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Beyond biopsychosocial: The keystone mechanism theory of pain

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ABSTRACT

Pain is a deeply personal experience, with interindividual differences in its chronification and treatment presenting a formidable healthcare challenge. The biopsychosocial model (BPSm) has been hugely influential within nascent attempts at precision pain medicine, steering the field away from a reductionist biomechanical viewpoint and emphasising complex interactions of biological, psychological, and social factors which shape the individuality of pain. However, despite offering a strong theoretical foundation and holistic perspective, we contend that the BPSm remains limited in its capacity to deliver truly mechanistically informed treatment of pain. We therefore propose the keystone model of pain which offers a pragmatic balance between the dimensionality expansive BPSm and overly reductive approaches, providing both theoretical and practical advantages for the transition from treating populations to individual people.

1. Introduction

Pain is a unique phenomenological experience. It is shaped by a myriad of genetic and environmental factors which determine the structure and function of systems throughout the neuroaxis, with micro-, meso-, and macro-scopic opportunities for interindividual differences spanning from dermal nerve endings to cortex. As such, any meaningful approach to understanding and treating pain must account for these individual differences that make pain personal (Fillingim, 2017). Crucially, this is not solely a theoretical problem but has enormous real-world impact. Pain is the second greatest cause of Years Lost to Disability worldwide (Rice et al., 2016) and current interventions are inadequate to manage this disease burden, with most analgesics having a number needed to treat (NNT) in order to produce 50% pain relief of between 3 and 10 (Borsook et al., 2018; Moore et al., 2014; Finnerup et al., 2015). Crucially, this may not solely represent an inherent inadequacy of the treatments, but also a failure to target the right treatment to the right patient (Fisher et al., 2018; Soliman et al., 2023). However, despite the shortcomings of current strategies targeting treatments at the population level, the best path forwards towards treating individual people remains unclear. Here, we first discuss the barriers that heterogeneity presents for the research and treatment of pain. Next, we overview attempts to address this heterogeneity utilising the biopsychosocial (BPS) model and contend that, whilst it has been a valuable foundation to build our understanding upon, the BPS model has several critical limitations that require addressing. Subsequently, we

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instead advocate for a modified framework which focuses on measurable keystone mechanisms that play a pivotal role in dictating individual pain phenotypes, offering a pragmatic and mechanistically grounded path towards the long-term goal of precision pain medicine. Finally, we use this model to provide a roadmap forward for translational pain science, with an emphasis on inter-disciplinary efforts to create robust composite biomarkers.

1.1. The challenges of heterogeneity in pain

The significant heterogeneity in pain-related physiology gives rise to inter-individual differences in the experience of pain, its chronification, and treatment responses. Crucially, these are theoretically and mechanistically intertwined; the (patho)physiology shaping pain experience and chronification likely also contribute to analgesic efficacy, for which treatment-based predictive biomarkers are needed to facilitate mechanistic stratification. As such, these can collectively be thought of as an individual's "pain phenotype". Furthermore, rather than being static, these phenotypes also fluctuate over time; precision medicine necessitates not only getting the right treatment to the right patient, but also at the right time. To take the example of pain perception, experimental paradigms largely look at a snapshot of behaviour (eg: a pain rating on a visual analogue scale) and try to make inferences as to the mechanisms that shaped it within the temporal context of an experimental session. However, the level of reported pain is also dictated by factors that span back hours (eg: how well did they sleep the previous night? (Lautenbacher et al., 2006; Schuh-Hofer et al., 2013) to years (eg: did they experience childhood mistreatment? (Pieritz et al., 2015; Simon et al., 2022) to millennia (eg: the evolution of their ancestors (Sneddon, 2018; Zeberg et al., 2020). Similarly, whether a given individual develops chronic pain following an injury or responds to an analgesic treatment is not determined in that moment, but rather shaped by innumerable life experiences interacting with a unique genome over time. Moreover, each contributory mechanism has a set of causes itself, collectively constituting a theoretically infinite causal chain of events (Coggon and Martyn, 2005). This overwhelming complexity presents a formidable clinical challenge with regards to treatment. This is perhaps best exemplified by that fact that whether or not a randomised controlled trial meets its primary efficacy endpoint can be due to a fundamental inadequacy of the intervention or a heterogeneous response across patients, with "non-responders" diluting out the benefit seen within a subset of "responders". A growing body of evidence suggests that under many circumstances the latter may be true, leading to the emerging consensus (Fisher et al., 2018; Soliman et al., 2023) that conventional diagnostic categories are too broad to effectively target treatment and mechanistic biomarkers are required to further characterise subpopulations whose neurobiological similarity may result in a greater likelihood of responding similarly to a given intervention. Taken to it its logical conclusions, truly precision pain medicine offers the tantalising opportunity to link mechanisms to targeted treatment at the individual level. To achieve these goals, basic and translational science must provide a robust characterisation of the aforementioned overwhelming complexity, which in turn necessitates a robust guiding model.

1.2. The biopsychosocial model of pain

Since the landmark 1977 paper in Science (Engel, 1979) criticising the reductionist biomedical model of disease, the biopsychosocial model has permeated and predominated within many aspects of medicine (White, 2005), including stratified treatment of pain (Fillingim, 2017; Bevers et al., 2016; Cheatle, 2016; Gatchel et al., 2007; Nicholas, 2022; Quintner et al., 2008; Pincus et al., 1976; Andrasik et al., 2005). In essence, the BPSm asserts that addressing any single aspect of pain, such as biology or psychology, is insufficient to fully explain, understand, or treat pain (Fillingim, 2017; Bevers et al., 2016). Moreover, there is a strong emphasis on the complex interactions of biological, psychological, and social influences, with potential for mediation, additive associations, and moderation amongst others (Fillingim, 2017). This has provided a foundation upon which to build our understanding and placed important emphasis on the individuality of pain experience, whose complexity cannot be circumvented through pure reductionism. This has led to patients being examined more holistically, providing a richer context for, and subsequent insight into, each individual's pain. Indeed, this reflects a paradigm shift which, alongside the gate-control (Melzack and Wall, 1979) and neuromatrix (Melzack, 1999) theories, was one of the most significant advancements in pain research and treatment of the last century. However, it has also not been without criticism. For example, the BPSm has been accused by some of reflecting the old biomedical model, despite it fitting within a seemingly holistic perspective (Quintner et al., 2008). Similarly, Carr and Bradshaw argued for a reframing to the "sociopsychobiological model" in order to counteract what they deem to be an overemphasis on biological aspects and underappreciation of social and psychological determinants of pain (Carr and Bradshaw, 2014). Moving beyond both the undeniable benefits of the BPSm as well as the criticisms that it remains reductionist, we contend that, in the move towards precision medicine, this approach is particularly limited in several practical aspects, which we discuss here in turn.

1.3. The BPSm fails to account for modern materialist views of the mind

The contemporary application of the BPSm is anachronistic given advances in our understanding of the relationship between mind and brain. Inherent within the BPSm is the assertion that psychological and social determinants of disease and its treatment are worthwhile distinguishing from biology. Whilst this has led to the important inclusion of previously underappreciated psychological and sociological viewpoints, such siloing can perpetuate unhelpful constructs. The separation of biological from the psychosocial is often conflated with the reasonable notion that disease arises from the summation or interaction of genetic and environmental factors – the former is often thought of as biological with the latter representing the psychosocial. However, "biological" factors such as diet can be environmental, and events of social or psychological consequence can impact disease or treatment response only to the extent that they influence the structure and function of the nervous system. As such, whilst the BPSm is entirely correct that social or psychosocial factors are influential in shaping pain and its treatment, these constitute poorly characterised biological mechanisms, and their separation represents a false dichotomy which perpetuates unhelpful dualistic perspectives. Specifically, it necessitates a theoretically problematic account of how psychological and biological processes are integrated or interact, rather than fully embracing them as two sides of the same coin. Additionally, it leaves explanations of what drives pain abstracted from the mechanisms underlying it and upon which treatments act.

1.4. The interaction of causal factors makes their identification in isolation meaningless

Stochastic, non-linear, and chaotic processes also play a key role in shaping disease (Coggon and Martyn, 2005; Denk et al., 2014). For example, despite the clear causal role of smoking in lung cancer, it remains neither necessary nor sufficient. Similarly, the vast majority of contributing mechanisms are neither necessary nor sufficient for the development of pain nor its alleviation. By definition, a cause must make a pathogenic contribution under at least one circumstance. However, in other circumstances it may produce no effect, or even prove protective. Identification of only one or several putatively causal factors will likely lead to an erroneous inference as to their functional consequences without sufficient context. Approaches that meaningfully characterise chronic pain must move beyond solely identifying causes, whose actual effects can be drowned out amongst the effects of stochasticity, and

towards elucidating the mechanisms through which causes manifest their effects. Moreover, it is these mechanisms to which we aim target treatment within stratified treatment of pain.

1.5. The BPSm identifies so many causal factors that it is rendered impracticable

The dimensionality imposed by the BPS approach is incompatible with precision pain medicine. It entails characterising the incomprehensibly numerous and multifaceted causes that occur and interact over vast time scales to yield interindividual differences in perception, chronification, and treatment efficacy. Indeed, this cannot be narrowed down much beyond every genetic polymorphism and experience an individual has ever had. This is especially problematic when coupled with the fact that the vast majority of these causes, such as genetic single nucleotide polymorphisms (Mogil, 2012), will explain only a tiny proportion of the variance in treatment responses. Given the practical constraints imposed in typical hospital settings, this combination of numerosity and small impact completely precludes a meaningful individual level characterisation. Moreover, even under the extreme assumption that we could overcome these logistical barriers, this knowledge would remain impracticable. Knowing the multifarious contributions of all the different BPS influences that give rise to an individual's pain phenotype, one paradoxically finds themselves less capable of identifying a clear intervention. How many investigations would patients be subjected to in order to characterise these and how many could a single intervention meaningfully impact?

Collectively, these limitations render the BPSm in its conventional form both a hinderance to a meaningful mechanistic understanding of pain as well as impracticable for truly effective targeted treatment of chronic pain clinically. Novel approaches that ground theoretical understanding of the complexity of interindividual differences in pain that the BPSm affords into a more realistically implementable framework are urgently needed to enable the transition from treating populations towards individual people.

1.6. Keystone mechanisms offer a pragmatic framework building upon the BPSm

Whilst a BPS perspective may offer too many explanatory variables, at the other end of the spectrum, it is infeasible that any single mechanism or biomarker will ever be sufficient to meaningfully stratify chronic pain cohorts. As such, personalised pain medicine necessitates a pragmatic middle ground. We contend that it is imperative to identify "keystone" mechanisms which are downstream of a substantial number of causal influences that may be biological, psychological, social, or more realistically, a combination. A keystone is placed at the summit of a freestanding arch, locking the structure together. It builds upon a much larger number of other stones, but plays a crucial role in the integrity of the system, with its removal causing the arch to collapse. Analogously, here "keystone" pain mechanisms are built upon a large number of causally upstream contributing factors, but play a critical role within the (patho)physiology of pain. This acknowledgement of the numerosity and complexity of contributing factors offers an important departure from strictly reductionist accounts, whilst being causally proximal to treatment mechanisms, overcoming the challenges of inferring the impact of abstracted and interacting causal factors within the BPSm. The long-term aim of this approach would be to identify the minimum set of these keystone biomarkers necessary to capture the majority of the variance in treatment responses between individuals *trans*-nosologically. These can then be incorporated into a larger framework in which clinical experience is used to direct patients through a subset of targeted investigations to probe different combinations of these keystone mechanisms (Fig. 1), providing a pragmatic balance between meaningful stratification and overburdening of patients with unrealistically intensive testing. For example, if a given patient has a set of symptoms that strongly implicates a potential keystone mechanism, investigation of this alone may be sufficient to guide treatment selection without the need for them to undergo a large number of additional assessments.

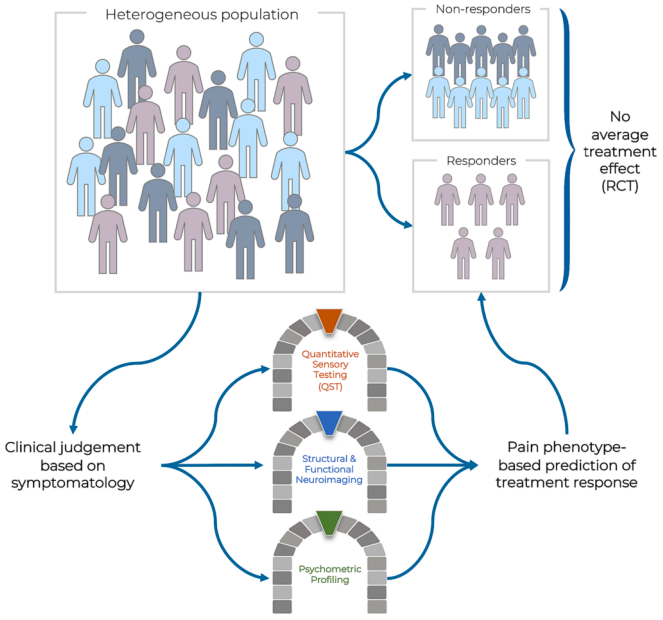

Fig. 1. Chronic pain populations exhibit substantial heterogeneity in underlying mechanisms (top left). In the context of a randomised control trial (RCT), some patients may derive substantial benefit from a given intervention whilst others show little-to-no improvement (top right). This results in diminished average treatment effects, with non-responders diluting out the primary efficacy endpoints met by responders. Stratified and personalised pain medicine involves prospective identification of responders, allowing for mechanistically informed targeted analgesic pharmacotherapy, transcending the challenges imposed by heterogeneity. The novel model of pain proposed here asserts that we must identify "keystone mechanisms" that capture diverse but pivotal aspects of pain processing (bottom), which can be examined in isolation or combination to provide phenotypic stratification. Crucially, these mechanisms must be downstream of a sufficient number of biological, psychological, and social causal factors to account for a meaningful proportion of the variance in treatment response whilst also remaining clinically practicable. Currently, these keystone mechanisms have yet to be identified, characterised, or tested and we therefore identify three methodological classes from which we envisage keystone mechanisms may emerge moving forward.

Several areas of pain neuroscience have shown initial promise to provide putative keystone mechanisms to date, including static and dynamic quantitative sensory testing (QST), neuroimaging, and psychometry (Fig. 1). Static QST is a streamlined battery of psychophysical tests that provide critical insights into multiple aspects of peripheral nervous system function, covering both loss and gain of function and addressing multiple possible mechanisms of pain generation (Rolke et al., 2006). This has been used to prospectively stratify individuals with peripheral neuropathies into an irritable nociceptor group and a deafferented group based on their sensory phenotypes, with the former showing a substantially improved number needed to treat with oxcarbazepine than the latter (Demant et al., 2014). Similarly, it has also shown potential to predict response to a TRPA1 inhibitor (Jain et al., 2022). The full capabilities of static QST for stratifying various classes of treatments remains unclear. However, it is theoretically particularly suited to target drugs which act primarily peripherally (Baron et al., 2017), rather than broad-acting interventions like psychological treatment or opioids. Conditioned Pain Modulation (CPM), a form of dynamic QST, is a "pain-inhibits-pain" paradigm which offers insights into the functionality of an individual's capacity to modulate pain (Ramaswamy and Wodehouse, 2021; Nir and Yarnitsky, 2015), a mechanism

often argued to be dysfunctional within chronic pain populations (Lewis et al., 2012; Yarnitsky, 2015). CPM has shown preliminary predictive value for treatment responses to duloxetine (Yarnitsky et al., 2012), spinal cord stimulation (Campbell et al., 2015), and diclofenac (Edwards et al., 2016). Whilst it remains contentious to what extent CPM measures additional mechanisms above and beyond its pre-clinical counterpart, diffuse noxious inhibitory controls (DNIC), top-down neuromodulation of pain in general engages key opioidergic, serotonergic, and noradrenergic mechanisms (Ossipov et al., 2014), with CPM potentially offering insights into the panoply of drugs which also act on these systems, such as opioids and serotonin/noradrenaline re-uptake inhibitors (Yarnitsky, 2015; Bannister and Dickenson, 2016). Similarly, neuroimaging measures at baseline are related to treatment responses to surgical intervention in trigeminal neuralgia (Hung et al., 2017; Hung et al., 2021; Hung et al., 2019; Danyluk et al., 2020; Tohyama et al., 2018), ketamine use in neuropathic pain (Bosma et al., 2018), duloxetine for osteoarthritis (Martins et al., 2022), occipital nerve block for cluster headache (Medina et al., 2021), and pregabalin as well as milnacipran for fibromyalgia (Harris et al., 2013; Schmidt-Wilcke et al., 2014). This diversity of treatments and conditions reflects the fact that pain ultimately only emerges as a conscious experience within supraspinal structures, with neuroimaging offering insights into the state of these systems. Moreover, alongside the plethora of pharmacological sites of action potentially amenable to characterisation through neuroimaging, it may offer particular potential in identifying predictors of non-pharmacological interventions such as mindfulness (Medina et al., 2022). Finally, psychometric profiling provides key insights into cognitive facets of pain processing. The Neuropathic Pain Symptom Inventory scores are related to treatment response to Botulinum Toxin A (Bouhassira et al., 2021), although not combination treatment efficacy in diabetic painful neuropathy (Tesfaye et al., 2022). Pain Catastrophizing and pain self-efficacy (Schumann et al., 20222022), emotional distress (Tesfaye et al., 2022), as well as post-traumatic stress and its positive counterpart, post-traumatic growth (Dyball et al., 2022), have all been shown to interact with pain levels and potentially predict treatment responses. Interestingly, measures like catastrophizing, mindfulness, and acceptance seem to overlap, with additional work required to distil these down to a meaningful core set (Turner et al., 2016) which may hold particular promise in stratifying patients who may respond to non-pharmacological interventions.

This is by no means an exhaustive account of treatment stratification work to date but highlights three diverse approaches which primarily assess the functionality of peripheral (static QST), spinal (CPM), and supratentorial (neuroimaging and psychometric profiling) pain systems. As such, they hold promise as methods for identifying putative keystone mechanisms which can capture diverse facets of pain (patho)physiology within the framework outlined here, providing overlapping yet distinct insights into critical facets of pain processing throughout the neuroaxis upon which multiple interventions act. Whilst these have shown significant promise to date, we do not claim these suggestions are necessary nor sufficient for the effective understanding or treatment of pain. The ongoing identification, characterisation, and inclusion of additional mechanisms such as neuroinflammation (Ji et al., 2014; Sideris-Lampretsas and Malcangio, 2021), genetics and epigenetics (Denk et al., 2014), as well as multiple-omics approaches will likely prove indispensable if this framework is to be applied truly *trans*-nosologically.

1.7. Moving forward with keystone mechanisms

Rather than being a readily implementable solution to the challenges presented by heterogeneity in treatment responses, the keystone mechanism model of pain outlined here serves to guide interdisciplinary translational research moving forwards. Not only does this provide advantages over and above the BPSm, but importantly it helps redirect the disparate work across disciplines to identify, characterise, and measure keystone mechanisms which can be combined into realistically implementable composite biomarkers. Once identified, a crucial next step to bring these keystone biomarkers towards clinical reality is to simplify their assessment such that they aren't prohibitively technical, costly, nor time consuming. Crucially, simplification must be achieved without significantly compromising the sensitivity or reliability of the biomarker. This is a non-trivial challenge, especially given that currently the sensitivity of putative biomarkers remains limited even in idealised experimental conditions. However, attempts to do this for QST are already underway (Reimer et al., 2020). CPM and neuroimaging remain significantly further from this goal, requiring substantial additional basic and translational work. A consensus on CPM experimental design is required before a simple and scalable version of this assessment can be explored clinically. Similarly, any imaging-based biomarker will need to be derivable from a short scan that does not require substantial additional expertise to run nor challenging tasks for the patients. Structural MRI and resting-state fMRI both fulfil these criteria, and with the rapid analytic methods development ongoing in the field (Lawn et al., 2023; Howard et al., 2023), these may offer practicable biomarkers in the longer term. Multiple efforts are ongoing to achieve consensus on patient-reported symptoms and outcomes with the aim of reducing questionnaire burden whilst preserving sensitivity (Wandner et al., 2023). Crucially, with the end goal of integrating these different assessments into a larger framework within which they contribute distinct insights into a given individuals broader pain phenotype, reducing the scope of each assessment to prioritise the separable and complementary aspects may help overcome individual reductions in sensitivity and maintain collective power to stratify. As such, it is imperative to build these assessments into studies investigating treatment outcomes to allow for identification, refinement, and application of these different keystone mechanisms to the prediction of treatment response. Additionally, open sharing of data may prove particularly important in showing that their predictive utility generalises. Subsequently, large scale studies examining the combination of different keystone mechanisms into composite biomarkers in the context of different chronic pain conditions and analgesic interventions will be required to meaningfully demonstrate the utility of this approach. Moving forward, implementation will require careful consideration of which combination of potential keystone mechanisms offers the greatest predictive value given their resource cost. For example, if an additional keystone mechanism under consideration provides significantly overlapping information to an existing keystone mechanism in the model whilst being time-consuming and costly, this would not be worthwhile. Conversely, a new keystone capturing substantial unique variance in treatment response that is easily implementable and cheap would be clearly important to utilise. This subsequent model optimisation will also move beyond mechanistic and statistical investigation and require significant patient, caregiver, clinician, and health economist input. Whilst ambitious, the challenge of implementing true precision medicine in enormous and the requirement of substantial interdisciplinary efforts to bring together composite biomarkers seems inevitable. The keystone mechanism model of pain outlined here provides a guiding framework towards this long-term goal, overcoming key theoretical and practical limitations of the BPSm.

2. Conclusion

The BPSm has been hugely influential in shaping nascent attempts at precision pain medicine. Whilst it continues to provide theoretic benefit and emphasise the need to consider pain holistically, it also fails to keep pace with modern materialist views in which psychological and social elements constitute poorly understood neurobiological mechanisms. Moreover, taken to its logical conclusions, the number of explanatory variables implicated within a truly BPSm are both immeasurably numerous and practically unimplementable. The approach outlined here builds upon the successes of the BPSm to provide a theoretical foundation for basic and translational pain science to move forward with a

strong emphasis on identifying facets of pain (patho)physiology (keystone mechanisms) that maximally capture the myriad of biological, psychological, and social factors that shape an individual's pain phenotype in a practically implementable manner. In doing so, this framework provides a practicable and mechanistically grounded translational path from treating populations towards treating individual people.

2.1. Search strategy and selection criteria

We searched PubMed for all articles published in English or German using the search terms "biopsychosocial" AND "pain". The search was most recently updated on the October 3rd, 2022. Articles were excluded if they related to treatment of a specific pain syndrome or population (e.g. dementia), listed treatment approaches in general, were diagnostic guidelines, or general statements (e.g. chronic pain should be treated using a biopsychosocial approach). We also considered the references of relevant articles. The final reference list was generated based on the relevance to the topics covered in this perspective piece.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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