Craniofacial Muscle Pain: Review of Mechanisms and Clinical Manifestations

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Epidemiologic surveys of temporomandibular disorders (TMD) have demonstrated that a considerable proportion of the population—up to 5% or 6%—will experience persistent pain severe enough to seek treatment. Unfortunately, the current diagnostic classification of craniofacial muscle pain is based on descriptions of signs and symptoms rather than on knowledge of pain mechanisms. Furthermore, the pathophysiology and etiology of craniofacial muscle pain are not known in sufficient detail to allow causal treatment. Many hypotheses have been proposed to explain cause-effect relationships; however, it is still uncertain what may be the cause of muscle pain and what is the effect of muscle pain. This article reviews the literature in which craniofacial muscle pain has been induced by experimental techniques in animals and human volunteers and in which the effects on somatosensory and motor function have been assessed under standardized conditions. This information is compared to the clinical correlates, which can be derived from the numerous cross-sectional studies in patients with craniofacial muscle pain.

The experimental literature clearly indicates that muscle pain has significant effects on both somatosensory and craniofacial motor function. Typical somatosensory manifestations of experimental muscle pain are referred pain and increased sensitivity of homotopic areas. The craniofacial motor function is inhibited mainly during experimental muscle pain, but phase-dependent excitation is also found during mastication to reduce the amplitude and velocity of jaw movements. The underlying neurobiologic mechanisms probably involve varying combinations of sensitization of peripheral afferents, hyperexcitability of central neurons, and imbalance in descending pain modulatory systems. Reflex circuits in the brain stem seem important for the adjustment of sensorimotor function in the presence of craniofacial pain. Changes in somatosensory and motor function may therefore be viewed as consequences of pain and not factors leading to pain. Implications for the diagnosis and management of persistent muscle pain are discussed from this perspective.

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Pain in the masticatory and craniofacial muscles has for a long time been recognized as a prominent symptom in many clinical syndromes, such as Costen's syndrome, myofascial pain dysfunction, mandibular pain dysfunction syndrome, craniomandibular disorders, or temporomandibular pain and dysfunction

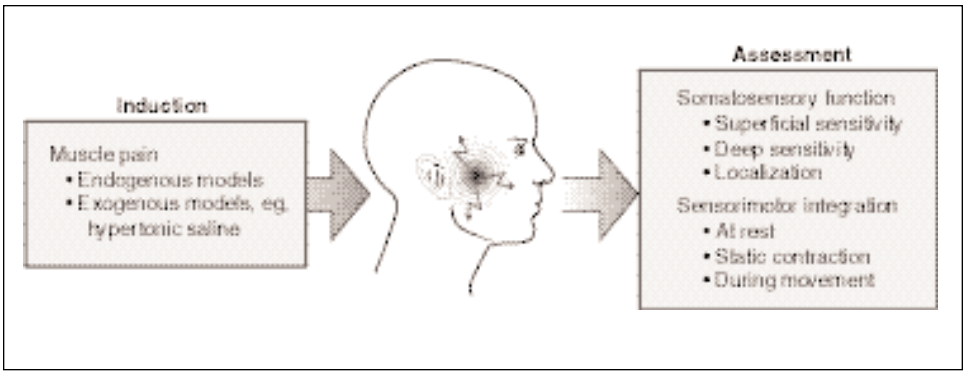

Fig 1 Principles in experimental pain research.

syndrome.[1] The different names probably reflect difficulties in establishing concise and validated diagnostic criteria. The term *temporomandibular disorders* (TMD) is currently viewed as "a collective term embracing a number of clinical problems that involve the masticatory muscles, the temporomandibular joint and associated structures, or both."[2] The Research Diagnostic Criteria for TMD appear to be the best, but perhaps not the perfect, option for a classification scheme of TMD.[3] Multifactorial models of TMD pain consider a series of initiating, predisposing, and aggravating biomechanical, neuromuscular, biopsychosocial, and neurobiologic factors. It is important, however, to note that the pathophysiology and etiology of most craniofacial muscle pain conditions are far from being completely understood, and the pain community is a long way from a mechanism-based classification of pain in the masticatory and craniofacial muscles.[4]

This review will try to synthesize recent knowledge of the neurobiology of craniofacial muscle pain obtained from human experimental pain models and basic studies in animals with the clinical correlates in patients. The advantage of experimental pain models is that the cause of pain is known and the effects of pain can be assessed under standardized, controlled conditions, with respect to both somatosensory consequences and sensorimotor integration (Fig 1). Therefore, experimental pain studies provide a direct insight into the nature of such cause-effect relationships, which is often difficult or even impossible to infer from clinical cross-sectional studies.

Experimental Muscle Pain Models

The first step in experimental pain research is the selection of a suitable technique for induction of pain. The next step is then to quantitatively assess the pain-induced responses (Fig 1). These topics have been described in several reviews.[5–7] The next 2 sections will briefly review techniques to induce pain in the craniofacial muscles. Experimental muscle pain models can be divided into techniques in which pain is provoked by a sustained or repeated voluntary motor task performed by subjects under controlled conditions (endogenous models) or by standardized application of various painful stimuli (exogenous models).[8]

Endogenous Muscle Pain Models

In conditions with heavy loading and insufficient relaxation periods, concentric dynamic and isometric contractions will produce muscle pain that probably involves the same pathophysiologic processes as ischemic pain.[9] Ischemia alone is not sufficient to evoke muscle pain, but in combination with contractions, strong pain develops in humans. Accumulation of metabolites such as lactate, potassium, or the lack of oxidation of metabolic products, in addition to mechanical factors (eg, the number of contractions, their duration and force), may play a significant role.[9,10] Moreover, hypoxia and the release of bradykinin (BK), prostaglandins (eg, prostaglandin E_2 [PGE_2]), and calcitonin gene-related peptide (CGRP), in association with a reduced pH, may sensitize muscle nociceptors and lead to pain evoked by mechanical stimulation during contractions.[11]

A combination of concentric dynamic contractions, eg, mastication and ischemic block of the

superficial temporal artery, produces a continuously increasing, dull, bilateral, frontal headache in healthy subjects.[12,13] Sustained or repeated static tooth-clenching tasks in different jaw positions may also lead to intense jaw muscle pain with a rapid onset.[14–19] It is notable that pain disappears quickly when clenching ceases, and most studies in healthy subjects have failed to show clinically significant levels of pain in the jaw muscles in the days following exercise. A recent study showed that even daily 15-minute tooth-clenching episodes at 25% of maximum voluntary contraction (MVC) for 5 days failed to elicit longer-lasting jaw muscle pain and soreness in healthy female subjects.[20] There is no evidence that a deep noxious input applied to an exercised jaw muscle has a stronger impact on the perceived pain intensity than the same stimulus applied to a non-exercised jaw muscle.[21] However, injection of hypertonic saline into leg muscles causes higher levels of pain when the muscles are fatigued as the result of prolonged standing.[22] Furthermore, patients with tension-type headache and migraine will more frequently develop headache following sustained tooth-clenching (< 30% MVC) than will healthy control subjects.[23,24] It has therefore been suggested that patients with headache have an increased sensitivity to afferent stimuli, which could be related to impaired endogenous inhibitory control mechanisms.[25]

In contrast to the immediate and rather short-lasting muscle pain evoked by concentric contractions, eccentric contractions are more effective in inducing a delayed onset of muscle pain or soreness in limb muscles.[26–28] The mechanisms underlying this kind of muscle pain are probably related to damage to muscle connective tissue.[29,30] Furthermore, disorganization of myofilaments and extensive disruption of muscle structures localized particularly in the regions of the Z discs have been demonstrated.[31] Forced lengthening of tetanic stimulated jaw muscles in mice has also been shown to decrease the contractile tension and elevate the levels of plasma creatine kinase as indices of muscle injury.[32] One classic study showed that experimental tooth-grinding for 30 minutes caused significant levels of jaw muscle pain lasting for several days in 9 healthy subjects.[33] However, it has been demonstrated more recently that 45 minutes of strong tooth-grinding activity at 50% MVC in 12 healthy subjects caused only low levels of pain and soreness the following 3 days.[34]

Thus, the results of exercise-induced activation of human muscle nociceptors show that excessive and strong contractions of the muscles can cause pain in the craniofacial region, but the pain is usually short-lasting and self-limiting. Furthermore, due to the nature of the experimental procedures, there may be a strong confounding factor of muscle fatigue. In addition, muscle pain is usually developed in a group of muscle synergists rather than in one specific muscle. Other techniques are therefore required to allow the study of both somatosensory effects of pain and the sensorimotor integration in the craniofacial region.

Exogenous Muscle Pain Models

Activation of muscle nociceptors can be accomplished by application of several different types of high-intensity stimuli. For example, intramuscular needle electrodes can be used to stimulate the human muscle afferents directly.[35–37] The elicited sensation is described as a cramp-like pain often in combination with a visible muscle contraction. Thus, the electrical stimulus may cause interference in electromyographic (EMG) recordings when motor functions are studied.

Intraneural microstimulation is an advanced although invasive and time-consuming technique for selective activation of single human muscle afferents.[38–40] It has been shown that the projected pain area enlarges as a function of stimulus duration (temporal summation) and as a function of a number of stimulated afferents (spatial summation).[41] To date, intramuscular electrical stimulation of craniofacial muscles or microstimulation of trigeminal nerves does not appear to have been attempted in human pain research.

Intense mechanical stimuli applied over a muscle activate nociceptors in muscle and potentially also in skin. Thus, the evoked pain sensation may have a component from both types of tissue. Anesthetizing the skin will cause no changes[42] or only a small elevation of pressure-pain thresholds in muscles,[43–45] suggesting a minor contribution to the evoked pain sensation from superficial tissues in healthy subjects. Application of special "head screw" devices to the scalp will gradually cause pain, starting from a non-painful pressure sensation until pain tolerance is reached.[46,47] The mechanism underlying this type of pain is probably related to local ischemic reactions, rather than direct mechanical stimulation of nociceptive afferents.

Intramuscular injection of algesic substances has also been used for chemical activation of human muscle nociceptors. There is substantial evidence from animal studies that BK and serotonin (5-hydroxytryptamine [5-HT]) activate nociceptive

group III and IV afferents.[48] However, non-nociceptive afferents may also be activated by such stimuli.[11] When injected into the human anterior temporalis or the tibialis anterior, low concentrations of 5-HT (40 μmol/L) do not induce significant levels of pain, and BK induces no or relatively low levels of pain.[49–51] Higher concentrations of 5-HT (1 mmol/L) have recently been shown to produce higher levels of pain than isotonic saline when injected into the masseter muscle of healthy subjects.[53] Furthermore, the combined injection of 5-HT and BK causes significantly higher pain ratings than injection of isotonic saline.[50,53] This finding supports the importance of sensitization with 5-HT for BK-induced neural activity.

Other neuropeptides and excitatory amino acids have recently been implicated in muscle nociception, especially glutamate and N-methyl-D-aspartate (NMDA) receptors.[54–56] Substance P has been studied extensively in cutaneous pain but does not appear to sensitize muscle nociceptors to mechanical stimuli.[11] Substance P in itself does not produce pain when injected into the human anterior temporalis or tibialis anterior.[51,57] However, in combination with CGRP and BK, it does induce muscle pain and a significant reduction of pressure-pain thresholds in the anterior temporalis.[57,58]

Intradermal or topical application of capsaicin (chili-pepper extract) is a widely used experimental model to study cutaneous pain and hyperalgesia,[59] but only 1 published study in humans has tested intramuscular injection of this substance. Capsaicin-induced muscle pain is described as severe and cramp-like and is associated with significant increases in neural activity of group III and IV muscle afferents.[40] This stimulus may prove to be useful in future studies of human muscle pain. Preliminary studies have demonstrated the ability of capsaicin to induce both local and referred muscle pain.[21,60]

Finally, an intriguing finding is that systemic administration of human nerve growth factor (NGF) in healthy subjects could induce pain, notably in the craniofacial muscles, that tended to worsen during function. The pain was more pronounced in women than in men.[61] There is evidence that estrogen and NGF may interact in the regulation of nociceptive processes, and this could be of importance in explaining the female preponderance in TMD pain.[62] Female reproductive hormones are increasingly being implicated as an etiologic factor in some types of TMD pain.[63] In accordance, it has recently been shown that nociceptive muscle afferents in female rats demonstrate a significantly greater response to injection of glutamate compared with male rats and that the pain responses to glutamate injections in the masseter muscle are significantly higher in women than in men (Cairns et al, unpublished data).

A substantial part of the present knowledge of peripheral and central craniofacial pain mechanisms is derived from elaborate and well-designed animal studies (for reviews see Dubner et al,[64] Sessle,[65–67] Capra and Dessem,[68] Hannam and Sessle,[69] and Lund and Sessle[70]). Injection of potent algesic substances such as mustard oil into deep craniofacial tissues has been particularly useful to document the neurobiology and neuropharmacology of brain stem reflex responses and hyperexcitability of central neurons.[55,56,71–80] These animal models nevertheless do not provide information on pain per se but on nociception or nocifensive responses only, because there is no direct way to know the correlation between nociceptive activity in anesthetized animal preparations and the subjective report of pain in conscious human beings. Therefore, there is a need to apply experimental pain models in healthy human subjects, with the purpose of bridging the basic information obtained in animal studies with the data from clinical trials in patients.

In summary, exogenous stimulation techniques help to characterize basic aspects of craniofacial muscle pain. The choice of model depends on the specific purpose of the study. For example, injection of specific algesic substances and excitatory neuropeptides may help outline the neuropharmacology involved in craniofacial muscle pain. For the study of sensorimotor interaction in the human craniofacial region, it is important that the stimulus is safe and induces a robust pain sensation that can be maintained for several minutes or longer. Kellgren and Lewis[81–83] demonstrated that intramuscular injection or infusion of hypertonic saline is a suitable and reliable model to evoke experimental muscle pain in healthy subjects. Since hypertonic saline has been used extensively as a painful stimulus, this technique will be described in more detail in the next paragraphs.

Induction of Muscle Pain by Hypertonic Saline. Hypertonic saline in a concentration of 4% to 6% has been the most commonly used chemical substance to induce muscle pain in humans.[22,35,44,81,82,84–122] A major reason for the widespread use of hypertonic saline is the safety of this technique; no side effects after numerous intramuscular injections have been reported.[99,124] In principle, the hypertonic saline can be administered either as a bolus injection or as a slow, continuous infusion with the help of computer-controlled syringe pumps[123,124] (Fig 2). Tonic infusion

of hypertonic saline has advantages over bolus injection in that muscle pain can be maintained for up to 15 or 20 minutes at a fairly constant level, the evoked pain is more similar to clinical muscle pain, and more experimental registrations can be performed.[44,104,112,116,117,119]

Hypertonic saline is unfortunately a non-specific painful stimulus, ie, not mediated by specific pharmacologic receptors, and non-nociceptive afferents may be activated concomitantly with the activation of nociceptive group III and IV afferents.[11,125] Many craniofacial muscles contain all classes of primary afferents[64,68,69] that potentially could be activated by injection of hypertonic saline. Iggo reported that muscle spindle afferents (group Ia) from the gastrocnemius and soleus muscles in cats responded to intramuscular injection of a small quantity of 5% hypertonic saline,[125] whereas Paintal concluded in another cat study that nociception following local infiltration of 6% hypertonic saline was unlikely to be mediated by muscle spindle afferents.[126] Intramuscular injection of 0.5 mL 6% hypertonic saline clearly evokes 2 to 5 minutes of neuronal activity in group III muscle afferents in cats, whereas isotonic saline does not induce detectable activity.[126] Convergent spinal dorsal horn neurons are strongly excited by intramuscular injection of 0.1 to 0.3 mL 6% hypertonic saline, and on the basis of the response characteristics, it was suggested that the excitatory response was primarily mediated by group IV afferents.[127,128] About 70% of the wide-dynamic-range neurons and nociceptive-specific neurons in the trigeminal subnucleus caudalis respond to injection of 7% hypertonic saline, whereas relatively few (25%) low-threshold-mechanoreceptive neurons respond.[129] Furthermore, neurons encoding nociceptive information in the nucleus submedius in the thalamus have been found to respond to intramuscular injection of hypertonic saline, and it has been argued that recruitment of group IV afferents would be necessary to elicit the response.[130] A recent human study showed that a differential block of myelinated nerve fibers did not significantly affect saline-induced muscle pain intensity, ie, mainly group IV afferents mediated the muscle pain sensation.[131] Finally, the dominant sensation caused by intramuscular injection of hypertonic saline in conscious humans is deep, diffuse pain.[35,81,96,99,113,124]

It is unlikely that increased intramuscular pressure should be the cause of the pain during infusion of hypertonic saline, since the maximum pressure measured at the tube does not exceed 100 to 110 mmHg.[19,117,120] During non-painful static contractions, the intramuscular pressure can increase up to more than 300 mmHg[132] in the limb muscles and up to 250 mmHg in the jaw-closing muscles.[133] Finally, infusion of isotonic saline with a pressure of 400 mmHg does not produce muscle pain,[93] and no differences in infusion pressure between isotonic and hypertonic saline have been reported.[107,117]

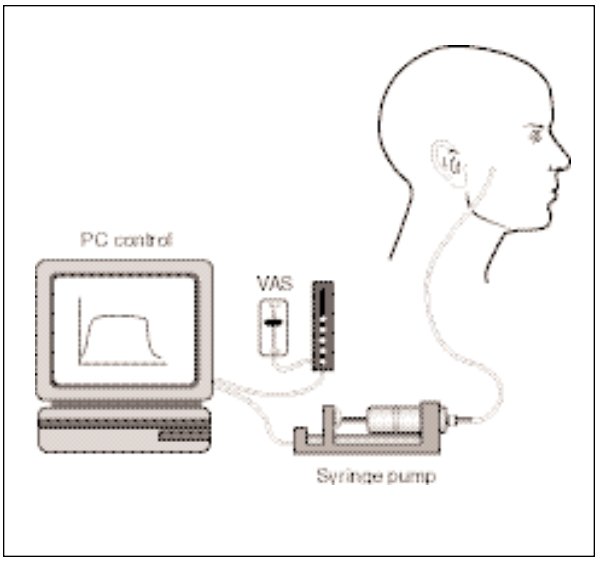

Fig 2 Setup used for induction of muscle pain by tonic infusion of hypertonic saline into the masseter. The computer (PC) controls the infusion rate of the syringe pump and samples the visual analog scale (VAS) scores of pain intensity.

In summary, the evidence strongly suggests that hypertonic saline is indeed a potent chemical stimulus for excitation of group III and IV muscle afferents and central neurons encoding nociceptive information along the neuroaxis. Therefore, it is reasonable to suggest that changes in somatosensory or motor function following hypertonic saline are primarily a result of activity evoked in nociceptive muscle afferents.

Somatosensory Effects of Muscle Pain

Human experimental pain models can be used to describe the effects of craniofacial muscle pain on somatosensory sensitivity. This is important because it had earlier been suggested that a low psychophysical threshold could contribute to the complaints of TMD pain.[134] Although some of the

clinical literature on somatosensory function in patients with craniofacial muscle pain suggests significant disturbances, there is at present no agreement on the direction of changes. The next sections will review the evidence for somatosensory changes in superficial and deep tissues in relation to experimental and clinical muscle pain in the craniofacial region.

Experimental Muscle Pain and Sensitivity of Superficial Tissues

Many human studies of experimental deep pain have reported increased cutaneous sensitivity to pricking mechanical or electrical stimuli in the local pain area,[35,83,94,135] but some reports have also shown decreased or unchanged sensitivity.[88,103,104,108] Lewis and Kellgren[83] noted that superficial hyperesthesia was not detected until about 5 minutes after injection of hypertonic saline and that it was usually very slight at first, but developed over time to become more profound. The sites of superficial hyperesthesia involved either the local pain area at the injection site or even more distant regions. Steinbrocker et al[135] reported that changes in superficial sensitivity were variable in occurrence following intramuscular injection of hypertonic saline, but that they usually consisted of hyperesthesia and rarely hypoesthesia in the local pain area. A recent detailed study showed that both hypoesthesia and hyperesthesia can occur, depending on the innervation area and the relation to the referred pain area.[136] Arendt-Nielsen et al[137] demonstrated significant superficial hyperalgesia to single and repeated electrical stimuli applied to the referred pain area. However, changes in somatosensory sensitivity in the referred pain area appear to be modality-specific, because both hyperalgesia to electrical stimuli and hypoalgesia to radiant heat stimuli can be observed.[104] Continuous infusion of hypertonic saline into the masseter muscle has been shown to produce significant hyperesthesia to punctate mechanical stimuli.[117] The significant changes occurred after more than 5 minutes of infusion, and this time profile is in agreement with the increase in excitability of second-order neurons that follows a nociceptive input.[72,74,138] Thus, the human experimental model has demonstrated that the processing of cutaneous mechanical stimuli is facilitated during ongoing jaw muscle pain, and it has been suggested that these findings could be related to the hyperexcitability of second-order neurons in subnucleus caudalis.[67]

Clinical Muscle Pain and Sensitivity of Superficial Tissues

A number of studies have examined the sensitivity of superficial tissues in patients with craniofacial muscle pain to various non-painful and painful stimulus modalities. It has been reported that the detection and pain thresholds to electrical stimulation of the facial skin or teeth are not significantly different between TMD patients and control subjects.[139,140] However, significantly increased detection and pain thresholds to electrical stimulation of the facial skin in TMD patients have also been reported, ie, hypoalgesia.[141] A significant impairment in vibrotactile function and discrimination abilities on the facial skin in TMD patients was recently described.[142,143] A detailed psychophysical study found that the vibrotactile function was differentially affected (amplitude discrimination was unchanged), but frequency discrimination sense was significantly impaired in TMD patients compared to control subjects.[143] Based on correlation analysis, it was suggested that the vibrotactile deficit and the clinical pain seemed to be nearly independent symptoms of an underlying disturbance in the processing of somatosensory information.[143] Interestingly, a case report was recently presented of a patient with TMD and with hyperesthesia to vibrotactile stimulation, both at the face and at the forearm.[144] The hyperesthesia was sensitive to administration of the NMDA receptor antagonist dextromethorphan, which suggests the involvement of central hyperexcitability in this condition.

Patients with craniofacial muscle pain may also demonstrate hyperalgesic responses to application of thermal heat within and outside the local pain area.[145] Thus, stimulus-response curves clearly indicated an augmented processing of thermal information, and it was argued that sensitized thermoreceptors were unlikely to explain this finding because the heat detection thresholds were unchanged. Instead it was suggested that integrative mechanisms in the central nervous system participated because of an augmented temporal summation of thermal stimuli on the hand.[145] Temporal summation mechanisms and wind-up phenomena in central neurons could be strongly related to the development of central hyperexcitability.[7,146] This indicates that some patients with craniofacial muscle pain may be in a state of generalized central hyperexcitability, which also was suggested by Sörensen et al for patients with fibromyalgia.[147] However, an earlier study by Price and Harkins reported that thermal nociceptive

processing was normal in patients with TMD pain.[148] Triangulation procedures demonstrated internal consistency in pain reports, and the slopes of stimulus-response curves were not significantly different between TMD pain patients and control subjects.[148] The age, duration of pain symptoms, and levels of pain were comparable between these 2 studies, leaving the possibility that specific subgroups of TMD pain patients could have differing responsiveness to thermal stimulation or that the methodology differed in some subtle aspects.[145,148] Findings in patients with chronic tension-type headache and fibromyalgia support the conclusion of generalized hyperalgesic responses to superficial somatosensory stimulation.[149–152]

In patients who have significant hyperalgesia to superficial stimuli applied outside the segment containing the local pain area, it is unlikely that peripheral sensitization and sensitization of second-order neurons can explain the findings. Rather, sensitization is probably occurring at higher levels in the central nervous system, and it has been suggested that the ascending reticular formation could be involved.[153] First, there are projections from dorsal horn and brain stem neurons via the spinoreticular/trigeminoreticular tract. Secondly, the many nuclear groups in the brain stem and basal forebrain areas project to other brain areas related to a wide range of functions, such as regulation of sensory perception, emotional responses, arousal, endocrine responses, somatomotor output, and autonomic function.[153] It has been suggested that disinhibition of the ascending reticular formation would be consistent with a generalized hyperalgesia as well as the many psychologic, sensory, motor, autonomic, and neuroendocrine changes often observed in TMD pain patients.[145,153] The activity of the ascending reticular formation is normally under the control of peripheral baroreceptor afferent input, and a dysfunction of the regulatory systems could be involved in craniofacial muscle pain.[154] An alternative but not mutually exclusive explanation for the generalized hyperalgesia could be an interaction between NGF and female hormones such as estrogen.[62] Such an interaction with up-regulation of NGF could probably explain both the widespread nature of deep pain and hyperalgesia[61,155] and the female preponderance among patients with TMD pain.[62] The sequence of events could be initiated by acute muscle inflammation,[156] but the long-term effects of NGF on pain and hyperalgesia are still not known.[155] Furthermore, the common complaint of pain in the craniofacial region can at this moment only be hypothesized to be related to the rich innervation of the tissues, the prominent representation in the somatosensory cortex, and the frequent use of the masticatory system.[153]

In summary, there are contradictions in the clinical literature regarding the valence of changes in superficial sensitivity in patients with craniofacial muscle pain. Studies have reported both hypo- and hyperalgesic responses. This controversy may be explained partly by differences in psychophysical techniques and by differences in diagnostic criteria for the patient population. However, the most recent studies with robust psychophysical techniques and the best described diagnostic criteria for inclusion have indicated both localized and generalized hyperalgesia to heat stimuli that is probably related to hyperexcitability of central neurons and deficiencies in the endogenous inhibitory control systems.[145] Findings in healthy subjects with experimental jaw muscle pain also indicate hyperesthesia to punctate mechanical stimuli.[117] It seems important that modality-specific changes in superficial sensitivity can be detected in referred pain areas during ongoing experimental muscle pain.[104] Cutaneous hyperalgesia in referred pain areas may resemble the phenomenon of cutaneous secondary hyperalgesia.[7] In conclusion, muscle pain in the craniofacial region seems to have a significant effect on superficial sensitivity that is reflected mainly in a facilitated processing of the afferent inputs.

Experimental Muscle Pain and Sensitivity of Deep Tissues

Mechanical stimuli have been used extensively to assess the sensitivity of deep craniofacial tissues in humans. The most widely used technique is pressure algometry.[6,157] Pressure algometry is recommended as one of the diagnostic procedures for evaluation of patients with tension-type headache,[158] but not for examination of patients with TMD pain.[2] Methodologic issues such as short-term and long-term reproducibility,[159–166] influence of pressure rates and muscle contraction levels,[167–169] and examiner expectancy[170] have been carefully addressed. Provided that proper standardization methods are followed, approaches using pressure-pain thresholds are generally considered an improvement on the manual palpation of muscles. Nonetheless, a palpometer device has recently been developed[171] and tested in patients with tension-type headache and fibromyalgia[172,173]; this device might also provide useful information in, for example, TMD patients.

Several authors have reported increases in deep tenderness following injection of hypertonic saline. A number of studies[35,81–83,86,88,95,109,135,174] measured intramuscular electrical pain thresholds following injection of 20% hypertonic saline into the human vastus lateralis muscle and observed significant decreases lasting for 24 hours. However, this finding could not be confirmed in a recent study with control injection of 0.9% isotonic saline into the tibialis anterior muscle.[108] Injection of 6% hypertonic saline into the infraspinatus muscle causes a significant decrease in pressure-pain thresholds at referred pain sites.[110] Additionally, Jensen and Norup showed that injection of hypertonic saline into the human anterior temporalis muscle significantly decreased the pressure-pain threshold during ongoing pain; but after about 5 minutes the pressure-pain thresholds had returned to baseline values.[96] This is in accordance with the lack of significant changes in pressure-pain thresholds 5 minutes after injection of 5% hypertonic saline into the masseter muscle.[113] However, the stimulus-response curves had shifted significantly upward, indicating increased deep sensitivity.[113]

The finding of deep hypoalgesia to intramuscular electrical stimulation proximal to the pain area in healthy subjects further complicates the interpretation of pain-induced effects on deep sensitivity,[7] as does the observation of deep hypoalgesia to pressure stimuli in referred pain areas and extrasegmental sites.[44,104] In human studies, the influence of endogenous inhibitory control systems may be considered an important factor to explain these hypoalgesic effects. Thus, in the normal somatosensory system, descending inhibitory controls and segmentally organized inhibitory mechanisms may partly counteract peripheral and central sensitization.[108,175–177] Indeed, animal studies have suggested that deep noxious stimulation can effectively trigger these inhibitory systems and inhibit nociceptive activity in spinal dorsal horn or brain stem neurons.[178–180] On the other hand, brain stem structures such as the ventral nucleus reticularis gigantocellularis may have coincident descending inhibitory and facilitatory effects on the development of hyperexcitability in spinal dorsal horn neurons.[181] Imbalance between such opposing descending modulating systems could be of importance for the variability of deep sensitivity.

Combined injection of BK and 5-HT or substance P and BK causes significantly lower pressure-pain thresholds, and injection of capsaicin into the masseter muscle also causes significant reductions in thresholds.[21,50,53,57] In contrast, hypertonic saline may not have a very strong or long-lasting sensitization effect; in fact, one study[126] found that nociceptive group III muscle afferents showed decreased responsiveness to pressure stimuli following the second administration of hypertonic saline. In conclusion, the effect of intramuscular injection of hypertonic saline on deep sensitivity is relatively modest in healthy human subjects, probably because of little or no potency to induce peripheral sensitization and a concurrent activation of endogenous inhibitory control systems.

Clinical Muscle Pain and Sensitivity of Deep Tissues

A large number of studies have consistently reported lower pressure-pain thresholds in the jaw-closing muscles of patients with TMD pain compared to control subjects.[114,145,162,182–187] Patients with episodic or chronic tension-type headache have also been reported to have lower pressure-pain thresholds in craniofacial muscles,[149,188,189] but other studies have failed to show this difference between tension-type headache patients and control subjects.[47,190–192] The degree of chronicity and probably daily levels of pain may influence the pressure-pain thresholds.[25,164] Furthermore, there might be differences related to measurements made at tender points or trigger points versus measurements made at fixed anatomic locations.[25,183]

The pathophysiologic mechanism responsible for lower pain thresholds in deep craniofacial tissues could be a sensitization of peripheral nociceptors. Animal studies have shown that a deep noxious input causes sensitization of the peripheral receptors.[193] Thus, endogenous substances released by tissue trauma, such as BK, 5-HT, PGE_2, and adrenaline, as well as hypoxia, lower the mechanical threshold of nociceptors into the innocuous range; as a consequence, weak stimuli are able to excite nociceptors and elicit pain.[11,48,194,195] Furthermore, experimental myositis in animals is associated with an increased density of substance P and NGF-immunoreactive nerve fibers, which could contribute to the peripheral sensitization process.[156] It is also an intriguing finding that persistent jaw muscle pain in humans seems to be associated with local changes in 5-HT levels, as revealed by microdialysis techniques.[196] Ernberg et al[196] suggested that peripheral 5-HT could be involved in the hyperalgesia to pressure stimuli in patients with persistent jaw muscle pain; this is in accordance with a direct hyperalgesic action of intradermally applied 5-HT in rats.[197] In contrast, intramuscular injection of low concentrations of 5-

HT does not seem to induce experimental muscular hyperalgesia.[51,53]

Although peripheral sensitization may cause deep tissue hyperalgesia, there is substantial evidence that sensitization of second-order neurons in the spinal cord or brain stem is also involved in the pathophysiologic process.[11,66,72,146,198,199] The neuropharmacology of central hyperexcitability has been described in detail, and the NMDA and neurokinin-1 receptors in particular, as well as the formation of nitric oxide, appear to play a crucial role in the hyperexcitability and spontaneous hyperactivity.[54,67,76] In fibromyalgia patients, the NMDA receptor antagonist ketamine significantly reduces spontaneous muscle pain and attenuates hyperalgesia to pressure stimulation,[200,201] probably because the NMDA antagonist suppresses central hyperexcitability. Based on studies of capsaicin-induced cutaneous hyperalgesia,[202] central summation of nociceptive inputs from muscles would be expected to be exaggerated in musculoskeletal pain conditions if central hyperexcitability is involved. In line with this suggestion, the efficacy of temporal summation of intramuscular electrical painful stimuli is increased in fibromyalgia patients compared to control subjects.[147] Moreover, the augmented temporal summation in fibromyalgia patients seems to be reversed by an NMDA antagonist.[203] Hence, the combination of pharmacologic modulation and experimental pain assessment might be a valuable tool in elucidating the possible involvement of central hyperexcitability in patients with craniofacial muscle pain.

The site-specificity and extent of deep hyperalgesia has been examined in several papers. One study[204] reported that the pressure-pain sensitivity in the finger was increased in patients with TMD pain. In accordance, Maixner et al[145,153] have presented good evidence that patients with TMD pain are hyperalgesic to stimulation of deep tissues outside the craniofacial region. They speculate that this state of generalized deep hyperalgesia could be caused by defects in endogenous inhibitory control systems, which could also account for observations of generalized hyperalgesia in tension-type headache patients[149,152] and fibromyalgia patients.[147,173,205–207] However, these results contrast with findings of Carlson et al[187] and Svensson et al,[113] where no significant differences were found in pressure-pain thresholds in the finger between patients with persistent jaw muscle pain and control subjects. It is difficult to explain the observed differences, since strict inclusion criteria for the diagnosis of TMD pain were followed[3] and comparable pressure algometers were used in these studies.[113,145,187] It should be noted that the pressure-pain thresholds were reduced relatively more (22% to 30%) in the jaw-closing muscles than in the wrist (12%) in patients with persistent jaw muscle pain.[145] This could imply a graded effect of changes in deep hyperalgesia. In contrast, more pronounced changes in deep pressure sensitivity were observed in the finger than in the anterior temporalis in patients with chronic tension-type headache compared to healthy controls.[152] Thus, it remains an open question whether the deep sensitivity to painful stimuli is site-specific or generally altered in patients with craniofacial muscle pain. Moreover, graded responses corresponding to transitions from localized pain complaints to more widespread pain complaints might be of importance. An interesting observation is that many fibromyalgia patients have a preceding history of localized muscle pain that develops into a more generalized pain condition.[208]

In summary, there is good evidence that the sensitivity to pressure stimuli within the local pain area is increased in patients with craniofacial muscle pain, ie, a localized deep hyperalgesia. One mechanism that could be responsible for the observation of deep hyperalgesia is sensitization of peripheral nociceptors. However, the observation of more generalized increases in sensitivity to pressure stimuli in some patients with craniofacial muscle pain suggests that changes in central hyperexcitability are involved as well. The finding of generalized deep hyperalgesia contrasts with the experimental muscle pain studies in healthy subjects, in which there is considerable evidence for deep hypoalgesia outside the local pain area. The development of persistent muscle pain and generalized deep hyperalgesia could be associated with a gradual decrease in the efficacy of endogenous inhibitory control systems[145] or an imbalance between descending facilitatory and inhibitory control systems.[181]

A practical implication of the psychophysical studies reviewed above is that stimulus intensity, stimulus modality, stimulus location, and rating scales must be carefully described and standardized to obtain useful information and allow comparisons between studies. There is a continual need to supplement the data from previous studies of craniofacial muscle pain with new data derived from extra-segmental stimulation to determine the extent and degree of somatosensory changes in well-defined subgroups of patients. An important note is that many patients with craniofacial pain may also have unrecognized pains in other parts of their body.[209] This could explain why some studies

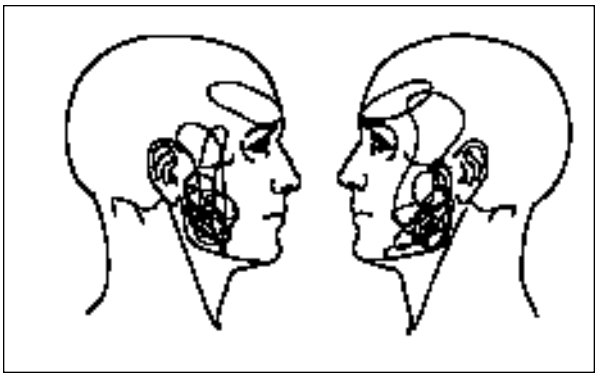

Fig 3 Examples of pain drawings following bilateral bolus injection of 0.2 mL 5% hypertonic saline into the masseter muscles in 10 healthy subjects. Note the diffuse distribution of pain.

show generalized changes in somatosensory sensitivity, and it also questions a simple cause-effect relationship if multiple pain loci are present. A wide variety of somatosensory changes can be expected in conditions with craniofacial muscle pain, ie, both hypo- and hyperalgesia and hypo- and hyperesthesia have been described in experimental and clinical pain studies. From a clinical point of view, psychophysical tests may nevertheless facilitate the differential diagnosis, eg, neurogenic pain disorders often have somatosensory deficits in discrete regions related to the nerve supply, whereas patients with craniofacial muscle pain are unlikely to demonstrate a strict somatotopic pattern of changes. Furthermore, the psychophysical studies imply that both peripheral sensitization and hyperexcitability of central neurons may be responsible for the observed effects of muscle pain. This means that the management of craniofacial muscle pain should target both peripheral and central sites. Finally, the experimental pain studies have clearly indicated that deep and superficial somatosensory sensitivity can change in the presence of jaw muscle pain,[113,117] which suggests that patients with persistent muscle pain do not a priori have lower psychophysical thresholds.

Localization of Experimental Muscle Pain

In contrast to superficial types of pain, pain from deep structures is typically described as diffuse and difficult to locate precisely.[11,85,198,210] Thus, the perceived localization of deep pain may be different from the original source of pain. Pain localized to the source of pain is termed *local* or *primary pain*, whereas pain felt in a different region away from the source of pain is termed *referred* or *heterotopic pain*.[210] Referred pain in the craniofacial region has been defined as pain in other structures or pain completely separated from the local pain areas.[99] Pain drawings are useful tools to illustrate the localization and extent of pain areas,[211,212] although the perceived size of body areas is labile and may be influenced by pain-induced changes in central somatosensory maps.[213]

Experimental human studies with infusion of hypertonic saline into the midportion of the masseter muscle have shown diffuse areas of pain within the muscle, which spread toward the temporomandibular joint, temple, and eye region on the ipsilateral side[99,100,116,117,119] (Fig 3). Preliminary maps of saline-induced pain from 6 different pericranial muscles showed that the masseter and anterior temporalis were consistently associated with referred pain patterns, whereas other pericranial muscles showed a less uniform pain distribution among subjects.[214] Gerber et al[109] documented that pain induced by experimental irritation of the acromioclavicular joint in healthy subjects could be distinguished from irritation of the subacromial space and that the corresponding pain patterns derived from pain maps could yield clinically relevant information for the differential diagnosis. In the craniofacial region it is clinically relevant that experimental jaw muscle pain can cause pain referred to the teeth.[99,113] This should be considered in the differential diagnosis of odontogenic pain problems. Likewise, it is well-established that odontogenic pain may mimic jaw muscle pain.[215] Teeth exposed to a past painful event under general anesthesia may be the site of referral when the maxillary sinus ostium is stimulated more than a week earlier.[216,217] This suggests that a strong barrage of nociceptive activity may prime central nociceptive neurons and bring about a central hyperexcitability that can persist for an extended period of time.

The frequency and area of referred pain is dependent on the perceived intensity of the experimental painful stimulus[96,100,103,105] and the duration of the stimulus.[38,40] The self-reported pain area also increases as a function of time; this illustrates the radiating or spreading character of deep craniofacial pain.[117] Moreover, sequential infusion of hypertonic saline has shown that the perceived intensity and area of muscle pain are influenced by temporal summation.[105] Interestingly, a larger number of subjects developed referred pain during sequential infusions given at 90-second interstimulus intervals compared to 360-second interstimulus intervals. Thus, it has been suggested that

temporal summation of afferent inputs onto common central neurons may be involved in the development of referred pain.[41,177]

The increase in self-reported pain areas in human models of experimental muscle pain is paralleled by the findings of an increase in receptive field size of spinal cord and brain stem nociceptive neurons in animal models of myositis.[72,138,218] Hoheisel et al[138] found a 40% increase in the size of mechanoreceptive fields 5 minutes after BK injection in rat hind limb muscles. Hu et al[72] and Yu et al[74] reported increases in mechanoreceptive field size between 20% and 300% following noxious stimulation of deep craniofacial tissues in rats. It is likely that there is an association between the increases in referred pain areas and the increases in receptive field size related to changes of the excitability of central neurons in the brain stem and spinal cord.

The various theories on referred pain mechanisms have been reviewed recently.[11,124] Referred pain is most likely a central mechanism, because it is possible to induce referred pain in limbs with complete sensory loss following spinal injury[219] or anesthetic blocks.[37,88,220] There is good evidence that a feature of the diffuse nature and poor localization of muscle pain is the central convergence of afferent fibers onto common central nociceptive neurons, because this feature would reduce the spatial resolution of somatosensory information.[221] Several studies in the craniofacial region[129,222,223] and in the spinal system[127,128,224,225] have shown that nociceptive afferents from muscles, joints, skin, and viscera converge onto common projection neurons. Mechanisms other than central convergence may also be involved in the expression of referred pain, since there is normally a time delay between the onset of local and referred pain.[37,81,94,104] One possibility is that the nociceptive barrage from muscle tissue opens up latent connections, ie, a form of central divergence. Thus, myositis-induced input from muscle nociceptors could lead to an expansion of the responding neuron population in the spinal cord or brain stem.[54] The synaptic connections between neurons that originally had no effective drive from the myositis-induced muscle now become effective. The neurobiology subserving such mechanisms is probably related to central sensitization of second-order nociceptive neurons and the development of hyperexcitability.[54] The diffuse nature of muscle pain and the "misinterpretation" of referred pain can also be related to other neurobiologic features, such as a small number of neurons that respond exclusively to noxious stimulation of muscle afferents[66,128,129,225] and few cortical neurons specifically responsive to deep nociceptive inputs compared to superficial inputs.[226,227] Furthermore, convergence of nociceptive inputs at the level of the thalamus and at higher cortical levels might also be important for referred pain.[228]

Localization of Clinical Muscle Pain

Pain drawings have not been applied on a regular basis for assessment of TMD pain.[212,229,230] A recent study showed that only about 19% of patients referred to a facial pain clinic have pain confined to the trigeminal region, whereas 66% have widespread pain outside the trigeminal and cervical regions.[212] Information on these concomitant sites of pain has largely been neglected, even though their presence draws attention toward the involvement of more widespread pathophysiologic mechanisms.[209,231]

Travell and Simons[232] presented the classical topographic distributions of jaw muscle pain. These maps were drawn from the clinical experience of the pain patterns produced by activation of trigger points in the jaw muscles. Depending on the location of the trigger points in the superficial part of the masseter muscle, pain may be referred to the mandible or maxilla (sinusitis-like pain), to the mandibular or maxillary molar teeth (toothache), to the gingiva, to the temple and over the eyebrow, or preauricularly to the region of the temporomandibular joint (earache). From the deep part of the masseter, pain can be experienced in the mid-cheek area and the ear (earache and tinnitus). In close accordance with this description, it has been found that the pain of trigger points in the deep part of the masseter may often (41.5% to 55.5% of the time) be referred to the temporomandibular joint or ear, whereas trigger points in the superficial part of the masseter can be referred to the jaw, cheek, gingiva, maxillary premolars, or mandibular molars.[233] Thus, there are fairly consistent and reliable patterns of referred pain from deep craniofacial tissues.[234–236] It is important to realize that referred pain per se is not a pathophysiologic phenomenon because it can be elicited in healthy subjects. However, this central mechanism may be modulated by chronic pain conditions. The referred pain area induced by hypertonic saline is enlarged in patients with chronic fibromyalgia and whiplash syndrome as compared to control subjects.[147,237] Saline injection both within and outside the painful region produces significantly larger referred pain areas. Interestingly, referred pain

proximal to the injection site has been observed in fibromyalgia and whiplash patients, whereas this is rarely found in healthy subjects. Hence, central hyperexcitability is most likely involved in the facilitated response of referred pain. In line with this notion are findings that the NMDA antagonist ketamine reduces the increased areas of saline-induced referred pain in patients with fibromyalgia.[203]

Experimental jaw muscle pain evoked by injection of hypertonic saline shares many of the clinical features of persistent muscle pain in the craniofacial region, with spread of pain to the temporomandibular joint, jawbone, and teeth. The perceived intensity and duration of muscle pain seem to be important factors in the spread and referral of pain. The underlying mechanisms responsible for this spread and referral of pain are most likely related to central convergence of afferent fibers and unmasking of new synaptic connections resulting from central hyperexcitability. Thus, human experimental pain models may be used to study in detail the underlying neural mechanisms of referred pain, eg, by blocking the peripheral input from the referred pain area.[37]

Pain drawings are useful tools in experimental and clinical research to map the extent of pain, but they cannot differentiate between local (primary) pain and referred pain (heterotopic). Furthermore, the current versions of pain drawings do not distinguish sufficiently well between superficial or deep types of pain. The clinical implications are the use of diagnostic blocks to differentiate between local and referred pain areas and early treatment to avoid the spread of jaw muscle pain.[210,238]

Sensorimotor Integration of Muscle Pain

There are good reasons to believe that jaw motor function and muscle pain are interrelated, mainly because the cardinal symptoms of TMD include both pain and tenderness in craniofacial muscles and restrictions and deviations in jaw movements.[239] Over the years, many pathophysiologic models have been presented to explain the interaction between jaw motor function and muscle pain.[210,239–243] A common denominator is increased muscle tension, muscle hyperactivity, or muscle spasms caused by psychologic, psychophysiologic, neuromuscular, or biomechanical factors. An important problem with clinical cross-sectional trials is the difficulty in identifying what is the cause and what is the effect of muscle pain. Experimental muscle pain models may therefore provide important insight into the nature of such sensorimotor interactions. The following sections will review the literature on the interaction between craniofacial muscle pain and various jaw motor functions, with the exception of jaw reflexes, which have recently been reviewed.[244]

Experimental Muscle Pain and Electromyographic Activity at Rest

The completely resting muscle is characterized by the absence of any EMG activity[245]; however, with the jaws at rest, there is weak EMG activity present in the human jaw-closing muscles.[246] This may serve to counteract the effects of gravity on the mandible, ie, postural activity. In the trigeminal system, the jaw-closing muscles serve as the physiologic extensors and the jaw-opening muscles as the flexors.[247] There is general consensus that healthy, non-painful jaw muscles will exhibit only very low levels of EMG activity in the range of 3 to 5 μV, but there is no scientific evidence for any exact threshold values.[248] Surface EMG recordings are influenced by position and types of electrodes,[246] position of the body,[249] thickness of subcutaneous layers,[247] and psychologic factors such as stress.[250–253] Methodologic problems regarding intraindividual and interindividual reproducibility have also been investigated.[246,254,255] Jensen[25] concluded that surface EMG recordings of craniofacial muscles were reliable and reproducible, but because of the high interindividual variability (> 30%) and the relatively lower intraindividual variability (14% to 18%), paired studies should be preferred.

To avoid a discussion of cause-effect relationship between muscle pain and surface EMG activity at rest, a number of human experimental studies have directly measured EMG activity in response to deep injection of hypertonic saline.[46,98,106,107,118,256–259] Some of these studies report increases in EMG activity but provide no quantitative measure or statistics to support the claim.[46,256,259] Cobb et al[257] used semi-quantitative EMG techniques and suggested a considerable degree of correlation between the time course of pain and increased EMG activity. However, no surface EMG activity could be detected in 2 of 7 subjects; 1 subject demonstrated increases in EMG activity before the onset of pain, and no increases in intramuscular EMG could be found. Moreover, the reported increases in surface EMG activity were small, in the range of 3 to 10 μV, and were sometimes obscured by electrocardiographic artifacts during recordings

from the paravertebral muscles. Nevertheless, the authors saw no reason to challenge the well-accepted concept of the pain-spasm-pain theory.[257] A more recent quantitative study revealed that the surface EMG activity of the sternocleidomastoid muscle increased significantly during a painful injection of hypertonic saline,[259] but the authors later ascribed the changes to mimetic responses from the platysma.[98] Stohler et al[98] found significant increases in surface EMG activity of the jaw-closing muscles at rest when they were exposed to painful infusion of hypertonic saline, but the EMG increases were not significantly different from those induced by actively recalling an experience of past pain and could again be contaminated with EMG activity from mimetic muscles. Graven-Nielsen et al[107] found an increase in intramuscular EMG activity following infusion of isotonic or hypertonic saline into the tibialis anterior muscle but reported no difference in EMG activity between the 2 infusions. Finally, it has been shown that hypertonic saline injection into the masseter and tibialis anterior causes a transient increase in both surface and intramuscular EMG activity, but this activity is not correlated to the perceived pain intensity as measured on visual analog scales.[118] It was suggested that part of the transient EMG increases could be explained by increased endplate noise and endplate spikes at the neuromuscular junction and less likely by recruitment of new motor units.[118]

Overall, these studies suggest that a number of factors may influence postural EMG activity, eg, electrode type and mimetic muscle activity. There is little experimental evidence to suggest a long-lasting increase in EMG activity in human subjects during ongoing experimental muscle pain. The weak and inconsistent signs of EMG increases in humans are in direct contrast to the robust EMG increases observed in the jaw muscles of animals exposed to injection of algesic substances into deep craniofacial tissues.[55,56,71,73,75,76,78,79] This type of physiologic response strongly suggests an initial (lasting 10 to 15 minutes) facilitatory effect of deep nociceptive afferents on alpha motoneurons, with a critical relay in the trigeminal subnucleus caudalis.[260] Moreover, intense group IV afferent inputs into the spinal cord can produce a prolonged increase in the excitability of the flexion reflex.[261] This facilitated reflex response was seen mainly after stimulation of muscle afferents and not after stimulation of cutaneous afferents. It should be noted that the jaw muscle responses evoked by noxious stimulation of deep craniofacial tissues involve strong responses in both the jaw-opening and jaw-closing muscles. This can be interpreted as a "splinting" reaction, with the physiologic purpose to limit jaw movements and allow rapid healing.[65,66]

Clinical Muscle Pain and Electromyographic Activity at Rest

There is no consensus on the level of EMG activity recorded by surface EMG electrodes overlying the jaw-closing muscles in conditions with craniofacial muscle pain. A number of studies have indicated no significant difference in postural activity between patients with TMD pain and control subjects.[253,262–265] Other studies have found a small increase[252,266–274] and some studies even reported a small decrease.[255,275] The same controversy is present for tension-type headache; some studies have reported significant increases in pericranial surface EMG activity,[276–281] and other studies have revealed no significant increases or relationships to pain.[282–284] Many of the studies have been criticized for a lack of proper matching between patient and control groups with regard to age, gender, cranial morphology, and oral habits like bruxism.[285] However, 2 recent and well-controlled studies showed a small, significant increase in surface EMG activity in patients with TMD pain[273] and chronic tension-type headache.[192] However, the specificity of a slightly increased surface EMG activity in the jaw-closing muscles has also been questioned because it could easily be contaminated with cross-talk of EMG activity from mimetic muscle, eg, eye muscles or platysma.[98,247,259] Pain is reflected in the facial expressions and mimetic responses,[286] which seems to support a potential contribution from mimetic muscles to the surface EMG recordings of jaw-closing muscles. Finally, the pathophysiologic importance of such small increases in postural EMG activity, if they exist, has been questioned,[98] especially since the described EMG increases are calculated to represent less than 1% of the MVC level, and there is no evidence that this can lead to the development of muscle pain.[98]

For a long time, increased postural EMG activity has been believed to play a very important role in the pathophysiologic mechanisms in many musculoskeletal pain disorders, including pain in the craniofacial region. Increased EMG activity in painful muscles would also intuitively explain the clinical impression of increased tension or hardness in the same muscles. Recently, evidence was presented for increased hardness of pericranial muscles in patients with tension-type headache.[287,288] Travell et al[289] are usually given credit

for the description of the "vicious cycle," which proposed a mutually reinforcing relationship between chronic pain and muscle hyperactivity. In this respect, confusion regarding terminology has long existed, since the terms "muscle tension," "muscle spasms," "muscle contractures," and "muscle hyperactivity" have been used interchangeably but may represent entirely different conditions.[290] De Vries[291] suggested that muscle pain and soreness were caused by tonic local spasm of motor units and that pain reflexly sustained the tonic muscle contraction, thus setting up a vicious cycle. Later, Johansson and Sojka[292] presented a model to explain the muscle tension and pain that integrated the gamma motoneuron system in the pathophysiologic mechanisms. Mense[11] discussed a modified vicious cycle concept in which the critical component was local ischemia. However, it was pointed out that at present there is no evidence for the suggested chain of events. Finally, Simons and Mense[290] have proposed that tension in painful muscles is electrically silent and that muscle contracture and not contraction could cause tension. The minute loci of trigger points could be associated with localized EMG activity,[293] but the question of increased EMG activity in trigger points of jaw-closing muscles has not yet been unambiguously answered.[25,294,295]

The topic of postural EMG activity in painful musculoskeletal disorders has for decades caused much speculation and discussion and continues to do so. There is at present no indisputable evidence in favor of increases in EMG activity of jaw-closing muscles in clinical or human experimental studies of craniofacial muscle pain. The same appears to be true for other musculoskeletal pain disorders.[247] Even if there were significant increases in postural EMG activity in patients with craniofacial muscle pain, then the absolute magnitude of such EMG changes would be very small and would provide no diagnostic information.[25,273] The pathophysiologic consequence of a small tonic increase in EMG activity, eventually corresponding to the recruitment of a few motor units, is not known. Finally, surface EMG recordings of human craniofacial muscles with the jaws at rest are susceptible to contamination by mimetic responses and should be interpreted cautiously. Intramuscular EMG recordings might avoid the problem of EMG crosstalk. The evidence of strong facilitation of EMG activity in jaw muscles of rats following injection of various algesic substances into deep craniofacial tissues indicates that excitatory pathways do exist to the alpha motoneuron pools of both the jaw-opening and jaw-closing muscles, and the co-contraction of the jaw-opening and jaw-closing muscles may serve as a "splinting" effect and reduce jaw movement. The discrepancy between the human and animal models of experimental pain might be related to the differences in recording conditions, jaw position, influence of anesthesia, and the magnitude of nociceptive activity. In conclusion, the human experimental studies have contributed to the discussion of the cause-effect relationship between pain and motor function by showing that jaw muscle pain at a clinically relevant level has little or no effect on postural EMG activity in jaw-closing muscles.

Experimental Pain and Static Electromyographic Activity

Measurement of the maximum EMG activity during static and concentric contraction of the jaw-closing muscles has been widely used to examine the motor function of the masticatory system. Maximum voluntary occlusal force can be measured reliably in healthy subjects by various intercclusal transducers, all of which, however, have some drawbacks because the bite is inevitably raised and the afferent input from the periodontal receptors can influence the maximum effort.[296,297] In addition, a number of other factors, such as age, gender, occlusal parameters, and facial morphology, are of importance in the maximum voluntary occlusal force.[297]

Jaw muscle pain induced by tonic infusion of hypertonic saline has been shown to reduce the maximum voluntary occlusal force[116] and the maximum EMG activity of jaw-closing muscles.[122] Comparable results have been obtained during tonic pain in the tibialis anterior, where the MVC is significantly reduced and the endurance time at 80% MVC is significantly reduced.[106] Ashton-Miller et al[260] found no significant effect of experimental pain in the sternocleidomastoid on submaximal contractions at 10% MVC. A decreased ratio between EMG activity in the tibialis anterior and the dorsiflexion torque around the ankle following injection of hypertonic saline was described by Graven-Nielsen et al.[106] This finding could suggest an effect of experimental muscle pain on the recruitment pattern of motor units, which is in line with the notion that pain inhibits the activity of the alpha motoneuron pool.[247]

In contrast to the significant effect of experimental jaw muscle pain on maximum voluntary occlusal force, sustained static or dynamic contractions have failed to induce significant changes in healthy subjects' ability to produce maximum

contractions.[34,298] Christensen[299] ascribed the reduced endurance of jaw-closing muscles to neuromuscular fatigue. In a well-designed study, Clark and Carter[298] argued, however, that the primary limiting factor of sustained submaximum contractions was the development of ischemic pain in the jaw-closing muscles. Furthermore, the relationships between occlusal force and EMG activity did not change during static contractions at various force levels, whereas the mean frequency of the EMG signal decreased significantly.[300] Thus, neuromuscular fatigue appears to develop later than pain in the jaw-closing muscles in experimental models of tooth clenching or tooth grinding.

Clinical Muscle Pain and Static Electromyographic Activity

In comparison to healthy subjects, patients with muscle pain in the craniofacial region have reduced maximum EMG activity[272,274,301–306] and reduced maximum voluntary occlusal force.[303,307–310] In addition, a shorter endurance time at submaximum contraction levels,[302,311] greater decreases in the mean power frequency content of the EMG signal during submaximum clenching,[274,304,311,312] steeper force-EMG curves,[309,313] and less steep curves of force versus mean frequency of the power spectrum[314,315] have been described in the jaw-closing muscles of patients with craniofacial muscle pain.

Muscle pain has been suggested to cause inhibition of the maximum voluntary output of the contracting muscles through actions within the central nervous system.[247,295,316] Alternatively, it has been argued that weak muscles have a greater risk of becoming painful, and consequently a higher proportion of patients with craniofacial muscle pain will have lower maximum voluntary occlusal force.[301,317,318] The suggested predisposition of weak muscles to become painful seems to be supported by the lack of significant increases in maximum EMG activity following treatment of patients with craniofacial pain.[310,317] In contrast, Helkimo et al[308] found that the maximum voluntary occlusal force increased following treatment of their TMD pain patients.

To address the question of a peripheral versus a central pathology for the reduced maximum voluntary force, the painful muscles can be stimulated electrically by the use of a twitch force technique to determine the "true" maximum muscle force.[319,320] This technique has not yet been applied to patients with craniofacial muscle pain. Fibromyalgia patients have lower maximum voluntary contraction forces, but unfortunately the use of electrical stimulation techniques has yielded equivocal results. Thus, the electrically evoked muscle force is either found to be the same in fibromyalgia patients and control subjects[321,322] or to be 20% to 50% lower in fibromyalgia patients.[323,324] A reduced "true" maximum muscle force could nevertheless develop following relative physical inactivity of the muscle or by unknown disturbances in microcirculation.[320] Finally, a longitudinal study related to chronic low back pain found that over a 10-year period, there was no association between the initial level of muscle function and the subsequent development of pain.[325] This supports the view that reduced occlusal force is the consequence, not the cause or predisposing factor, of pain. Thus, activity in nociceptive group III and IV muscle afferents can reduce the net output of the alpha motoneuron pool.

In summary, there is good evidence that the maximum EMG activity and voluntary occlusal force in patients with craniofacial muscle pain are reduced as compared to control subjects. It remains controversial to what extent these parameters return to normal values when muscle pain is successfully treated. Human experimental studies suggest that the reduced capacity to produce a maximum effort results from the acute effect of muscle pain. Thus, activity in nociceptive muscle afferents has inhibitory effects on the alpha motoneuron pool of the homonymous muscle during static contractions.[316] Furthermore, there appear to be signs of faster neuromuscular fatigue in patients with craniofacial muscle pain, but the patients are not in a constant state of fatigue.[311] Further studies are necessary to separate the underlying neurophysiologic mechanisms of jaw muscle pain and jaw muscle fatigue from each other.

Experimental Muscle Pain and Electromyographic Activity During Movement

The basic pattern and rhythm of mastication and the underlying neurophysiologic mechanisms have been carefully described in several papers and reviews.[246,326–328] Registration of jaw muscle EMG activity, combined with recording of jaw movements, is required to obtain a good understanding of the human masticatory process.[329–332] Thus, EMG activity can be determined, for example, in the fast-opening, fast-closing, and slow-closing phases of the masticatory cycles[333] and divided into phases with antagonist and agonist action of

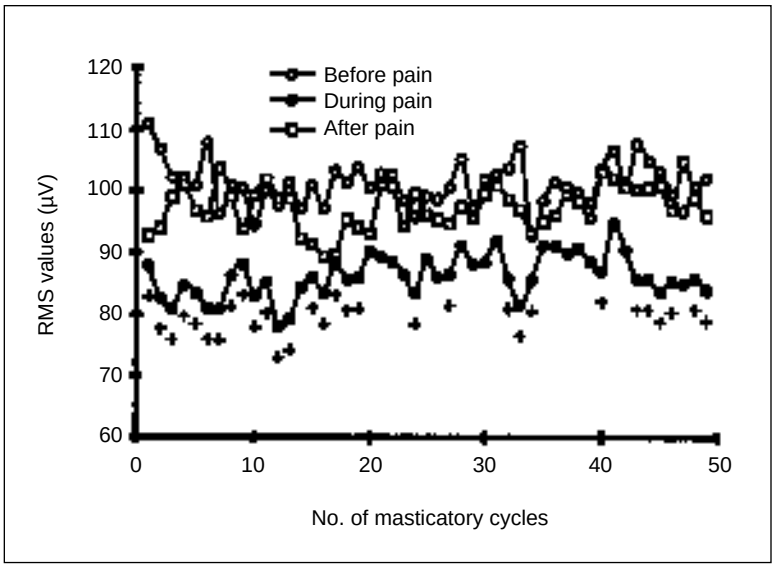

Fig 4 Quantitative EMG analysis of jaw-closing muscles during continuous mastication (n = 12). The effect of tonic experimental muscle pain can be seen as a significant decrease in the root-mean-square (RMS) value of the EMG burst in the agonist phase. + = $P < 0.05$. From Svensson et al[116]; reprinted with permission.

the jaw muscles. A kinematic analysis of jaw movements most often includes measurement of the maximum displacement in 3 dimensions, in addition to duration and velocity of movements.[334–336] Several studies have examined the reliability and reproducibility of surface EMG recordings and kinematic registration of the mandible.[331,337] In particular, the problems with non-linearity of magnet-based jaw-tracking devices have been pointed out,[338,339] although jaw movements during normal mastication are within the linear range of magnet-based devices, and resizing algorithms can be used.[114,115] The newer opto-electronic jaw-tracking devices have, however, increased the accuracy and sensitivity considerably compared to the magnetic-based devices.[340–342] Despite differences in the measurement techniques, it is generally established that factors such as gender,[343] age,[344] occlusion and facial morphology,[246] and bolus size and consistency[345,346] can influence the masticatory process.

Preliminary evidence was presented by Lund et al[247] that injection of hypertonic saline into the human masseter muscle causes a reduction of the agonist burst during empty open-close jaw movements. This was later confirmed in groups of healthy men exposed to hypertonic saline injection.[114–116] A single bolus injection induced significant levels of jaw muscle pain and reduced the maximum displacement of the mandible in the lateral and vertical axes and slowed down the maximum velocities during jaw opening and jaw closing.[114] This analysis was based on averaged masticatory cycles and therefore did not take into consideration the cycle-to-cycle variability. Subsequently, the analysis of the masticatory patterns was extended to include analysis of each single masticatory cycle[115,116] (Fig 4). Bilateral injections of hypertonic saline into the masseter muscles cause a significant reduction of the agonist EMG bursts and a significant increase in the antagonist EMG bursts in some of the masticatory cycles.[115] Svensson et al found no statistically significant effects of pain on the maximum displacements or duration of the masticatory cycles.[115] Later Svensson et al showed that mastication on the contralateral side to the painful side had a similar but smaller effect on the EMG activity in the agonist burst.[116] The duration of the masticatory cycles was not changed significantly in the presence of experimental jaw muscle pain.[114–116] Thus, a series of studies on the effects of hypertonic saline injection into the masseter muscle have consistently shown a decrease in agonist EMG activity

in the range of 10% to 15%, a small increase in antagonist EMG activity, and modest or no reductions in maximum displacements.

These findings are generally in accordance with experimental pain studies and muscle activity during gait and repetitive shoulder movements.[101,106,111] During saline-induced muscle pain in the lower back, the lumbar muscle EMG activity during gait is increased in phases where the EMG activity normally is silent and decreased in the phases with normally strong EMG activity.[101] Experimental models of muscle pain have also been used in occupational settings (low load, repetitive work), where it was found that hypertonic saline–induced neck muscle pain causes a decreased working rhythm and comparable changes in muscle coordination.[111]

The experimental findings in humans are supported by observations in animal preparations of mastication. In decerebrate rabbits with cortically induced mastication, noxious pressure applied to the zygoma or intramuscular injection of hypertonic saline caused a significant reduction in the agonist EMG burst, significant increases in the duration of the masticatory cycle, and significantly smaller amplitudes.[347,348] The difficulties that the human experimental pain studies have in showing changes in duration of the masticatory cycle could be related to the obvious differences in the human and animal studies. First, human studies are performed in conscious human beings, and the influence of higher-order brain centers cannot be ruled out. There is good evidence that the primary somatosensory and motor areas participate in the fine-tuning of mastication.[349] In addition, the motivational component of pain may influence sensorimotor interaction. The finding that mastication increases the perceived intensity of pain[350] also suggests that higher-order brain centers could contribute to pain-induced changes in mastication. Second, the human studies are performed with a bolus, whereas the animal studies look at empty open-close jaw movements evoked by electrical stimulation of the corticobulbar tract. The motor programs related to such different types of jaw movements could also be differentially influenced by pain. Nevertheless, the human experimental and animal studies are in general agreement with each other and have provided experimental evidence in support of specific pain-induced changes in dynamic motor function.

Clinical Muscle Pain and Electromyographic Activity During Movement

Patients with craniofacial muscle pain seem to differ in rather discrete ways in their masticatory pattern compared to control subjects. Mongini et al[351] found smaller and slower movements during mastication in patients with TMD pain. Feine et al[352] reported that the average and maximum opening velocities of the mandible were lower in patients with persistent jaw muscle pain than in matched control subjects, but found no differences in the maximum displacement during empty open-close movements. The lack of significant changes in the maximum displacement is consistent with several other studies that used jaw-tracking devices.[353,354]

Møller et al[355] found that TMD pain patients used their jaw-closing muscles significantly less during the agonist phase; however, the relative contraction strength was found to be higher, most likely because of a decreased maximum voluntary occlusal force as well. Nielsen et al[356] observed significantly less intense and less frequent EMG activity in the jaw-closing muscles in the agonist phase of patients with persistent jaw muscle pain compared to control subjects. However, the control groups in these 2 studies were not matched to the patient groups. In his complex analysis of masticatory patterns, Kumai[357] noted that TMD pain patients had more irregular muscle function and weaker activity of the jaw-closing muscles. Regarding the EMG activity of the jaw-closing muscles in the antagonist phase (during jaw opening), Stohler et al[358,359] found increased values during painful mastication, which is in accordance with the findings of Møller et al.[355] Finally, it has also been shown that TMD pain patients have a significantly longer duration of the masticatory cycle, ie, they chew more slowly than control subjects.[355]

Lund and colleagues[247,248,295] drew attention to the fact that comparable findings with slower movements and less EMG activity in the agonist phase and more EMG activity in the antagonist phase could also be observed during other dynamic motor tasks, such as gait, in other musculoskeletal pain conditions. These observations led to the formulation of the pain-adaptation model, which strongly contrasted with the "vicious cycle" model (see above). The pain-adaptation model predicts that the consequence of nociceptive inputs to premotoneurons in the brain stem would be facilitation of inhibitory pathways to the alpha motoneurons (during agonist function) and facilitation of excitatory pathways (during antagonist

function).[247] The essential prerequisite for the model is the collection of premotoneurons constituting the central pattern generator in the brain stem and groups of inhibitory and excitatory interneurons.[327,360,361] The pain-adaptation model elegantly explains the motor consequences of pain but does not provide any explanation for the origin of pain.

The dynamic jaw motor function exemplified by mastication seems to follow general principles in the presence of both clinical and experimental craniofacial muscle pain. Moreover, the behavior of other motor functions in the presence of pain, such as gait and complex upper limb tasks, can also be interpreted to be in accordance with the suggested pain-adaptation model. The main effect of muscle pain is a reduction of the agonist EMG burst and a facilitation of the antagonist EMG burst, which may lead to slower and/or smaller movements. This could allow more rapid healing and avoid further damage to the system, provided the motor function is given the possibility to adapt. The underlying neural circuits responsible for reorganization of jaw motor function are thought to be located mainly in the brain stem and to involve a central pattern generator and groups of inhibitory and excitatory interneurons.[247] However, the functional role of higher-order brain centers cannot be ruled out in conscious human beings. In conclusion, the experimental findings suggest that dynamic motor function is changed by the presence of pain, and hence a changed motor function (dysfunction) is not the cause of pain. Nonetheless, the long-term consequences of changes in dynamic motor function are not known.

Summary and Future Perspectives on Craniofacial Muscle Pain

At present, the etiology and pathophysiology of deep pain in the craniofacial region are unknown. However, a number of neurobiologic mechanisms have been described and discussed in the preceding sections.

High-intensity stimuli are associated with the release of endogenous inflammatory substances, which may cause sensitization of nociceptors within the muscle tissue. The peripheral sensitization of muscle nociceptors also has an impact on the second-order nociceptive neurons, which may become hyperexcitable.[198] In animals, central sensitization is observed as increases in receptive field size, spontaneous neural discharges, and lowering of firing thresholds of nociceptive neurons.[67] The clinical correlates of peripheral and central sensitization are spontaneous pain, localized deep hyperalgesia, superficial hyperesthesia, and allodynia. NMDA and neurokinin-1 receptors are implicated in myositis-induced hyperexcitability, whereas spontaneous hyperactivity may be related to the amount of nitric oxide.[54,67,76] Inhibitors of nitric oxide synthase could be an effective way to treat chronic tension-type headache[362] and other forms of craniofacial muscle pain. Furthermore, NMDA receptor antagonists could be used to manage central hyperexcitability, and alpha-2-agonists, for example, to augment inhibitory modulation.[4,363] Central convergence of peripheral afferents in addition to unmasking of latent synaptic connections onto second-order nociceptive neurons is likely to be the basis for referred pain and spreading of deep pain. Sensitization of higher-order neurons may also occur in association with impairment of endogenous inhibitory control mechanisms. This could lead to more generalized hyperalgesia and associated disturbances in somatosensory function.[145] Clinically, it is important that craniofacial muscle pain can cause significant somatosensory disturbances both within and outside the primary region of pain complaint.

The afferent barrage has consequences not only for somatosensory function but also for sensorimotor integration. There is little good evidence to support a "vicious cycle" with simple relationships between craniofacial muscle pain and muscle function. It is critical to distinguish between the specific type of motor function, because sensorimotor interactions can have different manifestations. Thus, animal studies have documented a strong facilitatory effect of muscle pain on the alpha motoneuron pool.[66] However, there is only weak evidence in patients with TMD pain in favor of an EMG increase, the increase is very small, and human experimental pain studies have been unable to demonstrate robust activation of jaw-closing muscles.[118] There is no evidence so far that a small increase in EMG activity can induce long-lasting pain in the masticatory muscles. During static contractions of the jaw-closing muscles, there is good evidence of an inhibitory effect of nociceptive muscle afferents on alpha motoneuron activity; this effect is probably not direct but rather likely involves a set of interneurons in the brain stem. The functional significance of this inhibition could be lowered endurance and reduced capacity to work against load in attempts to protect the painful muscle.[247] Studies of jaw reflex activity have indicated no direct effects of experimental jaw muscle pain on the excitability of the alpha

motoneuron pool (H-reflexes),[119] but a net excitatory effect on inhibitory reflex pathways.[120,121] The gamma motoneuron system seems to be facilitated in the presence of experimental muscle pain,[364] which suggests an increased reflex stiffness.[293] This would seem to be a useful physiologic mechanism to limit jaw movements. Finally, there is now good evidence from both animal and human experimental studies of decreased agonist EMG activity and increased antagonist EMG activity during painful mastication.[114,115] The underlying mechanisms are suggested to be mediated through sets of excitatory and inhibitory premotoneurons and a central pattern generator in the brain stem. The net effect is to cause reduced movement amplitude and slower movements, which may allow more rapid healing and protection of the injured and painful area.[247]

The experimental pain models have clearly shown that craniofacial muscle pain has significant effects on both somatosensory function and sensorimotor integration. Thus, these changes may be viewed as consequences of pain and not factors leading to pain; or, stated differently, the pain-induced changes represent a physiologic response rather than a pathophysiologic dysfunction.

What then causes craniofacial muscle pain in the first place? This is still unknown, but it seems clear that there is no single or simple cause in the majority of cases. There is no indication of a genetic predisposition for development of TMD pain.[365] Thus, in current multifactorial models of TMD pain, a series of initiating, predisposing, and aggravating biomechanical, neuromuscular, biopsychosocial, and neurobiologic factors have been considered. A recent hypothesis has highlighted some of the neurobiologic factors, such as an interaction between NGF and estrogen levels.[62] If jaw muscles were injured by accident or during function, this could trigger a sequence of critical events in the peripheral tissue that lead to sensitization of the afferent channels and perhaps even cause reorganization at the cortical level.[366] Further studies are needed to identify the factors responsible for the initiation of the events and for the transition from acute to persistent muscle pain.

The experimental pain studies presented in this review have at this point contributed to a more advanced understanding of both the somatosensory and motor effects of craniofacial muscle pain and added further caution to strict biomechanical thinking with untimely overemphasis on, for example, dental occlusion.[367] Tonic experimental jaw muscle pain has been shown to directly change the occlusal relationship,[102] which challenges the etiologic importance of occlusal factors in the development of TMD pain. Thus, it seems appropriate that treatment should be guided toward the management of pain rather than restoration of motor "dysfunction." Moreover, pain management should be directed both to the peripheral tissue, where pain may be initiated, and to the central nervous system, where pain is maintained.[198] A pharmacologic approach using molecules with dual drug actions may be one future way amongst others to pursue the goal of effective pain management.[363]

It is evident that human experimental pain research alone cannot solve the puzzle of persistent muscle pain in the craniofacial region, but it can be used to test and generate specific questions, which is not possible in animal or clinical research. Thus, human experimental pain research should remain a bridge between basic animal research and controlled clinical trials.

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