Principled Mechanistic Explanations in Biology: A Case Study of Alzheimer's Disease

In this paper, following a review of the significant problems faced by the Alzheimer's research field, I argue that various strands of clinical evidence point to the conclusion that the existing and widely-accepted 'amyloid cascade' mechanistic explanation of Alzheimer's disease appears to be fundamentally incomplete. I also provide evidence that even when alternative explanations are proposed for the disease, they are often pinned to the amyloid explanation.

In this context, I propose that a theoretical framework termed 'principled mechanism' (PM) has the potential to inspire new sets of empirical questions and novel avenues of investigation that can take a given mechanistic explanation at any stage of development as its starting point. PM is a two-pronged framework: on the one hand, using a short series of 'tests', it systematically compares different components of the mechanistic explanation against a paradigmatic set of criteria, and hints at various ways of making the mechanistic explanation more 'complete'. These steps will be demonstrated using the amyloid explanation, and its missing or problematic mechanistic elements will be highlighted.

On the other hand, PM makes an appeal for the discovery and application of 'biological principles' (BPs) relevant to the phenomenon being explained. BPs are 'principles' since they approximate what some philosophers mean by *ceteris paribus* laws or 'invariant generalizations', and 'biological' because they are operative at and specific to the level of a biological cell. As such, although thermodynamic, evolutionary, ecological and other laws or principles from chemistry and the broader life sciences could inform them, BPs should be considered ontologically unique. BPs could aid in several ways, such as augmenting different facets of the mechanistic explanation itself—for example the deficiencies picked out by the paradigmatic tests—but also allowing further *independent* nomological explanation of the phenomenon.

While this overall strategy can be complementary to certain 'New Mechanist' approaches, an important distinction of the PM framework is its equal attention to the explanatory utility of biological principles. PM can help to move cell biological investigations from what might be called a generally 'mechanistic-descriptive' state (the status quo) to a 'mechanistic-nomological' paradigm, entailing theoretic BPs alongside mechanistic accounts.

Lastly, I detail two hypothetical BPs, one having to do with time and the synchronicity of biochemical processes at the cellular level, and the other concerning the structure of 'disordered' protein domains. I will show how these two theoretical BPs could each inform and improve the potentially incomplete mechanistic aspects of the amyloid explanation and also how they could provide independent explanations of the cellular features associated with Alzheimer's disease.

In all, the goal of the PM approach, which could just as easily be applied to other mechanistic explanations of pathobiological conditions, is to lead to more complete mechanistic explanations but also deeper overall explanations of cellular phenomena afforded by a novel focus on a class of principles specific to cellular processes.

Representative References

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