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Expanding the notion of mechanism to further understanding of biopsychosocial disorders? Depression and medically-unexplained pain as cases in point

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Abstract

Evidence-Based Medicine has little consideration of mechanisms and philosophers for science and medicine have recently made pleas to increase the place of mechanisms in the medical evidence hierarchy. However, in this debate the notions of mechanisms seem to be limited to 'mechanistic processes' and 'complex-systems mechanisms,' understood as 'componential causal systems'. I believe that this will not do full justice to how mechanisms are used in biological, psychological and social sciences and, consequently, in a more biopsychosocial approach to medicine. Here, I propose, following (Kuorikoski, 2009), to pay more attention to 'abstract forms of interaction' mechanisms. The present work scrutinized review articles on depression and medically unexplained pain, which are considered to be of multifactorial pathogenesis, for their use of mechanisms. In review articles on these disorders there seemed to be a range of uses between more 'abstract forms of interaction' and 'componential causal system' mechanisms. I therefore propose to expand the notions of mechanisms considered in medicine to include that of more 'abstract forms of interaction' to better explain and manage biopsychosocial disorders.

Keywords: biopsychosocial disorders, evidence-based medicine, mechanisms

1. Introduction

Messiness is an integral part of science, from reality being messy and scientific explanation trying to provide some order to scientific approaches being messy themselves (Schickore, 2020). Here are considered as messy the many causal interactions between geno- and phenotypes as well as phenomena that show feedbacks at several levels, as for example in psychiatry, or that scientists consider to require much skill (Mellor, 2001; Mitchell, 2009). A mess can thus be thought of as “a system of problems” or "problem complex (Ackoff, 1974). Problem complexes have, historically, been addressed by multidisciplinary research in which the initial problems are decomposed into simpler problems that several disciplines then deal with and solve in parallel (Ackoff, 1974). In the alternative approach of interdisciplinary research, the problem complex is not divided into parts that different disciplines then try to solve, but rather considered in its entirety by several disciplines in collaboration (Ackoff, 1974).

Even though there is wide theoretical consensus that many problems regarding living systems in biology and medicine are difficult to decompose into parts (Bechtel and Richardson, 2010; Bruggeman et al., 2002; Mitchell, 2009; Wimsatt, 2007), in practice this seems to have been the major approach that has been followed. For this and the, often associated, collapsing of higher levels of perceived organization (social or behavioral) into lower ones (cellular or molecular), biological and medical research has repeatedly been criticized for being reductionistic (Joyner, 2011; Kaiser, 2011; Rose, 1999; Skurvydas, 2005; van Wietmarschen et al., 2018; Xavier, 2016). Therefore, it can be expected that, even regarding disorders for which decomposition is not straightforward, most of the biomedical evidence presented in favor of causal relationships or candidate treatments for a disease involves entities at a lower level of perceived organization.

From the mid-1990s onwards, important efforts have been undertaken to make medicine more evidence-based. Early on, four steps were proposed for Evidence-Based Medicine (EBM) according to which a physicians should frame a clinical question based on a patient’s report, examine the relevant literature for published articles, evaluate their validity and utility, and put these in in practice

(Rosenberg and Donald, 1995). EBM has typically highly valued 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 (Charlton and Miles, 1998; Solomon, 2011).

Not surprisingly, EBM has been criticized for its statistical view of causation that discounts important aspects of causal interpretation in both lay and scientific activities (Penston, 2005). Some philosophers of science and medicine have proposed to put mechanisms along with randomized clinical trials at the top of pyramid of biomedical evidence or to validate a causal claim only when the candidate cause and effect are correlated and can be explained by a mechanism (Bluhm, 2005; Bunge, 2013; Williamson, 2019). Such requirements have been motivated by cases in which correlation was not accompanied by causality, and *vice versa* (Williamson, 2019). However, it is also important here to remind that the initial motivation of EBM was to give basic science, which has been historically important in driving clinical decisions, less weight, because knowledge of (patho)physiological mechanisms was often not found to predict the outcome of a medical intervention (Andersen, 2012; Worrall, 2007).

Nevertheless, it has been argued that a stronger emphasis on mechanism could help mitigate the imbalance between internal and external validity in EBM. While internal validity refers to the validity of a causal claim in a controlled setting, external validity has to do with the extrapolation of findings obtained in one setting (often a laboratory or clinically-selected sample) to a broader more relevant situation or target population (Campbell, 1957; Cartwright, 2007, 2010; Jimenez-Buedo and Miller, 2010). It has thus been proposed that in EBM, and more broadly in the natural and social sciences, that extrapolation of findings obtained under laboratory conditions to real world situations can be warranted by showing that the causal mechanisms considered to be relevant are the same in both conditions (Clarke et al., 2014; Steel, 2008; Williamson, 2019).

Although proponents of so-called EBM+ have indicated that mechanisms play a role in clinical trials from drug quality and bodily distribution to patient adherence (Aronson et al., 2018), it is also important to point out that the role of evidence in medicine is not limited to treatments and interventions, even though that has been the main focus of EBM. Indeed, the notion of evidence is

broad and can be applied in many ways in and to many aspects of medicine. It can, however, be specified by trying to answer the questions of evidence of what and to what extent as well as for whom (Martini, 2021; Worrall, 2007). Importantly, it also concerns disease diagnosis and explanation. Indeed, the process of diagnosis itself includes generation of hypotheses and evaluating evidence in favor or against the hypotheses put forward (Stanley, 2019; Stanley and Campos, 2013). But, evidence is also essential for disease explanation to physicians and patients. While acute diseases, for example infectious diseases, can often be explained by a monocausal model, chronic diseases often require multifactorial thinking for their explanation (Broadbent, 2009; Fuller, 2018). Nevertheless, mechanistic evidence, for example regarding inflammation, can be useful in providing explanations both for presumed monocausal and multifactorial diseases (Bluhm, 2005; Broadbent, 2009; Furman et al., 2019; Nervi, 2010).

I welcome pleas in favor of trying to understand how and under which circumstances a medical intervention or treatment (best) works by considering mechanisms (Anjum et al., 2020). In addition, I am sympathetic to the idea that because the notion of mechanism seems to be used in a variety of ways since this opens possibilities to consider causation in a non-reductive manner that encompasses psychological and sociological factors (Anjum et al., 2020). Furthermore, the authors of the book *Evaluating evidence of mechanisms in medicine* stress that mechanisms in medicine and public health can be social in addition to biological (Parkkinen et al., 2018). They also distinguish mechanistic processes in which some characteristics are transmitted from one spatiotemporal point to another from complex systems mechanisms consisting of a particular organization of entities and activities that is considered to be responsible for an *explanandum*. However, this group of authors then concludes that, in medicine and the health sciences, mechanisms and mechanistic explanations often involve a combination of the two while leaving open the possibility that other types of mechanisms may be discovered in the social sciences (Parkkinen et al., 2018; Williamson, 2019).

While I agree that one ought to understand mechanisms broadly and that mechanisms relevant to medicine should include social processes, I believe that limiting the notion of mechanisms to

'mechanistic processes' and 'complex-systems mechanisms' without further specification may not do full justice to how mechanisms are used in psychological and social science studies addressing medical disorders. However the question is not so much what philosophers of science and medicine think, but rather how mechanisms are used in publications on complex medical disorders, such as depression and medically-unexplained pain. The working hypothesis regarding this question is that the notions of mechanisms that philosophers have proposed to be operating in medicine need to be better specified to account for how different scientists and physicians use mechanisms in publications on depression and medically-unexplained pain in particular when some phenomena are more relational in nature.

Here I want to take the claim by philosophers that EBM should include evidence of mechanisms as a starting point to discuss what is meant by mechanisms and in particular mechanistic processes and complex systems mechanisms. In a context in which evidence in medicine not only pertains to the evaluation of treatments but also to that of diagnosis and etiology, I will next question if considering mechanisms as mechanistic processes and complex systems mechanisms in medicine can do full justice to explanations that involve not only biological, but also psychological and social, factors. As explanations involving psychological or social factors are often relational in nature, I will discuss the notion of mechanisms as forms of abstract interactions proposed by Kuorikoski as a type of mechanism that can be considered as a form of complex causal system that is relevant in explanations of biopsychosocial disorders, like depression and medically-unexplained pain. I then propose an empirical study of the kind of mechanisms used in review articles on depression or medically-unexplained pain to conclude with a plea for the inclusion of more 'abstract forms of interaction' mechanisms in our explanations of biopsychosocial disorders.

The paper is organized as follows. After introducing in Section 1 the idea that some philosophers would like to include mechanisms in EBM, different notions of mechanism will be discussed in Section 2, in particular those of 'processes' and 'complex systems' mentioned by these philosophers. This will be followed by a specification of 'complex systems' mechanisms with the distinction between 'componential causal systems' and 'abstract forms of interactions' put forward by Kuorikoski. In

Section 3, the biopsychosocial model of medicine will be presented along with the question of how mechanisms are used in academic publications on the biopsychosocial disorders depression and medically unexplained pain. Section 4 will then specify some of the contents of the publications considered regarding the use of mechanisms. Section 5 will place these findings in a broader context of some mechanism-related discussions in philosophy before Section 6 concludes.

2. Different notions of mechanisms

2.1 Mechanisms as processes or complex systems

Biomedical researchers seem to employ the notion of mechanisms in addition to those of networks, pathways and processes, while still problematizing all of these notions as mechanisms in a second vaguer sense(Moss, 2012). Mechanisms and mechanistic explanations have been conceived of by philosophers as causal processes, reminiscent of Railton-Salmon mechanisms, or as complex systems, a notion developed by Bunge, Glennan, Bechtel and Richardson, and Machamer, Darden and Craver (MDC), in which mechanisms are stable organizations of parts and activities responsible for a function or behavior, It is thus important to first consider these two notions. Although MDC state that their view and that of Salmon have in common that mechanisms involve processes and interactions, they also suggest that Salmon's view is limited to fundamental interactions in physics and would be less relevant to the study by other sciences of what activities can bring about at other levels of organization (Machamer et al., 2000).

However, philosophers of science have also argued that, starting from a single general description, different notions of mechanisms and heuristic strategies can be employed in the natural and human sciences (Glennan and Illari, 2018; Kuorikoski, 2009; Stinson, 2017). According to a first, well-known, strategy, mechanisms can be considered "componential causal systems," (Kuorikoski, 2009), which would correspond to a particular take on mechanisms as complex causal systems. In a componential causal system mechanism the emphasis to explain a phenomenon of interest is more on the parts than on the organization, to which an analytic approach is then applied to gain more knowledge on the

properties of the parts (Kuorikoski, 2009). For componential causal systems the typical heuristic strategy is that of decomposition and localization (Bechtel and Richardson, 2010). In this strategy, the causal properties of the composing parts and their organization are supposed to determine causal directions and ultimately the properties of a system of interest (Kuorikoski, 2009). It has been argued that this strategy has been widely adopted in the life sciences such that an acceptable explanation of a phenomenon of interest consists in the description of mechanism, for which in turn parts or entities and activities as causes then need to be determined (Machamer et al., 2000). In the social sciences, the decomposition and localization strategy has been applied, for example when some operations are mapped on particular institutions (Kuorikoski, 2009).

However, and as has been pointed out repeatedly, considering mechanisms as componential causal systems seems to come with a tendency of always trying to determine a mechanism underlying a mechanism (Hedström and Ylikoski, 2010; Leuridan, 2010) and thus begs the question of where they bottom out. Different appreciations of what a complete mechanism is have been put forward. Some have endorsed a view in which higher-level mechanisms must be realized by lower-level mechanism until they bottom out in fundamental laws of physics (Glennan, 1996), whereas MDC have proposed that bottoming out occurs as a function of the interests of a scientific field (Machamer et al., 2000). But regardless of whether the bottom of a mechanism would be the fundamental laws of physics or depend on the interests of a scientific field (see above), it puts interdisciplinary research at the risk of never being considered mechanistic enough (Konsman and Reyes, 2020).

A somewhat related, yet distinct, question is whether componential causal systems mechanisms function as independent modules when they are taking out of the context in which they are embedded. It has been argued that a mechanistic explanation is complete when it designates a mechanism that is sufficient to produce a phenomenon of interest under experimental or natural conditions (Baetu, 2019). The notion of sufficiency that is referred to here is that of engineering in the sense that one should be able to build (*in vitro* or *in silico*) a system from parts that can produce the phenomenon of interest (Baetu, 2019). Thus considered, componential causal systems mechanisms can be thought of

as being largely context-independent and that explanations invoking these mechanisms are of the kind that one gets it if one can make it.

2.2 Abstract forms of interaction in complex systems mechanisms

However, how a mechanism works is not only determined by its parts and activities, but also by how these are organized (Glennan and Illari, 2018). Therefore, a second approach to mechanisms as complex systems consists of considering them as more "abstract forms of interaction," in which the emphasis to explain a phenomenon of interest is on the organization rather than on the parts, and to which a more upward-looking strategy going from the features of parts to the those of the organized system is applied (Kuorikoski, 2009). This strategy is often adopted after the realization that the known causal activities of parts of a mechanism cannot account for the phenomenon of interest or that it is mainly relational, as in natural selection (Kuorikoski, 2009). Moreover, it has been argued that for numerous social systems there are typically not a wide variety of parts with different causal activities and that is therefore unlikely to be helpful to consider lower level mechanisms in explaining the properties of the whole (Kuorikoski, 2009), p. 151). For example, even though in agent-based simulations of economic market situations, some activities like buying and selling are directly linked to the agent as a part, the decisive properties, such as preferences, strategies, demand and supply are in essence relational (Kuorikoski, 2009). Thus, these systems seem to correspond to forms of mechanistic organization in which the types of parts and activities matter less (Glennan and Illari, 2018).

These abstract forms of interaction mechanisms can be linked either to MDC's idea of a mechanism sketch or to that of a mechanism schema. While the former is typically seen as an intermediate temporary stage that needs to be abandoned when more mechanistic detail becomes available, the latter is a type of abstract account of mechanisms to which more detailed descriptions of recognized parts and activities could be added, but need not be, because scientists often care about kinds of mechanisms (Machamer et al., 2000). This distinction has also been interpreted as mechanism sketches corresponding to accounts that acknowledge breaks between operations and mechanism schemas consisting of accounts that display continuity of operations (Bechtel, 2011). Thus, as an

alternative strategy to obtaining more detail regarding parts and activities composing a mechanism, abstract schemas allow for explanatory transposition of a kind of mechanism from one domain to another (Darden, 2002). In addition to between-domain transposition of mechanisms, it may be sometimes be necessary to exclude details of a mechanism and to focus on its organization in order to explain why it displays a particular behavior (Bechtel, 2011; Levy and Bechtel, 2013). Indeed, the diagrams representing mechanisms in textbooks often lack detail to increase its explanatory force (Bechtel, 2011; Love and Nathan, 2015). But in this, mechanistic explanations are no exception to other types of explanation that only contain essential explanatory elements (Love and Nathan, 2015).

Although so-called topological explanations have been opposed to mechanistic explanations (Huneman, 2010), this opposition seems to concern foremost the componential view of mechanism. Instead, abstract mechanisms emphasize less the causal activities of parts and focus more on the abstract or topological characteristics of a system, which are then often described in mathematical terms in an attempt to explain these features (Huneman, 2010). Thus, it has been argued that the varieties of mechanistic organization can be termed topological (Glennan and Illari, 2018).

More abstract forms of interaction kind of mechanisms can be encountered in many different disciplines. Social scholars have distinguished relational mechanisms as those that change links between individuals, groups and larger networks from environmental mechanisms that correspond to external impacts on social life and cognitive mechanisms that occur as the result of changed perception by an individual or group (Tilly, 2001). In psychology, authors have claimed that psychological explanations appeal to mechanisms for which it is not necessary to know how these are realized in the nervous system (Gundersen, 2021). Moreover, William Bechtel has proposed that mechanisms can have their place in psychological explanation if one replaces the notion of material transformation associated with mechanisms in biology by that of information processing and if one adopts another approach to decomposition (Bechtel, 2008). Furthermore, it has been put forward that adopting a less componential causal view of mechanisms allows for cognitive explanatory models in psychology (Stinson, 2016). In line with this, multilevel mechanisms integrating more abstract aspects like

representation and computation can be argued to play an important role in neurocognitive phenomena (Boone and Piccinini, 2016). Interestingly, it has recently been acknowledged by some philosophers that in biology the notion of pathway is compatible with mechanistic accounts if one adopts a mechanism as abstract forms of interaction view (Ross, 2021). Finally, some philosophers of medicine have argued that the explanation of why people get sick involves instantiation of a causal network describing various factors (Thagard, 1998a). Not surprisingly, this approach has been qualified as involving abstract mechanism schemas (Darden, 2018). This brief overview suggests that relational or more abstract notions of mechanisms are at work in different scientific disciplines and are certainly not limited to the humanities.

The heuristic strategies for these abstract forms of interaction mechanisms include the use of abstraction and simple models (Kuorikoski, 2009), which then would be applied in those numerous scientific domains where the explanatory factors are not residing in more details about certain parts but instead in the relations between the parts (Glennan and Illari, 2018; Stinson, 2017). In addition, and as mentioned above, a more abstract view of a kind of mechanism can also be used for explanation when knowledge gained on one case of a kind is transposed to another case to help formulate a hypothesis regrading a phenomenon that is still to be explained as some explanatory template that be applied to different contexts or in different domains (Darden, 2002; Stinson, 2017). Thus, when it comes to biology, for example, the componential causal systems view of mechanisms may be present more in cellular and molecular biology, and the abstract forms of interaction view of mechanisms may be more prevalent in ecological and evolutionary biology.

2.3 Comparing abstract forms of interaction and componential causal systems mechanisms

Sets of heuristics strategies exist in and across scientific disciplines and are used to frame and approach a problem, produce, collect and analyze evidence as well as to formulate and evaluate hypotheses (Grüne-Yanoff, 2021). An interesting historical case of heuristics leading to the proposal of mechanisms is that of explanations involving so-called cancer genes. When it turned out that in many tumors the expression of ‘cancer genes’ was not changed and that the genes differentially expressed in various

tumors affecting the same tissue were often distinct from cancer genes, scientists realized that various genes could alter the same mechanism and proposed that such altered mechanisms were involved in the development of hallmarks of cancer (Bechtel, 2019).

Often, once a mechanism has been proposed, evidence that an entity fills in mechanistic detail in bringing about a phenomenon of interest, for example cell death, requires both showing that a putative entity is altered under conditions that induce the phenomenon and establishing that an intervention on that entity under inducing conditions modifies the outcome (Baetu, 2012). Interlevel mechanistic explanations that purport to explain phenomena at a perceived higher level of organization by localizing, identifying, and articulating mechanisms at a lower level of organization can be considered a legitimate heuristic strategy as long as one does not eliminate the higher level phenomena and one is aware of the boundaries of mechanisms both in terms of levels and context (Wimsatt, 2006).

For componential causal systems mechanisms the main assumption is to consider such systems as, at least partial, aggregates or compositions. However, in order for the property of a system to be considered aggregative and prone to decomposition into parts and their properties, these parts should not display feedback or feedforward interactions (Wimsatt, 1997), which is a typical feature of many living systems. Nevertheless, aggregativity is often, at least initially, assumed including in mechanistic models in the life sciences (Wimsatt, 1997, 2006). Moreover, considering a system as near aggregate or composed for which the properties of the parts can be studied in isolation by looking down levels of organization and filling in mechanistic detail is not always enough to explain the behavior of the whole. Indeed, it often needs to be complemented by looking up and around at organization when there is feedback between parts of a proposed mechanism or when there are indications that it cannot adequately account for the phenomenon to be explained such as relative stability after external perturbation or rhythmicity (Bechtel, 2009).

Mathematical models are one way to assess the completeness of mechanical explanations appealing to componential causal systems (Baetu, 2015). In addition, historical failures to explain biological

phenomena or treat certain medical conditions can also be argued to indicate a lack of complete understanding. The perceived failure of some mechanistic accounts to adequately explain certain biological phenomena has been proposed to be often related to the relative lack of attention to forms of organization (Bechtel, 2011). Thus, in scientific practice, abstract forms of interaction mechanisms are typically proposed after a componential causal system mechanism type of explanation has shown limitations. Evidence in favor of abstract forms of interaction mechanisms, for example feedback, can be obtained when the relative stability of a phenomenon after external perturbation is shown to depend on the action of a downstream entity in a sequence of events or on an element that is not part of that sequence. And even if filling in mechanistic detail for abstract forms of interaction mechanisms can add to the understanding of how things are brought about, most explanatory power is provided by organizational or relational aspects, for example by stating that the stability of a phenomenon is due to a feedback mechanism.

Precisely because different varieties of mechanisms can be distinguished, several taxonomies have been proposed. One way to classify mechanisms is to consider the relationship they bear to the phenomena they are purported to be responsible for, either in the sense of constituting or in the sense of producing them (Glennan and Illari, 2018). Thus, Salmon's notion of mechanisms as sequences of causal events or causal process are concerned chiefly with the production of a phenomenon along a horizontal axis of time (Glennan and Illari, 2018). In contrast, when mechanisms are proposed to underlie or constitute phenomena, which is a frequent claim in the work of Craver, then they seem to occur more along a vertical axis of links between wholes and parts (Glennan and Illari, 2018; Glennan et al., 2022). Complex system mechanisms can thus be thought of as constituting, but also producing, phenomena of interest. It is important to keep in mind that in the literature complex causal systems and componential causal systems are often considered as two slightly different terms for the same type of mechanisms. Here it is proposed that abstract forms of interaction emphasizing the organizational aspects of complex system mechanisms can also be considered when considering how phenomena are constituted or produced.

Given that, minimally, "[a] mechanism for a phenomenon consists of entities (or parts) whose activities and interactions are organized so as to be responsible for the phenomenon", other ways of classifying mechanisms concern the varieties of parts or entities and their interactions and activities or those of organization (Glennan and Illari, 2018, p. 92). Regarding both parts and their activities as well as interactions, one important trend in research is to try and make these more concrete and detailed. Although organization can vary to a large extent independently form the concrete parts and activities of a mechanism, the organization of mechanisms tends to be less studied (Glennan et al., 2022). Along the organization dimension, mechanisms as sequences of causal events or process would turn out be rather 'flat,' horizontal or one-dimensional. There is a tendency when it comes to componential causal systems to focus on the activities of parts as causes and to view the organization as constraints along which these causes operate. Indeed, such mechanism are often viewed as nested hierarchies, which implies some vertical movement towards lower level mechanism until they are considered to bottom-out because some fundamental level (physical or determined by the aims and interests of a scientific community has been reached (Machamer et al., 2000). Instead, the focus for abstract forms of interaction mechanisms is more on the form of organization rather than on the parts of complex system to account for a phenomenon of interest. As a consequence, there are typically no issues regarding the question of where such mechanisms bottom out.

Although there may be notions of mechanisms that are common to the natural and social sciences, it is likely that within the sciences different fields or domains attempt to differentially characterize the parts, activities and organization of mechanisms that are purported to play a role in phenomena of interest (Bunge, 2004; Dalkin et al., 2015; Illari and Williamson, 2012). Indeed, the concern has been expressed that because cell biology or neuroscience investigate more cohesive systems and evolutionary biology and social science address more distributed phenomena, the characterization of a mechanism that applies to the former may not be informative for the latter (Hedström and Ylikoski, 2010; Kuorikoski, 2009; Skipper and Millstein, 2005). However, it has also been argued that following a minimal account, according to which a "mechanism 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, 2018, p. 92), does not imply that thinking in terms of mechanisms comes down to radical reductionism, but can instead promote integration, for example between neuroscientific and psychological levels (Gundersen, 2021).

More specifically regarding medicine, some philosophers have expressed reservations concerning the use of mechanisms and have proposed to restrict its use to physical illness, because the mind-body problem has proven, at least until now, unsolvable (Gillies, 2017). Other philosophers have made the point that although mechanisms in medicine are likely to be both biological and social, important lacunas exist regarding mechanistic explanations of social phenomena (Parkkinen et al., 2018). Nevertheless, these authors predict that new mechanistic models will be proposed in medicine that include social factors and stress that these models should not be reductionist (Parkkinen et al., 2018). It is therefore interesting to investigate to what extent EBM and the calls for a more important place of mechanisms in EBM (Anjum et al., 2020; Bunge, 2013; Parkkinen et al., 2018; Williamson, 2019), can be informed by notions other than that of the componential causal systems mechanisms of drug action and etiological mechanisms of physical illnesses. In addition, the possibility that a more flexible use of the notion of mechanism can play an important role in the articulation of interfield relationships will also be explored regarding so-called biopsychosocial disorders.

3. Biopsychosocial medicine and mechanisms?

Even though it is the type of medicine we are most familiar with in Western societies, biomedicine does not simply correspond to the junction of biology and medicine (Valles, 2020). Rather, it is better characterized by an emphasis on biological, over psychological or social, determinants of disease and the adoption of a form of reductionism according to which complex phenomena displayed by some systems are thought to be due to one main factor ultimately derived from a single primary principle and can be best accounted for by the characteristics of the parts of the system (Engel, 1977; Krieger, 2011). Thus, in the biomedical framework, an illness is typically accounted for by some physical dysfunction at a lower level of organization (Rocca and Anjum, 2020).

Biopsychosocial disorders have often been described as being of multifactorial pathogenesis (Hauser et al., 2014; Meng et al., 2016; Van Oudenhove et al., 2011) and may therefore correspond to the kind of problem complexes or messes mentioned in the introduction. The biopsychosocial label refers to an alternative model of medicine proposed by George Engel to encourage physicians to be more educated and skilled in psychosocial domains and to thus counter the reductionist approach to identify causes of an illness (Engel, 1981). An example of such a reductionist approach has been the establishment of *Heliobacter pylori* as a main cause of peptic ulcers after decades of consensus that psychosomatic factors were at its origins (Levenstein, 2002; Thagard, 1998b). However, some authors have also come to conclusion that, overall, the evidence that psychological stress causes ulcers and reduces response to treatment is robust and that *Helicobacter* alone cannot explain ulcers since many individuals who are infected do not get ulcers (Levenstein, 1998).

The biopsychosocial model of medicine was initially framed to fit Von Bertanlanffy's general systems theory, according to which groups of linked phenomena can be considered as systems with functions and characteristics that are similar at various levels of organization, from molecules to society (Engel, 1977). In addition, the same principles are proposed to function at all levels of organization with the latter being linked in such a way that a transformation at one level brings about changes at other levels (Engel, 1977). Even though the biopsychosocial model of medicine can be considered as an elaboration of a complex problem space or a mess as indicated in the introduction, not much indication was provided on how scientific disciplines and fields studying different levels of perceived organization could or should interact. Importantly, biopsychosocial medicine, in contrast to biomedicine, admits downward or top-down causality, according to which changes in the whole system can bring about changes in its parts, thus making it impossible to understand the full phenomenon of interested displayed by the system just by analyzing parts separately (Rocca and Anjum, 2020).[1]

[1] The spirit of the biopsychosocial model of medicine can also be found in more recently formulated frameworks, such as the ecosocial theory (Krieger, 2005, 2014) and biosocial science (Alvarado, 2020; Roberts and Rollins, 2020). Although similar in spirit, there are also some differences between biopsychosocial medicine and these more recent frameworks. For example, while the biopsychocial model of medicine aspires to be useful both for medicine and the individual patient, the ecosocial and biosocial models foremost target population

In interfield theories, one field can provide a physical characterization, in terms of location, structure and nature, of parts or processes used in another field and even propose causal relationships between parts of interest to the two fields (Darden and Maull, 1977). Such activities at the interface between, and aimed at linking, disciplines are thought to require collaboration while at the same time each discipline pursues its own agenda (Abrahamsen, 1987; Bechtel and Richardson, 2010). However, other scholars have argued that bridging and integration between psychology and neuroscience, for example, is complicated by their different grain of abstraction (Hochstein, 2016).

In the more recent philosophy of science literature, mechanisms have been proposed to play a role in interfield integration when fields work on various features of one mechanism at a certain level or when scientists establish links that comprise the behavior of a mechanism as a whole and that of its parts (Craver and Darden, 2013). However, in adopting an approach based on levels of organization, social and psychological factors have to somehow interact with biological mechanisms or explanatory models, and one runs the risk of ending up with a rather loose patchworks (Baetu, 2019). In addition, it is important to keep in mind that in spite of the claim of some philosophers of science that mechanistic explanations are not reductionist (Andersen, 2014; Bechtel and Abrahamsen, 2005; Craver, 2005), mechanistic accounts in the life sciences have often been criticized for being reductionist (Konsman and Reyes, 2020; Kuorikoski, 2009; Soom, 2012; Stinson, 2017).

Moreover, if one adopts the idea that mechanisms play an important role in integration of scientific fields while accepting the idea that disciplines likes psychology and neuroscience constrain each other, this entails questions that mobilize metaphysical positions when designing experiments to determine which variables to intervene on and under which conditions and how to interpret findings obtained in certain models (Hochstein, 2019; Povich, 2019). Such questions regarding mechanisms and integration between scientific disciplines or fields are particularly relevant for biopsychosocial disorders and medicine. However, here the question of how notions of mechanisms are used in a more

health. Furthermore, and even though the ecosocial and biosocial models incorporate and are compatible with psychological factors, they do not indicate this in their very name. For these reasons, the term biopsychosocial will be employed here as a general label.

biopsychosocial approach of medicine was not addressed by examining theoretical papers, but rather by considering publications on depression and medically-unexplained pain, which are often thought of as biopsychosocial disorders.

Several authors have argued that depression corresponds to a rather stable clinical entity over time, even though there are some differences with, for example, melancholia (Horwitz et al., 2017; Kendler, 2020). Its explanation in the 19th and through much of the 20th century appealed mostly to psychological and contextual factors (Horwitz et al., 2017; Kendler, 2020). However, from the second half of the 20th century, depression was more and more proposed to be due to biological factors, in particular, reduced monamine release in the brain (Feighner, 1999; Heninger et al., 1996; Kraemer and McKinney, 1979). Some success in treating depression with pharmacological drugs along with the existence of the DSM diagnostic category of 'depression due to a medical condition' and research indicating that biological factors are important in the etiology of depression (Gilbert, 2001; Rantala et al., 2018) have further favored the emergence of a biomedical approach to depression.

However, and although biological explanations of the genesis of mental disorders have been found to be associated with reduced blame for schizophrenia, this was not the case for depression (Kvaale et al., 2013). Moreover, the biomedical model of depression has also been heavily criticized by clinicians and scientists (Deacon, 2013; Gardner and Kleinman, 2019; Kinderman, 2005). In addition, philosophers of science and medicine have pointed out that because biochemical, neurological and genetic levels are all causally relevant to major depressive disorder, it cannot be considered an aggregative complex system that would be nearly decomposable (Mitchell, 2008a; Schaffner, 2008). Although this debate is far from settled, it is safe to say that biological, psychological and social factors can all be relevant to depression and that, therefore, the latter ought to be considered a biopsychosocial disorder.

While acute pain is typically indicative of tissue injury and explainable biomedically (Goodwin and McMahon, 2021; Julius, 2013), chronic pain often remains medically unexplained, yet is thought to involve biological, psychological, and social factors (Cheatle, 2016; Gatchel et al., 2007; Pincus and

Castrejon, 2019). Indeed, many authors consider that biomedicine cannot explain cases in which an individual is ill, but does not show any objective signs of dysfunction (Rocca and Anjum, 2020) and call for an alternative causal approach that takes into account the complexity and sensitivity to context of medically unexplained symptoms, like chronic pain (Eriksen et al., 2013). Indeed, patients with medically unexplained symptoms show higher scores on catastropihizing cognition associated with bodily perceptions (Rief et al., 1998). Moreover, such patients think in terms of, and express the need for, explanations that link psychological and physical factors (Dowrick et al., 2004; Peters et al., 1998; Salmon et al., 2004). Interestingly, in proposing alternative accounts, several philosophers of science and medicine have taken the biopsychosocial model of medicine as a starting point (Baetu, 2019; Coninx and Stilwell, 2021).

The aim of the present work was to assess how notions of mechanisms are employed in relation to medically unexplained pain and depression. The methods employed to meet this aim included database searches and content analysis of articles to determine to what mechanisms refer and how the term is used. Expressions like “mechanism of action” or “underlying mechanism” were considered to indicate component causal systems if the interaction or relationship of mechanisms’ parts was fixed and direct and most of the explanatory work was done by appealing to properties of the parts (Glennan, 2002). For example, mechanisms of action often invoke cell membrane receptors coupled to intracellular biochemical pathways that serve as signal transducers for which the coupling is taken as given and the emphasis is on the intracellular molecules to explain the biological effects. The term underlying mechanisms is frequently used to refer to constituting or nested mechanisms. In nested mechanisms, parts are be obtained because the system is supposed to be nearly decomposable and are conceived of as causally independent, which, in turn, can give rise to the proposal that there are parts with activities within parts with activities (Povich and Craver, 2018). However, it is also important to point out that other authors deem it unlikely that a complex biological system, such as the brain, corresponds to a well-ordered hierarchy of nested mechanistic parts, because the boundaries of such mechanisms are often unclear (Stinson and Sullivan, 2018).

Alternatively, notions such as that of selective mechanism, feedback mechanism, cognitive mechanisms or integrative mechanism suggested a type of link or organization that was considered a more abstract form of interaction mechanism. In the discussion on natural selection, those who do not consider it a mechanism emphasize that it does not involve the same parts all the time, whereas those who view it as a mechanism can admit that the environmental factors exerting selective pressure do not need to be one entity and see it rather as an abstract activity (Skipper and Millstein, 2005). Indeed, natural selection and the related concept of fitness cannot be viewed as intrinsic properties of parts in that their causal characteristics are relational rather than decomposable (Kuorikoski, 2009). Furthermore, feedback mechanisms can also be considered to correspond to a form of organization that does not dependent on particular parts or activities that can be encountered in different versions in mechanistic process and systems at all levels of organization, from molecular to social (Glennan and Illari, 2018). Cognitive mechanisms are usually conceived of as multilevel with explanations typically abstracting away from detail (Boone and Piccinini, 2016). In addition, cognitive mechanisms often involve feedback and integrative mechanisms (Boone and Piccinini, 2016; Newen, 2017). For these reasons, cognitive mechanisms were considered as abstract forms of interaction mechanisms.

The notion of integrative mechanisms deserves some more discussion as it seems to be some mix of component causal systems and abstract forms of interaction. A distinction between constitutive and integrative mechanisms has been put forward, in which the latter gives an explanation of how a property of interest incorporated into causal or law-like relationships with other properties can form a complex of higher-level properties (Haug, 2010). Hence, the relational aspect is important in integrative mechanisms. In addition, the relationship between constitutive and integrative mechanisms is mostly that of many-many in the sense that one type of integrative mechanism can contain many constitutive mechanisms and that one constitutive mechanism can be part of several integrative mechanisms (Haug, 2010). Finally, different kinds of integrative mechanisms can be at work in different scientific fields and disciplines (Haug, 2010). For example, in physiology, integrative mechanisms are often used to explain how different stimuli can bring about a response (Cardinali et

al., 2000; Charkoudian et al., 2010; Hillyard, 1999). Similarly, in neuroscience, integrative mechanism typically account for the convergence of signals at the level of the synapse, neuron, brain structure or nervous system (Bassolino et al., 2019; Jacobs et al., 1986; Saper and Levisohn, 1983; Schmidt-Hieber and Nolan, 2017; Watts and Sanchez-Watts, 2002; Zoli et al., 1993). In all of these cases integrative mechanisms seem to involve both organizational or relational aspects and constitutive mechanisms.

Finally, the notion of integrative mechanisms has also been employed between sciences, for instance as an attempt to bridge the discrete and abstract descriptions of mental processes by cognitive science and their more continuous and concrete neural network implementations studied by neuroscience (Maurer, 2016). Such discussions about interfield integrative mechanisms are often framed in terms of relations between different levels of analysis and explanation without much emphasis on constituting mechanisms (Maurer, 2016). However, some authors have argued that multidisciplinary integration should be considered as models that assemble results regarding correlated and causally relevant factors in a level-neutral manner (Baetu, 2019). These causal models differ then from complete mechanism explanations in that the former indicate constraints and causal relevant factors and the latter stipulate the sufficient causes to bring about a phenomenon on interest (Baetu, 2019). But, if interdisciplinary integrative mechanisms are taken as mechanism schemas or abstract forms of interaction mechanisms, then the proposed organization and relationships between factors types of explanation can accommodate causal constraints and relevance. So while the relational or network aspect is important in integrative mechanisms and is reminiscent of abstract forms of interaction, they often appeal to and can incorporate component causal system mechanisms.

In view of the above, the claim investigated here is that in the literature on depression and medically-unexplained pain, which are often considered biopsychosocial disorders, mechanisms are not always merely construed as mechanistic processes or component causal system mechanisms that bottom-out to account for these disorders, but that aspects of abstract forms of interaction mechanisms are also present.

4. Use of mechanisms in reviews on depression and medically-unexplained pain

So, philosophers of science have spent some effort on specifying the notion of mechanisms and may even have come to some kind of consensus (Glennan et al., 2022). However for biomedical researchers mechanisms may refer to something less-well specified anywhere in between having a susceptibility to explain in a rather general sense and being (metaphorically) related to know-how concerning the use of machines in more narrow sense (Moss, 2012). Accordingly, there may be a risk of disconnection between philosophers, on the one hand, and physicians and researchers, on the other hand, regarding mechanisms in the health and life sciences. Indeed, while work in philosophy of science on mechanisms may come across as a reflective extension of science, one needs to keep in mind that it is mostly based on cases taken from neuroscience and cell biology in the late 20th century and may therefore not be representative of biology and medicine more broadly speaking. Consequently, it is key to study if the notions of mechanism put forward by philosophers emphasizing the importance of mechanisms in medical evidence correspond to those used in medical and scientific articles. Moreover, the biopsychosocial model aims to become an alternative to biomedicine, not only in terms of care, but also when it comes to explanation of illnesses. Thus, it is important to get a better insight into how mechanisms are used in publications on two conditions, namely depression and medically-unexplained pain, which can be considered biopsychosocial disorders.

The articles considered here were restricted to reviews for several reasons. First, so-called systematic reviews as archived by the Cochrane Library are highly ranked in the EBM pyramid of evidence (Atkins et al., 2004; Grant and Booth, 2009; Moreira, 2007). This seems, at least in part, to be motivated by the worry that individual studies may be subject to biases and the belief that these can be mitigated by considering several studies according to a standardized protocol (Chandler and Hopewell, 2013; Moher et al., 2009; Moreira, 2007). One could be left with the impression, based on the introduction that clinical trials, and, in turn, systematic reviews never mention mechanisms. However, it is important to keep in mind though that mechanisms often constitute essential elements in the justification and interpretation of a clinical trial (Agencies, 1998; Aronson et al., 2018; Parchment and

Doroshow, 2016; Parkkinen et al., 2018). Furthermore, several authors consider that the justification of clinical trials for different generations of antidepressants moved from serendipitous findings to progressively more mechanism-of-action-based pre-clinical evidence (Feighner, 1999; Lopez-Munoz and Alamo, 2009; Robinson, 2018). In this context it is interesting to observe that recent antidepressant strategies consist of developing drugs which can increase the availability of cerebral monoamines by interfering both with transporter reuptake and feedback mechanisms (Butler and Meegan, 2008; Millan, 2009). More generally, targeting feedback mechanisms alone or in combination with signal transducing cascades have been proposed to lead to a new era of discovery of therapeutic options (Araujo et al., 2007). In this sense, different notions of mechanisms, including more abstract ones like feedback mechanisms, can be thought to have fed and to continue to feed the production of biomedical evidence.

Second, less standardized, narrative reviews do not only tend to present the state of the art in a specific field or regarding a specific question, but also collect relevant published findings to present them as a comprehensive framework (McMahan and McFarland, 2021). Narrative reviews can thus propose certain links between findings and topics, and in some cases even promote the authority of new research fields (Blümel and Schneiderman, 2020). It has therefore been argued that reviews offer the best occasions for presenting novel claims (Sinding, 1996).

Third, in practice, an individual original research paper as a unit of publication often only contributes one or two elements to a mechanism proposed by the work of others. Review articles, instead, often synthesize many of these contributions into a more complete mechanistic explanation. Accordingly, review articles can be expected to deal less with the experimental details involved in elaborating a particular mechanism than would primary research articles in the life and medical sciences.

Finally, and as has been repeatedly pointed out, the number of original scientific articles has rapidly increased in the life and health sciences over the past decades (Ketcham and Crawford, 2007; Sinding, 1996), making it often close to impossible to keep up with the state of the art in a field. Thus, by focusing on reviews here, the idea was to put less emphasis on how scientists obtain bits of evidence

in favor of some parts of mechanism that is related to a phenomenon of interest, but more on how researchers seem to utilize mechanisms in their reasoning once mechanisms have been established to some extent to propose certain links between findings and disorders.

To collect review articles on "depression and mechanism" and "medically unexplained pain and mechanism," several online databases were used. The biomedical literature database PubMed supported by the US National Institutes of Health yields reproducible search results and contains over 30 million articles that have been indexed by humans (Blümel and Schneiderman, 2020; Klopfenstein and Dampier, 2021). Similarly, PsychInfo is a database with its own thesaurus and indexing provided by the American Psychological Association that covers psychological and psychiatric as well as social topics to a larger extent than PubMed (Eady et al., 2008). Finally, SocINDEX with full-text is a database with its specific thesaurus and indexing that covers all subdisciplines of sociology, and in particular peer-reviewed articles in journals, some which go back to 1895 (Tyler et al., 2017). Another important database, is the Cochrane Database of Systematic Reviews that contains systemic reviews "undertaken by teams of volunteer authors, who have access to free training resources, reference texts and software for preparing and maintaining their review" (Henderson et al., 2010, p. 617). Searches were limited to publications in English and performed on March 29, 2021.

The search string "medically unexplained pain and mechanism" as part of an advanced search in title, abstract and keywords on Cochrane Reviews did not yield any hits. A more specific search was therefore done for the most well-known condition characterized by medically unexplained pain, namely fibromyalgia, which resulted in 3 hits. A search on PubMed with the keywords "medically unexplained pain and mechanism and review" yielded 47 hits while the same string entered on PsychINFO gave 7 publications, with 4 in common with those found on PubMed. In addition, a more specific search was done with fibromyalgia as a condition characterized by medically unexplained pain. Since a PubMed search with the keywords "fibromyalgia and mechanism and review" resulted in over 500 publications, this search was limited to publications with "fibromyalgia" as a title word, which resulted in 235 publications. A PsychInfo search with the keywords "fibromyalgia and mechanism and

review" resulted in 104 publications with 11 in common with those found on PubMed. Finally, searches with "medically unexplained pain and mechanism and review" or "fibromyalgia and mechanism and review" did not yield any publications on SocINDEX.

For medically unexplained pain, identified reviews spanned the period from 1993 to 2021. Among the different reviews on medically unexplained pain, different uses of mechanisms regarding etiological factors were encountered, for example between "mechanisms by which emotion … or social factors impact physical disease" and "brain mechanism of functional somatic syndromes" (Kano et al., 2020, p. 139; Kube et al., 2020a). Many authors emphasized the relevance of psychological mechanisms, such as emotional and failure-focused avoidance, catastrophizing, denying or minimizing pain, as being relevant for fibromyalgia (Beneitez et al., 2020). Other authors actually pointed out that biological, cognitive and social mechanisms need to be considered when it comes to pain sensitivity (English, 2014) or that the neural mechanism of central sensitization (see below) cannot explain all fibromyalgia-associated comorbidities (Arnold et al., 2019). A few authors also put forward the idea that "a biopsychosocial perspective … permits integration of complex biologic and psychosocial mechanisms" (Masi et al., 2002, p. 81) or "propose[d] a preliminary conceptual model using a biopsychosocial perspective to integrate what is known about biologic and psychosocial mechanisms in the etiology of [juvenile primary fibromyalgia syndrome]" (Kashikar-Zuck et al., 2000, p. 388). Similarly, pleas were made for "more research … to better understand the psychosocial mechanisms of cognitive-emotional sensitization and interpersonal sensitization," without which "the likely outcome will be a further strengthening of biomedical treatment options and a weakening of the biopsychosocial approach" (English, 2014, p. 537).

Numerous studies adhered to the idea that treatments would be more successful or could be improved "if they follow the results of mechanism research" or "unravel the specific cognitive behavioural mechanisms responsible for the development and maintenance of chronic pain" (van Koulil et al., 2007, p. 578; Rief and Martin, 2014; Van Houdenhove et al., 2010, p. 359). Similarly, some publications made pleas to better understand the mechanisms of action of different so-called alternative medicine

therapies for medically-unexplained pain (Guidelli et al., 2012). While some studies indicated that one should move from the social and psychological mechanisms to the neurobiological mechanisms to "investigate the mechanism of disease" (Kano et al., 2020, p. 147), others envisioned integration or convergence of these different mechanisms, often under the label of 'central sensitization' (see also below) (den Boer et al., 2019; English, 2014; Kube et al., 2020a; Nijs et al., 2014).

An advanced search for "depression and mechanism" in title, abstract and keywords on Cochrane Reviews resulted in 53 publications of which 13 were further analyzed based on the relevance of the title and abstract. In these publications, mechanism referred to either a mechanism of action of some form of therapy or to a putative etiological mechanisms. As a PubMed search with the keywords "depression and mechanism and review" resulted in more than ten thousand publications, this search was rendered more specific by limiting "depression and mechanism" to the title. In this case, 50 publications were obtained. Interestingly, a search for reviews using "depression" and "mechanism" as title words on PsychINFO resulted in 166 hits for publications with only about a dozen in common with those found on PubMed for the same search. Entering "depression and mechanism and review" on SocINDEX yielded 76 publications.

Regarding depression, reviews found spanned the period from 1983 to 2021. The vast majority of publications dealt with candidate etiological biological or neural mechanisms or mechanisms of action of treatment options, including pharmaceutical drugs, electroconvulsive therapy and transcranial neurostimulation, but also psychotherapy, cognitive therapy, physical activity, omega-3 polyunsaturated fatty acid supplementation and St. John's Wort (Butterweck, 2003; De Raedt et al., 2015; DeRubeis et al., 2008; Disner et al., 2011; Gujral et al., 2017; Hsu et al., 2018; Kandola et al., 2019; Marwood et al., 2018). More specifically, with regard to mechanisms of action of different forms of therapy, such as "[c]ognitive therapy and antidepressant medication," the idea that they "probably engage some similar neural mechanisms, as well as mechanisms that are distinctive to each" seemed to prevail (DeRubeis et al., 2008, p. 788).

Concerning potential etiological mechanisms, a few publications discussed socio-economic or psychological mechanisms, like those related to income inequality and socials networks (Marroquin, 2011; Patel et al., 2018; Ridley et al., 2020; Schaefer et al., 2011). For example, one study was interested in "disentangling selection mechanisms responsible for [similarity in] depression" among friends considering preference, avoidance and withdrawal (Schaefer et al., 2011, p. 765). The authors of this study pointed out that "[d]elineating which mechanisms are in operation is vital to appropriately target interventions to counter negative consequences of depression for social integration" (Schaefer et al., 2011, p. 780). However, most publications focused on attentional or cognitive mechanisms and their possible neural correlates within the framework of a cognitive model of depression (Clark et al., 2009; Cortes-Garcia et al., 2020; Disner et al., 2011; Mennen et al., 2019; Roiser et al., 2012). As mentioned, it has been argued that, in part, similar neural mechanisms mediate the favorable consequences of cognitive therapy and those of antidepressant medication in the treatment of depression (DeRubeis et al., 2008) or that common neural mechanisms allow for integration of the beneficial effects of transcranial neurostimulation and neurocognitive strategies on depression (De Raedt et al., 2015).

Regarding the use of mechanisms in publications on depression and medically unexplained pain, the componential causal systems view of mechanisms seemed to be more frequent than the abstract forms of interaction notion of mechanisms. But abstract forms of interaction mechanisms were not absent from these publications, as one can encounter authors that mentioned mediating or linking mechanisms without necessarily seeking to identify lower level mechanisms (Cortes-Garcia et al., 2020; Ridley et al., 2020; Rief and Martin, 2014; Sampson et al., 2002; Van Ee et al., 2015). For example, it has been proposed that neighborhood conditions in American cities "appear to vary in systematic and theoretically meaningful ways with hypothesized social mechanisms such as informal social control, trust, institutional resources and routines" (Sampson et al., 2002, p. 473). Moreover, "a more relational or transactional framework" beyond "mechanisms such as mentalization, attachment,

physiological factors, and the cycle of abuse" has been called for to "enhance our understanding of the relation between trauma and parenting" (Van Ee et al., 2015, p. 13).

In addition, some of the reviews also contained considerations on the very notion of mechanism. Thus, one could read in a review invoking attentional and cognitive-perceptual mechanisms in the context of medically unexplained symptoms that "psychiatric terms … such as "conversion", "dissociation", and "somatization", have been criticized for implying unproven psychological mechanisms for the symptoms in question" (Brown, 2007, p. 773). Others stated that they "use[d] the term "mechanisms" to refer to the cognitions, affects, and behaviors displayed by children and adolescents in their friendships" (Beneitez et al., 2020, p. 28). Regarding sociological mechanisms relevant for depression, some authors have specified that "[t]hese proposed mechanisms represent middle-range theory (Merton 1968) that can be extended to dimensions beyond depression" (Schaefer et al., 2011, p. 779). Finally, some authors clarified that, concerning the "mechanisms underlying psychotherapeutic change," the identification of mediators is essential with the understanding that "[a] mediator is a variable that statistically explains why and in what way a treatment has an effect on outcome, and [that] can be seen as a potential mechanism" (Lemmens et al., 2016, p. 96). These few examples illustrate that some scientists also provide operational definitions of mechanisms that do not necessarily easily fit the distinction between abstract forms of interaction and componential causal systems mechanisms.

Interestingly, cognitive mechanisms can be thought of as more abstract forms of interaction of neural mechanisms. Long-term potentiation in hippocampal and cortical circuits proposed to underlie some forms of memory has been compared to mechanisms of central sensitization consisting of peripheral nociceptor activation increasing the excitability and synaptic efficacy of local nociceptive pathways in the spinal cord (Ji et al., 2003). Later accounts of central sensitization incorporated reduced local inhibition among the mediating mechanisms and put thus less emphasis on peripheral nociceptor activation (Latremoliere and Woolf, 2009; Woolf, 2011, 2014) and may thus be considered as more abstract mechanisms. Many accounts of medically unexplained pain typically present central

sensitization as being due to impaired activation of descending supraspinal pain-modulating pathways or top-down influences (Cagnie et al., 2014; den Boer et al., 2019; Meeus and Nijs, 2007; Nijs et al., 2014). Somewhat similarly, initial mechanisms proposed to mediate so-called predictive coding or processing, based on the idea that the brain actively anticipates or projects sensory inputs, involved local neuronal circuits within columns of the cerebral cortex (Bastos et al., 2012). However, the proposed mechanism rapidly became more abstract as predictive coding explanations were more generally conceived of as integrating bottom-up and top-down influences in the context of emotional awareness (Gu et al., 2013), pain (Hechler et al., 2016; Kube et al., 2020a) and depression (Kube et al., 2020b; Schutter, 2016). Thus, after an initial detailed cellular or molecular description of mechanisms underlying central sensitization or predictive coding some form of abstraction occurred to take into account other factors.

In summary, and while most publications, especially those identified on the biomedical database PubMed, considered biological mechanisms, the notions of psychological and social mechanisms were also encountered and with some studies even proposing ways in which these could converge or be integrated. For example, several authors related the idea that psychological factors could contribute to sensitization of nociceptive mechanisms (English, 2014; Ursin and Eriksen, 2001). Finally, the majority of the publications seemed to adhere to the idea that identifying mechanisms underlying disorders or mechanisms of action of therapeutic options contribute to making treatments more successful.

5. Regarding biopsychosocial disorders, scientists and physicians use mechanisms flexibly and sketch some interfield articulations

Using the recent plea for a more important place of mechanisms in EBM by several philosophers of medicine and biology and their claim that mechanistic explanations often involve complex systems mechanisms and mechanistic process (Anjum et al., 2020; Bunge, 2013; Parkkinen et al., 2018; Williamson, 2019) as starting points, the aim of the present work was to investigate how mechanisms

are used in review articles on depression and medically unexplained pain. These disorders are often considered biopsychosocial disorders, meaning that they are thought to be of multifactorial pathogenesis (Hauser et al., 2014; Meng et al., 2016; Van Oudenhove et al., 2011).

Given that the 'componential causal systems' notion of complex systems mechanism seemed the most prevalent in reviews on depression and medically unexplained pain, it is relevant to discuss to what extent the assumption that systems of interest are easily decomposable into their components may hold. Several authors have argued that a decomposability criterion is not easily met when it comes to explanations of psychological and cognitive phenomena (Bechtel and Richardson, 2010; Bechtel, 2002; Bruggeman et al., 2002). Other authors have made the more general point that causal modularity, according to which the various causal factors contributing to an effect can be separated, does not apply to biological systems (Mitchell, 2008b).

In this respect it is also interesting to consider that full descriptions of all the possible physical and chemical interactions alone do not necessarily provide biological explanations, but rather constrain the range of possibilities (Mitchell, 2009). Interestingly, some neuroscientists have also proposed that the prevalent hunch of causal reduction among scientist is mistaken precisely because it does not take into account mechanism that cannot be reduced to their parts and activities (Grasso et al., 2021). It is therefore not surprising that some authors promote the idea that a causal account should not only include physical and chemical principles, but also biological, psychological and social processes to yield a model of causation that incorporates many interacting factors (Bolton and Gillett, 2019).

Although Von Bertalanffy in his *General Systems Theory* did not seem to address the question of the articulation between disciplines in great detail, he did point out similarities in the ways systems of interest to the different disciplines are organized and behave. He also indicated that network theories and cybernetic approaches could be used to study systems (Von Bertalanffy, 1968). Concerning the latter, Von Bertalanffy invoked diagrams to illustrate what may, in hindsight, be considered as mechanism sketches or schemas. Indeed, he argued that cybernetics allow to account for the

organization of regulatory mechanisms, so that the structure of such organizations can be acknowledged, even when the complete mechanisms are still elusive (Von Bertalanffy, 1968).

Regarding interfield mechanism discovery, application of an abstract mechanism or instantiation of a mechanism schema has been proposed to play an important role (Darden and Craver, 2002). In this context diagrams are often used to visually illustrate the organization of mechanisms (Darden and Craver, 2002). Furthermore, scientists often use diagrams, which leave out mechanistic details to represent how the general state of a system evolves over time (Sheredos et al., 2013). Thus, in addition to text, diagrams can be expected to characterize both componential causal systems mechanisms and abstract forms of interaction mechanisms types of explanations in reviews on depression or medically unexplained pain. Indeed, many publications contain diagrams that represent both types of mechanisms However, and even though many reviews considered both types of mechanism, one seemed to only employ the abstract forms of interaction notion of mechanism and presented in a figure as the main mechanism the causal links between poverty and mental illnesses (Ridley et al., 2020).

Here the adjective biopsychosocial was considered rather loosely to refer to conditions that are thought as being of multifactorial origin and for which biomedicine so far has been considered to not have provided satisfying explanations. It was found that when clinicians and scientists use mechanism in their reviews on depression or medically unexplained pain, this notion does not only refer to componential causal systems requiring more lower level detail. Indeed, it seemed that clinicians and scientists did not always have in mind more detailed causal components when they talk about mechanisms in the context of depression or medically unexplained pain, contrary to what has been suggested recently for biochemistry (Ross, 2021).

Our findings seem to imply that, in medicine, mechanistic accounts can display some flexibility. Flexibility in the use of mechanism, in the sense that the term can refer to different notions and uses, in medicine has already been acknowledged between mechanistic processes à la Railton-Salmon and complex systems mechanisms promoted by MDC as well as others (Parkkinen et al., 2018; Williamson,

2019). Here, however, the proposal is to expand that flexibility to the abstract forms of interaction notion of complex systems mechanisms to better account for how biopsychosocial disorders and their treatments are explained. Moreover, this expanded flexibility in mechanistic accounts seemed to often occur between disciplines or fields that are broadly considered to be part of biopsychosocial medicine. Indeed, based on review articles considered here, some transitions from an abstract forms of interaction notion of mechanisms, with a relative paucity of detail, to a componential causal systems notion of mechanism, with more detail, seemed to take place between fields or disciplines, like for example, between psychology and neuroscience. Indeed, such transitions were frequently invoked between cognitive and neural mechanisms involved in the etiology of depression (Clark et al., 2009; Cortes-Garcia et al., 2020; Disner et al., 2011; Mennen et al., 2019; Roiser et al., 2012). But it was also encountered, albeit in a less articulated way, regarding medically unexplained pain, for example when psychosocial and neural mechanisms of heightened pain sensitivity in fibromyalgia were mentioned together in a table (English, 2014). For the future, it would be interesting to study to what extent relational mechanistic or abstract forms of interaction notions continue to be applied both in explanation and clinical practice, for example when cognitive models are being mobilized. In particular, one would like to know if abstract forms of interaction mechanisms will continue to be used in explanations or if they will be progressively replaced by componential causal systems notions.

Such transitions between different fields or disciplines are reminiscent of the notions of interfield theories and mechanisms, the function of which has been proposed to be the articulation and explanation of relationships between different scientific fields (Darden and Craver, 2002; Darden and Maull, 1977). Accordingly, biological integration can be thought to involve the proposal of mechanism schemas that cover different levels of organization with varying time scales and fulfil disciplinary criteria of several fields in biology, in addition to those of some in chemistry and physics (Craver and Darden, 2013). In this effort to integrate between levels, scientists link the behavior or functioning of whole mechanisms to those of their parts (Craver and Darden, 2013). Thus, the transitions from abstract forms of interaction mechanisms, with a relative paucity of detail, to componential causal

systems mechanism that occur between different fields or disciplines in interdisciplinary research can be considered as interfield mechanisms.

In case of interfield mechanisms, it is important, however, to acknowledge the possibility that actors in different fields may have varying views on what a mechanism could or should be. As indicated above, for some psychologists, a mediator is a variable that can be considered a potential mechanism when it both explains why (based on statistical analyses) and how some treatment induces on outcome (Lemmens et al., 2016). Interestingly, when these authors evaluated which factors could mediate treatment effects and serve as potential mechanisms, they concluded that none did based on the fact that not any of the included studies attempted to experimentally vary the hypothesized mediator (Lemmens et al., 2016). While this seems compatible with the view that many philosophers of biology hold regarding mechanisms, these authors also remarked that questions can and should be raised about the importance of manipulability as a criterion. In particular, they argue that the relevance of experimental conditions in which can intervene on a proposed mechanism varying its components one by one while keeping the others constant is limited (Lemmens et al., 2016).

Instead, philosophers of biology have frequently emphasized the importance of decomposition, localization and manipulation to establish mechanisms. In such a perspective, psychology typically offers approaches for decomposition of cognitive functions, but much less for the localization and manipulation of those in the brain (Wright and Bechtel, 2007). Thus, these functional decompositions have been proposed by some philosophers of science to correspond to mechanism sketches for which neuroscience is expected to fill in the missing detail (Piccinini and Craver, 2011). In addition, these philosophers emphasize the importance of manipulability in establishing mechanisms (Craver, 2007). Therefore, the level of detail is likely not to be the only dimension on which the appreciation of mechanisms differ between fields or disciplines.

Although the componential causal systems notion of mechanism was most prevalent in the corpus of review articles on depression and medically unexplained pain considered here, it is important to acknowledge that this heuristic stance also comes with some biases. One of these is reductionism of

a phenomenon of interest to the entities and activities of a proposed mechanism (Kuorikoski, 2009). Another potential bias of the componential causal systems notion of mechanism is related to the rejection of the possibility of top-down causes by some of its most prominent advocates (Craver and Bechtel, 2007). However, in the review articles considered here, many authors seemed to acknowledge top-down influences in terms of causes. Finally, the abstract forms of interaction notion of mechanism, along with the componential causal systems view on mechanism, may both be at risk of some reductionistic bias related to the attribution of a border between a system of interest and the environment of such a system (Kuorikoski, 2009). Thus, besides constituting heuristic strategies, notions of mechanisms also come with potential biases that need to be considered.

The main finding of this empirical survey is that, even though componential causal systems mechanisms are the most prevalent, more abstract forms of interaction mechanisms are often present in review articles on depression and medically-unexplained pain as well. This is a welcome perspective in the context of a broader consideration of the notion of evidence in medicine. As mentioned in the introduction, evidence is an important part of disease explanation, although it is often ignored in discussions of EBM that tend to focus more on the role of evidence in the evaluation of potential therapeutic interventions. However, for many chronic conditions, among which many can be considered biopsychosocial disorders, there are typically very few interventions with long-lasting therapeutic benefits for the patients. Thus, it is likely that, along symptom management, satisfying disease explanations are of utmost importance for patients to accept their condition. In this context, abstract forms of interaction mechanisms are more likely provide satisfying explanations for patients' concerns than componential causal systems explanation with their emphasis on more mechanistic detail.

But the review articles considered here were not written primarily for patients, but for academic or clinical colleagues. The presence of abstract forms of interaction mechanisms in these reviews suggests that among clinicians and scientists explanations highlighting organizational aspects are important to account for phenomena framed in the contexts of their disciplines or for relationships between

phenomena studied by different disciplines. Furthermore, in an EBM perspective of evidence concerning the evaluation of interventions, it was also found in the reviews considered that the notion of mechanism of action, thought to typically indicate componential causal systems mechanism, could also refer to more abstract forms of interactions such as cognitive mechanisms. This is an interesting observation in the context of the debate around mechanisms and external validity in EBM. Indeed, critics of the position that mechanisms contribute to the external validity of findings of a clinical trial have remarked that understanding of mechanisms is often incomplete and limited to laboratory conditions (Howick et al., 2013a, b). However, proponents of the position have argued that not every mechanistic detail needs to be known and that mechanisms can be the basis for analogies that increase the external validity of evidence (Guala, 2010; Steel, 2010; Williamson, 2019).

And while this latter point seems to suggest that philosophers promoting the consideration for mechanisms in medicine may implicitly acknowledge more abstract forms of interactions mechanisms, I do think it is important to distinguish these more explicitly from other types of mechanisms. One important distinction, for example, pertains to the completeness of mechanisms with bottoming-out being important for componential causal systems mechanisms but making less sense for abstract forms of interaction mechanisms. I think that, overall, approaches emphasizing more abstract forms of interaction mechanism should be saluted as they are complementary to those emphasizing parts of a system and their activities in attempts to reframe phenomena at the lowest level of organization considered by a discipline or in terms of fundamental physics.

6. Conclusions

Here, the use of mechanisms regarding the messy or problem complex biopsychosocial disorders, depression and medically unexplained pain, was assessed in review articles identified on academic and clinical databases. While philosophers of science have been very good at conceiving of and distinguishing between different types of mechanisms, this may be less the case for scientists and physicians. Instead, they may use mechanisms often as shorthand for some causal processes. So far,

philosophers have argued that in medicine, mechanisms represent either determinate linear arrangements of causes (Gillies, 2017), reminiscent of Salmon's mechanistic processes, or a combination of that notion and complex-systems mechanisms, in particular the componential causal view promoted by MDC (Parkkinen et al., 2018; Williamson, 2019). Here, the proposal is to expand the notions of complex systems mechanisms at work in medicine to include the abstract forms of interaction notion of mechanism to allow for better explanations of biopsychosocial disorders both to physicians and their patients and their treatments.

In the corpus of review articles on depression and medically unexplained pain considered, componential causal systems mechanisms were more prevalent than abstract forms of interaction mechanisms. However, both notions were often present in reviews that discussed the neural mechanism correlates or substrates of some cognitive mechanisms with the latter being more abstract. These more abstract outlines of mechanisms have been coined mechanism schemas and are considered to comprise place-holders for the entities and activities of mechanisms and to specify the organization of the components of mechanisms (Darden and Craver, 2002). Thus, the use of mechanism by scientists and physicians can be thought to correspond to more or less abstract notions of mechanisms distinguished by philosophers of science and medicine. In turn, it is evidence indicating that such mechanisms often play an important role as an explanation of symptoms both for physicians and patients. And in this context it is of utmost importance that medical explanations are articulated to lay conceptions about disease and illness (Nordby, 2008). Thus, more abstract forms of interaction mechanism can be thought to facilitate communication about disease explanation to patients but also to clinical or academic colleagues from other disciplines in an interdisciplinary dialogue. Interestingly, philosophers promoting the place of mechanisms in EBM have also argued that not every mechanistic detail needs to be known for mechanisms to serve as a basis is for analogies that increase the external validity of evidence (Guala, 2010; Steel, 2010; Williamson, 2019).

Moreover, in the case where neural mechanisms are proposed to be correlates or substrates of cognitive mechanisms, as in the case of quite of few review articles on depression, the notion can be

argued to function as an interfield mechanism. Finally, regarding the perceived plausibility of proposed mechanisms, it may be important to keep in mind that for the social sciences, the 'closedness' of a system of interest and the extent to which entities can change the system are important in determining how plausible a mechanistic approach can be (Dalkin et al., 2015). Instead, for the natural sciences, the filling in of detail has been argued to make a mechanism more plausible (Craver, 2007; Machamer et al., 2000). These two readings of the plausibility of mechanisms are, in fact, complementary and can be used in concert regardless of field or discipline.

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