CHAPTER 6

Pharmacological Approaches to Pain and Consciousness Using Functional Neuroimaging

Irene Tracey and Katie Warnaby

BACKGROUND

Powerful ways for better understanding pain, analgesia, relief, and altered states of consciousness are offered via pharmacological neuroimaging paradigms. This is where a drug is administered to volunteers alongside neuroimaging data acquisition. Most experiments to date have used functional magnetic resonance imaging (oftentimes called phFMRI), though there exists a strong early and periodic literature deploying positron-emission tomography (PET). Two modes of application are commonly used: (1) imaging the brain's response after acute or chronic administration of the drug and without any concurrent stimulation (i.e., no pain or sensory/cognitive task), and (2) imaging how the brain's response to a sensory stimulus or cognitive task is altered due to the concurrent presence of a drug (acutely or chronically administered). Relatedly, you can degrade the state of consciousness during anesthesia to determine how this impacts perception and awareness. The second mode of application is more commonly employed these days. The first mode is generally limited to PET studies where questions are focused on where and to what extent the drug binds within the human brain.

The popularity of phFMRI is growing as researchers recognize what a powerful tool it is for manipulating and probing the "state" of pain or consciousness to reveal underpinning mechanisms. Similarly, industry has long recognized the value of phFMRI and PET for the analgesic drug discovery process and has been pivotal in driving forward this field with their academic collaborations. We should note that although FMRI has been the predominant tool in such studies, there are many other physiological measures from the human brain that the MR modality can obtain which lend themselves to pharmacological studies—that is, neurochemical (magnetic resonance spectroscopy), structural, resting state networks (connectivity patterns and changes), arterial spin labeling, and diffusion imaging (white matter integrity/tracts). These measurements are now starting to be combined in "traditional" pharmacological imaging studies, and so the field generally refers to phMRI studies. Also, the reader should be aware that phMRI is used in preclinical studies, though to a lesser extent than human studies.

NEUROIMAGING ANESTHESIA–INDUCED ALTERED STATES OF CONSCIOUSNESS

Copyright © 2016. Wolters Kluwer Health. All rights reserved.

Garcia-Larrea, Luis, and Philip L. Jackson. Pain and the Conscious Brain, Wolters Kluwer Health, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/oxford/detail.action?docID=4931411.
Created from oxford on 2019-07-01 03:42:46.

Here, we will limit the discussion to studies exploring how anesthetic agents influence brain processing to produce altered states of consciousness. As the triad of anesthesia (analgesia, muscle relaxation, and hypnosis/awareness) has pain and awareness at its core, we will explore how such changes impact nociceptive processing and an awareness of pain alongside other sensory stimuli. This field is relatively young and very few laboratories work in this challenging arena. Conducting neuroimaging while subjects are under general anesthesia is one of the most difficult types of experiment to perform—both from a safety and practical perspective. This explains why the literature is relatively sparse compared to pain neuroimaging and phMRI. Understandably, there are far more electrophysiological-based studies, but we will discuss only a few of those briefly here. The interested reader is referred to the following reviews that summarize key aspects of this literature and relate it more broadly to issues surrounding consciousness, anesthesia, coma, and vegetative states [7, 29, 32, 37].

Fig. 6-1 nicely illustrates the complex relationship between behavior and increasing dose of anesthetic agent. Key features of this journey that neuroimaging/electrophysiological approaches might help identify and are relevant to the anesthetist, neuroscientist, and patient include the following:

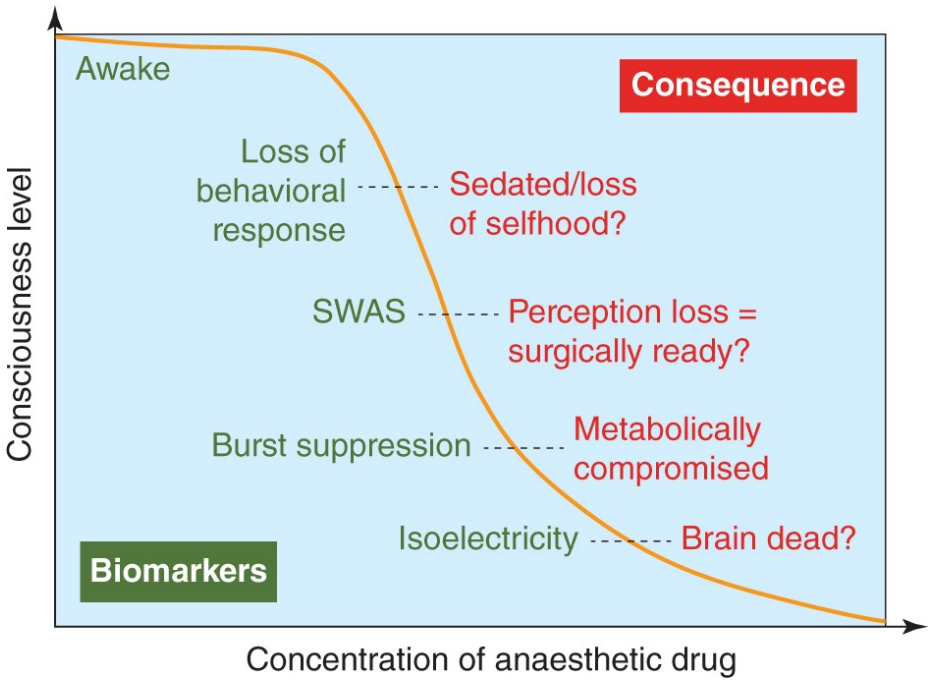

FIGURE 6-1 Schematic illustrating the relationship between state of consciousness, loss of behavioral response, and concentration of general anesthetic (GA) agent.

1. What neural event(s) underpin loss of behavioral responsiveness (LOBR) and what does this mean in terms of interoceptive awareness?
2. What brain changes occur during further increases in dose of anesthetic agent that might indicate loss of perception to sensory events (e.g., nociceptive inputs and pain)? An efficacious *individualized brain-based biomarker* is much needed as most anesthetics are administered based upon population responses (“average”) using

Copyright © 2016. Wolters Kluwer Health. All rights reserved.

Garcia-Larrea, Luis, and Philip L. Jackson. Pain and the Conscious Brain, Wolters Kluwer Health, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/oxford/detail.action?docID=4931411.
Created from oxford on 2019-07-01 03:42:46.

nonbrain and indirect (e.g., heart and respiration rate) changes to indicate when it might be safe to start the surgical procedure without fear of pain, awareness, or movement.

3. How robust are these measures across different anesthetic agents?
4. How variable are these measures based upon other subject parameters (e.g., age, sex, presence of other drugs, brain damage)?

Early Data—Is There a Thalamocortical "Switch" in Anesthesia?

Many models have been proposed to explain "consciousness," as discussed in the reviews recommended and this book. The "information integration" theory of consciousness states that when a percept, such as pain, is constructed then synchronous activity in distinct distributed nodes, each processing the discrete components of that percept, is necessary [10, 41]. Any breakdown of communication or connectivity between the nodes of these networks is thought to underlie loss of consciousness and will by definition impact that percept. Various studies have shown that changes in connectivity between discrete nodes occur during an anesthetic state [26, 27, 33]. An FMRI study performed by ourselves that examined the awake state and two propofol-induced sedated states (mild and moderate) in healthy subjects during concurrent auditory and nociceptive stimulation illustrates nicely how the connectivity of the thalamus and putamen to subcortical and cortical regions variably and independently changes at each of these transitional states.

When we group averaged the subjects' brain's responses to sensory stimulation at each of these states (awake, mild, and moderate sedation), we showed that this loss of connectivity decreased brain activity the deeper the subjects were sedated. As such, this data lends support to this theory, but the key to all these studies is our inability to know what the subjects *actually perceive* when sedated (as we have no behavioral measure or report). We have to *infer* from the brain activity map what subjects are likely perceiving based upon how these maps relate to the awake brain or a subject experiencing analgesia (if stimulus of interest is pain). Reverse inferences are fraught with assumptions—but right now it is commonly how neuroimaging studies interpret such data. Machine learning tools, discussed in the Machine-Learning Applications in phMRI section below, will undoubtedly play an important contribution to this problem going forward.

Several earlier studies (PET and FMRI) identified what was assumed to be a specific reduction in thalamic activity. This observation led to the concept of a "thalamocortical switch," whereby thalamic suppression blocks information flow and further processing of incoming sensory stimuli within cortical regions [2, 23, 48]. While this is an attractive and intuitive construct, it is starting to be questioned within the remit of anesthesia-induced unconsciousness [3, 31]. It should be remembered that there is an order of magnitude more connections from the cortex to the thalamus than vice versa. Therefore, the reduction observed during impaired consciousness in thalamic metabolism and blood flow may be secondary to the reduced inputs from cortex or brain stem to the thalamus producing a "functional thalamic deafferentation"-like state. Alternatively, failure of information integration may be due to

Copyright © 2016. Wolters Kluwer Health. All rights reserved.

Garcia-Larrea, Luis, and Philip L. Jackson. Pain and the Conscious Brain, Wolters Kluwer Health, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/oxford/detail.action?docID=4931411.
Created from oxford on 2019-07-01 03:42:46.

disruption of corticocortical communication, as recently shown using advanced analysis methods [16, 22, 34] and reduction in thalamic connectivity [1, 17, 33]. Either way, based upon current literature the verdict is that thalamic deactivation is more likely to be a consequence of impaired consciousness rather than the cause.

We should stress this seems to be the case only for pharmacologically induced or "provoked" loss of consciousness, while in physiological unconsciousness (e.g., natural sleep) the thalamus deactivates earlier than the cortex [28]. This potential dissociation between "natural" and "provoked" unconsciousness, as discussed in Chapter 5, is extremely interesting and warrants further investigation and confirmation. Certainly, anesthesia-induced altered states of consciousness appear to share some brain processes with sleep-induced unconscious states, as discussed below. Interestingly, the mechanisms underlying induction of and emergence from anesthesia-induced states of altered consciousness might be different. They might have quite separate relationships to sleep-like states, and this is the focus of current research in some laboratories such as ours.

Current Data—Multimodal Imaging and Slow Waves

Previous work using pharmacological sedation, as a model for the study of consciousness, has been largely constrained by the assumptions underlying the application of population-based pharmacokinetic models to individuals. Therefore, it is unsurprising that no *individualized* neurophysiological marker of perceptual loss (e.g., to pain) has been identified. The approach used in many published neuroimaging studies of consciousness or anesthesia is to deliver the anesthetic agent at specific effector-site concentrations and collect data in response to sensory stimulation for all subjects at that dose. While this has been a valuable starting point for many studies and has provided valuable data showing how the brain's responsivity to sensory stimulation alters with increasing dose of anesthetic agent (see examples for ketamine [39] and propofol [33]), the subjects are at varying states of consciousness at each dose. The problem being that the averaged brain activation map at each dose cannot inform us about the specific link between a certain state of consciousness and the nociceptive processing relevant to pain perception. In order to achieve that understanding, we must examine each individual slowly as they transit in a continuous fashion down the curve described in Fig. 6-1. In short, we need a fundamentally different paradigm.

Due to the large and robust literature using electrophysiological measures (EEG) to explore how neural oscillations (e.g., α, δ, γ waves) alter during sleep and anesthesia [11, 35, 38], it is important to integrate these changes into any paradigm as they can inform the neuroimaging analysis. Further, we have known for a long time that under hyperpolarizing influences, including endogenous sleep drive and anesthetic drugs, cortical neurons oscillate at ~1 Hz, measurable as slow waves in the EEG. Also, it has been recently shown that in later stages of non-REM sleep, which are defined by the presence of slow waves, thalamic, and cortical responses to stimulation become less consistent [13]. Therefore, we hypothesized that the amplitude of slow-wave activity (SWA) upon reaching its maximum *for an individual* is the electrophysiological signature of an unresponsive yet active brain during anesthesia.

We used an ultraslow induction of propofol anesthesia (over 40 minutes induction rather

Copyright © 2016. Wolters Kluwer Health. All rights reserved.

Garcia-Larrea, Luis, and Philip L. Jackson. Pain and the Conscious Brain, Wolters Kluwer Health, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/oxford/detail.action?docID=4931411.
Created from oxford on 2019-07-01 03:42:46.

than a few seconds—that is, allowing for a slow motion "video" of the brain as it transits through altered states of consciousness) and simultaneous EEG and FMRI during nociceptive and auditory stimulation—asking subjects to respond to the stimulus [36]. We showed that after LOBR each individual's EEG SWA rises to saturation (SWAS), and remains constant despite increasing drug levels. Impressively, the magnitude of SWAS response correlated positively with their prefrontal gray matter volume. Simultaneously collected FMRI and EEG during nociceptive/painful and auditory stimulation allowed us to interrogate the FMRI responses to auditory and nociceptive stimulation during time windows guided by behavior and the EEG slow-wave patterns. Pre-LOBR there is normal activity within the brain, and this is largely sustained post-LOBR but pre-SWAS (i.e., when SWA is still low). However, during the behavioral unresponsive transition to SWAS we see a dramatic change in brain activity in response to auditory and nociceptive stimulation—in effect, perception loss and thalamocortical isolation occur. Interestingly, based upon spindle patterns, we found that an internal thalamocortical exchange persists at this stage (possibly contradicting the "thalamocortical" switch hypothesis), and an alternative more fundamental cortical network occurs that includes precuneus activation to sensory stimulation. We have established for the first time the relationship between changes in SWA and functional imaging of the brain's response to sensory stimulation during anesthesia. From these results, we conclude that SWAS is a potential *individualized* biomarker for perception loss with profound implications for anesthesia and the study of altered states of consciousness [36].

This study nicely illustrates the potential for multimodal neuroimaging to reveal novel and important mechanisms related to states of consciousness and how they impact pain perception. We hope such studies provide a catalyst for other groups to work in this exciting arena.

phMRI STUDIES OF PAIN AND ANALGESIA

Stratification and Personalized Medicine

To date, most phMRI pharmacological studies have averaged the drug-induced neural response changes to a range of painful stimuli/experimental models (e.g., capsaicin model of secondary hyperalgesia and ongoing pain) within a group of approximately 20 healthy subjects to ascertain the "analgesic mechanism" [21, 25, 49, 53], or have combined FMRI with a pharmacokinetic model of the analgesic to explore the time course of its effect on pain processing [51]. As a whole, such studies show a good correlation between analgesia and reduced activity in response to these painful challenges within regions commonly found active in many pain studies (e.g., thalamus, S1, S2, anterior, mid, and posterior insula, anterior cingulate, brainstem nuclei, and prefrontal cortices). More complex mechanisms of analgesia can be identified—such as the amygdala-sensory uncoupling of connectivity during cannabinoid analgesia that correlated with the discrepancy between the change in pain intensity and unpleasantness ratings [25]. While such phMRI studies provide some validity for the neuroimaging measure relating to pain they do not confirm the specificity of these regions for pain (see below). Further, important individualized variances in network responses across

Copyright © 2016. Wolters Kluwer Health. All rights reserved.

Garcia-Larrea, Luis, and Philip L. Jackson. Pain and the Conscious Brain, Wolters Kluwer Health, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/oxford/detail.action?docID=4931411.
Created from oxford on 2019-07-01 03:42:46.

these and other regions are commonly averaged out from the response, unless specific analyses are done as for the cannabinoid study. More recently, studies are being published that highlight how neuroimaging measures (functional, network, and neurochemical) at baseline, pretreatment, and posttreatment can contribute toward predicting and measuring behavioral and neuroimaging treatment responses at an *individualized* level. One example from our group showed that individual baseline reward system regional brain responsivity to painful stimulation predicted subsequent opioid analgesia [47]. Another study showed that posterior insula glutamate and glutamine levels and insula connectivity to other brain regions at baseline predicted subsequent pregabalin but not placebo analgesia [19]. Importantly, such studies can disambiguate drug from placebo mechanisms plus what might explain variances in the placebo response. As such, the personalized medicine and stratification goals that are much needed might be aided with the inclusion of neuroimaging. Further, they inform us about what role these brain regions contribute to pain perception and pain relief. This is important fundamental neuroscience.

The more we identify the neural systems involved in drug action and validate such markers as the ones affected by treatments in patients, the better we can generate novel hypotheses about combined treatments based on targeting complementary brain systems. Also, the better can we match individuals to appropriate treatments based on their brain systems that show abnormal responses and those targeted by a candidate treatment.

Verifying Pain Mechanisms Using phMRI—Drugs As "Probes"

This brings us to an important aspect of phMRI. Neuroimaging has powerfully contributed to our understanding of the mechanisms involved in developing, sustaining, and exacerbating a chronic pain state (e.g., central sensitization, alterations in descending pain modulation [DPMS], anxiety, catastrophizing, and depression). Further, neuroimaging has highlighted how the chronic pain condition itself directly and indirectly changes the brain and spinal cord. One way to test the clinical significance of any of these neuroimaging-based measures is to treat the patient pharmacologically and see how the specific measure changes relative to gold-standard clinical or behavioral measures. Such an approach is increasingly being used psychophysically without neuroimaging (e.g., aberrant conditioned pain modulation as indication of poor DPMS relating to increased duloxetine analgesia) [55]. However, given the differences in sensitivity between behavioral and neuroimaging measures, the issue discussed below regarding effect sizes alongside the complex relationship between brain processing of nociceptive inputs and subjective pain ratings, it is possible that a treatment can change structure, function, or neurochemistry in the absence of a significantly altered pain rating or behavior. If a patient's brain is "normalized" post pharmacological treatment to that of an age-matched healthy control subject, but there is no pain relief, is that meaningful and does it make the measure/mechanism any more or less relevant? This is discussed in a recent editorial [42]. Correcting identified mechanisms with or without concomitant pain relief is now measurable because of brain imaging, but it raises interesting questions for the community. What has certainly been shown, thankfully, is that even patients with years of chronic pain and measurable changes in chemistry and structure when treated (pharmacologically or surgically) for their pain successfully

Copyright © 2016. Wolters Kluwer Health. All rights reserved.

Garcia-Larrea, Luis, and Philip L. Jackson. Pain and the Conscious Brain, Wolters Kluwer Health, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/oxford/detail.action?docID=4931411.
Created from oxford on 2019-07-01 03:42:46.

reverse these changes and have "normal"-looking brains from a structural and functional perspective [18, 19, 40].

Are the phMRI Changes "Clinically Significant"?

The potential "disconnect" between what phMRI might show up as a significant effect on neural networks in the absence of any analgesia—sometimes explained away as imaging having an improved SNR—should be considered in the light of the fact that MRI and FMRI images have measures anywhere between 50,000 and 200,000 voxels approximately. This means there is activity in coherent, but spatially distributed systems across the brain—akin to other measures distributed across many variables, such as genome-wide scans. As such, MRI analyses may show many statistically significant differences that are not large enough to be clinically significant. This can lead to an overestimation of effect sizes for brain correlations. Some machine-learning approaches (discussed further below) integrate brain information across regions to make a *single* prediction about a patient's level of pain (whether on drug or not), and as such can robustly track acute pain magnitude [46], and even provide diagnostic information [43]. Such approaches powerfully contribute to our basic understanding of what brain regions are important for conscious pain perception.

Machine-Learning Applications in phMRI

There is a many-to-one mapping between psychological or physiological processes and activity in each voxel, which it should be remembered integrates activity across hundreds of thousands to millions of neurons with distinct functional properties [54]. fMRI correlates of pain have been identified in the anterior cingulate and insula (among other regions)—these regions are important for pain, but they are often activated in many other tasks (e.g., emotion, decision-making). As such, when reported as single brain regions they are not *specific* to pain or any other function for that matter, questioning their utility as a single diagnostic marker. However, whereas any one voxel in a region such as the anterior cingulate may not be highly diagnostic of pain, a particular local pattern across voxels within the anterior cingulate may be highly diagnostic and biologically relevant to pain [46].

To circumnavigate this problem, "machine-learning" algorithms that identify distributed patterns of fMRI activity within and across regions are being increasingly used in neuroimaging. Such "multivoxel pattern analysis" has been applied to pain and identified patterns maximally predictive of a pain state [9, 30, 43, 46]. As such, these patterns are potentially better suited to diagnostic development and testing because they are designed to optimize the prediction of outcomes such as pain (e.g., be sensitive to pain) and differentiate pain from related conditions (e.g., be specific to pain). Similarly, they can be applied in phMRI studies to better inform us about what constitutes a pharmacological-related "analgesic network" versus a "placebo or no treatment network," as highlighted in a recent study from our group [15]. Here, we pooled many phMRI studies across a range of drug classes tested in either experimental pain models, healthy controls, or patients and developed a novel machine-learning paradigm ideally suited for analgesic drug development. It allows single subject and

Copyright © 2016. Wolters Kluwer Health. All rights reserved.

Garcia-Larrea, Luis, and Philip L. Jackson. Pain and the Conscious Brain, Wolters Kluwer Health, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/oxford/detail.action?docID=4931411.
Created from oxford on 2019-07-01 03:42:46.

single cohort prediction of drug or placebo treatment. Further, the study design also enabled us to examine across drugs and types of painful experiences the "averaged" brain network subservient to pain and drug-induced analgesia. This is illustrated in Fig. 6-2.

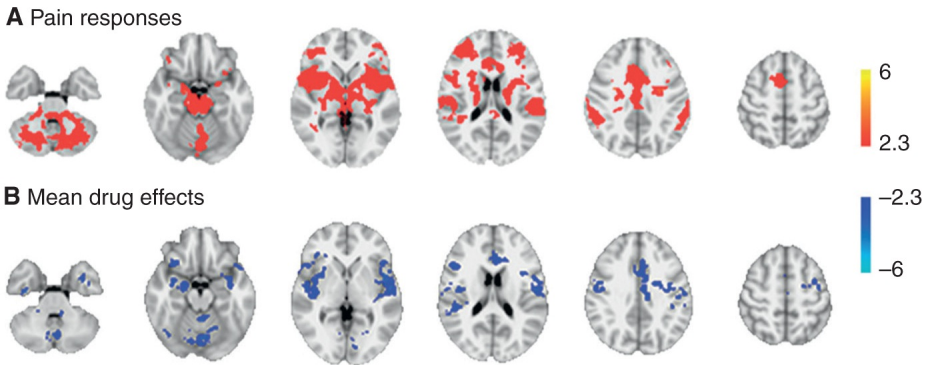

FIGURE 6-2 Multistudy activation maps. **A:** *Z*-statistic maps of a mixed-effects analysis of the average pain response across eight phMRI studies. Red corresponds to brain regions showing significant response to the painful stimuli. **B:** Mixed-effects analysis of modulation of pain responses by analgesics across all eight analgesic studies. Blue corresponds to regions showing a significantly reduced response to the painful stimuli in the analgesic sessions = "analgesic network." (Adapted from Duff et al. [15].)

In summary, many examples now exist of brain markers based on distributed patterns of activity within and across brain regions that can be used to predict forms of acute pain [9, 30, 43, 46], identify brain targets of analgesic drugs (e.g., remifentanil; [46]), identify placebo responders [20, 45], and predict whether a subject is on drug or placebo arm [15].

Specificity versus Sensitivity in phMRI

Currently, there is growing interest on the diagnostic value of brain patterns for clinical pain conditions [4] and treatment responses using the accepted criteria of *specificity and sensitivity*. For acute nociception-driven pain, a distributed pattern of regions that matches well with prototypical "pain-processing" regions in humans accurately tracks the magnitude of pain [46]. If two conditions are moderately different in pain (e.g., two points on a 10-point VAS), activity in the "neurologic pain signature" (NPS), as coined by Wager, can correctly predict which is more painful for an individual person with 90–100% accuracy. It has been successfully tested across different sites, and in addition, it was shown to have 90% or greater sensitivity and specificity to somatic pain in comparison with nonpainful warmth, pain anticipation, pain recall, and emotionally evocative images. This "NPS" responded to remifentanil administration; however, it was not affected by a placebo treatment suggesting it is sensitive to certain aspects of pain. Again, such approaches in phMRI are contributing in fundamental ways to our understanding of what brain networks are core to the complex and subjective experiences that are pain and analgesia.

Analgesic Drug Discovery

Copyright © 2016. Wolters Kluwer Health. All rights reserved.

Garcia-Larrea, Luis, and Philip L. Jackson. Pain and the Conscious Brain, Wolters Kluwer Health, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/oxford/detail.action?docID=4931411.
Created from oxford on 2019-07-01 03:42:46.

Industry has suffered from a lack of tools that provide objective in vivo information on whether their drugs have, first, target engagement and, second, efficacy toward the mechanism being targeted. Over-reliance on subjective ratings that are influenced or biased by several extraneous factors means that novel compounds with genuine antinociceptive, antihyperalgesic, and so forth activity are discarded in early phase studies. The attrition rate for analgesics is larger than for any other disease area. Many factors contribute, but one relates to the problem that pain is a multifactorial experience subject to many influences. Therefore, irrespective of the nociceptive input or even the presence of strong analgesics divergences and complex relationships occur between what a subject reports and what is measured using regional brain activity [14].

The fact that subjects might not show a statistical improvement in subjective rating when using any of our developed pain scales is not a binary reason to discard the drug at very early stages of drug development, and yet this happens. Recent studies highlighting how negative expectation can mask true analgesic efficacy [6, 24], and how correction of aberrant neurochemistry and network connectivity can occur in patients without necessarily good analgesia [19], illustrate these points well.

The sad truth is that few drugs make it to Phase IV testing in humans; therefore, it is important that an appropriate range of tools are used to assess potential efficacy at this stage. From what has been previously discussed in this chapter, it should be apparent that imaging can provide the following novel insights into a new compound:

1. CNS penetration and drug dosing
2. Identification of neural circuits targeted
3. Assessment of potential efficacy, based on neural circuitry of activation and its connectivity
4. Potential side effects based on changes in brain regions involved with sleepiness, addiction, and nausea/vomiting

The use of imaging in early clinical trials (and drug evaluation for analgesia) is increasing: of the 70 drugs reported on clinicaltrials.gov that included imaging, 10 involved analgesics. Currently, there are few phase 3 imaging analgesia studies; however, this situation is likely to change [8, 44].

Additionally, the ability of phMRI to measure the responsivity of neural circuits with respect to pharmacological manipulation means these circuits provide “a language of translation” between preclinical species and humans, and as such phMRI studies allow for extrapolation of efficacy from preclinical models to humans more objectively [5, 8] and identification of potential side effect profiles based upon circuitry affected (e.g., nausea and vomiting) [12].

For the interested reader, several excellent reviews provide a comprehensive overview of phMRI’s potential application and benefit for analgesic drug development [8, 50, 52]. Neuroimaging is being slowly adopted into analgesic drug development in both translational and clinical trials. Many large companies have realized the benefit of phMRI to provide objective readouts and, as such, help with their “go/no-go” decision-making processes. En

Copyright © 2016. Wolters Kluwer Health. All rights reserved.

Garcia-Larrea, Luis, and Philip L. Jackson. Pain and the Conscious Brain, Wolters Kluwer Health, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/oxford/detail.action?docID=4931411.
Created from oxford on 2019-07-01 03:42:46.

route, we are learning more about how our drugs work and fundamental aspects regarding pain and analgesic mechanisms.

CONCLUSION

From the literature discussed, phMRI is a significant and growing component of neuroimaging-based studies, exploring pain and altered states of consciousness. Such paradigms provide insight into the neural bases of analgesia and pain relief, in the context of pain-related drugs, as well as enable a translational agenda by aiding analgesic drug development within industry. phMRI will play an increasing role in both clinical decision-making and drug discovery in the years to come. Further, as we improve our neurobiological understanding of the neural networks core to consciousness, pain perception and analgesia through phMRI studies alongside new analysis approaches, such as machine learning, so we can better interpret brain patterns generated during anesthesia-induced altered states of consciousness during surgical procedures. The link between pain and the conscious brain is an old but complex one. Our hope is that phMRI can continue to unravel and simplify this relationship.

REFERENCES

1. Akeju O, Loggia ML, Catana C, Pavone KJ, Vazquez R, Rhee J, Ramirez VC, Chonde DB, Izquierdo-Garcia D, Arabasz G, et al. Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. eLife 2014;3:e04499.
2. Alkire MT, Haier RJ, Fallon JH. Toward a unified theory of narcosis: brain imaging evidence for a thalamocortical switch as the neurophysiologic basis of anesthetic-induced unconsciousness. Conscious Cogn 2000;9:370–86.
3. Alkire MT, Hudetz AG, Tononi G. Consciousness and anesthesia. Science 2008;322:876–80.
4. Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat Neurosci 2012;15:1117–9.
5. Becerra L, Navratilova E, Porreca F, Borsook D. Analogous responses in the nucleus accumbens and cingulate cortex to pain onset (aversion) and offset (relief) in rats and humans. J Neurophysiol 2013;110:1221–6.
6. Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, Tracey I. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med 2011;3:70ra14.
7. Boly M, Sanders RD, Mashour GA, Laureys S. Consciousness and responsiveness: lessons from anaesthesia and the vegetative state. Curr Opin Anaesthesiol 2013;26:444–9.
8. Borsook D, Becerra L, Fava M. Use of functional imaging across clinical phases in CNS drug development. Transl Psychiatry 2013;3:e282.
9. Brodersen KH, Wiech K, Lomakina EI, Lin C, Buhmann JM, Bingel U, Ploner M, Stephan KE, Tracey I. Decoding the perception of pain from fMRI using multivariate pattern analysis. Neuroimage 2012;63:1162–70.
10. Buzsaki G. Neuronal oscillations in cortical networks. Science 2004;304:1926–9.
11. Casali AG, Gosseries O, Rosanova M, Boly M, Sarasso S, Casali KR, Casarotto S, Bruno M-A, Laureys S, Tononi G, Massimini M. A theoretically based index of consciousness independent of sensory processing and behavior. Sci Transl Med 2013;5:198ra105.
12. Chin C-L, Fox GB, Hradil VP, Osinski MA, McGaraughty SP, Skoubis PD, Cox BF, Luo Y. Pharmacological MRI in awake rats reveals neural activity in area postrema and nucleus tractus solitarius: relevance as a potential biomarker for detecting drug-induced emesis. Neuroimage 2006;33:1152–60.
13. Dang-Vu TT, Bonjean M, Schabus M, Boly M, Darsaud A, Desseilles M, Degueldre C, Balteau E, Phillips C, Luxen A, et al. Interplay between spontaneous and induced brain activity during human non-rapid eye movement sleep. Proc Natl Acad Sci U S A 2011;108:15438–43.
14. Denk F, McMahon SB, Tracey I. Pain vulnerability: a neurobiological perspective. Nat Neurosci 2014;17:192–200.
15. Duff EP, Vennart W, Wise RG, Howard MA, Harris RE, Lee M, Wartolowska K, Wanigasekera V, Wilson FJ, Whitlock M,

Copyright © 2016. Wolters Kluwer Health. All rights reserved.

Garcia-Larrea, Luis, and Philip L. Jackson. Pain and the Conscious Brain, Wolters Kluwer Health, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/oxford/detail.action?docID=4931411.
Created from oxford on 2019-07-01 03:42:46.

et al. Learning to identify CNS drug action and efficacy using multistudy fMRI data. Sci Transl Med 2015;7:274ra16.
16. Ferrarelli F, Massimini M, Sarasso S, Casali A, Riedner BA, Angelini G, Tononi G, Pearce RA. Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness. Proc Natl Acad Sci U S A 2010;107:2681–6.
17. Gili T, Saxena N, Diukova A, Murphy K, Hall JE, Wise RG. The thalamus and brainstem act as key hubs in alterations of human brain network connectivity induced by mild propofol sedation. J Neurosci 2013;33:4024–31.
18. Gwilym SE, Filippini N, Douaud G, Carr AJ, Tracey I. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: a longitudinal voxel-based morphometric study. Arthritis Rheum 2010;62:2930–40.
19. Harris RE, Napadow V, Huggins JP, Pauer L, Kim J, Hampson J, Sundgren PC, Foerster B, Petrou M, Schmidt-Wilcke T, Clauw DJ. Pregabalin rectifies aberrant brain chemistry, connectivity, and functional response in chronic pain patients. Anesthesiology 2013;119:1453–64.
20. Hashmi JA, Baria AT, Baliki MN, Huang L, Schnitzer TJ, Apkarian AV. Brain networks predicting placebo analgesia in a clinical trial for chronic back pain. Pain 2012;153:2393–402.
21. Iannetti GD, Zambreanu L, Wise RG, Buchanan TJ, Huggins JP, Smart TS, Vennart W, Tracey I. Pharmacological modulation of pain-related brain activity during normal and central sensitization states in humans. Proc Natl Acad Sci U S A 2005;102:18195–200.
22. Jordan D, Ilg R, Riedl V, Schorer A, Grimberg S, Neufang S, Omerovic A, Berger S, Untergehrer G, Preibisch C, et al. Simultaneous electroencephalographic and functional magnetic resonance imaging indicate impaired cortical top-down processing in association with anesthetic-induced unconsciousness. Anesthesiology 2013;119:1031–42.
23. Kaisti KK, Metsahonkala L, Teras M, Oikonen V, Aalto S, Jaaskelainen S, Hinkka S, Scheinin H. Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. Anesthesiology 2002;96:1358–70.
24. Kessner S, Wiech K, Forkmann K, Ploner M, Bingel U. The effect of treatment history on therapeutic outcome: an experimental approach. JAMA Intern Med 2013;173:1468–9.
25. Lee MC, Ploner M, Wiech K, Bingel U, Wanigasekera V, Brooks J, Menon DK, Tracey I. Amygdala activity contributes to the dissociative effect of cannabis on pain perception. Pain 2013;154:124–34.
26. Lee U, Mashour GA, Kim S, Noh G-J, Choi B-M. Propofol induction reduces the capacity for neural information integration: implications for the mechanism of consciousness and general anesthesia. Conscious Cogn 2009;18:56–64.
27. Liu X, Lauer KK, Ward BD, Li S-J, Hudetz AG. Differential effects of deep sedation with propofol on the specific and nonspecific thalamocortical systems: a functional magnetic resonance imaging study. Anesthesiology 2013;118:59–69.
28. Magnin M, Rey M, Bastuji H, Guillemant P, Mauguière F, Garcia-Larrea L. Thalamic deactivation at sleep onset precedes that of the cerebral cortex in humans. Proc Natl Acad Sci U S A 2010;107:3829–33.
29. Marchant N, Sanders R, Sleigh J, Vanhaudenhuyse A, Bruno M-A, Brichant JF, Laureys S, Bonhomme V. How electroencephalography serves the anesthesiologist. Clin EEG Neurosci 2014;45:22–32. doi:10.1177/1550059413509801.
30. Marquand A, Howard M, Brammer M, Chu C, Coen S, Mourão-Miranda J. Quantitative prediction of subjective pain intensity from whole-brain fMRI data using Gaussian processes. Neuroimage 2010;49:2178–89.
31. Mashour GA, Alkire MT. Consciousness, anesthesia, and the thalamocortical system. Anesthesiology 2013;118:13–5.
32. Mashour GA, Alkire MT. Evolution of consciousness: phylogeny, ontogeny, and emergence from general anesthesia. Proc Natl Acad Sci U S A 2013;110:10357–64.
33. Mhuircheartaigh RN, Rosenorn-Lanng D, Wise R, Jbabdi S, Rogers R, Tracey I. Cortical and subcortical connectivity changes during decreasing levels of consciousness in humans: a functional magnetic resonance imaging study using propofol. J Neurosci 2010;30:9095–102.
34. Monti MM, Lutkenhoff ES, Rubinov M, Boveroux P, Vanhaudenhuyse A, Gosseries O, Bruno M-A, Noirhomme Q, Boly M, Laureys S. Dynamic change of global and local information processing in propofol-induced loss and recovery of consciousness. PLoS Comput Biol 2013;9:e1003271.
35. Mukamel EA, Pirondini E, Babadi B, Wong KFK, Pierce ET, Harrell PG, Walsh JL, Salazar-Gomez AF, Cash SS, Eskandar EN, et al. A transition in brain state during propofol-induced unconsciousness. J Neurosci 2014;34:839–45.
36. Ni Mhuircheartaigh R, Warnaby C, Rogers R, Jbabdi S, Tracey I. Slow-wave activity saturation and thalamocortical isolation during propofol anesthesia in humans. Sci Transl Med 2013;5:208ra148.
37. Owen AM. Detecting consciousness: a unique role for neuroimaging. Annu Rev Psychol 2013;64:109–33.
38. Purdon PL, Pierce ET, Bonmassar G, Walsh J, Harrell PG, Kwo J, Deschler D, Barlow M, Merhar RC, Lamus C, et al. Simultaneous electroencephalography and functional magnetic resonance imaging of general anesthesia. Ann N Y Acad Sci 2009;1157:61–70.
39. Rogers R, Wise RG, Painter DJ, Longe SE, Tracey I. An investigation to dissociate the analgesic and anesthetic properties of ketamine using functional magnetic resonance imaging. Anesthesiology 2004;100:292–301.
40. Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Ouellet JA, Stone LS. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. J Neurosci 2011;31:7540–50.
41. Tononi G. An information integration theory of consciousness. BMC Neurosci 2004;5:42.

Copyright © 2016. Wolters Kluwer Health. All rights reserved.

Garcia-Larrea, Luis, and Philip L. Jackson. Pain and the Conscious Brain, Wolters Kluwer Health, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/oxford/detail.action?docID=4931411.
Created from oxford on 2019-07-01 03:42:46.

42. Tracey I. “Seeing” how our drugs work brings translational added value. Anesthesiology 2013;119:1247–8.
43. Ung H, Brown JE, Johnson KA, Younger J, Hush J, Mackey S. Multivariate classification of structural MRI data detects chronic low back pain. Cereb Cortex 2014;24:1037–44.
44. Upadhyay J, Anderson J, Baumgartner R, Coimbra A, Schwarz AJ, Pendse G, Wallin D, Nutile L, Bishop J, George E, et al. Modulation of CNS pain circuitry by intravenous and sublingual doses of buprenorphine. Neuroimage 2012;59:3762–73.
45. Wager TD, Atlas LY, Leotti LA, Rilling JK. Predicting individual differences in placebo analgesia: contributions of brain activity during anticipation and pain experience. J Neurosci 2011;31:439–52.
46. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo C-W, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med 2013;368:1388–97.
47. Wanigasekera V, Lee MC, Rogers R, Kong Y, Leknes S, Andersson J, Tracey I. Baseline reward circuitry activity and trait reward responsiveness predict expression of opioid analgesia in healthy subjects. Proc Natl Acad Sci U S A 2012;109:17705–10.
48. White NS, Alkire MT. Impaired thalamocortical connectivity in humans during general-anesthetic-induced unconsciousness. Neuroimage 2003;19:402–11.
49. Wise RG, Lujan BJ, Schweinhardt P, Peskett GD, Rogers R, Tracey I. The anxiolytic effects of midazolam during anticipation to pain revealed using fMRI. Magn Reson Imaging 2007;25:801–10.
50. Wise RG, Preston C. What is the value of human FMRI in CNS drug development? Drug Discov Today 2010;15:973–80.
51. Wise RG, Rogers R, Painter D, Bantick S, Ploghaus A, Williams P, Rapeport G, Tracey I. Combining fMRI with a pharmacokinetic model to determine which brain areas activated by painful stimulation are specifically modulated by remifentanil. Neuroimage 2002;16:999–1014.
52. Wise RG, Tracey I. The role of fMRI in drug discovery. J Magn Reson Imaging 2006;23:862–76.
53. Wise RG, Williams P, Tracey I. Using fMRI to quantify the time dependence of remifentanil analgesia in the human brain. Neuropsychopharmacol 2004;29:626–35.
54. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis of human functional neuroimaging data. Nat Methods 2011;8:665–70.
55. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. Pain 2012;153:1193–8.

Copyright © 2016. Wolters Kluwer Health. All rights reserved.

Garcia-Larrea, Luis, and Philip L. Jackson. Pain and the Conscious Brain, Wolters Kluwer Health, 2016. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/oxford/detail.action?docID=4931411.
Created from oxford on 2019-07-01 03:42:46.