

Functional magnetic resonance imaging is a powerful approach to probing the mechanism of action of therapeutic drugs that act on the central nervous system

Shu-Feng Zhou

Department of Pharmaceutical Science, College of Pharmacy, University of South Florida, Tampa, FL, USA

In the paper by Pickering et al¹ published in this issue of *Drug Design, Development and Therapy*, the authors explore the brain areas actively involved in the mechanism of action of acetaminophen as an analgesic in healthy subjects using functional magnetic resonance imaging (fMRI). In this randomized, double-blind, crossover, placebo-controlled study, healthy subjects were exposed to experimental thermal stimuli with acetaminophen or placebo. fMRI experiments were performed on a General Electric Discovery MR 750 3.0 T using a 32-channel head coil with subjects lying supine. A standard whole-brain gradient echoplanar imaging sequence was utilized for the functional scans. The neuroimaging data were preprocessed and analyzed using Statistical Parametric Mapping version 8 (Wellcome Department of Imaging Neuroscience, London, UK) in Matlab 7.12 (MathWorks). The blood oxygenation level dependent (BOLD) images were then spatially normalized into the Montreal Neurological Institute and Hospital (MNI) space using trilinear interpolation, with the normalization parameters determined during normalization of the structural images. Subsequent spatial smoothing using an isotropic 8 mm full-width half maximum Gaussian kernel was applied to the functional images to increase the signal-to-noise ratio. On the basis of a priori hypotheses regarding the involvement of the anterior cingulate cortex (ACC), insula, prefrontal cortices, thalamus, and periaqueductal gray (PAG) in the pain-reducing effect of acetaminophen, Pickering et al¹ applied structurally defined region of interest analyses to compare neural activity in these regions between groups during a thermal pain stimulus. Regions of interest, ie, the PAG, ACC, insula, prefrontal cortices, and thalami, were defined using the Marsbar tool in Statistical Parametric Mapping version 8. Beta extractions were then performed, in order to assess group differences in neural activity in these regions during a thermal noxious stimulus. The study has shown that activity in response to noxious stimulation was suppressed with acetaminophen compared with placebo in the prefrontal cortices, insula, thalami, ACC, and PAG. The correlation between the fMRI signal for diminution of activation (T100–T0) and the diminution of pain intensity was significant for acetaminophen ($P=0.002$) but not for placebo. The imaging results are consistent with the behavioral analgesic effects of acetaminophen.

The above study provides evidence in healthy subjects that acetaminophen reduces the pain-related BOLD signal responses arising from noxious thermal stimulation in several brain areas of the pain matrix. The reduction of perceived pain intensity scores

Correspondence: Shu-Feng Zhou
Department of Pharmaceutical Sciences,
Colleges of Pharmacy and Medicine,
University of South Florida, 12901 Bruce B
Downs Boulevard, Tampa, FL 33612, USA
Tel +1 813 974 6276
Fax +1 813 974 9885
Email szhou@health.usf.edu

simultaneous with the reduction in pain-related activity is consistent with the observed changes in BOLD signal resulting from the analgesic effect of acetaminophen. Compared with placebo, acetaminophen reduces significantly the pain-related BOLD signal responses arising from the noxious thermal stimulation in the selected regions of interest, ie, insula, ACC, thalamus, and prefrontal cortices. This suggests an inhibitory effect of acetaminophen on spinothalamic tracts, leading to decreased activation of higher structures and a resulting antinociceptive effect of acetaminophen.¹ The authors have proposed a “top-down phenomenon” with an active engagement of the PAG for the mechanism of action of acetaminophen as an analgesic and a specific action on the midbrain neurotransmission system.

This interesting study by Pickering et al¹ demonstrates the significance of fMRI application in probing the mechanisms of action of therapeutic drugs, especially for those that act on the central nerve system (CNS). Recently, there has been a large number of published studies of fMRI in healthy volunteers or patients that aimed to explore the mechanisms of action of CNS drugs.²⁻⁴ fMRI is able to characterize the effects of CNS drugs associated with conditions and disorders such as pain, schizophrenia, epilepsy, depression, drug addiction, Alzheimer’s disease, stroke, alcoholism, and obesity.² fMRI has shown potential for distinguishing effective from noneffective compounds (placebo) and for predicting the clinical efficacy of drugs. These capabilities suggest that fMRI could provide a complementary, noninvasive adjunct to molecular imaging for detecting drug-related modulation of brain activity.² fMRI may also represent a useful approach to improving the success rate of CNS drug discovery whereby CNS drug failures can be avoided at the early stages of development.

A number of fMRI studies with analgesics have demonstrated the coupling between subjective pain intensity ratings and objective BOLD responses measured in central structures.^{2,3,5-8} Analgesics studied using fMRI include alfentanil,⁹ methadone,¹⁰ buprenorphine,¹¹ morphine,^{12,13} parecoxib,¹⁴ oxycodone,¹⁵ naproxen,¹⁶ lidocaine,¹⁷ pregabalin,¹⁸ naloxone,^{19,20} nalbuphine,²⁰ indomethacin,²¹ aspirin,²² remifentanil,²³ propofol,²⁴ and ketamine.²⁵⁻²⁷ For example, it was found that nalbuphine (an opioid agonist), like morphine, attenuated activity in the inferior orbital cortex but increased activity in the temporal cortex, insula, pulvinar, caudate, and pons in healthy male volunteers.²⁰ In addition, nalbuphine induced functional connectivity of the caudate and multiple regions in the frontal, occipital, temporal, insular, middle cingulate cortices, putamen, and many areas in the cerebellum.²⁰

Coadministration of naloxone selectively blocked activity in the pulvinar, pons, and posterior insula. These studies have provided new insights into how analgesics act on CNS-specific areas, and the image information from fMRI may be used as new biomarkers for monitoring the effects and side effects/toxicities of analgesics. fMRI offers new opportunities to evaluate and compare the effects of existing and new analgesics on human brain activity and to provide system-level predictions for how new drug candidates for chronic pain will affect the brain, thus accelerating drug discovery and allowing repurposing of existing drugs for new indications.³

However, when we understand the usefulness and applicability of fMRI in the functional pharmacology of CNS drugs, several limitations to this study by Pickering et al¹ have been noted. First, the resultant data from fMRI is just structural, not really functional, and thus functional validation studies are often needed to confirm the fMRI data. Second, this study is a single-dose one, and does not include the regimens for chronic usage of acetaminophen. The dose-response relationship is not explored, and the time course is not well characterized. Third, the study was carried out in healthy volunteers, not patients. Finally, variation in study protocols and analysis techniques has made fMRI difficult to produce consistent data on the associations between subtle modulations of brain activity and the clinical efficacy of CNS drugs. fMRI does not quantify physiological variables directly associated with drug action, so identifying evidence for the efficacy of compounds must be based on empirically established associations between brain activity patterns and measurable clinical variables, such as clinical therapeutic outcomes.² It is important that imaging tools are able to offer predictive capabilities beyond what can be obtained from clinical measures alone. Direct brain correlates of available behavioral and clinical measurements, which may be affected by factors unrelated to long-term efficacy, will not necessarily provide substantial additional predictive value for evaluations of CNS drugs. Therefore, as the authors have pointed out, further binding and connectivity studies are warranted to assess how the analgesic effect of acetaminophen relates to cerebral and descending modulation of pain, especially in chronic dosing of acetaminophen in patients.

Since evaluations of the therapeutic potential of CNS drug candidates in humans are often difficult and expensive, with efficacy unreliable, hard to measure, and slow to manifest, fMRI represents a noninvasive imaging technique that can complement molecular imaging for systemic studies of new and existing CNS drugs. fMRI is also widely used to explore the molecular mechanisms of pain and other disorders.⁴

A deep understanding of how CNS drugs act on specific brain regions is important for optimized use of these drugs and may provide a base for precise medicine. fMRI may help with the development of more selectively targeted CNS drugs.

Disclosure

The author reports no conflicts of interest in this work.

References

- Pickering G, Kastler A, Macian N, et al. The brain signature of paracetamol in healthy volunteers: a double-blind randomised trial. *Drug Des Devel Ther.* 2015.
- Duff EP, Vennart W, Wise RG, et al. Learning to identify CNS drug action and efficacy using multistudy fMRI data. *Sci Transl Med.* 2015; 7(274):274ra216.
- Wager TD, Woo CW. fMRI in analgesic drug discovery. *Sci Transl Med.* 2015;7(274):274fs6.
- Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. *N Engl J Med.* 2013; 368(15):1388–1397.
- Baliki MN, Geha PY, Fields HL, Apkarian AV. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. *Neuron.* 2010;66(1):149–160.
- Wise RG, Rogers R, Painter D, et al. Combining fMRI with a pharmacokinetic model to determine which brain areas activated by painful stimulation are specifically modulated by remifentanyl. *Neuroimage.* 2002;16(4):999–1014.
- Wise RG, Williams P, Tracey I. Using fMRI to quantify the time dependence of remifentanyl analgesia in the human brain. *Neuropsychopharmacology.* 2004;29(3):626–635.
- Upadhyay J, Anderson J, Schwarz AJ, et al. Imaging drugs with and without clinical analgesic efficacy. *Neuropsychopharmacology.* 2011; 36(13):2659–2673.
- Oertel BG, Preibisch C, Wallenhorst T, et al. Differential opioid action on sensory and affective cerebral pain processing. *Clin Pharmacol Ther.* 2008;83(4):577–588.
- Marvel CL, Faulkner ML, Strain EC, Mintzer MZ, Desmond JE. An fMRI investigation of cerebellar function during verbal working memory in methadone maintenance patients. *Cerebellum.* 2012;11(1): 300–310.
- Upadhyay J, Anderson J, Baumgartner R, et al. Modulation of CNS pain circuitry by intravenous and sublingual doses of buprenorphine. *Neuroimage.* 2012;59(4):3762–3773.
- Khalili-Mahani N, Zoethout RM, Beckmann CF, et al. Effects of morphine and alcohol on functional brain connectivity during “resting state”: a placebo-controlled crossover study in healthy young men. *Hum Brain Mapp.* 2012;33(5):1003–1018.
- Becerra L, Harter K, Gonzalez RG, Borsook D. Functional magnetic resonance imaging measures of the effects of morphine on central nervous system circuitry in opioid-naive healthy volunteers. *Anesth Analg.* 2006;103(1):208–216.
- Maihofner C, Ringler R, Herrndobler F, Koppert W. Brain imaging of analgesic and antihyperalgesic effects of cyclooxygenase inhibition in an experimental human pain model: a functional MRI study. *Eur J Neurosci.* 2007;26(5):1344–1356.
- Gorka SM, Fitzgerald DA, de Wit H, Angstadt M, Phan KL. Opioid modulation of resting-state anterior cingulate cortex functional connectivity. *J Psychopharmacol.* 2014;28(12):1115–1124.
- Gimenez M, Pujol J, Ali Z, et al. Naproxen effects on brain response to painful pressure stimulation in patients with knee osteoarthritis: a double-blind, randomized, placebo-controlled, single-dose study. *J Rheumatol.* 2014;41(11):2240–2248.
- Letzen JE, Craggs JG, Perlstein WM, Price DD, Robinson ME. Functional connectivity of the default mode network and its association with pain networks in irritable bowel patients assessed via lidocaine treatment. *J Pain.* 2013;14(10):1077–1087.
- Kim SH, Lee Y, Lee S, Mun CW. Evaluation of the effectiveness of pregabalin in alleviating pain associated with fibromyalgia: using functional magnetic resonance imaging study. *PLoS One.* 2013;8(9): e74099.
- Taylor JJ, Borckardt JJ, Canterberry M, et al. Naloxone-reversible modulation of pain circuitry by left prefrontal rTMS. *Neuropsychopharmacology.* 2013;38(7):1189–1197.
- Gear R, Becerra L, Upadhyay J, et al. Pain facilitation brain regions activated by nalbuphine are revealed by pharmacological fMRI. *PLoS One.* 2013;8(1):e50169.
- Rasmussen M, Juul N, Christensen SM, et al. Cerebral blood flow, blood volume, and mean transit time responses to propofol and indomethacin in peritumor and contralateral brain regions: perioperative perfusion-weighted magnetic resonance imaging in patients with brain tumors. *Anesthesiology.* 2010;112(1):50–56.
- Misra UK, Kalita J, Nair PP. Role of aspirin in tuberculous meningitis: a randomized open label placebo controlled trial. *J Neurol Sci.* 2010; 293(1–2):12–17.
- Bingel U, Wanigasekera V, Wiech K, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanyl. *Sci Transl Med.* 2011;3(70):70ra14.
- Amico E, Gomez F, Di Perri C, et al. Posterior cingulate cortex-related co-activation patterns: a resting state FMRI study in propofol-induced loss of consciousness. *PLoS One.* 2014;9(6):e100012.
- 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(2): 292–301.
- Driesen NR, McCarthy G, Bhagwagar Z, et al. The impact of NMDA receptor blockade on human working memory-related prefrontal function and connectivity. *Neuropsychopharmacology.* 2013;38(13): 2613–2622.
- Niesters M, Khalili-Mahani N, Martini C, et al. Effect of subanesthetic ketamine on intrinsic functional brain connectivity: a placebo-controlled functional magnetic resonance imaging study in healthy male volunteers. *Anesthesiology.* 2012;117(4):868–877.

Drug Design, Development and Therapy

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which

Submit your manuscript here: <http://www.dovepress.com/drug-design-development-and-therapy-journal>

has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.