Which mechanism for mechanisms in medicine?

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Mechanisms in Medicine

University of Kent, 3-5 July 2017

Four Decades of Mechanisms

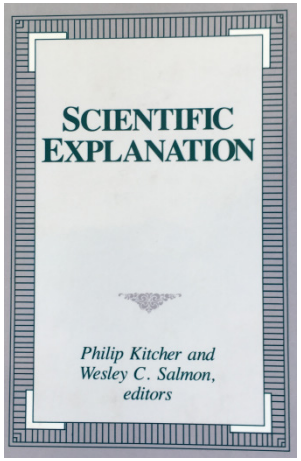
- Beginning of the “revival” of mechanism:
  - Wesley Salmon: “the time has come to put the ‘cause’ back into ‘because’” (1977).
    - “A Third Dogma of Empiricism”, 1977
    - “An ‘At-At’ Theory of Causal Influence”, 1977
    - “Why Ask ‘Why?’?”, 1978

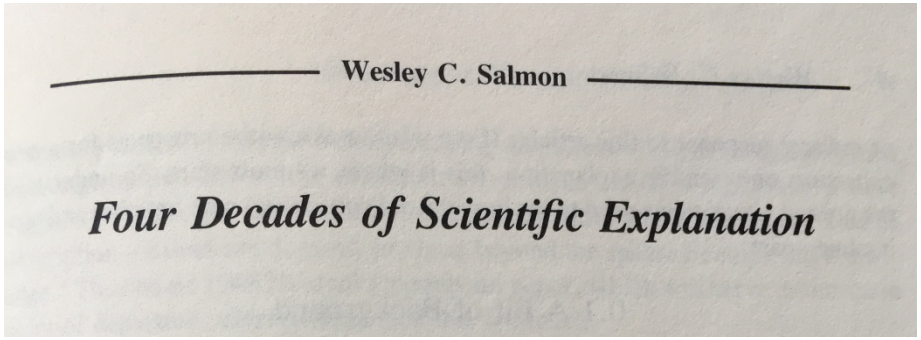
- Wide literature and proliferation of theories and definitions

Four Decades of Mechanisms

1948-1989: *Four Decades of Scientific Explanation*

1977-2017: Four Decades of Mechanisms





Outline

- 1. From “the causal structure of the world” to “the new mechanical philosophy”: What’s new?

- 2. Mechanism and the Sciences.

  Issues from Psychiatric Sciences

- 3. *“New Mechanical Philosophy” e*ntering the fifth decade: which mechanism for mechanisms in medicine?

The “roots”

- *Scientific Explanation and the Causal Structure of the World*, 1984, last chapter (ch. 9): “The Mechanical Philosophy”:

  “The theory here proposed appeals to causal forks and causal processes; these are, if I am right, the *mechanisms of causal production and causal propagation that operate in our universe*. These mechanisms, it has been emphasized, may operate in ineluctably stochastic ways. Scientific explanation, according to the ontic conception, consists in *exhibiting the phenomena-to-be-explained as occupying their places in the patterns and regularities which structure the world*”.

Shared concerns…

- It is both "statistical *and* causal relations [which] constitute the patterns which structure our world" (Salmon 1982, "Comets, Pollens and Dreams")

- To explain in causal terms is to:

1) Identify all and only statistically relevant relations (S-R);
2) Specify the mechanism responsible for the explanandum (causal step)

Statistical relevance relations without causal processes would not explain **&** causal processes are identified on the basis of S-R relations.

- Crucial issue: identify *genuine* causal relations

- We should “treat […] evidence of mechanisms alongside evidence of correlations in medicine. […] a causal claim in medicine should in general only be accepted if it is supported both by evidence of correlation, and evidence of mechanisms. [They] need to be taken together in order to establish causal claims” (Clarke, Gillies, Illari, Russo, Williamson, “Mechanisms and the Evidence Hierarchy”, 2014)

- *New* attention to, e.g.,: biological plausibility; external validity; evidential pluralism; …

… and *not* shared concerns

- Salmon: process ontology (spatio-temporally continuous) and MT as a ***criterion*** to tell genuinely causal from pseudo-processes.

- MDC (2000): “Mechanisms are entities and activities organized such that they are productive of regular changes from start-up to finish or termination conditions”.

- Bechtel and Abrahamsen (2005): “A mechanism is a structure performing a function in virtue of its component parts, component operations and their organization. The orchestrated functioning of the mechanism is responsible for one or more phenomena”.

- Illari and Williamson (2012): “A mechanism for a phenomenon consists of entities and activities organized in such a way that they are responsible for the phenomenon”.

- Glennan (forthcoming, 2017): “A mechanism for a phenomenon consists of entities (or parts) whose activities and interactions are organized so as to be responsible for the phenomenon”.

Varieties of …

- Entities and activities (Field-relative);

- Mechanistic accounts with some explanatory power (e.g. mechanisms' sketches or schemata (see MDC 2000), or how-possibly, how-plausibly, how-actually explanatory models (see Craver 2006); ..);

- Systems that can be deemed "mechanisms"
  (e.g. Skillings (2015): we might be "dealing with mechanistic diversity", "more or less paradigmatic" of a mechanism defined along a continuum by different parameters; Glennan (forthcoming), ch. 7: "Kinds of mechanisms", "expansive conception of what a mechanism is", "understood permissively")

New …

- Aim: To have some notion which can work for "mechanisms across the sciences" (Illari and Williamson 2012), and which is "grounded in the details of scientific practice" (Machamer, Darden and Craver 2000).

- Not only search for "the causal structure of the world"/"open the black box of nature", to explain *how things work*, but also focus on *how the search for mechanisms works* (discovery of mechanisms; explanatory strategies; modelling, abstraction, idealization …).

Ontic conception:

> "a conception of explanation is a version of the *ontic* conception only if it takes explanations to be extant entities that subsist in re" (Wright, "The Ontic Conception of Scientific Explanation", 2015)

But also:

> "statements about the relations between causes and effects are usually highly selective, and they are typically context-dependent" (Salmon 2002, "A Realist Account of Causation");
>
> "to believe that the 'cause-effect' terminology is heavily context-dependent – involving human background knowledge, interests, and purposes" (Salmon 2010, "The Causal Structure of the World").

On Ontic/Epistemic (Wright 2012, 2015; Illari 2013; Craver 2014; van Eck 2015; …)

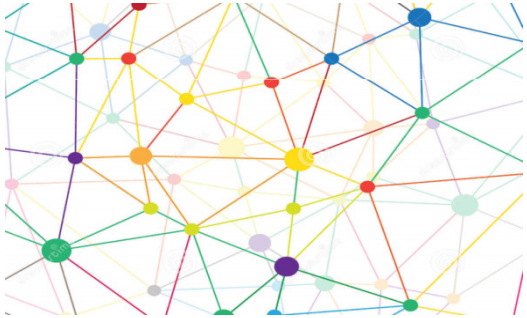
Neo-mechanism: On the representational character of explanations.

And:

- Craver (2001, "Role Functions, Mechanisms and Hierarchy"): "describing an item's mechanistic role is a *perspectival affair*"
- Darden (2008, "Thinking Again about Mechanisms"): "when [scientists] identify mechanisms, there is an *inherent perspectival aspect* as to what is picked out of interest from all the goings on in the world".

Mechanisms to the test

- Four decades of mechanisms: Towards actual scientific practice; complex systems; multi-dimensional frameworks



- Psychiatric sciences

  Neurology, neuropsychiatry, psychiatric epidemiology, genetics, pharmacology, neuroanatomy, clinical psychology, …

- Reflections *on*, and *from within*

Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression

D. Jeffrey Newport, M.D., M.S., M.Div., Linda L. Carpenter, M.D., William M. McDonald, M.D., James B. Potash, M.D., M.P.H., Mauricio Tohen, M.D., Dr.P.H., M.B.A., Charles B. Nemeroff, M.D., Ph.D., The APA Council of Research Task Force on Novel Biomarkers and Treatments

Am J Psychiatry 172:10, October 2015

Nat Neurosci. 2015 October ; 18(10): 1386–1393. doi:10.1038/nn.4113.

Neuroimmune mechanisms of depression

Georgia E. Hodes[1], Veronika Kana[2], Caroline Menard[1], Miriam Merad[2], and Scott J. Russo[1,*]

© 2017. Published by The Company of Biologists Ltd | Disease Models & Mechanisms (2017) 10, 451-461 doi:10.1242/dmm.027623

RESEARCH ARTICLE

Towards trans-diagnostic mechanisms in psychiatry: neurobehavioral profile of rats with a loss-of-function point mutation in the dopamine transporter gene

Valentina Vengeliene[1,*], Anton Bespalov[2,*], Martin Roßmanith[1,*], Sandra Horschitz[3], Stefan Berger[4], Ana L. Relo[2], Hamid R. Noori[1], Peggy Schneider[1], Thomas Enkel[4], Dusan Bartsch[4], Miriam Schneider[1], Berthold Behl[2], Anita C. Hansson[1], Patrick Schloss[3] and Rainer Spanagel[1,‡]

Insights *on* and *from within* psychiaty

Explanatory issues - Kendler ("Explanatory Models for Psychiatric Illness", 2008). A mechanistic approach can fit psychiatry insofar as:

- It can grasp a multicausal framework;
- Mechanisms can be decomposed, investigated as separate sub-units; re-assembly in order to study the behaviour of the system as a whole;
- No privileged set of entities over the others; hence, in principle, "middle ground between hard reduction and hard emergence".

Kendler, Zachar and Craver ("What Kinds of Things Are Psychiatric Disorders?", 2011): mechanistic approach to identify mental disorders through different social and cultural contexts, by focusing on *some shared physiological mechanisms*

- "Shift from the quest for essence of psychiatric kinds […] to a quest for the complex and multi-level causal mechanisms that produce, underlie and sustain psychiatric syndromes".
- "There are robust explanatory structures to be discovered underlying most psychiatric disorders".

- MPC – Mechanistic property cluster kinds
  - "…psychiatric disorders are *objectively grounded features of the causal structure* of the mind/brain. MPC kinds are fuzzy sets defined by mechanisms at multiple levels that act and interact to produce the key features of the kind"
  - "… *grounded in common features of the causal structure of the world*, not merely imposed upon the world by psychiatrists through their classificatory practices" (italics added)

- *Research Domain Criteria* project (RDoC, 2008; 2015): nimh.nih.gov/research-priorities/rdoc/index.shtml

https://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml

"RDoC integrates many levels of information (from genomics to self-report) to better understand basic dimensions of functioning underlying the full range of human behavior"

" It is centered around dimensional psychological constructs (or concepts) that are relevant to human behavior and mental disorders, as measured using multiple methodologies"

- 5 “domains” of the RDoC matrix:
  - Negative Valence Systems (responsible for anxiety, fear and loss)
  - Positive Valence Systems (resp. for reward seeking, habit learning, …)
  - Cognitive Systems (resp. for, e.g., language, attention, perception)
  - Systems for Social Processes (mediate responses in interpersonal settings)
  - Arousal/Regulatory Systems (regulate, e.g., sleep and balance)

- Units of analysis of constructs: genes, molecules, cells, circuits, physiology, behaviours, self-reports, paradigms

Psychiatrists on RDoC:

- Pathologies “as disruptions of the normal-range operation of these systems, with an emphasis *on the mechanisms* that serve to result in dysfunctions” (Cuthbert and Insel, “Toward the future of psychiatric diagnosis: the seven pillars of RDoC”, 2013).
- Investigations “– from molecular factors to social determinants – to understand normal and abnormal behaviour, based *on a deep understanding of mechanisms*” (Insel, “The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry”, 2014)

Tabb and Schaffner (2017 “Causal pathways, random walks and tortuous paths: Moving from the descriptive to the etiological in psychiatry”), “over the last decades a consensus position has formed among psychiatrists and philosophers that progress in psychiatric nosology consists in the validation of descriptive categories through the discovery of underlying causal mechanisms”

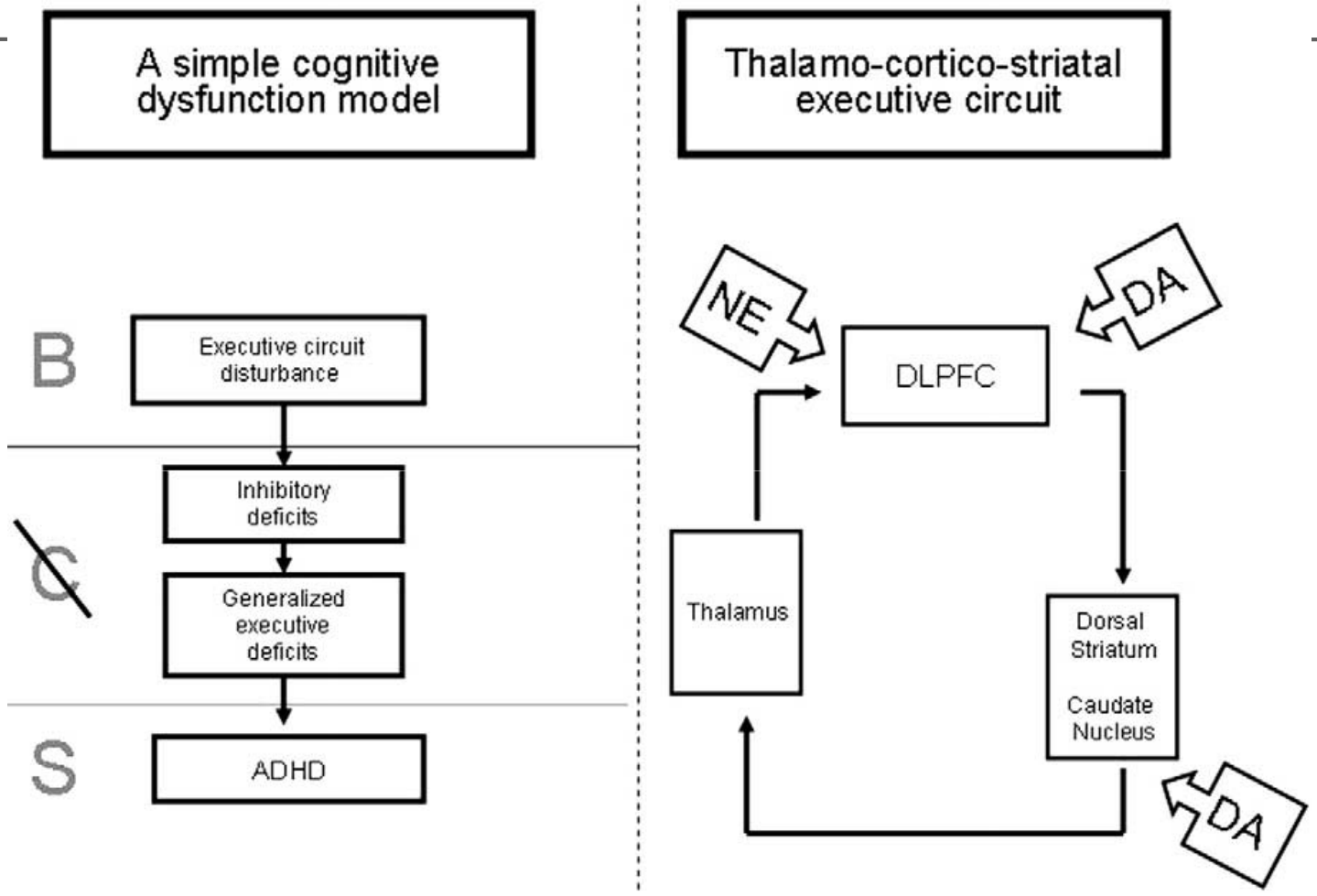
- Why searching for “mechanisms”?
- Which “mechanisms”?

An example: ADHD

- **DSM V** (2013): “a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with development, has symptoms presenting in two or more settings (e.g. at home, school, or work), and negatively impacts directly on social, academic, or occupational functioning”.

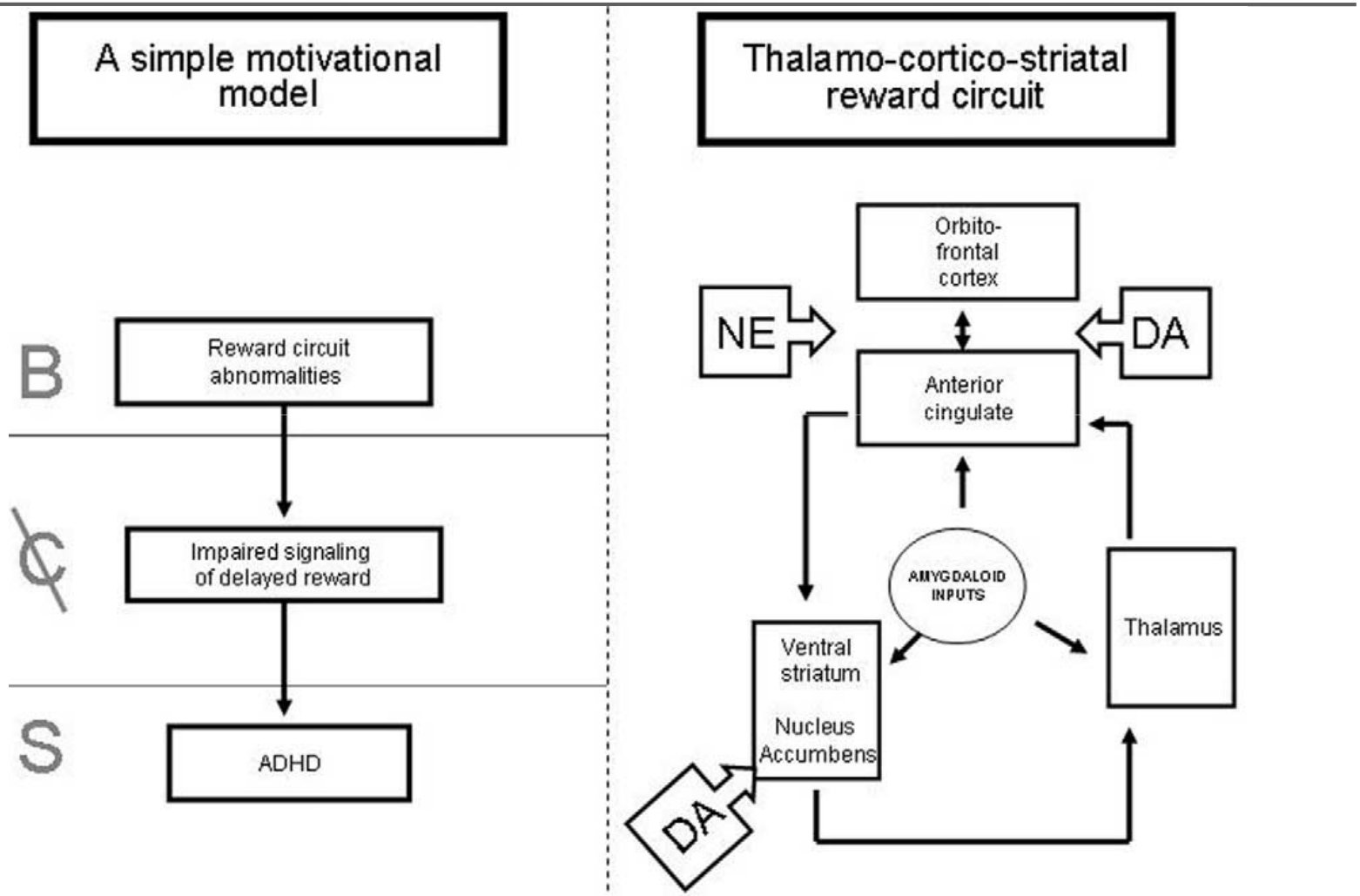
- **DSM I** (1952): no mention of the disease
- **DSM II** (1968): introduction of a pathology characterized by: short attention span, hyperactivity and restlessness, labeled “hyperactivity reaction to childhood”
- **DSM III** (1980): ADD, i.e. attention deficit disorder, seen mainly as a problem of attention deficit, not hyperactivity
- **DSM IV** (1994): ADHD, 3 possible manifestations: a) hyperactive/impulsive; b) attention deficit; c) combination of a) & b)

The executive dysfunction model

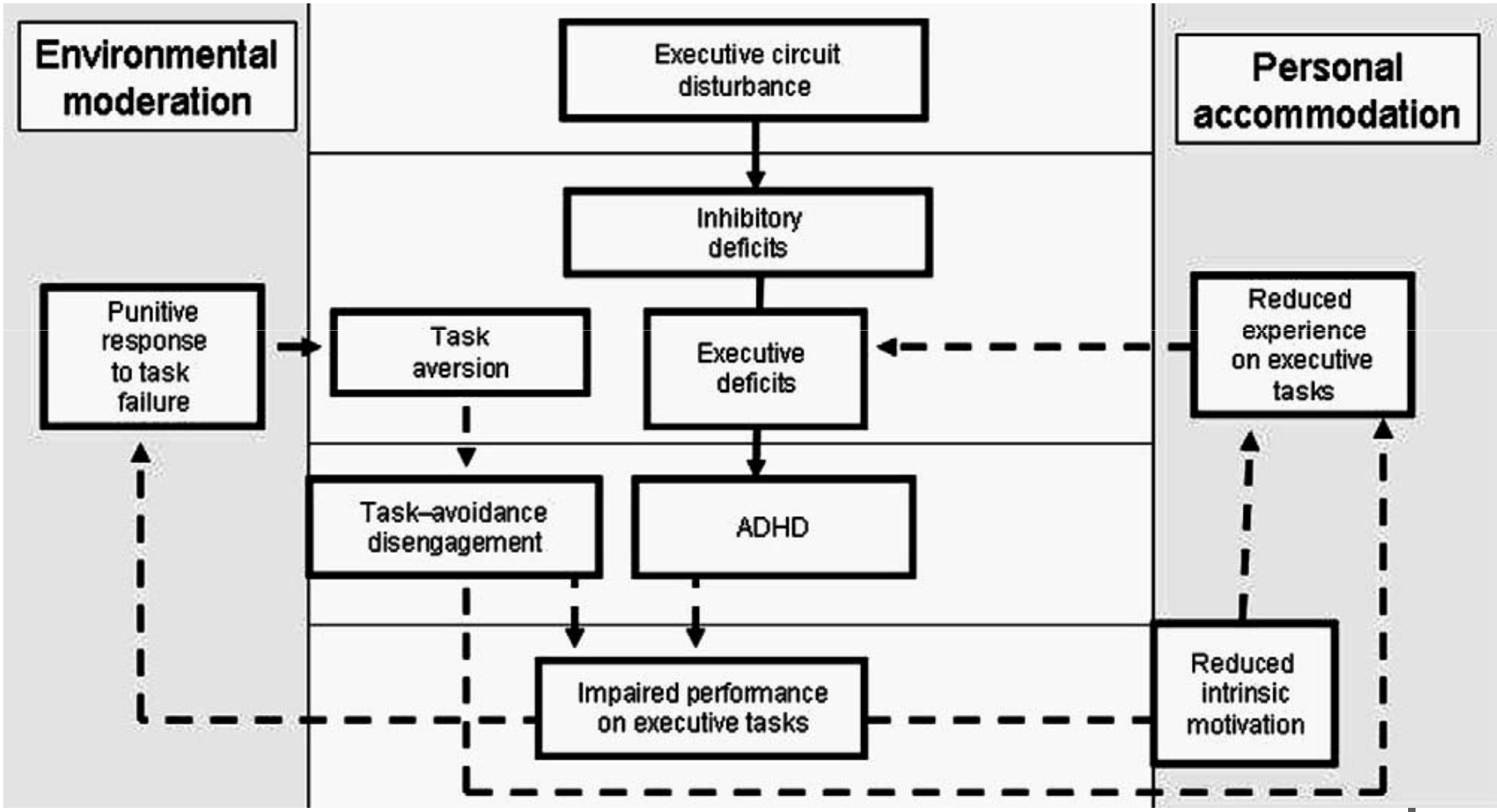


B: biology; C: cognition; Slashed C: cognitive deficits; S: symptoms
DLPFC: dorso-lateral prefrontal cortex; DA: dopamine; NE: norepinephrine

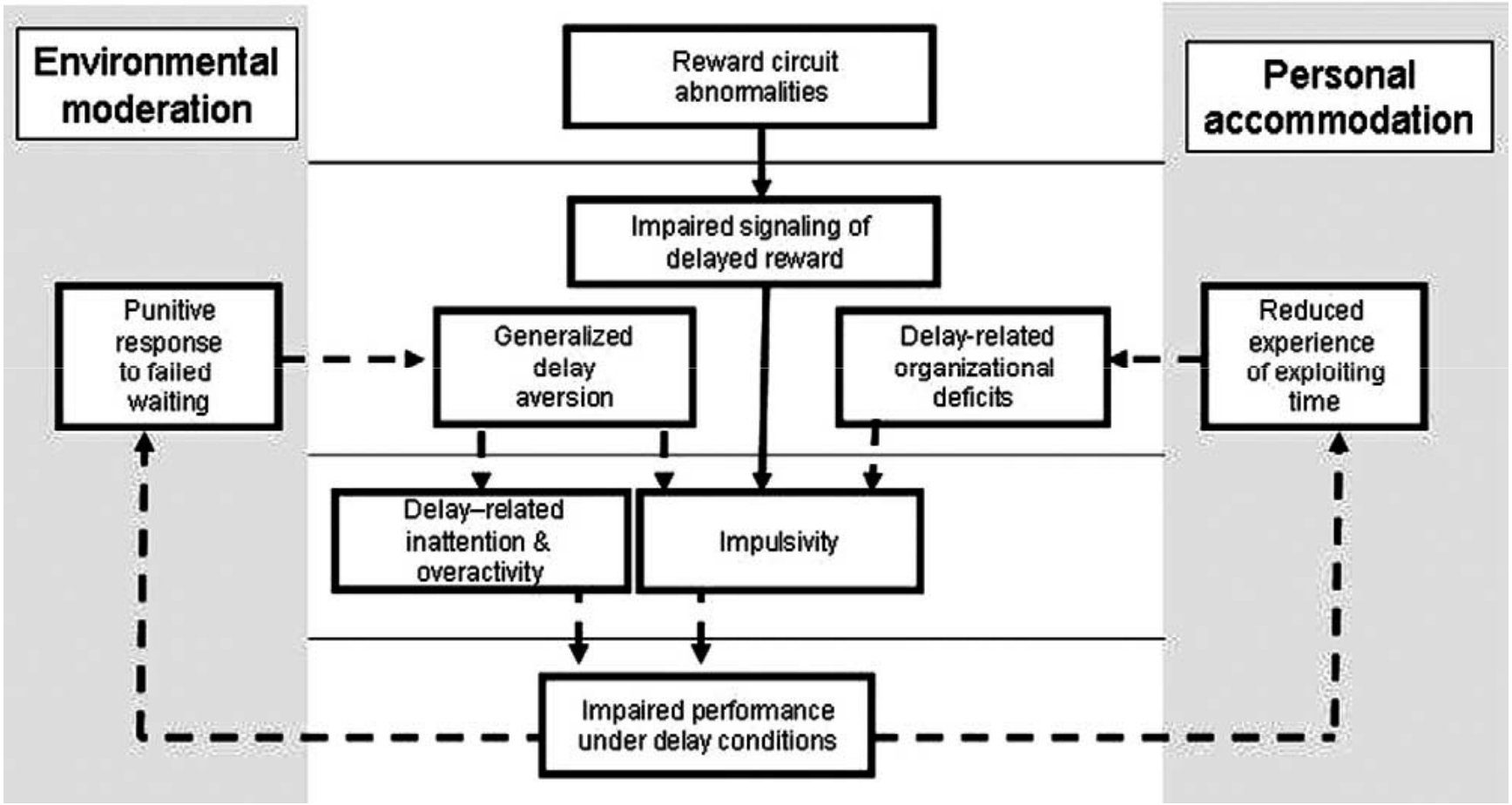
The motivational model



Extended cognitive model



Extended motivational model (delay aversion model)



Evidence from, e.g.:

- genetic research on *genetic mutations*, heritability and susceptibility (e.g., twin studies);
- epidemiological research on environmental risk factors and *gene x environment interactions* (family, twin and adoptees studies; e.g. pre- and peri-natal exposure to maternal smoking and alcohol addiction);
- neuroimaging studies (structural imaging showing *brain volume reduction* in various areas; functional MRI reports showing *decreased functional connectivity* in long-range connections linking different brain regions);
- clinical-observational studies, including behavioral tests and questionnaires (e.g. on interactions between child and significant adults, as parents or teachers).

a) Which mechanism?

- *Simple Causal Models / Extended causal models*
- *Shift from common simple deficits models* **to** *multiple neurodevelopmental pathway models, meant as potentially "powerful explanatory tools".*

What is the mechanistic model a model of?

Disease: network of impairments

Identification of the mechanism. Which boundaries?

- "A mechanistic explanation must begin with an accurate and complete characterization of the phenomenon to be explained. […] To characterize the phenomenon correctly and completely is the first restrictive step in turning a model into an acceptable mechanistic explanation" (Craver 2006, "When Mechanistic Models Explain")

- No single and shared definition of an isolated phenomenon, no single, "accurate and complete characterization" of the system under investigation.

- *Choice* of a minimum set of characterizing features, taken to define the disease *provisionally*; will impinge on what will be identified as the *explanans*.

- *Descriptions* of the disease evolve along with *causal explanatory practice*.

- Boundaries of the mechanism: drawn and re-drawn

- Behavioural descriptions and mechanical accounts co-evolve

- Inclusion of different entities and relations: drawing a different mechanism; not just putting into context, not just an “extended pathology”, but a different pathology altogether.

  (Campaner, “Mechanistic Models and Modeling Disorders”, 2016)

- Franklin-Hall (2016, "New Mechanistic Explanation and the Need for Explanatory Constraints"): mechanistic models should meet "the carving standard": "models should carve mechanisms 'at their joints', describing them in terms of the appropriate set of parts (Craver 2006, p. 367; Bechtel and Abrahamsen 2005)."

- Psychiatry calls for more stable definitions and explanations, to improve classification, diagnosis and treatment
- Strong dependence on the initial drawing of the boundaries of what is taken as the mechanistic system itself.

- Different "carving" of the "causal structure of the world"

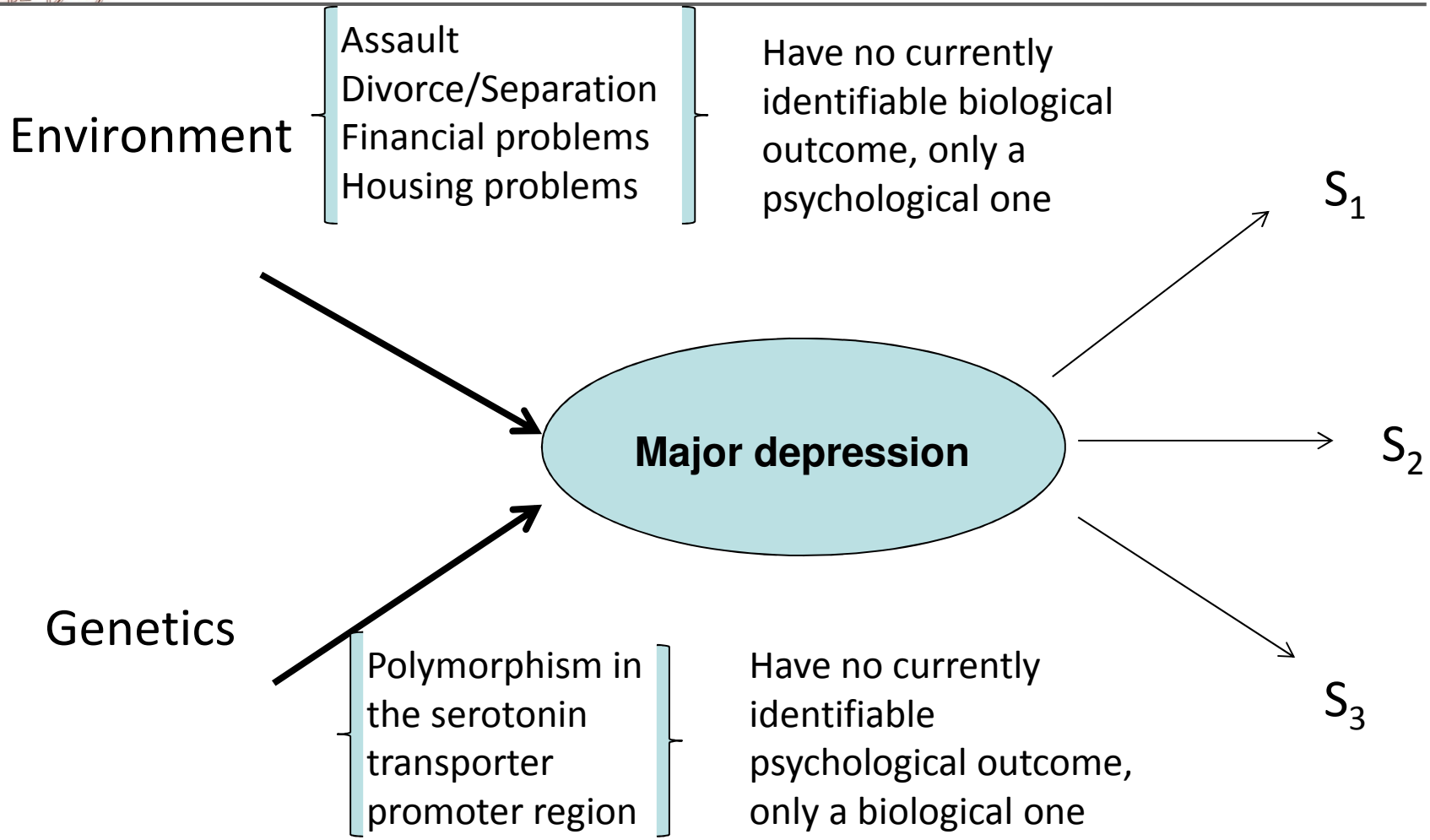
b) How does it work?

"Organization": it "involves an internal division of causal labor whereby different components perform *different causal roles* […]. Given some effect or behavior, a system is organized with respect to that effect or behavior if (i) different components of the system make different contributions to the behavior, and (ii) the components' differential contributions are *integrated*, exhibiting *specific interdependencies* (i.e. each component interacts in particular ways with a particular subset of other components)" (Levy and Bechtel, "Abstraction and the Organization of Mechanisms", 2013).

Components playing *different, specific and interdependent causal roles*.

- General point of a mechanistic account: make explicit how the parts of a systems and the ways in which they act conspire to produce its overall behavior.

- Organization as the "relation between a mechanism as a whole and its components", by virtue of which they "work together to do something" (Clarke et al., "Mechanisms and the Evidence Hierarchy", 2014) is usually still largely unknown in psychiatry – plus we often do not know to what extent an understanding of organizational features is essential – or not – to an understanding of the disease's overall functioning.



From Campbell, "Validity and the causal structure of a disorder" (2017)

- E.g. *How* does a polymorphism in a (dopamine) risk-gene for ADHD translate into a neurobiological substrate and result in behaviors that warrant a diagnosis of ADHD in a developing child? (Durston & Konrad, "Integrating genetic, psychopharmacological and neuroimaging studies", 2007).
- Or: *How* does the blocking of striatal dopamine transporters, achieved through pharmacological treatment, alleviate behavioural symptoms?

- "How social context and environmental factors translate into biological changes at the level of gene expression" (Arbuckle et al., "Integrating a Neuroscience Perspective into Clinical Psychiatry Today", JAMA 74, 2017) still pretty obscure.

- Some account of *organization* must count as a bar set on any explanatory mechanistic model *once the explanandum has been singled out*

- On the one hand, mechanistic evidence – e.g. of neurophysiological circuits – is often taken as the "core of the disease".
- On the other hand, some demanding idea of mechanistic organization, to switch *from mechanistic evidence to the mechanism of the disorder* as such, currently seems mostly a (provisional?) "sign of our epistemic limits" (Kuorikoski and Ylikoski, "How Organization Explains", 2013).

- How many black boxes are we willing to admit?

c) What's responsible for…?

- Accommodation and compensation strategies, that might – or might not – get activated.

- Concepts as "cognitive reserve" or "neural compensation" introduced to "account for the frequent discrepancy between an individual's measured level of brain pathology and her expected cognitive performance" (Barulli and Stern 2013, "Efficiency, Capacity, Compensation, Maintenance, Plasticity: Emerging Concepts in Cognitive Reserve")

- These and related concepts are introduced to explain why patients with relatively equal conditions can then turn out to have very different functional manifestations and, hence, perform differently on cognitive tests – thus meeting, or not, the definition of given pathology.

- Conceptualization of different kinds of reserve and compensation, what activates them, which roles possible modulations and thresholds play, which their boundaries can be, and whether their activities can be described in some specific “organizational” terms: far from clear.

- How are we to account for the causal efficacy of compensation and accommodation strategies? Can/Should they be isolated as separated mechanisms? Or not?

- Do they affect the identification of the mechanisms of brain pathologies?

- Which elements count as “responsible” for the behaviour of the mechanism of the pathology here?

- Pathology: some “orchestrated functioning” which is responsible for some “non-functioning”.

- Mechanistic explanation of a disease: reveal the specific contributions of causal factors involved in the *working of the pathology as a system*, insofar as such specific working is dysfunctional with respect to some higher level of organization – which is taken as typical of a health condition.

- Amongst issues from psychiatry:
  - the identification of the mechanism's boundaries and its impact on explanatory content, and definition of disorder;
  - the mutual organization of components and its explanatorily relevance;
  - the precise identification of what is "responsible" for relevant acting and organization.

- How do we get *from mechanistic evidence* – supporting the presence of a causal, productive link (e.g. regarding the functioning of the dopamine or norepinephrine circuits) – *to evidence of the mechanism of the pathology* as such?

- “Four decades of mechanisms”:
  - from a process ontology to complex systems and multidimensional frameworks;
  - from the ontic conception to a focus on a range of mechanistic models;
  - from the definition of genuine causal processes to open the “black box of nature” (Salmon), to the idea that “to distinguish [some] types of phenomenon (and thereby types of mechanisms) we employ the models-first strategy, classifying mechanisms by the models that we use to represent them” (Glennan, forthcoming).

- Minimal notion: quite limited informative import; poorly meets the demand for a reduction of variability of definitions of mechanistic systems and of discretional choices.

- Some specific and detailed notion of mechanism: more likely to highlight the current gaps in psychiatric knowledge than its achievements.

- Issue: does mechanism actually grasp what psychiatry is currently like, or what it would like to be and – at least in part –aims to become?
- Is a mechanistic perspective meant to describe how the different psychiatric sciences actually proceed, or should it help them to rethink/reframe some of their working concepts?

To wrap up:

Which relation between mechanistic discourse *on* and *in* the sciences?

✓Various versions of *neo-mechanism*: fit to describe at least some current features of psychiatric research, such as the variety of phenomena and conditions it encounters

✓If the purpose is to describe conceptual tools and ways of reasoning sciences *should* adopt, neo-mechanist definitions will also make gaps and puzzles emerge.

✓If we focus on reflections *from within* psychiatry: it seems that it is an ontic idea that still guides the appeal to mechanistic notions, as something to aim at in order to reach its most ambitious goals and overcome present limits.

Which mechanism for mechanisms in psychiatry?

- From the standpoint of psychiatry and the enduring dilemmas in that field: still "old-mechanistic", ontic stances drive current research and capture ultimate goals.

- "New-mechanistic" mechanisms give a sense of the *methodology* employed, also by making explicit that "ontic constraints are discovered epistemically" (van Eck 2015, "Reconciling Ontic and Epistemic Constraints on Mechanistic Explanation, Epistemically").

- Further stretching of mechanical philosophy, or, in psychiatry, shall we rest content with robust patterns, with a range of pathway sketches, and, finally, perhaps with no need for mechanisms at all? (see Tabb and Schaffner 2017)

Glymour (1982, “Causal Inference and Explanation”):

> “Those of us who know and admire Salmon know also that he is really a son of the Enlightenment, a man who belongs in spirit to the age of reason, not to this mad time. And there is an integrity of sensibility and intellect, for Salmon will have none of model realism, necessary connections, action at a distance, discontinuity or occult powers. *He is, I believe, the last Mechanical Philosopher*” (italics added).

After four decades:
Too much mechanism, or not enough (yet)?

- Who's afraid of mechanisms?

- I am not.

Knowledge of mechanisms for:

  - Explanation
  - Methodological decomposition
  - Reduce possible alternative plausible stories
  - Improve treatment and prediction
  - Limit adverse effects
  - …

- But I think that if philosophy of mechanisms is to dialogue with the sciences, the modes of the interactions and respective expectations in talking about mechanisms are also to be made clear.

- Worries:
  - A one-notion-fits-all situation
  - Lose sight of interesting features of specific phenomena we're trying to capture in mechanistic terms

What's next?

In the agenda for the fifth decade:

- Make explicit the relations between the philosophical discourse on mechanisms in medicine, and the medical discourse on mechanisms (when looking and when not looking at philosophy)

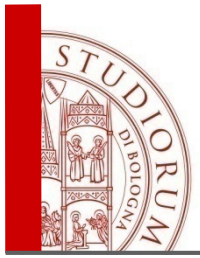
- What is philosophy of mechanisms addressing in medicine?
  - Some/All medical fields?
  - Some/All medical issues?
  - Some/All diseases?

-

- Investigate how evaluations of mechanistic evidence and evidence of “sub-mechanisms” can impact on the identification of what is taken as the overall mechanism of the disease as such.

- Investigate the impact of *both* mechanistic knowledge and “mechanistic ignorance” in modeling diseases in medicine.

- …. And possibly much more …



THANK YOU