Center for
Precision Psychiatry
MGH Department of Psychiatry

CAUSAL DIVERSITY IN PRECISION PSYCHIATRY

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DISCLOSURES

Center for
Precision Psychiatry
MGH Department of Psychiatry

I do not have a relevant financial relationship with a commercial interest to disclose.

IN SEARCH OF PRECISION BIOMARKERS

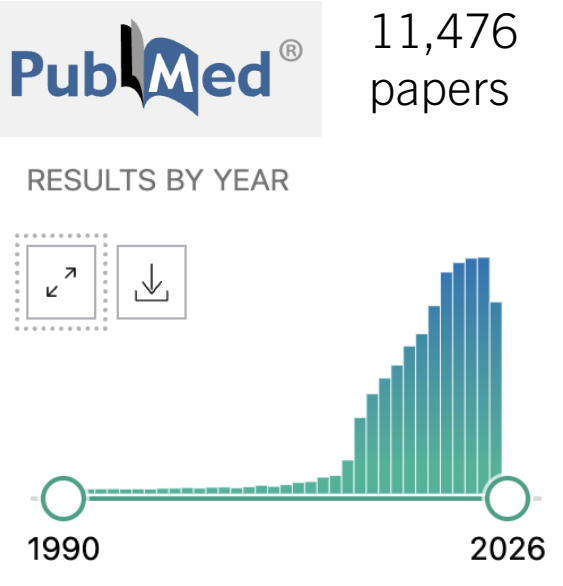
measurable indicators in the body that signify a psychiatric condition or predict response to treatment

use brain mapping to identify regional markers of disease or response

use network approaches to identify connectivity markers of disease or response

❖ aligning detection with factors relevant for information transmission

NETWORK NEUROSCIENCE FOR PSYCHIATRY



11,476 papers

Psychosis (Odkhuu et al., 2023 Mol Psychiatry)
Bipolar (Demirlek et al., 2024 Psychiatry Res)
Borderline (D'Adda et al., 2025 Sci Rep)
Depression (Kim et al., 2025 J Affect Disord)
Functional neurological disorder (Westlin et al., 2025 Brain Commun)
Post traumatic stress (Lan et al., 2023 Cereb Cortex)
...
..
.

The paradigm shift has been driven by the lack of evidence for a single focal “lesion” in these disorders, in concert with mounting evidence for disruption of large-scale brain networks.

THE APPROACH

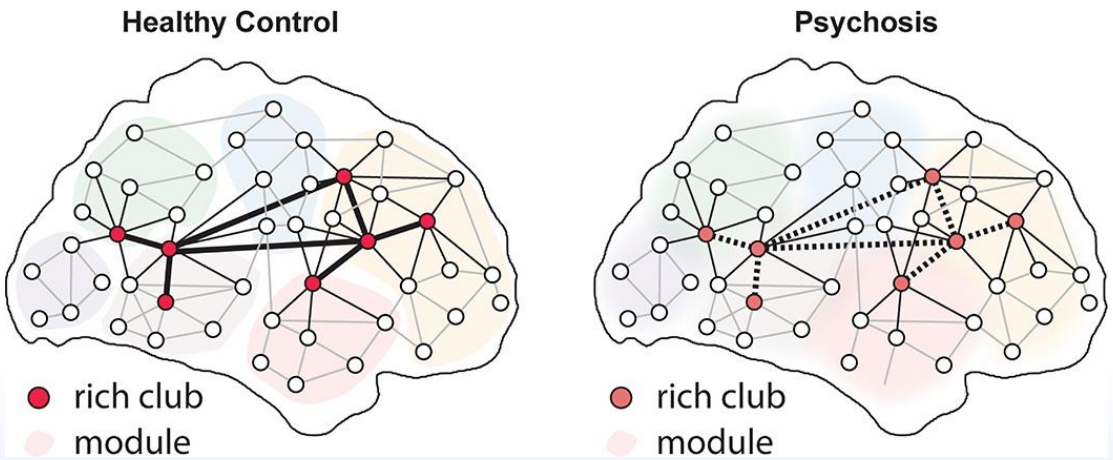


Figure from Bassett et al., 2018 Biol Psychiatry.
See also Van Den Heuvel et al., 2013 JAMA Psychiatry

Describe networks

- At different scales
- In different brains
- In different groups
- Under different conditions
- Using different modalities
- In both humans and animal models
- Over time

Graph Theory

Network Science

Topological Data Analysis

STRETCHING BEYOND DESCRIPTION

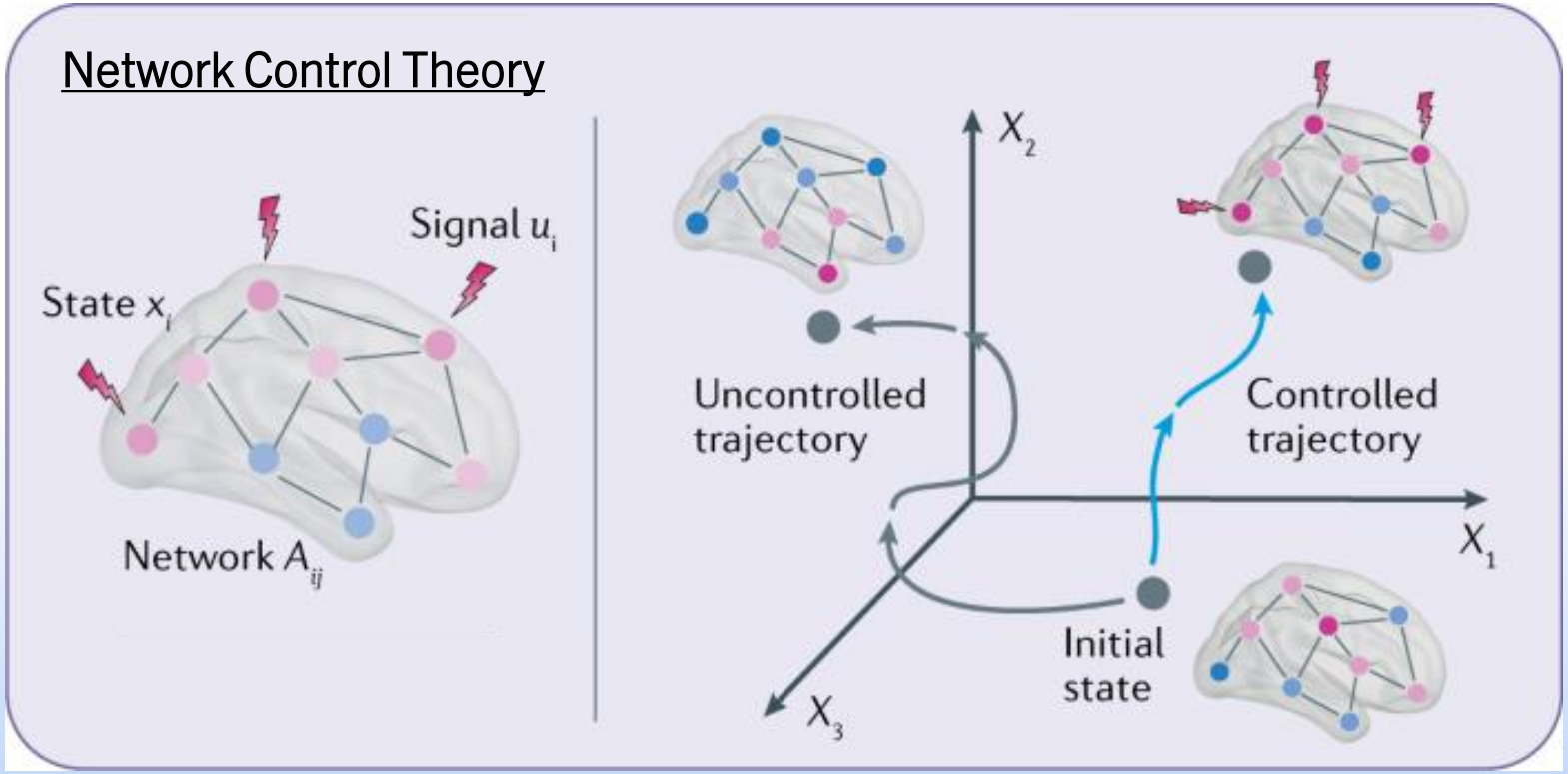


Figure from Lynn & Bassett (2019) Nature Reviews Physics.
See also Parkes et al., 2024 Nature Protocols.

Network control theory is a branch of engineering that aims to understand how to control the behavior of a dynamical system.

Enables a systematic, theory-driven evaluation of the difficulty in inducing system changes by altering nodes or edges.

Metrics: controllability, control points, control energy, state stability, maintenance energy, etc.

NETWORK CONTROL THEORY IN PSYCHIATRY

(EXAMPLES)

2021

2025

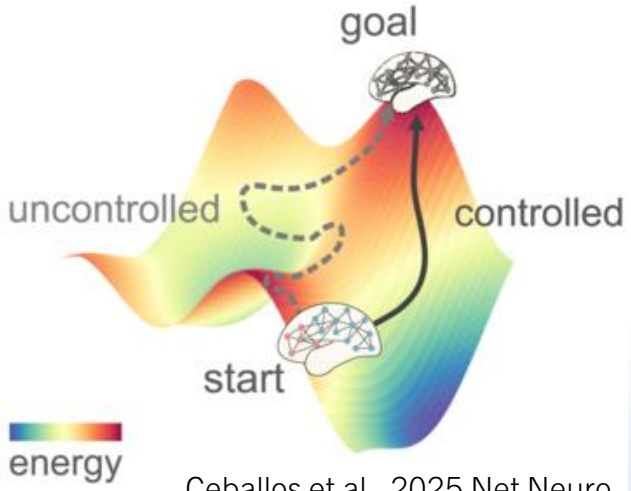
Braun et al., (2021) Nat Commun: “Brain network dynamics during working memory are modulated by dopamine and diminished in schizophrenia”

Parkes et al., (2021) Biological Psychiatry: “Network controllability in transmodal cortex predicts positive psychosis spectrum symptoms”

Singleton et al., (2022) Nature Communications: “Receptor-informed network control theory links LSD and psilocybin to a flattening of the brain's control energy landscape”

Hahn et al., (2023) PNAS Nexus: “Towards a network control theory of electroconvulsive therapy response”

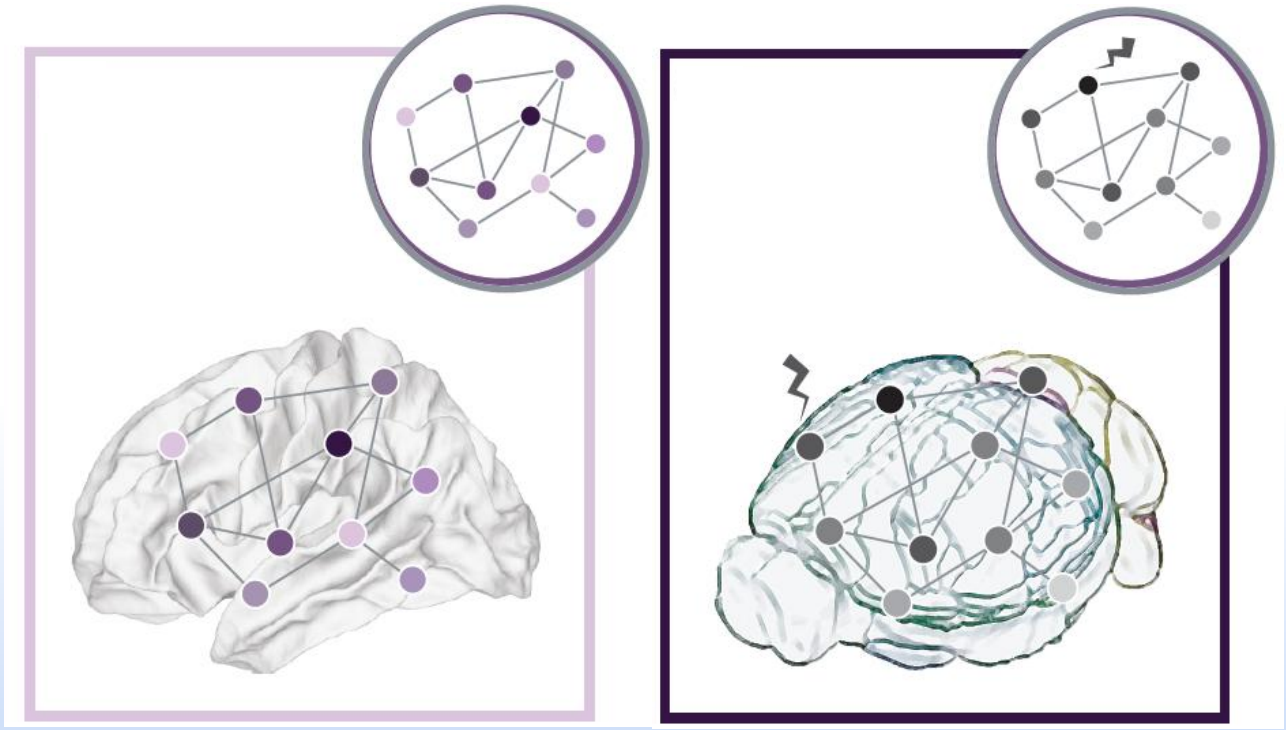
Zhang et al., (2025) Biological Psychiatry: “Sleep deprivation effects on brain state dynamics are associated with dopamine D(2) receptor availability via network control theory”



Ceballos et al., 2025 Net Neuro

◊ How the network determines possible dynamics and constrains their ease vs. difficulty.

FROM DESCRIPTION TO PREDICTION



Bassett, Zurn, Gold, 2018 *Nat Rev Neurosci*

Network Control Theory presses on from description to prediction:

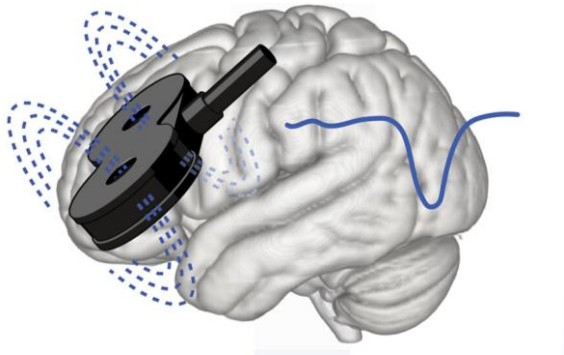
an organism-model correlation in response to a perturbation, such as a drug, electrical or chemical stimulation, neurofeedback, or training.

WHAT SORTS OF EXPLANATIONS ARE ACCESSIBLE?

Constraint-Based Explanation --- factors that are explanatory in virtue of the fact that they constrain the system in some way

- how the network (the explanans) "makes a difference" to the system's behavior (the explanandum), in which this difference-making relation (dependency relation) is the structural constraint of where network edges exist.

- Causal Constraint-Based Explanation --- as above but where the network constraint is a causal constraint (e.g., network edges constrain dynamics and circuit behavior by determining available causal pathways for information)



vlPFC → amygdala

Sydnor et al., 2022 Science Advances

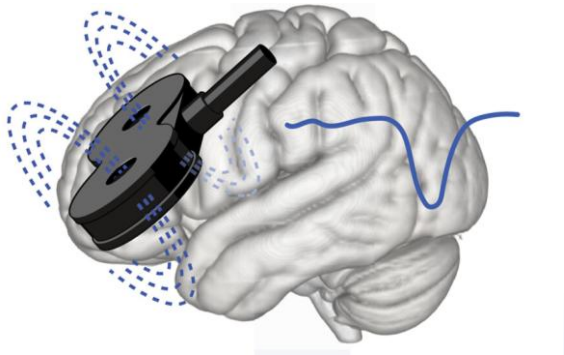
Lauren Ross, 2023, Philosophy of Science

WHAT SORTS OF EXPLANATIONS ARE ACCESSIBLE?

Topological Explanation --- from topological properties of a system, one draws mathematical consequences that explain behavior

- how the topology of the system (the explanans) "makes a difference" to the system's behavior (the explanandum), in which this difference-making relation (dependency relation) is specified mathematically.

- Causal Topological Explanation --- as above but where some edges in the network indicate causal relations, and the difference-making relation (dependency relation) is specified both mathematically (topology) and empirically (cause).



vlPFC → amygdala

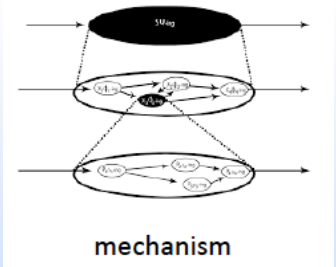
Sydnor et al., 2022 Science Advances

Lauren Ross, 2019, Synthese

CAUSAL STRUCTURES IN NETWORK PSYCHIATRY

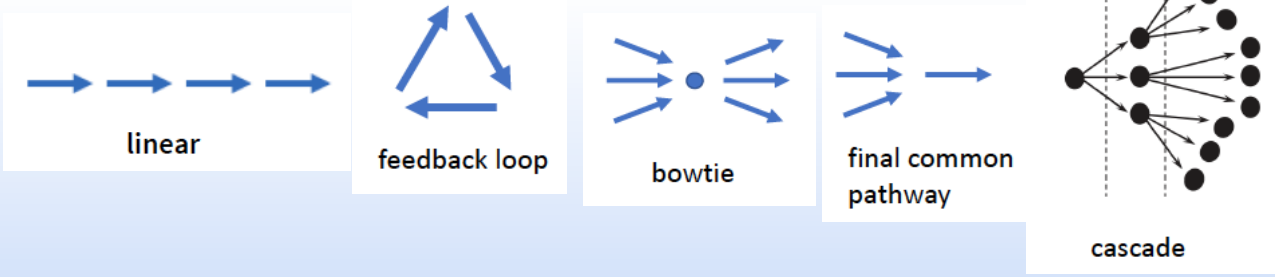
Causal structures can exist across a variety of scales, and myriad causal structures can contribute to causal topological and causal constraint-based explanations.

Lower-level:



mechanism

Same-level:

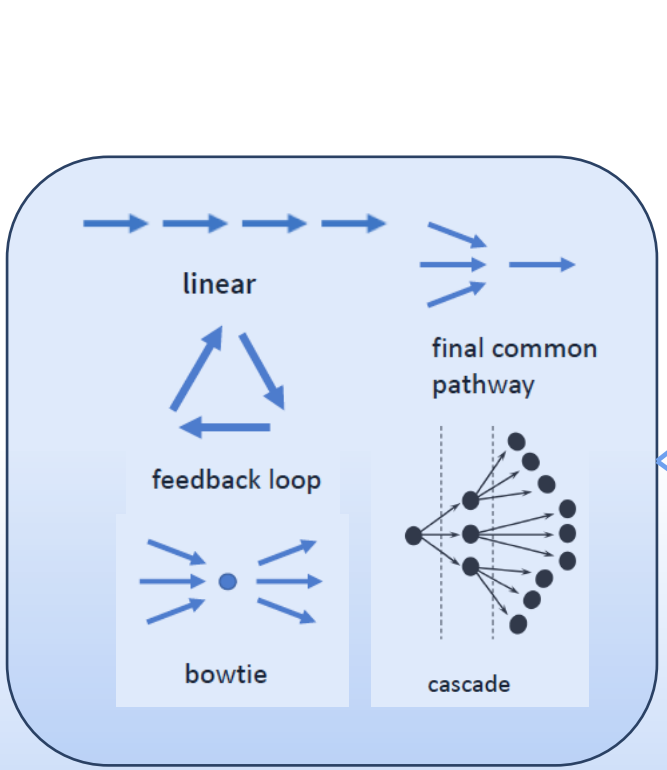


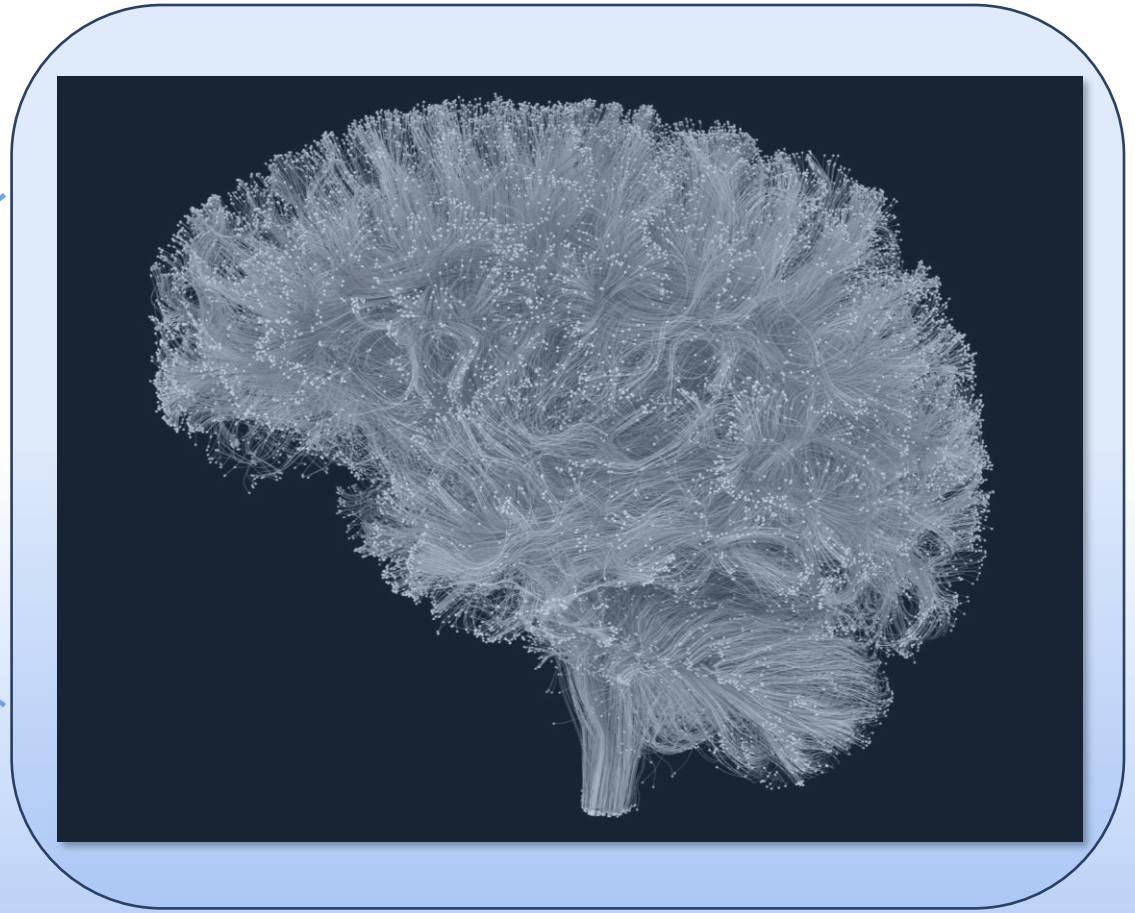
Higher-level:

(e.g., social structure)

Lauren Ross, 2022, The British Journal for the Philosophy of Science

CAUSAL NETWORK STRUCTURES IN THE BRAIN





Dani S. Bassett

CAUSAL DIVERSITY AND PLURALISM

In considering network explanations in psychiatry, it is important to consider causal diversity, with many potentially different causes all playing a key role.

(1a) monocausality (one cause)	(2a) causal homogeneity (same causes)
(1b) multicausality (many causes)	(2b) causal heterogeneity (different causes)

Lauren Ross, “Explanation in Contexts of Causal Complexity”

CAUSAL DIVERSITY IN PRECISION PSYCHIATRY

Causal explanations for psychiatric disease or response to treatment.

- Can exist across scales (from molecules to social factors)
- Can be topological, constraint-based, mechanistic, or structural
- Can include a variety of causal structures in brain networks

Identifying these explanations will require us to embrace causal diversity in the biological sciences and have approaches for holding the complexity of causal heterogeneity in our investigations.

Lauren Ross & D. S. Bassett (2024) Nature Reviews Neuroscience

What are the possible explanatory factors accessible to modern instruments?

What features of the disease or response are we seeking to understand?

explanans	dependency relation	explanandum
“	“	“
“	“	“
“	“	“
“	“	“
“	“	“
“	“	“
“	“	“
“	“	“

What kinds of dependency relations could exist?

What are the possible explanatory factors accessible to modern instruments?

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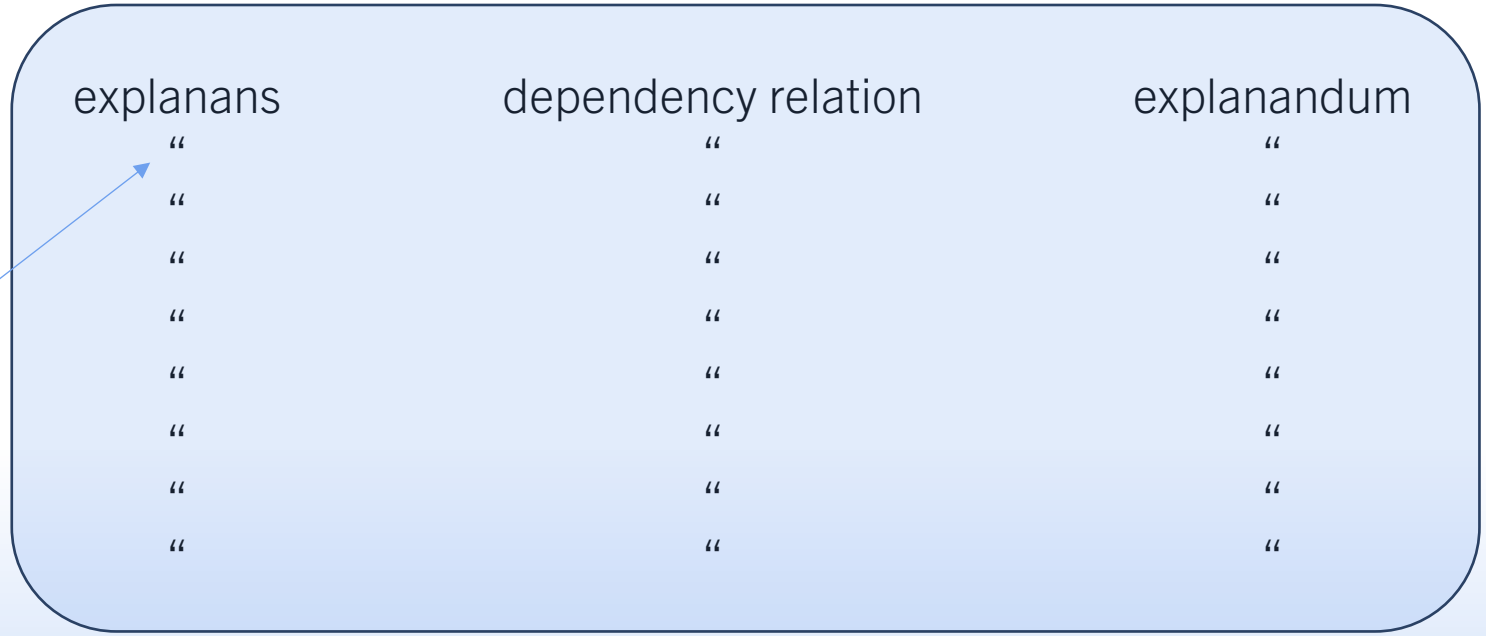

biomarker?
(single scalar value)

What kinds of dependency relations could exist?

A focus on biomarkers within of this broader context (for what? how? among which others?) could provide a deeper understanding and enhanced potential to intervene, thereby supporting precision psychiatry.

… AND PERHAPS MORE GENERALLY

explanans	dependency relation	explanandum
“	“	“
“	“	“
“	“	“
“	“	“
“	“	“
“	“	“
“	“	“
“	“	“
“	“	“

What might happen if we considered this entire table as a BIOMARKER?

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THANK YOU!

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