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Topical review

Neuroethical issues related to the use of brain imaging: Can we and should we use brain imaging as a biomarker to diagnose chronic pain?

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1. Introduction

There is increasing pressure from the general public, clinical and scientific circles, insurance companies, and legal, government, and military agencies to adopt brain imaging for chronic pain and other health-related diagnostics [27]. Brain imaging is being considered as a diagnostic tool for neurological and psychiatric conditions, particularly for conditions that by their very nature rely on self-report. However, in our experience, we find that most clinicians and other stakeholders do not have a sufficient understanding of the limitations of the technology, despite the enormous impact its misuse could have. The diagnosis of chronic pain can be particularly challenging because, by definition, pain is a subjective experience. Thus, chronic pain "biomarkers" or "predictors" based on brain imaging findings are being sought. Such applications require clear understanding of the technical and physiological capabilities of brain imaging as well as ethical and policy considerations. This review highlights limitations of single-subject functional magnetic resonance imaging (fMRI) and the need to address public understanding of neuroimaging and responsibility of researchers, patient vulnerability, regulatory issues, and discrimination.

2. Defining and diagnosing pain

Fundamentally and by definition, pain is a subjective experience (International Association for the Study of Pain [IASP]: http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm), and as such can be measured only by self-report. Pain diagnostics, and treatment decision-making and effectiveness critically rely on subjective self-evaluated pain. For the most part, a simple self-evaluation of pain suffices, but there are compelling reasons to develop an objective measure as a proxy for pain self-reporting, especially when self-report is not possible (e.g., in patients in whom understanding is difficult).

A concept related to but not synonymous to pain is that of nociception. Nociception is a neurophysiological event defined by the IASP as an objective measure of the "neural process of encoding noxious stimuli" (http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm). The IASP definition further states that the "consequences of encoding may be autonomic (e.g., elevated blood pressure) or behavioral (motor withdrawal reflex or more complex nocifensive behavior). Pain sensation is not necessarily implied." The latter part of this definition is the critical roadblock to the dependence of nociceptive measures as an absolute proxy for pain measures, and underscores the need to integrate subjective dimensions of pain.

Health care professionals, insurance companies, lawyers, and other stakeholders must rely on patient self-report because pain, by its very nature, is subjective. Without a method for objective validation, patients can be dismissed as malingerers, exaggerators, or as having a mental health issue as opposed to actually experiencing pain. The consequences for a patient who is not believed to have "real pain" can include major obstacles to the receipt of adequate pain management, and can also have financial and social consequences.

3. Can brain imaging identify chronic pain?

The explosion of brain imaging studies of pain has re-opened the issue of whether an objective proxy for pain can or should be developed. If such a biomarker is used for the diagnosis and

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treatment of pain, then we must understand the technical limitations and ethical implications of such a test.

There are 2 major barriers to establishing neuroimaging biomarkers for processes such as pain: the problem of reverse inference and the possibility of false negatives. Poldrack discussed the reverse inference problem (i.e., backwards logic that the presence of a brain activation must mean that a particular cognition occurred) and offered insight into approaches to minimize the problem [28,29]. A false-negative finding (ie, Type II error) arguably represents the greatest neuroethical roadblock for pain diagnostics. For example, if an imaging test mistakenly concluded that an individual is not experiencing pain (when in fact they are), then that individual could suffer dire consequences such as denied medical treatment, time off work, insurance coverage, etc. Therefore, the adoption of any new diagnostic test must meet criteria of specificity, sensitivity, accuracy, positive and negative predictive values, and the likelihood ratio [17,36]. A careful assessment of these criteria as pertains to brain imaging of pain indicate that many are not met with current imaging technologies. Rather than attempt to provide data to prove or disprove these mathematical

Defining a Putative Pain "Biomarker"

❑ Imaging technique

- ❖ fMRI: BOLD (evoked, resting state connectivity), perfusion (rCBF)
- ❖ PET: rCBF (water), glucose metabolism, receptor binding

❑ Activation features

- ❖ presence or absence of an evoked response
- ❖ magnitude of response
- ❖ sign (i.e., increase or decrease from baseline)
- ❖ anatomical location
- ❖ size and spatial extent
- ❖ connectivity with other brain areas
- ❖ behavioural correlation (e.g., pain intensity)

❑ Imaging parameters

- ❖ MRI field strength (e.g., 1.5T, 3T)
- ❖ pulse sequence (e.g., echoplanar, spiral)
- ❖ acquisition parameters (spatial and temporal resolution, etc.)

❑ Protocol design

- ❖ stimulus modality (heat, mechanical, electrical, laser, etc.)
- ❖ stimulus intensity (fixed stimulus, fixed evoked pain intensity)
- ❖ control condition (no stimulus, non painful (e.g., thermal, mechanical))
- ❖ duration and number of trials (block versus single trial design)

❑ Preprocessing and statistical criteria

- ❖ hemodynamic response (stimulus-related vs percept-related)
- ❖ spatial (Gaussian) and temporal filters
- ❖ height and extent (cluster) threshold
- ❖ correction for multiple comparisons
- ❖ whole brain versus region of interest analysis
- ❖ fixed effects versus random effects analysis

❑ Physiological issues

- ❖ brain areas are non-specific and multi-responsive (fear, attention, salience, emotion, pain, etc.)
- ❖ overlap of pain and non-pain responsive neurons for touch, etc. (i.e., no brain area contains only pain-responsive neurons)
- ❖ BOLD, rCBF ceiling effects

Fig. 1. The definition of a putative pain "biomarker" based on neuroimaging must be based on a set of standardized technical, design, and analysis criteria that are validated across a large population of subjects, considering sex, age, and other individual characteristics, and must also address physiological issues of specificity and sensitivity. fMRI, functional magnetic resonance imaging; BOLD, blood oxygen level dependent; rCBF, regional cerebral blood flow; PET, positron emission tomography.

constructs, we review here 4 fundamental concerns at the heart of these standard criteria most relevant to the adoption of brain imaging as a valid diagnostic test of pain (Fig. 1).

3.1. Operational definition of pain biomarkers: Defining a "pain activation"

Medical tests determine whether an individual's measured value is outside the range of normal values based on population data. Therefore, any "pain biomarker" used for diagnostic purposes must be based on knowledge of the range of normal values across a large sample representative of the population, and must consider variability due to individual factors such as sex, age, and ethnicity. To date, there are no such large-scale brain-imaging studies of pain, although the consensus of numerous studies conducted for cohorts of typically <30 individuals is that several brain areas are normally "activated" by painful stimuli, some of which may be abnormal in chronic conditions [2]. The critical issue not yet resolved is the capability of imaging in terms of specificity, sensitivity, and accuracy of such findings for an individual person and how to actually measure this.

There is no consensus as to which imaging criteria to use to make critical decisions about imaging findings. At least 7 features can characterize a brain-imaging finding (typically an "activation" in fMRI or positron emission tomography [PET]) [8,10,22]: 1) response presence or absence, 2) magnitude of response, 3) sign (increase/decrease from baseline), 4) anatomical location, 5) size/spatial extent, 6) connectivity with other brain areas, and 7) behavioural or perceptual correlation (e.g., to pain intensity). Most imaging studies consider a finding to be simply present in a simple analysis (criteria 1) or some more sophisticated analysis (criteria 6 or 7), but these are based on statistical tests that may or may not incorporate the other criteria and are critically dependent on nuances of subtraction technique (see [8] for details).

3.2. Technical issues

Technical imaging details vary across laboratories but are critical in producing imaging "maps" and contribute to sensitivity and specificity of any imaging "test" (Fig. 1). Imaging parameters can critically impact MRI signal and noise (and hence the signal-to-noise ratio) that impact detectability. fMRI activations are derived from a statistical comparison between the hemodynamic responses to these conditions. Thus, other critical factors include the test itself, including the protocol design, choice of test, and control stimuli, as well as the myriad of statistical analysis decisions [30].

3.3. Physiological issues

Physiological issues contribute to and complicate interpretation of pain imaging studies (Fig. 1). Most important is that no known brain area responds only to pain. Brain areas that show pain-related responses are also associated with nonnoxious sensory functions like touch, and cognitions such as fear, stress, attention, salience, and various emotions [8,9,11,14,37]. Furthermore, nonnociceptive neurons are intermingled with and likely outnumber nociceptive neurons in pain-responsive areas [3,6,13,19,20], and so statistical subtraction may not allow for identification of pain responses [7]. Additional physiological issues that are not well understood are the limitations of hemodynamic responses. For example, chronic pain presumably is reflected by spontaneous activity in nociceptive neurons, which pose a potential hemodynamic ceiling effect that would limit fMRI responses to external stimuli. Patients with cerebrovascular response impairments (e.g., post stroke) also have limited ability to show normal fMRI responses.

3.4. Choice of imaging technique

Patients with chronic pain conditions suffer from ongoing (spontaneous) pain and/or stimulus-evoked pain (e.g., initiated by light touch or movement). Therefore, the choice of imaging technology and protocol needs to consider the type of pain characteristic to study. For example, classical stimulus-evoked fMRI and PET could be used to assess allodynia/hyperalgesia, but approaches such as resting state fMRI, or regional cerebral blood flow (e.g., PET, MRI perfusion) must be used to assess activity related to ongoing pain. These later approaches are still under development for use in individual subjects.

4. Ethics and policy considerations in brain imaging for chronic pain

4.1. Public understanding of neuroimaging and responsibility of researchers

Potential uses and misuses of brain imaging-based pain biomarkers will likely be shaped by how the public, clinicians, and other stakeholders understand the limitations of the technology. Important shortcomings of media reports on neuroimaging techniques have been observed, such as limited methodological and design-related details [32,35]. Further, neuroimaging findings are typically over-interpreted in the form of neuroessentialism (interpretations that the brain is the self-defining essence of a person) and neurorealism (interpretations that neuroimaging research yields direct data on brain function) [33,35]. Neuroimages can also sway beyond their legitimate scientific value [25,38]. Many neuroimagers are concerned about public over-interpretations and consequent pressures to use neuroimaging results [12]. Simple strategies have been proposed, such as asking reporters to allow a review of citations prior to publication, stressing the incremental nature of neuroscience research, and to avoid hyping the results [31]. More complex schemes involve 1) academic institutions and funding bodies valuing the contribution of researchers to public outreach similarly to teaching and research; 2) developing experts in both neuroscience and journalism; 3) supporting more evidence-based research on communication [18]; and 4) fostering self-reflection on precedent use of imaging and neuroscience [34].

4.2. Patient vulnerability and expectations for neuroimaging

Patients suffering from chronic pain constitute a vulnerable population because for some, their hope and desperation for a clear diagnosis or better treatment may thwart their appreciation of the capabilities of neuroimaging. The powerful impressions made by media messages can impact expectations of patients [4]. General guidance about how to respond to requests of overly hopeful patients emphasize the need for continuity in health care [26] and for nurturing a climate of trust with patients, to avoid dismissing their requests but being receptive to their views and expectations [5]. Consolidating the understanding of nonexpert health care providers will also be important.

4.3. Regulatory issues and discrimination based on interpretation of neuroimaging

There are numerous regulatory and legal issues pertaining to the possible access of neuroimaging findings by third parties like insurers and employers [21]. Given the challenges of public understanding of neuroimaging techniques and longstanding concerns

about discrimination of pain patients [26], it is not clear how this health information would be interpreted. Would abnormal responses to pain be interpreted as clear signs of the legitimacy of chronic pain? Would, on the contrary, the absence of any abnormal imaging finding be held against a patient for insurance coverage or other health benefits? Important lessons come from the introduction of fMRI as a lie detection device in the public and legal arena. In this case of scientifically unwarranted use of neuroimaging, and in spite of responsible and cautionary responses from the scientific community [16,39], private companies are offering services for fMRI-based lie detection, and attempts have been made to introduce it in American courts in Tennessee and New York. So far, American courts have not accepted fMRI-based findings [23,24], but a case of electroencephalography use for a murder conviction in India has been reported [15]. Thus, significant efforts must come from the pain research community to avoid pitfalls that can jeopardize patient interests. Further discussion could examine the benefits and challenges of nondiscrimination legislation introduced in the context of genetics [1].

5. Conclusions: Pros and cons of brain imaging of pain

Potential contributions of brain imaging of clinical pain, and consequences that must be considered in moving forward with this approach are summarized in Fig. 2. In summary, brain imaging can provide tremendous scientific insight into pain. The strength of brain imaging lies in its ability to reveal how, in general, the brain is engaged during a particular state for a study cohort. However, technical and physiological obstacles must be addressed to establish whether there are sensitive, specific, and reliability "pain biomarker" readouts that are valid in an individual subject, and that considers the range of normal interindividual differences across

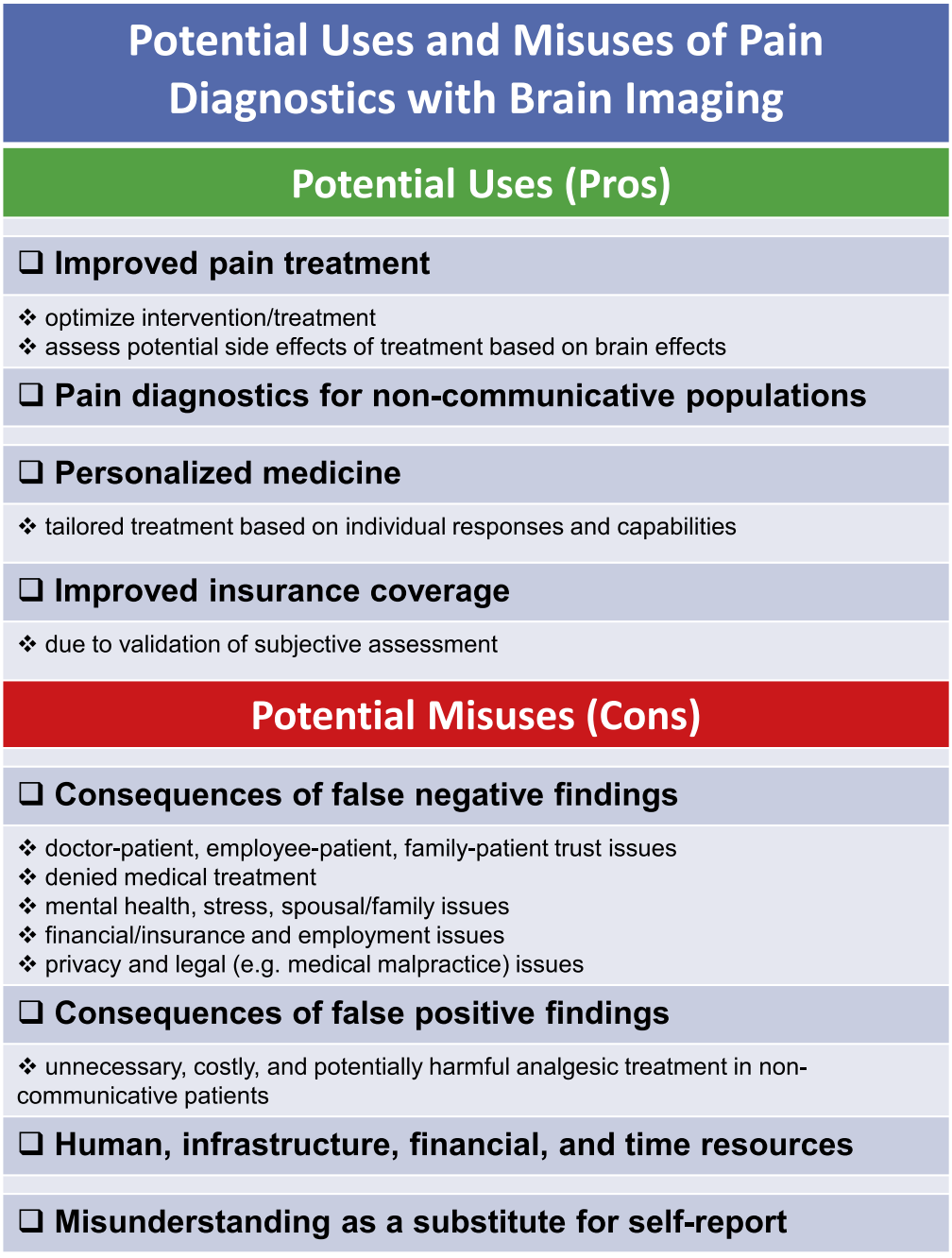

Fig. 2. There are several potential uses and misuses of brain imaging for the diagnosis of clinical pain.

different populations. Therefore, like any new technology, serious efforts are needed to determine if and how brain imaging is applicable to clinical medicine pertaining to chronic pain.

Conflicts of interest statement

The authors have no conflicts of interest to disclose.

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