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The effect of psychological factors on pain outcomes: lessons learned for the next generation of research

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Abstract

Big data and machine learning techniques offer opportunities to investigate the effects of psychological factors on pain outcomes. Nevertheless, these advances can only deliver when the quality of the data is high and the underpinning causal assumptions are considered. We argue that there is room for improvement and identify some challenges in the evidence base concerning the effect of psychological factors on the development and maintenance of chronic pain. As a starting point, 3 basic tenets of causality are taken: (1) cause and effect differ from each other, (2) the cause precedes the effect within reasonable time, and (3) alternative explanations are ruled out. Building on these tenets, potential problems and some lessons learned are provided that the next generation of research should take into account. In particular, there is a need to be more explicit and transparent about causal assumptions in research. This will lead to better research designs, more appropriate statistical analyses, and constructive discussions and productive tensions that improve our science.

Keywords: Pain, Causality, Biopsychosocial model, Psychological, Psychosocial

1. Introduction

Pain is a complex sensory and emotional experience, which can occur in relation to actual or potential tissue damage, or perceptions of such damage.[65] In addition, the role of social and behavioral processes in the experience of pain is also acknowledged.[89] Although pain is most often temporary, sometimes an episode of pain persists and becomes chronic. Yet, why the transition to chronic pain occurs for some but not others remains poorly understood. Identifying factors that initiate or exacerbate chronic pain problems is needed, as chronic pain is prevalent,[7,27,79] reduces quality of life, and has tremendous societal and economic costs.[21,61] For example, low back pain is among the leading causes of disability worldwide.[87]

Biomedical approaches that focus on the development and maintenance of chronic pain primarily target structural or biomedical abnormalities. These approaches remain insufficient to understand the myriad of problems that individuals with chronic pain experience. A biopsychosocial perspective has, therefore, been advanced recognizing the complexity and multifactorial nature of pain and related suffering.[17,52] This perspective takes into consideration biomedical variables, psychological (eg, beliefs, emotions, and behavior), and social variables (eg, cultural norms and values and social support). An important scientific and clinical endeavor is to identify risk/protective factors that account for the initiation, exacerbation, maintenance, and recovery of pain problems.[18]

There is a wealth of empirical research that substantiates the role of psychological variables in the experience of pain. Numerous experimental studies in the laboratory have unequivocally shown that factors, such as attention, expectation, and pain-related fear, have a profound impact on pain, distress, and disability.[41] Several theoretical models have been developed

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to explain how exactly these factors affect pain, distress, and disability.[19,37,84,86] Evidence is accumulating that these factors are also relevant beyond the laboratory. Longitudinal research has revealed that psychological factors make a difference in the development and maintenance of chronic pain, distress, and disability.[1,71,80] Several reviews have been published substantiating the role of psychological risk factors in developing persistent pain and increased disability.[42,75] For example, the systematic review of Sobol-Kwapinska et al.[75] concluded that "pain catastrophizing" (better labeled as "pain-related worrying,"[14] which is the term that will be used in this paper), optimism, expectation of pain, anxiety (state and trait), negative affect, and depression were associated with acute postsurgical pain. In sum, there is consensus that psychological factors make a difference in the development and maintenance of chronic pain, pain-related distress, and disability.

Notwithstanding this consensus, there is room for improvement. The evidence base concerning the effect of psychological factors on the development and maintenance of chronic pain could and should be better and stronger.[44,83] The research is, however, challenged by the reliance on observational or longitudinal designs as it is often impossible to experimentally manipulate psychological factors. In these designs, we, thus, have to rely on the variations in the psychological states that occur in individuals in the real world and on their relationships to the variations on the outcomes of interest. This implies that causal inference is difficult and complicated by the potential presence of several biases, among which the role of confounding factors is the best known.[29]

Advances in "big data" and "machine learning techniques" are exciting and promising to address these challenges for several reasons. First, chronic pain has become recognized as an important public health problem to address.[24] Several research agencies have funded large multidisciplinary and (inter)national projects to provide a better understanding of the drivers of chronic pain.[18,55] These consortia and initiatives are collecting data sets consisting of a large number of participants and a large number of variables at different system levels (-omics, physiology, neurology, psychology, and society). These data sets can without doubt be considered as big data, offering higher complexity and increased statistical power than generally smaller data sets from traditional research projects. Second, the field of data processing and statistical analyses has moved forward. Pipelines for integrating and processing of large data sets have been developed and are in use. Machine learning and artificial intelligence (AI) have entered the arena holding promise of new discoveries, better understanding, and faster identification of new intervention targets.[6]

However, these advances in big data and machine learning techniques may blind us by too great expectations, and we may lose sight of some "basic" research tenets. Indeed, high-quality conclusions always depend on a combination of well-articulated assumptions, proper conceptual thinking, and appropriate measurement. The advances in big data and machine learning are supportive of but not sufficient for making high-quality conclusions. First, big data can only deliver when the quality of the data is high. If the quality of big data is poor, the results will also be poor. Second, machine learning and AI offer unprecedented opportunities to analyze data, but we should avoid "black box" approaches that maximize performance (prediction accuracy) at the cost of explaining how performance was achieved. In that context, there is a call for "white box" approaches and explainable AI (XAI). Our approaches should be transparent, interpretable, and explainable.[2] Third, the use of big data holds a risk of "mathwashing," ie, the belief that because mathematics is involved, algorithms of artificial intelligence are automatically objective, truthful, and trustworthy.[46] Hence, we should be sensitive to unduly and hasty applications that may put particularly vulnerable groups at a disadvantage.[10] It is important to remind ourselves that human intelligence (in many situations) still outperforms AI in solving complex, open-system problems.[72]

We, therefore, argue that the advances offered by the availability of big data and machine learning should go hand in hand with conceptual and methodological rigor to reach its full potential. Therefore, we should do better in designing and analyzing observational studies that aim to identify and assess the *effects* of psychological factors on pain outcomes. The word "effects" in italics has been carefully chosen. It refers to the putative causal role that a factor might play, either directly or indirectly through mediating pathways. These "effects" are important for researchers in theory building but equally relevant for clinicians who aim to identify and change the factors that are causally related to relevant pain outcomes. One must keep in mind that such causal questions are different from merely predictive questions,[3,66] which only aim to predict but not to explain. Indeed, predictive questions, including those of screening instruments that aim to predict which individuals with acute pain will develop chronic pain in principle, do not have causal claims. As such, using predictive instruments for theory building or to match interventions is misguided.

In this paper, the message of the need to improve designing and analyzing observational studies when attempting to identify the *effect* of psychological factors on pain outcomes is translated into several lessons learned. These lessons stem from challenges encountered in our own research and from literature reviews.[83] We believe that these lessons can guide the next generation of pain research. As a starting point, we take 3 basic tenets of causality: (1) the cause and the effect are different, (2) the cause precedes the effect within reasonable time, and (3) alternative explanations are ruled out. Building on these tenets, we illustrate potential problems that can occur in efforts to identify *effects* of psychological factors on pain outcomes. In doing so, we bring together various established fields of research, ie, (1) the scholarly approach of the philosophy of causality in the sciences in general and in medicine in particular;[34,68,69,70] (2) the influential tradition in epidemiology about causal inference, stemming from the seminal work of Bradford Hill[32] and its update;[33] and (3) the flourishing field of causal modeling in statistics.[30,56]

2. Three basic tenets

2.1. The cause and effect are different

It may seem obvious that cause and effect should be dissimilar because there is no phenomenon to be explained if cause and effect are identical, similar, or highly overlapping. Cause and effect would then belong to the same class of events, or the cause would be part of the effect. The dissimilarity between cause and effect is not always self-evident in psychological research, especially when it comes to defining and measuring causes and effects. Indeed, psychological factors are typically not discrete events but complex individual characteristics or dimensional states (eg, personality, desires, motivation, attitudes, beliefs, emotions, stress, and quality of life). Psychological factors are constructed based on *consensual definitions* within a particular field in a particular era. Often self-report questionnaires are then developed and validated to assess these defined constructs. Yet, far too often, it is forgotten that these constructs are not real entities and only exist by their proper definitions and conventions.[60] We argue that to clearly separate cause and effect, there is a need for precise definitions and measures.

First, different researchers have different research cultures, academic training, and theories, leading to different definitions. The problem is not so much the variety of these definitions but their hidden nature.[59] Far too often, definitions used for psychological constructs are broad and lack precision. Yet, using precise definitions is a prerequisite to correctly model causal relationships between constructs and to develop and select the appropriate measures. Here, the use of ontologies, which are formal, computer-readable and agreed on sets of constructs, definitions, and their relationships to represent a domain, may be a promising avenue to accelerate research and spread knowledge in pain research. Ontologies may help us to be explicit and transparent about constructs and their definitions and to structure the interrelationships.[51]

Second, cause and effect may become conflated or contaminated in measuring constructs, jeopardizing the validity of causal claims. For example, if a causal claim is made that "self-efficacy leads to less disability," one may have doubts about the causal role of "self-efficacy" if it is operationalized by items that largely measure the reverse of "disability" (self-efficacy item: "I can do most of the household chores, despite the pain"[53]); disability item: "Pain interferes with both work outside the home and housework."[11] In this example, the cause (self-efficacy) and effect (disability) may be too semantically intertwined. Similarly, if a causal claim is made that "poor sleep increases pain interference," one could have doubts about the effect of "sleep" on "pain interference," when the latter is measured by the Brief Pain Inventory, which contains a sleep-related item.[10] In this example, the cause (sleep) is part of the effect (disability). Such critical analysis of the precise content of self-report questionnaires and their implications for analysis is often overlooked. This problem may easily arise with big data. The large number of variables often requires a variable reduction approach, where the labels of the measured constructs are often taken for granted.[62]

This line of reasoning stresses the importance of being aware of the definition of the constructs that one measures and carefully analyzing the content of the questionnaires that are used to measure these constructs.[14] Several methods have been developed to evaluate the (dis)similarity of questionnaires. One approach is to investigate the intercorrelations between the items of the cause and the items from the effect. Current data visualization techniques, such as heatmaps and network approaches, may help identify problematic items that are too similar. Another useful approach was developed for investigating the content validity of questionnaires.[14,40] In the study of Lauwerier et al.,[40] all items that measured pain acceptance were collected and categorized by experts as a function of their content into categories that are considered key components of acceptance or into categories that are not considered part of acceptance. The results highlighted important challenges for making causal inference about the role of acceptance based on these questionnaires. Of particular worry was that acceptance instruments often contain items that reflect engagement in valued activities despite pain. The content of such items (eg, "When my pain increases, I can still take care of my responsibilities,"[49]) can be understood as the reverse of items on a disability questionnaire (eg, "describe how pain has interfered with your normal work"[11,36]). Another method to research the content validity of questionnaires has been developed by Johnston et al.[35] To prevent problems of similarity between cause and effect in the future, we propose to systematically analyze the content of questionnaires measuring causal characteristics or states and focus on the potential overlap with the measures of the relevant outcomes.[81,82] Besides allowing us to detect overlap between cause and effect, these methods also allow us to investigate whether a questionnaire captures a construct in a comprehensive and comprehensible manner.[50]

Within this tenet, there are 2 further issues to be elaborated. First, a content analysis may be performed by expert researchers in the field, providing a fine-grained, detailed, and nuanced analysis of concepts. However, we also recommend involving individuals with lived experience of the condition under study. After all, one would expect that those living with a condition should be able to comprehend the items and be able to differentiate between questionnaires that measure cause and effect. Second, we have to remember that questionnaires may well capture the experience of individuals, but are not particularly successful in transforming these experiences into diagnostic labels that by definition require contextualization and expert opinion. For example, in a previous analysis of so-called somatization, we have found that none of the empirical research on somatization fulfilled the scientific criteria for somatization: "… the tendency to experience and communicate somatic distress and symptoms unaccounted for by pathological findings, to attribute them to physical illness, and to seek medical help for them…"[43] Indeed, "somatization" instruments simply measure the experience of multiple bodily symptoms.[13] We argue, therefore, to label instruments and their subscales in relation to what is actually measured and not to what the researcher or clinician had in mind.[13,14]

Cognitive interviewing techniques[4] are useful for this purpose. In cognitive interviewing, an interviewer follows up the answering of questionnaire items by a participant, and asks specific questions about the comprehension of the item; the processes used by a participant to retrieve relevant information from memory; and the response processes used by the participant. As such, this technique can help determine whether the questions are generating the information the authors aimed to target and whether the response scales used are appropriate.

2.2. The cause precedes the effect within time

Not many will dispute the idea that a cause should precede the effect and not the other way around. Such time asymmetry has become the operational definition of a risk factor.[39] Without the demonstration of a time asymmetry, we may only speak of a "correlate," a measure somehow associated with the outcome. A "risk factor" is then defined as a correlate shown to precede the outcome. Nevertheless, a time asymmetry between cause and effect is not undisputed.[63] Researchers have pointed at the possibility of bidirectional effects of psychological factors and pain, such as between low mood and pain.[54] Bidirectional effects are problematic for approaches that require unidirectionality between cause and effect,[31,57] but they are not insurmountable. First, there may be bidirectionality at a group level but not at an individual or subgroup level. For some, the causality works one way; for others, it works the opposite way. Second, findings may appear to indicate bidirectionality but are unidirectional when taking into account a smaller, fine-grained time scale or unit of analysis. For example, many will agree that a discussion with a colleague is bidirectional. Both influence each other. However, this is the likely conclusion when considering the whole conversation as the unit of analysis. When using smaller units of analyses (utterances, words, and nonverbal expression) and a smaller timescale, one may detect that the conversation consists of many unidirectional influences, albeit dynamic and complex ones. So, we accept the necessity of a time asymmetry between events as a consideration to infer causality.[32] This example show that is of importance to elaborate on the importance of using an appropriate time scale to investigate cause and effect. Most causes "work" and realize their effect within a particular time frame. For example, the rain today may have an effect on sprouting in the upcoming days but not the sprouting of the following year. Distracting yourself from pain may work during that moment, but its effects wane when the use of the coping strategy is stopped. The importance of using the appropriate timescale is often underestimated in longitudinal studies.[74] Causes may manifest their effects only within a particular time frame.[28] A large interval between measuring risk factors and its effects is not by definition a feature of a high-quality study. It may well be that many psychological factors have a short-lived effect or can operate in different ways in the short-term and long-term. Pain-related fear may in the short-term lead to less back pain as back-straining activities are avoided, but the pain-related fear may lead to more pain in the long-term by decreased levels of physical activity. One should, therefore, always be able to reasonably explain how and why a particular psychosocial factor may have an effect within the selected time frame.

2.3. Alternative explanations are ruled out

When an association is found between a putative cause and its effect, the observed association can be spurious and accounted for by alternative explanations.[26] In longitudinal and observational studies, the role of confounding factors[29] is a well-known problem. Carefully deliberating on the role of confounding factors should be common practice in both designing studies and analyzing data.[20,77] Not considering confounders at the design phase may turn out to be a missed opportunity. In the long list of factors that researchers are interested in, the selection of factors is often based on empirical ("Factor A has been shown to predict a pain outcome") or theoretical ("There is a reasonable explanation for why factor A might impact a pain outcome") arguments. The focus is often not on attempting to rule out alternative explanations.[20] We argue this is also the case for studies investigating the role of psychological factors of (chronic) pain and provide 2 examples.

2.3.1. Example 1

Numerous studies have observed that pain-related worrying at baseline is predictive of pain-related outcomes later on.[47,90] It makes sense that pain severity at baseline is considered a confounding factor, having both an effect on pain-related worrying at baseline and the pain outcomes later on. Accounting for such obvious confounding factors should be common practice in original research and systematic reviews and meta-analyses about these factors.[29,48]

2.3.2. Example 2

Recovery or pain expectations are one of the most consistent and reliable predictors of pain outcomes, becoming key factors in research and clinical practice. Peerdeman et al.[58] provided an integrative review on the role of expectancies on pain and discuss the possible theories that explain why expectancies may affect pain. Chief among these is the response expectancy theory of Kirsch.[37] That theory states that expectancies are powerful in themselves and may become a kind of self-fulfilling prophecy. His response-expectancy theory hypothesizes a direct causal link between expectancies and pain. Experimental research on nocebo and placebo has corroborated this view.[5,12,67] Nevertheless, there is also substantial evidence that pain expectancies track the past experiences of pain.[15,16] It may thus be that the predictive power of pain expectancies in observational and longitudinal studies is simply based on the human ability to capture and integrate information from different sources (current pain, physical condition, family history, reports of GP). In the latter scenario, expectancies do not play a causal role at all but reflect the presence of confounding factors.

The latter example illustrates a further critical point. Decisions and discussions about the causal status of risk factors and about the role of alternative explanations do not occur in a vacuum. They take place against a background of (scientific) knowledge and (sometimes competing) theoretical understandings.[34] Indeed, to many philosophical scholars, causal claims do not only rely on data ("difference making argument") but also include explanatory arguments as key ingredients.[22] It is then not surprising that there can be reasonable, well-informed differences in opinion and explanation. Such differences should be welcomed as they can lead to productive tensions and the development of better research designs and analyses of data. However, this is only possible if we are transparent about the assumptions that we make. Directed Acyclic Graphs (DAGs) are knowledge graphs allowing researchers to summarize expert knowledge and a priori assumptions in an intuitive way. Such DAGs may help in visualizing the assumed causal structure between key variables. As a result, it becomes clear which variables may confound the relations of interest. Consequently, causal DAGs are important resources for guiding study design and performing causal analyses.[20,77]

3. Different forms of causality

Risk factors most often work in combination with other factors,[68] or in a causal field, reflecting relevant background factors that enable a cause to have its effect.[45] To acknowledge that complexity, the biopsychosocial perspective distinguishes between predisposing, initiating, and maintaining factors.[17] Other terms have also been used, including precipitating, exciting, perpetuating, and exacerbating factors. Although commonly used, there is no precise definition of these terms or debate on their definition available. Predisposing factors most often refer to the genetic, personal, or environmental make-up of an individual. Reviews on predisposing factors generally list factors that are relatively stable over time or are often rather unspecific.[64] Precipitating or exciting factors are factors, which in combination with a predisposing factor may initiate the pain problem. Maintaining or perpetuating factors are then factors that are associated with a prolonged course of the pain problem. Relatedly, exacerbating factors are those which increase the pain problem over time.

Although it may seem obvious to assign each risk factor to one of the categories, we easily run into difficulties. The distinguishing feature between these factors is their temporal relation with the onset of the problem. For predisposing variables, the time between the presence of the factor to the onset of the problem is in the distant past. These variables can be considered as part of the causal field.[45,68] Exciting or precipitating factors are close in time to the onset of the problem. They can be considered as the last risk factor that was needed in a constellation of other factors.[45,68] Finally, maintaining factors play a role once the problem has occurred.

Table 1

Recommendations for the next generation of pain research of psychological factors.

1. Use and report precise definitions of your constructs.[57] Ontologies may help to manage and structure constructs, definitions, and their relationships.[51]
2. Critically appraise whether the (self-report) instrument actually measures the intended construct and is not conceptually overlapping with the outcome. This can be achieved using content validity methods.[14,35]
3. Investigate whether participants understand the self-report items as intended by the researcher. This can be achieved by cognitive interviewing techniques.[4]
4. Select an appropriate timescale that allows to detect the effect of the cause.[28] The effect of some causes may only emerge after a large time scale. Other causes have immediate and short-lived effects, in which more time-intensive designs (Ecological Momentary Assessment methods and measurement burst designs) should be preferred.[73]
5. Take into account alternative explanations (eg, confounders) in designing a study and analyzing data.[26] Graphic visualizations such as knowledge graphs and causal directed acyclic graphs have proven to be useful tools.[20,77]
6. Reflect on whether and how other (background) causes might interact.[45,68] If insufficient knowledge about the causal relationships and synergies between risk factors exists within the literature or experts (top-down), they may also be identified from the data (bottom–up) with causal discovery methods.[23]
7. Be transparent and explicit about your causal thinking. Prediction and causation are 2 different objectives in data science. When the aim is to prevent or intervene on pain problems, the interest is in causation.[20,77]

Except for some stable factors such as genetics and personality traits, it may prove difficult to order them along such a temporal dimension. In that context the sufficient component cause model, also known as the causal pie model,[68] is instructive. The onset of a health problem is the result of the accumulated exposure to several risk factors. Some may be already present at birth, and others may have been acquired during life. Whenever the combination of necessary components is present, the pie is complete, and the health problem will occur. The last factor in the constellation may then be seen as the initiating or exciting factor. Yet, which factor is last may vary across individuals and is, therefore, relatively arbitrary.

More important than classifying factors as predisposing, initiating and maintaining may be the investigation of synergistic effects of factors. The basic assumption underlying the categorization in predisposing, initiating, and maintaining factors may indeed be the interplay between risk factors. Some factors may be equally necessary for the effect to occur. The investigation of such synergies is largely lacking in research. Most often a black box approach is adopted, in which multiple risk factors are entered into the equation (ie, regression models). Researchers then investigate which factors "explain" the largest part of the variance, or which factor has a unique "explanatory" value, ignoring the fact that interpreting these multiple adjusted effect estimates is often misleading.[88] Instead, we need to investigate the complex relationships between variables, as these might reveal causal interdependencies.[85] We, therefore, argue for a systematic investigation of the synergistic or joined effect of risk factors.[6,38] Many of these synergistic effects still need to be uncovered. This may make the construction of causal models solely based on expert knowledge and the literature a difficult enterprise (top down approach). In this case, a bottom–up approach in which machine learning techniques are used to infer causal structure from the data (ie, causal discovery, for a review see Ref. 23) can be helpful. Once possible causal structures are uncovered, structural equation modeling (SEM; for an overview see Ref. 76) may be used to determine the most suitable causal model and estimate the magnitude of the relationships.[9]

4. Conclusions

Big data and machine learning techniques offer great opportunities to investigate the effects of psychological factors on pain outcomes. Nevertheless, these advances can only deliver when the quality of the data is high and the underpinning causal assumptions are explicitly considered. We have argued that there is room for improvement. In our analysis, 3 basic tenets of causality were taken as a starting point: (1) the cause and effect are different, (2) the cause precedes the effect within reasonable time, and (3) alternative explanations are ruled out. Throughout, we identified some problems, provided some lessons learned, and proposed some ways forward, which we summarize here as our recommendations for the next generation of pain research (**Table 1**). These recommendations may have value in providing structure and guidance in avoiding many of the pitfalls described. However, they should not be treated as prescriptive "criteria" but rather as "viewpoints" (see Ref. 30 for a similar case). Our approach can guide researchers to make informed decisions and to be transparent about these decisions.[59,77] We consider this essential for a rigorous science of pain. Only when we are explicit and transparent about our causal assumptions, will we be able to have constructive discussions and productive tensions that improve our thinking and science. There are several graphic tools that may help us with this endeavor (such as knowledge graphs[8] and directed acyclic graphs[25,78]). It might be time to have a conversation about whether such visualizations of our causal assumptions should become a necessary ingredient of research and publications.

Disclosures

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