

Pharmacological fMRI

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In the early days of fMRI, if a study incorporated an acutely or chronically administered drug either alone or in combination with a task (i.e. giving a painful stimulus) it was referred to as a pharmacological MRI study (or phMRI). Many paradigms now include a drug challenge as part of the overall design or manipulation and so there is nothing particularly 'special' about phMRI; yet, the expression and term remains and will be employed here. Several recent reviews provide a comprehensive overview of the field and the potential application and benefit for analgesic drug discovery in the industrial setting (Wise & Tracey, 2006; Wise and Preston, 2010; Borsook et al., 2013; Borsook et al., 2006). Although other technologies could be used alongside drug administration, it is true that the field is led by clinical functional magnetic resonance imaging but with more preclinical studies now occurring. The key feature of fMRI use is its ability to measure alterations and responsivity of neural circuits with respect to pharmacological manipulation. Neural circuits provide '*a language of translation*' between preclinical species and humans (Borsook et al., 2006), and as such phMRI studies allow for extrapolation of efficacy from preclinical models to humans more objectively. Before we explicitly discuss the use of phMRI for analgesic drug discovery, we shall discuss some more generic aspects of how phMRI informs our understanding of pain, pain mechanisms and their modulation as well as analgesia.

Background

Whether neuroimaging information is neurochemical, structural or functional a range of CNS disorders have undoubtedly benefited from an improved scientific understanding of the mechanistic changes that occur *in vivo* and over time as the condition develops or improves naturally or with treatment. This is particularly true for acute and chronic pain where dramatic strides in our understanding of underpinning mechanisms have

occurred, as discussed extensively in other chapters. We must remember that **functional** imaging is a powerful tool for measuring how the brain is processing and modulating nociceptive inputs to produce pain perceptions and not, as is often stated, the 'holy grail' and objective 'surrogate' of pain ratings. Rather, it is a 'behind the scenes' measure distinct from, but obviously related to, subjective descriptions and ratings of pain – a process that uses its own tools for assessment. Many factors contribute to pain ratings that irrespective of the nociceptive input or even the presence of strong analgesics mean divergences and more complex relationships can occur between what a subject reports and their measured regional brain activity (Denk et al., 2014). This has tremendous value for drug discovery and can provide confidence that your compound has target engagement or is attenuating nociceptive processing *in vivo*, so long as the conditions discussed at the end of this chapter are borne in mind and met.

The fact that subjects might not show a statistical improvement in subjective rating when using any of our developed pain scales is not an exclusive reason to throw the drug out at this stage of early development (e.g. at Phase II), and yet this has very likely happened. A recent study by Harris and colleagues alongside the study by Bingel and colleagues illustrates this point well (Tracey, 2013; Harris et al., 2013; Bingel et al., 2011, 2012)

CNS Modification versus Analgesia

Additional measures, for example structural or neurochemical, provide clues as to the underlying mechanisms sustaining and exacerbating a chronic pain state (e.g. central sensitization, alterations in descending pain modulation, anxiety, catastrophising and depression). Further, neuroimaging has powerfully illustrated how the pain condition itself changes the brain and spinal cord (both directly (via nociceptive inputs and sensitisation) and indirectly via changes in lifestyle, biomechanics, etc). Undoubtedly, neuroimaging highlighted the impact of unmanaged chronic pain on the brain and raised the stakes regarding better treatment and management. To test the clinical relevance of any of these neuroimaging based measures one can treat the patient, say pharmacologically, and see how the measures change relative to gold-standard clinical/behavioural measures. This helps our understanding of neuroimaging-based measures from being purely correlative to more causal in their nature. However, given the differences in sensitivity of behavioural and neuroimaging measures 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 on a particular scale chosen. This possibility throws up an interesting question. If neuroimaging shows that a patient's

brain is 'normalised' post treatment to that of an age-matched healthy control subject, but there is no pain relief – is that a good thing? This is discussed in a recent editorial (Tracey, 2013). Correcting aberrant 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 for their pain successfully reverse these changes and have 'normal' looking brains from a structural perspective (Rodriguez-Raecke et al., 2009; Gwilym et al., 2010) – highlighting the tremendous plasticity of the CNS and our ability to intervene still.

Early or Baseline Predictors of Response.

The next challenge for neuroimaging is to deliver statistically robust information at an individual level, rather than group averaging neural responses, which has been the common approach to date for phMRI studies examining analgesic mechanisms (Wise et al., 2002, 2004, 2007; Iannetti et al., 2005; Lee et al., 2013). Individualized measures allow identified mechanisms with their concomitant neuroimaging markers to be related to your patient and their particular set of symptoms, possibly even providing measures that predict treatment response. Studies are now being published that highlight how neuroimaging measures (functional, network and neurochemical) at baseline and pre-treatment can contribute towards predicting treatment response (both behavioural and neuroimaging responses - (Wanigasekera et al., 2012; Harris et al., 2013). These studies firmly support the notion that the personalised medicine and stratification goals we need to aid clinical trials and treat our patients more effectively might be better realised using neuroimaging alongside other measures, such as quantitative sensory testing, being tested. Further, these studies and others highlight how brain imaging can be used to distinguish drug from placebo effects in patients. Much has been learnt about the CNS mechanisms relevant to acute and chronic pain from human neuroimaging studies and there is an opportunity to reverse-translate this knowledge to aid refinement of our preclinical models. If done, the following may be realized: (1) new targets within the CNS to assay for drug related analgesic effects and (2) brain regions to record from that reflect symptoms difficult to measure from preclinical behavioural assessments (e.g. ongoing or tonic pain). Hopefully in the coming years by concerted effort and creation of consortia to share data and knowledge progress in this domain will occur. Meanwhile, a number of studies have been done with the specific aim to improve analgesic drug discovery and they span the preclinical to phase 3 spectrum.

Preclinical phMRI

A number of analgesic drugs have been evaluated using phMRI in rats (for a review see Jenkins, 2012) using either preclinical chronic pain models or examining the effects of the drug on whole brain systems (e.g., gabapentin on spinal nerve ligation model (Hooker et al., 2013); celecoxib in an osteoarthritis model (Upadhyay et al., 2013); buprenorphine in healthy rats (Becerra et al., 2013); ketamine in healthy rats (Chin et al.,); and remifentanyl in healthy rats (Liu et al., 2007)). In short, the studies have asked where the drug acts in the brain and what brain systems relevant to chronic or acute pain do the drugs modulate.

The use of preclinical models allows for better comparisons with humans and the likelihood that such data are relevant to the patients, as illustrated by recent examples showing similar brain changes and responses to drug or pain across species (Becerra et al., 2013; Becerra et al., 2013). Further advantages proffered by use of preclinical models include, amongst others, help with dosing as well as identifying potential side effect profiles based upon circuitry affected (e.g. those circuits involved in nausea and vomiting (Chin et al., 2006) or sedation (Liu et al., 2013).

Clinical phMRI for analgesic drug discovery

Phase 1:

The reality is that few drugs make it to Phase I testing in humans (approximately 1 in 10). While most Phase I trials enroll healthy subjects there is a move to have earlier involvement of patients. Imaging can provide a number of novel insights into Phase I evaluation of a novel compound, including: (1) CNS penetration validation and guidance on drug dosing (Upadhyay et al., 2012); (2) Identification of neural circuits targeted (see Upadhyay et al., 2011); (3) Assessment of the predictive qualities of Phase I vs. Phase II; (4) Assessment of potential efficacy, based on neural circuitry of activation and its connectivity (Upadhyay et al., 2011); (5) Potential side effects based on changes in brain regions involved with sleepiness, addiction and nausea/vomiting.

Phase 2:

Involving small groups of patients in Phase 2 based imaging studies will not only define similar features to those listed for Phase 1, but potentially also the following: (1) new drug vs. best in class or comparator; and (2) responders vs. non responders. For example, the psychiatric side effects now noted for the antimalarial mefloquine (Ritchie et al., 2013), may have been determined prior to its marketing if an imaging based study was done early in its development. There is no doubt that the use of imaging in early clinical trials and drug evaluation for analgesia is increasing (Borsook et al., 2013). Of

the 70 drugs used and reported on clinicaltrials.gov that involved an imaging component, 10 involved analgesics (including for rheumatoid arthritis, migraine, fibromyalgia, osteoarthritis) (Borsook et al., 2013).

Phase 3:

At this time, there are very few Phase 3 studies that use imaging to aid drug development (Borsook et al., 2013; Clinical trials.gov). At this stage of a drug's evaluation, imaging may provide insights into the temporal course of drug effects (functional and morphological), potential long term negative effects (e.g., opioids (see Upadhyay et al., 2012; Jarred et al., 2012), disease modification, placebo/responder vs. non-responder issues, as well as baseline stratification to predict treatment response.

It is evident from the above that neuroimaging is being slowly adopted into analgesic drug development in both translational and clinical trials. Remaining issues to be cognizant of, include: (1) Integration of imaging into trials without confounding regulatory processes and including added risks to the trial. If this approach shows valid outcomes, due to the increased power of the study, this could lead to fewer patients to be exposed to new drugs, particularly in Phase II studies; and (2) Applying good imaging practice in trials (Schwarz et al., 2011; Schwarz et al., 2011) to ensure standards across the industry; and imaging may evolve into the validation of surrogate end points.

To implement these measures some additional considerations are required, as discussed below.

Implementing Neuroimaging for Analgesic Drug Discovery

Better practices for using neuroimaging to identify targets for drug development and evaluation are evolving rapidly. Over the past several years, the neuroimaging field across the neuroscience space has begun to mature from early proof-of-concept work and methods development into larger-scale efforts to use neuroimaging in translational science, including datasets with multiple sites, cohorts, and outcome domains (Mueller, et al., 2005; Poldrack, et al., 2013; Van Essen, et al., 2013; Yarkoni, Poldrack, Van Essen, & Wager, 2010). This maturation includes a growing recognition of four kinds of needs: (1) Outcome specificity; (2) Clinically significant effects; (3) Replication and (4) Evaluation of diagnostic properties. These four needs and their relevance to analgesia and measuring analgesic effects in pHMRI studies will be discussed briefly below.

Outcome Specificity

It has long been recognized that distinct types and aspects of pain are not highly correlated, necessitating the targeting of specific behavioral and functional outcomes of interest. For example, sensitivity to different pain assays are uncorrelated or sometimes negatively correlated across mouse strains (Mogil, et al., 1999a, 1999b) and effects on pain vs. cognitive performance under pain can be unrelated (Buhle, Stevens, Friedman, & Wager, 2012). It is now increasingly recognized that brain patterns that predict one pain-related outcome are not necessarily the patterns that predict another pain-related outcome. For example, placebo effects on pain reports are in some cases uncorrelated with placebo effects on brain responses to acute noxious events (Wager, Atlas, Leotti, & Rilling, 2011). In addition, the brain patterns related to different kinds of acute and chronic pain in different patient groups may be distinct (Apkarian, Hashmi, & Baliki, 2011). Such specificity motivates the need to identify brain markers related to specific outcomes of interest, and the evaluation of their construct validity as measures of those outcomes.

It is also critical to identify specific brain targets, and this is an ongoing challenge in the field. A central problem in identifying brain predictors of specific outcomes is that the smallest unit of analysis in fMRI, the “voxel” (about 1/100,000 of the volume of the brain), integrates activity across hundreds of thousands to millions of neurons with distinct functional properties. Thus, there is a many-to-one mapping between psychological processes and activity in each voxel (Sarter, Berntson, & Cacioppo, 1996; Yarkoni, et al., 2011), which complicates the use of voxel-wise activation as a marker for pain. For example, fMRI correlates of pain have been identified in the anterior cingulate and insula (among other regions). While these regions are certainly important for pain, they are the most frequently activated regions in the brain across all types of tasks (including emotion, judgment and decision-making, and tasks requiring mental effort; (Yarkoni, et al., 2011)). Thus, activity in the anterior cingulate as a whole is not *specific* to pain or any other function, and is therefore unlikely to be useful as a diagnostic marker.

An important trend in the neuroimaging literature is the use of “statistical learning” or “machine learning” algorithms to identify distributed patterns of fMRI activity within and across regions (e.g., (Horikawa, Tamaki, Miyawaki, & Kamitani, 2013; Mitchell, et al., 2008)), and this approach is increasingly being applied to pain (Brodersen, et al., 2012; Cecchi, et al., 2012; Marquand, et al., 2010; Ung, et al., 2012; Wager, et al., 2013). This approach, also called “Multi-Voxel Pattern Analysis,” identifies patterns designed to be maximally predictive of a specific outcome. The algorithms can also be constrained to produce *neuroscientifically interpretable* patterns that can be used in reverse translation. They are 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).

Another, powerful idea is that patterns derived from machine learning can circumvent some of the limitations in spatial resolution of fMRI, because patterns can be sensitive to the local structure of functional columns and differential functional organization across microvascular beds (Chaimow, Yacoub, Ugurbil, & Shmuel, 2011; Kriegeskorte, Cusack, & Bandettini, 2010). Pattern information about functional topography is often preserved at a mesoscopic level, and is detectable even when the voxels sampled are larger than the columns themselves (Chaimow, et al., 2011; Kamitani & Sawahata, 2010; Kamitani & Tong, 2005; Swisher, et al., 2010). In addition, mesoscopic organization is often preserved across individuals, permitting accurate inferences about individuals based on normative group-level data (Rissman, Greely, & Wagner, 2010; Shinkareva, Malave, Just, & Mitchell, 2012; Shinkareva, et al., 2008; Wager, et al., 2013). This means that distributed local patterns of activity can be sensitive to the differential distribution of different types neurons across a brain region. Thus, whereas any one voxel in a region such as the anterior cingulate may not be highly diagnostic of pain (van Snellenberg & Wager, 2009; Yarkoni, et al., 2011), but a particular local pattern across voxels within the anterior cingulate may be diagnostic (Wager, et al., 2013).

Recent studies have suggested that brain markers based on distributed patterns of activity within and across brain regions can be used to predict forms of acute pain (Brodersen, et al., 2012; Cecchi, et al., 2012; Marquand, et al., 2010; Ung, et al., 2012; Wager, et al., 2013), identify brain targets of analgesic drugs (e.g., remifentanyl; (Wager, et al., 2013)), and identify placebo responders (Hashmi, et al., 2012; Wager, et al., 2011). Related measures based on brain connectivity may identify individuals that will develop chronic back pain (Baliki, et al., 2012). These findings are promising in terms of the ability to identify markers useful for multiple aspects of treatment development. Brain markers for outcomes (e.g., acute pain) can be used in reverse translation to identify animal models with homologous brain features and develop new treatments. Markers for neural systems involved in drug action can be used to identify the brain components affected by treatments. Combined with a scientific understanding of the aspects and types of pain that these brain components reflect, these markers can be used to a) generate novel hypotheses about combined treatments based on targeting complementary brain systems, and b) match individuals to appropriate treatments based on the match between the brain systems that show abnormal responses and those targeted by a candidate treatment.

Clinically significant effects.

MRI and fMRI images are a complex source of information, consisting of measures of on the order of 50,000 – 200,000 voxels or more, reflecting activity in coherent, but spatially distributed systems across the brain. Like other measures distributed across many variables such as genome-wide scans, MRI analyses may show many statistically significant differences that are not large enough to be *clinically* significant. This has emerged as an important issue in the literature, as there have been widespread criticisms that effect sizes for brain-behavior correlations are often dramatically over-estimated (Lieberman, Berkman, & Wager, 2009; Vul, Harris, Winkielman, & Pashler, 2009; Yarkoni, 2009). Though machine-learning fMRI approaches based on local patterns do not address this issue, some machine-learning approaches can provide unbiased estimates of effect size and establish that brain patterns are robust enough to be meaningfully useful for prediction and diagnosis. These approaches integrate brain information across regions (and potentially imaging modalities) to make a *single* prediction about a patient's status or level of pain. Such approaches suggest that brain information can provide very robust markers that track acute pain magnitude (Wager, et al., 2013), and may provide useful diagnostic information about patient status in pain (e.g., (Ung, et al., 2012)) and other types of psychopathology (e.g., (Brodersen, et al., 2011; Cuingnet, et al., 2011; Du, et al., 2012; Zeng, et al., 2012)).

Replication.

Another important problem in the development of brain markers is that the search for effects across many brain voxels and modalities has resulted in high false-positive rates, and there is an increasing recognition of the need for replication of results across laboratories (Ioannidis, 2005; Pashler & Wagenmakers, 2012). This is true across multiple fields that deal with complex data, including both neuroimaging (Button, et al., 2013) and genetics (Duncan & Keller, 2011), and in other fields as well (Simmons, Nelson, & Simonsohn, 2011). A second, related problem is that what constitutes a replication in neuroimaging studies has been unclear. Regions that are often treated as units of analysis in publications—such as the amygdala or dorsal anterior cingulate—include hundreds or thousands of voxels, and it is insufficient for replication purposes to find “anterior cingulate activity” in two or more studies.

When used in specific ways, machine learning-based approaches can circumvent both problems. These approaches use part of the data to estimate a distributed pattern that serves as a provisional brain marker, and another part of the data to test the diagnostic accuracy of that specific pattern. In some cases, brain predictors of pain may be identified in a group of individuals that provide information diagnostic of pain in other individuals, even when collected at different sites. Because the pattern is fixed

across training and testing, this strategy provides an exact replication test of the brain marker (e.g., (Wager, et al., 2013)).

Thus, whereas results in most previous neuroimaging studies are not used prospectively to quantitatively test responses in new samples and individuals, machine learning-derived patterns have shown promise in this regard.

Evaluation of diagnostic properties

Dominant paradigms in neuroimaging data analysis have not focused on diagnostic properties, which may be captured in part by analysis of the sensitivity and specificity of a specific brain pattern for a specific class of outcomes. However, as neuroimaging is increasingly used in clinical studies, there is increasing focus on the diagnostic value of brain patterns for clinical conditions using such criteria (Baliki, et al., 2012; Brodersen, et al., 2011; Cuingnet, et al., 2011; Du, et al., 2012; Zeng, et al., 2012) and treatment responses (e.g., (Doehrmann, et al., 2013; Miller, et al., 2013)).

Another important concept is that brain markers that can be applied across individuals can be easily tested for generalization across samples and sites, which is essential if neuroimaging markers are to be validated and used clinically. In addition, the generalization and specificity of such markers—with respect to types of pain, body sites, and pain vs. related psychological states—can be tested on existing data, accelerating the development-test cycle for brain markers.

There are now several promising candidate markers emerging for pain. For acute nociception-driven pain, a distributed pattern of regions that matches well with prototypical ‘pain-processing’ regions in humans and animals can accurately track the magnitude of pain (Wager, et al., 2013). If two conditions are moderately different in pain (e.g., 2 points on a 10-point VAS), activity in this pattern, the “neurologic pain signature” (NPS), as it has been termed 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 work examining the transfer across types of pain (e.g., heat, cold, mechanical, inflammatory) is ongoing. In addition, it was shown to have 90% or greater sensitivity and specificity to somatic pain in comparison with non-painful warmth, pain anticipation, pain recall, and emotionally evocative images, and it responded to remifentanyl administration with a time course predicted by pharmacokinetic models of remifentanyl.

However, the NPS is likely to be sensitive to only certain aspects of pain. In initial tests, it was not affected by a placebo treatment. In addition, a brain pattern that was optimized to predict placebo effects relied on very different systems from the NPS, including frontal cortical activity during pain anticipation (Wager, et al., 2011). Finally, recent work has suggested that brain markers can predict the transition from acute to

chronic back pain with moderate accuracy (80% in a holdout sample; (Baliki, et al., 2012)). However, like the placebo-predictive pattern, it relies on very different brain systems from the NPS: It is based on connectivity between the ventromedial prefrontal cortex and nucleus accumbens, neither of which responds strongly to increases in noxious stimulus intensity. Together, these preliminary results suggest that there may be distinct, predictive markers for acute pain driven by nociceptive input and psychological factors. The development of acute back pain, in addition, is accompanied by a shift in the correlates of pain away from 'nociception-centered' pain systems and towards systems broadly associated with value, emotion, stress, and autonomic regulation.

These markers hold promise for both providing new explanations of pain and clinical translation, though they must continue to be tested for replicability across samples and specificity vs. generalization across types of pain, types of patients, and other contextual factors.

Conclusion:

From what is presented in this chapter and the literature discussed it is evident that phMRI is a significant and growing component of neuroimaging based studies. 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. It is our belief; phMRI will play an increasing role in both clinical decision-making and drug discovery in the years to come.

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