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A FUNCTIONAL MAGNETIC RESONANCE IMAGING APPROACH FOR STUDYING CENTRAL EFFECTS OF ANALGESIC DRUGS

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Recent functional imaging studies in humans using positron emission tomography (PET) aimed at investigating the brain effects of opioid agonists and the central correlates of the opioid analgesic effect. However, the adopted techniques did not allow to dissociate the effects on processing somatosensory stimuli from that on anticipation of pain, that may induce selective changes of activity in cortical systems.

In the present work, we aimed to develop a new experimental approach for investigating changes of activity in the cerebral cortex during anticipation of, and following mechanical stimulation of the skin, using functional magnetic resonance imaging (fMRI). fMRI is characterized by a better spatial and temporal resolution than PET, but few fMRI studies have been published on the central effects of analgesic drugs. The experimental protocol was approved by the University Committee on Ethics, and each participant gave his/her written informed consent before the experiment. Volunteers were healthy right-handed subjects aged 21-47 y. Each volunteer was paid for participation and was studied only once.

We adopted an event-related fMRI experimental design to investigate the time course of cortical activity related to single somatic inputs. Each trial lasted 40 s. It began with a warning signal that was followed 10 s later by the mechanical stimulation of the dorsum of the right hand, that could be either non-noxious or noxious. Stimuli were delivered through a custom-made, computer-controlled device in four adjacent sites of the skin, and they lasted two seconds. Twelve seconds after the stimulus, another visual cue prompted subjects to signal the perceived intensity of the stimulus. This was done by rotating a knob controlling the position of a cursor on a scale visible through mirrors inside the magnet, using the left (unstimulated) hand. A first group of volunteers underwent two runs, each consisting of 24 events, without drug administration. In a separate group of volunteers, a bolus of the μ -opioid receptor agonist fentanyl (1.2 μ g/kg), or an equivalent amount of saline, was intravenously injected 3 minutes before each single run. Stimuli were presented in a pseudo-random sequence, and the order of drug injection was randomized between subjects. Respiratory and cardiovascular functions were monitored continuously during the experiments.

Functional images were obtained using a General Electric Signa LX Echospeed MR system at 1.5 T (ASL Modena), by a T2*-weighted echo-planar sequence (TR=2 s, 12-14 axial planes covering the parietal cortex of both hemispheres, 3.75x3.75x5 mm), sensitive to the local changes in blood oxygenation accompanying neuronal activation (the so-called BOLD effect). For image processing and statistical analysis of the fMRI time series data we used SPM99. All images were realigned to the first, corrected for motion artifacts, normalized into the Montreal Neurological Institute (MNI) stereotactic space and smoothed with a 8-8-10 mm gaussian kernel. Activated voxels were identified with the general linear model approach for time series data using the hrf model function. Data for each individual were analyzed to detect signal changes significantly related to cortical neural events occurring during the waiting phase, following somatic input and following hand motor activity. A F-statistic was used to determine significance on a voxel-by-voxel basis and the data were transformed into a normal distribution (Z statistic). Regions of significant condition-associated signal changes were then displayed with a statistical threshold based on the amplitude ($p < 0.05$, corrected for the number of comparisons).

All subjects were able to discriminate between noxious and non-noxious stimuli and gave consistent responses throughout the experiment. Anticipation of pain induced increases in BOLD signals in the posterior and anterior cingulate cortex on both hemispheres, and in the putative hand region of the contralateral primary somatosensory cortex (SI). Both non-noxious and noxious stimulation increased activity in the contralateral, and to a lesser extent in the ipsilateral, SI. A bilateral activation of the secondary somatosensory cortex and of the anterior cingulate was also found in most subjects. As expected, left hand movement induced a complex pattern of activity in parietal and frontal areas, mainly on the right (opposite) hemisphere, and clearly different from the ones related to either anticipation or somatosensory input.

Opioid administration resulted in a significant reduction of the anticipation-induced activity in the posterior cingulate cortex. In most instances, somatosensory-induced activity was not significantly modified, although a trend towards an increase was found in the anterior cingulate and parietal regions. Motor-related activity was unaffected by fentanyl.

These findings demonstrate for the first time a selective effect of opioid agonists on different components of the brain response during potentially threatening (noxious) events. Specifically, the reduction of anticipation-

related activity may be related to the well-known opioid reduction of affective reactions to painful stimuli, given that anticipation of pain may directly influence the activity of nociceptive networks and the role of the cingulate cortex in the pain matrix. The results during noxious input are in line with previous studies, suggesting that the analgesic effect of drugs or techniques such as acupuncture can not be simply ascribed to reduced input to the cerebral cortex, but rather to a complex change in the activity of cortical systems. Due to its ability to discriminate between different aspects of the brain response, the proposed approach appears a promising tool for investigating the effects of different kinds of drugs on central pain networks.

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