American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 14, No 4 (April), 2013: pp 323-327
Available online at www.jpain.org and www.sciencedirect.com

Pain Measurement and Brain Activity: Will Neuroimages Replace Pain Ratings?

Michael E. Robinson,* Roland Staud,† and Donald D. Price‡

*Departments of *Clinical and Health Psychology, †Medicine, and ‡Oral and Maxillofacial Surgery, University of Florida, Gainesville, Florida.*

Abstract: Arguments made for the advantages of replacing pain ratings with brain-imaging data include assumptions that pain ratings are less reliable and objective and that brain image data would greatly benefit the measurement of treatment efficacy. None of these assumptions are supported by available evidence. Self-report of pain is predictable and does not necessarily reflect unreliability or error. Because pain is defined as an experience, magnitudes of its dimensions can be estimated by well-established methods, including those used to validate brain imaging of pain. Brain imaging helps to study pain mechanisms and might be used as proxy measures of pain in persons unable to provide verbal reports. Yet eliminating pain ratings or replacing them with neuroimaging data is misguided because brain images only help explain pain if they are used in conjunction with self-report. There is no objective readout mechanism of pain (pain thermometer) that is unaffected by psychological factors. Benefits from including neuroimaging data might include increased understanding of underlying neural mechanisms of treatment efficacy, discovery of new treatment vectors, and support of conclusions derived from self-report. However, neither brain imaging nor self-report data are privileged over the other. The assumption that treatment efficacy is hampered by self-report has not been shown; there is a plethora of treatment studies showing that self-report is sensitive to treatment. Dismissal of patients' self-reports (pain ratings) by brain-imaging data is potentially harmful. The aim of replacing self-report with brain-imaging data is misguided and has no scientific or philosophical foundation.

***Perspective:** Although brain imaging may offer considerable insight into the neural mechanisms of pain, including relevant causes and correlations, brain images cannot and should not replace self-report. Only the latter assesses the experience of pain, which is not identical to neural activity. Brain imaging may help to explain pain, but replacing self-report with brain-imaging data would be philosophically and scientifically misguided and potentially harmful to pain patients.*

***Key words:** Brain-imaging, self-report, neuroimage.*

Recent publications have suggested that brain imaging of pain has the potential to replace self-report of pain. The following excerpts from 3 representative publications highlight the intent and rationale for using functional brain imaging as a substitute or replacement for self-report:

1. "Unfortunately, its (pain) assessment is based solely on subjective self-report, using limited scales or measures, which are unsuitable for elucidating the different types and causes of pain (i.e. pain endophenotypes) and for rigorously evaluating the impact of targeted interventions. Self-report measures also hamper progress in the monitoring required to precisely dose a medication and then evaluate its comparative effectiveness among different individuals."[9]
2. "The big question for neuroimaging in pain research is whether these methods can be used as a read-out of pain experience independent of behavioural ratings. Neuroimaging has the potential to become an objective measure of pain and replace subjective report. Using neuroimaging to characterize pain without a need to rely on subjective pain ratings or descriptions of pain would be also of great benefit for measuring treatment efficacy."[24]
3. "Moreover, it [anatomical and functional specificity in distinct chronic pain conditions] suggests that such therapies can be tested with very specific

Funding for this project was provided by the National Institutes of Health (NCCAM) grant 5R01AT001424-06 to M.R.
The authors have no conflicts of interest to report.
Address reprint requests to Michael E. Robinson, PhD, Department of Clinical and Health Psychology, University of Florida, P.O. Box 100165 HSC, Gainesville, Fl 32610-0165. E-mail: merobin@ufl.edu
1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2012.05.007

objective brain-derived markers, *even bypassing self-report* (Italics ours)."[1]

Our main thesis is that despite new insights into mechanisms of pain provided by neuroimaging, it is highly unlikely (and inappropriate) that neuroimage data can replace self-report or even improve it. We address erroneous and misguided reasoning underlying the rationale for replacing self-report with neuroimaging data. This reasoning not only is becoming embedded in the scientific literature but has formed part of the rationale for funding research (see excerpt 1 above).

Erroneous Assumptions About Self-Reported Pain and Neuroimaging

The first assumption apparent in these arguments is that self-report of pain is unreliable. The error in this thinking is based on empirical data that clearly show that self-report of pain is variable. There are a number of reasons for variability in self-report. The authors quoted above apparently make the assumption that measurement error is the chief source of this variability. The fallacy of this assumption is well addressed in the literature. First, pain experience is variable. Therefore, some variability of self-report of pain stems from the true fluctuations in the pain experience, and not just error in its measurement. There are a number of empirical reports of the reliability and repeatability of self-report pain scales (eg,[2,17]). Second, a large proportion (eg, 50%) of the variability in self-report of clinical pain is predictable.[19,20] That level of predictability, by definition, demonstrates that the variability cannot be all error (unreliability).

The next assumption to address is that functional neuroimaging is more reliable and less error prone than self-report. This is sometimes couched in terms of objective versus subjective measures. There are few data that even address the reliability or psychometrics of neuroimaging measures. Those who seek to replace self-report with neuroimaging seem to assume that neuroimaging measurement is error free and/or perhaps perfectly reliable. We contend that the reliability of neuroimaging data, including functional connectivity, is at best unknown, and certainly not established enough to replace the known reliability of self-report.

It is also important to remember that the validity of pain-related neuroimaging was established by the correlation of brain images with self-report of pain![2] By definition, if the self-report is predictable, it cannot be error. In addition, the upper limit of the validity of neuroimaging validated against self-report would be limited by the reliability of self-report (known to be good) and the reliability of neuroimaging (not yet established).

The contention that neuroimaging would be superior to self-report because it will be more sensitive to inter- and intraindividual responses to interventions again appears to be based on an erroneous assumption that self-report of pain is insensitive to treatment effects. There is a plethora of well-conducted studies showing that self-report of pain is quite sensitive to a large range of treatments.[5,6,16,21] The sensitivity of functional neuroimaging to treatments is still relatively unknown and predicated on first establishing the reliability of functional neuroimaging of pain. The assumption that the assessment of treatment efficacy is hampered by self-report has not been demonstrated. The lack of ability to detect a treatment difference with a standardized self-report instrument is more likely the result of a weak treatment effect than poor measurement.

Validating Self-Report and Brain-Imaging Methods: Are the Validations Interrelated?

Pain is defined as a specific type of human experience that contains multiple dimensions (pain sensation intensity, qualities, cognition, and affect). The magnitudes of these dimensions can be estimated in individuals and groups by well-established psychophysical and other psychometric methods. Brain activations often strongly correlate with ratings of pain dimensions in widely distributed areas of the brain. These correlations validate brain-imaging methods and also provide some external validation of pain ratings. Yet most of the validation of self-report measures remains within the domains of psychophysics and the rest of psychology. Validation of pain scales includes analyses of both clinical and experimental pain. For example, the demonstration that a type of visual analog scale has ratio scale properties required direct ratings of both clinical and experimental pain and matching temperatures to multiple levels of clinical pain.[15] This approach reflects converging and multiple lines of evidence, similar to strategies used in science in general.

Brain-imaging data provide important mechanistic information such as the neural representations of pain sensation intensity and unpleasantness and information about functional connections. General mechanisms of analgesia and hyperalgesia are also confirmed using brain imaging (eg, general mechanisms of placebo and hypnotic analgesia).

Brain-imaging measures may possibly be used in the future as proxy measures of pain in persons unable to provide verbal quantitative representations of their pain (eg, ratings), such as individuals who are minimally conscious as a result of partial anesthesia or paralysis or individuals who are unable to provide verbal ratings (eg, very young or some elderly people with dementia). Thus, brain imaging is a highly valuable and evolving scientific technology.

Yet it would be absurd to eliminate pain ratings or replace them with neuroimaging data as a general principle because conclusions about brain mechanisms and neural representations only explain pain if self-report is included in the study (using different types of pain scales)! The following sections provide foundations for our position on this issue and are guided by several questions.

Are Patterns of Brain Activity or Self-Reports Better Accounts of the Experience of Pain?

If it could be demonstrated that specific patterns of brain activity are the same thing as pain (ie, ontological

identity), this identity might be used to establish a biomarker of the experience of pain itself, thereby providing an extreme variant of the use of biomarkers. Yet to our knowledge no one has demonstrated that the experience of pain and pain-related neural activity are the same phenomenon. It has been argued elsewhere that such a demonstration would verify that all the properties of pain are the same as all of the properties of pain-related neural activity.[13,23] Yet pain is fundamentally an experience whose properties cannot be exactly the same things as, for example, C-fibers firing or action potentials within somatosensory and insular cortices (see discussion in references[13,23]). Measures of brain activity provided by neuroimaging provide indirect information about neural representations and mechanisms of pain, while self-report measures provide indirect information about the experience of pain. Although neuroimaging data and self-report contribute complementary information about pain states, they are mutually irreducible to each other, and neuroimaging data do not have an epistemologically privileged status over pain ratings (or questionnaires). Self-report and brain-imaging data are imperfect accounts of pain.

A perfect brain account of pain would depend on demonstration of several types of subjective influences known to affect pain. Paradoxically, this would require considerable self-report measures. If, unlike subjective measures, brain activity remained the same under different subjective influences, then the brain measures would be less trustworthy than self-report. If, on the other hand, a perfect correlation was found, then one could use the far less expensive and less time-consuming self-report. There does not appear to be an objective readout mechanism of pain that is independent of the thoughts, feelings, desires, meanings, and attitudes of the person who is experiencing the pain—there is no pain thermometer in the brain that registers a physical output like body core temperature or amount of impending tissue damage.

Would Neuroimaging Data Benefit the Measurement of Treatment Efficacy?

Possible benefits from including neuroimaging data might include increased understanding of underlying neural mechanisms of treatment efficacy, discovery of new vectors for treatment, and corroborative confirmation of conclusions derived from self-report. However, a major problem would arise when the results of neuroimaging and self-report diverge. This divergence has been highlighted in discussions about using neuroimages in medico-legal contexts and has been rejected on both scientific and legal grounds.[7,12,18] Neither brain imaging nor self-report data are epistemologically privileged over the other, and neither type of data is observer free (ie, a god's eye view from nowhere); thus, there are no a priori reasons to dismiss one type of data or replace self-report with brain images.

A General Network for Pain

Based on over 20 years of human neuroimaging research, there is consensus that neural activities within a network of brain regions positively correlate with pain intensity. Some of the correlations are quite strong (r^2 = .8–.9) and even include clinical pain.[1,8] This network is sometimes termed a pain matrix. These areas include various parts of the medial and posterior thalamus, somatosensory cortices (S1 and S2), insular cortical areas (posterior, mid, and anterior insula), cingulate cortical areas (subgenual and pregenual anterior cingulate, anterior midcingulate, and less often posterior cingulate areas), caudate/putamen, and cerebellar areas. Although most if not all of these regions increase their neural activity during various types of pain, no single region seems to be exclusively dedicated to processing pain. To put it simply, there doesn't appear to be a pain center in the brain.

Are There Neural Signatures for Pains or Can the Same Type of Pain Be Represented by More Than 1 Pattern of Brain Activity?

It has been suggested that functional interactions between brain structures specifically characterize pain and even different types of pain.[1] Thus, pain signatures may include specific functional interactions between relevant brain structures and/or levels of neural activity within the brain structures themselves. A major problem with the concept of objective neural signature is abundant evidence from many sources that the same type and intensity of pain can be generated by different brain regions,[10] different central nervous system pathways,[22] and perhaps even different functional interactions.[3] Thus, individuals who are missing an entire cerebral hemisphere can localize and rate pain intensities on both sides of the body,[10,11] and patterns of pain-related brain activity can change across 2 baseline conditions wherein the pain intensity remains unchanged.[14] Clearly, neural signatures are not at all immutable, because pain-related patterns of brain activity and directions of functional connectivity change as a result of subtle psychological and biological factors. These kind of results will only be fully explained when questions about pain experience are answered by awake human beings. Functional interactions between pain-related brain areas decrease and even change direction when there is no statistical change in the level of pain.[4] The neural representation of pain in the brain can occur in multiple and often radically different ways across subtly different conditions (eg, repeat resting state imaging). Thus, neural activity within defined anatomical regions and the number of regions activated do not seem to precisely characterize an invariant and objective pattern of brain activity (ie, signature) for a given type and intensity of pain. If no single brain area is exclusively dedicated to processing pain and no pattern of functional interaction uniquely characterizes an intensity or type of pain, then exactly what constitutes a neural signature of pain, one that can be said to be an objective measure of pain that can replace pain ratings?

Are There Areas of the Brain That Represent Pain Itself Distinct From Brain Areas That Are About Reporting or Expecting Pain?

Although clearly there is much more to learn about the answer to this question, there are now multiple studies that show partial overlap between areas involved in expecting pain and areas involved in the direct experience of pain, and there is 1 study that shows activation in S1 and other pain-related areas during pain and again several seconds after the pain subsides and during the pain rating.[8] Although there may well be a distinction between biases about pain levels and pain levels themselves, it still has not been established whether biases about pain intensity can occur without changing pain intensity itself. But even if that could happen, there remains a lot to understand about the distinction between brain areas and mechanisms that are involved in biases and reporting pain and brain areas that represent pain itself.

Conclusions

The assertion that objective brain images would greatly benefit measuring treatment efficacy involves magical thinking. There are poor and excellent methods of self-report, similar to all empirical methods. There is a plethora of treatment studies showing that self-report is sensitive to treatment. Moreover, there are no reasons to assume that all self-report methods are intrinsically flawed because they are subjective. For example, eye tests are psychophysical yet they correct vision to within a fraction of a diopter. Phenomena such as report bias are reflected in brain activity, so that brain measures would be influenced by them as well (as discussed above). Inappropriate dismissal of patients' self-reports (eg, pain ratings) by brain-imaging data is potentially harmful to patients. In this respect, it is similar to dismissing chronic back patients' pain ratings because of lack of objective physical orthopedic evidence. There are good reasons for retaining self-report in pain measurement and assessment. Self-report measures are good predictors of treatment outcomes from patients' perspectives. They also determine when and who seeks care or terminates care. The assumption that treatment efficacy is hampered by self-report is not supported by empirical evidence and it may be guided by results that show that many treatments have small-to-negligible effects. If so, then the assumption is fallacious. Although brain imaging greatly advances understanding of pain and its mechanisms, the aim of replacing self-report data with brain-imaging data is misguided and has no scientific or philosophical foundation.

References

1. Apkarian AV, Hashmi JA, Baliki MN: Pain and the brain: Specificity and plasticity of the brain in clinical chronic pain. Pain 152:S49-S64, 2011

2. Coghill RC, McHaffie JG, Yen YF: Neural correlates of interindividual differences in the subjective experience of pain. Proc Natl Acad Sci U S A 100:8538-8542, 2003

3. Craggs JG, Price DD, Perlstein WM, Verne GN, Robinson ME: The dynamic mechanisms of placebo induced analgesia: Evidence of sustained and transient regional involvement. Pain 139:660-669, 2008

4. Craggs JG, Price DD, Verne GN, Perlstein WM, Robinson MM: Functional brain interactions that serve cognitive-affective processing during pain and placebo analgesia. Neuroimage 38:720-729, 2007

5. Flor H, Fydrich T, Turk DC: Efficacy of multidisciplinary pain treatment centers: A meta-analytic review. Pain 49: 221-230, 1992

6. Hoffman BM, Papas RK, Chatkoff DK, Kerns RD: Meta-analysis of psychological interventions for chronic low back pain. Health Psychol 26:1-9, 2007

7. Miller G: Neuroscience. Brain scans of pain raise questions for the law. Science 323:195, 2009

8. Moulton EA, Keaser ML, Gullapalli RP, Greenspan JD: Regional intensive and temporal patterns of functional MRI activation distinguishing noxious and innocuous contact heat. J Neurophysiol 93:2183-2193, 2005

9. NIH: Biomarkers for chronic pain using functional brain connectivity. commonfundnihgov, 2011

10. Olausson H, Ha B, Duncan GH, Morin C, Ptito A, Ptito M, Marchand S, Bushnell MC: Cortical activation by tactile and painful stimuli in hemispherectomized patients. Brain 124: 916-927, 2001

11. Olausson H, Marchand S, Bittar RG, Bernier J, Ptito A, Bushnell MC: Central pain in a hemispherectomized patient. Eur J Pain 5:209-217, 2001

12. Phan KL, Magalhaes A, Ziemlewicz TJ, Fitzgerald DA, Green C, Smith W: Neural correlates of telling lies: A functional magnetic resonance imaging study at 4 Tesla. Acad Radiol 12:164-172, 2005

13. Price DD, Barrell JJ: Inner Experiences and Neuroscience. Merging the two perspectives. Cambridge, MA, MIT Press, 2012

14. Price DD, Craggs J, Verne GN, Perlstein WM, Robinson ME: Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. Pain 127:63-72, 2007

15. Price DD, McGrath PA, Rafii A, Buckingham B: The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 17:45-56, 1983

16. Price DD, Staud R, Robinson ME, Mauderli AP, Cannon R, Vierck CJ: Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. Pain 99:49-59, 2002

17. Rosier EM, Iadarola MJ, Coghill RC: Reproducibility of pain measurement and pain perception. Pain 98:205-216, 2002

18. Simpson JR: Functional MRI lie detection: Too good to be true? J Am Acad Psychiatry Law 36:491-498, 2008

19. Staud R: Predictors of clinical pain intensity in patients with fibromyalgia syndrome. Curr Pain Headache Rep 9: 316-321, 2005

20. Staud R, Robinson ME, Vierck CJ Jr, Cannon RC, Mauderli AP, Price DD: Ratings of experimental pain and pain-related negative affect predict clinical pain in patients with fibromyalgia syndrome. Pain 105:215-222, 2003

21. Staud R, Vierck CJ, Robinson ME, Price DD: Effects of the N-methyl-D-aspartate receptor antagonist dextromethorphan on temporal summation of pain are similar in fibromyalgia patients and normal control subjects. J Pain 6:323-332, 2005

22. Stein BE, Price DD, Gazzaniga MS: Pain perception in a man with total corpus callosum transection. Pain 38: 51-56, 1989

23. Velman M: Understanding Consciousness. Philadelphia, PA, Routledge/London, 2009

24. Wortolowska K: How neuroimaging can help us to visualise and quantify pain? Eur J Pain 5:323-327, 2011