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Methodological advice for the young at heart investigator: triangulation to build better foundations

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Abstract

In medicine and science, one is typically taught the main theories in a discipline or field along with standard models before receiving more instructions on how to apply certain methods. The aim of this work is not to address one method, but rather methodology, the study and evaluation of methods, by taking a philosophy of science detour. In this, a critique of biomedicine will be used as a starting point to address some positions regarding reductionism, specifying notions such as systems and mechanisms, as well as regarding the mind-body problem discussing psychosomatic medicine and psychoneuroimmunology. Some recommendations to make science more pluralistic, robust and translationally-relevant will then be made as a way foster constructive debates on reductionism and the mind-body problem and, in turn, favor more interdisciplinary research.

Introduction

Students are typically taught the main theories in a field along with standard models and experiments before receiving more instructions on how to apply methods in the collection and analysis of 'data' (Grüne-Yanoff, 2014). In addition, experimental life scientists develop aptitudes to recognize mechanisms, which constitute a highly-valued type of causal explanation in their domain, without necessarily understanding why and how. These conventions and implicit ways of understanding of what good research questions and appropriate methods are different between disciplines and make interdisciplinary research challenging. For example, so-called neurovascular coupling constitutes the basic principle for functional brain imaging that is used as a tool by psychologists (Dolcos et al., 2011; Just and Varma, 2007; Rissman and Wagner, 2012), while it is an active research topic for neuroscientist who try to understand under what circumstances and how electrophysiological neuronal activity can increase local blood flow and oxygen delivery (Drew, 2022; Lecrux et al., 2019; Logothetis, 2008).

Studying pain with brain imaging can illustrate how some differences in approach can play out. Many scientists have addressed the question whether or not an objective cerebral signature for pain perception can be obtained with functional brain imaging (Davis et al., 2017; Derbyshire, 2011; Hu and Iannetti, 2016; Legrain et al., 2011; Malfliet et al., 2017; Schweinhardt and Bushnell, 2010; Tracey and Mantyh, 2007; Wager et al., 2013; Wiech, 2016). Others, however, have answered this question in the affirmative early on and used functional brain imaging to explain why some conditions hurt (Eisenberger and Lieberman, 2004).

These matters are relevant to psychoneuroimmunology as an interdisciplinary research endeavor aiming at the integration of psychology, neuroscience and immunology within the broad framework of biopsychosocial medicine (Ader, 2000; Zachariae, 2009). Thus, some articles indicate that brain imaging indicate altered neural processing of peripheral stimuli in chronic painful conditions, such as irritable bowel syndrome, or during acute experimental inflammation (Benson et al., 2015; Elsenbruch, 2011), while others suggest that brain imaging patterns can explain why inflammation is painful (Karshikoff et al., 2016). This, in turn, raises questions about the extent to which sensations, feelings or moods can be reduced to brain circuits or inflammatory processes and how to integrate the latter.

Experimental scientist often attempt to acquire the most recent methods by doing or hiring a post-doc. However, as an alternative to running a rat race for implementing a new method, it could also be helpful to have some guidance in determining the advantages and limitations of different approaches in order to be able to make well-informed and, therefore defendable, choices of methods. Indeed, the latest method is often only perceived the best because its limitations are not yet widely known.

Philosophy of science has studied widely-used constructs like genes, natural selection, levels and mechanisms as well as research strategies and integration of explanations and methods in and between different fields and disciplines (Bechtel and Richardson, 2010; Brigandt, 2013; Craver, 2007; Fox-Keller, 2000; Mitchell, 2002; Potochnik et al., 2018; Potochnik and McGill, 2012; Skipper and Millstein, 2005; Sullivan, 2009, 2018). Philosophers of science typically approach a science method or practice by analyzing it and specifying the conditions in which it is employed or they analyze a study or project in which the methods were used in relation to that study's or project's aim, conceptual starting point and relevant evidence (Grüne-Yanoff, 2014). Philosophers of science can thus be complementary to scientists in making clear the justifications for using particular methods and comparing these across disciplines (Grüne-Yanoff, 2014). Indeed, "[m]ethodology—the analysis and critical evaluation of scientific methods" is now part of the core activities of philosophers of science and can be insightful for scientist in many ways, including for interdisciplinary research and science communication (Grüne-Yanoff, 2014), p. 123).

Interestingly, many clinicians and scientists seem to agree that epistemology, the branch of philosophy interested in knowledge acquisition, can contribute to their disciplines as well as to interdisciplinary research (Marshall, 1997; Moon and Blackman, 2014; Rudnick, 1990; Saad, 2020; Samsonovich and Ascoli, 2005). Furthermore, when philosophers of science and scientist can agree that there is no such thing as a single scientific approach, they can jointly work in the choice and coordination of different approaches to create a fuller and more complete understanding by practicing a form of scientific pluralism[1] (Chang, 2004, 2012; Mitchell, 2002, 2004; Veigl, 2022). Such joint work can take the shape of philosophy of science as a complementary science "ask[ing] scientific questions that are excluded from current specialist science" (Chang, 2004), p. 3) or that of philosophy in science in which a scientific problem is addressed with tools, like logic, for which philosophers are experts, to propose an original solution to scientists (Pradeu et al.). Philosophers can, thus, contribute to scientific pluralism.

The aim here is not to address just one method, but rather to discuss motivations that may underlie the choice of certain methods by taking some philosophy of science detour. This detour is intended to contribute to discussions on, for example, reductionism that have been ongoing in several disciplines as well as in different interdisciplinary fields. As such, it will hopefully provide guidance to junior and senior scientists in their choice of methods to address questions related to health and disease, in particular in the context of interdisciplinary research projects, with a pluralist mindset.

To do so, we first introduce approaches such as reductionism and interventions as well as notions like mechanisms, biological systems, biomedicine and systems biology, which are all at work, at least in the background, in psychoneuroimmunology. Next, we discuss different scientific positions relative to the so-called mind body problem, namely psychosomatic medicine, psychoneuroimmunology, immunopsychiatry and microbiota gut brain axis research. Finally, we recommend to adopt a more

[1] Scientific pluralism can be defined "as the doctrine advocating the cultivation of multiple systems of practice in any given field of science" Chang, H., 2012. Is Water H2O? Evidence, Realism and Pluralism. Boston Studies in the Philosophy and History of Science., p. 260) or "as the position that certain natural phenomena need more than one explanation, theory, or method, to be fully understood" Veigl, S.J., 2022. Scientific Pluralism in Practice: Responses to Anomaly in the Sciences. Philosophy, Theory, and Practice in Biology 14., p. 2). These general definitions cover both theoretical (for example, explanations and model choice) and empirical (methods and findings) aspects. If philosophers of science have been mostly been dealing with the theoretical aspects of scientific pluralism, scientists are more likely to be interested in its empirical aspects. Humility regarding the pretentions of a particular scientific approach is a fundamental motivation for scientific pluralism (Chang, H., 2012. Is Water H2O? Evidence, Realism and Pluralism. Boston Studies in the Philosophy and History of Science.. However, this does not mean that scientific pluralism leads to an "anything goes" relativism characterized by a refusal to judge ibid., p. 261). Instead, a "many things go" pluralism "takes a clear stance against absolutism" ibid., p. 261). Scientific pluralism is minimally a form of tolerance in which many systems co-exit, and maximally a place of interaction via ad-hoc integration, co-option of elements or competition between different systems of practicing science ibid., Mitchell, S.D., 2002. Integrative pluralism. Biol. Philos. 17, 55-70..

pluralist stance and we propose ways to attain more pluralism both in psychoneuroimmunology and in the life sciences more generally.

1. A 'divide, reduce and conquer' story of science

The aim of this first part is to provide some background on the general questions of reductionism and interventions before addressing notions like mechanisms, biological systems, biomedicine and systems biology that specifically apply to the life sciences. Since the 17th century, science has been a rather successful enterprise in providing explanations for all kinds of phenomena of interest to us. However, it has also been criticized for a division of labor between scientific disciplines and fields that loses the bigger picture and cannot adequately address the 'real' problems including disease and climate change that we are facing. In particular, biology has been deemed to have succumbed to reductionism. Using one of these critiques of reductionism as a starting point, an overview will be provided of how biology has organized and explained phenomena of interest by appealing to the notions of systems and mechanism.

a. Biomedicine and reductionism

Although its positive contribution to care and research remains debated, the initial formulation of biopsychosocial model of medicine by the internist and psychiatrist George Engel as a critique against reductionism and mind-body dualism of biomedicine (Engel, 1977) seems to be widely shared. Indeed, several authors consider that biomedicine assumes 1) that disease causes are restricted to "biological, chemical, and physical phenomena," 2) that "phenomena are best explained by the properties of their parts" and 3) that findings obtained in experimental models contribute to useful knowledge (Krieger, 2011; Massoud et al., 1998), p. 130).

In the context of Engel's criticism of biomedicine, it may be insightful to distinguish different forms of reductionism[2], even though many life scientists seem foremost committed to so-called "methodological reduction," which is the idea that biological systems are best studied at the lower levels to discover molecular and biochemical causes (Brigandt and Love, 2008). An example of that would be the current interest in 'omics' and systems biology approaches, as discussed below.

b. Proposing a short and selective history of biological systems and compartments

If one focuses on structure-function relationships in biology, one can distinguish a strategy of decomposition and localization that first focused on organs and organ systems (Minelli, 2021) and has progressively shifted, in some reductionist move, to cells and molecules (Nicholson, 2010; Schmidt-Rhaesa, 2007; Strasser and de Chadarevian, 2011). Notions of organ systems can often be described anatomically or functionally, for example the circulatory or cardiovascular system and the digestive or gastrointestinal system. In this respect, Ramon y Cajal around 1900 is interesting in that his "neuron doctrine" proposed functional properties based on anatomical observation of stained tissue, along with the notion of the synapse proposed by Sherrington and an idea of a structure-function relationships based on a sensory-motor distinction that was established decades earlier (Fulton, 1960).

[2] The main issue regarding reduction(ism) is whether the properties, explanations or methods from one field of science addressing higher levels of organization can be accounted for by (and hence reduced to) the properties,, explanations, or methods of another field of science interested in lower levels of organization Brigandt, I., Love, A., 2008. Reductionism in biology. In: Zalta, Z. (Ed.), The Stanford Encyclopedia of Philosophy.. Philosophers have long been mostly interested in "ontological reduction," or the assumption that a system of interest is constituted only by molecules and their interactions as well as in "epistemic reduction," according to which the knowledge of some phenomena at a higher level in one domain can be reduced to or explained by that of processes at a lower level of another domain ibid., Kaiser, M.I., 2011. The limits of reductionism in the life sciences. Hist Philos Life Sci 33, 453-476, Kaiser, M.I., 2015. Reductive Explanation in the Biological Sciences. Springer.. It is interesting to note that mechanistic accounts, which are popular with both philosophers and scientists, do not correspond to classical full theory reduction, but rather to a 'compositional' reductionism in the sense that they propose that the properties and processes at a higher level of composition are thought to be reducible to activities of entities at a lower level Bertolaso, M., 2016. Philosophy of Cancer: A Dynamic and Relational View. Imprint: Springer, Gillett, C., 2007. Understanding the new reductionism: the metaphysics of science and compositional reduction. Journal of Philosophy 104, 193-216, Rosenberg, A., 2020. Reduction and Mechanism. Cambridge University Press..

The molecular turn in the 20th century with the use of more (bio)chemical approaches enabled to envision systems that were not based on anatomical continuities. Although the role of certain cells and molecules in the neutralization of foreign material had been known since the end of the 19th century, an explicit formulation of the immune system emerged only in the second half of 20th century when it was characterized as a diffuse organ or network displaying "partly antagonistic interactions" among its elements (Jerne, 1974), p. 382).

Besides the different organ and functional systems that life scientist have identified over the centuries, it is important to remind ourselves that a multicellular body often contains many cavities and compartments. Such spatial separations have been proposed to enable the emergence of more specialized organs, increased homeostatic regulation as well as physiological and behavioral flexibility (Rosslenbroich, 2005, 2009). Epithelial tissue layers often play an important role in separating the parenchyma of organ systems from other biological compartments and thus contribute to maintain specific extracellular environments (Leys and Riesgo, 2012; Spadoni et al., 2017).

c. Describing and intervening in biological systems

The distinction between observation and intervention is an important when it comes to the study of living systems. According to a popular 'broad-stroke' history of science, the ancient Greeks just observed and it was only Francis Bacon who introduced the experimental method in the 16th century (Byrne, 2020; Gower, 1996; Malik, 2017). Aristotle's reservations about experimentation seem to be linked to the possibility that an intervention can prevent a natural substance from exerting transformations of itself or its surroundings (Byrne, 2020). Instead, Francis Bacon considered that experiments allow to reveal truths in nature that, otherwise, would remain hidden (Gower, 1996).

Centuries after Aristotle, descriptive approaches are now in the spotlight again with the emergence of so-called omics approaches (genomics, transcriptomics, proteomics and metabolomics) that aim to provide full 'maps' of the landscape of genes, transcripts, proteins or metabolites. While the use of high-throughput operational protocols is relatively new in biology and opens new possibilities, some scientists and philosophers of science have also argued that such approaches are partly dependent on and can be relatively easily articulated with more traditional approaches, such as the mechanistic approach of molecular biology (Ratti, 2015; Welch and Rogler, 2003).

An intervention allows us to propose causal relationships by observing the outcome of changing one variable in a system of interest while ideally keeping all the others constant (Woodward, 2003). So-called top-down experiments typically study the effects of an intervention at a higher level of (perceived) organization of living systems, for example putting an animal in a behavioral test, on lower level components (cells and molecules). Conversely, bottom-up experiments usually address the consequence of an intervention at a low (cellular or molecular) level on higher level physiological or behavioral parameters (Craver, 2002).

The use of optogenetics to control cellular activity with light pulses by introducing light sensitive molecules, such as channelrhodopin, into the membranes of cells of interest (Deng et al., 2014; Jiang et al., 2017) is a good example of a recent bottom-up experimental approach. However, the innocuity of viruses and derived vectors to deliver transgenes to mammalian cells continues to be debated (Bessis et al., 2004; Jooss and Chirmule, 2003; Lowenstein, 2002; Lowenstein and Castro, 2002; Sakurai et al., 2008; Wood et al., 1996). Another issue concerns the non-specific effects of light stimulation, such as heat generation (Deng et al., 2014; Jiang et al., 2017). While optogenetics clearly offers unprecedented ways of intervening on biological systems, both scientists and philosophers of science have argued that the possible caveats associated with optogenetics, for example related to the use of viral constructs to infect target cells, remain to be fully determined (Bernard, 2020; Sullivan, 2018).

d. Adjusting mechanisms

Intervening on biological systems allows to establish causal relationships, which, in turn, can easily be incorporated into mechanistic explanations (Woodward, 2002, 2011). In present-day science, "a mechanism [responsible] for a phenomenon consists of entities (or parts) whose activities and interactions are organized so as to be responsible for the phenomenon" (Glennan and Illari, 2018a), p. 2). It is insightful to consider different kinds of mechanisms. Underlying and producing mechanisms are two kinds of mechanism that give rise to processes and end products, respectively (Craver and Darden, 2013). A third kind would be that of maintenance mechanisms, which account for the maintenance of a certain process or property of a biological system within a certain range after a perturbation (Craver and Darden, 2013).

Given the emphasis on parts of mechanisms and the importance of decomposition as strategy in the mechanism discovery, one may wonder at what level of organization one is allowed to stop looking for lower level components of mechanism to explain a phenomena. Some have argued that the decomposition of a system into parts should only end at the level of the fundamental laws of physics (Glennan, 1996). Others, after having pointed out that "[a]ctivties are causes," have claimed that bottoming-out should be relative and determined by where the scientific field in question "stops when constructing mechanisms" (Machamer et al., 2000), p. 6, p. 13). The notion of interfield mechanism has been put forward to account for integration in biology by proposing "mechanism schemas that span many different levels [or] bridge across many different time scales" and by "satisfy[ing] evidential constraints from many areas of biology" (Craver and Darden, 2013), p. 162).

Some theoretical biologists like Howard Pattee, have also proposed that higher level structural or functional properties constrain responses of lower level entities. He remarked that for living systems constraints are often taken for granted and that the important issue seems to be to show how the system works taking into account its parts (Pattee, 1969). Some contemporary philosophers of science, such as William Bechtel, refer to Pattee's work. Bechtel proposes to 'flatten' mechanisms into something that looks like a graph theory or a network with nodes representing mechanisms and functional or structural connections edges that constrain (Bechtel, 2017). In addition, regarding mechanisms, Bechtel and colleagues distinguish constraints that determine the possible behaviors of a system from controls that can alter the flexible constraints operating on a mechanism (Winning and

Bechtel, 2018). Biological constraints and controls are thus ways to conceive of top-down causation when it comes to mechanisms (Bechtel, 2017; Winning and Bechtel, 2018).

It is perhaps time to revise what is valued in mechanistic explanations. Indeed, several authors have pointed out that explanatory power also often comes from considering how entities and activities are organized (for example in the case of natural selection of feedback loops) (Glennan and Illari, 2018b; Kuorikoski, 2009; Machamer et al., 2000). Mechanisms in the latter kind of explanations have been referred to as "mechanism schemata" or "abstract forms of interaction mechanisms" (Kuorikoski, 2009; Machamer et al., 2000). Interestingly, some neuroscientists have recently criticized "the widespread assumption that there is no room for additional causes once we have accounted for all elementary mechanisms within a system," because such "causal reductionism misses out on causes and effects that clearly are important, both conceptually and biologically" (Grasso et al., 2021), p. 1348, p. 1353). So, philosophers of science as well as scientists have come to the conclusion that causal reduction consisting of identifying causes in the activities of entities at lower levels of mechanism can be mistaken because it does not take into account mechanisms that cannot be reduced to their entities and activities.

e. Organizing systems biology

The difference between biology of systems and systems biology is related to the question of reductionism. Systems biologists claim that they their work is non reductionistic, because they do not engage in theory reduction (Gatherer, 2010). In addition, they consider that they cannot be declared guilty of explanatory reductionism as they are precisely after discovering emergent patterns that cannot be derived from previous knowledge obtained by molecular biology. However, systems biology seems committed to methodological reductionism as it typically takes as starting points lower level biological components, such as DNA or proteins. And if one accepts the methodological reductionism that biological systems are best studied at a molecular level, then one should also be prepared to deal with more reductionism-related questions like how knowledge of higher level biological phenomena and process relates to that obtained on molecular components.

Some authors have urged systems biology to take into account not just a systems' components, but also its more general or higher level properties, such as feedback loops, and to consider some characteristics of the whole system (for example demand and supply for metabolic systems) (Cornish-Bowden, 2006; Cornish-Bowden and Cardenas, 2005). And even if the interactions between lower level components of a system of interest turn out to be sufficient for a function or behavior of that system, understanding it in an organismal and ecological context most likely will require considering higher levels of organization as well.

2. Who has the presence of mind and body?

The aim of this second part is to discuss some scientific positions relative to the so-called mind body problem, namely psychosomatic medicine, psychoneuroimmunology, immunopsychiatry and microbiota gut brain axis research. The mind-body problem deals with questions like how bodily condition can give rise to the subjective feelings of pain and hunger and how psychological factors can influence somatic disease. While such questions have long been debated by philosophy, science and medicine have embraced these question as well. In the 20^{th} century, psychosomatic medicine and psychoneuroimmunology have played important roles in, while, more recently, immunopsychiatry and the gut microbiota brain axis have emerged as new takes on aspects of the mind-body problem (Figure 1). These different fields will be illustrated below with respect to the direction of causation that they favor regarding psychological factors and bacteria in the context of disease. It is, however, important to keep in mind that, while all of the field co-exist in some shape or form today, they can be considered to have built on each other. Indeed, minimally, a field that was emergent or actively promoted at a certain time has indicated how and why it was different from the then more dominant scientific approach of the mind-body problem.

a. Biomedicine and dualism

George Engel already criticized Descartes for promoting mind-body dualism (Engel, 1977), but a more recent reproach can be found in the book “Descartes’ error” written by the neurologist Antonio Damasio’s book in the 1990s. The dualism that Descartes put forward in the 17th century was one of substances according to which the body is a physical thing and the mind is not (Westphal, 2016). There is now a large consensus that such a position is not tenable because it implies that explanations of interactions between mind and body do not follow fundamental laws of physics. If adopting a dualism of properties position between mental and physical properties allows to be compatible with the laws of physics, it still raises the question of how to explain mind-body interactions (Westphal, 2016).

Although monism, the position opposed to dualism regarding the mind-body problem, raises questions regarding reductionism, philosophical debates of it also touch upon many other aspects. One of the best known quasi-monist positions is behaviorism that posits that the mind is behavior and that has dominated experimental psychology in North-America in the first half of the 20th century (Westphal, 2016). Another monist physicalist position is that of the so-called identity theory according to which mental events are identical to brain states (Westphal, 2016).

b. Psychosomatic medicine

In the early 20th century it appeared that not all diseases could be explained by infectious microbes or nutritional deficiencies. Among the illnesses that still lacked explanations at the time were asthma, rheumatoid arthritis, peptic ulcer, and ulcerative colitis. Today, we would readily consider entities such as chronic fatigue syndrome, fibromyalgia and irritable bowel syndrome (Brown, 2007; Scott et al., 2022). Psychosomatic medicine proposed in the mid-20th century that specific personalities or emotional conflicts could give rise to dysfunction of certain organs and somatic symptoms (Kimball, 1970). Interestingly, the editors of the first board of the journal *Psychosomatic Medicine* also made it clear that the field “is not concerned with the metaphysics of the mind-body problem” and that the guiding idea should be “that there is no logical distinction between the ‘mind and body’, mental and physical.” (Alexander et al., 1939), p. 4). So, in this sense, early psychosomatic medicine would ideally like to monist regarding the mind-body problem (Westphal, 2016).

Several proponents of psychosomatic medicine have nevertheless promoted a better understanding of the interactions and integration of mind and bodily processes (Alexander, 1962; Brown, 1989; Reiser, 1979). This was also the spirit of George Engel’s biopsychosocial medicine (Engel, 1977). So over time, psychosomatic medicine thus seems to have shifted to some form of property dualism (Westphal, 2016).

However, the psychogenic causation of peptic ulcer, put forward initially by psychosomatic medicine, was challenged when the physicians Barry Marshall and Robin Warren showed in the 1980s and 1990s that the *Helicobacter pylori* bacterium was present in most patients with gastric inflammation, duodenal or gastric ulcer and that *Helicobacter pylori* eradication treatment was associated with lower long-term incidence of duodenal ulcers (Forbes et al., 1994; Marshall and Warren, 1984). These findings were awarded the Nobel Prize in 2005 for the “discovery that … ulceration of the stomach or duodenum (peptic ulcer disease) is the result of an infection of the stomach caused by the bacterium Helicobacter pylori” at a time when “stress and lifestyle were considered the major causes” (Institutet, 2005). Thus, the language of the Nobel Prize committee suggests a monocausal vision, which contrasts with that of some contemporary scientists and physicians who seem to have adopted accounts that allow for and integrate multiple causes, including revised views on the role of psychological factors (Jones, 2006; Levenstein, 1998; Lewin and Lewis, 1995; Overmier and Murison, 2013).

c. Psychoneuroimmunology

Over time, psychosomatic medicine has welcomed broader explanations that invoked multiple causal factors, including less specific ones, such as psychological stress. Thus, caring for a spouse with dementia was considered a chronic stressor and shown to be associated with more respiratory tract infections and lower cellular immunity as compared to control subjects (Kiecolt-Glaser et al., 1991). So, in the second half of the 20th century, psychological stress was accepted in fields like psychoneuroimmunology as contributing to the vulnerability to infectious diseases.

Interestingly, another line of research emerged in the 1980-90s showing that administration of non-infectious lipopolysaccharide fragments of Gram-negative bacteria induces many non-specific disease symptoms, such as fever, reduced food intake, anxiety and depressed mood (Hart, 1988; Reichenberg et al., 2001). These findings, which have fed a second line of research in psychoneuroimmunology indicate that while specific bacteria cause specific disease symptoms in multicellular hosts, the host response to the presence of bacteria can also alter the host's physiology and psychology in non-specific ways.

So, while psychoneuroimmunology was initially rather focused on determining how psychological stress can influence disease, it has progressively incorporated the study of how infection, inflammation and tumor growth can affect the host's physiology and behavior. As a consequence, this field considers both top-down and bottom-up approaches and seems to adopt a form of property dualism regarding the mind-body problem.

d. Immunopsychiatry

The more recent field of immunopsychiatry can be considered as a spin-off of the bottom-up approach of psychoneuroimmunology to make its insights useful for psychiatric disorders, such as depression and schizophrenia. The working hypothesis of immunopsychiatry is that immune process and molecules, such as inflammation and auto-immune antibodies, alter the brain and cause depression or other mental disorders. It thus reflects a position according to which mental properties emerge from brain features that is very close to monist physicalism (Westphal, 2016). The findings of clinical trials seem to support some etiological role of inflammation in depression and schizophrenia (De Picker, 2021). However, the most precise interventions targeting prototypical pro-inflammatory cytokines have so far not shown beneficial effects on depression (Knight et al., 2021; Raison et al., 2013). It therefore seems too early to conclude that every type of inflammation is causing depression, just like not every case of an auto-immune antibody gives rise to a mental disorder.

e. Gut microbiota brain axis research

The causal specificity of particular microbes in disease has been questioned by recent findings obtained by DNA- and RNA-sequencing techniques that enable the identification of many microbial species (Fraher et al., 2012; Staley et al., 2018). The resulting characterization of microbiota in multicellular host compartments systems made it possible to associate gut microbial compositions to different diseases and disorders, including mental disorders (Nikolova et al., 2021), often with the assumption that certain intestinal bacterial make-ups are causing such disorders (Dinan and Cryan, 2016; Rogers et al., 2016). And while the gut-microbiota-brain axis had received the most attention, it is important to keep in mind that gut microbiota also influence other tissues and organs (Anand and Mande, 2022) and that microbiota communities of other body parts are also relevant to host physiology and disease (Takada et al., 2023).

However, several authors have pointed out that correlation is not causation, that the host can influence its microbial contents and that the evidence presented in favor of the causal direction from gut microbiota to depression is based on animal studies with transplantation of microbiota and hence different from evidence presented in support of the claim the *Helicobacter pylori* causes peptic ulcers (Loniewski et al., 2021; Lynch et al., 2019; Madison and Kiecolt-Glaser, 2019; Martins-Silva et al., 2021). The guiding hypothesis of gut microbiota brain axis research is that microbial composition alters brain function and, hence, contributes to mental disorders (Berding and Cryan, 2022). Like immunopsychiatry, it also reflects an emergentist position regarding the mind-body problem according to which mental properties emerge from brain features (Westphal, 2016).

3. A realistic future of pluralism?

The aim of this third and last part is to sketch some possible ways to foster scientific pluralism, which is of particular relevance for interdisciplinary fields like psychoneuroimmunology. As indicated above, several philosophers of science have already made pleas for pluralism in science (see also footnote 1) (Chang, 2004; Mitchell, 2002, 2004). With regards to interdisciplinary scientific fields addressing mind-body interactions, such as psychoneuroimmunology, it is important to minimally adopt a form a pluralism that tolerates a plurality of methods and approaches (for example those of neuroscience and psychology) and to maximally work toward a form of pluralism that tolerates and integrates different kinds of explanations.

a. Let's not go to extremes and be aware of reductionistic stances

The life sciences seem to have gone between extremes or to have framed questions in terms of extremes for decades, without necessarily exploring the in-betweens in depth (Stotz, 2008). One illustration of scientific questions being framed in terms of extremes can be found in the structure-function debate about the brain between 'localists or modularists', who believe that mental functions can be precisely localized in the brain, and 'holists', who consider that mental functions instead require widespread brain regions. An important impetus for the localist view of mental functions was given by Franz Gall at the start of the 19th century, when he proposed a theory according to which certain mental faculties are related to differences in size of the cerebral cortex. This idea of function localization in cortical regions was corroborated by Paul Broca's finding that aphasia, or the inability to speak, could be linked to lesions of the left frontal lobe of the cerebral cortex (Fingler, 2000). Later, in the early 20the century the neurosurgeons Harvey Cushing and Roger Penfield systematically stimulated cortical areas to determine their functions during surgery in epilepsy patients. This allowed them to elaborate ‘motor’ and ‘sensory’ homunculi cortical maps that are still found in modern neuroscience textbooks (Fingler, 2000; Folzenlogen and Ormond, 2019).

However, Pierre Flourens in in the 19th century and Karl Lashley in the 20th century, challenged localization theories based on their findings obtained with brain lesioning techniques in animals (even though the techniques employed were quite different between the two). This resonated with the criticisms of clinicians like Jackson, Head and Goldstein who warned against the dominant interpretation that some loss of function associated with a lesion in a particular brain region reveals the endogenous role of that cerebral structures. However, it is important to keep in mind that strictly opposing modular or localist visions held by Broca, Cushing and Penfiled and a more holistic organization of the brain promoted by Lashley, Jackson, and Goldstein is “rather artificial” (Nazarova and Blagovechtchenski, 2015) as the latter were often simply expressing some reservations regarding conclusions of the former.

Indeed, scientists have repeatedly argued in favor of more ‘connectionist’ views of structure-function relationships in the brain, in which both connections between brain regions and a degree of local functional specialization play a role (Geschwind, 1965; Mesulam, 1998; Spratling, 2002). While some connectionist visions, such as parallel distributed processing, can of course, again be frontally opposed to pure localist views, more nuanced frameworks have also been proposed (Bowers, 2002; Page, 2000; Roy, 2012). Furthermore, MRI findings can be interpreted to indicate that “the nervous system is [organized in a way that is] both highly specific and densely interconnected” (Sutterer and Tranel, 2017), p. 972). However, it is intriguing that some of the networks that seem to be activated by the latest brain imaging approaches, under certain experimental conditions have been given names, such as attentional network reward circuit and salience network (Seeley, 2019), that are reminiscent of the kind of function-structure attributions that localists have often been criticized for in the past (Nazarova and Blagovechtchenski, 2015). Interestingly, in this and other debates, technological innovations have been presented as having solved a long-standing disputes by enabling findings and insights that were not possible previously. However, in many cases, the currently prevailing consensus can be considered to have emerged already as a result of critical thinking about findings obtained with older techniques.

Some extreme positions in scientific debates may be considered as expressions of reductionism, which, in the end, seems to be better off being recognized as a heuristic strategy that comes with certain biases. However, as a starting scientist, it may seem close to impossible to grasp all the details of debates regarding reductionism and how it influences research. Nevertheless, one certainly has intuitions about specific approaches or one may be part of a bigger research environment in which some of these issues regarding reductionism arise. To end this first part of recommendations, we would like propose some specific guiding questions that may be useful to keep in mind when a scientist explores a new body of scientific literature on a complex system of an organism and would like to avoid the reductionistic positions discussed above. A first question is if the original function attributed to an organ systems dripples down all the way down to cells and molecules proposed to comprise it in the sense that, for example, all cells and molecules attributed to the immune systems would only have immune functions? A second useful question to ask oneself to what extent a mediator's biological function is dependent on the body compartment or system in which the mediator is encountered? And regarding the kinds of approaches encountered in different scientific disciplines or fields interested in similar phenomena, one could ask if these interact in fruitful ways. Finally, one may want to know to what extent scientific disciplines and fields that are dominated by reductionistic approaches of complex systems have established relationships with ecological and evolutionary approaches of the same complex systems to better take into account the environmental and historic factors that may determine the behavior and function of an organism or its biological systems (Cannon and Greenamyre, 2011; Paulson, 1977; Seebacher and Franklin, 2012; Tshala-Katumbay et al., 2015).

b. Let's increase science robustness by 'triangulating' between disciplines

The philosopher of science, William Wimsatt has pointed out that "[t]he use of multiple means of determination to "triangulate" on the existence and character of a common phenomenon, object, or result has a long history in science" (Wimsatt, 2012), p. 61). Indeed, given that each experimental approach comes with both opportunities and biases, it can be claimed to be more important to compare findings obtained by different techniques on a particular phenomenon rather than to repeat the same experiment or to collect big data sets using the same method (Munafo and Davey Smith, 2018).

However, questions have also been raised about the comparability of evidence obtained with different methods and the actual use of triangulation[3] by scientists (Hudson, 1999; Kuorikoski and Marchionni, 2016; Stegenga, 2009; Stegenga and Menon, 2017). Indeed, the use of different methods often depends on diverse, and potentially divergent, scientific perspectives. Perspectives in science can refer to many things that seem to have in common "at least some of the properties of being "from a point of view"" (Wimsatt, 2007), p. 227). One of the major challenges for (philosophy of) science is therefore to determine if different perspectives can lead to some "collective cosmopolitan ability to contribute to scientific knowledge" by 'interlacing' them and, in turn, how to choose between and bridge perspectives put forward by different sciences (Massimi, 2022), p. 335).

[3] "Triangulation is the combination of at least two or more theoretical perspectives, methodological approaches, data sources, investigators, or data analysis methods" Thurmond, V.A., 2001. The point of triangulation. Journal of Nursing Scholarship 33, 253-258., p. 253). Through the use of triangulation, one can decrease and counterbalance the limits and biases associated with following one single strategy. This, in turn, increases the robustness of findings and one's ability to interpret them. In the experimental sciences in particular, "methodologic triangulation has the potential of exposing unique differences or meaningful information that may have remained undiscovered with the use of only one approach or data collection technique in the study" ibid., p. 255). As such, triangulation is an active strategy to maintain and foster scientific pluralism (see also foot note 1).

c. Let's transform translational research

The prevailing view after World War II was that medical progress stems from discoveries in areas of basic research, which thus set the pace for technological progress (Fang and Casadevall, 2010; Maienschein et al., 2008). In the 21st century, translational research has been proposed as "a new social contract for the way science works in society" to accelerate the transformation of basic research discoveries into novel diagnostic, therapeutic or preventive strategies of disease (Maienschein et al., 2008), p. 43).

Several authors have since pointed out that clinical conditions or technological applications can also raise new fundamental research questions and that therefore translation research should be viewed as a bidirectional process that can be mutually beneficial for applied science and basic research (Fang and Casadevall, 2010; van der Laan and Boenink, 2015). Other authors have expressed the worry that incentives for unilateral translation research have contributed to many research papers making bold claims that seems poorly justified (Kaelin, 2017). Therefore, making findings as robust as possible by corroborating them with different approaches and in different conditions can be considered as part of a basic scientist's and funding agencies' 'moral obligation' to favor translational research. In addition, actors on the applied sciences side should be less tied to commercial interests or strict guidelines in order to be able to engage more easily in collaborations with basic scientists to evaluate the translational potential of findings.

d. Let's better divide and share labor

Based on declared author contributions, scientific work seems more divided in the biomedical than in the social sciences (Lariviere et al., 2016). Indeed, those performing experiments tend to be of younger academic age than those designing the experiments, analyzing the findings and writing the paper (Lariviere et al., 2016). This combined with the trend that junior scientists typically only have temporary contracts raises the risk of junior scientists being used as 'cheap' labor in biomedical research who are unable to critically reflect on the approaches they are using.

While the system and the pressure it exerts are not likely to change overnight, individuals can still contribute to an exchange-based productive division of labor. Students and junior scientists are encouraged to not lose their curiosity while finding their way in research. Senior scientists with more job security can be considered to have some moral obligation to form and guide their more junior colleagues based on their experience, also as a way for them to stay in touch with what is going on in the lab. Furthermore, senior scientist and their institutions are invited to value teaching as to promote understanding of principles underlying biology and medicine (Fyrenius et al., 2007; Gluckman et al., 2011). Finally, institutions are urged to reduce the administrative load put on scientists and think of themselves as supporting rather than managing research (money).

e. Let's consider some guidance

Evidence-based medicine (EBM) was motivated by the desire to standardize care across hospitals and recommends physicians to follow several steps: 1) frame a clinical question based on a patient's report, 2) examine the relevant literature for published articles, 3) evaluate their validity and utility, and 4) put these in practice (Rosenberg and Donald, 1995). For the evaluation of the literature, EBM proposes a hierarchy of evidence in which *in vitro* and animal studies along with opinions and editorials are considered of low value and clinical trials of high value (Blunt, 2015; Sackett, 1997). Indeed, EBM highly values clinical trials comparing groups of volunteers or patients after interventions to which both the subjects and the clinicians and scientists running the trial are blind or masked as well as systematic reviews and meta-analyses of such trials (Charlton and Miles, 1998; Solomon, 2011).

Intriguingly, one can also observe an increase in systematic reviews and meta-analyses in preclinical research and basic science (Duque-Quintero et al., 2022; Kat et al., 2022; Menting et al., 2019; Sep et al., 2021; Varholick et al., 2020). For example, animal models in which the effects of new molecules are tested can benefit from systematic reviews and meta-analyses if the model can be standardized (O'Hagan et al., 2018; Sena et al., 2014). However, in many cases of basic science, researchers judge reliability (reproducibility) and external validity (relevance) of model systems differently (Sullivan, 2009), meaning that there is often no consensus on model choice. In these cases, it may be worthwhile considering systematic reviews approaches that enable researchers to address multiple topics, such as scoping and umbrella reviews (Ioannidis, 2023).

Regardless of whether it concerns clinical or basic science findings, there is a need to secure a place for critical appraisal by the physician or researcher (Montori and Guyatt, 2008). Guidelines, such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Guyatt et al., 2008; O'Connor and Sargeant, 2014; Upshur, 2009) have been developed with the idea of appealing to the experience of the physician or researcher. These, thus, seem to acknowledge that more tacit considerations are also important in the application of guidelines (Thornton, 2006; Wieringa et al., 2021). Another important and related point is that guidelines should stay guidelines and not become dogmatically-applied rules (Anjum and Mumford, 2017).

The United States' National Institutes of Health are an important sponsor of both clinical and preclinical research and have established guidelines with the idea of improving rigor, understood as "the strict application of the scientific method to ensure unbiased and well-controlled experimental design, methodology, analysis, interpretation and reporting of results" and reproducibility of biomedical research (Collins and Tabak, 2014). However, the so-called replication crisis in science is not necessarily only due to lack of rigor and reproducibility. Indeed, individual researchers often consider a trade-off between external validity (relevance) and internal validity (reliability) (Sullivan, 2009), meaning they can choose to prefer relevance over replicability even though they will perform their studies with rigor.

f. Let’s be more engaged and open-minded for better science practice

When the genome of SARS-CoV-2 was made public, many observers were optimistic about being able to limits its impact across the globe. It is indeed often assumed that a genome sequence reveals some essential properties or “powers of genes” causing a pattern of effects in a rather linear way (Dupré, 2010), p. 19). Instead, it is important to acknowledge that the functions of a genome can only be fully understood if one considers the many structures with which it interacts and that enable it to play a role in an organism (Dupré, 2010). It can therefore be more fruitful to view a virus not as something that can be reduced to its genome, but more as a process in interaction with the host (Dupré and Leonelli, 2022). In this broader perspective on viral disease, it is also important to not consider the immune system as a system whose exclusive role would be to destroy infectious microorganisms in order to protect the host (Zach and Greslehner, 2022). Yet, the immune system sometimes favors disease tolerance and, consequently, reduces host tissue damage or, conversely, contributes to host disease by mounting inflammatory reactions (Zach and Greslehner, 2022).

Even though sharing the SARS-CoV-2 genome was important for vaccine development, the long-term outcome of SARS-CoV-2 infection invites to adopt a broader interaction and pluralist perspective. How else can we hope to better understand that many individuals, including vaccinated ones, go on to develop symptoms, including loss of smell or taste, cognitive impairment and weakness that can last up to a year after diagnosis of a mild SARS-CoV-2 infection (Mizrahi et al., 2023)? In such efforts, it will be important to include patient histories and to communicate what we think we understand and how rather than dismissing some phenomena out of hand. Such an effort could prove mutually beneficial for both clinical science and basic research.

Conclusion

We have tried to indicate some motivations, advantages and limitations of forms of reductionism to help scientists reach better informed decisions on research strategies. In particular, we propose that reductionism is often relative to disciplinary standards of what would be the relevant lowest level of perceived organization and can, therefore, raise particular problems for interdisciplinary research. Medical and scientific fields addressing mind-body interactions often encounter questions regarding reductionism and would benefit from constructive debates on these matters. We humbly hope to have contributed to keep such debates lively and to have provided starting points for young (at heart) investigators to engage in these.

Figure legend

Figure 1: Timeline situating psychosomatic medicine, psychoneuroimmunology, microbiota-gut-brain axis research and immunopsychiatry. Years indicate institutional recognition, in the form of journal or book publications with 1939 being the year in which the first issue of the journal *Psychosomatic Medicine* appeared (Alexander et al., 1939), 1981 the year in which the monograph entitled *Psychoneuroimmunology* was published (Ader, 1981), 2011 the year in which the words “microbiota-gut-brain axis” and “microbiome-gut-brain axis” first appeared in titles of published biomedical articles (Bercik, 2011; Cryan and O'Mahony, 2011), and 2015 the year in which the term “immunopsychiatry” was first used by several authors in titles of published biomedical articles (Leboyer, 2015; Pariante, 2015). The different fields are compared with respect to the direction of causation they favor regarding mind and body. Thus, mind -> body indicates a form of top-down causation while body -> mind designates a type of bottom-up causation.

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