

What can imaging techniques tell us about orofacial pain?

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Orofacial pain is a major challenge for the clinician treating the patients and the researchers studying the basic mechanisms of pain. The reason for this is mainly due to an interaction between the complex neurophysiology of orofacial pain and the special psychological importance of the trigeminal region. In this article, we will review briefly the basic peripheral and central mechanisms of pain which is necessary in order to appreciate the crucial role of the brain for the perception of pain, including orofacial pain. We will then introduce the brain imaging technique termed positron emission tomography (PET) and discuss the current and possible future role of PET in advancing our basic understanding of pain and its management in the clinical setting.

The International Association for the Study of Pain (IASP) defines pain as »an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage« (1). This definition captures the rich complexity of the pain experience, which includes the sensory capacity to localize and identify the physical characteristics of the painful stimulus, the affective (hedonic) component of unpleasantness that is intrinsic to pain, and the emotional and motivational drive that compels somatomotor action and accompanies autonomic and neuroendocrine responses (2, 3).

As might be expected, the neural mechanisms activated by noxious stimuli and mediating pain are complex and distributed widely throughout the nervous system. Although each of the components of pain mentioned above is mediated by specialized neural mechanisms, they interact with one another and with other neural systems in important ways that we are just beginning to discover. For example, the perceived intensity of pain can be strongly influenced by previous experience, conditioning, fear, attention, and by other somatic or visceral stimuli. Recent advances in human brain imaging are just now beginning to reveal the brain structures and pathways that are activated during different types of pain and how the activity in these brain regions is modified in a variety of conditions and by different disease states. By learning how the brain processes neural information to produce the sensation of pain, we may be able to develop more effective means of controlling acute and chronic pain.

Peripheral aspects of pain

Afferent nerve fibres innervating nociceptors are activated most effectively by stimuli that are normally painful. Psychophysical studies, including recording the action potentials of single fibres in alert humans, have correlated the activity of afferent fibres with the intensity of pain sensation (4). The nociceptive fibres include both finely myelinated A-delta afferents and unmyelinated afferent fibres (C fibres), both without corpuscular endings. These nociceptive fibres have been identified in virtually all orofacial tissues including skin, mucosa, muscle, joint, periodontium and tooth pulp (5). One of the special features of the trigeminal system as compared to the spinal system is the high density of primary afferents and the high proportion of unmyelinated fibres.

A-delta fibres innervate primarily high threshold mechanoreceptors and some heat nociceptors. C fibres innervate receptors that respond to either heat (above 45°C), cold (below 40°C) mechanical, or chemical stimuli that are normally perceived as painful. Some of these nociceptive afferents respond only to one type of stimulus, such as noxious heat or

noxious cold, but others are »polymodal«, responding to all noxious stimulation, regardless of the physical agent. Some C fibres respond to tactile stimuli or to chemical or mechanical stimuli that produce itching.

C polymodal nociceptors respond to substances produced during inflammation, such as H^+ , K^+ , bradykinin, prostaglandin, leukotrienes, cytokines, and other compounds produced in response to tissue damage (6). Nociceptor activation is not attributable to the action of only one molecular species. Rather, the products of inflammation appear to facilitate mutually each others' excitatory effect on nociceptive activity. The chemical environment provided by the inflammatory process can cause »sensitization« of nociceptors so that stimuli that were previously ineffective now become effective in evoking the discharge of nociceptive afferents. Nociceptor sensitization is probably responsible for the tenderness of damaged tissue. The cellular physiological and molecular basis for nociceptor sensitization is not known.

Joint capsules and ligaments are innervated primarily by A-delta and C afferent fibres. The great majority of these afferents are nociceptors, responding to extremes of joint position or stretch. Many are »silent« nociceptors – never firing unless they are sensitized by inflammation and tissue damage (7).

The majority of tooth pulp afferents are unmyelinated and have undifferentiated endings in the dentinal canals. These afferents innervate polymodal nociceptors, which are activated by inflammation or by mechanical, thermal, or chemical stimuli. Periodontal tissues, like the skin, are innervated by sensory afferents that cover the range from large-diameter tactile to small-diameter nociceptive fibres (5).

The major contractile portion of the muscle and the surrounding muscle fascia are innervated by nociceptive A-delta and C fibre afferents with undifferentiated »free« nerve endings dispersed throughout the extracellular tissue space (8). These afferents respond to extremes of stretch, ischemia, chemical stimuli, and inflammation. Although the innervation density of muscle and other deep tissues is rather sparse when compared to that of skin, the pain is often more unpleasant and severe than skin pain.

The major innervation of the viscera and internal organs is provided by A-delta and C fibre afferents which run primarily in sympathetic nerves with projections to the CNS via the autonomic rami communicantes to the dorsal root (9). Some of these afferents serve regulatory functions that are specific for the innervated organ (e.g. gut motility, urinary bladder reflexes, baroreceptor functions), but others undoubtedly serve a nociceptive function during extremes of distention, stretch, or during ischemia.

Central aspects of pain

Brain stem

A-delta and C fibres from the sensory root of the trigeminal nerve terminate mainly within the substantia gelatinosa at the dorsal apex of the caudal portion of the trigeminal sensory nucleus (subnucleus caudalis), which is sometimes referred to as the medullary dorsal horn (in reference to the dorsal horn of the spinal cord) (5) (Fig. 1). Some of these afferents branch for several millimetres before making synaptic contact with dorsal horn neurons. This wide distribution of nociceptive input is thought to underlie the perceived spatial radiation of severe pain beyond the site of injury.

Thermal and nociceptive afferents activate two anatomically and physiologically distinct types of trigeminal nucleus neurons that contribute axons to the trigeminothalamic tract (10, 11). Nociceptive specific (NS) neurons are found within the substantia gelatinosa and receive input exclusively from A-delta and C fibres. As the name implies, NS neurons respond only to noxious stimuli; thermal or mechanical stimuli may be differentially effective for some, but others respond to

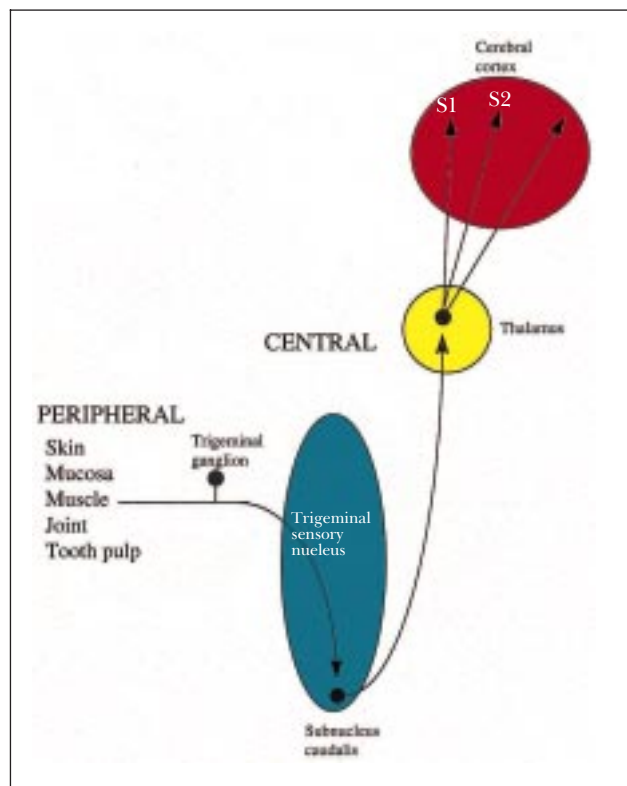


Fig. 1. Simplified presentation of the peripheral and central aspects of orofacial pain. Modified after (5).

Fig. 1. Schematisk og forenklet fremstilling af de perifere og centrale aspekter ved orofacial smerte.

all forms of noxious stimulation. NS neurons represent a form of labeled line coding for noxious stimuli in the central nervous system. Wide dynamic range (WDR) neurons have their dendrites within the substantia gelatinosa, but their cell bodies are located ventrally. In accordance with this designation, WDR cells respond to both innocuous and noxious somatic stimuli. WDR neurons receive synaptic input from tactile, thermal, and nociceptive afferents. The action potential discharge frequency of WDR cells increases progressively as the intensity of a somatic (or visceral) stimulus increases from innocuous to noxious levels. WDR cells thus represent a form of central nervous system pattern, or frequency, coding for noxious stimuli.

Thalamus

Axons of cell bodies in the caudal trigeminal nucleus cross the midline near their point of entry and project directly to the ventral posterior medial thalamus (VPM). In the VPM, synaptic endings are found on neurons that also receive input from tactile pathways. This anatomical finding underlies the physiological observation that WDR type responses of VPM neurons have been recorded from the VPM thalamus of humans and experimental animals (12, 13). In addition, anatomical and physiological studies have shown that there are NS type thalamic neurons ventral and posterior to the VPM thalamus. Thus, the parallel representation of NS and WDR encoding of noxious stimulation in the caudal trigeminal nucleus is preserved at the thalamic level.

Cerebral cortex

Thalamocortical neurons in the ventral posterior thalamus receive spinothalamic input and send axons to the S1 cortex, where both NS and WDR type neurons have been recorded from experimental animals (14, 15). However, experimental and clinical observations have shown that, although the selective destruction of S1 cortex impairs the ability to discriminate different intensities of noxious stimulation, it does not eliminate the ability to perceive noxious stimuli as painful. There are at least two possible anatomical and physiological explanations for this observation. One is that thalamic neurons also send axons to the second (S2) somatosensory and insular cortices, which are adjacent to the lateral (Sylvian) fissure. A second explanation is that neurons in the trigeminothalamic tract send collateral fibres and terminal endings medially into the reticular formation of the brainstem and into the medial thalamus. From these medial thalamic and brainstem sites, nociceptive information is transmitted widely throughout the forebrain. Studies of pain-induced cerebral activity in animals and humans have shown, for example, that

noxious stimulation activates prefrontal, premotor, posterior parietal, insular, and medial limbic cortical areas (16-20). These cortical structures mediate the cognitive, mnemonic, motivational, and emotional aspects of pain perception and prepare autonomic and somatomotoric responses. At these thalamic and cortical levels, it becomes most apparent that nociceptive processing is distributed among neuronal circuits that mediate different aspects of pain experience and response.

Imaging of pain with PET

Physiological basis

There is substantial evidence that regional CBF is highly positively coupled to synaptic activity (21), although the degree of this coupling shows some regional variation (22). One major factor controlling regional CBF is the local production of nitric oxide (NO) (23). This, in turn, is produced in neurons by calcium-calmodulin activated NO synthase. Calcium influx is the triggering event for presynaptic neurotransmitter release, so NO production reflects predominantly the activity within the synaptic neuropil. However, NO synthase is not evenly distributed among neurons; therefore, the absence of a CBF increase may not mean synaptic inactivity. Recently, evidence has been presented that NO may not be the link between neuronal activity and regional CBF in the rat somatosensory system and that adenosine may be important in mediating this effect.

Data acquisition

In PET, CBF is computed from the coincidental counts of gamma rays emitted by the annihilation of positrons from a radioactive compound in the blood and electrons within the surrounding media. In most current studies, water (as H_2^{15}O) is injected intravenously (Fig. 2) or carbon dioxide (as C_{15}O_2) is inhaled and converted in the lungs to H_2^{15}O . The ^{15}O has a half-life of 122 sec. This is sufficient for CBF measurements because, at the CBF levels being measured in human studies, a bolus injection (e.g. 50 mCi) of this compound is nearly completely diffused into brain tissue on the first arterial pass. The counts of emissions from a given volume of brain tissue is therefore a good estimate of the amount of blood within that brain region during the counting period. The difference in the number of counts between sequential counting periods provides an estimate of CBF within that volume of brain tissue. The location of that volume (a voxel) within the brain is computed from the intersection of the radial lines formed by the set of opposing (180°) detectors that have registered the gamma emissions from that site (Fig. 2).

The volume within which counts are made is the voxel.

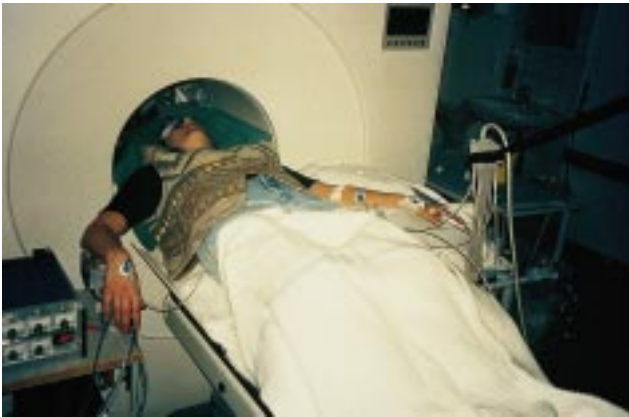


Fig. 2. A subject lying in the PET scanner. The radioactive tracer ($H_2^{15}O$) is injected intravenously in the left arm. Painful stimulation of the volar surface of the right arm is started ten seconds before the PET scan which lasts 50 seconds.

Fig. 2. Liggende forsøgsperson i skanneren på PET-centret i Århus. Det radioaktive sporstof ($H_2^{15}O$) injiceres intravenøst i venstre arm, mens højre arm påvirkes med smertefulde varmepåvirkninger. Disse påvirkninger starter 10 sek. før PET-skannet startes og varer 50 sek.

There are approximately 95,000 voxels in the gray matter of the average human brain. However, the spatial resolution of PET is limited by the ability of the radiation detectors to differentiate the radiation emitted from two separate point sources. Because the radioemissions spread outward from each point source, there is a spatial limitation on the detectable distance between them. For PET, this distance is the width of the distribution of radioactivity at one-half of the maximum counting rate, called the »full width at half maximum« (FWHM). The FWHM defines the spatial resolution for PET scanners; for a typical scanner today, this is between 6 and 9 mm. However, the spatial resolution can be increased considerably (to less than half the FWHM) when subtraction images are made.

Each image set is then normalized to whole brain counts (24), and mean radioactivity concentration images are created estimating regional cerebral blood flow across all subjects by stereotactic anatomical standardization techniques. We align CBF images onto the coordinates of a standard stereotactic atlas (25), using anatomical landmarks identified within the PET images of each individual so that the CBF differences are compared within the same brain regions (for references see 26). To determine whether a task or a stimulus has produced an increase in regional CBF, the rCBF computed during a control condition is subtracted from that computed during the test condition. Areas of significant CBF changes and the locations

of volumes of interest (VOI) are determined stereotactically. The resulting subtraction image, then, shows those brain regions with differences in CBF between the two conditions.

Data analysis

A voxel-by-voxel statistical subtraction analysis (Z-score) with adjustment for multiple comparisons is performed by estimating the smoothness of subtraction images following three dimensional Gaussian filtering to enhance signal-to-noise ratio and compensate for anatomical variance. Voxels showing a significantly increased CBF compared to the average noise variance computed across all voxels (pooled variance) are identified (27). The critical level of significance is determined by adjusting $p = 0.05$ using this information (27). Typically, only those voxels with normalized CBF values larger than 60% of the global value are analyzed because these represent the gray matter of the brain.

In addition, volumes of interest (VOI) may be established within brain structures selected because of a priori hypotheses and the results of previously published PET studies (16-20). The size and shape of each VOI may be standardized across studies or determined separately according to functional criteria. To determine the statistical significance of rCBF increases, a paired t-statistic is computed for each VOI from the average percentage increase in CBF across all subjects. Levels of significance are established based on the Bonferroni correction for multiple comparisons among VOI.

Interpretation of PET images

A statistically significant increase in rCBF can reasonably be assumed to be due to increased synaptic activity. Thus, it is the synaptic neuropil, rather than the neuronal cell bodies, that generates the measured response. There is currently no method for distinguishing between increased inhibitory and excitatory synaptic activity with PET CBF studies. Increases in local metabolism are seen during increased inhibitory synaptic activity, so increases in regional CBF would be expected during the activity of either excitatory or inhibitory synapses. The neurophysiological significance of decreases in regional CBF is less clear; presumably, this could reflect a decrease in synaptic activity induced by active synaptic inhibition elsewhere. In subtraction images, of course, an apparent decrease in rCBF may be due to an increased rCBF in the »baseline« condition that is subtracted from the »test« or »experimental« state. Assuming this has not occurred, the »test« condition may be associated with an actual decrease in rCBF. The evidence presented above would suggest that the removal of excitatory synaptic activity (disfacilitation), due to a spatially separate active inhibition of excitatory projection neurons, could pos-

sibly result in a focal reduction in rCBF. However, even this possibility is not yet supported by direct evidence. This leaves open the possibility that a reduction in rCBF due, for example, to an active or passive redistribution of rCBF to synaptically active regions, could result secondarily in a reduction in local synaptic activity. Unfortunately, evidence on this possibility is also lacking, complicated in part by our ignorance of the relationship between synaptic activity and an imposed reduction in rCBF. One would obviously like to establish a mathematical relationship between rCBF increases and the amount of synaptic activity. Recent PET studies have begun to establish quantitative stimulus-response relationships between increases in rCBF and measurements of behavioural performance. For example, a logarithmic relationship between the force of finger flexion and the increases in rCBF in the primary motor cortex, posterior cingulate motor area, and the ventral posterior supplementary motor area (28). These results suggest that similar stimulus-response relationships could be expected for other behavioural performance measures, including measurements of various aspects of orofacial pain.

Interpreting the functional significance of increases in rCBF in any single region or in a pattern of brain regions currently depends upon prior information obtained from other studies (lesions, stimulation, anatomy) and from correlation with performance measures obtained at the time of PET data acquisition. In the case of studies of sensory function, including orofacial pain, it is essential to obtain measures of the sensory experience so that this may be correlated with the observed pattern of rCBF. It is likely that some behavioural performance measures may not be related to the rCBF in one or a few regions, but will correlate better with measures of the activity within all or part of the inter-regional network of activated areas. Put another way, the function of any given brain region may be best defined in terms of its function within the interregional network. Network function, then, becomes the important unit of measurement in establishing brain-behaviour relationships. Finally, it must be kept in mind that we may be detecting only part of the network of activity evoked by the stimulation. There are obvious technical limitations, as with any technique, and these limit the volume and intensity of activity that can be detected with PET rCBF studies.

Recent PET studies of pain

In a recent survey of 11 PET rCBF studies of pain (26), 50% or more of the studies revealed pain-related activations of the contralateral insular and anterior cingulate cortex, ventral posterior thalamus, lenticular nucleus, and the medial dorsal midbrain (in the region of the periaqueductal gray) and cere-

bellum. Nearly half of the investigations showed significant rCBF increases in the contralateral second somatosensory (S2) and primary sensorimotor (M1/S1) cortex, and approximately one-third reported pain-related activation of the contralateral posterior parietal, lateral prefrontal, and premotor cortex, and the ipsilateral thalamus. This degree of concordance is remarkable, given the marked heterogeneity of the subject populations, the methods of stimulation, data acquisition and analysis among the studies.

These results suggest that there is an underlying pattern of forebrain activation that is common to all types of pain. This question has been addressed in recent PET studies comparing cutaneous heat pain with deep cold pain (17) and cutaneous heat pain evoked by infra-red laser with deep intramuscular pain in the arm (19). In the latter study significant increases in rCBF to both noxious cutaneous and intramuscular stimulation were found in the contralateral S2 cortex and inferior parietal lobule. In addition, comparable levels of rCBF increases were found in the contralateral anterior insular cor-

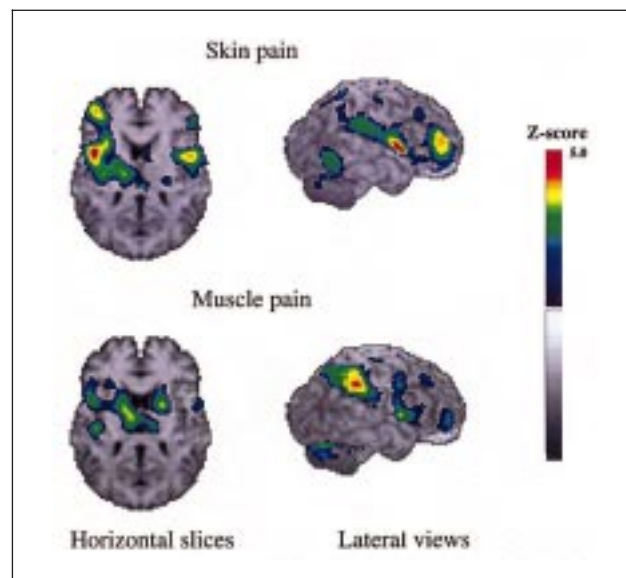


Fig. 3. Examples of the PET subtraction images (painful minus non-painful stimulation). The PET images (horizontal sections and lateral views) are superimposed on MRI to enhance the anatomical accuracy. A network of neural structures are activated both with skin and muscle stimulation. The colour scale indicates the significance level of blood flow changes.

Fig. 3. Eksempler på billeder fra en PET-undersøgelse af raske forsøgspersoner. Billederne viser forskellen mellem en ikke-smertefuld og en smertefuld påvirkning af henholdsvis hud og muskel. For at øge den anatomiske præcision er PET-billederne sammenholdt med MRI-skanninger (horisontalt snit samt set fra siden). Der kan iagttages et netværk af strukturer der viser signifikant øget blodgennemstrømning (farveskala).

tex, thalamus, and in the ipsilateral cerebellum (Fig. 3). Direct comparisons of the two different noxious stimulation procedures showed that the brain activation pattern was similar, but not identical. The common pattern may represent the cerebral structures with the lowest threshold for nociceptive activation because both forms of stimuli were near-pain intensity threshold. The differences in cerebral activation patterns suggest that the perceived differences between acute skin and muscle pain are mediated by variations in the intensity and the temporo-spatial patterns of neuronal activity within similar sets of forebrain structures.

Thus, PET studies have clearly illustrated the fact that there is no »pain center« in the human brain, but there is a distributed network of neurons which differentially can be engaged in the processing of painful stimuli.

Imaging of orofacial pain

So far very few PET studies have specifically addressed the orofacial pain problem. In one study the brain responses to non-painful and painful thermal stimulation of the arm were studied in control subjects and in patients with the diagnosis »atypical facial pain« (29). The atypical facial pain patients demonstrated significantly more activity in the anterior cingulate cortex and less activity in the prefrontal cortex. The authors suggested that atypical facial pain could be a hyper-emotional reaction to incoming sensory information with increased anxiety and perturbed attentional mechanisms.

Another PET study examined patients with episodic cluster headache and found a right-lateralised increase in rCBF in the anterior cingulate cortex (30). Thus, the anterior cingulate seems to be the key structure within the pain-processing network; probably with a preferential role in the affective-cognitive dimension of clinical pain.

No PET studies have, however, demonstrated the extent of the neural network involved in the processing of e.g. tooth pain or jaw-muscle pain. There are reasons to believe that the network will share many characteristics of the network described for the processing of pain from other sites in the body. However, the orofacial region has classically been described to occupy a large proportion of the somatosensory cortex (31), and the psychological impact of orofacial pain might also contribute to differential responses. At the PET Centre in Aarhus the first experimental study of jaw-muscle pain has just been completed, so hopefully in the near future a more detailed description of orofacial pain can be provided.

Future aspects of PET and orofacial pain

Besides the important possibilities to advance the basic understanding of the human brain in the processing of orofacial

pain, there are fascinating clinical implications as well. One potential application of the PET technology in the future is to develop analgesics which specifically are targeted towards critical components of the pain network. Another possibility will be to identify the cortical reorganization that takes place in the nervous system following damage to the peripheral or central nervous system (26). If such changes can be objectified and imaged, they might also be prevented by either physical or pharmacological treatments. Finally, the intriguing possibility exists that PET could be used in the diagnosis of chronic pain conditions. If the described technical limitations of the current PET technique can be solved and if the many neurophysiological and psychological factors and conditions which influence the activity of the pain-processing network can be adequately described, then in the future we might be able to look at a PET scan of a patient with chronic orofacial pain and say: »This patient indeed suffers from moderate to strong cramping pain from her right jaw-muscle«.

Today PET may best be described as a valuable research tool which just has started to allow us to gain insight into the extremely complex mechanisms involved in the physiological processing of e.g. orofacial pain.

Dansk resumé

Hvad kan billeddannende teknikker fortælle om orofaciale smerter?

Orofacial smerte er en stor udfordring for klinikerne der behandler patienterne, og for forskerne der undersøger basale smertemekanismer. En af årsagerne hertil er samspillet mellem en kompleks neurofysiologi og de specielle psykologiske forhold ved smerter i trigeminus-området. I denne artikel beskrives væsentlige dele af det perifere nervesystem der spiller en rolle ved fx orofacial smerte. Information om et smertevoldende stimulus transmitteres gennem specialiserede nervefibre der kan sensibiliseres ved vævsskade og derved medføre en øget smertereaktion. I de centrale dele af nervesystemet findes der ligeledes specialiserede nerveceller med karakteristiske egenskaber der kan forklare de kliniske fænomener som spredning af smerte og meddelte smerter. For at kunne forstå smertens fysiologi er det i høj grad også nødvendigt at studere hjernens funktion. I dag er det muligt med moderne afbildningsteknikker at visualisere hvilke områder af hjernen der medvirker ved bearbejdning af smerte. Den såkaldte positron-emissions-tomografi (PET-teknik) kan med god nøjagtighed vise de lokale ændringer af blodgennemstrømningen bevirket af standardiserede smertepåvirkninger. Man antager således at der ikke er ét smertecenter i hjernen, men at der er et helt netværk af strukturer der alle bidrager med forskellige aspekter til den komplekse sanseoplevelse som smerte også udgør. Ved systematisk

kortlægning af disse strukturer samt beskrivelse af hvilke forhold der kan modificere deres aktivitet, vil det måske i fremtiden være muligt at fremstille målrettede smertestillende stoffer, samt mere objektivt at vurdere ændringer af det normale smertereaktionsmønster. I dag kan PET bedst betragtes som et fascinerende højteknologisk forskningsredskab der bidrager til en større indsigt i den orofaciale smertes fysiologi.

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