Simultaneous fMRI-PET Imaging of the Opioidergic Pain System in Human Brain

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Introduction BOLD fMRI has been used extensively in neuroscience research. During a task, fMRI probes functional hyperemia, which is assumed to be closely related to neural activity. However, fMRI lacks the ability to image neurotransmitter specific neural activation. Having an approach that is sensitive to neural responses and, at the same time, provides information about the underlying neurochemical events could be extremely helpful to better understand brain function. In this study, we present the first simultaneous fMRI-PET study in humans that investigated the engagement of the opioid system during experimental pain and how it compares to functional responses. We hypothesized that BOLD fMRI could identify brain regions related to pain perception and modulation, while changes detected by PET would be limited to regions involved in opioid-mediated pain modulation.

Methods Eight healthy volunteers (4 males, 4 females; age: 24.1±2.7; *N=16 scans*) were included in this study. Each subject underwent two MR-PET scans in a pseudo-randomized order – one as a baseline (pressure, no pain) and the other with calibrated pressure pain applied.

MR-PET: All images were acquired on a 3T Siemens TIM-Trio with a BrainPET insert. The fMRI and PET scans, and pain stimuli were synchronized to tracer injection in order to achieve maximum response. A PET-compatible CP transmit/8-channel receive array was used. GE-EPI was used for BOLD imaging with the following parameters: TR/TE=3000/30 ms, matrix = 72x72, field of view = 21.6x21.6 cm (3 mm isotropic resolution), and 47 slices. A high-resolution anatomical image was acquired using ME-MPRAGE (1mm isotropic). A dual ultra-short echo sequence was run for deriving the PET attenuation map. Up to 12 mCi (10.83±1.45 mCi, N=16) of [^{11}C]Diprenorphine, a non-selective opioid receptor antagonist, was injected i.v. as a quick bolus for each study. PET data were acquired for 90 min in list mode format and binned into 44 frames of progressively longer duration. The corresponding images were reconstructed using the 3D OP-OSEM algorithm with detector efficiency, decay, dead time, attenuation, and scatter corrections applied.

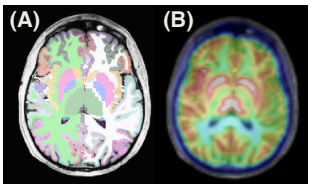

Fig 1. (A) FreeSurfer segmented ROIs and (B) mean dynamic PET data overlaid on T1.

Pain Stimulation: Calibrated pressure cuff pain was determined in a separate behavioral session and confirmed on the scan date. Pressure cuff was placed around the subject's left calf muscle. Intermittent calibrated pressure to achieve a "moderate-to-high" pain (15 out of 20 Gracely intensity scale) level was delivered for a total of 30 min (42 sec ON with variable interstimulus intervals). Subjects rate the intensity of each given stimulus using a botton box, and the pressure was adjusted in real-time to account for potential habituation. During baseline scan, stimuli at very low, non-painful, pressure were given to match the experimental conditions.

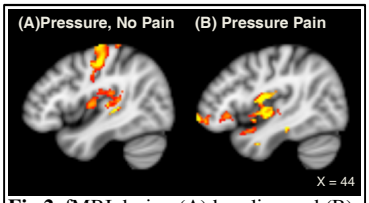

Fig 2. fMRI during (A) baseline and (B) pain.

Data Analysis: Data were processed using FSL, SPM8, FreeSurfer, and PMOD. ***MRI***: fMRI data was motion and slice-time corrected, skull stripped, and spatially smoothed with an 8mm FHWM Gaussian kernel. A standard GLM was used to generate fMRI activation map. Statistical group analysis was performed using single-group average and two-group paired t-test ($Z>2.3$, cluster corrected $p<0.05$). Individual subject's anatomical image was processed through FreeSurfer reconstruction pipeline to generate atlas-based segmentations to be used for PET kinetic modeling (**Fig 1**). ***PET:*** PET data was analyzed using a non-invasive Logan model with bilateral occipital cortices as the reference tissues[1]. Quantitative binding potential maps (BP_{ND}), which represent the relative amount of specifically bound radioligand to that of non-displaceable radioligand, were calculated. The resulting BP_{ND} images were then co-registered to the MNI152 brain. Statistical group analysis was performed using a two-group paired t-test and threshold at voxel-wise $Z>1.96$ and cluster level of $p<0.05$ to account for multiple comparisons.

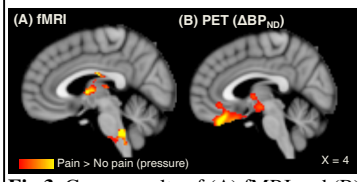

Fig 3. Group results of (A) fMRI and (B) PET.

Results and Discussion The pressure delivered to induce muscle pain was 310±90 mmHg, which resulted in a mean intensity pain rating of 13±2. During baseline scan, a low pressure of 40 mmHg was given and all subjects confirmed no pain was experienced. fMRI showed robust responses to both pressure (no pain) and pain stimulation (**Fig 2**). Only painful pressure activated the frontal/prefrontal area. The group contrast of pain>no pain demonstrated significant activations in bilateral caudate, putamen, thalamus **(Fig 3A)** and brainstem.

Statistical comparison of BP_{ND} images revealed pain induced decreases in [^{11}C]DPN binding (interpreted as radioligand being displaced by the release of endogenous opioid peptides or by receptor internalization) in bilateral amygdala/parahippocampal area, insula, nucleus accumbens, hypothalamus, rostral anterior cingulate cortex, thalamus, and contralateral orbitofrontal cortex (**Fig 3B**). Both fMRI and PET changes were observed in regions of the basal forebrain, such as nucleus accumbens/caudate, with a percent BP_{ND} change of ~13% (**Fig 4**). These results suggest there is a connection between the neural circuitry underlying pain and reward[2].

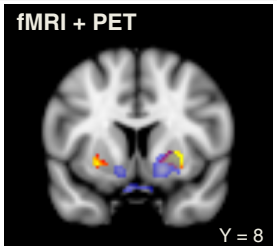

Fig 4. fMRI (red) and PET (purple) shows overlapping activation in NAc/Caudate.

This novel technology confers multiple advantages. First and most important is the ability to investigate specific neurotransmitter contribution to dynamic changes in regionally specific brain activity. Second, MRI provides sufficient information for PET attenuation correction obviating the need for CT[3], and could potentially improve the quality of PET data. Third, simultaneous MR-PET avoids the need for image co-registration; therefore, MRI images are readily available for ROI definition to be used in PET kinetic modeling **(Fig 1)**. Until now, pharmacological MRI was the method of choice to investigate neurochemical function at the receptor level. Simultaneous fMRI-PET provides a great alternative and opens a new horizon for neuroimaging research.

Conclusions We presented the first simultaneous fMRI-PET study of the human opioid system and showed fMRI-PET activations in regions related to opioid-mediated pain modulation. Simultaneous fMRI-PET data acquisition provides the unique opportunity to relate neurochemical events (such as endogenous opioid release) to the functional responses (likely related to neural activation), and as such provides a powerful tool for studying the biology and pathology of the human brain.

References: 1. Logan J, et al., JCBFM, 1996. 2. Leknes S. and Tracey I., Nature Rev. Neurosci., 2008. 3. Catana C., et al., JNM, 2010.

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