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Beyond metaphor: contrasting mechanisms of social and physical pain

Gian Domenico Iannetti[1], Tim V. Salomons[2], Massieh Moayedi[1], André Mouraux[3], and Karen D. Davis[4,5]

[1] Department of Neuroscience, Physiology and Pharmacology, University College London, London, UK
[2] Department of Psychiatry, University Health Network, Toronto, Canada
[3] Institute of Neuroscience, Faculty of Medicine, Université Catholique de Louvain, Brussels, Belgium
[4] Division of Brain, Imaging, and Behaviour – Systems Neuroscience, Toronto Western Research Institute, University Health Network, Toronto, Canada
[5] Department of Surgery and Institute of Medical Science, University of Toronto, Toronto, Canada

Physical pain can be clearly distinguished from other states of distress. In recent years, however, the notion that social distress is experienced as physically painful has permeated the scientific literature and popular media. This conclusion is based on the overlap of brain regions that respond to nociceptive input and sociocultural distress. Here we challenge the assumption that underlies this conclusion – that physical pain can be easily inferred from a particular pattern of activated brain regions – by showing that patterns of activation commonly presumed to constitute the 'pain matrix' are largely unspecific to pain. We then examine recent analytical advances that may improve the specificity of imaging for parsing pain from a broad range of perceptually unique human experiences.

Beyond metaphor: does social exclusion really 'hurt'?

Poets, novelists, and philosophers have, for centuries, attempted to make seemingly intangible emotional states more tangible by comparing them to sensory states. A common example of this literary device is the comparison of emotional distress to physical pain. Although both states may involve suffering, it is undeniable that physical pain is perceptually distinct from the emotional experiences to which it is commonly compared. Thus, a 'broken heart' from a failed relationship does not 'feel' like angina pectoris (unless the failed relationship causes a coronary artery spasm), nor does the experience of being 'stabbed in the back' by a once-trusted associate feel like the pain evoked by stepping on a sharp object. Thus, it is clear that such metaphors are a literary device and not grounded in physical reality.

In an influential study published in 2003, Eisenberger and colleagues attempted to go beyond metaphor by proposing that physical pain and social distress share a common neurobiological substrate. This conclusion was based on the observation that when participants perceived that they were being socially excluded from participating in a video game, brain activity sampled by functional MRI (fMRI) was observed in regions also activated during experimental acute pain, thus 'paralleling results from physical pain studies' [1].

In the aftermath of this study, the notion that this similarity in brain responses indicates that social distress is experienced as physically painful gained traction in both the scientific literature and the popular press. A 2005 review article claimed that 'social exclusion is experienced as painful because reactions to rejection are mediated by aspects of the physical pain system' [2] and a recent article in the *New York Times* stated that 'being socially rejected doesn't just feel bad, it hurts' (*New York Times*, 15 May 2011; www.nytimes.com/2011/05/15/fashion/is-rejection-painful-actually-it-is-studied.html). The attraction of the popular press to this field of research is understandable because neuroimaging evidence that seemingly demonstrates that emotional distress 'hurts' represents a glamorous marriage of metaphor and modern science. From the standpoint of both clinical and basic science, however, greater conceptual, taxonomic, and linguistic precision is critical.

In this opinion article, we discuss the arguments that have been used to demonstrate experiential overlap between social distress and physical pain. We provide compelling evidence that these arguments are logically and technically flawed, and not substantiated by empirical data. Indeed, the overlap between brain regions responding to social and physical pain can be entirely explained by the fact that both experiences trigger multimodal cognitive processes involved in detecting, orienting attention towards, and/or reacting to salient events. Furthermore, recent results have identified fine-grained differences in the spatial patterns of fMRI activation during social and physical pain, highlighting the fact that these experiences are likely to be distinct at a neuronal level.

The arguments for social 'pain': commonalities in neurochemistry and brain activation

Two arguments have been put forth to support the hypothesis that social distress is physically painful: common

Corresponding author: Iannetti, G.D. (g.iannetti@ucl.ac.uk).
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neurochemistry and common patterns of brain activation. Given that functional neuroimaging studies have propelled this hypothesis into the spotlight, the focus of this review is on common patterns of brain activations.

Common neurochemistry

There is evidence that social distress and physical pain can be modulated by analgesic pharmaceutical interventions, such as opiates [3] and acetaminophen [4]. The suggestion that this suffices as evidence that social and physical pain share common neuropharmacological mechanisms disregards the fact that these agents have differential effects depending on the population of cells they are targeting. For example, the described effect of opiates on the experience of social distress [5,6] could be explained by their effect on the circuits involved in reward and motivation [7] – proposed to subtend its euphoric effect – rather than through a specific effect on nociceptive pathways. Similarly, acetaminophen appears to exert a variety of poorly understood effects on the central nervous system [8] and the effects explaining analgesia do not necessarily correspond to those explaining reduced social pain.

Common patterns of brain activation

The report by Eisenberger and colleagues [1] was followed by several other studies that replicated the observation that experiencing social distress activates the insular, cingulate, and secondary somatosensory (S2) cortices [2,6,9–11], that is, the brain regions that are also activated by nociceptive somatosensory stimuli (Figure 1) [12–15]. Evaluating the degree to which activation in these regions implies physically painful percepts requires an examination of the crucial assumption that this pattern of brain responses reflects cortical processes exclusively involved in pain perception.

The myth of the 'pain matrix': a construct based on reverse inference

In a seminal study that introduced the use of laser-evoked brain potentials to study nociception in humans, Carmon *et al.* concluded that 'it is possible that only the arousing and alerting effect of pain is responsible for the electroencephalographic phenomenon observed' [16]. A few years later, Chapman *et al.* stated that these responses 'cannot be considered neurophysiological representations of pain sensations' [17]. In the past 20 years, studies conducted with different types of *in vivo* functional neuroimaging techniques have shown that transient nociceptive stimuli consistently elicit activity within an array of subcortical and cortical brain structures, including the thalamus, the primary somatosensory cortex (S1), S2, the cingulate, and the insula [18–20]. As the number of such studies increased exponentially, investigators became less cautious in interpreting the functional significance of these activations. Indeed, at present, many consider that these activations are at least partially pain-specific because (i) they are consistently obtained when the stimulus elicits a sensation of pain, (ii) their magnitude often correlates strongly with the perceived intensity of pain, and (iii) factors modulating pain can also modulate their magnitude. Therefore, the activity within these brain structures would be 'mediating pain experience itself' [21] and constitute a cortical 'representation' [22] or 'signature' [23] for pain, reflecting the neural processes underlying pain function and dysfunction in humans [19]. However, as explained below, this interpretation is often made without considering matters of specificity, sensitivity, and significant technical issues (such as the poor spatial and temporal resolution, and the indirect sampling of neural activity through the hemodynamic response of fMRI or positron emission tomography) [24,25]. Furthermore, the heterogeneity of pain is also overlooked. Noxious stimuli evoke various qualities of sensation with unique temporal signatures that vary across individuals [26,27], requiring percept-related fMRI approaches [28–30] to distinguish brain signals associated with different qualities of sensation.

Box 1. Reverse inference

In propositional logic, the *modus ponens* is a valid form of argument that takes the following form:

Example 1
* When John does laundry, he uses more electricity.
* John is doing laundry.
* Therefore, he is using more electricity.

A superficially similar but fallacious form of argument known as 'affirming the consequent' takes the following form:

Example 2
* When John does laundry, he uses more electricity.
* John is using more electricity.
* Therefore, he is doing laundry.

The logical problem with Example 2 is clear. There are many potential explanations for why John is using more electricity (e.g., he is baking a cake or using his electric razor). Thus, greater power usage is not sufficient evidence that he is doing laundry.

Inferences based on affirming the consequent are commonly used in functional neuroimaging research. These are known as reverse inferences and commonly involve inferring a particular mental state (e.g., the perception of pain) from a given pattern of brain activation (e.g., the so-called pain matrix) [32].

The following provides an example germane to the current discussion:

Example 3
* If an individual feels pain, the pain matrix is activated.
* The pain matrix is activated.
* Therefore, the individual is experiencing pain.

Although the form of such an argument is logically flawed, Poldrack has argued that such arguments should be treated probabilistically, with the likelihood of the inference being correct depending on the degree of exclusivity of the relationship between the cognitive state and activation in the brain region [32]. It is common to take a one-sided approach when assessing the exclusivity of the relationship between a brain region and a given cognitive state. We assess how often the brain region is activated when the physical/cognitive state is present. An accurate assessment of the probability of a reverse inference being true, however, also requires an assessment of false alarms, that is, of how often the area is active when the cognitive state is not present. In other words, it is not enough to simply ask how often the pain matrix is activated when pain is present; we must also ask how often the pain matrix is activated in situations in which physical pain is not present. As reviewed in this article, although the so-called pain matrix is nearly always active in pain studies, it is also frequently active in studies in which pain is not present, which suggests that the reverse inference that pain is experienced because the pain matrix is activated is unlikely to be true.

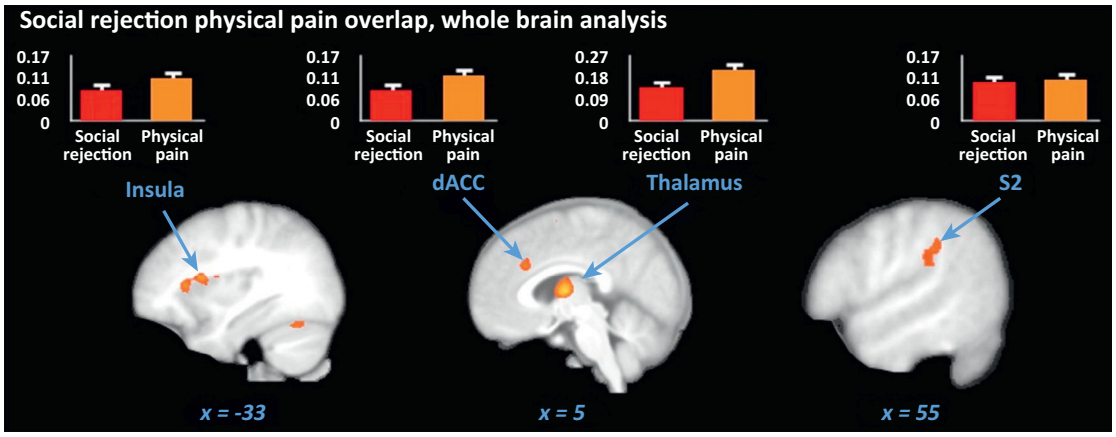

Figure 1. Common activation for social rejection and physical pain. Comparison of brain responses elicited by nociceptive stimulation and by pictures evoking recent romantic rejection. On the basis of the similarity of the active regions (i.e., thalamus, insula, cingulate cortex, secondary somatosensory cortex), the authors concluded that 'rejection and physical pain share a common somatosensory representation'. Reproduced, with permission, from [11].

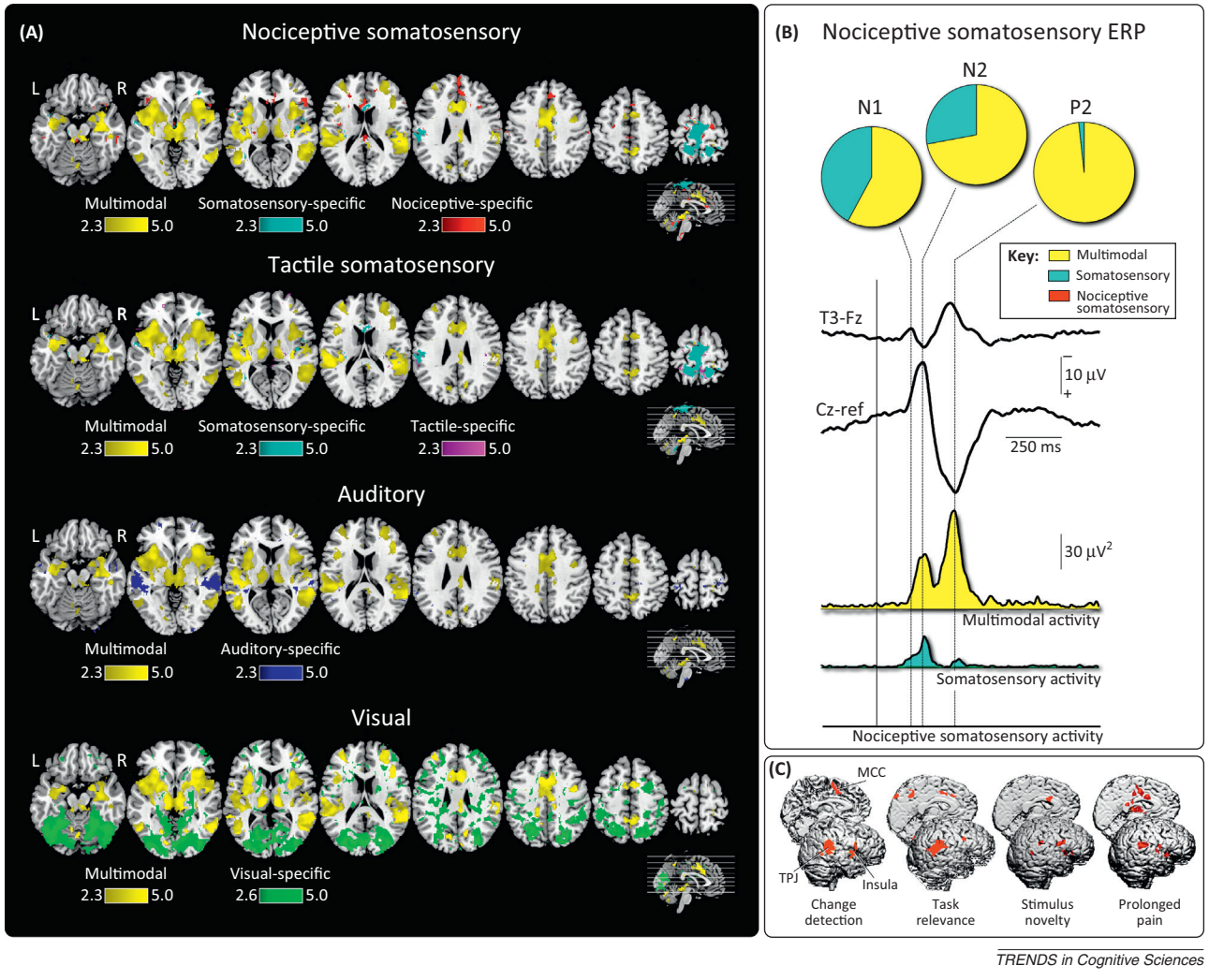

Figure 2. Multimodal neural responses to sensory stimuli. **(A)** Functional MRI responses elicited by transient nociceptive, tactile, auditory, and visual stimuli. Voxels responding to all four types of sensory stimuli are shown in yellow (adapted from [37]). **(B)** Electroencephalographic responses elicited by nociceptive-selective laser stimuli are largely explained by multimodal neural activity (activity also elicited by stimuli that belong to other modalities). The contribution of somatosensory-specific activity (activity elicited by both nociceptive and non-nociceptive somatosensory stimuli) is confined to the earlier part of the time course (adapted from [38]). **(C)** Change detection, task relevance, and stimulus novelty in various sensory modalities elicit a similar pattern of neural activation to prolonged pain (adapted from [39–41,66]).

The fundamental argument that social neuroscientists put forward to claim that 'social exclusion is experienced as painful' [2] relies precisely on the assumption that the pattern of brain activity elicited by a nociceptive stimulus perceived as painful actually reflects the mechanism through which physical pain emerges within the human brain. However, inferring an experiential state such as physical pain from a pattern of neural activity is a typical example of reverse inference (Box 1), in which a mental state is inferred from a pattern of neural activation. The validity of a reverse inference drawn from neuroimaging depends on the exclusivity of the relationship between the mental state and the activated brain region [31,32]. Thus, the validity of the inference in Example 3 of Box 1 is dependent on whether the pain matrix regions are exclusively activated during the experience of physical pain. In other words, the claim that 'social pain hurts' because it triggers the same brain activity as physical pain is justified if, and only if, this brain activity is exclusive to the perception of physical pain.

This crucial assumption is contradicted by a growing body of evidence demonstrating not only that the bulk of brain activity used to justify the experiential link between physical and social pain is, in fact, unspecific for pain, but also that, when more sophisticated and sensitive analysis approaches are used (e.g., multivariate pattern analysis, MVPA), the patterns of brain activity elicited by physical and social pain have clearly different fine-grained spatial patterns [33].

Although several previous studies have shown significant correlation between the magnitude of the brain responses elicited by nociceptive stimuli and the intensity of perceived pain, this relationship is by no means obligatory and can be dramatically disrupted. For example, the repetition of a nociceptive stimulus at a short and constant interstimulus interval markedly reduces the magnitude of the elicited brain responses without affecting the intensity of perceived pain [34,35], and the analgesia induced by visual observation of the body is not paralleled by a reduction in the elicited brain responses [36]. Furthermore, salient visual, auditory, and tactile stimuli elicit brain responses with a regional spatial configuration similar to that of the brain responses elicited by a transient nociceptive stimulus [37,38] and therefore similar to the pattern of brain activity observed during the experience of social rejection. A series of early studies demonstrated that these brain responses are more related to the detection of environmental change [39] and its relevance [40] and novelty [41] than to the generation of any particular perceptual state. For all these reasons, we recently proposed an alternative interpretation of the functional significance of the pain matrix, namely, that it reflects the activation of a system involved in detecting, processing, and reacting to the occurrence of salient sensory events, regardless of whether they elicit perception of pain (Figures 2 and 3) [34,37,39–42]. Such a multimodal network, sometimes referred to as the saliency network [43–45], would reflect some of the basic operations through which the brain detects and reorients attention towards behaviorally salient events, such as stimuli that represent a potential threat to the integrity of the body [43].

Thus, at the macroscopic scale of fMRI or electroencephalographic (EEG) signals analyzed using traditional univariate approaches, stimulus-evoked activity within these brain regions does not appear to be exclusive to the perception of physical pain. This lack of exclusivity renders unjustified the reverse inference underlying the claim that social pain 'hurts' because it elicits activity within the same brain regions active during physical pain. In fact, if we consider that these brain responses may be mainly related to saliency processing, it is not surprising that an event that triggers social distress elicits activity within these brain regions. Indeed, events such as viewing the photograph of an ex-partner we still care about [11] are likely to be as salient as an actual nociceptive stimulus [46].

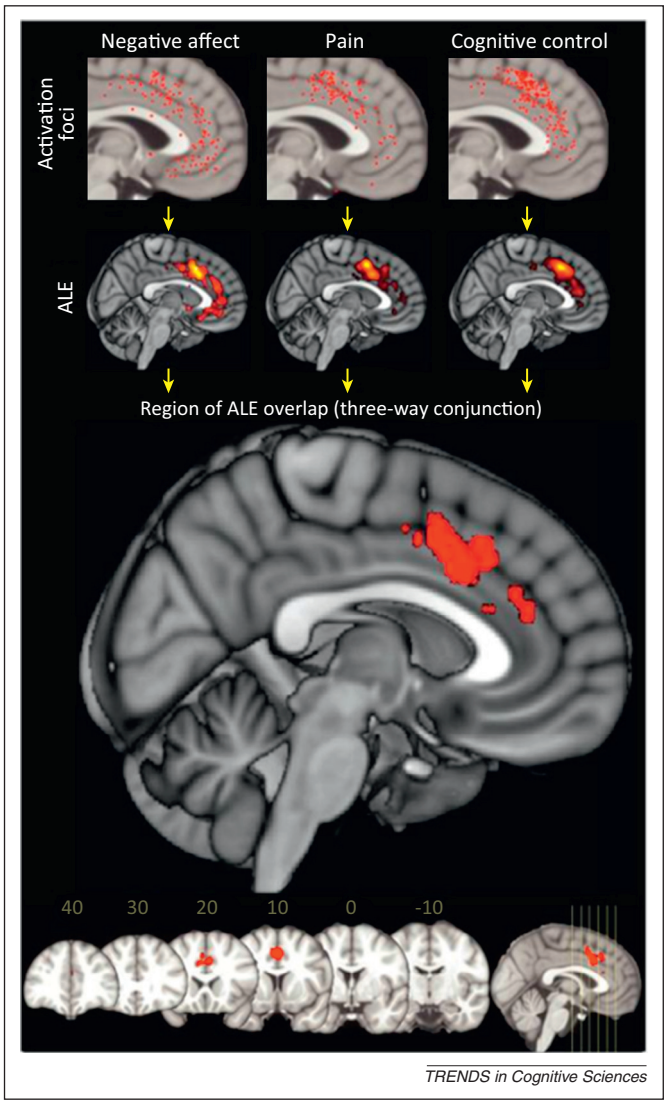

Figure 3. Overlap in anterior mid-cingulate cortex (aMCC) activity during pain, negative affect, and cognitive control. A recent meta-analysis showed that aMCC, a key 'pain matrix' region frequently activated in social pain studies, is also activated by a wide range of cognitive-control- and negative-affect-generating tasks that do not elicit physical pain [67].

Social and physical pain: mechanistic similarities and differences

Despite the reviewed evidence prompting a more cautious interpretation of the apparent similarities between brain responses to social and physical pain, we maintain that examining the neural overlap between these experiences is an important endeavor. First, such overlap provides a

critical window into how evolutionary pressure might foster efficiency by developing a common system for detecting and responding to potentially threatening environmental events, regardless of their origin.

Perhaps more importantly from the perspective of pain research, data that demonstrate activation in the so-called pain matrix in response to social distress represent a critical challenge in terms of elucidating how the brain specifically encodes the experience of physical pain. Individuals are able to clearly distinguish between experiences that are physically painful and those that are socially or emotionally distressing, and such a clear perceptual difference must be subserved by a different pattern of neural activity. Accordingly, the perception of physical pain emerges from activity within the nociceptive system, a submodality of the somatosensory system. The nociceptive system has dedicated peripheral receptors with specific molecular transduction mechanisms [47–51], as well as specific spinal and supraspinal projections [52–54]. This system provides the ability to extract the basic attributes of a nociceptive stimulus, such as its spatial location, with remarkable acuity [55] and involves activity within neuronal populations that are finely somatotopically organized [56]. Although a prominent feature of nociceptive-specific neurons in the central nervous system is their scarcity, they do exist [57–61] and could subtend the emergence of painful percepts [42].

The ease with which individuals can distinguish between the perception of painful and non-painful sensations, as well as between the experience of physical and social pain, raises the following question: why have functional neuroimaging techniques, such as EEG and fMRI, largely failed to identify obvious differences between the patterns of brain activity elicited during these different

Box 2. Multivariate pattern analysis (MVPA)

MVPA is a machine learning technique that uses a pattern classifier to identify the representational content of fMRI responses elicited by, for example, different stimuli. Whereas conventional fMRI analysis approaches (such as mass-univariate analyses using general linear modeling, GLM) detect regional-average activations and consider a single voxel at a time within a given brain region, MVPA detects patterns of activity across many voxels and thus tests whether a stimulus is specifically represented in the spatial pattern of activity sampled across the multiple voxels of a given brain region. Therefore, MVPA is more sensitive than conventional univariate analysis in disclosing fine within-region spatial differences in brain activity across experimental conditions, and may detect changes in the spatial distribution of fMRI signals even when regional-average activity does not differ across different conditions. MVPA often takes the form of solving a classification problem, for example, guessing whether an fMRI response is elicited by physical pain or social pain. In within-subject MVPA, the fMRI data set obtained from an experiment is divided into a training data set (constituted by, e.g., three out of four fMRI runs) and a test data set (constituted by, e.g., the fourth run). The training data set, together with the known labels (identifying the different stimulus categories, e.g., social pain and physical pain), is used to train a classifier that learns the spatial pattern of responses to each stimulus category. This classifier is then applied to the test data set to assess its ability to predict the category of the stimulus eliciting the responses for each sample. Good classification accuracy implies that the data (i.e., the spatial distribution of the fMRI signal within a given brain region) contain sufficient information to distinguish correctly the different stimulus categories or experimental conditions. A leave-one-run-out cross-validation approach is commonly used in which the procedure is repeated using each single run as a test data set and all other runs as the training data set. In between-subject MVPA, the classifier is trained on the fMRI data set for all but one subject and is tested on the fMRI data set for the remaining subject. This cross-validation step is repeated until each participant has been used as the test data set. Within- and between-subject MVPA address fundamentally different questions. Within-subject MVPA examines whether the different stimulus categories have reliably distinct cortical representations at single-subject level, independently of whether these representations are consistent across subjects. By contrast, between-subject MVPA requires the spatially distinct representations to be consistent across subjects (Figure I).

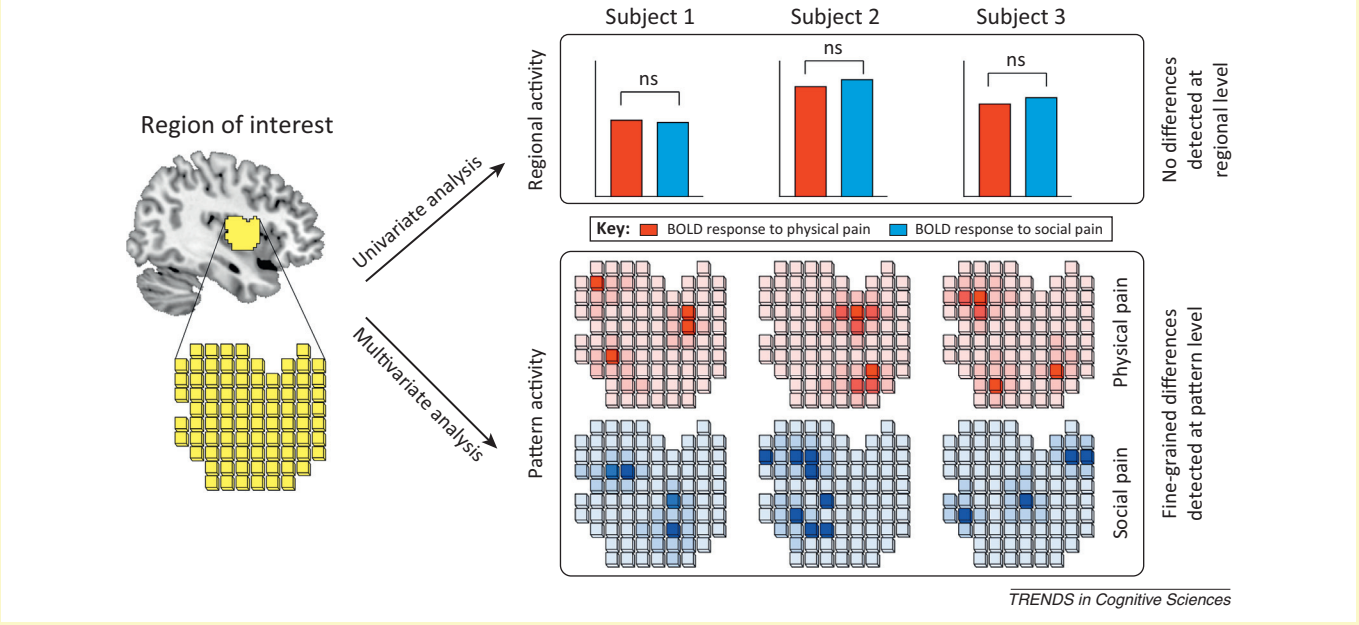

Figure I.

experiences? One explanation is that the magnitude and spatial extent of the so-called pain matrix responses have prevented the identification of weaker, possibly pain-specific sources of neural activity. Another explanation is that analysis methods based on the identification of regional changes in cortical activity fail to isolate the activity of nociceptive-specific neurons because these neurons are not organized in a spatially segregated cortical region, but instead are intermingled with neurons that respond to non-nociceptive sensory inputs. As detailed in the following paragraphs, recent results obtained using novel neuroimaging analysis techniques, such as time–frequency decomposition of EEG/MEG data and multivariate pattern analysis (MVPA) of fMRI data (Box 2), provide support for these explanations.

Most of the EEG responses elicited by a nociceptive stimulus are related to the saliency content of the stimulus, as demonstrated by the observation that they correlate with pain perception only when stimuli are presented in isolation and not when their saliency is reduced by repetition [34,35,62]. However, it has recently been shown that gamma band oscillations, a small and elusive feature of the electrocortical response induced by a nociceptive stimulus in human S1 [63], predict the intensity of pain perception even when the saliency of the stimulus is reduced by repetition [64]. These results provide evidence that cortical activity more directly subtending the perception of pain can be effectively discriminated.

Similarly, MVPA is more sensitive than univariate analysis in detecting fine-grained differences in the spatial patterns of fMRI activity elicited in different experimental conditions (Box 2). Very recently, two studies have attempted to exploit this technique in order to isolate pain-specific patterns of neural activity [33,65]. Wager *et al.* used MVPA to discriminate between responses elicited by application of a transient nociceptive stimulus to the forearm and those elicited by viewing a headshot of their former partner in 40 individuals who felt intensely rejected as a result of a recent unwanted romantic relationship break-up [33]. They showed that MVPA of signals sampled within the pain matrix was able to distinguish between responses elicited by the two stimulus types, indicating that they differed in their fine spatial features [33]. Importantly, the demonstration that the two stimulus types actually elicit spatially distinct patterns of brain activity – that is, that 'specificity may be driven by fine grained differences in activity patterns in regions activated by both physical and social pain' [33] – amends the previous, more contentious interpretation by the same authors of the same data set, when they concluded that 'rejection and physical pain are similar not only in that they are both distressing – they share a common somatosensory representation as well', and that these 'results give new meaning to the idea that rejection "hurts"' [11].

Liang *et al.* performed MVPA [65] on fMRI responses elicited by brief and similarly salient nociceptive, tactile, auditory, and visual stimuli [37]. They observed that whereas the traditional analysis of these responses identified activation in the same areas of the so-called pain matrix, MVPA revealed striking differences in the fine-grained activity patterns in regions activated by the four stimulus types, regardless of the overall level of fMRI activation. This demonstration of consistent differences in the spatial pattern of activation indicates that, within these different brain regions, the different stimuli do not activate the same neuronal populations. From the perspective of pain research, these results indicate that the neural activity elicited by stimuli perceived as painful can actually be distinguished from the neural activity elicited by other stimuli and, hence, that a specific signature for pain does exist. Interestingly, MVPA was able to effectively distinguish painful from non-painful sensations using the signals sampled in several other brain regions than those constituting the pain matrix, including unexpected regions such as the primary visual or auditory cortex. Therefore, it could well be that the perception of pain does not only emerge from activity within the areas commonly activated by nociceptive stimuli.

Concluding remarks

In sum, the experimental evidence that has been used to support the view that social and physical pain are experientially similar because they share a common neurophysiological substrate is questionable. Indeed, the overlap between the brain regions responding to social pain and those responding to physical pain can be entirely explained by the fact that the two experiences are salient and hence trigger multimodal cognitive processes involved in detecting, orienting attention towards, and/or reacting to salient events. Furthermore, recent observations that MVPA of fMRI data is able to identify fine-grained differences in the spatial patterns of activation during social and physical pain, or during painful and non-painful sensory experiences, indicates that these distinct experiences activate distinct neuronal populations. Given the inherent subjectivity of pain, making judgments about the presence or absence of pain without regard to self-report is unwarranted. Nevertheless, these techniques offer hope that neuroimaging will finally be able to distinguish between experiences, such as physical and social pain, that are clearly distinct at the perceptual level (Box 3).

Box 3. Questions for future research

- Multivariate pattern analysis of fMRI data can differentiate neural activity during social and physical pain. However, the functional significance of the neural activity underlying these fine-grained spatial differences remains entirely unknown. What is the functional significance of these differences? Do they reflect neural processes critical to these experiences or are they merely unrelated by-products of such experiences?
- Previous research has focused on comparing neural responses to transient experiences of social distress and physical pain. Do these neural responses become more divergent as social and physical pain become chronic?
- Identification of patterns of activation that uniquely characterize social and physical pain requires not only that these experiences be matched for salience but also that we can reliably measure perceptual features that make these experiences distinct. Given the widespread use of the term 'pain' to describe socially and emotionally aversive experiences, how can we improve our psychophysical assessments to reflect unique perceptual aspects of social versus physical pain?

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