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The lost cause of not being mechanistic enough?

A perspective inspired by philosophy of science

Jan Pieter Kongsman and Teresa M. Reyes

Biomedical research advances explanations of biological phenomena relevant for health and disease, and proposes therapeutic strategies to intervene in disease processes and promote health. The identification of causal factors and description of mechanisms are important both for explanation and development of therapeutic strategies.

There is discussion regarding an increase in critiques of biomedical grants and manuscripts according to which a project or a finding “is not mechanistic enough” (Anonymous, 2012; Siegel, 2018) or “lacks mechanistic insight” (Halpert, 2001; LeMasurier, 2015). Such critiques seem to be motivated by a growing belief that studies that are “more mechanistic” or focus on lower level mechanisms are necessarily more important and/or worthy of funding. Interestingly, and so far mostly in parallel, philosophy of science has debated the concept of mechanism in biology (Craver, 2006; Nicholson, 2012; Weber, 2008; Woodward, 2004), has discussed the differences between cause and mechanism, and has addressed the question of the completeness of mechanistic explanations. Here we attempt to initiate a dialogue between science and philosophy of science in the discussion of mechanism, particularly as it relates to interdisciplinary fields such as psychoneuroimmunology. We come to the conclusion that the belief that more detailed mechanistic studies are more explanatory or impactful than studies that are “less mechanistic” is often misguided, because of (1) failure to distinguish between cause and mechanism and (2) mistaken acceptance of misconceptions regarding the completeness of mechanisms.

Therefore, it is important to consider the (respective) contribution(s) of cause and mechanism when seeking to explain a biological phenomenon. Some philosophers of science propose 1) that “a satisfactory explanation requires ... a description of a mechanism”, 2) that description of mechanism requires the identification of both activities, which “are the producers of change” (for example, bind, phosphorylate, etc.) and entities (e.g., cells and molecules) which are “the things that engage in activities, and 3) that “activities are types of causes” (Machamer et al., 2000), p. 1, p. 3).

However, others adhere to a so-called difference-making account of causation in which intervention studies are used to establish causal claims and “that causal relationships are often established in the *absence* of information about ... mechanisms”. (Woodward, 2004, 2011). Consequently, these philosophers warn against the temptation to merely describe mechanisms and instead advocate for the necessity of controlled intervention accounts of causation (Woodward, 2004), p. 66).

Consider, for example, fever. Recombinant interleukin-1beta (IL-1beta) administered to rodents was shown to cause fever (Dinarello et al., 1986). This finding against the background knowledge that bacterial fragments (e.g., lipopolysaccharide, LPS) stimulated IL-1 release by macrophages (Gery et al., 1981), indicated that IL-1beta could be an endogenous pyrogen. Subsequent experiments using antisera to IL-1beta or the IL-1 receptor antagonist (IL-1ra) definitively showed that IL-1beta was an endogenous pyrogen mediating LPS-induced fever (Long et al., 1990; Luheshi et al., 1996). Hence, a causal relationship was established between IL-1beta and LPS-induced fever, but in the absence of definitive knowledge about *how* IL-1beta brought about such fevers.

Numerous potential mechanisms were proposed to explain how IL-1beta could induce fever. As IL-1beta binds to brain endothelial cells and stimulates the synthesis of prostaglandins (Cao et al., 1996; Van Dam et al., 1996), which were already known to raise body temperature when administered into the preoptic area (Splawinski et al., 1978), this seemed a plausible mechanism. However, follow-up intervention experiments (in this case pharmacological inhibition of or genetic deficiency for prostaglandin synthesis enzymes) were necessary to determine that prostaglandin synthesis was required (the difference-maker) for both IL-1beta and LPS-induced fever (Engblom et al., 2003; Li et

al., 2001; Li et al., 1999; Saha et al., 2005). This example illustrates how description of (potential) mechanisms and identification of difference-making causal factors are complimentary and necessary approaches for furthering explanation in biology and medicine (Russo and Williamson, 2007; Woodward, 2004, 2011). Thus, while it is interesting to do “experiments directed towards figuring out how a mechanism operates”, it is important to emphasize “that often experiments are required to delineate the phenomenon for which a mechanism is responsible” (Bechtel, 2008), p. 37).

For some, identification of a cellular level mechanism (brain endothelial cells releasing a diffusible mediator, which then acts on thermosensitive neurons of the preoptic hypothalamus) was sufficient, while others required identification of the molecular components (IL-1 β acting on IL-1 receptors inducing cyclooxygenase-2 (COX-2) thus giving rise to prostaglandin production, which diffuse to nearby and bind to prostaglandin EP3 receptors). And beyond these examples of mechanism, even lower level mechanisms could be sought (e.g., downstream molecules phosphorylated to bind DNA and affect transcription) which then raises the question of what is mechanistic enough? Interestingly, with regard to explanations involving mechanisms, a distinction can be made between ‘how-possibly explanations’ and ‘how-actually explanations’ (Craver, 2006; Machamer et al., 2000), with the former capturing *potential* and/or partial mechanisms and the latter representing a *complete* mechanistic description of a biological response. However, it has also been noted that a, “complete how-actually model [...] is a philosopher’s fiction” and that, “sciences would be utterly paralyzed if complete how-actually explanations were the guiding objective” (Kaplan and Craver, 2011), pp. 609-10). So if the search for a complete mechanism would be paralyzing or senseless for science, why then do more detailed mechanistic accounts seem to be favored?

Identifying the lowest level mechanism may be valued because of the belief that it leads to the development of a more targeted therapeutic strategy of intervention. Some clinicians and life scientists welcome a situation wherein a particular biological response would be brought about by a highly specific mechanism involving only one defined ligand/receptor/ intracellular signaling cascade or where biologically-active molecules, from food components to drugs, would have only one relevant active metabolite and one site and mechanism of action. However, we generally find out

(the hard way) that this is not at all the case. We suggest that mechanistic studies should also emphasize (patho)physiological relevance along with lower-level molecular details. That is to say, it is critical to evaluate variables such as sex, age, past experience and the environment, all of which can impinge on and alter specific mechanisms, in an effort to best describe the pathophysiological relevance of specific mechanisms.

This resonates with the ideas of some philosophers of science who emphasize that “a mechanism is always contextually situated” and that “its behavior is often altered by conditions in the environment” (Bechtel, *Mental mechanisms: philosophical perspectives on cognitive neuroscience*, 2008, p. 17). Therefore, “the mechanistic perspective is inherently multilevel” with higher-level sciences providing insights into “the causal factors affecting the mechanism as a whole” that are “not accessible with the tools of more reductionistically oriented investigators” (Bechtel, 2008), p. 17, p. 22). The challenge of interdisciplinary research is to then articulate and possibly integrate these different levels of (mechanistic) explanations.

Finally, some philosophers of science state that “the orchestrated functioning of the mechanism is responsible for one or more phenomena” (Bechtel and Abrahamsen, 2005), p. 423). To illustrate this point consider that similar mechanisms are proposed to explain different and even contrasting conditions. For example, the same entities, namely cytokines, glial cells and neurons, and activities, such as neuroinflammation, have been proposed to account for the lack of appetite and weight loss associated with infectious and inflammatory diseases on the one hand and obesity on the other (Besedovsky and Del Rey, 2014; Burfeind et al., 2016; Guillemot-Legris and Muccioli, 2017; Thaler et al., 2010). But since anorexia and obesity are on opposite sides on the energy ‘balance’ spectrum, it is clear that using “neuroinflammation” as a mechanistic explanation is not adequate to explain both situations. Here appealing to (patho)physiological relevance may help to ultimately get a differential explanation for anorexia and obesity that involves causes and mechanisms specific for each condition. In these cases, instead of pursuing a complete “how actually” mechanistic explanation at lower and lower reductionist levels, a more complete explanation of the phenomenon of interest

may well be obtained by going back to “how-possibly” mechanisms and determining the (patho)physiological conditions under which these operate.

With these examples, we illustrate how establishing causes and describing mechanisms are complimentary in improving understanding of biological systems. It is our proposal that across the biological sciences, and particularly within interdisciplinary fields like psychoneuroimmunology, vague critiques that some model or explanation is “not mechanistic enough” should be replaced by more constructive commentaries regarding specific concerns about causal inferences or (patho)physiological relevance.

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Figure 1

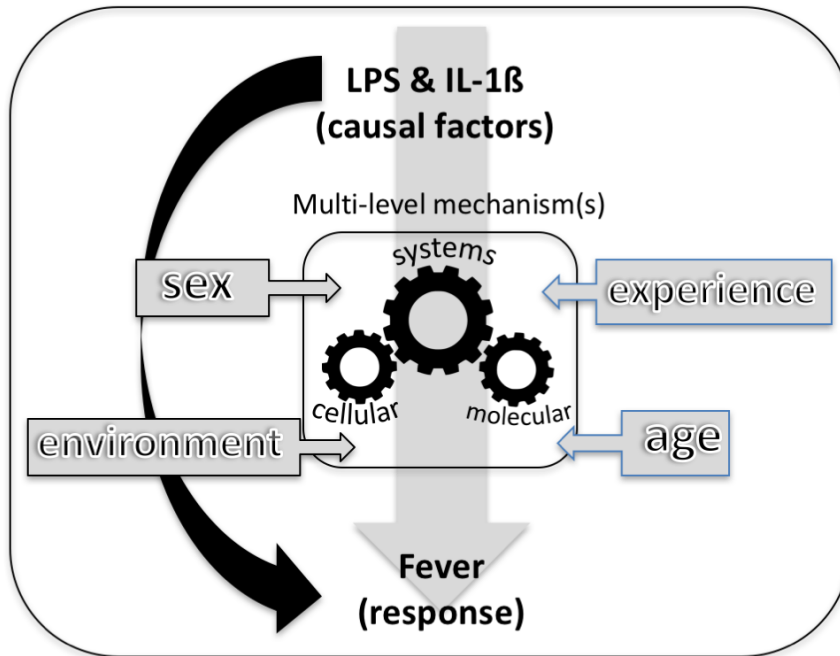


Figure legend: Both the identification of causal factors without description of mechanism (black arrow), as well as description of the underlying mechanism(s) are necessary for explanation of biological responses. Mechanisms exist on multiple levels, and must be considered in the context of (pathophysiologically) relevant factors (e.g., age, sex, experience, and environment), which have the potential to alter mechanisms.