Can fMRI Imaging Techniques be Used as a Biomarker for Pain Identification?

Vanessa Weir

Executive Summary

Pain is a subjective and complex entity which continues to be a public health epidemic. Its difficulty to objectively measure has led to challenges in both the legal sphere as well as in clinical pain management settings. Some researchers posit that neuroimaging could provide an objective measurement tool, referred to as a “biomarker,” to be utilized as an alternative to verbal reports. However to be a good biomarker, a tool must satisfy specific criteria, such as having high sensitivity and specificity for its outcome measure. Furthermore, is this technology reliable enough to be a deceptive factor in penal punishment or other clinical applications? This paper investigates the appropriateness of neuroimaging to measure pain and what compliance with that use could mean in healthcare diagnosing and law. Although neuroimaging could be used as a supplemental biomarker to assess for and verify pain in a clinical application, technological limitations prevent it from appropriate use in higher stakes incidences, like the judicial system.

Introduction

Truck driver Carl Koch was filling his tank with molten tar one afternoon when the hose broke and tar seared his face and arm, causing second degree burns. When his pain was persistent one year later, he opened a personal injury lawsuit against Western Emulsions, his employer, claiming he suffered from chronic neuropathic pain. Western Emulsions tried to deny his pain claims, prompting Koch’s lawyers to reach out to Joy Hirsch, a neuroscience professor at Columbia University. He conducted a fMRI scan to prove the presence of pain in Koch’s arm. Hirsch’s exam revealed that pain-mediating neural circuits were activated when Koch squeezed a ball with his injured right hand, but not for the same task on his unaffected left arm. The judge on the case ruled this evidence admissible in court. This raises the question: does the science indicate that fMRI technology is an accurate enough measure of pain to be used in court? Furthermore, could this technology be used clinically in the drug discovery process?

Background

The current standard for clinical pain assessment almost exclusively relies on subjective self-report. Although verbal rating scales are reliable in well-informed individuals, it has not been shown to be as efficacious in cognitively impaired or non-verbal patients. Furthermore, although verbal rating scales and picture scales can be sensitive to treatment effects and pain intensity, they are less accurate at measuring long term changes in pain. Perhaps most importantly, these measures are completely dependent on the integrity of the patient, which can be compromised when patients are motivated to lie, such as to win personal injury suits or access commonly abused pain medication. Thus, there is a clear need for a valid and reliable measurement tool to objectively quantify an individual’s pain experience. Some scientists, clinicians, and even attorneys are hoping to use brain imaging, such as fMRI, to serve as that objective diagnostic tool.
Two clinically relevant areas where biomarkers could be useful in pain management is 1) as an outcome measure to validate subjective pain reports and 2) as a tool to improve treatment outcomes in the drug discovery process.

Pain and its neurological mechanisms
The use of fMRIs as a tool in pain identification rests on the assumption that the neural mechanisms for pain are well understood. Imaging studies and well as animal research have greatly increased our understanding of pain perception and its mechanisms. However, pain is a complex and varied condition, which is why it has often been so difficult to assess – and thus treat - with a single diagnostic tool. Broadly, pain is the conscious interpretation of nociceptive input (i.e., tissue damage) which can be influenced by cognitive factors such as memories, emotions, context, or genetics. However, experienced pain does not have to be directly correlated with noxious input from damaged tissues, and can be experienced as neuropathic pain (when nerve communications are impaired). Although there is no distinct “pain center,” the network believed to be responsible for pain consists of integration of neural signals from the thalamus, insular cortex, primary and secondary somatosensory cortices, anterior cingulate cortex, and prefrontal cortex. Since scientists have identified neural correlates of pain, in theory fMRI techniques could be used as biomarkers to identify and verify pain in an individual.

What is a biomarker?
A biomarker is an objective indication of a medical state that can be accurately and reproducibly measured. The use of biomarkers has become commonplace in medicine and helped to contribute to the efficacious optimized ‘individualized medicine’ used in cancer and heart disease treatments. The hallmark of these different types of biomarkers are that they are both biologically informative and can be objectively measured in a specific and sensitive way.

fMRI use as a tool to improve measurement of treatment outcomes
fMRI data has become increasingly relevant in the drug discovery process, as scientists hope that they can provide clinical outcome measures for novel pharmacotherapies. Specifically in this sphere, biomarkers aim to be informative by confirming areas of the brain where drugs act, predicting clinical outcomes when given a drug, and demonstrating those drug effects in a patient. For example, fMRI has been used in depression treatment research to demonstrate drug effects in the brain, which correlate with behavioral reports of the participants. Some scientists believe that fMRI could be used as an objective outcome measure for pain treatment studies to replace subjective verbal reports, which would be particularly useful for determining effective doses of medication. This would also be particularly pertinent in increasing how well animal research translates to humans, because the biomarker is measurable in both species.

In order to use fMRI for this kind of measurement, activation of the pain network should show high correlation to subjective verbal reports. Some research has found this. In one study of the efficacy of opioid analgesic compounds, fMRI detected decreases in pain-related brain areas and these correlated strongly with analgesia reported by volunteers. Beyond correlation, can fMRI improve upon verbal reporting? A separate study demonstrated that
reduction in pain regions of the brain was greater than reduction in subjective pain scores for an increasing dose of an opioid analgesic,12 suggesting fMRI biomarkers may be more sensitive than verbal pain reporting. Additionally, the pharmacologically induced changes in pain centers may help to reveal the mechanistic processes that underlie the disease rather than the compensatory or alternative processing output.10 Taken together, these studies indicate that fMRI technology may be uniquely beneficial in providing biologically informative information where verbal reporting falls short.

Using fMRI data as a biomarker in drug development could have huge potential implications for increasing efficacy of novel pharmacotherapies. Furthermore, by using fMRI to provide proof of concept early on in small cohorts of humans, one could decrease overall costs of the drug discovery process with an early “go decision” to move ahead to the next phase of FDA approval10

**fMRI use as an outcome measure to validate subjective pain reports**

In order to be a useful biomarker to validate verbal pain reports, fMRI must have high specificity and sensitivity (Figure 1). Specificity indicates the proportion of negative individuals that are correctly identified (i.e., people who are not experiencing pain who are correctly labelled as not experiencing pain), while sensitivity indicates the proportion of positive individuals correctly identified (i.e., people who are experiencing pain and correctly labelled as experiencing pain). In this way, the ideal biomarker aims to completely separate diseased from non-diseased populations.13 Although sensitivity and specificity studies of utilizing fMRI in pain have been limited, one study showed that an algorithm using fMRI data could distinguish warm sensations from painfully hot sensations with 71.11% accuracy, and could predict the participants’ reports of their maximum tolerable pain threshold (the temperature at which the sensation was too painful) with 91.67% accuracy14. Furthermore, there was a moderate correlation between the subjective pain threshold predicted from the fMRI data and the patients’ subjective pain intensity. Taken together, this indicates that machine learning algorithms can use fMRI data to distinguish warm and painfully hot stimuli with decent accuracy. However, it is important to note that thus far fMRI predictions of pain are limited to a couple cases.

Discussions for the validity of using an fMRI technology as a biomarker for pain diagnosis is particularly important due to the social implications that accompany it. For

![Figure 1. Statistical Performance of Biomarkers](from Veronese, M. Imaging Biomarkers: General Principles and Applications in Brain Research. (2017).)
$4,500, companies like Millennium Magnetic Technologies use fMRI technology to detect pain signatures to be used in a personal injury lawsuits. This practice is gaining traction as the company has provided reports for dozens of plaintiffs, although all cases have ended in settlement. Current tort doctrine sets high thresholds for invisible harms, like pain, because of the lack of current objective measures to identify them. This raises the question of how accurate (i.e. sensitive and specific) should these measures be to be admissible in court? While a 71% and 91% correct prediction may be decent, 29% and 9% incorrect prediction is too high to be admissible in court when large financial risks are at stake.

Recommendations

Taken together, the emerging literature shows that there is a potential for neuroimaging as a biomarker to assess for pain, but the specific way in which it is used is pertinent to the decision-making. In drug discovery, it has the potential to be used as an outcome measure in order to refine dosing and measure efficacy. However, when brought into the legal sphere, fMRI techniques should not be used to verify pain because they do not have the level of sensitivity and specificity to be completely accurate when big financial implications are at stake.

Conclusion

Carl Koch’s case never went to trial, as the company settled out of court. We do not know how a jury would have interpreted his fMRI data, but the prospect of its use was enough to dissuade the defendants from going to trial. Until higher courts decide upon the use of fMRI in pain detection, there are no rules nor regulations surrounding their use in court. Therefore, it is paramount that there be an increased scientific and societal dialogue surrounding this topic to ensure that our scientific technologies are used in fair and just ways. However, emerging research looks promising that fMRI could be uniquely biologically informative in improving the drug discovery process for pain medications.

Works Cited