Sensing the Unknown: Historicising the Discoverability of the Olfactory Receptors within the Life on an Experimental System

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The notion of scientific discovery is traditionally associated with the introduction of novelty into a scientific discourse. It has been central to the philosophy of science, especially in relation to the concept of evidence and the context of justification. The topic of this paper is a discovery that has not been dealt within philosophical debate and that poses an interesting case to formulate another notion of discovery as pertaining to historicity and procedures of epistemic iteration integral to scientific practice, rather than novelty. The case with which I am concerned with is the discovery of the olfactory receptors and its role in the life of an emerging experimental system surrounding the molecular basis of smell perception.

A considerable debate in olfaction theory surrounds the yet unknown mechanism of primary odour recognition. It is hoped that this mechanism will explain why a particular molecule has a particular smell. For almost the entire 20th century any hypothesis about the molecular basis of odour perception remained speculative, simply because the receptors were unidentified. Nonetheless, being considered as part of a wider group of ligand binding processes such as digestion, metabolism and immune responses, primary smell perception was assumed to act according to a shape-sensitive mechanism. Demonstrating the adequacy of this hypothesis appeared to be a local scientific problem and subject to further advancements in technology and measurement. With the discovery of the olfactory receptors (ORs) by Linda Buck and Richard Axel in 1991, the key element for research on the olfactory mechanism was identified at last. Knowing what kind of protein is associated with olfactory responses, it was believed, should enable us to identify what kind of perception mechanism is at work. Fast forward to the present day, however, and insight into the details of the recognition process has not improved greatly. The problem is the experimental inaccessibility of the OR binding site. Studies of transmembrane proteins are notoriously difficult and only very few breakthroughs in elucidating the structure of their binding sites have been made. ORs present a particularly difficult case as standard methods of crystallisation, an essential requirement for protein modelling, have so far been unsuccessful.

Nonetheless, this discovery had important implications for further olfactory research, because it identified smell receptors as a class of 7 transmembrane G-coupled proteins, which strongly suggested that molecules (causing a particular odour) dock on a specific primary receptor according to some kind of shapesensitive mechanism. It was the background of advancements in genetics and growing experimental evidence for an involvement of a G-coupled protein that paved the way for this groundbreaking discovery. Previous studies on olfactory responses already indicated the presence of cAMP (cyclic AMP), a messenger molecule that activates ion channels when a cell is activated. Because of its function of stimulating the formation of cAMP, the involvement of a G-coupled protein was considered to be likely before its ultimate discovery. Although G-coupled proteins take part in a variety of physiological processes, ranging from vision to the regulation of behavioural and immune responses to digestion, those proteins active in chemical ligand binding were all considered to act according to a shape-sensitive mechanism. For this reason, the theoretical implications of Buck and Axel's discovery were not a complete surprise but, rather, reflected orthodox opinion about primary smell perception, which had always taken aspects of molecular shape to be the key feature responsible for odour detection.

It is against the background of the trajectory of olfaction theory that I will analyse the role of this

discovery within the life of an emerging experimental system. To understand how this discovery was made and, moreover, to further show how it relates to the past and future course of olfaction theory, I will trace the reasoning that governed the methods and interpretations and that fostered a laboratory culture most integral to turn previously dispersed olfactory studies into an organised modelling context. Drawing on Hans-Jörg Rheinberger's notion of an "experimental system" and Hasok Chang's concept of "epistemic iteration", I will trace the gradual entrenchment of conceptual assumptions and experimental strategies underlying Buck and Axel's search for the olfactory receptors. The thereby outlined reasoning resonates with the concept of "discoverability" as introduced by Thomas Nickles.

Discoverability describes a process of generative justification, meaning a rational reconstruction of the strategies involved in the path of discovery. In contrast to "discovery" as the original generation of, for instance, theories or hypotheses, the concept of discoverability is also related to the context of justification. Whereas discovery is understood historically as a particular event that resists methodological generalisation, discoverability reflects its post hoc rationalisation that needs not to coincide with the original actions undertaken.

The aim of this paper is to present an argument why not only the event of discovery but also its epistemic reconstruction within justification strategies needs to be historicised. The question by which I am going to address the historicity of discoverability is as follows: what is it for which a discovery is reconstructed in terms of its discoverability? Rather than primarily justifying a theoretical framework, I claim, the impact of the olfactory receptor discovery lies in its historical and changeable role within the life of an experimental system. Discoverability as a rational reconstruction implies the question for what exactly it is supposed to provide a generative justification. The purpose of such a narrative, however, is dependent on the stage of scientific discourse within which it is placed and, given the growth of knowledge, subject to revision as well. The presented genealogy of a discovery as related to the live of an experimental system will aid me to further explore what a historicised perspective on discoverability implies for philosophical analysis of scientific discoveries.