Invited review

Neurophysiological evaluation of pain

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Abstract

Neurophysiological techniques for the evaluation of pain in humans have made important advances in the last decade. A number of features of neuroanatomy and physiology of nociception qualifies pain as a multidimensional phenomenon which is rather unique among the sensory systems and which poses a number of technical and procedural requirements for its appropriate diagnostic assessment. Various stimulation techniques to induce defined pain in humans and used in combination with the methodology of evoked electrical brain potentials and magnetic fields are presented. Most recent knowledge gathered from scalp topography and dipole source analysis of pain-relevant evoked potentials and fields is discussed. Particular emphasis is put upon laser-evoked potentials and their application for diagnosis, pathophysiological description and monitoring of patients with neurological disorders and abnormal pain states. Future perspectives in this growing field of research are discussed briefly. © 1998 Elsevier Science Ireland Ltd. All rights reserved

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1. Introduction

Pain subserves an essential function for the organism to guarantee immediate awareness about actual or threatening injury enabling the individual to adopt a protective behavior; experience of pain is complex and primarily subjective. It involves sensory, affective, cognitive and motivational components and is associated with autonomous activity, nocifensive reflexes and reactions as well as with aversive emotions and avoidance behavior (for a definition see Merskey, 1991). The anatomical substrate of pain, the so-called nociceptive system, has been the scope of other reviews (Willis, 1985, 1995; Willis and Coggeshall, 1991; Willis and Westlund, 1997) and various chapters in the Textbook of Pain edited by Wall and Melzack (1994). It consists of cutaneous and visceral nociceptors (Aδ- and C-fibers) and spinal cord neurons which transmit the peripheral input to supraspinal structures like brain-stem, thalamus, cortex and limbic system, and pass it to motoneurons which mediate withdrawal reflexes, or to autonomous efferents which modify, e.g., cardiovascular and respiratory activity. The pain signal is subject to a variety of facilitatory and inhibitory modulation all along its way from the nociceptor to brain structures involved in perception and cognition.

Endogenous pain suppression includes phenomena of stimulation-induced antinociception as formulated, e.g. in the theory of gate control (Melzack and Wall, 1965), diffuse noxious inhibitory control (DNIC; Le Bars et al., 1979; for review see Le Bars et al., 1995), descending inhibition and stress-induced analgesia (SIA; for review see Fields and Basbaum, 1994). Also, higher brain functions regulating consciousness and attention significantly contribute to endogenous pain control (for a comprehensive presentation of this issue see Bromm and Desmedt, 1995). Considerable fluctuations of pain can occur over very short periods of time: during a sporting competition or a combat, for example, a subject may completely fail to be aware of even severe tissue damage which, in the next moment, may become increasingly painful if the victim releases more and more his attentional involvement in these activities. From a teleological point of view the endogenous inhibition of pain during stress can be assumed to serve for survival if fight or flight are necessary at the presence of severe injury.

There is also endogenous facilitation of pain which

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involves sensitization of the nociceptor and their spinal and supraspinal projection neurons on the basis of tremendous neuronal plasticity exhibited under certain stimulation patterns or pathophysiologic conditions, such as skin or muscle inflammation and nerve injury (for reviews see Mense, 1993; Handwerker et al., 1994; Levine and Taiwo, 1994; Dubner and Babasaum, 1994). Long-lasting hypersensitivity upon existing tissue damage obviously serves to promote healing by forcing the victim to take special care of injured body parts. However, pain loses any apparent benefit if hypersensitivity outlasts the process of healing, and becomes itself a disease. Even severe pain states may appear although the patient never presented any appropriate objective signs of tissue damage, e.g. in patients with hysteria (Merskey, 1995), stroke and seizures (Boivie, 1994), phantom limb pain (Melzack, 1990), fibromyalgia (McCain, 1994), and even cases of low back pain (Cavanaugh and Weinstein, 1994). These pains are usually termed ‘neuropathic’ or ‘psychogenic’ in contrast to ‘nociceptive’ where physical reasons, a noxe, trauma or inflammation, are present.

As the basic vehicle of pain is the neuronal system, neurophysiological techniques have been developed or adapted for the evaluation of pain in human subjects and patients (for reviews see Bromm, 1984; Chapman and Loeser, 1989; Treede et al., 1995a; Dotson, 1997; Arendt-Nielsen, 1997). One approach relates human pain sensation to neurophysiological phenomena in the periphery, e.g. microneurography of nociceptor discharges (for reviews see Vallbo et al., 1979; Handwerker and Kobal, 1993), or electromyography of withdrawal reflexes (Willer and Le Bars, 1995). Other approaches pertinent to the scope of the present review use spontaneous and evoked electro- (EEG) and magnetoencephalography (MEG). These latter methodologies have in particular experienced significant advances in the past 10 years, the decade of the brain. They allow noninvasive access to brain processes at an integrative level of the central nervous system (CNS) with high degree of spatiotemporal resolution. A comprehensive source of literature about EEG and MEG studies in human volunteers and patients examined by standardized techniques of pain stimulation or during clinical pain states is attempted to be covered in this review. Pharmacological modulation of EEG and MEG is outside the primary scope of this paper; it is reviewed elsewhere (Scheirin and Bromm, 1998). However, selected findings of drug effects are included if they contribute to the neurophysiological understanding of pain, such as, e.g., the elaboration of the pain specificity of evoked potential components or their modulation in varied states of consciousness.

2. The pain apparatus

2.1. The nociceptor

The identification of nociceptors all over the body including skin, cornea, viscera, muscles, joints, bones, tendons, vessels and meninges substantiated the specificity theory of pain. Basic differences in the periphery between nociceptive and mechanoreceptive afferents, the latter subserving tactile, vibration and joint position sense, concerns both morphological and functional properties. Low-threshold mechanoreceptors belong to Aδ-fibers which can perfectly be investigated using electrical nerve stimulation in electro- neurography and evoked potential application; they conduct with 30 to 60 m/s in man, enter the dorsal horn and project within the dorsal column to lower brain stem nuclei gracilis and cuneatus. After synaptic transmission, second-order neurons of the medial lemniscal tract convey the signal to the contralateral ventrobasal and lateral nuclei of the thalamus from where third-order neurons project into the primary somatosensory cortex of the postcentral gyrus. This so-called lemniscal system is ideal for sensory-discriminative quality of sensation due to the rapid transmission and the strong stimulus-response correlations along its synaptic relays stations in terms of small somatotopically-organized receptive fields, clear intensity dependency, and modal specificity.

In contrast, the anatomy of the pain system contains important structural properties which constitute the dual nature of pain being composed of both sensory-discriminative and motivational-affective components (Melzack and Casey, 1968). It is the purpose of this review to give an overview of the literature about this issue, yet without giving a claim to completeness. Comprehensive presentations are given elsewhere (Willis, 1985; Willis and Coggeshall, 1991; Willis and Westlund, 1997). With particular reference to visceral nociception, the reader might be referred to reviews by Cervero (1995) and Vahlé-Hinz et al. (1995).

When natural stimuli, often heat or pressure, are applied at adequate intensities to the skin, two sequential pain sensations are elicited: first and second pain relate to activation of thin myelinated Aδ-fibers (4–30 m/s) and unmyelinated C-fibers (0.4–1.8 m/s), respectively (for conduction velocities in man see Vallbo et al., 1979). These nociceptors could be subdivided into groups according to differences in stimulus modalities. One currently used terminology denotes by CMH and AMH mechanical and heat sensitivity of high-threshold C- and A-fibers, respectively (for review see Meyer et al., 1994). C-fibers of the human skin with heat sensitivity exhibit in more than 60% also chemosensitivity (Handwerker et al., 1994) so that CMH often refers to the term ‘C-fiber polymodal nociceptor’ coined by Bessou and Perl (1969). A high degree of congruence of chemo- and heat sensitivity of nociceptors is also supported by the recent discovery of an ion channel, the vanilloid receptor subtype 1 (VR1), which is activated by both capsaicin and noxious heat, and which is specifically expressed in nociceptive neurons (Caterina et al., 1997).

With respect to myelinated fibers, there are two types of AMH nociceptor – differentiated by their response latencies and thresholds to heat stimuli (e.g. Campbell and Meyer, 1986). They differ in abundance at hairy and glabrous skin
of the monkey hand, and were termed type I and II AMH (for review see Meyer et al., 1994). Differential response properties of these two types of A-afferents have been studied in the monkey hand by Treede et al. (1995b): type I AMH conducts with 25 m/s (mean), has a high heat threshold (53°C), starts to respond not before several seconds of a long-lasting heat stimulus, and develops slowly increasing discharge rates. Type II AMH conducts with 15 m/s, a lower heat threshold (45°C) and starts to respond much earlier, at 120 ms, with an early peak discharge between 1 and 3 s. Whereas the hairy skin of a monkey’s hand has both types of AMH, only type I AMH is found in glabrous skin. The two types of A-nociceptors, furthermore, differ with respect to sensitization following intense heat stimulation which lowered the threshold of type I AMH, but increased the threshold of type II AMH.

Based on the above classification and given similar conditions in man, type II AMH fibers correspond to Aδ-nociceptors, most likely responsible for first pain after a brief radiant heat stimulus, delivered, e.g., by a laser stimulus applied to the hand dorsum. By conduction velocity criteria, type I AMHs fall into the category between that of Aδ- and Aβ-fibers; due to its extremely long receptor utilization time it should not be relevant for an evoked potential correlate averaged over repeated heat stimuli (see below). However, an electrical stimulus bypasses the receptor and directly activates the nerve. Thus, type I AMHs may well contribute to experimental pain and the brain potential evoked by transcutaneous or intracutaneous electrical stimulation at painful stimulus intensities.

### 2.2. Spinal and supraspinal projections

The functional anatomy of the dorsal horn projection pathways transmitting the peripheral nociceptive signals to higher CNS structures is a matter of permanent updating. Its comprehensive discussion would certainly go beyond the scope of this review. We will limit the introduction to basic features based on a sound experimental and clinical evidence, being aware of some inherent simplification.

Nociceptive afferents enter the spinal cord via the dorsal roots and synapse with cell bodies of crossing fibers of the spinothalamic tract (STT) which are mainly located in Rexed’s laminae I and V. There is some functional differentiation of STT neurons, in that cells in lamina I are specifically activated by noxious stimuli, called nociceptive-specific (NS) neurons, whereas lamina V cells respond to a ‘wide dynamic range’ (WDR) of stimulus intensities. WDR neurons receive convergent input from mechanoreceptive Aδ-fibers and from nociceptive Aδ- and C-fibers (for review see Dubner and Basbaum, 1994). Aδ- and C-fibers of the trigeminal nerve subserving cranial nociception descend in the spinal tract and terminate mainly in the pars caudalis of the spinal trigeminal nucleus in the upper cervical dorsal horn, where they synapse with crossing STT fibers joining the anterolateral tract projections of the body.

Nociceptive signals of spinal and trigeminal nerves which are transmitted by STT cells located in laminae I and V mainly project into ventro posterolateral (VPL) and ventro posteromedial (VPM) nuclei of the lateral thalamus from where information directly proceeds to somatosensory cortex (SI and SII). Deeper STT neurons project to the medial thalamus (intralaminar nuclei, the central lateral nucleus and the medial dorsal nucleus) which exhibit strong fiber connections to the anterior cingulate gyrus. There are also some nociceptive and thermoreceptive STT neurons of superficial dorsal horn projecting into the medial thalamus which have been suggested as being relevant for the mechanisms of central pain (Craig et al., 1994), as will be discussed in more detail below. Medial thalamus and cingulate cortex receives, furthermore, input from spinoreticular and spinothalamic fiber tracts. These systems exhibit numerous synaptic connections with ascending and descending pathways, particularly involving the periaqueductal gray matter (PAG) and the raphe nuclei which exert antinociceptive actions (e.g. DNIC, see above). The separation of STT neurons projecting to either medial or lateral thalamic nuclei and terminating in either somatosensory or limbic cortex gave rise to a global differentiation of a medial and a lateral pain system (for reviews see Vogt, 1985; Albé-Fessard et al., 1985; Vogt et al., 1993; Jones and Derbyshire, 1996). The lateral pain system is regarded as important for discrimination and identification of noxious stimuli allowing precise determination of their epipritical attributes such as localization, time and intensity. A key role of the medial pain system is thought to emotionally ‘color’ nociceptive sensation by signaling aversion which motivates escape, avoidance and protective behavior.

It is evident that both the medial and the lateral pain system have manifold reciprocal connections by which they interact so that any pain, be it experimental or clinical, acute or chronic, always contains both sensory-discriminative and motivational-affective aspects. Yet, the dominance of either component may surely differ among pain states. It should also be noted that mechanoreceptive fibers and the lemniscal system also contributes to sensory-discriminative processing of painful stimuli, as this system is most often coactivated. Interneuronal networks both in the dorsal horn and the thalamus give rise to manifold modulations both in the direction of enhanced or reduced nociceptive transmission. The balance of excitatory and inhibitory processes which can be manipulated by certain input patterns form the basis of general theories on endogenous pain control mechanisms such as the ‘gate-control-theory’ by Melzack and Wall (1965) or the mechanisms referred to as ‘diffuse noxious inhibitory controls’ by Le Bars et al. (1979). Furthermore, the notion that nociception is only transmitted via STT of the anterolateral corner of the spinal cord has been challenged recently by Berkley and Hubsch (1995), who provided evidence that particularly visceral nociception also activates the dorsal column pathway.
Knowledge about the central mechanisms of nociceptive processing have long been coupled with the understanding of the ‘thalamic pain syndrome’ first described by Dejerine and Roussy (1906) and Head and Holmes (1911) on the basis of stroke-induced analgesia and thermoanesthesia associated with thalamic lesions. The term ‘thalamic pain’ has been, however, more and more abandoned in favor of the term ‘central pain’ (CP) accounting for the clinical experience that brain lesions outside the thalamus can produce virtually the same pain syndrome. For example, CP occurs in patients with lateral brain-stem infarcts, known as the Wallenberg syndrome, with a relatively high incidence of 25% (MacGowan et al., 1997). CP is also well-known as complication of spinal lesions, e.g. in syringomyelia (for review see Boivie, 1994). The general feature of CP after lesions at various locations along the central afferent neuraxis seems to be the affection of the pain pathway itself. For in most CP patients the typical paradox exists that body parts in which pain and temperature sensitivity is lost develop abnormal freezing or burning, extremely unpleasant types of pain, or allodynia to cold and touch stimuli.

Craig et al. (1994) described two specific regions in the thalamus suggested to be important for a central integration of temperature and pain sensation. One, referred to as the posterior part of the ventral medial nucleus (VMpo), mainly projects to the insula and receives input from spinothalamic parts in which pain and temperature sensitivity is lost.

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2.3. Central pain

The anterior cingulate cortex and receives input from spinothalamic ‘COLD’-neurons of lamina I which cold-sensitive peripheral Aδ-fibers synapse. Activation of this channel produces sensation of cold. Another, referred to as the ventral caudal part of the medial dorsal nucleus (MDvc), projects to the anterior cingulate cortex and receives input from nociceptive STT neurons of lamina I which respond to polymodal input from peripheral Aδ- and C-fibers sensitive for heat, pinch and cold (‘HPC’-neurons). Its activation leads to a sensation of heat or pain. A central integration system coordinating transfer of input from these two channels to somatosensory and limbic cortices is postulated because not the absolute magnitudes of either COLD or HPC inputs determine whether cold or pain are sensed but their relative difference of impulse rates (Craig and Bushnell, 1994). An interesting experimental model supporting the existence of the proposed central mechanism of pain and temperature integration is seen in the ‘pain illusion’ produced by the Thunberg grill, a phenomenon already described in the last century by a Swedish physiologist (Thunberg, 1896). A grid of contact thermodes consisting of interlaced innocuous cool (20°C) and innocuous warm bars (40°C) produces a sensation of pain in healthy subjects. Craig et al. (1996) recently demonstrated by positron emission tomography (PET) imaging that this grill illusion of pain is accompanied by an activation of the anterior cingulate. Both pain and PET activation of anterior cingulate failed to appear when either warm or cold stimuli were presented alone. The reason for the grill illusion of pain is seen to be due to the interlaced warm bars reducing the activation of the neuronal COLD channel without changing the HPC channel. Their difference of impulse rates (HPC minus COLD) is therefore shifted by the Thunberg grill to a value as if a noxious cold stimulus of 11°C is applied alone which induces a burning pain. According to this model, CP and cold allodynia in the analgesic and thermoanesthetic body part are explained by lesions in VMpo or STT neurons impinging upon it by which COLD input is reduced and the MDvc transmission of HPC input to anterior cingulate becomes disinhibited (see also Craig, 1994).

Hyperactivity of the medial thalamus on the basis of an imbalance between lateral and medial thalamus as cause for CP has also been postulated by Cesaro et al. (1991); in fact medial thalamotomy was among the first and most efficient stereotactic operations against CP (Sano, 1977). Although Jeannin et al. (1994, 1996) regard the disturbed balance between medial and lateral thalamus as an initially important event as well, they particularly emphasized that CP is finally determined by rhythmic bursting of lateral and medial thalamic neurons as a consequence of a loss of STT input to the lateral thalamus. The development of thalamic bursting activity is furthermore emphasized by Lenz et al. (1987, 1989) to be closely associated with CP based on intracerebral electrophysiological studies in neurosurgical patients. There are still controversies in the concepts of CP with respect to the importance and anatomical basis of the various postulated interactions and phenomena. However, there is a broad agreement that damage of the spinal and supraspinal pain and temperature pathways causes an imbalance of the system which leads to disinhibited spontaneous nociceptive activity and pain in response to innocuous stimuli at the presence of decreased physiological exteroceptive function (for a comprehensive review see Boivie, 1994).

2.4. Neuronal plasticity

Sensitization is a basic feature of the entire nociceptive system starting in the periphery where it particularly concerns C-nociceptors (for reviews see Handwerker and Reeh, 1991; Perl, 1996). It is mediated by algogenic substances, such as bradykinin, prostaglandins, serotonin and histamine, which are released from inflamed and injured tissue. Intraocular application of exogenous substances like capsaicin into human skin also sensitizes C-nociceptors and leads to burning pain (Handwerker et al., 1994). Low pH has long been implicated to account for excitation of nociceptors. Recent studies showed that low pH effects upon nociceptor activation are potentiated in the presence of inflammatory mediators (for review see Reeh and Steen, 1996). Algogenic substances lower the threshold of nociceptors and activate second-messenger systems which in turn induce gene expression in the cell nuclei. This way production and transmission of some excitatory amino acids and neuropeptides and their receptors are upregulated sensitizing the nociceptor over longer periods of time. Some of these algogenic neuropeptides, e.g. substance P, calcitonin-gene-related
peptide (CGRP) and neurokines, are released by the peripheral and central endings of nociceptive C-fibers themselves and induce neurogenic inflammation. Antidromic neurosecretion, originally called axon reflex by Lewis (1935), and described in detail by Hardy et al. (1952), mediates the neurogenic flare reaction by increasing vascular permeability and inducing vasodilatation. These effects are eliminated by injection of local anesthetics into the receptive field of the C-nociceptor. Hot skin, burning pain and tenderness to touch as features of sensitized C-nociceptors are also exhibited by some painful neuropathies, a condition which Ochoa (1986) termed ‘angry backfiring C-nociceptor syndrome’ (ABC syndrome).

Enhanced intensity and anatomical extension of pain has further been described to be due to ‘awakening’ of normally ‘sleeping nociceptors’ reflecting the phenomenon that they only fire spontaneously or become responsive for peripheral stimulations when inflammation is present (Schaible and Schmidt, 1985; Schmelz et al., 1994). Ongoing pain and tenderness as clinical features of inflamed tissue involves the sensitization of spinal WDR neurons by which a convergent Aβ-fiber input becomes capable of signaling mechanical (secondary) hyperalgesia and allodynia in unaffected skin surrounding the lesion (for review see Treede et al., 1992). Referred pain which is the phenomenon that a visceral lesion produces somatic pain, e.g. in the left arm due to angina pectoris, may be regarded as a special type of secondary hyperalgesia due to the existence of visceral-somatic convergence of peripheral afferents upon spinal pain signaling projection neurons. Supraspinal and cortical areas also seem to be involved in long-lasting changes of pain sensitivity. Plastic reorganization within the primary somatosensory cortex has been recently implicated to be involved in the development of chronicity of pain syndromes (Flor and Birbaumer, 1994; see also Bromm, 1994; Flor et al., 1995, 1997; Birbaumer et al., 1995, 1997).

3. Brain electric and magnetic activity during experimental and clinical pain

The primary topic of this review is a comprehensive presentation of the literature on human physiological studies which aimed to identify pain-relevant information in spontaneous electroencephalogram (EEG), typically quantified by power spectral density analysis, as well as in evoked potentials (EP) and their magnetic counterparts magnetoencephalography (MEG) and evoked magnetic fields (EF). It does not include all varieties of studies of patients with pain in whom EEG/MEG analysis was performed as part of a broader neurophysiological diagnostic or in order to study pathophysiological mechanisms related to the underlying disease rather than to the concomitant pain, e.g. in migraine (for review see Sand, 1991), in pain associated with seizure disorders, in neurosurgical pain patients or central pain syndromes (see above). Selected articles in patients with these pathologies were only considered if they addressed EEG/MEG as correlates of pain perception and related cognitive and emotional phenomena, or of pain sensitivity.

3.1. Pain correlates in the spontaneous electro- or magnetoencephalogram

A quantification of effects of experimental pain upon the spontaneous EEG of healthy volunteers by analysis of power spectral density (PSD) after Fourier transformation was performed in only 5 studies so far (Table 1). Although some differences among these studies may be related to different pain stimuli and pain duration, as well as in the classifications of the bandwidths, the most striking similarity concerned a decrease of alpha and an increase of beta activity under pain. Interestingly, Backonja et al. (1991) observed the alpha decrease under pain, induced by ice water, only during the first minute after stimulation onset, which turned into an alpha augmentation upon further pain stimulation, particularly in the low alpha range (8–10 Hz). To our knowledge, no study so far examined spontaneous MEG during pain.

Desynchronization of alpha upon sensory stimulation is a well-known phenomenon since Berger’s description of the visual alpha blocking effect, later examined in more detail by Pfurtscheller and Aranibar (1977) who coined the term event-related desynchronization (ERD). The opposite phe-

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<th>Reference</th>
<th>Pain stimulus</th>
<th>Stimulated location</th>
<th>Delta</th>
<th>Theta</th>
<th>Alpha</th>
<th>Beta</th>
<th>Other effects</th>
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<tr>
<td>Chen et al. (1989)</td>
<td>Ice water</td>
<td>Hands</td>
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<td>↑</td>
<td>Differences between pain sensitive and pain tolerant</td>
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<td>Backonja et al. (1991)</td>
<td>Ice water</td>
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<td>Initial ↓ Later ↑</td>
<td>↑</td>
<td>EMG contamination of beta, same effects with feigned pain</td>
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<td>Veerappan and Stohler (1992)</td>
<td>Hypertonic saline i.m.</td>
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<td>Increase of local and inter-hemispheric coherence</td>
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<td>Chen and Rappelsberger (1994)</td>
<td>Ice water</td>
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<td>Delta after left hand &gt; after right hand stimulation during 2nd minute</td>
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<td>Delta after left hand &gt; after right hand stimulation during 2nd minute</td>
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nomenon of event-related synchronization (ERS) in the alpha band also occurs (Pfurtscheller, 1992). According to this author both phenomena depend upon the scalp location where being recorded pointing to their association with certain topopspecifically organized cortical functions: for example, at occipital leads, ERD can be observed during vision whereas at the same time ERS occurs at a fronto-central electrode over the supplementary motor area. In turn, during movement the opposite constellation may be present: ERS appears fronto-centrally and ERS occipitally. ERD and ERS, therefore, fluctuate over very short time periods which may depend on the various brain areas engaged in a particular task at a given moment. Based upon these considerations, alpha reduction and augmentation during pain are unlikely pain-specific and may indicate changes of the dominance and selectivity of perceptual cues being utilized during orienting and organization of adaptive motor behavior in response to pain as an obtrusive stimulus. The second consistent effect of tonic experimental pain on EEG power spectra is an increase of beta activity. However, this high-frequency PSD enhancement can also hardly be regarded as a specific phenomenon. It may directly be related to the desynchronization of alpha being replaced by faster rhythms. Moreover, special care has to be applied to avoid muscle activity from head, face and neck movements in response to experimental pain; spreading of muscle activity (measured by electromyography, EMG) contaminates EEG, especially in the high-frequency range.

The nature of EEG changes observed in clinical pain states, particularly in the heterogeneous group of headache and migraine patients, is very difficult to relate to perceptual, emotional or cognitive processes linked to pain itself. For example, enhanced slow wave activity, focal or generalized spike paroxysms are all common EEG abnormalities in headache and migraine, but may rather indicate an intrinsic feature, such as the hyperexcitability, of these diseases (for reviews see Sand, 1991; see also Chen, 1993a). Furthermore, enhanced slow wave activity in the theta band (4–7 Hz) may also indicate an active reaction of a subject to lower the perception of pain (Larbig et al., 1982). These latter authors described augmented PSD in the theta band in a fakir during self-induced hypnosis-like states in expectation of painful electrical shocks. High-amplitude theta waves were also observed in the fakir during execution of his ‘professional’ pain control demonstrations (see also Larbig, 1994). It is interesting that the appearance of high amplitude and regular theta activity has also been related to efficient stress coping in human subjects exposed to extreme environmental conditions, such as experimental deep diving (Lorenz et al., 1992) or prolonged isolation and confinement in a simulated space-flight (Lorenz et al., 1996). Therefore, it is evident that not only the perception of pain or stress, but their active control by the subject applying trained mental skills may be indicated by EEG phenomena as well.

3.2. Pain-related evoked electric and magnetic activity

The poor utility of spontaneous brain electric or magnetic activity to extract pain-specific information by the traditional frequency bandwidths certainly reflects the fact that brain produces many activities at the same time which are not related to the actual event, e.g. pain. Much more successful are investigations of evoked brain potentials (EP) and fields (EF) in response to stimuli inducing phasic pain. In these experiments ongoing brain activity, the spontaneous EEG or MEG, may be regarded as ‘noise’ which can easily be diminished by conventional averaging techniques. The clinical usefulness of the visual, auditory, or somatosensory evoked cerebral potential is widely established in the diagnosis of pathological alterations of the sensory channel examined. In the following the assessment of the nociceptive system in humans by means of pain-relevant changes in evoked brain potentials will be reviewed.

In particular, so-called long latency components have been identified as correlates of pain perception; with respect to earlier literature the reader may be referred to, e.g., Chapman et al. (1979), Chudler and Dong (1983), or Bromm (1984). Early somatosensory evoked brain potentials reflecting the entrance of the stimulated afference in the cortex (S1) have not been observed in response to pain inducing stimuli so far, which should not – in the case of Aδ-fiber activation – appear before 80 ms, on average, in the case of hand stimulation. The following major reasons for the lacking observation of SI responses in EEG analyses have been discussed. The nociceptive system projects mostly to SI area 3b, located in the deep posterior wall (layers II through V) of the central sulcus (for review see Kenshalo and Douglass, 1995). Nociceptor terminations tend to be organized in aggregations, intermingled with those of low-threshold neurons belonging to the mechanoreceptive system. Therefore, nociceptive afferents represent only a small subpopulation of the afferent somatosensory volley into SI, rendering the degree of neuronal synchronization very small in response to noxious stimuli. Furthermore, the large variability of activation times and conduction velocities among peripheral nociceptive fibers fails to yield a sufficiently exact time-locking to the stimulus onset for primary responses in order to be revealed by averaging techniques (Bromm, 1985).

However, late components are broadly agreed to reflect cognitive processing of the stimuli, for example, stimulus localization or magnitude estimation (for review see Picton, 1988; Handwerker and Kobal, 1993). They can be induced, in principle, by all kinds of stimuli, electrical nerve stimulation, visual, auditory, or olfactory stimulation. Therefore, the late brain potentials investigated in pain research are by no means specific for pain in the sense that they only appear if pain is felt (for review see Bromm, 1985, 1989). They depend on the activated sensory channel, on the neuronal distance to be conducted, on body area and fiber spectra stimulated. They also depend on the arousal level of the
subject, on his vigilance, on attention and distraction. By means of highly sophisticated statistical methods, e.g. application of the principal component analysis (PCA) which decomposes the average wave form into statistically independent factors, so-called principal components, Bromm and Scharein (1982a) defined two components as pain-relevant, since they correlate significantly and exclusively with the subjects reported pain and were specifically attenuated by analgesic drugs (for details see Scharein and Bromm, 1998). These two pain-relevant components are part of the late N2-P2 complex. With an appropriate pain model which selectively or predominantly activate the thin fibers of the nociceptive system, and with adequate experimental designs which control the vigilance level of the subject being investigated, the N2-P2 amplitude differences can be used as an objective estimate for the induced degree of phasic pain.

Table 2 summarizes the most important demands on a pain-inducing stimulus in evoked potential designs. The first two statements are self-explaining. Moreover, stimulation should be possible at any anatomical location and should not exceed neurophysiological standards of technical ease and costs regarding personnel and equipment. The easiest and most successful way of stabilizing vigilance in our opinion is the random application of stimuli varying with respect to intensity and interstimulus interval. The patients are informed about the design with different stimulus intensities so that they will anticipate each stimulus as potentially most painful. They are furthermore instructed to carefully rate the perceived pain sensation after each stimulation with a delay of several seconds prompted by the occurrence of an acoustic signal. This latter auditory stimulus may also serve to average vertex potentials to control vigilance level from a non-nociceptive event (for details see Bromm and Meier, 1984; this way the epidemis serves as electrical insulator channeling the current directly into the immediate vicinity of the superficially located cutaneous nociceptors. Once the stimulating electrodes are properly mounted there is good reliability of pain intensity over repeated stimulation blocks. These properties rendered this pain model particularly valid to investigate basic psychophysiological questions related to pain or to test efficacy of analgesic substances (for review see Scharein and Bromm, 1998).

A chemical nociceptive stimulation is feasible by application of algogenic substances or lowering pH within a circumscribed skin area (for review, see e.g. Reeh and Steen, 1996). The very slow onset and disappearance of the response, e.g. after topical applications of substances like capsaicin or mustard oil are, however, incompatible with evoked potential applications. Sufficiently rapid local pH reductions have been achieved in the human nasal mucosa by brief changes of CO2 concentrations in a constant flow of air as carrier gas, a method originally developed for assess the olfactory sense (Kobal, 1985; Kobal and Hummel, 1988; Hummel et al., 1992, 1994). This model has also been applied in studies to evaluate analgesics (for review see Handwerker and Kobal, 1993).

Contact heat administered with peltier element in a probe that is held upon the skin has also been used in pain research (Fruhstorfer et al., 1976). It has been developed meanwhile into powerful tools with modern computer-assisted apparatus for quantitative sensory testing in clinical neurophysiology (Verdugo and Ochoa, 1992). However, contact heat lacks sufficient steepness of the stimulus time profile so that it is largely inappropriate for an evoked potential application.

In our opinion the best ‘career’ among all candidates of pain stimuli that have been used for the neurophysiological evaluation of pain in human subjects has been made by the brief radiant heat pulse delivered by a laser beam. Since the first report by Mor and Carmon (1975), a great number of working groups from theoretical and clinical areas adopted and refined the method of laser-evoked potentials (LEPs). The applicability of the laser stimulus all over the human

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Table 2

| Experimental prerequisites for the measurement of pain-relevant evoked potentials |
|---------------------------------|---------------------------------------------------------------------------------|
| 1.                              | The stimulus should induce defined pain without damaging the tissue             |
| 2.                              | The stimulus has to be steep and short in order to induce a defined activation time for stimulus-locked averaging |
| 3.                              | Repeated test blocks should be balanced over different dermatomes in patients (e.g. unaffected-affected-affected-affected) |
| 4.                              | Interstimulus intervals should randomly vary (e.g. 8-20 s) in blocks not longer than 15 min |
| 5.                              | At least two different intensities (e.g. 1.5- and 2-fold pain threshold) should be randomly applied within a block in order to stabilize vigilance and attention |
body rendered LEPs particularly appropriate for clinical neurophysiologists concerned with the assessment of sensory deficits in neurological patients. A modern generation of stimulators and their computer surroundings meanwhile fulfill the properties of equipment with which a clinical neurophysiologist is used to work. We will review the literature on LEPs in detail in Section 4.

3.3. Scalp topography and brain sources.

Knowledge about brain areas involved in the processing of pain has mostly been accumulated by invasive techniques in animals or in man subjected to surgery partially to alleviate intractable chronic pain. Recently, modern neuroimaging techniques have been developed and refined to monitor normal and disturbed cerebral function noninvasively in the awake human being, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), multi-lead electro- (EEG) and magnetoencephalography (MEG). PET and fMRI do not directly measure neuronal brain activity itself, but secondary changes in metabolisms and local blood circulation in reaction to the event, appearing with a delay in the range of seconds. In contrast, EEG and MEG monitor neuronal synchronization of brain activity concomitant to processing of external or internal events in the range of milliseconds.

With the fulminant development and refinement of hardware and software for measuring topographical brain maps of electrical potentials and magnetic fields, source analyses have become the most promising tool to identify and localize structures in the human brain which are active during a given mental process. In principle, high synchrony of activation in assemblies of neurons, particularly those which form large parallel columns of cortical axons and dendrites (e.g. pyramidal cells), produce local currents which are modelled by an ‘equivalent current dipole’ (ECD) or ‘generator,’ identified by the produced potential differences and magnetic fields and defined by its site, strength and orientation (6 coordinates); for a more detailed description of the physical background of these terms the reader may be referred to, e.g. Williamsen and Kaufmann (1981), Scherg (1989), or Hämäläinen et al. (1993). Physically spoken, the dipole is part of a closed circuit: currents strive through the surrounding tissues back to their origin. The extracellular currents are the so-called volume currents; they play the decisive role in the generation of the EEG but do, of course, also modify the magnetic fields.

The first modern technique to gather information about brain processing of perceived stimuli was brain potential mapping. Multi-lead data were picked up with as many electrodes as possible, e.g. 124 (Gevins et al., 1994), from which potential distributions were interpolated at each site of the scalp and at each time point measured. This way an enormous amount of data was collected for all sensory channels (for review see Duffy, 1986; Pfurtscheller and Lopes da Silva, 1988; Lehmann, 1989). With respect to pain, the first brain maps in response to painful tooth pulp stimuli were presented by Chatrian et al. (1975), illustrating a bilateral symmetrical distribution of both the late negative (N2) and positive (P2) components at 150 ms and 230 ms, respectively. Their maximum at the vertex was assumed to stem from deep brain structures, e.g. the limbic system (see below). This scalp topography was confirmed by many laboratories, e.g. for painful electrical skin stimuli (Buchsbaum and coworkers, for review see Buchsbaum, 1984), for LEPs derived from hand or foot stimulation (Treede et al., 1988a), or temple (Bromm and Chen, 1995; Treede et al. (1988a), in addition, observed an earlier negative component which appeared after 170 ms maximally over contralateral temporal electrode positions (N1; middle latency component). In further studies, especially with multichannel MEG, negative components were localized in primary and secondary somatosensory cortex areas (Hari et al., 1983; Hutton et al., 1986; Kunde and Treede, 1993; for more recent literature see below).

An essential improvement in functional brain map interpretations was the introduction of BESA, the brain electrical source analysis (Scherg, 1989), which allows the calculation of multiple dipoles with a spatio-temporal overlap in activity, based on the assumption that brain potentials are generated by multiple cortical regions being simultaneously active. BESA applied to LEPs in response to left temple stimulation in repeated measurements with 31 scalp electrodes resulted in 4 generators with a surprisingly high intra-individual constancy (Bromm and Chen, 1995; Bromm et al., 1996): a prefrontal dipole with peak maxima between 80 and 130 ms was seen in the prefrontal cortex, probably indicating premotor activity or blink reflex contamination in response to the stimulus (see also Ellrich et al., 1997). Two dipoles were localized bilaterally in the upper banks of the Sylvian fissure and adjacent regions of the corresponding secondary somatosensory cortex (SII; peak latencies between 100 and 130 ms, ipsilaterally about 5 ms later than contralaterally). A long latency dipole 4 was identified in the middle section of the cingulate gyrus (Brodmann’s area 23/24), which bound most activity of both the large vertex negativity at 150 ms and the subsequent positivity around 250 ms. Table 3 presents the dipole coordinates, mean values and standard deviations, in the BESA coordinate system. The intraindividual standard deviation in site coordinates of each generator was as low as 4 to 6 mm, thus meeting the lower theoretical boundary of 5 to 10 mm depending on dipole depth in the cortex (Mosher et al., 1993). Of course, the interindivdual variability was considerably larger with standard deviations in site of up to 24 mm, since all sources were evaluated in a uniform spherical head model.

Comparable results with BESA applied to LEP data from hand stimulation were found by Valeriani et al. (1996); Fig. 1 illustrates LEPs of one representative subject (on the left) and the resulting 5 ECD solutions from grand mean data calculated by BESA (right). Four components were identi-
negative values indicate left hemisphere; Q

collected from 10 subjects in repeated sessions; re-detection accuracy is mean power averaged over the analysis period (70 to 250 ms). Data were

indicated by angles (the skull at Cz). Dipole orientation (from positive to negative polarity) is

and in the cingulate gyrus (135–160 ms, the latter more

to painfulness), 3 other sources in bilateral hippocampus

and Darcey, 1994) identified as many as 7 generators of

SEP in response to electrical sural nerve stimulation of

bound variance of N2b.

Dipole IV has two maxima with antiparallel orientations describing N150

a phase reversal in frontal regions. In contrast to Treede et

al. (1988a) and Bromm and Chen (1995), the N2 component

is split by the authors into N2a with maximal amplitude at

the vertex and higher amplitudes ipsi- than contralaterally to

stimulation, and N2b with a more frontal distribution. Finally, P2 again exhibited a vertex maximum. BESA eva-

luation (from positive to negative polarity) is

indicated by angles (Φ = xy plane, anticlockwise from the nearest x-axis, negative values indicate left hemisphere; Ψ = zy plane). Strength is the

mean power averaged over the analysis period (70 to 250 ms). Data were collected from 10 subjects in repeated sessions; re-detection accuracy is
given as standard deviations within (SDx) and between (SDy) subjects calculated from the individual maps.

Dipeole IV has two maxima with antiparallel orientations describing N150

and P220 (for details see Bromm and Chen, 1995).

Unlike EEG and MEG, PET does not depend upon high
degree of neuronal synchronization. The early notion by Penfield and Boldrey (1937) who failed to elicit any painful sensation in conscious neurosurgical patients when electrically stimulating SI does not really disprove its importance

in nociception. In fact, later authors described alterations of pain sensitivity in patients after discrete lesions of the soma-
tosensory cortex, both in terms of hypoalgesia (Marshall, 1951) or hyperalgesia (Sweet, 1982). Complete excision of SI in monkeys resulted in transient increases of pain threshold to pinprick, yet more prominent was a long-term inability to localize any stimuli on the contralateral body side irrespective of their painfulness (Peele, 1944). Also, the ability to perform intensity discriminations were found to be impaired in monkeys after bilateral ablation of SI areas 3a, 3b and 1 (Kenshalo et al., 1988; for review see Kenshalo and Willis, 1991). These findings point to the importance of the somatosensory cortex for the sensory-discriminative aspects of pain perception such as its decoding for spatial, intensity and temporal properties which we delineated above as the functional elements of the lateral pain system. An interesting new aspect of SI function, recently discussed by Mau-
guïere et al. (1997a), is a kind of top-down control of somatosensory input through serial feedforward and back-
ward projections, explaining unusually late SI activations in dipole source analysis of electrical SEPs, a phenomenon similarly observed after painful laser stimuli (Tarkka and Treede, 1993; Kohlhoff et al., 1997).

Another promising way of studying brain areas involved in nociception is perhaps the investigation of modulating effects of evoked potentials after phasic innocuous stimuli by simultaneous application of interfering tonic noxious stimulation. In the past, the interference approach identified interesting so-called ‘gating’ effects or cortical-cortical interactions at early cortical levels within the somatosensory system (e.g. Jones, 1981; Kakigi et al., 1995a, 1996; Schnit-

zler et al., 1995). Lorenz and Bromm (1997) adopted a similar approach to study later, perceptual-cognitive levels

### Table 3

Dipole coordinates of LEPs after trigeminal stimulation

<table>
<thead>
<tr>
<th>Site</th>
<th>Contralateral</th>
<th>Ipsilateral</th>
<th>Frontal</th>
<th>Vertex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency</td>
<td>106.3</td>
<td>112.1</td>
<td>130.4</td>
<td>150.6/220.5</td>
</tr>
<tr>
<td>Location (mm)</td>
<td>1.77/4</td>
<td>1.77/2</td>
<td>1.0/10.1</td>
<td>0.4/4.9</td>
</tr>
<tr>
<td>Lateral, x</td>
<td>-36.7</td>
<td>50.2</td>
<td>6.4</td>
<td>-1.4</td>
</tr>
<tr>
<td>SDx/SDy</td>
<td>0.9/13.5</td>
<td>2.7/6.6</td>
<td>5.0/10.9</td>
<td>2.07/1.1</td>
</tr>
<tr>
<td>Frontal, y</td>
<td>28.1</td>
<td>20.6</td>
<td>42.5</td>
<td>3.2</td>
</tr>
<tr>
<td>SDx/SDy</td>
<td>1.3/13.7</td>
<td>4.6/12.9</td>
<td>4.5/19.7</td>
<td>6.2/14.7</td>
</tr>
<tr>
<td>Vertical, z</td>
<td>21.5</td>
<td>15.2</td>
<td>16.2</td>
<td>36.7</td>
</tr>
<tr>
<td>SDx/SDy</td>
<td>2.6/12.7</td>
<td>1.7/14.8</td>
<td>5.0/23.9</td>
<td>2.8/11.1</td>
</tr>
</tbody>
</table>

Orientation (°)

Φ        | 24.8          | -21.5       | 82.7    | 59.059.0 |
Θ        | -119.4        | 117.3       | 106.3   | 16.1/-164.2 |
Strength | 5.3           | 1.8         | 1.7     | 8.77/6.7 |
(α/ω)     | 0.8/3.0       | 0.7/1.8     | 0.6/2.1 | 0.54/2.0 |
| SDx/SDy  |              |             |         |          |

Site parameters of dipoles are given in BESA coordinates evaluated from the grand mean maps (zero point = center of the best-fitting sphere; x = left to right; y = occipital to frontal; z = vertical direction penetrating the skull at Cz). Dipole orientation is given as standard deviations within (SDx) and between (SDy) subjects calculated from the individual maps.

Dipole IV has two maxima with antiparallel orientations describing N150 and P220 (for details see Bromm and Chen, 1995).
of interferences of different sensory modalities (visual, auditory) with tonic experimental pain.

With the introduction of MEG source analysis the fundamental capacity of secondary somatosensory cortices (SII) in the processing of afferent information, also of pain, became increasingly evident. SII areas were first described by Adrian (1941) in the cat, and still most findings stem from anatomical and microelectrode investigations in animal, mainly on monkey (for review see Brodal, 1981); it encircles cortical areas along the superior bank of the Sylvian fissure, lateral and posterior to the face representation in SI and anterior or medial to the primary auditory areas, the medial wall of temporal lobe, frontal parts of insula, and the parietal operculum. It exhibits some somatotopic organization though with a large overlap in space: the face is presented rostrally, the legs most caudally (Burton, 1986; Yang et al., 1993). SII receives input from SI, though the direct nociceptive innervation by the VPL thalamus is probably more dense (Stevens et al., 1993).

Obviously the SII dipoles in response to somatosensory stimuli exhibit a strong tangential direction, ideally detected in MEG source analysis. This is true for electrical medianus and tibialis nerve stimulation (Kakigi, 1994; Kakigi et al., 1995c; Maguieré et al., 1997a), chemical nasal stimuli (Huttunen et al., 1986; Hari et al., 1997), intracutaneous shocks in the finger tip (Joseph et al., 1991; Howland et al., 1995; Kohlhoff et al., 1997), or laser stimuli applied at the hand (Laudahn et al., 1995; Kakigi et al., 1995b; Maguieré, 1997). In the case of laser stimuli applied to the temple the dipoles exhibit a more radial component and could, therefore, more easily be detected in EEG source analysis (Bromm et al., in preparation), a finding which supports the somatotopy in SII with the manifold foldings and sulci.

In full agreement with the BESA results all authors found a bilateral coactivation, whereby the ipsilateral SII was generally activated 5 to 10 ms after contralateral SII. Recently Maguieré (1997) proved the involvement of human SII in the processing of laser stimuli by intracerebral recordings in selected patients demonstrating a reasonable agreement between results of source location analyses and direct invasive measurements. Activity in SII seems furthermore to depend on the arousal level of the subject and on the news value of the stimulus: It was considerably enlarged with stimuli delivered at long and random interstimulus intervals ranging up to 20 s (Wikström et al., 1996; Maguieré et al., 1997b), an essential prerequisite for the extraction of pain related components (see Table 2). Moreover, in a recent study Kohlhoff et al. (1998) demonstrated a short-duration attenuation of bilateral SII activity if subjects were anesthetized by ketamine, whereas clonidine led to dose-dependent sustained suppression, raising the evidence of a compound
reactivity of SII to analgesic and sedative effects of anaesthetics.

SII activity induced by noxious stimulation has been referred to the so-called sensory-discriminative component of pain because of its somatotopic organization, its stimulus response characteristics, the bilateral processing of afferent information, and its dependency on arousal and attention. This view is supported by the finding that after circumscribed lesions of the parietal operculum pain thresholds were augmented, whereas certain mental abilities, such as texture recognition, were decreased (Greenspan and Winsfield, 1992). Sinclair and Burton (1993) suggested that SI, representing a lower level of the somatosensory hierarchy, decodes the physical component elements of a somatosensory stimulus within a specific topography, whereas SII, at a higher processing level, but less topographically precise, contributes to a 'neural picture' of the complete object. Dong et al. (1994) suggested that pain-related deficits after lesions in SII may be a sign of somesthetic neglect, consistent with the hypothesis of Mishkin (1979) that SII might serve a role in somatosensation similar to that of the inferior temporal cortex in vision mediating object discrimination.

The other consistent phenomenon of brain source analysis with painful stimuli is the localization of long latency activity in the gyrus cinguli (GC). This generator strongly accounts for both, the large vertex negativity (N2) and the subsequent positivity (P2), observed in multi-lead EEG evoked by various kinds of noxious stimuli, and is most relevant for pain, the topic of this review: both components have been shown to correlate significantly with the painfulness of the stimulus, estimated by the subject; both components moreover are strongly attenuated by centrally acting analgesics and under narcosis (for review see Scharein and Bromm, 1998), as well as in patients suffering from a local loss in pain perception, as will be reviewed below. GC activation, therefore, is broadly agreed to reflect the aversive-emotional component of pain.

This most impressive late brain activity, however, cannot consistently be seen with MEG, probably due to the mainly radial direction of equivalent current dipoles as already shown in Fig. 1 (dipole 3; $\phi = 165^\circ$ for right hand stimulation) from the data of Valeriani et al. (1996) and documented in Table 3 (dipole IV; $\phi = 16^\circ \pm 164^\circ$ for right temple stimulation) from the data of Bromm and Chen (1995). In fact, the extracephalically measured magnetic fields in this latency range are very weak. Yet, modern software for source analysis such as ‘CURRY’ developed by Philips which uses the individual cortex morphology, scanned by MRI, can also be applied to multi-lead EEG data and is thus well able to identify radial brain sources in the deep cingulate gyrus. Fig. 2 illustrates results using CURRY in a healthy subject who was repeatedly stimulated by painful laser pulses at the left temple. EEG

![Fig. 2. Equivalent current dipole in the cingulate gyrus. LEPs in response to painful left temple stimulation were recorded with 31 EEG electrodes distributed over the scalp and evaluated by brain source analysis on the individual cortex anatomy. In the upper line the subject looks to the left, in the lower line to the front; electrode positions are marked in the MRI scans. In a latency range between 220 and 280 ms after stimulus onset a mass discharge in the cingulate gyrus was found which could be fitted by one moving dipole with an accuracy of 90% over the entire analysis period; maximum activity, however, changed in space moving from posterior to anterior sites (from Bromm et al., 1996).](image-url)
was recorded from 31 electrode positions. A one moving dipole could be fitted which explained more than 90% of total variance within the entire latency range between 220 and 280 ms. Interestingly, this dipole was nearly constant in direction, but the maximum neuronal activity moved in space, changing from more caudal sites (at 220 ms) towards the front, and disappearing at around 280 ms. The space solution was not sufficient to decide whether it arose from left or right hemispheric GC. This variability of location along the caudal-rostral extension of cingulate cortex can well be seen in context with functional neuroanatomical evidences described in animal and man (Brodal, 1981): The posterior parts of GC are broadly agreed to control emotional experiences in stimulus recognition, whereas medial and anterior parts exhibit intimate fiber connections with the septal nuclei and the amygdala and may probably play a role in behavioral responses to the stimulus applied.

Cingulate cortex has further been shown to be implicated in acute and chronic pain states by postison emission tomography (PET) studies in healthy subjects using experimental pain (Jones et al., 1991; Talbot et al., 1991; Coghill et al., 1994; Casey et al., 1994, 1996b; Vogt et al., 1996), or in patients with atypical face pain (Derbyshire et al., 1994), with painful mononeuropathy (Hsieh et al., 1995), and under dobutamine-induced angina pectoris (Rosen et al., 1984; for review see Chen, 1993b; Casey and Minoshima, 1997). PET studies also revealed the cingulate cortex to be involved in reduction of pain affect by hypnotic suggestions which were thought to have selectively diminished unpleasantness, but not intensity perception of noxious stimuli (Rainville et al., 1997).

The roles of the amygdalar nuclei and hippocampal formation in pain perception are not yet clearly elucidated. It is interesting, however, that nearly all subcortical and cortical nociceptive structures mentioned so far have connections with the amygdaloid complex: ascending and descending pathways of the brain-stem, medial thalamus, insula and cingulate cortex (Nieuwenhuys et al., 1988). Electrical stimulation of the amygdala produced somatic, cardiovascular and respiratory components of stress and emergency (Schwaber et al., 1980). Kuypers (1982) postulated that the amygdala may activate the descending antinociceptive pathways, suppressing pain transmission during the execution of motor actions of vital priority. Also, Bernard and Besson (1990) speculated that this system could be involved in the emotional-affective, behavioral and automatic responses to noxious events as mediator of the general defense reaction. The close relationship of hippocampus and amygdala may point to the importance of learning and memory for these reactions. A great variability of involvement of amygdala and hippocampus in phasic experimental pain can certainly be related to the fact that most stimuli, especially phasic thermal pain, elicit more pronounced sensory-discriminative rather than affective reactions (Rainville et al., 1992).

4. Laser application in clinical neurophysiology

4.1. The method of laser-evoked potentials (LEPs)

The wavelength of infrared radiation has to meet one of the water absorption maxima of the tissue to be stimulated. This way heat energy is completely absorbed within the most superficial skin layers and activates nociceptors rather specifically (Kenton et al., 1980; Bromm et al., 1984), presumably through capsaicin-sensitive ion channels (Caterina et al., 1997; Kirschstein et al., 1997). Most investigations on LEPs were performed with the CO₂-laser (10.6 μm); usually pulse durations between 20 and 60 ms are applied (for review see Bromm and Treede, 1991). Recently, a thulium crystal laser was designed for neurological applications (Kazarians et al., 1995; Spiegel et al., 1996; Weiss et al., 1997); the short radiation of 1.8 μm can still be conducted by glass-fiber optics for the examination of any body site necessary; pulse durations are between 1 and 3 ms. Willer et al. (1979) used visible argon laser light as pain stimulus which Arendt-Nielsen and co-workers refined for LEP measurements using pulse durations of 200 ms (Arendt-Nielsen and Bjerring, 1988). However, the wavelength of 488–515 nm does not meet a water absorption maximum, is in the visible range and strongly depends upon skin pigmentation.

Within certain limits of stimulus durations (5–50 ms), the threshold energy (intensity times duration) of CO₂-pulses to elicit pain was found to be constant (Biehl et al., 1984). Longer pulse durations need higher energies due to heat conduction into neighboring tissue. Similarly, density of threshold energy (energy per skin area) was found to be constant for areas between 5 and 40 mm². Smaller and greater areas require higher and lower energy densities, respectively, because of interaction with the size of the receptive fields and spatial summation. Within these limits of the two parameters the mean pain threshold energy density of infrared laser stimuli was documented by various groups in the range between 9 and 14 mJ/mm² for the CO₂-laser (Biehl et al., 1984; Kakigi et al., 1989; Bromm and Treede, 1991; Gibson et al., 1991; Kakigi and Shibasaki, 1991), or around 12 mJ/mm² for the thulium laser (Kazarians et al., 1995; Spiegel et al., 1996). These values, furthermore, fit well the recent report of energies between 8–12 mJ/mm² to induce a withdrawal response and a reproducible vertex potential in monkeys (Beydoun et al., 1997). In contrast, visible argon laser light requires approximately twice as much energy to induce pain (Arendt-Nielsen and Bjerring, 1988).

Laser stimuli are felt as sharp, pungent pain, less localizable and scalable with respect to intensity than the conventionally applied pinprick. Simultaneously, the stimulus evokes late brain potentials which consist of a negativity (usually called N2) followed by a large positive component (P2) both with vertex (Cz) position maxima. The peak latencies depend on the body site stimulated, the conduction velocity of the fiber spectrum activated, and the kind of
laser stimulator used. Table 4 summarizes results among various laboratories with respect to norm values and standard deviations of latency and amplitude. Usually 1.5- to 2-fold individual pain threshold intensity is used in order to elicit reliable pain and brain potentials. Peak latency differences of the vertex negativity N2 between the different laser types reflects the importance of different stimulus durations used. Rise times to temperature maximum are in the order of 2 ms, 20 ms and 200 ms for thulium, CO2 and argon laser, respectively. Same laser stimuli applied to different body sites, on the other hand, give evidence for the fiber spectrum activated by infrared radiant heat pulses: CO2-laser stimuli administered to distal and proximal parts of the upper limb in 11 healthy subjects resulted in a latency difference of N2 which yielded a conduction velocity estimate of 14 m/s, which is in the range of A-fibers (Bromm and Treede, 1987b). The relatively short latency difference between N2 after hand (249 ms) and foot (273 ms; see Table 3) stimulation in the data of Bromm and Treede (1991) is ascribed to a shorter nociceptor activation time due to the thinner skin at the foot (see also Treede et al., 1988a).

The reliability of thulium-evoked LEPs and laser pain ratings over repetitive stimulus blocks and sessions was studied by Kazarians et al. (1995) in 10 healthy subjects. In order to minimize peak latency jitter they used upper trigeminal nerve stimulation (left temple) to make the neuronal distance between stimulation and recording sites as small as possible. Typically, N2 was found around 150 ms, P2 around 230 ms. The variances in the LEP waveforms within subjects in repeated sessions and blocks up to 3 weeks apart were found to be extremely small. Obviously, given a good experimental control of the recording condition, the LEPs are a stable response of an individual. One of the most important prerequisites is a careful control of vigilance and attention even in the long-lasting sessions, as will be discussed below. In contrast, the variability of LEPs between subjects was large: obviously each subject generates his own typical LEP in response to painful radiant heat stimulation. As a consequence, LEPs are required to be investigated in the individual, which is important for both experiments with drugs or other pain-reducing modulations and in patients examining healthy versus distorted body areas, as will be reviewed below.

Evoked potential correlates of second pain mediated by C-fibers in man using brief laser stimuli were first described and substantiated through continuing work by Bromm and colleagues (Bromm et al., 1983; Bromm and Treede, 1987a,b; Treede et al., 1988b; Lankers et al., 1991). Obviously, reliable elicitation of the so-called ultralate LEPs in the healthy volunteer is only achieved if the A-fibers are blocked, e.g. by pressure, and latency-adaptive averaging of the EEG is performed (Bromm and Treede, 1987b). As will be described below, ultralate LEPs can also be demasked in patients if damage to the nociceptive fibers predominantly involves A-fibers while sparing the C-fibers.

Second pain of burning character could also be elicited when using repeated stimuli of short intervals both with electrical shocks (Price, 1972) and thermal contact heat (Price et al., 1977). Such stimulations produce ‘wind-up’ of C-fibers by temporal summation. Similar to the results with brief radiant heat, application of a pressure block of A-fibers yielded progressive attenuation of an electrically elicited late component (N140/P220) in parallel with reduction of first pain sensitivity while at the same time a positivity at 1200 ms as correlate of preserved second pain through C-fiber activation appeared (Harkins et al., 1983).

The reason why myelinated fibers have to be blocked for ultralate LEPs components to appear reflects the physiological phenomenon that perception of first pain, being a novel event, dominates over second pain being always announced by first pain (for detailed discussion see also

### Table 4

<table>
<thead>
<tr>
<th>Reference</th>
<th>Stimulation site</th>
<th>Stimulation area (mm²)</th>
<th>Pulse duration (ms)</th>
<th>Intensity (mJ/mm²)</th>
<th>Latency N2</th>
<th>Amplitude N2</th>
<th>Latency P2</th>
<th>Amplitude P2</th>
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</thead>
<tbody>
<tr>
<td>Arendt-Nielsen and Bjerring (1988)</td>
<td>Hand</td>
<td>7</td>
<td>200</td>
<td>48.58</td>
<td>400</td>
<td>500</td>
<td>19.0 ± 6.0</td>
<td>7.3 ± 2.8</td>
</tr>
<tr>
<td>Bromm and Treede (1991)</td>
<td>Hand</td>
<td>20</td>
<td>20</td>
<td>14-16</td>
<td>249</td>
<td>391</td>
<td>5.5 ± 5.2</td>
<td>17.4 ± 7.3</td>
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<tr>
<td></td>
<td>Foot</td>
<td>20</td>
<td>20</td>
<td>14-16</td>
<td>273</td>
<td>427</td>
<td>5.8 ± 5.1</td>
<td>14.5 ± 6.6</td>
</tr>
<tr>
<td>Kazarians et al. (1991a)</td>
<td>Hand</td>
<td>3</td>
<td>20</td>
<td>18-20</td>
<td>240</td>
<td>335</td>
<td>2.1 ± 1.2</td>
<td>6.7 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>Foot</td>
<td>3</td>
<td>10</td>
<td>18-20</td>
<td>296</td>
<td>407</td>
<td>1.5 ± 0.8</td>
<td>4.4 ± 2.8</td>
</tr>
<tr>
<td>Gibson et al. (1993)</td>
<td>Hand</td>
<td>20</td>
<td>33-66</td>
<td>25</td>
<td>277</td>
<td>400</td>
<td>12.1 ± 9.0</td>
<td>25.0 ± 7.0</td>
</tr>
<tr>
<td>Beydoun et al. (1995)</td>
<td>Hand</td>
<td>28</td>
<td>60</td>
<td>8-13</td>
<td>233</td>
<td>369</td>
<td>15.8 ± 8.1</td>
<td>25.8 ± 14.0</td>
</tr>
<tr>
<td>Kazarians et al. (1995b)</td>
<td>Temple</td>
<td>20</td>
<td>2</td>
<td>16-20</td>
<td>150</td>
<td>230</td>
<td>11.6 ± 6.0</td>
<td>12.8 ± 5.6</td>
</tr>
<tr>
<td>Spiegel et al. (1996b)</td>
<td>Hand</td>
<td>20</td>
<td>3</td>
<td>27</td>
<td>208</td>
<td>328</td>
<td>30.4 ± 10.8</td>
<td>12.3 ± 6.9</td>
</tr>
<tr>
<td></td>
<td>Foot</td>
<td>20</td>
<td>3</td>
<td>27</td>
<td>248</td>
<td>378</td>
<td>22.3 ± 6.9</td>
<td>13.7 ± 7.0</td>
</tr>
</tbody>
</table>

- Argon laser of wavelength 488 nm (blue) and 515 nm (green) used.
- Only peak-to-peak amplitude differences reported.
- Thulium crystal laser (1.8 μm) used.
- These high intensities were applied to study responses in SII.
Bromm and Desmedt, 1995). Short intervals between successive stimuli are known to diminish long-latency evoked potentials (e.g. Angel et al., 1985). Bromm and Treede (1987a) applied laser double pulse stimulations at the dorsum of the hand and observed a 40% amplitude reduction of LEPs if elicited 900 ms after a preceding stimulus of same intensity. This interstimulus interval corresponds to the delay between first and second pain. Presuming that the central generators of first and second pain are largely the same, one may argue that the short interval between both pain sensations does not allow the activated processes to fully return to prestimulus conditions. When using a nerve block, however, C-fibers are the only afferents transducing and conducting the pain stimulus and can therefore recruit the full central response.

The relative activation of Ad- and C-fibers seems to depend upon intensity of the laser beam. Using the temperature-controlled CO2-laser both in monkeys and human subjects Treede et al. (1994) were able to compare the stimulus-response curves of human LEPs and the correspondent pain ratings with recruitment curves of Ad- and C-nociceptors of monkeys (Fig. 3). At 48°C, 50% of Ad-fibers were activated, and more than 50% of the stimuli were perceived as pricking pain. However, for a good elicitation of an LEP, stimuli of 50°C were needed at which more than 90% of the stimuli were rated as pricking pain. Interestingly, the recruitment curves of C-nociceptors were about 4°C to 6°C shifted to lower temperatures as were the 50% incidence of any sensation relative to a detection as pricking pain. Comparative stimulus-response functions for ultralate and late LEPs could not be studied due to the reasons mentioned above. However, in good agreement with the evidence of intensity-dependent differences of recruitments of C- and Ad-fibers, Bragard et al. (1996) demonstrated greater reliability of ultralate LEPs when using lower intensities and smaller stimulated areas. With respect to the latter effect the authors argued that C-fibers have a higher relative density in the skin compared with Ad-fibers, thus the probability to selectively hit a C-fiber is higher with smaller stimulus areas.

4.2. Exogenous and endogenous components within LEPs

Current terminology of evoked potentials denotes components as ‘exogenous’ if they primarily depend on physical characteristics of the eliciting stimulus (e.g. quality, intensity, duration) and contrasts them against ‘endogenous’ components which reflect predominantly psychological categories of stimulus content (e.g. novelty, task relevance). As a general rule, one can say that the longer the latency of a component the more likely does it depend upon endogenous factors (Picton and Hillyard, 1974). Pain-relevant evoked potentials are late or long-latency brain potentials which appear in the time range in which cognitive potentials are usually observed, such as the P300 (P3), first described by Sutton et al. (1965). Several authors, therefore, conducted studies with the aim to discriminate exogenous and endogenous components in pain relevant evoked potentials (Miltner et al., 1989; Becker et al., 1993; Towell and Boyd, 1993; Siedenberg and Treede, 1996; Kanda et al., 1996a; Zaslansky et al., 1996a,b; Yamamoto et al., 1996; Lorenz et al., 1997a,b, 1998b; García-Larrea et al., 1997).

In fact, pain-relevant evoked potentials show several properties which are usually ascribed to endogenous components, such as the dependence on the arousal level of the subject, on attention towards the stimulus event, or habitua-
tion in response to repeated stimuli. All these features, however, are also characteristic for the stimulus-induced pain (Bromm and Scharein, 1982b; Bromm, 1985; Kobal and Hummel, 1988; Bromm and Treede, 1991; Arendt-Nielsen, 1994). For an adequate discussion of this issue it is, therefore, necessary to clearly differentiate different aspects of attentional effects on brain potentials: on the one hand, sensory activity has been shown to depend upon tonic and phasic fluctuations of arousal and attention even at rather early cortical processing stages (Desmedt and Tomberg, 1989), probably indicating a kind of priming of modality-specific neurons (e.g. in SI) in order to enhance their functional efficiency. On the other hand, sensory specificity of the evoked neuronal activity becomes weaker at later stages, indicating higher hierarchical levels (e.g. cingulate cortex) at which the involved processes serve the purpose of perception and cognition for any sensory channel being scanned at a given moment through the mechanisms of orienting and focusing of attention.

As latency criteria are generally important for the distinction between exogenous and endogenous components, it is mandatory to carefully consider differences in conduction time between different stimulus qualities and sites (auditory, electrical, visual), or different fiber spectra involved in order to differentiate whether P2 of LEPs might be a P3-like component. P2 belongs to the biphase wave form often referred to as the ‘vertex potentials’ known for any sensory modality. However, P2 of electrical somatosensory evoked potentials (SEPs), for example, appears about 120 ms earlier than the P2 of LEPs (Treede et al., 1988a) due to different conduction velocities of activated fibers (Aβ- versus Aδ-fibers). Given the occurrence of a P3 after electrical finger stimuli at 400 ms (Desmedt and Robertson, 1977), a P3 after laser stimulation should be expected at a latency of 520 ms. In fact, using the typical ‘oddball’-paradigm a laser P3 after hand stimulation appeared around 600 ms, which could clearly be separated from the P2 (Towell and Boyd, 1993; Kanda et al., 1996a; see also Siedenberg and Treede, 1996). For these reasons one may criticize the suggestion of, e.g., Zaslansky et al. (1996b) who regarded the P2 of LEPs as a typical P3 wave indicating implicit cognitive appraisal of obtrusive painful stimuli, merely based upon the dependency of its amplitude upon the oddball factors. These authors, furthermore, failed to even differentiate P2 and P3 in their auditory oddball control task (for more details see Lorenz, 1997).

Though LEPs in patients will be reviewed in the next sections, evidence for the dissociation of P2 of LEPs and P3 may be obtained by their differential sensitivity towards effects of certain diseases or drug treatment. An example is given in Fig. 4 from a study with 25 demented patients (Yamamoto et al., 1996). The degree of cognitive decline, assessed by psychological tests, correlated stronger with auditory P3 latency than with P2 latency of LEPs. Half of the patients had absent P3 whereas only the 4 most severely demented patients additionally failed to show an LEP. Furthermore, unlike the auditory P3 latency, the laser P2 latency did not correlate with age. Thus, the authors concluded that pain perception is altered in severely demented patients, but this aspect of decline of mental function is apparently different from their cognitive deficits as measured by the auditory oddball P3. Clear divergence of the P2 of LEPs and auditory P3 has been furthermore reported in chronic pain patients under the effect of morphine (Lorenz et al., 1997b) and in a patient with a circumscribed total loss of sensitivity in one arm due to a conversion disorder (Lorenz et al., 1998b). To sum up, there is sound evidence that P2 of LEPs and P3 do not represent identical neurophysiological phenomena. Yet, a laser P3 may well appear occasionally without the classical oddball instructions, but in our experience it is not a regular phenomenon over repetitive stimuli in a standard laser paradigm.

4.3. LEPs in patients with disturbed pain sensitivity

The LEP method has meanwhile achieved predominance in neurological applications concerned with the documentation of pain sensitivity disturbances in patients. As already described, the laser beam offers the advantage of a natural pain stimulus with very good experimental control and application all over the human body surface including accessible parts of the oral mucosa (Svensson et al., 1992). The diagnostic rationale of using LEPs in adjunct to standard transcutaneous electrical SEPs stems on the neuroanatomical and functional divergence of nociceptive and mechanoreceptive fibers and their projecting pathways which are distinctly activated by these two types of stimuli (Treede et al., 1988a). Principally, any differential pathol-
ogy or lesion of mechanoreceptive and nociceptive fibers or of their projections, clinically presenting with a so-called dissociated sensory loss, are expected to yield a divergence of SEP and LEP findings.

As mentioned above, comparison of affected with unaffected dermatomes within a patient, typically on the contralateral side, is generally preferable to interindividual comparisons. Based on 18 patients with dissociated sensory losses of various etiologies, Bromm et al. (1991) regarded side differences in LEP amplitudes of 50% as pathological, a value also adopted by Hansen et al. (1996) in patients with lateral brain-stem lesions. Beydoun et al. (1993; n = 20) and Hansen and Treede (1995; n = 10) reported 28% and 35% as abnormal side differences, respectively, calculated as 3 standard deviations above the mean relative side differences derived from healthy subjects. There is some age dependency in LEP latencies and amplitudes (Gibson et al., 1991). Subjects above 80 years exhibit a delay of about 50 ms compared to subjects between 20 and 40 years, and amplitudes were found to decline about 50% for subjects above 60 years compared with those below this age.

4.3.1. Polyneuropathy and peripheral nerve disease

Polyneuropathies (PNP) are complex diseases of the peripheral nervous system with various underlying etiologies comprising sensory, motor and autonomous fibers. Clinically, stocking- and glove-like patterns of sensory deficits are typical for PNP which may impose as uniform or dissociated sensory impairment. The reason for dissociation of sensory deficits in PNP is not fully understood. There is some evidence that thin afferents are more vulnerable to ischemia than thick afferents (Parry and Brown, 1982). Some types of hereditary sensory-autonomous neuropathies exhibit characteristic predominance of thin myelinated afferent fiber affections.

Kakigi et al. (1992c) examined 30 patients with PNP of different etiologies and found a significant correlation between the latency of the LEP positive component (P400) after foot stimulation with the degree of clinical impairment of the pain sense. No correlation was present with clinical measures of mechanoreception. In contrast, latencies of N20 and P40 from SEPs exhibited the expected opposite constellation of correlation with mechanoreception, but not with nociception. These results extended the authors’ earlier findings in 10 PNP patients in whom histopathologically examined densities of small and large myelinated fibers of the sural nerves showed a positive relationship with LEPS and SEPs, respectively (Kakigi et al., 1991b). They concluded that the combined analysis of SEPs and LEPS may serve to delineate the afferent fiber specificity of PNP manifestations providing information which are otherwise only available by invasive nerve biopsy. Consistent with this view, Cole et al. (1995) as well as Yamamoto et al. (1997b) verified selective large myelinated fiber affections in single cases with neuropathies by finding abnormal SEPs together with normal LEPS.

Some PNP patients may exhibit ultralate LEPS as correlate of preserved C-fiber function when the Aδ-mediated input is strongly reduced or lost due to demyelination. Such a patient who suffered a hereditary motor and sensory neuropathy (type I) exhibited attenuated late, but pronounced ultralate LEPS after stimuli applied to both upper and lower limbs (Lankers et al., 1991). In this patient, an altered balance in favor of stronger relative C-fiber spinal input due to peripheral demyelination is thought to have mimicked the effects of an experimental nerve block, characterized by the attenuation of late LEPS and unmasking of ultralate LEPS. Clinically, the patient showed dysesthesia and pain and a phenomenon of abnormal summation or ‘wind-up’ in response to repetitive pinprick stimulation at a 1-Hz rate. At such a stimulation rate, healthy subjects perceive each pinprick as a single and sting ing pain. The patient, however, reported very soon a sensation of ongoing burning pain and inability to discriminate single pinpricks.

We think that wind-up as a typical feature of spinal processing of C-fiber input (Mendell, 1966) may contribute to ongoing pain and dysesthesia in some PNP patients, and that unmasking of ultralate LEPS in these patients may be a cortical correlate of enhanced C-fiber response after laser stimulation (see also Treede et al., 1995a).

Nerve-block experiments supported the view that mechanical pressure affect thick fibers more than thin fibers, whereas their vulnerability towards ischemia may be just opposite. In an attempt to delineate the involvement of thin afferents in carpal tunnel syndrome to indicate the importance of ischemia rather than pressure for this condition, Arendt-Nielsen et al. (1991) examined LEPS after Argon laser stimulation. The LEP amplitudes (measured as power between 0.5 to 7.5 Hz of the evoked response) of 13 patients with carpal tunnel syndrome after stimulating their most affected third fingers innervated by the median nerve were significantly lower than those of matched controls, whereas responses related to finger 5 innervated by the ulnar nerve did not differ between groups. There was no correlation between LEP power and electrophysiological markers of thick afferent and efferent fibers (sensory and motor conduction velocity). SEPs were not included in this study. The study provided evidence of thin afferent fiber involvement in this type of peripheral nerve disease which the authors related to the importance of intraneural ischemia.

Another important location for manifestation of peripheral nerve affection is the dorsal root. It is documented in the literature that SEPs can fail to verify the sensory deficits of a dorsal root affection, e.g. by herniated discs or spondylolisthesis, if only one or two spinal segments are involved (Aminoff et al., 1985; Schmidt et al., 1988). Textbooks of neurology describe the clinical experience of a narrow analgesic stripe as a typical feature of sensory loss in monoradiculopathy with or without a broader band of painful dysesthesia in the corresponding dermatome of the affected root (Mumenthaler and Schiack, 1993). A complete dermatomal anesthesia occurs only when 3 or more adjacent spinal segments are
involved. In a patient with unilateral radiculopathy, Lorenz et al. (1996a) could verify this evidence by the observation of a very sharp border between dermatomes of affected and unaffected dorsal roots as indicated by psychophysical measures of pain sensitivity and LEPs (Fig. 5). In contrast, SEPs after electrical and mechanical stimulation showed no or only minor changes. The reason for this differential manifestation of mechanoreceptive and nociceptive deficits in mono- or oligosegmental dorsal root lesions is seen in greater overlap of tactile dermatomes compared to pain dermatomes. The LEP method may, therefore, be applied in cases where an objective documentation of the spinal level of a dorsal root lesion is required.

4.3.2. Spinal and supraspinal lesions

The previous section demonstrated that in distinct peripheral nerve pathologies a dissociation of nociception and mechanoreception may be present, yielding LEPs as relevant source of information about thin fiber function supplementing SEPs. However, due to the close anatomical association of thin and thick afferents within a mixed nerve trunk, circumscribed structural neuronal damage in the periphery exhibits in most cases a uniform sensory deficit. In contrast, within the spinal cord there is a clear separation of mechanoreceptive and nociceptive fibers which is the basis for typical spinal syndromes characterized by a dissociated sensory disturbance. The anatomical extension of an intramedullary spinal damage will, therefore, determine the degree of dissociation of sensory symptoms.

LEPs have been documented as distorted or lost in patients with spinal pathologies clinically presenting with dissociated sensory loss. Bromm et al. (1991) investigated LEPs and SEPs in 18 patients suffering from dissociated sensory deficits due to syringomyelia, angioma, fistulae, myelitis, multiple sclerosis, Wallenberg and Brown-Séquard syndromes. In all patients the side differences of LEP amplitudes served perfectly to identify the body area with severest disturbances in pain and temperature sensitivity, whereas no alterations in SEPs were found, in agreement with the normal mechanosensitivity. The degree of LEP abnormality correlated best with degree of sensory deficits in those patients who suffered a localized destructive process in the anterolateral projection tracts, whereas smallest LEP changes were found in patients with inflammatory lesions despite the presence of considerable dissociated sensory deficits. Interestingly, in multiple sclerosis and HTLV-I-associated myelopathy, LEPs were also found to be abnormal without sensory symptoms (Kakigi et al., 1992a,b). Subclinical LEP abnormalities were further reported by Yamamoto et al. (1997a) in patients with Machado-Joseph disease, a subtype of cerebellar ataxias. Generally, it seems to hold that structural lesions yield greater correlations than inflammatory lesions between disturbed pain sensitivity, as detectable by clinical methods, and LEP abnormality, as already stated by Bromm et al. (1991).

In a group of 10 patients with syringomyelia, Treede et al. (1991) found absent LEPs in 8 cases and a significantly reduced LEP amplitude in one case. Interestingly, in the remaining patient, who had well-configured LEPs, only temperature sensitivity was lost, but pain sensitivity was intact. This can be reasonably explained by the fact that late LEPs are correlates of nociceptive Ad-fiber activation whereas warm sensation after laser stimulation is mediated by C-fibers. Also Ragazzoni et al. (1993) described a case of syringomyelia were LEPs were preserved in accordance with intact pain sensitivity despite the presence of a large syrinx extending from spinal level C2 to S3. LEPs were also lost in 7 of 8 syringomyelia patients in parallel with disturbed pain and temperature sensitivity examined by Kakigi et al. (1991a). A syringosubarachnoid shunt operation performed in 2 of these patients markedly improved sensory function rendering LEPs obtainable in postoperative sessions (see Fig. 6).

Evoked potential experience in syringomyelia agrees with the common view that electrical SEPs as correlate of thick fiber activation and dorsal column transmission misses abnormalities in the anterior commissure and anterolateral quadrant (Halliday and Wakefield, 1963; Desmedt and Noël, 1975; Chiappa, 1990). However, several working groups provided convincing evidence that the spinal N13 potential after electrical median nerve stimulation indicates dysfunction in spinal cord gray matter in syringomyelia that often coincides with clinical pain deficits (Urasaki et al., 1990; Restuccia and Mauguire, 1991; Kakigi et al., 1991a), but may also stay asymptomatic (Ragazzoni et al., 1993). N13 seems to reflect postsynaptic activity from a horizontally arranged ventro-posterior dipole in the spinal cord (Restuccia and Mauguire, 1991; Jeannond et al., 1991). Though obviously indicating different functional aspects, the combination of spinal SEPs and LEPs appears most promising to detect centromedullary spinal cord damage such as in syringomyelia.

Another lesion site typically affecting the nociceptive but sparing the mechanoreceptive system is the lateral brain-stem. In Wallenberg’s disease there is an infarction in the territory of the posterior inferior cerebellar artery (PICA), a branch of the vertebral artery, which supplies neuronal structures of the dorsolateral medulla oblongata, i.e. the spinthalamic tract, the descending spinal tract of the trigeminal nerve, the central descending sympathetic tract and pontocerebellar pathways. Accordingly, Wallenberg’s disease involves contralosional dissociated sensory loss of trunk and limbs, ipsilesional dissociated sensory loss of the face, ipsilesional Horner’s triad (miosis, ptosis, enophthalmus) and ipsilesional cerebellar ataxia. Hansen et al. (1996) recorded LEPs and SEPs in lateral brain-stem affections among which were 4 cases with Wallenberg’s disease and 1 case with brain-stem encephalitis. These authors reported the degree of recovery of pain sensitivity upon re-examination as being reflected in the extent of LEP normalization irrespective of whether the lesions were of
Fig. 5. Early somatosensory evoked potentials (SEPs) and laser evoked potentials (LEPs) in cervical radiculopathy. Top: early SEPs were recorded after electrical stimulation of the ulnar and median nerve at the wrist as well as after brief pressure pulses applied to all finger tips of the affected hand using a mechanical stimulator (Somedic TS 120). The 'numb' area in the dermatomes of C7 and C8 are indicated. Electrical SEPs were normal, mechanical SEPs showed only little changes in configuration and latency of P50 from digits IV and V. Bottom: in contrast to SEPs, absence of LEPs demarcated very sharply the border between affected and unaffected dermatomes indicating that radicular 'pain' dermatomes do not overlap as much as radicular 'touch' dermatomes (modified from Lorenz et al., 1996, with permission).
inflammatory or vascular origin. The peak-to-peak amplitude of the late LEPs correlated significantly with subjective scores for pain sensitivity. In contrast, early and late SEPs were normal upon both test sessions, as were the scores for mechanosensitivity. In accordance with these results Kanda et al. (1996b) found a good correlation of LEP abnormality and pain sensitivity deficits in Wallenberg’s disease.

At the level of the thalamus, the nociceptive and mechanoreceptive system converge again. Patients with thalamic stroke generally show a uniform sensory deficit which correlates well with median nerve N20 and tibial nerve P40 attenuation of SEPs (Wessel et al., 1994). Yamamoto et al. (1995) recorded LEPs and SEPs in 12 stroke patients. Two patients, both with thalamic strokes, had the constellation of delayed or absent LEPs with normal SEPs. The patient with delayed LEPs had a hemorrhagic posterior tha-
lamic lesion and displayed correspondent reduction of pain (determined by pinprick), but intact joint position and vibration sensitivity in the affected limb. The patient with absent LEPs suffered a posterolateral thalamic stroke and exhibited hyperalgesia in response to pinprick and normal mechano-sensitivity except some reduction for light tactile stimuli. In fact, laser hyperalgesia can well occur in parallel with marked mechanical or cold allodynia in central post-stroke pain, indicating damage of central nociceptive pathways and mediation of the pain through Aβ-fibers and mediallemniscal projection (Vestergaard et al., 1995; Casey et al., 1996a; Lorenz et al., 1998a).

4.3.3. Hypersensitivity and chronic pain
The experience with LEPs in patients primarily concerned the documentation of reduced pain sensitivity in various neurological pathologies. A few applications examined patients with hyperalgesia and chronic pain. Gibson et al. (1994) and Lorenz et al. (1996b) found augmented LEP amplitudes in patients with fibromyalgia syndrome who suffer a characteristic musculoskeletal pain and typical mechanical hypersensitivity at so-called tender points. The LEP findings in fibromyalgia supported the view of a more general hypersensitivity or pain modulation disorder. The already mentioned evidence that central post-stroke pain exhibits reduced or absent LEPs renders the LEP method appropriate to verify the non-nociceptive nature of pain in these patients which is abnormally signaled by the low-threshold mechanoreceptive system. Unlike a laser beam, a painful pinprick tested with a needle always contains activation of both low- and high-threshold mechanoreceptors which may pose particular difficulties to disentangle mechanical allodynia (Aβ-mediated) and hyperalgesia (Aδ-mediated) in neuropathic pains.

In this context, a patient with a circumscribed itching skin area after herpes zoster manifestation may be mentioned in which distinct hyperalgesia was observed in terms of increased subjective laser pain intensity and LEP amplitudes compared to the unaffected contralateral dermatome (Darsow et al., 1996). Thus, psychophysical and evoked potential evaluation with laser stimuli underlined the close relationship between itch and heat hyperalgesia as sequela of post-zosteric neuralgia in this patient.

5. Conclusions
The major motivation for a neurophysiological evaluation of pain in a clinical context concerns the objective documentation of normal and disturbed pain sensitivity; this information helps to verify the functional significance of a neurological disease with respect to involvement of the nociceptive system as neuroanatomically distinct part of the afferent neuraxis. After a brief review of this system starting with the peripheral nociceptor and ending with the attribution of different cortical structures to sensory, emotional and behavioral aspects of pain, this article identifies electrically or magnetically measured brain responses to phasic pain stimuli as a valid tool to assess the pain system noninvasively in volunteers and patients. The infrared laser stimulus has the particular advantage of highly specifically activating slowly conducting Aδ- and C-fibers of the nociceptive system and can be applied at any site of the body skin. The application of laser-evoked potentials (LEPs) in the various pathological conditions validated their power for diagnosis, pathophysiological description and follow-up monitoring of patients with neurological disorders and abnormal pain states. There is a natural constraint of the LEP method to detect early responses at the level of the spinal cord, brainstem or primary somatosensory cortex because slowly conducting nociceptive fibers exhibit a comparably low neuronal synchronization at these sites for applying conventional averaging techniques. So far, the first stage of sufficient neuronal synchronization to elicit evoked potential components after laser stimuli, referred to as N1 and early portions of N2, seems to be the secondary somatosensory cortex (SII). These areas play an important role in the entire somatosensory system; it is the first stage of a bilateral organization of the body scheme. Because of its somatotopy, though less impressive than in SI, and its major features (stimulus-response characteristics, stimulus specificity, dependency on arousal), SII activity evoked by pain-inducing stimuli reflects a significant role in the so-called sensory-discriminative component of pain. Later LEP components with vertex amplitude maxima (N2 and P2) have been found to vary significantly with the subjective report of the experienced strength of pain. The sources of these pain-relevant components have been identified in deep cortical structures, particularly in the cingulate gyrus. This topology and the clear relationship to dynamic aspects of attention (orienting, focusing) suggests the association of these potentials to the motivational and cognitive component of pain.

Though LEPs are cerebral correlates of phasic pain, they also can be applied in chronic pain states to examine pathologically disturbed nociception. LEP measurements help to verify whether an alteration of pain sensitivity, being generalized or localized, constitutes an important feature of the patient's pain state. With the particular aid of source analysis of multilead EEG and MEG in response to laser stimulation, future studies may reveal the involved brain areas to account for the state of hypersensitivity and pain, and disentangle sensory-discriminative from cognitive-emotional processes by looking at activations in different brain areas subserving either component (e.g. SII and cingulate cortex). In central pain, there is the paradox of severe pain in an analgesic region. In these cases absence of LEPs allows to document the damage of the nociceptive system and to verify the importance of an abnormal mediation of pain through Aβ-fibers, dorsal column and mediallemniscal projection. Damage of the nociceptive system seems to be closely associated with the mechanisms by which central pain develops. An early, subclinical diagnosis would be extre-
mely useful to prevent central pain known as extremely resistant against treatment once being manifest.

Finally, it should be mentioned that LEPs as well as any other phasic pain model are neurophysiological tools investigating particular aspects of nociceptive function. They surely cannot elucidate all varieties of cognitive, motivational and emotional features characterizing tonic pain states encountered in most clinical pains. Here, alternative neuromaging techniques, such as fMRI and PET, integrating slow metabolic and hemodynamic reactions over longer periods of time, may be first-choice candidates to study these aspects.

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