Towards an Ontology of Pain

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ABSTRACT. We present an ontology of pain and of other pain-related phenomena, building on the definition of pain provided by the International Association for the Study of Pain (IASP). Our strategy is to identify an evolutionarily basic canonical pain phenomenon, involving unpleasant sensory and emotional experience based causally in localized tissue damage that is concordant with that experience. We then show how different variant cases of this canonical pain phenomenon can be distinguished, including pain that is elevated relative to peripheral trauma, pain that is caused neuropathically (thus with no necessary peripheral stimulus), and pain reports arising through deception either of self or of others. We describe how our approach can answer some of the objections raised against the IASP definition, and sketch how it can be used to support more sophisticated discrimination of different types of pain resulting in improved data analysis that can help in advancing pain research.

1 Background: The Physical Basis of Disease

Increasingly, ontologies are being used to support the retrieval, integration and analysis of a variety of different kinds of biomedical data. Ontology-based technology has been successful especially in support of data-driven research in the basic biological sciences and in model organism studies, and efforts are now being made to extend these successes to the domain of human disease and diagnosis. The most successful ontologies, above all the Gene Ontology [Bodenreider 2008], rest on objective classifications of biological phenomena primarily at the molecular and cellular levels, and we face difficulties in applying the same approach where we are dealing with clinical data pertaining to pain and to other symptoms of human disease marked by the feature of subjectivity. The goal of this communication is to provide the beginnings of an ontological account of pain and of those phenomena closely related to pain that are commonly described as pain in patient reports. Because pain has subtly complex characteristics, we believe that its examination will have heuristic value for ontological accounts of symptoms (such as feelings of nausea, fatigue, depression) more generally.
Our strategy is to pursue a view of pain as resting in every case on some physical basis that is perhaps as yet unknown. This is part of a more general strategy, defended in [Scheuermann et al. 2009], which views all clinically relevant phenomena on the side of the patient as having some physical basis within the organism. By ‘physical basis’ we understand any configuration of one or more physical components within the organism at any level of granularity, from a single nucleotide to an arthritically deformed joint. Where they are non-disordered – which means: such as to reflect the coordinated expression of the corresponding structural genes for an organism of the given type [Rosse et al. 2007] – such configurations support those dispositions in the organism which are realized in normal, ordered functioning. Where they are disordered, such configurations support dispositions to abnormal functioning, one family of which is manifested in experiences of pain. We then use the term ‘disorder’ to refer to the physical basis of such a disposition to abnormal functioning. Thus a disorder is some physical part of the organism that gives rise to a potential for a clinically significant departure from normal functioning of one or other kind. As we shall see, abnormal functioning may have beneficial characteristics for the patient, above all – in the case of pain with concordant tissue damage (PCT) – in signaling the presence of tissue damage. When, for example, there is a persistent pain in a patient’s left temporomandibular joint (TMJ), then this is because some physical structure or substance in the organism is disordered (for example, the TMJ is deformed because of arthritis so that it serves as a direct source of nociception). As a result of this disorder, the organism acts in a certain way that is consistent with the presence of pain. When pain is acute, the behavioral manifestations of the organism follow a generally predictable pattern that is oriented towards self-protection and help-seeking: the pain excites the organism to some action to relieve the suffering involved in the experience. In the case of chronic pain, multiple components of the central nervous system are affected; behavioral manifestations will vary from patient to patient and will fluctuate over time in a pattern difficult to predict on the basis of only the reported pain but generally understandable when the multiple affected CNS components are identified.

‘Symptom’, as we here use this term, covers a restricted family of phenomena (including pain, anxiety, nausea, anger, drowsiness, itchiness), which are of their nature such as to have features which can be experienced only in the first person. (In Table 1 below these are labeled as ‘Subjectively Observable Features’.) Symptoms can be reported to, and associated behaviors and bodily qualities can be observed by, the clinician; but symptoms themselves cannot be observed (except by the patient) and they cannot be objectively measured. The absence of objective measurement does not, however, imply that symptoms cannot be reported reliably and so have objective validity. To say of pain that it has features that can be observed only subjectively is therefore consistent with the fact that given pain reports can be objectively true or false.

2 The IASP Definition of Pain

Pain is defined by the International Association for the Study of Pain (IASP) as follows:

\[
\text{pain (IASP)} = \text{def. an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [Merskey et al 1979].}
\]

This definition has proved to be of considerable value, having led to 50 years of highly productive fundamental research on pain. On the other hand it has certain problems, as
recently reflected by significant discussion by an IASP task force (http://www.iasp-pain.org/source/eforum). The definition ascribes a common phenomenology (‘unpleasant sensory and emotional experience’) to all instances of pain, together with the recognition of three distinct subtypes of pain involving, respectively:

1. actual tissue damage,
2. what is called ‘potential tissue damage’, or
3. a description (in some patient report) involving reference to tissue damage.

Clause 3. may be interpreted to mean that a mere description of a certain sort provides sufficient evidence that pain is present. The intent, as we understand it, is to assign those patient reports of pain that are not sufficiently grounded in observable manifestations of tissue damage to some other (for example psychological) realm albeit while still requiring reference to an experience anchored within the body. This causes problems in the classification of cases for example of the following sort: A patient presenting with pain and associated tissue damage was prescribed pain relief medication. While moderate tissue damage remains, the medication is effective, so that there is no longer pain. But because the patient has become addicted, he claims that there is still pain in order to obtain more medication. Such cases are not pain; yet as we shall see they will often be so classified by the clinician. Until recently the headache classification system would not permit a headache diagnosis if the patient was effective in use of medication for treating the headache. While this problem has been fixed, clinicians still face problems because of the ambiguous use of ‘pain’ and cognate terms to mean either pain as experienced or the underlying physical basis in the body of the patient. The latter may give rise to a disposition to pain which may survive even though it is not being realized as a result of effective medication.

3 Strategy for Defining Pain

In providing a modified version of the IASP definition in what follows we define, first, what we shall call ‘pain with concordant tissue damage’ (PCT), which we hold to be the canonical (normal, prototypical) and evolutionarily most basic case of pain. We then describe a number of variant phenomena which are defined in terms of, and involve specific kinds of departures from, this canonical case. Our strategy is thus comparable to the way in which the results of genetic mutations or injuries affecting, for example, the human hand, are most effectively described in terms of specific kinds of departures from, the anatomical structure of the normal human hand (with its 5 fingers, 10 metacarpal bones, etc.). This strategy has been pioneered by the Foundational Model of Anatomy (FMA) Ontology, a scientifically well-established reference ontology of human (and more generally of mammalian) anatomy [Rosse et al. 2007] which describes the ‘canonical’ structure of the human organism and various ‘variant’ structures arising, for instance, through amputation or genetic defect. Its implementation here, which draws on an approach to mental functioning-related anatomical structures advanced in [Ceusters et al. 2010], sees the nociceptive system as involving multiple components, including a reflex protective component, a sensory component, and an emotional component, the latter involving many non-cortical brain systems (e.g. amygdala) that together produce in the organism a sense of crisis, activate the autonomic nervous system, and organize the behavioral response to the pain stimulus. (Compare also [Melzack 2001].)
Against this background we can now distinguish the following five different sorts of cases of pain and of pain-related phenomena (see Table 1 and Figure 1):

**PCT: pain with concordant tissue damage:** the patient experiences pain of the evolutionarily most basic sort, which is to say: pain in response to and in concordance with simultaneously existing tissue damage. This tissue damage is both the experienced target and the cause of the pain experience. Here the nociceptive system and the peripheral trauma are aligned; clear signals connect the one with the other.

**PNT: pain without concordant tissue damage:** the patient experiences pain that is associated with some disorder outside the nociceptive system, a disorder existing either now or in the past. In some cases (for example myofascial pain) this disorder is predominantly associated with peripheral trauma; in other cases (for example tension headache) predominantly not. But in every case PNT pain is marked by the fact that it is discordant in terms of some attribute, such as intensity, spatial extent, or episode frequency or duration, relative to the state of the underlying tissue. Here the nociceptive system is intact, but signals associated with a stimulus at a peripheral site are either (1) ramped up relative to what would be the normal (PCT) case, or (2) ramped down, for example in individuals with coping styles which have the effect of diminishing either nociceptive transmission or some feature of experienced pain, or in cases of pain asymbolia, a condition in which pain is experienced (perhaps in a manner otherwise consistent with the PCT case) but does not cause suffering.

**NN: neuropathic nociception:** the patient experiences pain, as in the above, but here the pain is caused by some disorder in the nociceptive system. The latter is, as it were, derailed from its normal functioning and is firing on its own. Thus the patient is experiencing pain, which may be experienced as having a peripheral cause, but the pain is the result of a neuropathic disorder of the nociceptive system. An example is phantom limb pain, where pain-system components in the brain which had been laid down through the PCT experiences activated earlier by tissue damage in the once present limb are re-activated. Some types of cancer patients fall under the NN heading, where the nociceptive system has been derailed by a peripheral cancer disorder.

In addition, we distinguish two related cases of non-pain-phenomena:

**PBWP: pain behavior without pain:** there is, for example, a mere report in a medical record attributed to the statements of a patient, but no pain is being experienced by the patient (a fact which may or may not be detectable by an external observer).

**TWP: Tissue-damage without pain:** tissue damage normally of the sort to cause pain does not activate the pain system (as contrasted with pain asymbolia, where pain is experienced, so that the pain system is activated, but the patient does not experience the pain as something that is suffered).
case of a cut, a local burn, an abrasion; each involves a brief duration stimulus and
evokes a brief, intense experience of pain with accompanying reflex withdrawal that
moves the body away from the stimulus. Following the injury there is a continued expe-
rience of usually less intense pain associated with inflammation that gradually recedes
as healing occurs. Subtype 2. is chronic pain, a long-lasting sequence of experiences of
pain that emerge from acute pain that did not resolve, which may extend over many
years without relief, and which may involve the patient visiting many specialists (e.g.,
ENT, headache specialist, neurologist, dentist, psychologist) with no positive results.

4 Canonical Pain as an Evolutionarily Basic Mechanism

The canonical pain phenomenon reflects the fact that mammals have central nervous
system components that are associated with signals to the organism indicating that some
part of their peripheral structure is damaged or is in danger of being damaged. Such
signals result in various consistent outcomes on the side of the organism. This is the
sensory signalling system for pain.

It is canonical to have pain in a joint when the joint is inflamed. Coordination be-
tween tissue damage and pain is then part of the core orienting function of pain, which
is to protect the organism from harm. A patient can thus usually direct the clinician to a
particular site on or in the body where the pain is experienced.

The resultant definition of this evolutionary most basic, ‘canonical’ type of pain, in-
volving an aversive reaction towards that which is causing tissue damage, reads:

\[
pain \text{ with concordant tissue damage (PCT)} = \text{def.}
\]

\[
(1) \text{ a bodily process in an organism S involving two integrated levels:}
\]

\[
(1a) \text{ activation of the nociceptive system including the pain-associated emotion-}
\]
\[
\text{generating brain components of S, and}
\]

\[
(1b) \text{ a simultaneous sensory and aversive experience on the part of S}
\]

that is

\[
(2) \text{ caused by damage to tissue located in a region R of the body of the subject S,}
\]

\[
(3) \text{ experienced by S as being caused by this damage,}
\]

\[
(4) \text{ such as to involve an aversive reaction on the part of S directed towards that which is}
\]
\[
\text{presumed by S to be causing this damage,}
\]

\[
(5) \text{ concordant with the tissue damage on both levels (1a) and (1b),}
\]

and also

\[
(6) \text{ such that the sensory experience is sufficiently intense to communicate the presence}
\]
\[
\text{of tissue damage to the subject.}
\]

Pain is thus a bodily process that has both a subjective or mental level, consisting of a
sensory and emotional experience, and an objective or physical level, comprising the
workings of the nociceptive system and of those parts of the sensory and emotional
systems that are narrowly involved in the realization of this pain; each can exist without
the other. But in the case of pain both must exist together, and they are then mutually
dependent parts within a single whole [Smith et al. 1982]. In the case of canonical PCT
pain both must further be concordant with the peripheral tissue damage that causes
them. ‘Experience of pain’ in its primary meaning refers to the sensory and emotional
experience that is an integral part of the pain process itself; in a secondary meaning it may refer to optional cognitive representations of pain which may in certain circumstances be associated therewith. Animals and infants may experience pain in the former sense but it is not clear whether they can do so also in the latter.

The canonical pain process will involve activity in many components of the central nervous system. Part of the physical basis for this process is localized in the pain sensory system and associated emotional centers. In addition, PCT pain has a physical basis in simultaneously existing peripheral tissue damage. The tissue damage is localized in some part of the body, and the sensation is a sensation of processes in that part of the body. The definition of PCT pain is ‘canonical’ also in the sense that it reflects the default understanding brought to each new case by the clinician, who first assumes, on the basis of medical necessity, that the experience of pain reported by the patient is the result of simultaneous tissue damage.

PNT cases such as allodynia, in contrast, occur not only with tissue damage but also often occur in a site where there was an injury that has healed. A non-noxious stimulus to the site or an area surrounding the site produces pain. The mechanism for this could be the local sprouting, during the healing process, of excess nerve terminals, and/or permanent changes in the sensory system leading to the cortex that have nothing to do with cognitive mechanisms associated with threat that are activated in the case of PCT.

5 A General Definition of Pain

We can now advance the following general definition of pain, which comprehends both canonical pain and the distinguished variant phenomena:

\[
\text{pain} = \text{def. a bodily process in an organism } S \text{ involving two integrated levels:}
\]

(a) activation of the nociceptive system and associated emotion generating brain components of } S, and

(b) a simultaneous aversive sensory and emotional experience on the part of } S, where (b) is phenomenologically similar to the sort of aversive experience involved in PCT pain.

Here ‘phenomenologically similar’ means inter alia: (1) that the experience is ‘of’ or is targeted towards’ some region } R of the body of } S, so that all pain is in this sense (and however diffusely) localized; (2) that the experience involves a dimension of unpleasantness which – as is shown by the case of pain asymbolia – is not necessarily of the sort that involves suffering or aversion on the part of the subject } S.

This definition is formulated in such a way that small children and even some animals can experience canonical pain, even though they do not have the cognitive resources to represent their experience as one that is caused in this or that way. This addresses one recognized shortcoming of the IASP definition [Rollin 2006].

6 Problems of Diagnosis with PNT and NN Pains

Pain results in behavioral responses in animals similar to those observed in humans; but, trivially, only humans experience pain in a way that is linked to the ability to speak of it – the latter reflecting the contribution that cognition has in affecting our basic percepts.
It is for this reason that the IASP definition gives a prominent role to descriptions containing reference to tissue damage of varying states. Such descriptions are central to the clinician’s understanding of pain phenomena of both the PNT and NN types, neither of which necessarily has apparent tissue damage at the putative locus of pain, because the corresponding experiences are heavily influenced by processes independent of direct stimulus transmission.

Clinicians have significant problems with evaluating (quantifying) pain intensity, or the presence of pain itself, in those cases where no observable tissue damage or malfunctions in any component of the patient’s body can be observed. Indeed, even if tissue damage or malfunctions can be observed, pain intensity cannot be quantified in a purely objective manner for the same reason that other feelings cannot be quantified. While other attributes such as episode frequency or duration are more amenable to quantification (because they are more readily observable in an objective manner), the attribute of intensity is often the most salient one due to its greater susceptibility to change as well as the suffering aspect of pain which appears to be heavily influenced by intensity.

One such case is that of the well-known disorder referred to as ‘regional myofascial pain’, in which the fibers in the muscles of the jaw, neck or lower back, affected by a myofibril disorder that is putatively due to some form of trauma [Mense 1993], but where biochemical exploration has largely failed to find signs of overt inflammation suggestive of such trauma or of tissue damage. Many theories are associated with both the phenomenon and why it is painful, but controversy is considerable. We believe that this comes close to what IASP means by ‘potential tissue damage’. For us it is a case of PNT, because while the pain is intense, the peripheral physical disorder – a disorder in myofibrils – would not normally be of the sort to give rise to a pain of this intensity.

Another example is provided by PNT pains with the dominant characteristic of ‘al-lodynia’. The clinician applies non-noxious pressure to a tooth; the patient senses the increase in pressure and reports ‘pain’. Examination of the tooth, via direct observation and radiographs, fails to disclose any evidence of pathology (tissue damage), and yet the patent clearly localizes the pain of complaint in the tooth; moreover, the pain evoked by the examination replicates the pain of complaint.

This disorder was, for many years and in particular prior to the IASP definition, attributed to psychiatric cause; but when better knowledge emerged regarding an underlying neuroscience for allodynia, the psychiatric causation was transformed into a diagnostic entity currently referred to as ‘atypical odontalgia’ – pain that feels like a toothache but that is not due to peripheral damage of the tooth. It is one implication of our discussion above, that atypical odontalgia must be divided into two distinct kinds, representing pain, respectively, of the PNT or of the NN sort. In the first case, for example, a tooth has been treated for caries and the process affected the nociceptive system of the patient in such a way that the patient feels discordant pain that is (for the patient) localized in the corresponding tooth. In the second case, the relevant portions of the patient’s nociceptive system have become disordered for example in virtue of some virus infection, in such a way that the patient feels pain that is localized in just the same way as in the PNT case, but which involves no tissue damage at the corresponding locus.
7 Ontology of Pain and Ethics of Pain Diagnosis: Problems of Diagnosis with PBWP

Certainly there are behavior-based measures of pain, for example in terms of loudness and frequency of overt expressions. Given the PBWP phenomenon, however, these are in fact measuring two different things, since in the case of PBWP there is by definition no pain to measure. Science based on comparing the two sets of data appears empirically ungrounded.

Such cases make diagnosis in matters of pain especially difficult, and although the types of pain-related phenomena described here can be clearly distinguished in general ontological terms, identifying which type is exemplified in any given instance is by no means trivial.

For good, diagnostic reasons the IASP definition is standardly interpreted in such a way as to allow even mere descriptions of pain to warrant pain classification; there are also essential ethical reasons for the degree of permissiveness allowed by the IASP definition with regard to clinician action. When an experience is described by the patient in terms of peripheral tissue damage, the clinician will standardly not be in a position to assert that the reported experience is not correctly so described. It is precisely due to this feature of the IASP definition that pain research has progressed so significantly in the past 50 years. Data could be collected at the margins of pain without the clinician (investigator) having to be judge and jury regarding the patient’s reports of his experience. But factitious pain poses significant problems, and if research into the gigantic problem of pain that is experienced as being localized but is without localized tissue damage is to be successful, then some supplement to the IASP definition is needed, of the sort which, we believe, ontology can provide.

Our goal here is to initiate the development of an approach which allows the clinician or researcher to better understand the physical basis underlying a report of pain and not just to stay at the level of reports and of the assumption that, if the patient says that it is pain (within the limits of language relating to tissue damage of one sort or another), then therefore it is pain (or, as pain-clinicians will often say, for the benefit of patients, ‘all pain is real’).

If the clinician expects concordance between stated intensity (the symptom as reported) and the clinical findings (the signs), but concordance does not occur, then significant problems will ensue, either in the form of dismissing the disorder, or in labeling the patient as ‘psychiatric’. If, in contrast, the clinician understands the neuropathic and other non-peripherally localized contributions to pain experience, then this may serve a more adequate diagnosis.

8 Practical Applications of the Pain Ontology

Increasingly, progress in pain research and in diagnosis of pain will require analysis of new types of data, including:

1. PET or fMRI data;
2. data linking genotype risk to present pain in the interest of making prognostic statements, including predicting likelihood of future relapse on the basis of identified pain genes;
(3) classification structures that will incorporate multiple axes (including data already available concerning pain history, hard and soft tissue imaging, psychological data) so as to generate a multi-dimensional classification, producing clarification of pain subtypes as for example in the case of pains strongly characterized by alldynia, which we believe may be applied also in the troubled field of cancer pain [Hjermstad et al. 2009].

We believe that ontology-based research has already shown its value in supporting the integration that is required for full exploitation of such bodies of multi-dimensional data, and ontologies in a range of biomedical domains are now being developed in ways designed to serve such integration [Smith et al. 2007]. In the pain domain the ontological approach will in addition provide considerable value in allowing us to differentiate the categories involved even where we do not know to which categories given patients belong, because on the basis of the available clinical evidence we do not know the degree of match – or mismatch – between reported experience and the underlying neural processes. Knowing what these categories are then allows us to analyze the different types of data in ways which are unavailable on a more diffuse approach by allowing statistical analysis on the basis of alternative hypotheses as to the proportions of different sorts of mismatch in any given batch of patient reports.

9 Conclusion

A number of pain-related disorders found in specific, localized regions of the body and currently classified, for example, separately as temporomandibular disorders, orofacial pain, mucosal pain, odontogenic pain, regional neuropathic pain, and headache span the types of pain described in the above. Many of these phenomena are marked by a similar array of medically unexplained symptoms. The primary goal of the work described in the foregoing is to support research directed towards a better understanding of such phenomena and thereby also a better classification of patients according to susceptibility of responding positively to different kinds of therapy. Barriers to improved classification and subsequent research have thus far been due, in part, to the difficulty associated with going beyond traditional clinical perspectives and assumptions. At issue is the emerging recognition that many body regions have associated chronic pain disorders that are more alike than they are different, whereby one of the primary characteristics is: presence of persistent dysfunctional pain disproportionate to the observed pathology (here labeled PNT). Repeated observation has indicated that many of these disorders appear to co-occur at a higher rate than chance would suggest; yet research into this complex domain has, we believe, had trouble moving forward in part due to the inadequacy of the classification of pain and related phenomena that is implied by the IASP definition.

We believe that our ontological account of pain, and of those phenomena closely related to pain commonly described as pain in patient pain reports, can significantly contribute to advancing our ability to more successfully understand, diagnose and treat pain and related phenomena.
Acknowledgements

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References


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<td><strong>Canonical Pain</strong></td>
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<td><strong>Variant Pain</strong></td>
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<td>NN: neuropathic nociception</td>
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Figure 1: Top-Level Ontology of Pain and Pain-Related Phenomena