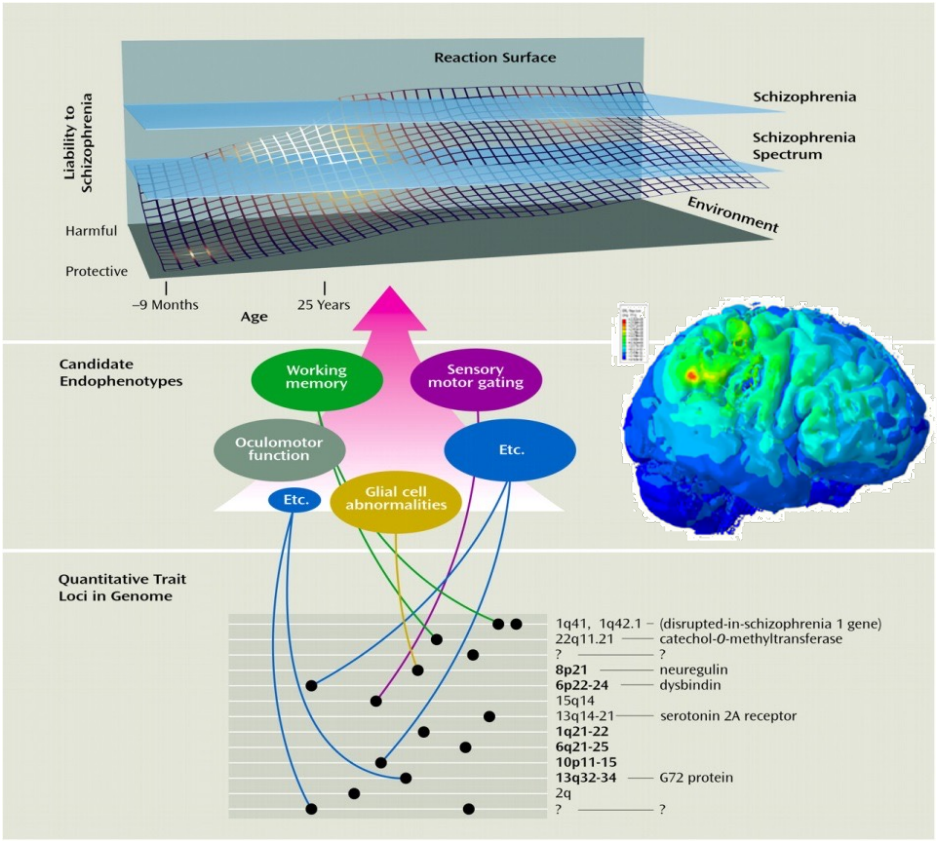
- Systems of neurons that project to broad regions of target neural tissue to modulate subsequent neural responses in those regions.

- Neuromodulatory systems typically have cell bodies situated in the brainstem and basal forebrain and deliver neurotransmitters, such as serotonin, dopamine, acetylcholine and norepinephrine, to target regions.

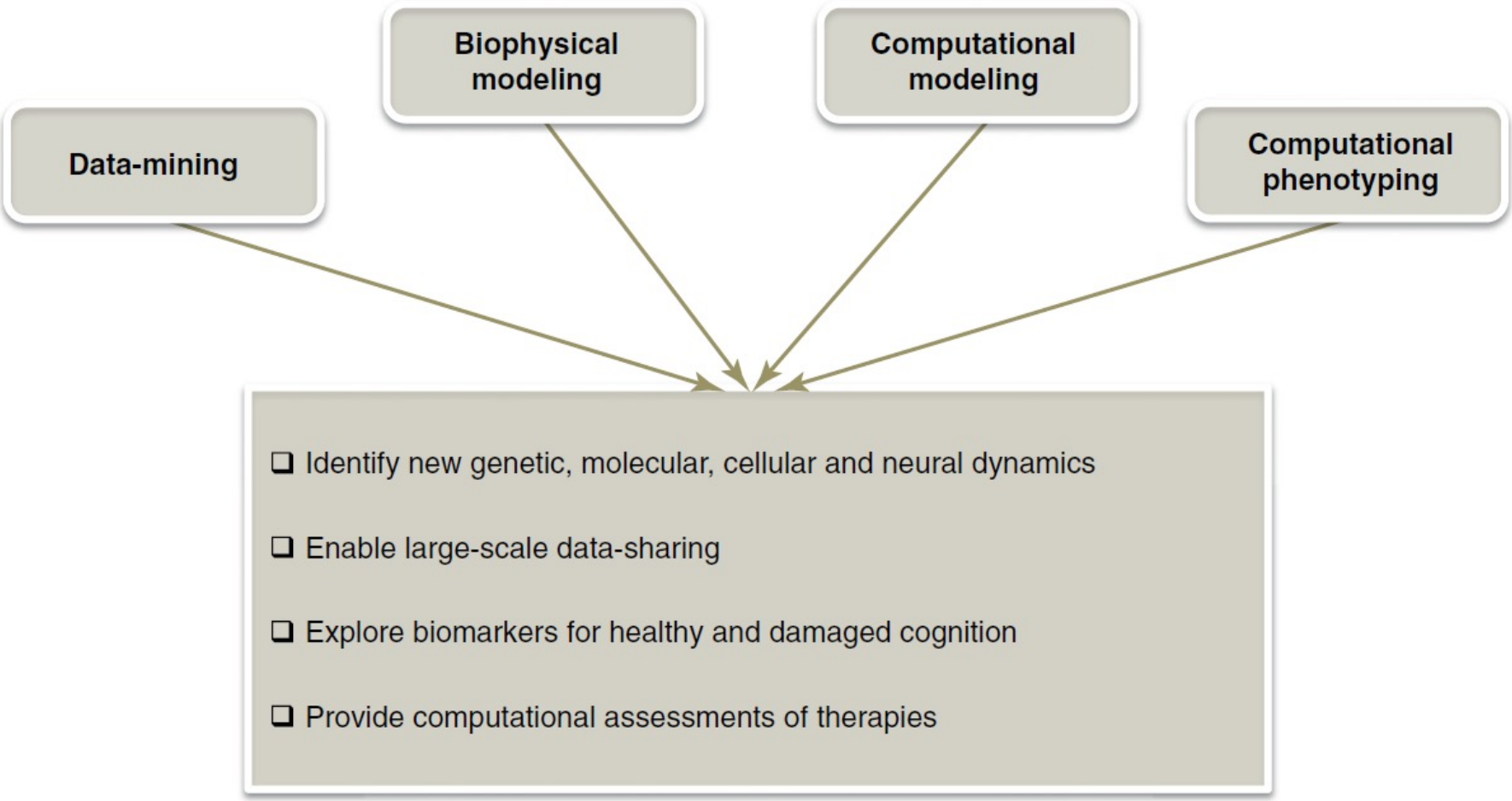
- They are called modulatory because their impact is typically much longer lasting than fast synaptic effects mediated by glutamate and they are much more widely distributed

Computational Psychiatry

"Broad and deep skills across cognitive neuroscience, computational neuroscience, cellular and molecular neuroscience, pharmacology, neurology, and psychiatry itself, in addition to this **computer science and engineering**, are required for the emergence of the richly interdisciplinary field of computational psychiatry"



Computational Psychiatry



Montague et al. TRENDS in Cognitive Sciences 2012

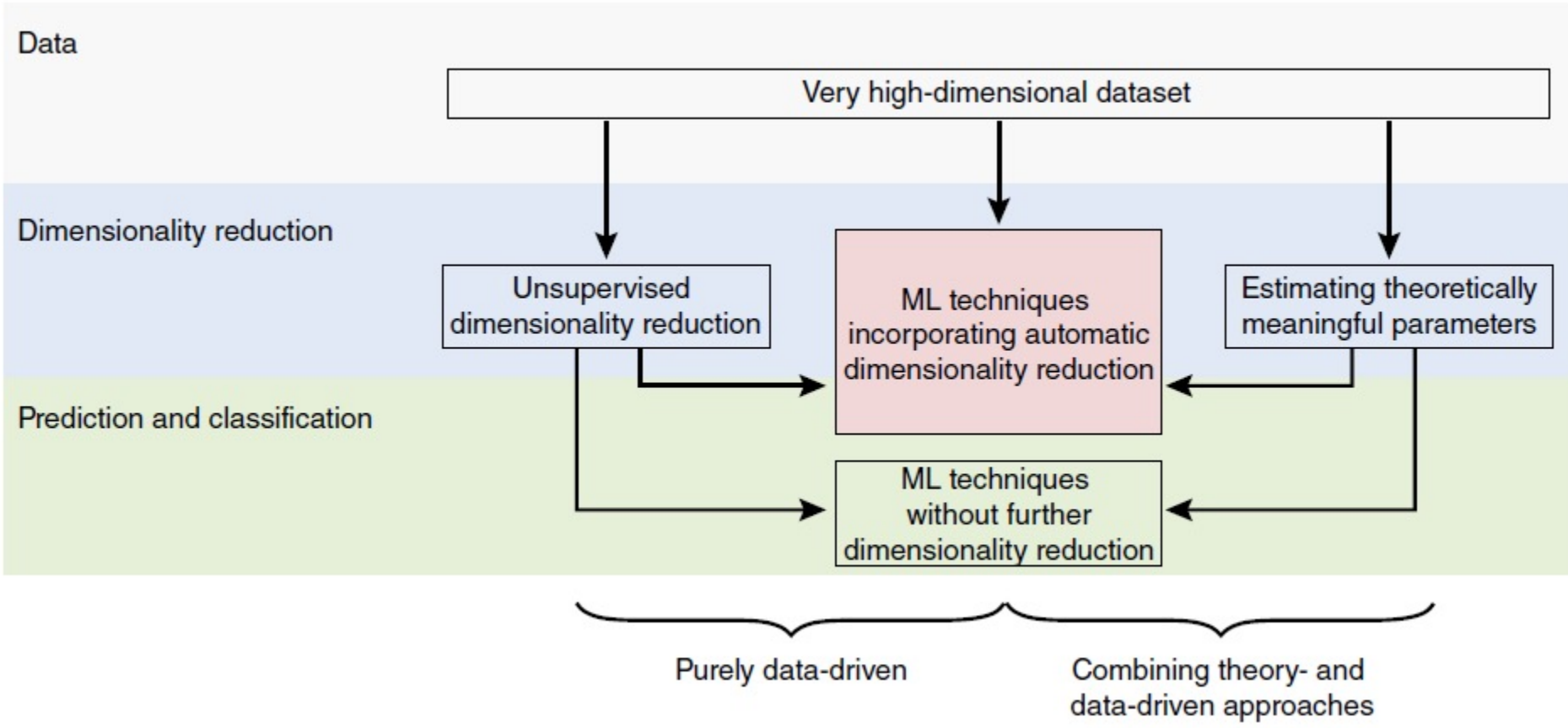
Computational psychiatry as a bridge from neuroscience to clinical applications

Computational psychiatry encompasses two approaches:

- Theory-driven models that mathematically specify mechanistically interpretable relations between variables (often including both observable variables and postulated, theoretically meaningful hidden variables).

- Data-driven, theoretically agnostic data-analysis methods from machine learning broadly construed (including, but extending, standard statistical methods), and

Computational psychiatry as a bridge from neuroscience to clinical applications



Huys et al 2016

Predictive Coding & Psychosis

The Bayesian brain

Bayesian brain can be conceptualized as a probability machine that constantly makes predictions about the world and then updates them based on what it senses.

In this way brains can be considered prediction machines that use information from previous experiences (memory) to predict future events (intelligence) in order to reduce uncertainty, which is important for survival.

“Predictive Coding” is a proposed mechanism of processing in the “Bayesian Brain”

Ridder et al Neuroscience Biobehavioral Reviews 2014;
Friston, 2010; Quartz & Sejnowski, 2002

Jack and Jill event up the hill

The last event evas cancelled

Jack and Jill event up the hill

event

The last event evas cancelled

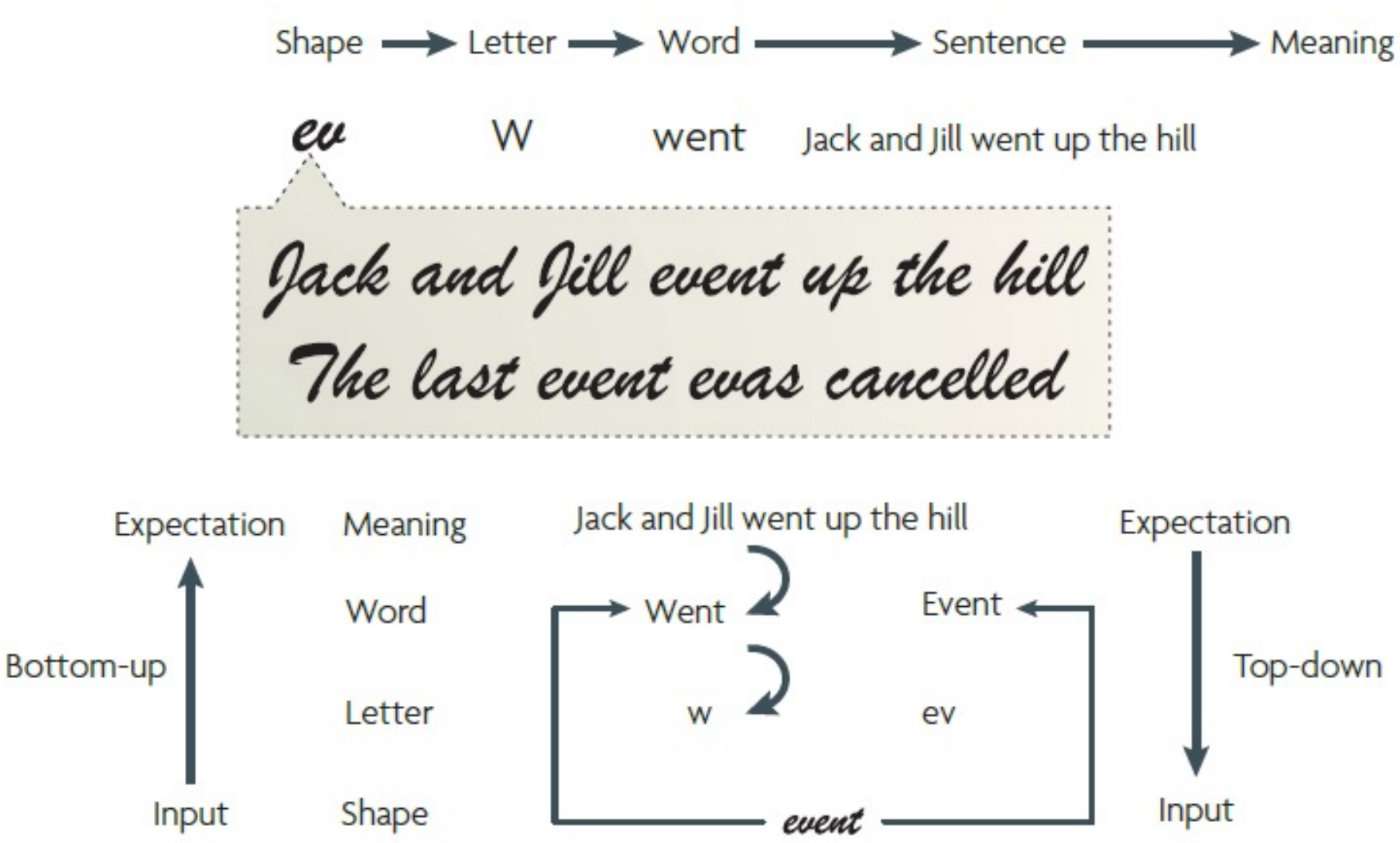
Predictive Coding

Predictive coding is a theory of cognition in which the brain is constantly generating and updating a mental model of sensory input.

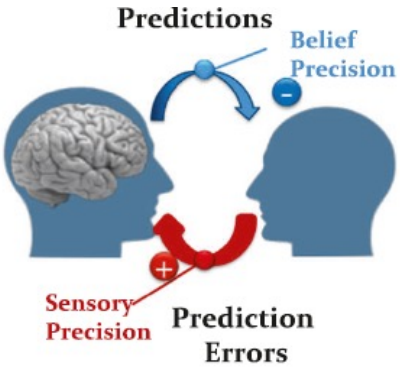
Predictive coding is based on the simple but powerful idea that instead of representing the input directly, it is often preferable to represent the prediction error, the difference (or sometimes the ratio) between a sensory input and a prediction

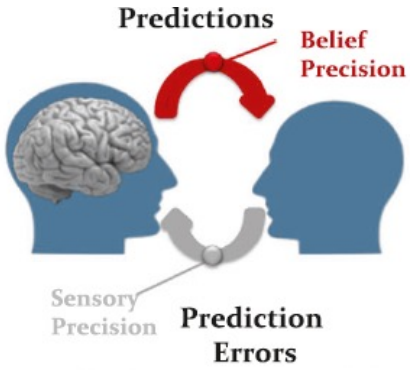
Ridder et al Neuroscience Biobehavioral Reviews 2014;
Friston, 2010; Quartz & Sejnowski, 2002

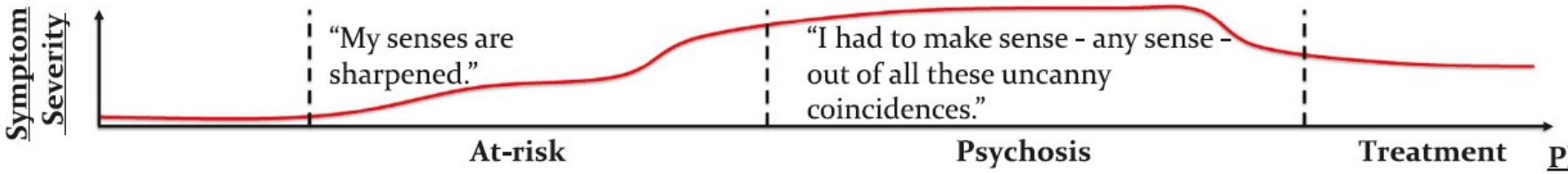
Bayesian Hierarchical Processing – An Illustration

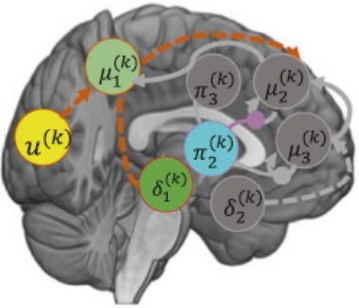


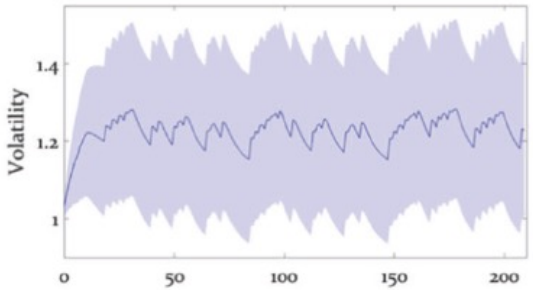
Predictive Coding & Origin of Delusion

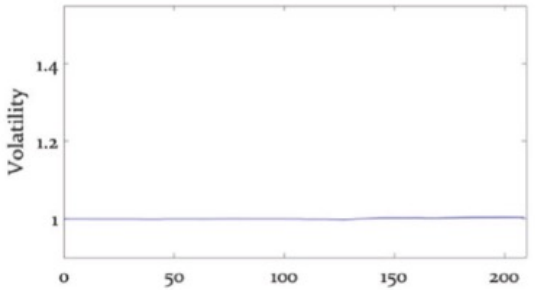


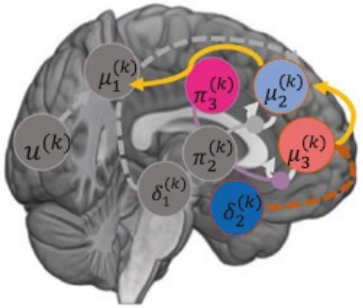


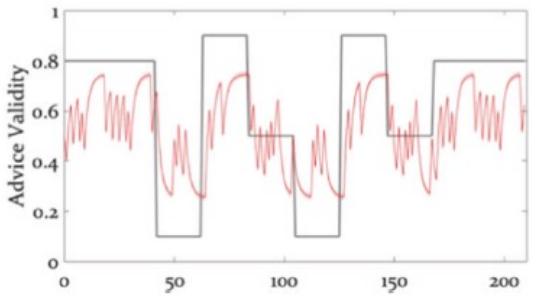


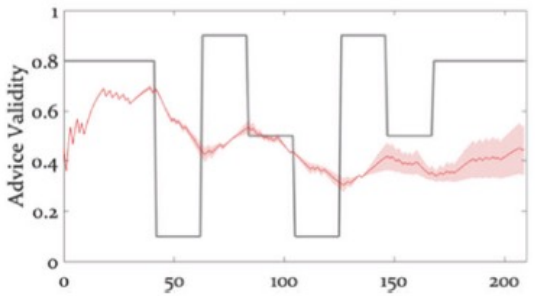












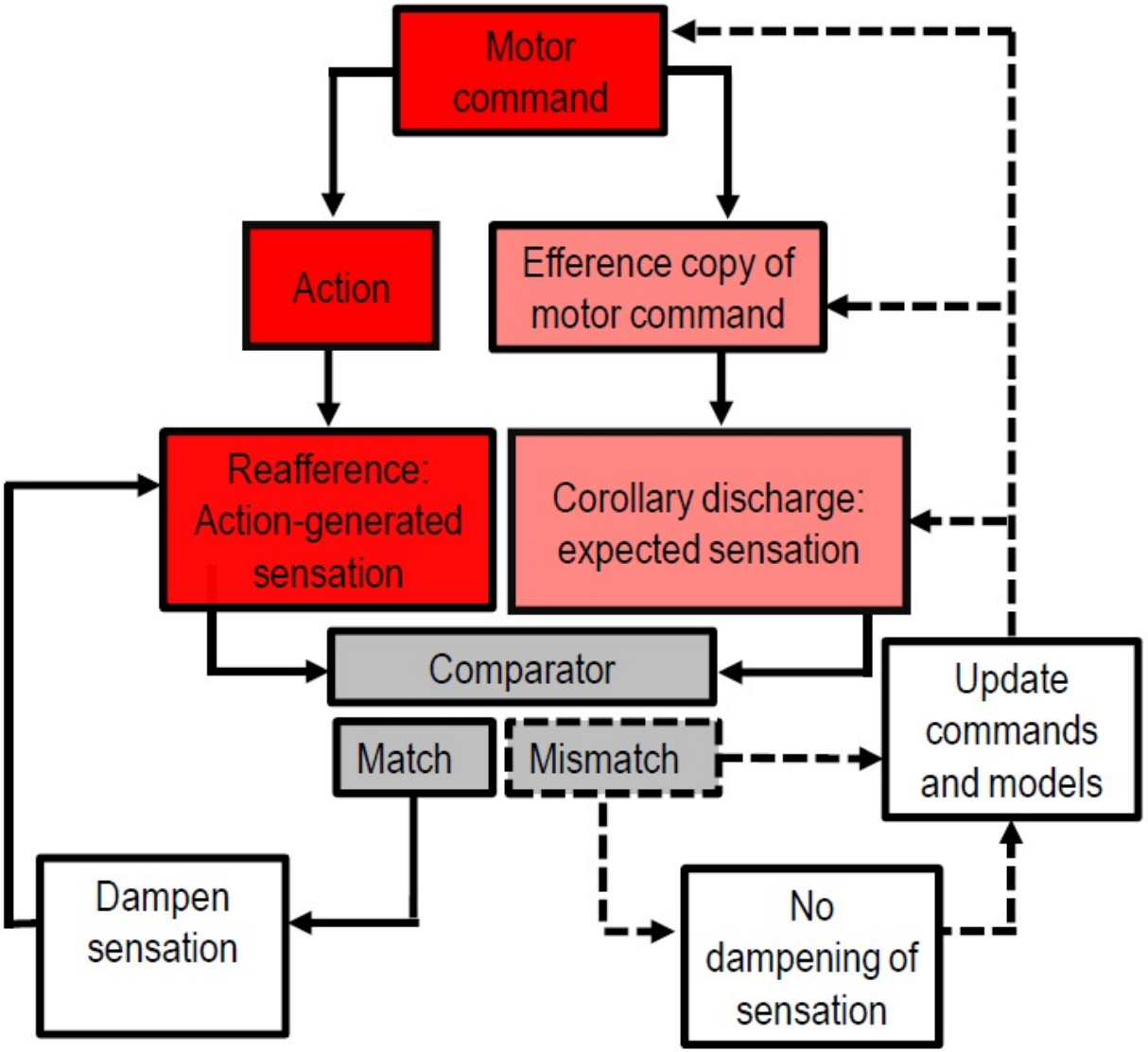
Diaconescu et al. Molecular Psychiatry 2019

Corollary Discharge & Psychosis

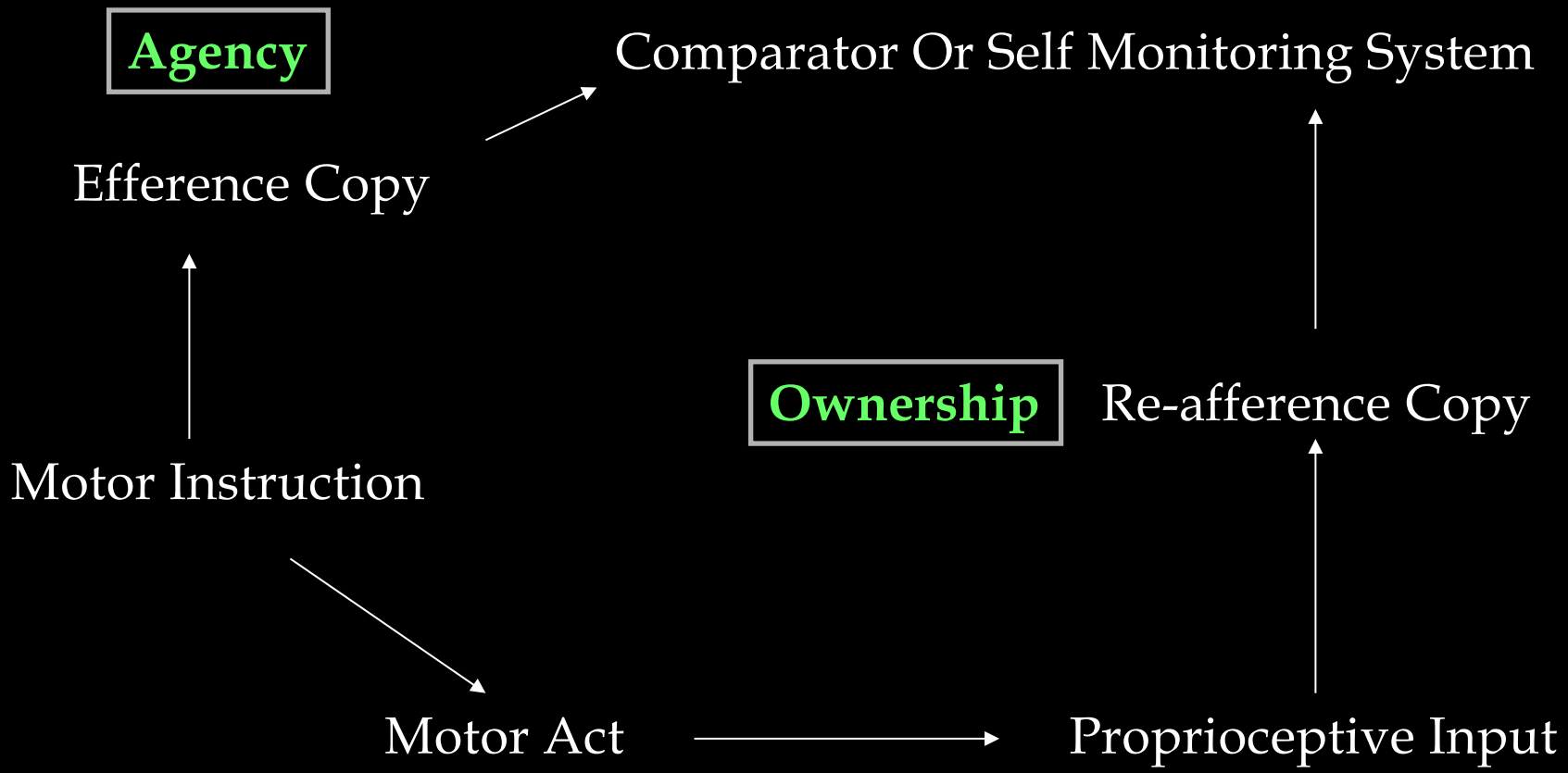
Corollary Discharge: Differentiating Self versus Non-Self

Corollary discharge mechanism refers to the suppression of sensory consequences of self-generated actions;
this serves to distinguish between self and non-self based on discrimination of origination of action

Corollary Discharge – An Example of Motor Action

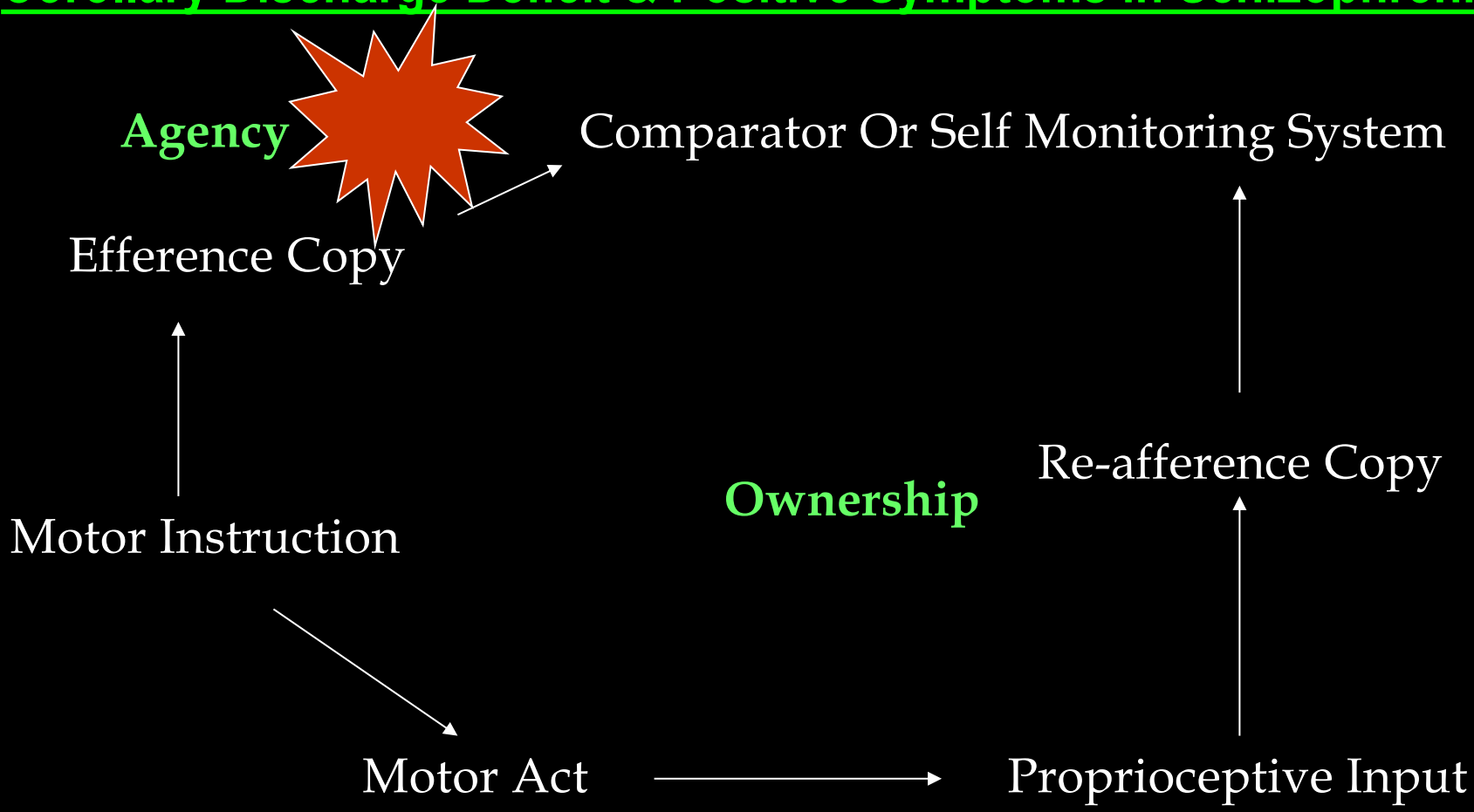


Corollary Discharge



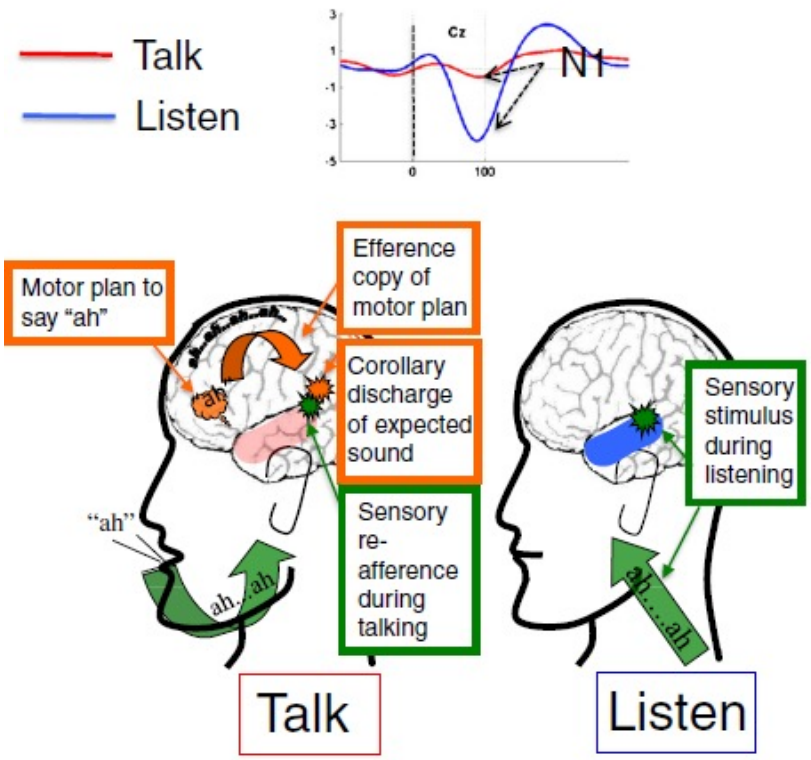
Parlikar, Bose, Venkatasubramanian 2019

Corollary Discharge Deficit & Positive Symptoms in Schizophrenia



Parlikar, Bose, Venkatasubramanian 2019

Corollary Discharge – Vocalization



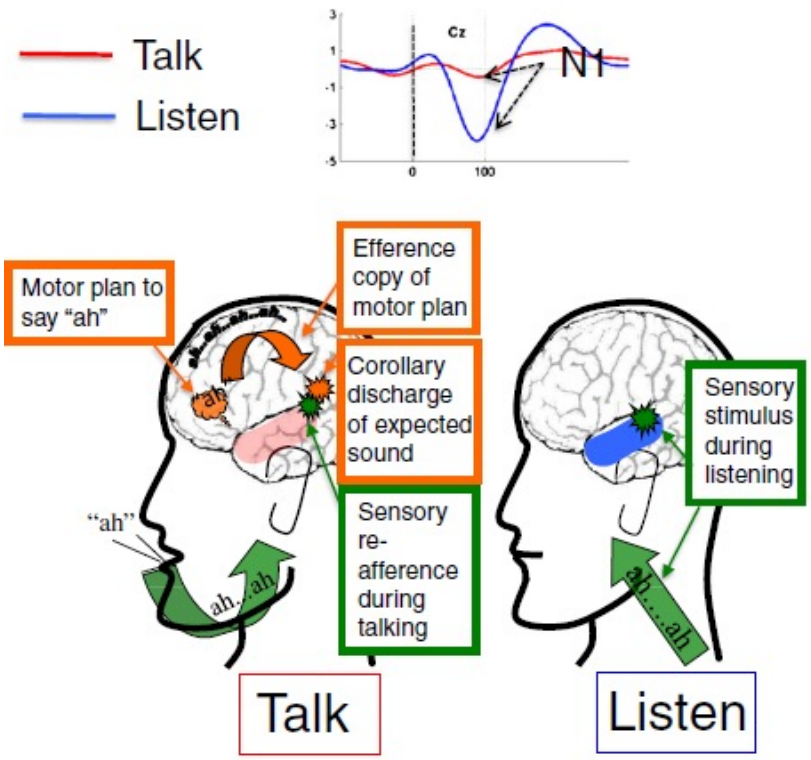
During vocalization, efference copy of the motor plan is generated in the vocalization regions in frontal cortex.

This efference produces a corollary discharge of the expected sensation in auditory cortex

When the expected sensation (corollary discharge) matches the actual sensation (sensory reafference) in auditory cortex, perception is suppressed.

Ford & Mathalon, I J Psychophysiology 2012

Corollary Discharge – Vocalization



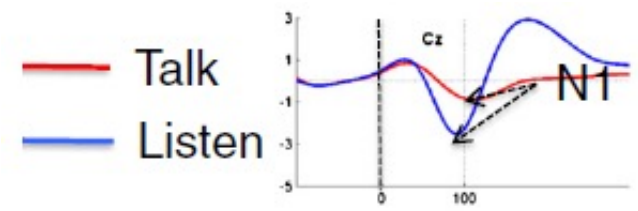
During talking, N1 to the speech sound is suppressed relative to N1 to the same sound during listening

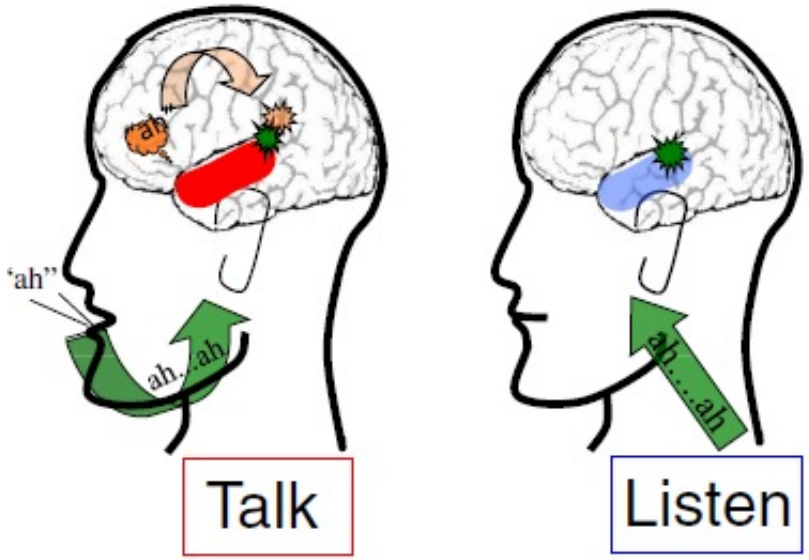
This applies to covert sub-vocalization as well

Corollary discharge provides a mechanism to differentiate "self-generated" versus "externally-generated"

Ford & Mathalon, I J Psychophysiology 2012

Corollary Discharge Deficits in Schizophrenia





In schizophrenia patients, with a relative failure of the efference copy and corollary discharge is deficient.

Lack of attenuation of N1.

This results in relatively less suppression of the auditory cortical response to the spoken sound.

Hence, self-generated talk (for example sub-vocalization) might be perceived as externally generated.

Ford & Mathalon, I J Psychophysiology 2012

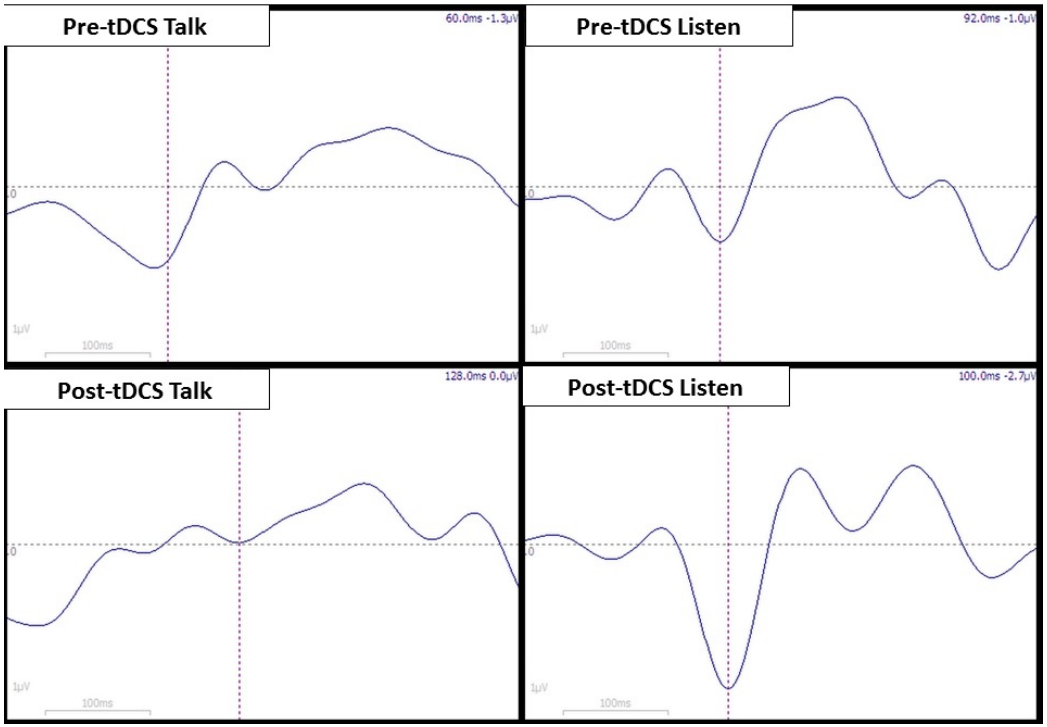
Genesis of Hallucinations: Integrating Predictive Coding & Corollary Discharge

- Deficient corollary discharge drives (possibly compensatory) generation and maintenance of predictions about sensory events that are less susceptible to modification by prediction errors.

- Thus, deficient corollary discharge may result in the overreliance on predictions (Bayesian "prior probabilities") that auditory events have occurred (which, in reality, have not occurred) in individuals with auditory verbal hallucinations

Ford & Mathalon 2019

Effect of tDCS:
Correcting Corollary Discharge Deficits in Schizophrenia



Hema

Anushree

There was a significant effect of tDCS on the N100 during the talk versus listen conditions indicating correction of a corollary discharge abnormality in schizophrenia with associated significant reduction in severity of auditory hallucinations

Nawani et al. Brain Stimulation 2014

Effect of fronto-temporal transcranial direct current stimulation on corollary discharge in schizophrenia: A randomized, double-blind, sham-controlled mediation analysis study☆

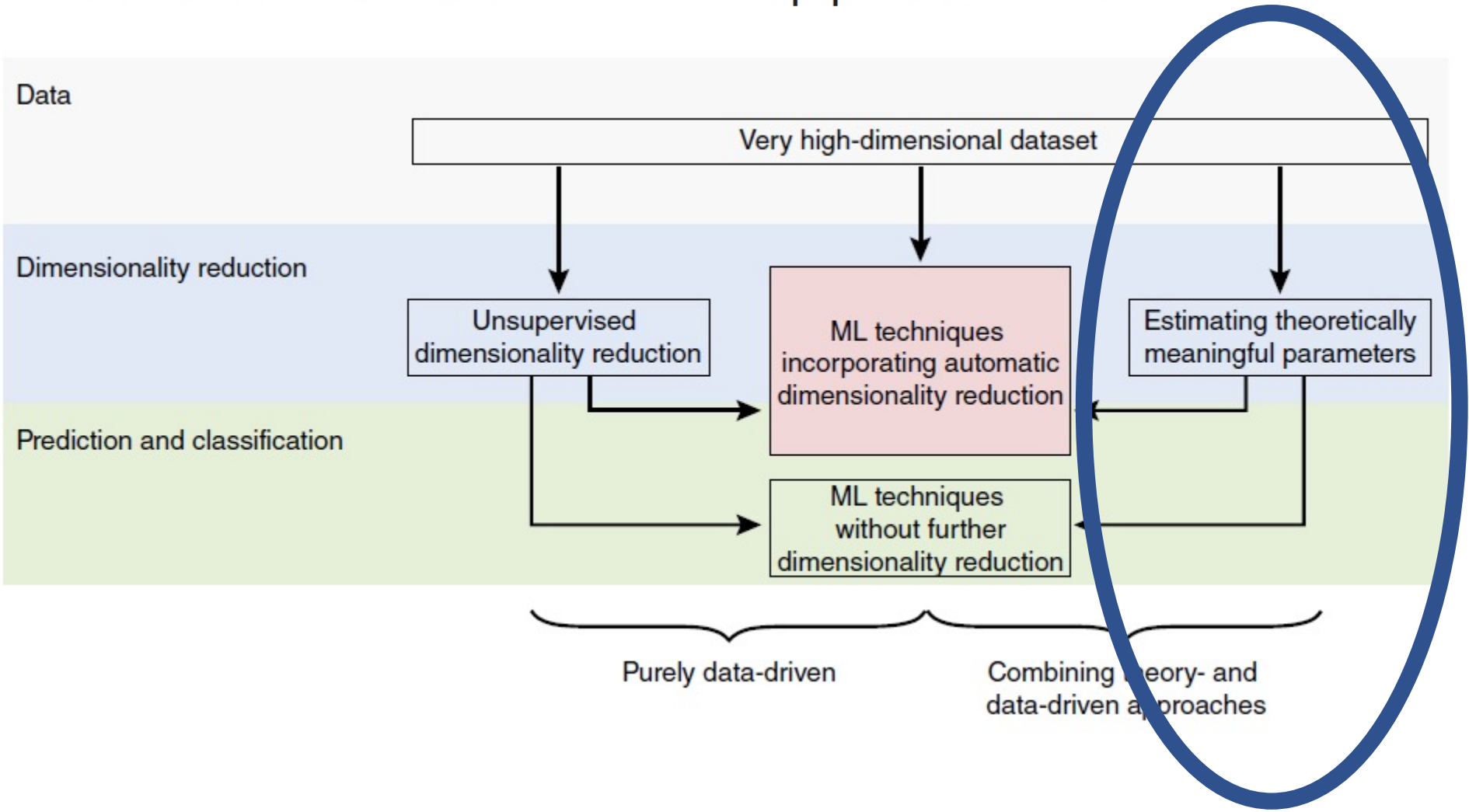
Anushree

Hema

"correction of the deficient corollary discharge might be one of the mechanisms underlying the beneficial effects of add-on frontotemporal tDCS on auditory verbal hallucinations in schizophrenia"

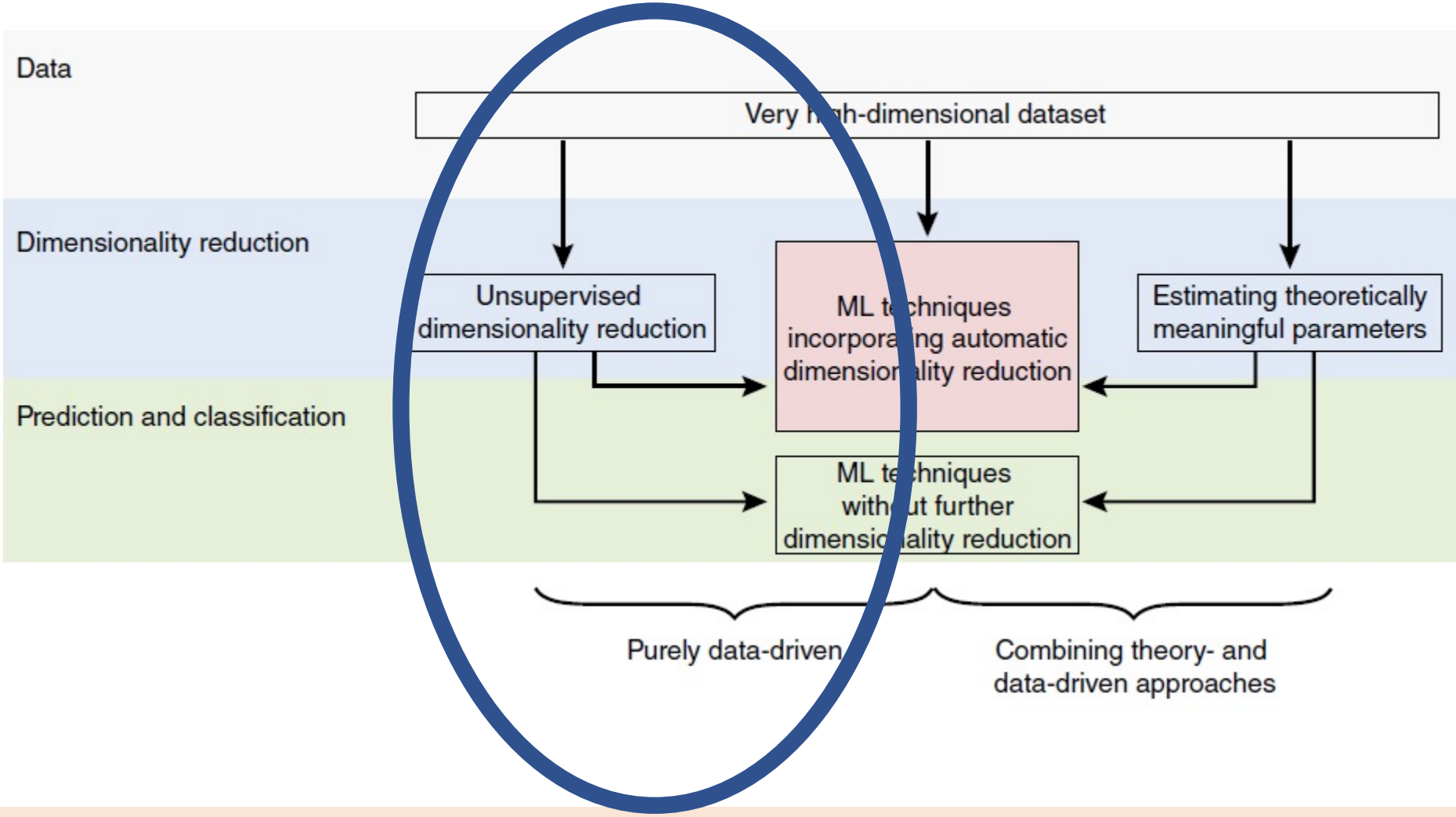
Bose et al 2018

Computational psychiatry as a bridge from neuroscience to clinical applications



Huys et al 2016

Computational psychiatry as a bridge from neuroscience to clinical applications



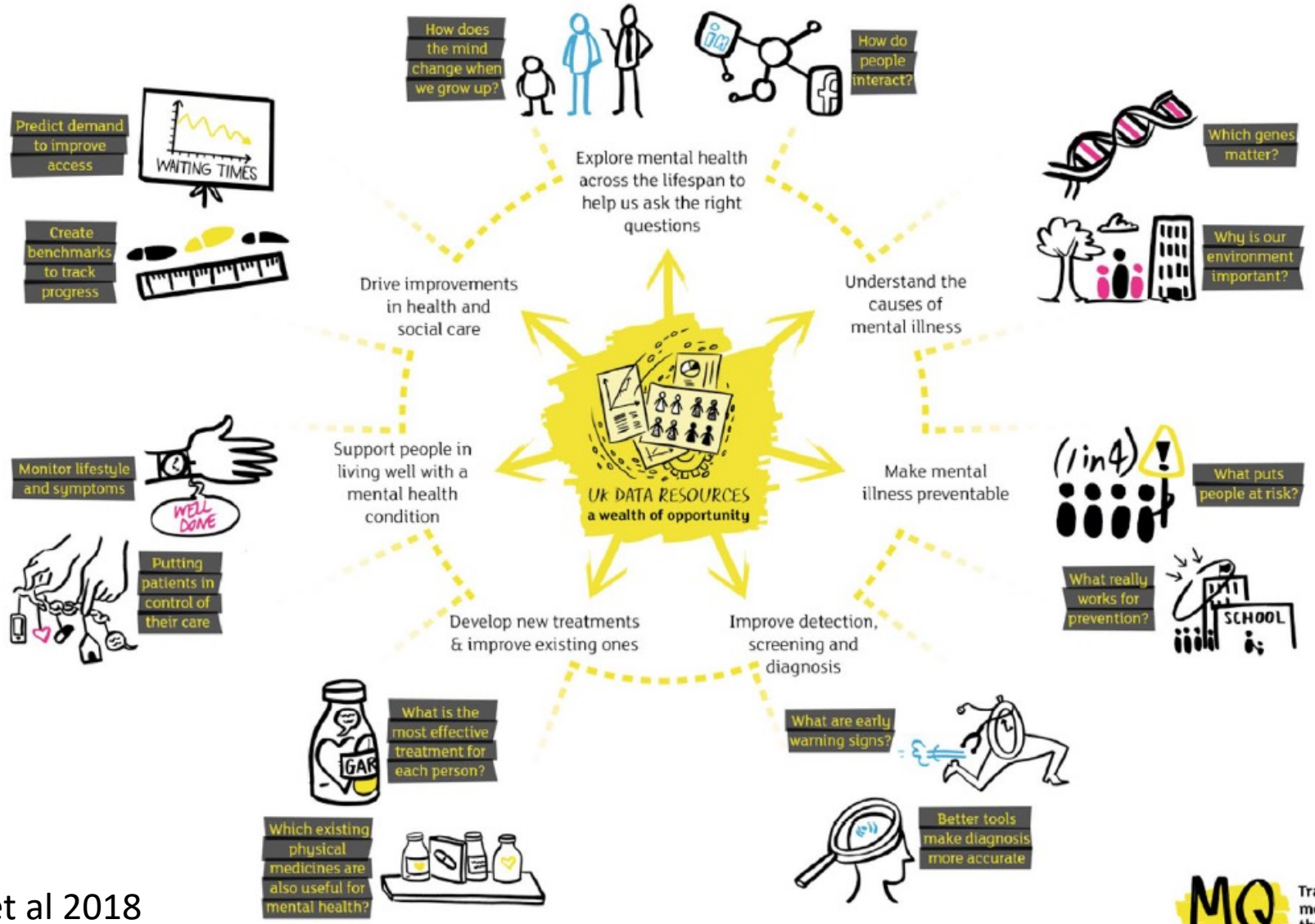
Huys et al 2016

Data Science & Psychiatry

nature human behaviour

What can data science do for mental health research?

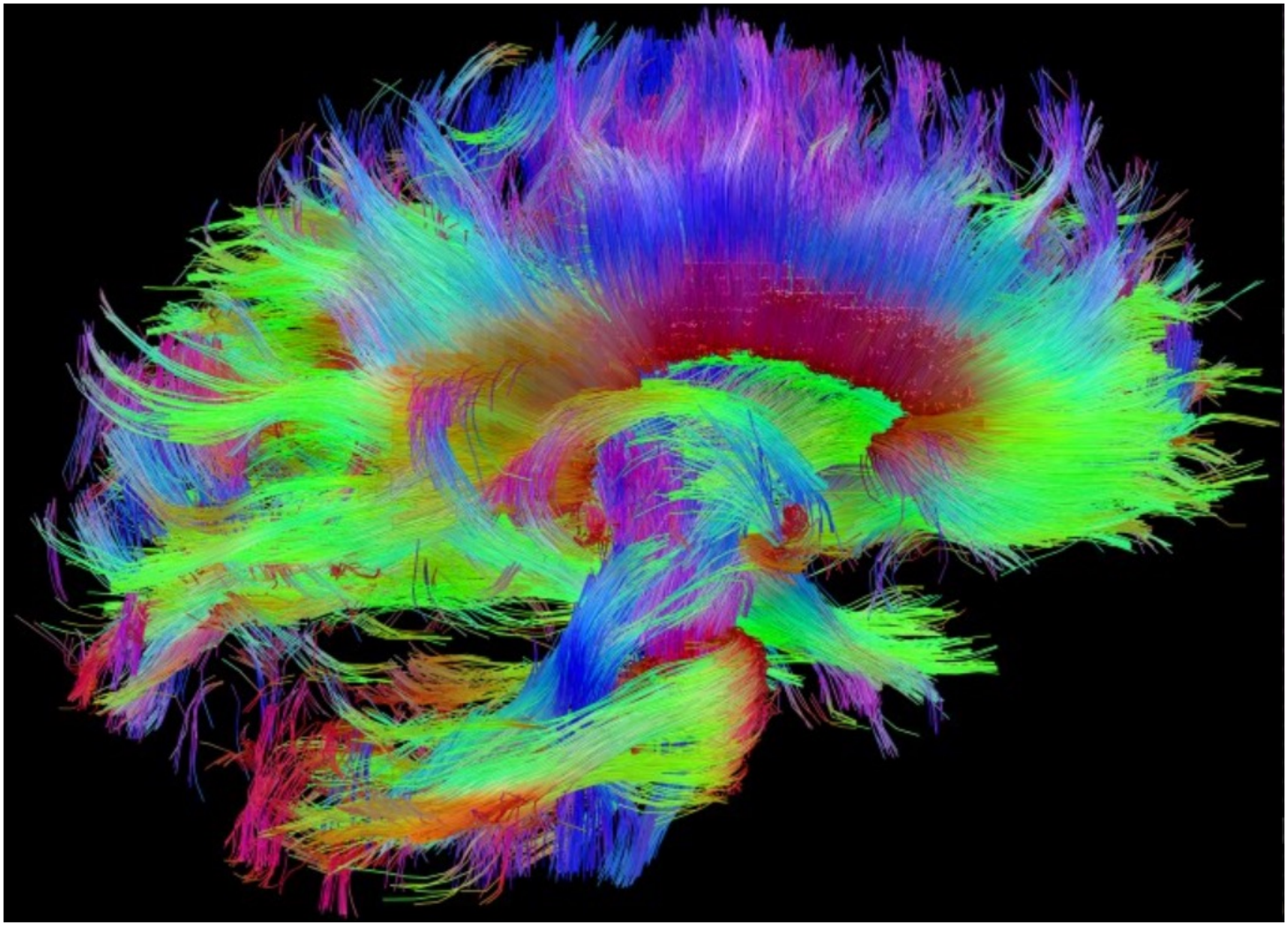
Data science and is key to improving diagnosis, transforming treatments, and ultimately making mental illness preventable.



Russ et al 2018

MQ Transforming mental health through research

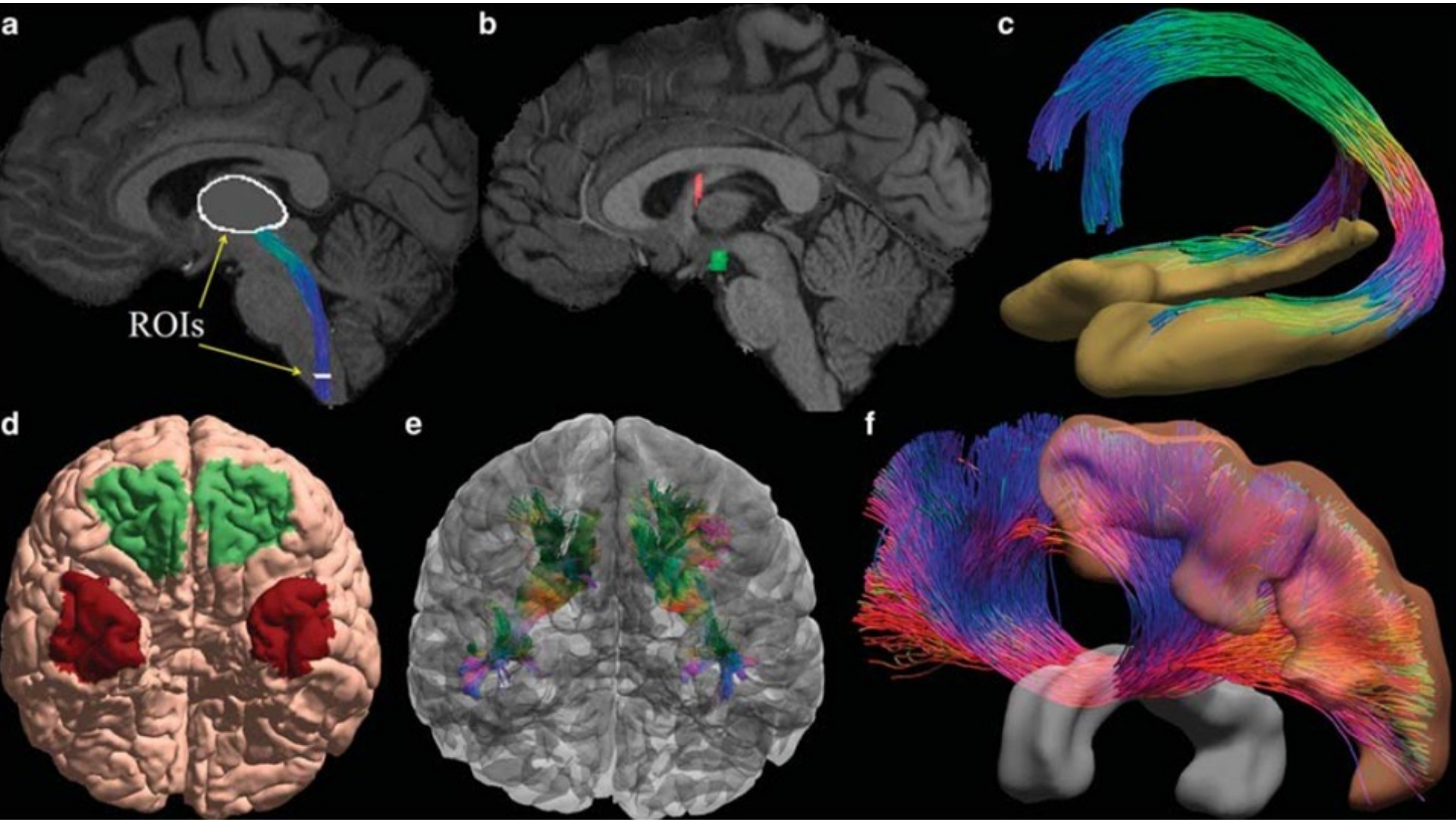
Brain – A Complex System of Networks



Human brain, perhaps the most complex network, comprises about 100 billion (10^{11}) neurons connected by about 100 trillion (10^{14}) synapses packed within the skull volume of 1.5 L

Buzsaki, Rhythms of the Brain; http://www.humanconnectomeproject.org

Brain – “The Connectome”



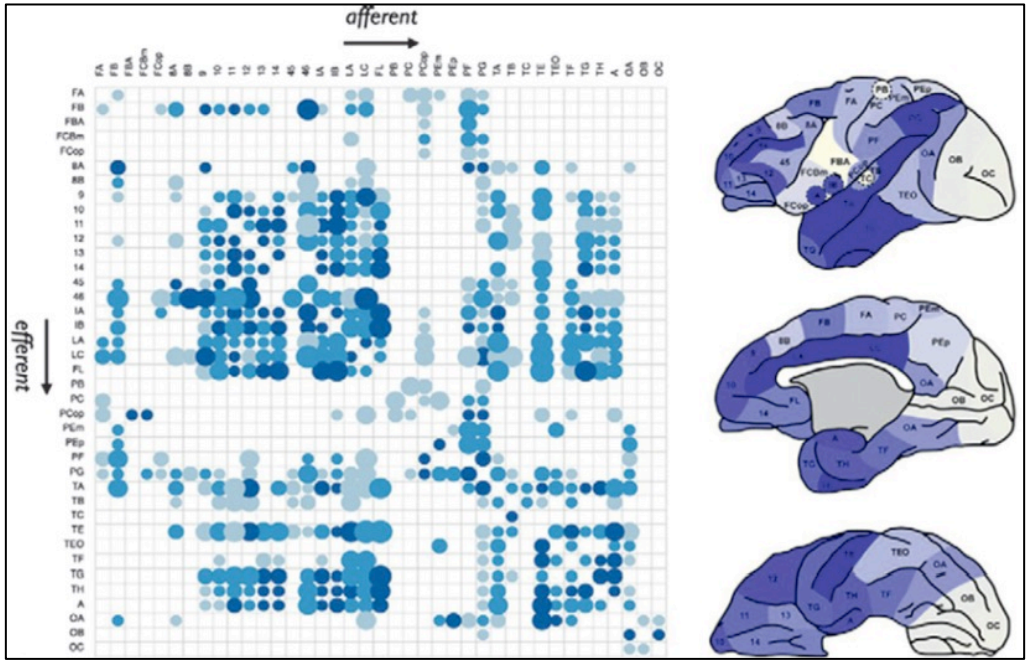
Connectome – A comprehensive Map of Neural Connections in the Brain

http://www.humanconnectomeproject.org

Brain Connectome

Connectome defines a matrix representing all possible pairwise anatomical connections between neural elements of the brain

A consistent conceptual focus on quantifying, visualizing, and understanding brain network organization across multiple scales of space and time is a fundamental characteristic of the burgeoning field of connectomics (Bullmore and Sporns, 2009).



The convergence of two powerful trends underlies the emergence of connectomics:

1. The mathematical and conceptual developments in complex network science
2. The evolution of technologies for measuring nervous systems

Fornito, Zalesky & Bullmore. Fundamentals of Brain Network Analysis 2016

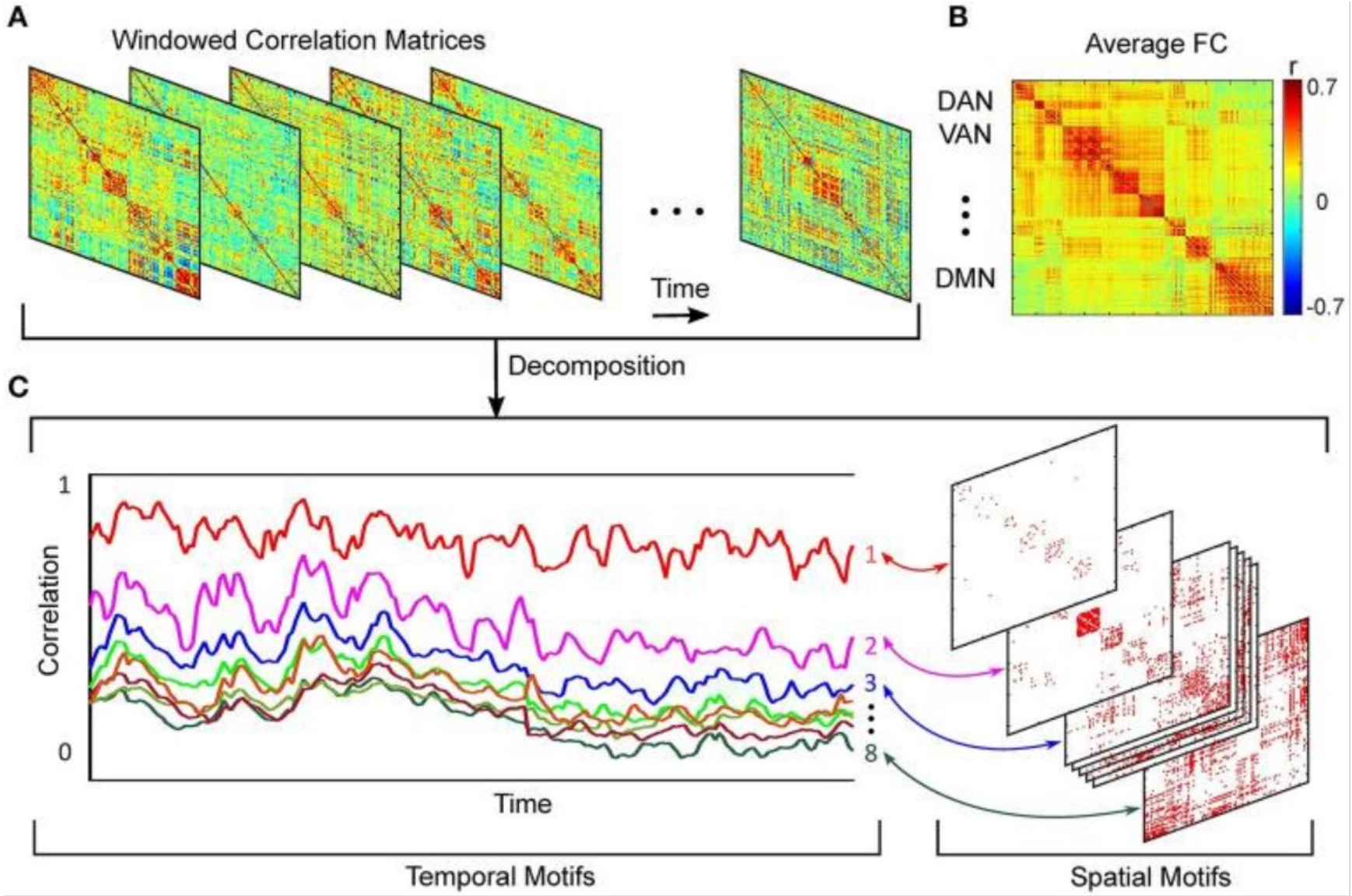
Beyond Connectome: The Brain Dynome

Beyond the Connectome: The Dynome

- The human connectome will provide a detailed mapping of the brain's connectivity, with fundamental insights for health and disease.
- However, further understanding of brain function and dysfunction will require an integrated framework that links brain connectivity with brain dynamics, as well as the biological details that relate this connectivity more directly to function.
- This integrated framework is called as the brain's "**dynome**".

Kopell et al 2014

Brain: Dynamic Functional Connectome



Kafashan et al 2016

Data Science & Psychiatry
Big Data Analysis

Distinct Subcortical Volume Alterations in Pediatric and Adult OCD: A Worldwide Meta- and Mega-Analysis

ENIGMA OCD

Study Principal Investigator	Site	Field Strength (teslas)	Age (years)				Male (%)		Control Subjects (N)	OCD Patients (N)	Total (N)
			Control Subjects		OCD Patients						
			Mean	SD	Mean	SD	Control Subjects	OCD			
Reddy	Bangalore I	1.5	27.2	6.4	27.5	6.3	74	59	46	44	90
	Bangalore II	3.0	26.3	5.0	29.6	8.0	62	52	156	208	364

T1 images from 1,830 OCD patients and 1,759 control subjects were analyzed, using coordinated and standardized processing, to identify subcortical brain volumes that differ between OCD patients and healthy subjects

The pallidum and hippocampus seem to be of importance in adult OCD, whereas the thalamus seems to be key in pediatric OCD. These findings highlight the potential importance of neurodevelopmental alterations in OCD and suggest that further research on neuroplasticity in OCD may be useful.

Boedhoe et al 2016

Cortical Abnormalities Associated With Pediatric and Adult Obsessive-Compulsive Disorder: Findings From the ENIGMA Obsessive-Compulsive Disorder Working Group

ENIGMA OCD

T1-weighted MRI scans of 1,905 OCD patients and 1,760 healthy controls from 27 sites worldwide were processed locally using FreeSurfer to assess cortical thickness and surface area

The parietal cortex was consistently implicated In both adults and children with OCD.

More widespread cortical thickness abnormalities were found in medicated adult OCD patients, and more pronounced surface area deficits (mainly in frontal regions) were found in medicated pediatric OCD patients.

These cortical measures represent distinct morphological features and may be differentially affected during different stages of development and illness, and possibly moderated by disease profile and medication

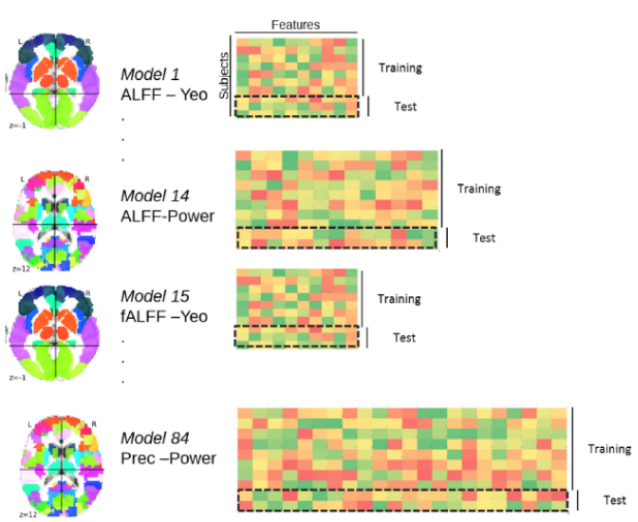
Boedhoe et al 2018

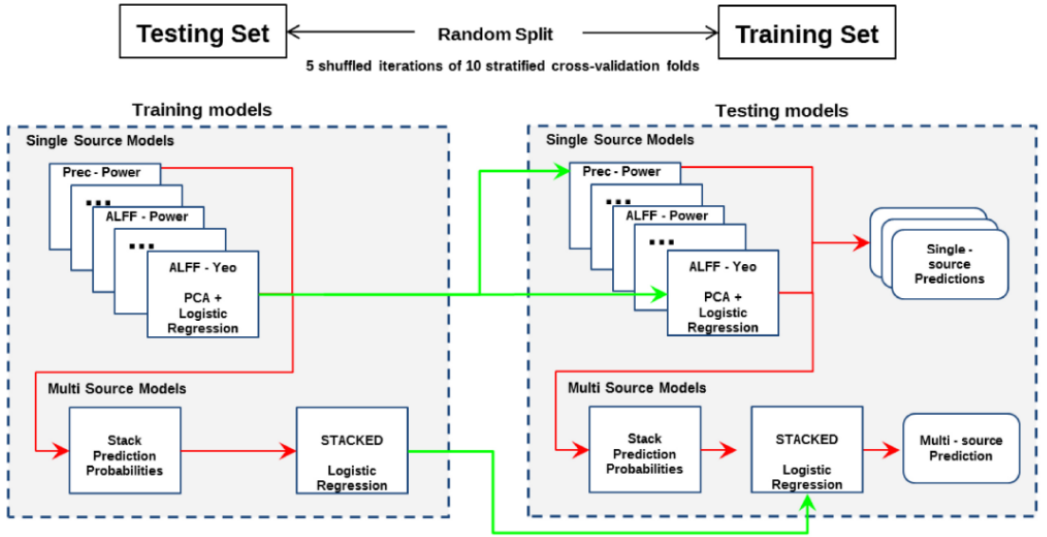
D-SNIP Program
Data Science informed Neurobiology & Interventions in Psychiatry

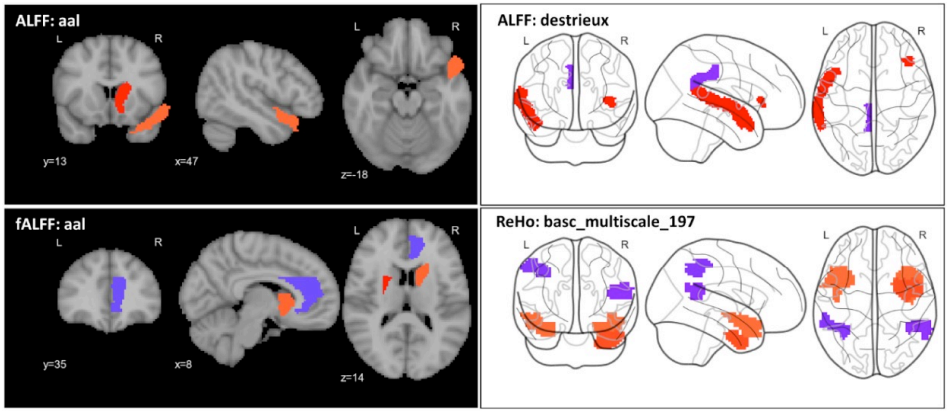
Diagnosis of Schizophrenia through Machine Learning

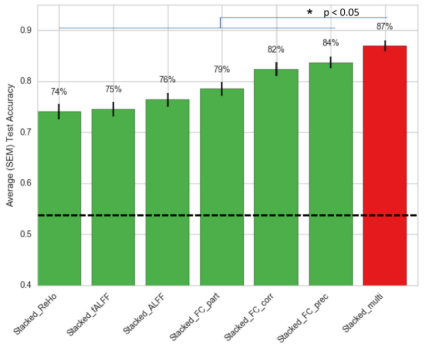
Computational Psychiatry: Illustrative Application of Machine Learning

Resting State fMRI Data Analysis using Machine Learning:
Schizophrenia vs Controls (87% Classification Accuracy)
Differentiating Brain Regions are implicated in predictive coding & corollary discharge





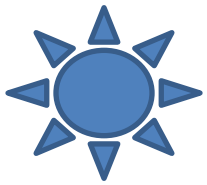




Kalmady… Venkatasubramanian, NPJ Schizophrenia 2019

D-SNIP Program
Data Science informed Neurobiology & Interventions in Psychiatry

Personalized Neuromodulation with tDCS



D-SNIP Program
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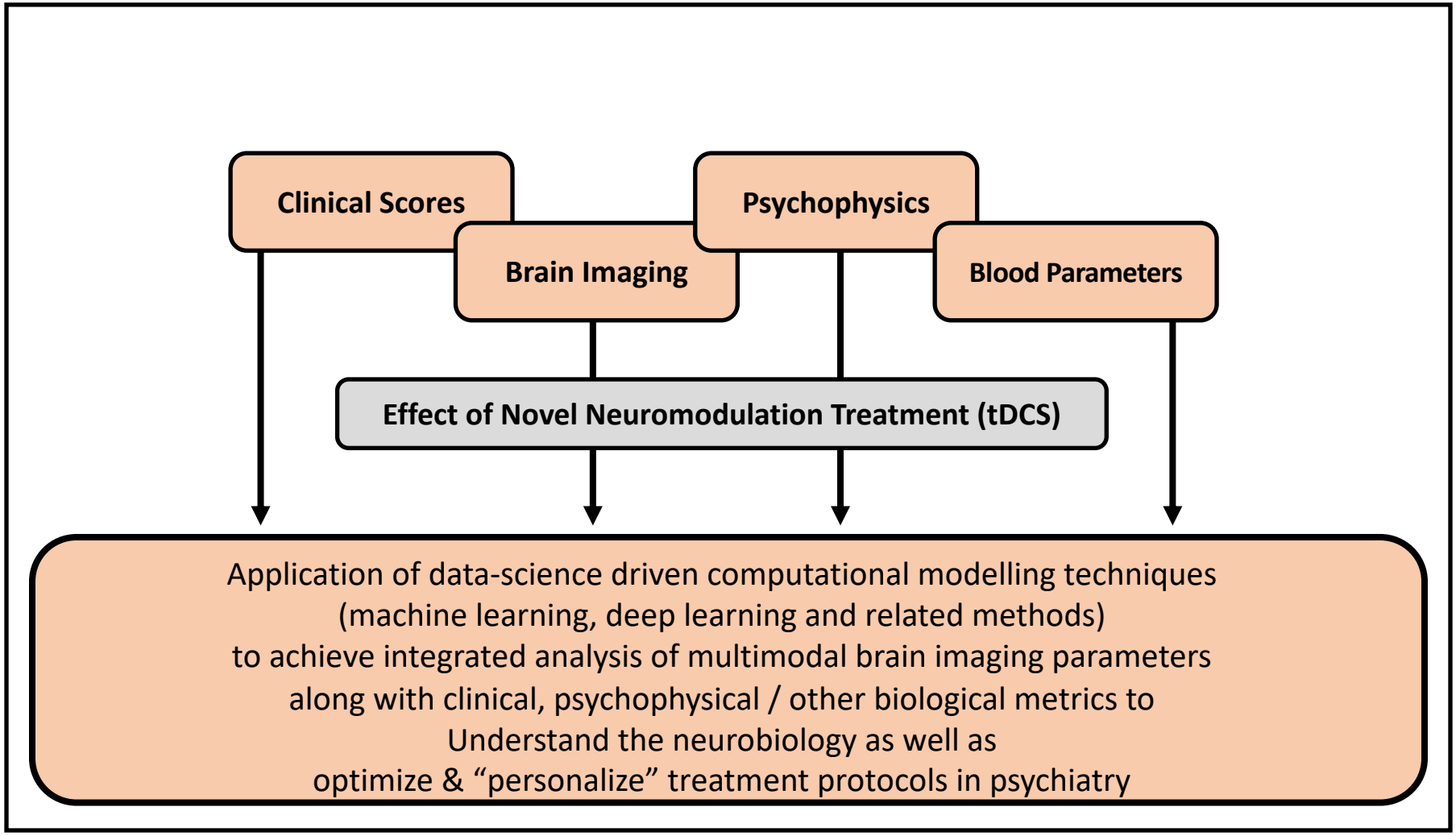


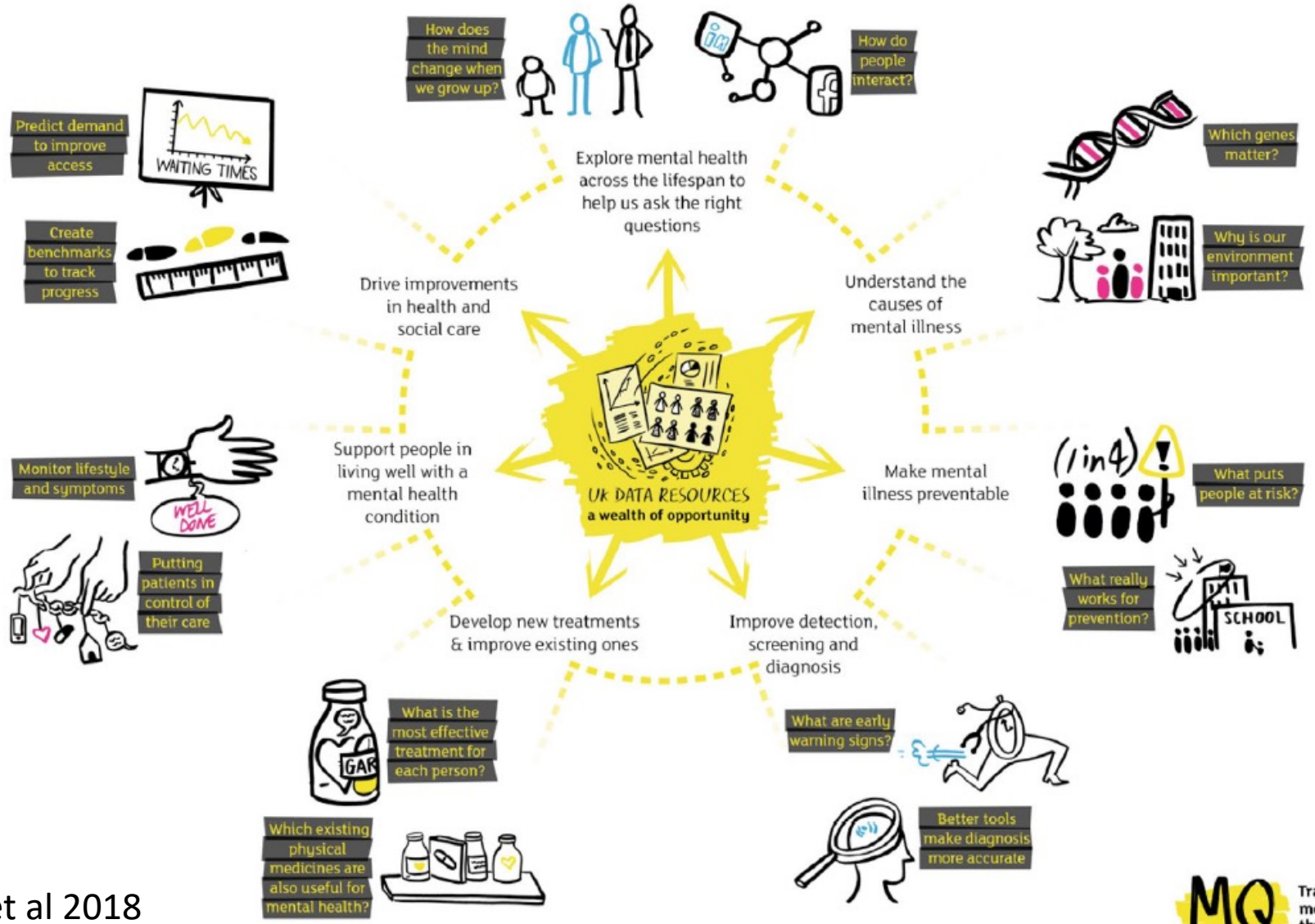
Data Science & Digital Psychiatry

Opportunities & Challenges

nature human behaviour

What can data science do for mental health research?

Data science and is key to improving diagnosis, transforming treatments, and ultimately making mental illness preventable.

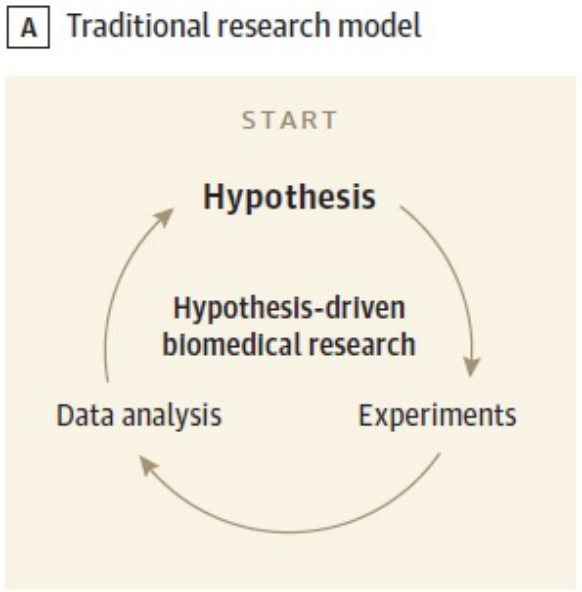


Russ et al 2018

MQ Transforming mental health through research

Informatics, Data Science, and Artificial Intelligence

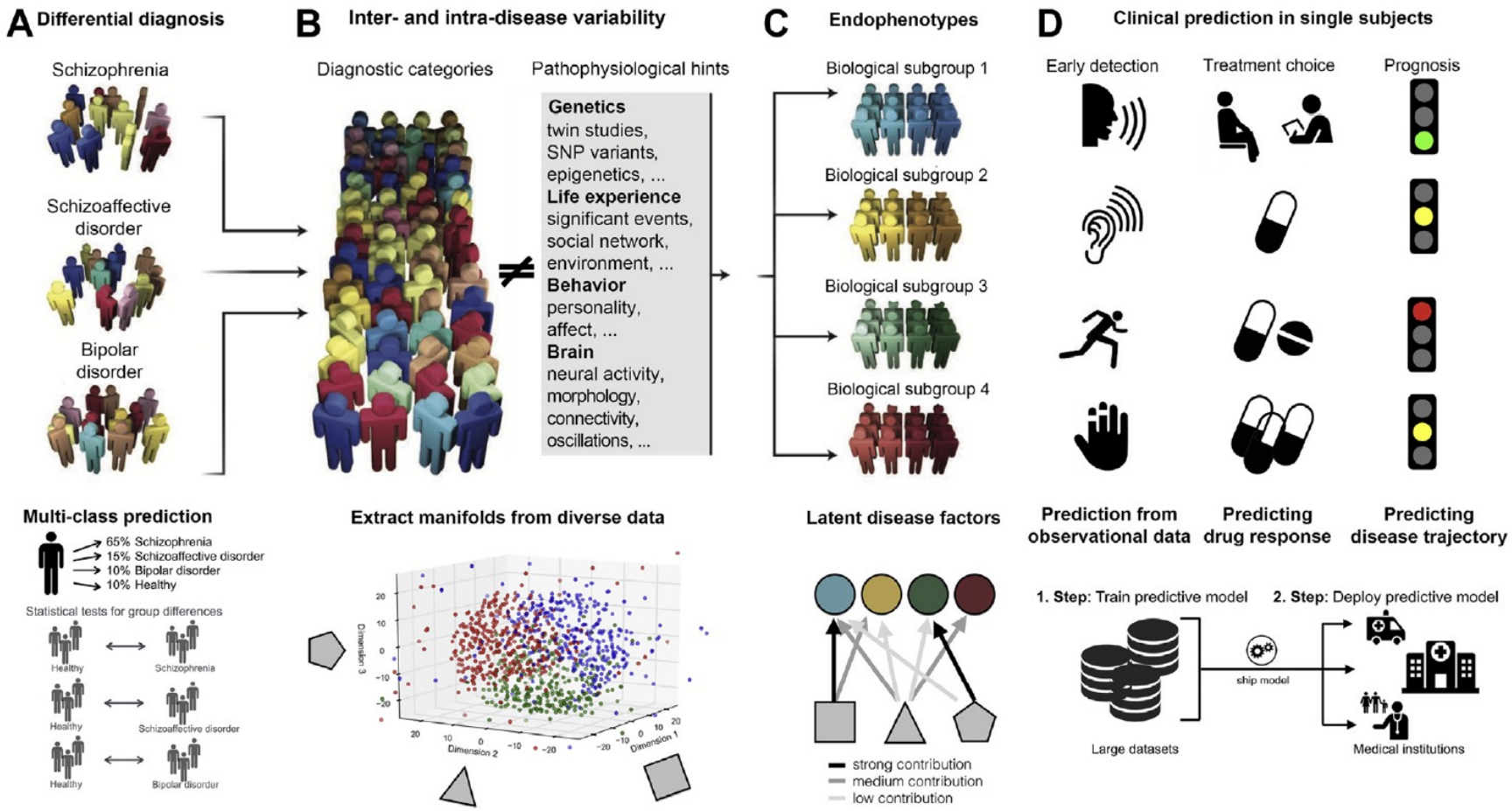
Traditionally, most biomedical researchers use their knowledge to generate a hypothesis, design experiments or clinical studies to test the hypothesis (Model – A).
With huge amounts of data becoming available, and advanced analysis tools such as artificial intelligence, biomedical research is driven more and more by data (Model – B).



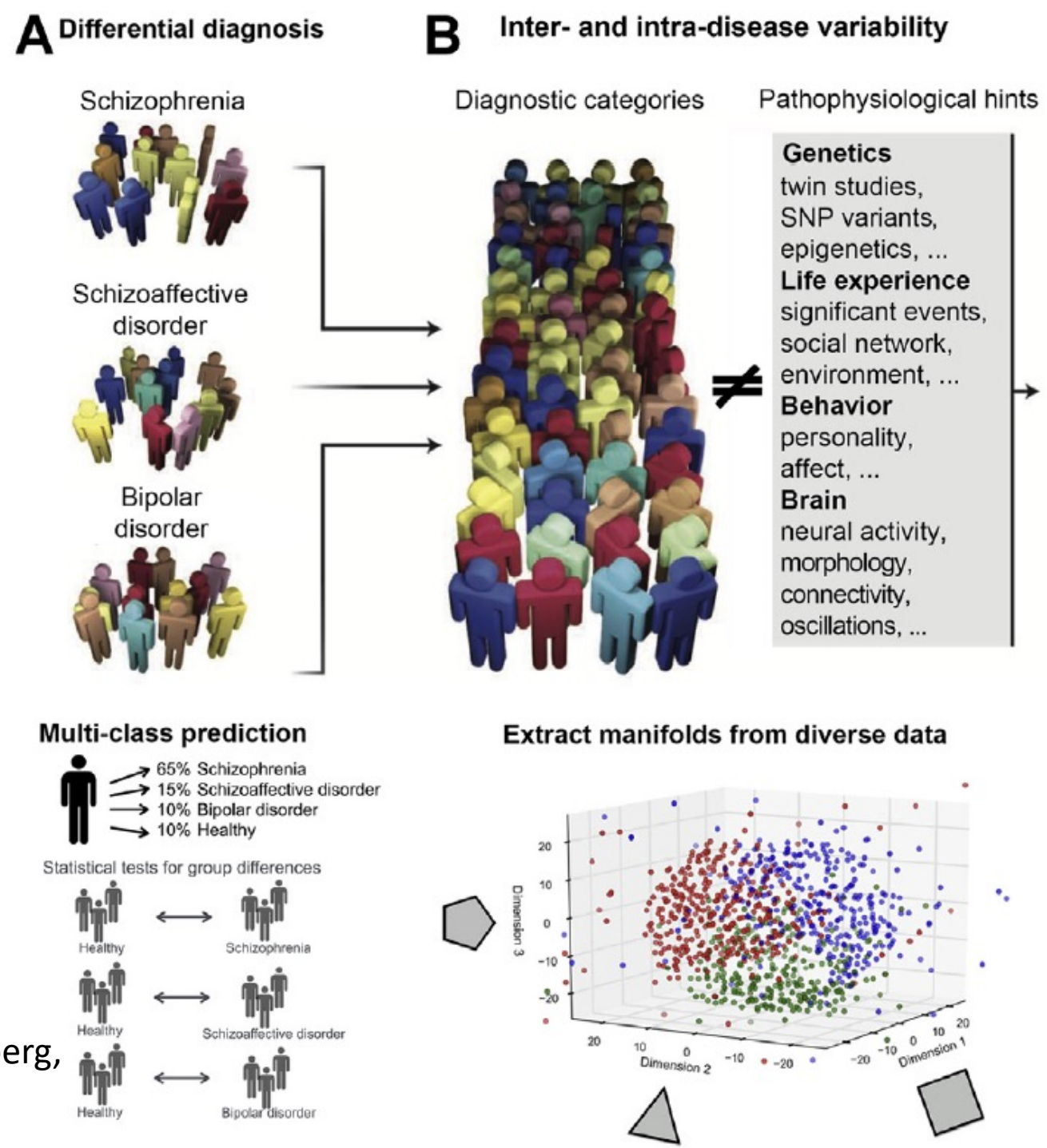
Zhu & Zheng, 2018

Machine Learning for Precision Psychiatry: Opportunities and Challenges

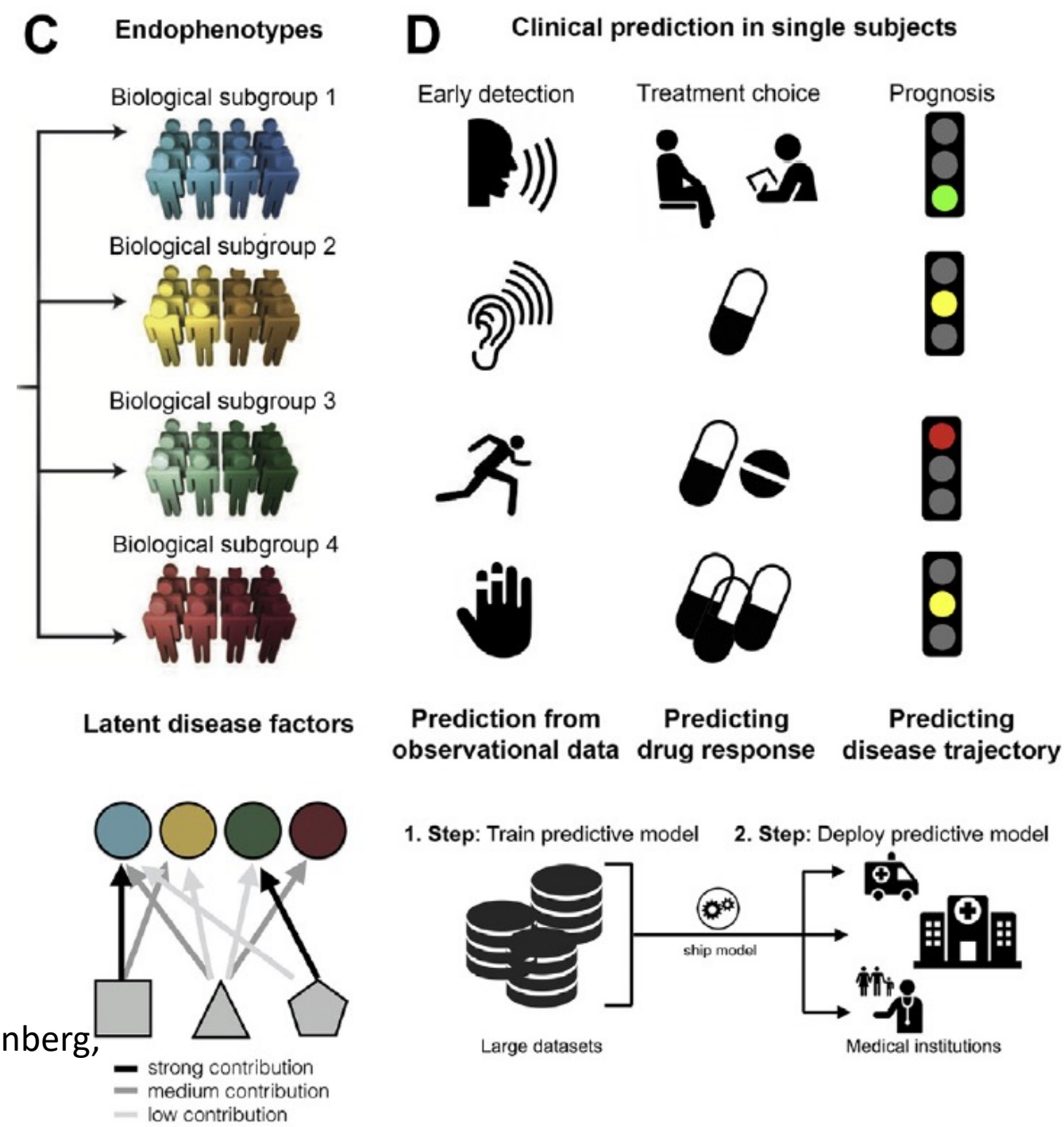
Bzdok and Meyer-Lindenberg, 2018



- Reproducibility
- Data Availability
- Heterogeneous & Incomplete Data
- Longitudinal Data
- Data Management
- Confounding Factors



Bzdok & Meyer-Lindenberg, 2018



Bzdok & Meyer-Lindenberg, 2018

Unintended Consequences of Machine Learning in Medicine

Cabitza et al 2017

Potential to reduce the skill of physicians

Intrinsic Uncertainty in Medicine

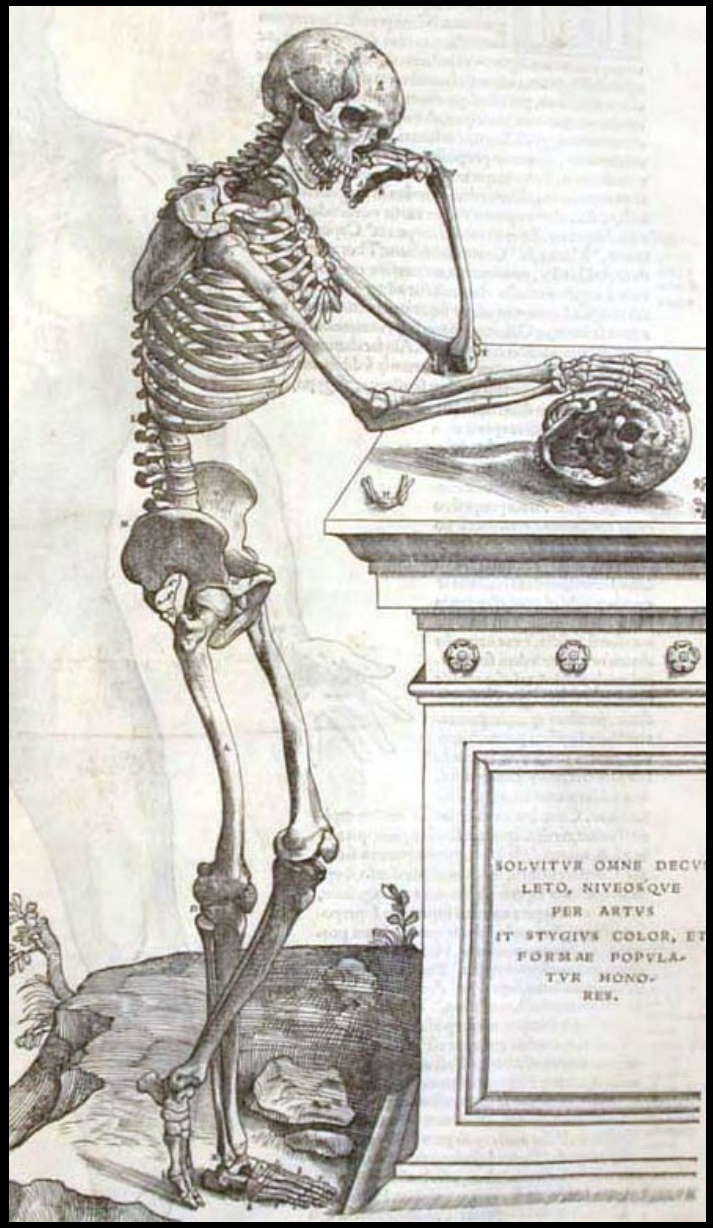
Need to open the ‘black box’ of machine learning

What This Computer Needs Is a Physician

Humanism and Artificial Intelligence

The 2 cultures—computer and the physician—must work together.

Verghese et al 2018



“ If the brain were so simple
we could understand it,
we would be so simple
we couldn't ”

Lyall Watson

Summary

- Digital Psychiatry – Increasing influence in contemporary research
- Computational Psychiatry: “Theory” as well as “Data” driven
- Psychosis: Predictive Coding & Corollary Discharge
- Connectome: Important approach to understand brain connectivity
- Beyond Connectome: Dynamic Functional Connectivity
- Brain Imaging: A time series of matrices – “big data”
- D-SNIP Program: Diagnosing Schizophrenia by Machine Learning
- D-SNIP Program: Personalized Neuromodulation
- Precision Medicine in Psychiatry: Opportunities & Challenges
- Blend of “Machine” & “Mind” based approach in Medicine

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wellcome trust DBT INDIA ALLIANCE
Department of Biotechnology
Ministry of Science and Technology
Department of Science & Technology
Ministry of Science & Technology

Thank You

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WISER Program

http://www.instar-program.org/wiser-program.html

www.transpsychlab.org