NEUROIMAGING

fMRI in analgesic drug discovery

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Functional magnetic resonance imaging offers an unprecedented opportunity to evaluate and compare drug effects on human brain activity and to provide systems-level predictions for how new drugs for chronic pain will affect the brain, thus accelerating drug discovery and repurposing (Duff *et al.*, this issue).

YOUR BRAIN ON DRUGS: BROAD AND COMPLEX MECHANISMS

Disorders of the brain are particularly complex, and finding drugs that treat them effectively is a major challenge (*1*). Chronic pain, in particular, has been a focus in medicine for thousands of years; but in spite of a wealth of knowledge about pain physiology, it has proven extraordinarily resistant to prevention and treatment. This is no less true of substance abuse, schizophrenia, depression, and other central nervous system (CNS) disorders with complex causes. Large-scale efforts to identify effective drugs have yielded only modest gains.

Surprisingly little is known about how drugs commonly used to treat pain and other disorders work at a systems level. Take morphine, for example. It is arguably the oldest effective drug in modern allopathic medicine. Its pharmacology has been studied in detail (it is mainly a μ-opioid agonist), and its molecular mechanisms have been characterized. However, we have much more to learn: Only a small number of studies have used whole-brain neuroimaging—mainly functional magnetic resonance imaging (fMRI) and positron emission tomography (PET)—to characterize the effects of morphine and other analgesic drugs on the interacting systems that comprise the human brain [reviewed in (*2*)]. These studies suggest that the targets of drug action are varied and complex. They are not limited to nociceptive systems—those primarily involved in conveying pain-related information to the brain—or even those rich in μ-opioid receptors. Rather, analgesics affect prefrontal and forebrain systems broadly implicated in mood, emotion, decision-making, planning, and even the construction of our self-identity (*3*). In addition, endogenous opioid function in these systems can be modified by behavioral as well as pharmacological interventions (*4*, *5*).

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These pervasive effects point to the tremendous gap between the cellular mechanisms of drug action and drug effects in the context of the living, functioning human brain. Their breadth and complexity might help explain why the same drugs are used to treat disorders that we think of as very different from one another and why very different classes of drugs are used to treat the same disorders. For example, patients with neuropathic pain might receive pregabalin, which acts on voltage-gated calcium channels; naproxen, a nonsteroidal anti-inflammatory drug that acts on cox enzymes; or tramadol, an opioid that also inhibits reuptake of serotonin and norephinephrine. There is little overlap in their molecular mechanisms, but might they affect brain representations of pain—or emotional, cognitive, and social processes related to health and well-being—in similar ways? And does their clinical efficacy relate to effects on nociceptive systems or to effects on brain representations of the broader emotional and cognitive context?

In this issue of *Science Translational Medicine*, Duff *et al.* (*6*) provide a framework for beginning to answer these questions systematically. Using fMRI, they compared drug effects on pain-related brain responses across eight studies of six different CNS drugs. Rather than simply assessing the commonalities and differences in brain activation across the drugs, they outlined a series of tests that are directly aimed at translation, using fMRI to assist in providing "Go/Stop" decisions on whether to continue costly clinical trials of a drug. Such decisions are critical at early stages of drug development (for example, in phase 2a trials) because there are substantial economic benefits of both accelerating the development of promising drugs and abandoning those likely to fail in later, more costly phase 2b and phase 3 trials (*2*). In one recent analysis of 24 experimental medicine drug trials from Merck, using biomarkers to make early Go/Stop decisions resulted in a realized value of $272 million, with 180% return on investment in biomarker development (R. Hargreaves, personal communication).

STOP AND GO

fMRI can help answer several critical mechanistic questions that preclinical animal studies cannot answer alone. First, does the drug penetrate into the human brain, and does it produce reliable pharmacodynamic effects on brain activity? And second, does it affect brain systems in ways comparable with other, established drugs?

To address these questions, Duff *et al.* used support vector machines (SVMs), a type of machine-learning algorithm suited to finding reliable patterns in complex multivariate data sets such as fMRI data, to estimate drug effects (*6*). They then used those estimates to make Go/Stop recommendations in two ways. First, they assessed pharmacodynamic effects by asking whether a candidate drug produces brain activity that is clearly different from placebo (Fig. 1A). Second, they assessed measures that served as proxies for clinical efficacy, operationalized in two ways: (i) the degree to which drug effects on fMRI activity are similar to those of known drugs ("Clinical Efficacy A") and (ii) the degree to which a drug "normalizes" pain-related brain responses ("Clinical Efficacy B"). Their framework also included quality-control checks that could help determine whether poor results are due to the quality of neuroimaging data rather than the drug itself. Such checks are standard in biological assays, and their incorporation into neuroimaging protocols will be critical for translational applications.

Using this approach, Duff *et al.* found evidence that the six drugs they tested—gabapentin, pregabalin, tramadol, remifentanil, tetrahydrocannabinol (THC), and naproxen—share common features in terms of their effects on brain responses during pain (*6*). Notably, the brain features that discriminated drug and placebo conditions were distributed across many brain systems. Some of these, such as the anterior cingulate and insula, are strongly associated with somatosensation and pain as well as decision-making and emotion. Others—including the amygdala and the orbitofrontal, parahippocampal, and lateral prefrontal cortices—do not appear to have a straightforward relationship with nociception per se but are strongly implicated in aspects of emotion, expectation, and affective learning. These results provide new clues about

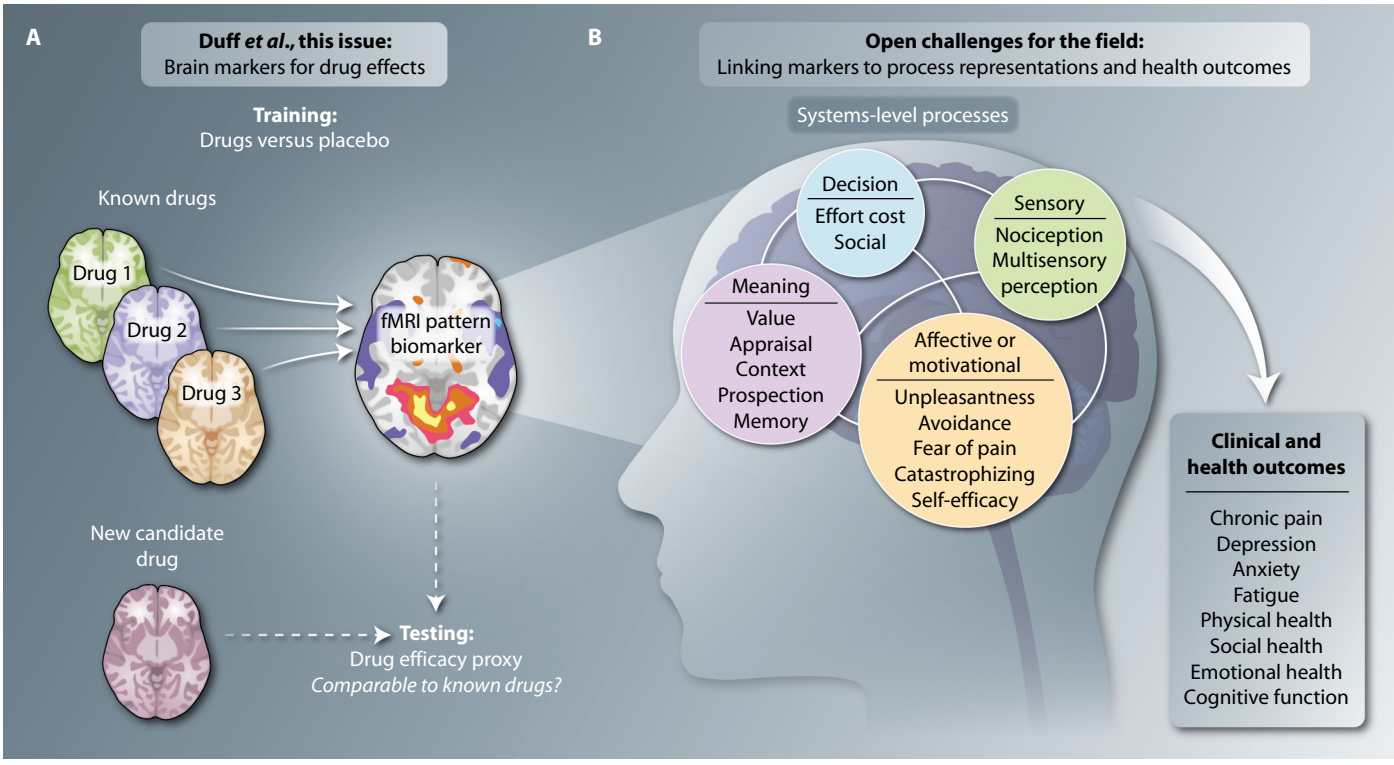

Fig. 1. Examining brain mediators of drug effects. (**A**) Duff *et al.* provide a framework for assessing new candidate drugs in terms of whether their effects on the brain are comparable with other, known drugs (*6*). (**B**) Open challenges for the field include understanding how drugs influence multiple, systems-level brain processes; how these processes mediate the drug effects on clinical and health outcomes (such as chronic pain, depression, or fatigue); and how fMRI markers for these processes can be used to predict those health outcomes.

the complexity and organization of brain systems affected by these drugs.

The findings by Duff *et al.* also suggest notable differences across drugs, which could shed light on their differential effects across types of pain and individuals. Some drugs, such as gabapentin and remifentanil, appeared to affect pain-related responses and normalized provisional markers of pain (Clinical Efficacy B), whereas other drugs, such as pregabalin and THC, did not. Perhaps surprisingly, most or all effects of pregabalin, THC, and naproxen were found in brain systems not clearly associated with nociceptive pain, but rather those associated with decision-making, meaning, and motivation. Overall, the results provide the first, preliminary assessment of the similarities and dissimilarities across multiple drugs in their effects on the brain. These findings were made possible by aggregating data across studies and drugs, which increased both the sample sizes and stability of estimates of drug effects across the brain, and allowed for comparison across conditions. Such multistudy efforts will be increasingly important in applications that emphasize the diagnostic and translational value of neuroimaging results.

RETHINKING DRUGS, OLD AND NEW ALIKE

The framework described by Duff *et al.* provides a launching point for drug evaluation and discovery, permitting new types of answers to old and fundamental questions (Fig. 1B). For example, by further characterizing common and distinct drug effects on the brain, we might be able to better understand which effects are linked to specific pharmacological mechanisms, and which are not strongly tied to one particular class of drugs. Some effects might also be linked to the drug-taking context itself (*7*, *8*) or common vascular effects. Future studies on pharmacological effects might benefit from the estimation of dose-response curves for multiple drugs, replacing the two-class SVM proxy measures in Duff *et al.* with formal pharmacodynamic dose-effect models (*8*, *9*).

The framework in this study (*6*) also provides a means for discovering new uses for old and new drugs alike. A definitive characterization of the similarities and differences between drugs at the brain systems level—carefully controlling for placebo effects and vascular confounds—could allow researchers to test new candidate drugs, evaluating their similarity to "best-in-class" compounds with known efficacy (*2*). Such comparisons can also be used to repurpose existing drugs, an essential strategy given the high costs of new drug development. For instance, gabapentin was initially developed for seizures but is now widely used to treat pain. Likewise, promising new treatment opportunities for other "old" drugs, such as propranolol and D-cycloserine, are currently being pursued. These drugs were originally used as treatments for high blood pressure and tuberculosis, respectively, but are now being studied as treatments for fear-related disorders. Comparing the effects of a drug on functional brain responses to a "library" of best-in-class drugs could accelerate the discovery of new drug effects and therapeutic uses.

WHITHER NOW? OPEN CHALLENGES AND OPPORTUNITIES

Moving forward, a critical goal of future research will be to understand how the complex brain-drug patterns revealed by Duff *et al.* relate to health outcomes and the mind/brain processes that mediate them (Fig. 1). These brain patterns are more than just

markers: They offer a rich window into the neurophysiological systems that underlie perception, motivation, decision-making, emotion, and other processes. As the results from the multistudy effort by Duff *et al*. and many others suggest, drugs may affect any or all of these processes, with diverse consequences for health. Understanding the mappings between drug effects, mediating mind/brain processes, and observable health outcomes is a major, open challenge for the field, and the framework by Duff *et al*. (*6*) provides a concrete way of bringing drug effects into the picture.

In this endeavor, at least two strategies might be fruitfully employed. The first is to link drug effects to brain patterns that are sensitive and specific for particular health-related processes. Duff *et al*. take a step toward this by identifying regions sensitive to high versus low pain in their studies (Clinical Efficacy B) and testing whether drug effects influence activity in these "pain-sensitive" patterns. However, such pain-sensitive patterns do not constitute representations of pain because they may reflect general negative arousal, attention to salient events, response preparation, and other processes distinct from pain itself. Testing drug effects on brain patterns that are sensitive and specific to nociceptive pain [for example, (*10*)] could provide additional insight into what kinds of pain-related processes these drugs affect.

Second, establishing direct associations between drug effects and clinical outcomes is another crucial piece of the puzzle. Only some of the clinical efficacy effects Duff *et al*. observed are likely to be related to specific clinical outcomes (such as allodynia); others may be related to functional and emotional outcomes (such as fatigue and anxiety) that are indirectly associated with pain but important in their own right. And yet others may be clinically irrelevant. Health is much more than the absence of disease, and recovering from pain may often involve more than reducing nociception. Thus, there is an array of functional outcomes that play vital roles in health and well-being, including multiple aspects of emotional, social, and physical health (Fig. 1B). As the field moves forward, we have an opportunity to examine the relationships between drug effects on brain systems–level dynamics and each of these health-related outcomes. Doing so will promote innovation and expand our conception of what drugs can do for us and how they do it.

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Competing interests: T.D.W. has performed consulting activities for Janssen Pharmaceutical related to fMRI imaging. The authors declare no other competing financial or other interests.

10.1126/scitranslmed.3010342

Citation: T. D. Wager, C.-W. Woo, fMRI in analgesic drug discovery. *Sci. Transl. Med.* **7**, 274fs6 (2015).