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Brain Images of Pain

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Combined magneto- and encephalography proves the sequential involvement of multiple cortical structures in pain processing. Bilateral activity in secondary somatosensory cortices reflects the sensory-discriminative component and is reduced in states of unconsciousness. Later activity in the posterior cingulum reflects the emotional-aversive component, which is blocked by narcocainalgesics.

Pain is a completely subjective phenomenon with all of the characteristics of mind: self-experience, representational, and cognitive states. Attention given to the noxious event plays the decisive role in pain experiences and is an essential key to understanding the neuroplastic mechanisms that make pain chronic. These statements sound trivial, but not until the past 10 years has systematic research into the close connection between pain experience and states of consciousness been addressed in neurophysiology.

Without consciousness there is no pain. This fact is best known by the anesthesiologist: general anesthesia makes the patient unconscious; he doesn’t feel pain, though the nociceptive impact evoked by the operation may still reach pain-relevant structures in the brain, eliciting nocifensive responses, withdrawal reflexes, and changes in blood pressure, circulation, and heart action. These reactions that accompany an operation are suppressed by the physician by additional, primarily nonanallytically acting means. Moreover, the vegetative responses are commonly used to estimate the depth of narcosis, although they do not reflect pain. Under general anesthesia, the relevant brain structures are not able to translate cerebral activity into conscious pain experience (for review, see Ref. 2).

Many examples in pain research and therapy address the issue of the neurophysiological basis of consciousness. Do newborns feel pain? In the first months of life the central nervous system is still developing; relevant thalamocortical projections are unmyelinated and should be too slow for a conscious handling of external or internal events. Should we then use general anesthesia with infants, although we know it destroys neurons and interferes with neuronal development? Of course, western physicians do not hesitate to recommend anesthesia, very flat anesthesia. Or, regarding modern pharmacological pain therapy, there is the question of why centrally acting narcocainalgesics exhibit sedative effects as well. Decrease in vigilance means weakening of consciousness. Is there an inherent correlation between pain decrease and decrease in arousal?

With these questions we touch the mind-body problem. Though we are far away from any solutions to this great challenge in thinking, the novel functional brain imaging techniques, such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), are first attempts at attributing representational states of the self to circumscrip cortical activity that is active during mental tasks. The following overview briefly describes these techniques and focuses on recent results with magneto- and electroencephalography applied to cortical reactions concomitant to pain. The studies were performed under controlled experimental conditions in healthy male volunteers selected for maximal homogeneity. Pain was induced by brief infrared laser stimuli (for review, see Treede et al. in Ref. 2) or by the intracutaneously applied current pulse (for review, see Ref. 12). Both types selectively activate the most superficial skin afferents, the thin myelinated A and unmyelinated C-fibers that belong predominantly to the nociceptive system. The brief stimuli (1–20 ms) induce pure pain sensations, pin-prick like, well localizable, and rated with high reliability even in long-lasting sessions (12).

Windows into brain functions

Exploration of central pain mechanisms entails major difficulties. Invasive experiments in the awake animal are excluded for ethical reasons. Under general anesthesia, however, nociceptive functions are changed, in particular with respect to pain. Moreover, integrative brain functions and cognitive mechanisms are species specific; findings in animals therefore can hardly be transferred to the human brain. A certain methodology has been developed through experiments on animals with chronically implanted electrodes, but until now our main body of knowledge has been accumulated by careful observations in selected patients under neurosurgery.

The past 10 years have provided research with a series of novel, noninvasive imaging techniques that monitor normal and disturbed cerebral functions in humans. Most of these techniques do not measure neuronal brain activity itself but instead measure the changes in metabolism that are initiated by increased neuronal activity in response to experimentally given tasks (Table 1). Enhanced neuronal activity changes the balance of oxygen supply (blood flow) and demand (extractions by tissue). Capillaries are dilated in the referred region, which changes the regional cerebral blood flow, measured by sonography, Doppler sonography, microthermography, single photon emission computer tomography (SPECT), and PET. Other approaches use radioactively labeled glucose or other substances metabolized by the working neurons that are also measured by PET or SPECT. Changes in blood oxygen can furthermore be assessed, without any markers, by the blood oxygenation level-dependent (BOLD) contrast in fMRI: when deoxygenized oxyhemoglobin gives up its oxygen, the resulting
desoxymoglobin changes the local magnetic fields, which leads to a marked signal loss.

The systematic delay between increased neuronal activity and increase in metabolism is on the order of seconds. During this delay blood has moved, thus changing the site of the signal. In addition, these techniques need different-length time intervals for data sampling, as given in the Table 1. Therefore brain imaging methods that are based on metabolic functions are mainly used to examine cerebral activity during long-lasting events, e.g., in states of persistent pain induced in volunteers by ischemia, heat, or cold, or in few cases in patients with headache or back pain (for latest reviews, see Casey et al. or Forster et al. in Ref. 11).

**Electrical and magnetic brain source analysis**

Brain source analysis of electro- and magnetoencephalograms (EEGs and MEGs) traces neuronal activity directly and in real time. With the fulminate development of highly sophisticated techniques for measuring and evaluating extracephalic potentials and magnetic fields, electrical and magnetic brain source analyses are the most promising tools for visualizing feelings by localizing the cortical columns or assemblies of neurons (for review, see, e.g., Ref. 4) that are active during defined experimental tasks. Brain source analysis calculates the “generators” within the brain that might be responsible for the signals measured outside the head, assuming that circumspect cortical activation can be approximated by “equivalent current dipoles,” defined by their site, strength, and orientation (6 coordinates per dipole; for the physical background of these terms the reader may refer to the reviews in MEG research, e.g., Ref. 14). In physical terms, the dipole is part of a closed circuit: currents flow through the surrounding tissue back to their origin. These extracellular currents are the so-called “volume currents.” Volume currents play the decisive role in the generation of the EEG but also, of course, modify the magnetic fields measured in MEG.

Electricity causes magnetism (Fig. 1). The electrical currents accompanying brain activity are extremely weak; the resulting magnetic fields are 100 fT, about seven orders of magnitude smaller than the magnetic field of the earth. Nonetheless, these tiny fields can be measured by utilizing supraconducting quantum interference device (SQUID). The measuring sensors are placed into cryostats (“Dewars”) and cooled down to, e.g., −269°C (fluid helium). At this time, −100 MHz centers worldwide are working on problems of functional brain imaging.

Besides the experimental tasks of measuring those tiny signals, two major problems must be solved: 1) the head has to be kept constant in space during the sometimes long-lasting experiments, especially if averaging techniques are applied to increase the signal-to-noise ratio, and 2) a clear, well-defined data transformation is needed between the cryostat system (scanner) in which the fields are measured and the individual brain anatomy in which the activated neuronal assemblies are to be identified. PET studies use, for example, individual facial masks or other equipment to fix the head under investigation and relate their scanner recordings in general to standardized head coordinates (13) by using the ears, eyes, nasion, and inion as external markers. In MEG research, magnetic markers (coils) are fixed at any head position; these positions are exactly localized in the individual head MRI (see below) as well as in the cryostat system by broadcasting their positions with tiny calibrating currents between the measurements.

Attempts to identify generators from their broadcasted signals meet the “inverse problem,” which is principally unsolvable as already stated by Helmholtz more than 150 years ago. To achieve unique solutions, additional assumptions have to be inserted that are derived from current physiological and anatomic knowledge, e.g., about the number of generators, the cortex areas presumably involved, or at least their depth, laterality, or orientation, etc. We use the CURRY software (8), which presets the individual cortex anatomy as mathematical space for the solutions, determined by ongoing MRI (for details

**TABLE 1. Functional brain imaging techniques**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Principle</th>
<th>Resolution</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT</td>
<td>Neuronal activity increases rCBF measured by single photon emitters, e.g., technetium</td>
<td>20-5, 10-1</td>
<td>7, 5, Casey et al. in Ref. 11</td>
</tr>
<tr>
<td>PET</td>
<td>Increased rCBF and metabolite consumption measured, e.g., by 14C-labeled deoxyglucose</td>
<td>20-5, 10-1</td>
<td>5, Forster et al. in Ref. 11</td>
</tr>
<tr>
<td>fMRI</td>
<td>Increased rCBF and O2 consumption measured by local BOLD effect</td>
<td>10-2, 1-0.1</td>
<td>5, Chen et al. in Ref. 2, and Bromm et al. in Ref. 11</td>
</tr>
<tr>
<td>EEG</td>
<td>Neuronal electrical activity is measured as maps with scalp electrodes</td>
<td>10-1, 0.001**</td>
<td>10, 14, and Bromm et al. in Ref. 11</td>
</tr>
<tr>
<td>MEG</td>
<td>Neuronal magnetic activity is measured as isocontour plots with gradiometers</td>
<td>10-1, 0.001**</td>
<td></td>
</tr>
</tbody>
</table>

SPECT, single photon emission computer tomography; PET, positron emission tomography; fMRI, functional magnetic resonance imaging; EEG, electroencephalography; MEG, magnetoencephalography; rCBF, regional cerebral blood flow; BOLD, blood oxygenation dependency. *Expressed as seconds of data collection. **Depends on bandwidth and sampling rate only.
Multiple representation of pain experience

Pain is processed in multiple brain areas with large overlap in space and time. All imaging studies stress the involvement of the secondary somatosensory cortex (SII), the cingulate gyrus, and the frontal cortex in the experience of pain. Some PET, fMRI, and other BOLD studies found, in addition, subcortical structures in the medial midbrain, thalamus, lentiform nucleus, and cerebellum, which are active in subacute and chronic pain states. The multiple representation reflects the fact that sensory, motor, associative, autonomous, and limbic systems are involved in the processing of the many perceptive and nociceptive components of pain (for a recent review, see articles in Ref. 11).

Surprisingly, the primary somatosensory cortex (SI) has been minimally explored as part of the pain system. The postcentral gyrus is believed to receive the earliest somatosensory input, with latencies of 20 ms and more, depending on the body site and fiber spectrum activated. SI neurons exhibit a distinct somatotopic organization and stimulus response characteristic, with accentuation in the hemisphere contralateral to the stimulated body side, as broadly investigated in animals and humans, and its examination in patients by evoked potential measures is clinically routine. But with respect to pain, precise investigation of the involvement of SI has just begun. From animal experiments, we know that area 3a receives thalamic input from nociceptive Aδ- and C-fibers (for review, see Ref. 1 and articles in Ref. 2). This region is small and very deep in the posterior wall of the sulcus centralis; moreover, the nociceptive input is only a minor part of total somatosensory information, and initial SI activation is assumed to be very brief. It therefore seems reasonable that pain-relevant signals from the SI are too weak to be measured outside the head. In any case, large numbers of stimulus repetitions are needed to increase the signal-to-noise ratio, too large in the case of painful stimulation.

In contrast, the involvement of secondary somatosensory cortices (SII) in the processing of pain is also clearly documented in humans. The relevant structures are in the parietal region, located along the superior bank of the lateral sulcus, inferior to the face presentation in SI, medial to the primary auditory areas, and in the upper operculum, altogether in parts of the cytoarchitectonically defined Brodmann’s areas 2, 3a, 3b, 41, and 43 (1, 6). A certain somatotopy has already been reported for SII organization from experiments in monkeys and cats, in which the face is represented laterally and the legs more medially. The SII assemblies involved in the processing of pain are very superficial and orientated, on the average, in a direction tangential to the skull; consequently their magnetic fields can easily be picked up by the MEG, as already shown in the first application of MEG with painful tooth pulp stimuli (9).

Unilateral stimulation induces bilateral SII activity

We know that pain-related SII activity starts ~80 ms after stimulus onset and lasts for ~40 ms (“lifetime of the SII generator”). Peak latencies range between 80 and 150 ms, depending on the neuronal distance to be conducted. However, whereas in SI the neuronal information is processed contralaterally to the stimulated body side, all MEG research unequivocally confirms that SII is activated in both hemispheres. In other words, though the stimuli are administered strictly unilaterally, bilateral SII activity occurs at corresponding locations. This fact is illustrated in Fig. 2 with painful laser stimuli applied anteriorly to the dorsum of the left or right hand; maximum activity is expressed by arrows (dipoles). For either stimulus site a pair of dipoles emerges in the corresponding SII area of the hand; the locations in SII are slightly (but significantly; see below) different depending on whether the left or right hand of the same subject is stimulated.

Some studies report an earlier SII activation of several milliseconds in the contralateral hemisphere. However, experiments with intracutaneously applied electrical stimuli of left middle finger tip in 10 (right-handed) subjects, each experiencing 3 sessions with 4 repeated stimulus blocks, did not point to a basic preference of left or right hemisphere (Bromm et al. in Ref. 11). In four subjects, the contralateral hemisphere was activated first, ~5 ms earlier than the ipsilateral site; in three others it was the ipsilateral SII that received the information first; and in the remaining three both SII cortices were simultaneously active within the accuracy of determination. In

FIGURE 1. The physical basis of magnetoencephalography (MEG). Circumscript brain activity, modeled as a current dipole, induces magnetic fields according to the right-hand rule. These fields are ~7 orders of magnitude smaller than the magnetic field of the earth but can be measured by the superconducting quantum interference device (SQUID) technique at low temperatures of, e.g., ~269°C. Each gradiometer (we currently use 62) picks the field up as a function of time, and at any given time we measure the field distribution over the head in the form of brain maps, here with blue lines indicating entrance and red lines indicating exit of the fields at this time point.

of measurement and calculations, see Kohlhoff et al. in Ref. 2 or Bromm et al. in Ref. 11). In this way generators are preset, and the fields calculated at the points of measurement (“forward calculation”) are compared with the measured signals. This leads to an iterative procedure of readjusting the sites and characteristics of the preset sources and repeated calculations. In MEG or EEG analysis, normally 20–50 numerical iterations are needed to achieve sufficient agreement between calculated potentials or fields with the measured ones.

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other words, there is no discrepancy from the reported findings of others, which incidentally are mostly from single case studies. Because of the large differences in brain anatomy between individuals, generalizations are difficult. Repeated investigations in the same subject are needed to describe the accuracy of determination and reliability of results if higher brain functions are examined. In a very late step, general statements may be derived on the grounds of the intra- and interindividual variabilities.

SII activity reflecting the sensory-discriminative pain evaluation

SII is the first cortical stage that processes somatosensory information from both body sites. The stimulus obviously calls corresponding SII areas in both hemispheres for comparative evaluation. This way the side that hurts may be determined. Bilateral activation presumably does not occur via transcallosal fibers because of the more-or-less simultaneous activation in both hemispheres. Pain-related activity exists in bilateral thalamic relay stations that receive information from bilateral spinothalamic projections (see Willis in Ref. 2). SII neurons project to SI (10), to the parietotemporal cortex, to the posterior insula, and into deep cortical structures like amygdala and hippocampus (1). Most of these projections are reciprocal; consequently, a variety of feedback loops are possible.

Repeating the experiments in same subjects by varying the stimulus intensity and the body area stimulated demonstrates a distinct stimulus response characteristic in bilateral SII activity and somatotopic organization. When stimuli are shifted to neighboring body sites, neighboring areas become active in SII of both hemispheres. This can best be shown by observing the shifts of the isocontour maps (Fig. 1) if stimulus conditions are changed. But it is extremely difficult to generalize these findings over subjects.

To sum up, the earliest cortical activity in response to painful somatosensory stimuli can clearly be seen in bilateral SII with somatotopy and stimulus response characteristics. These are the features of the lemniscal nervous system. Bilateral activation enables the brain to differentiate the hurting body site from the unaffected site; somatotopy allows the localization of the hurting event (presumably in context with SI); stimulus response characteristics let the brain rate the magnitude and character of the pain. Thus, following the nomenclature of psychologists, pain-induced activity in SII might reflect the “sensory discriminative component of pain.”

Pain processing in anterior and posterior cingulum

All functional imaging studies measuring neuronal metabolism concomitant with persistent pain (PET, fMRI) emphasize the involvement of the anterior cingulate cortex, characterized by Brodmann’s areas 23, 29, 30, and 31. The anterior cingulate gyrus (CGa) receives its dominant input from the spinothalamic tract, which is believed to conduct almost all pain information (Fig. 3). Activity of the CGa is under the control of the insula, which in turn exhibits reciprocal fiber connections with SII. These connections provide the basis for a function in motivation, initiation of behavior, and modulation of autonomic...
reactions. It is broadly agreed that associative nuclei in the CGa control nocifensive reactions, not only in the coordination of motor reflexes and behavior but in particular autonomic functions, like sweating, respiration, heart action, blood pressure, or circulation, via nuclei in the hypothalamus.

Direct tracing of pain pathways by combined MEG/EEG source analysis elaborated the decisive role of posterior parts of the cingulum in the processing of phasic pain, which extend to parts of Brodmann’s areas 24, 25, and 32. It is this generator in particular in the posterior cingulate gyrus (CGp) that is responsible for the so-called “pain-related” brain potentials that appear with peak latencies between 200 and 350 ms after stimulus onset (depending on the stimulated body site) and consist mainly of a vertex positivity. Subjecting this vertex positivity to multivariate statistical methods resulted in two factors that vary greatly with the magnitude of perceived pain. It therefore has been used for decades in the clinical examination of failures in the pain system (for review, see Treede et al. in Ref. 2) as well as in competitive evaluations of the analgesic potency of drugs (for review, see Ref. 12).

Because of its predominantly radial direction, the pain-related CGp generator impresses very little in MEG recordings but can be easily identified in multilead EEG measurements. CURRY software applied to the long latency vertex positivity, including the boundary element method model for volume currents (important in EEG evaluations), clearly identified the relevant generator in the CGp despite the large interindividual variability in brain anatomy. The initiation of pain-induced activity in the CGp has been found in all brain electrical source analyses based on multilead EEG responses to phasic pain stimuli (for literature, see Bromm et al. in Ref. 11). On the other hand, the pain-relevant vertex positivity is very broad, covering a latency range between 200 and 350 ms. CURRY analysis of the entire latency range resulted in the finding that different sites in the cingulum are active at different poststimulus times.

Figure 4 shows an example with painful left temple laser stimuli in one individual. CG activity starts in the posterior region, then “moves” toward rostral parts and disappears in the prefrontal cortex at latencies >280 ms. It is unlikely that this movement is mediated through transcingulate fibers because of its slowness, though they exist (Fig. 3). Instead it may express the involvement of multiple structures in the large cingulum that are successively activated in the course of pain perception. The spatial resolution, even with the highly sophisticated method used here, is not sensitive enough to decide whether the ipsi- or the contralateral CG, or both of them, is involved.

The CGp and the aversive emotional pain component

There is no doubt that the CGp receives nociceptive information (1), as already indicated in Fig. 3. The dominant inputs stem from the hippocampus and the amygdala via the anterior and laterodorsal thalamic nuclei. The laterodorsal nucleus receives multimodal inputs from the superior colliculus, which is activated by projections from the dorsal column, including postsynaptic dorsal column neurons. Their projections originate in laminae IV and V and carry nociceptive and wide dynamic range responses, mainly from Aβ-fibers (for details, see Ref. 1). There is no discrepancy between this and the findings of PET studies emphasizing the CGa in the processing of pain. PET and other imaging studies based on metabolism mainly apply tonic stimuli and investigate periods of painfulness on the order of minutes or more. Then the anterior spinthalamic tract may predominantly be accentuated. Moreover, the rather long periods for signal sampling may miss the brief but essential involvement of CGp in the processing of pain.

The posterior parts of the cingulum with activation from the amygdala and reciprocal fiber connections to broad regions of the parietal and temporal cortices are assumed to play an interactive role in affective “coloring” of perception and in transforming aversive inputs into movements, thereby providing maintenance of spatial orientation, pain memory, attention,
and evaluation of the significance of stimuli for the organism. We therefore may attribute pain-induced activity in the posterior cingulum to the so-called “emotional-aversive component of pain,” reported at the subjective level of measurement.

**Outlook: the clinical relevance of studies imaging pain**

Imaging studies are essential tools for exploring how the brain works, particularly in humans. But these techniques also have an immediate use in applied brain physiology, for example by documenting results in psychological treatment of persistent pain, such as distraction or coping mechanisms. This overview therefore ends with some remarks concerning the clinical relevance of brain imaging methodology in the investigation of pain. Several studies have already been performed in patients suffering from various pain states. Patients with central neuropathic pain sometimes show thalamic hyperactivity if the abnormal side is stimulated (for review, see articles in Ref. 11). We observed a patient with poststroke central pain who developed allodynia in the right leg during the observation period of more than a year (for literature, see Bromm et al. in Ref. 11). Repeated investigation by MEG documented neuroplastic changes in the projections from the thalamus to the cingulum, which switched tactile information directly into the CGp.

Another application is the documentation of the sites and strengths of centrally acting drugs in the treatment of pain, e.g., of narcoanalgesics or anesthetics. Obviously, SII activity in response to painful stimuli depends strongly on the arousal level of the investigated brain. Tranquilizers or hypnotics that make the subject drowsy significantly decrease SII activity in response to experimental pain test stimuli. This has also been shown in a study of the dissociative anesthetic ketamine, performed in collaboration with the Hamburg Clinic for Anesthesiology (for literature, see Bromm et al. in Ref. 11). During the brief period of unconsciousness, SII activity in response to intracutaneous pain stimuli was drastically reduced in both hemispheres (7 subjects). As soon as the subjects regained consciousness, mean global field power in SII was completely restored. In contrast, activity in the cingulum was only marginally attenuated during unconsciousness.

On the other hand, cingulate activity in response to pain-inducing stimuli is remarkably decreased by opiates. This has been shown in all studies that use the pain-related vertex positivity in EEG recordings, as mentioned above. The newest experiments with brain source analysis in the individual cortex anatomy evidenced the site of morphine action clearly in the CGp (Scharein et al., unpublished observations). The CGp generator activity was drastically attenuated in parallel with the decrease in the pain ratings when morphine had overcome the blood-brain barrier (~10 min after iv injection). The experiments in the first subjects so far document a large interindividual variability of morphine effects on CGp and pain ratings, and we are still in the process of looking for reasons. In all cases, the morphine effect on CGp activity lasted for little more than 2 h. In patients, morphine-induced pain relief lasts much longer. The reason might be that quick relief of pain may retard the development of neuroplastic changes concomitant to persistent pain.

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**References**