

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

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In the paper by Pickering et al<sup>1</sup> 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 al<sup>1</sup> 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

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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.<sup>1</sup> 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 al<sup>1</sup> 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.<sup>2–4</sup> 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.<sup>2</sup> 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.<sup>2</sup> 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.<sup>2,3,5–8</sup> Analgesics studied using fMRI include alfentanil,<sup>9</sup> methadone,<sup>10</sup> buprenorphine,<sup>11</sup> morphine,<sup>12,13</sup> parecoxib,<sup>14</sup> oxycodone,<sup>15</sup> naproxen,<sup>16</sup> lidocaine,<sup>17</sup> pregabalin,<sup>18</sup> naloxone,<sup>19,20</sup> nalbuphine,<sup>20</sup> indomethacin,<sup>21</sup> aspirin,<sup>22</sup> remifentanil,<sup>23</sup> propofol,<sup>24</sup> and ketamine.<sup>25–27</sup> 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.<sup>20</sup> 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.<sup>20</sup>

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.<sup>3</sup>

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 al<sup>1</sup> 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.<sup>2</sup> 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.<sup>4</sup>

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.

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