Topical Review: Modulation of Trigeminal Sensory Input in Humans: Mechanisms and Clinical Implications

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In this review, the modulatory effects of tooth and implant loading, orofacial pain, and psychological factors on somatosensory and jaw-motor function in humans are assessed. Experimental studies on the control of jaw actions have revealed that patients with prostheses supported by osseointegrated implants show an impairment of fine motor control of the mandible. One possibility is that this may be related to the loss of afferent information from periodontal ligament mechanoreceptors, which results in considerably higher and more variable forces to hold and manipulate food between the teeth. However, psychophysical investigations have shown that patients still perceive mechanical stimuli exerted on osseointegrated implants in the jawbone. The use of somatosensory evoked potentials may reveal what specific receptor groups are responsible for this so-called osseoperception phenomenon. Orofacial pain is another modulator of trigeminal system functioning. Experimental jaw muscle pain has several effects on the somatosensory and motor function of the masticatory system, all of them serving to warn the individual about the ongoing damaging of tissues. Finally, the influence of mental state on the sensory and motor functions of the trigeminal system will be addressed. While some animal studies suggest that psychological stress can reduce acute pain, less speculative are the findings in human subjects that the anticipation of receiving a painful stimulus or undertaking difficult mental tasks can modulate jaw reflexes, including those evoked by mechanical stimuli applied to the teeth. Since such stimuli occur regularly during normal oral activities, the study of the resulting motor effects may yield clinically meaningful results in the context of other variables that modulate mandibular function.

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Somatosensory and motor functions of the human trigeminal system have been studied extensively during the past few decades. However, many of the normal and pathophysiological aspects of the trigeminal pathways still need to be clarified. This need is dictated partly by oral health care, especially with the use of endosseous implants, in which the domains of periodontology, orofacial pain management, prosthetic dentistry, and others are confronted with questions that can be answered only by the relevant neurophysiologic research. In this review, some recent developments in the functional behavior of the (human) trigeminal system will be presented. Specifically, the modulatory effects of tooth and implant loading, orofacial pain, and psychological fac-

Fig 1 Responses of human periodontal afferents to steady state forces of various amplitudes applied to the receptor-bearing tooth in the most responsive direction.

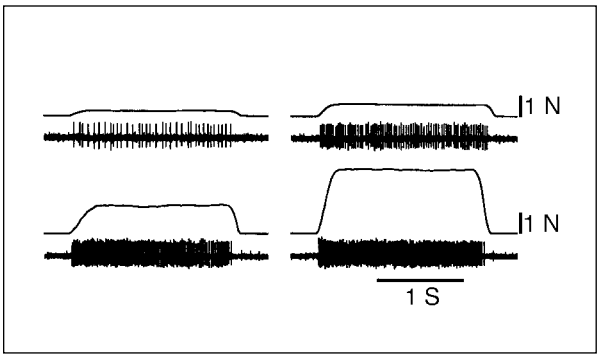


Fig 1a Examples of force stimulation and nerve recordings of a single afferent during stimuli of four different amplitudes.

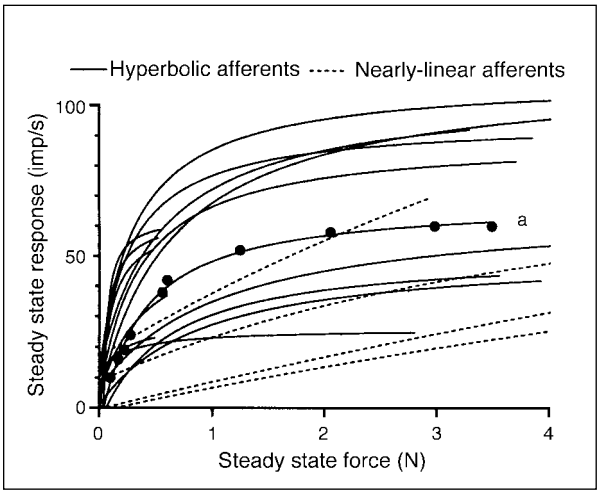


Fig 1b Stimulus-response functions for 19 periodontal afferents. The curves fitted to the data are defined by the F/(F+c) transform, where F represents the force, and c the force at which half the estimated maximum discharge rate is attained. This transform implies that the discharge rate increases more or less linearly until F approaches c and then levels off. Solid and dashed curves refer to afferents showing a "hyperbolic" stimulus-response relationship (n = 15; c value < 1.2 N) and a "nearly-linear" relationship (n = 4; c value between 5 and 22 N), respectively. The curve labeled *a* refers to the same afferent as illustrated in 1a. (After Trulsson and Johansson.[10])

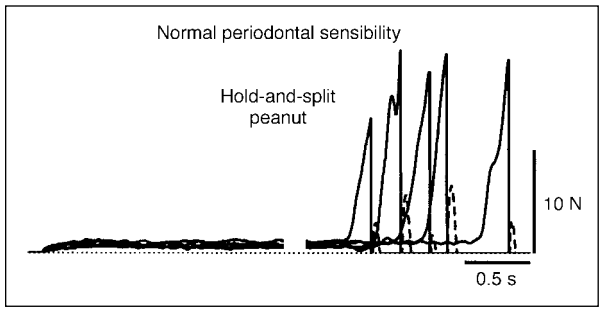
tors (eg, attention, stress, and anxiety) on somatosensory and jaw-motor function will be assessed. The influence of these factors on both clinical practice and planning of future research will be emphasized.

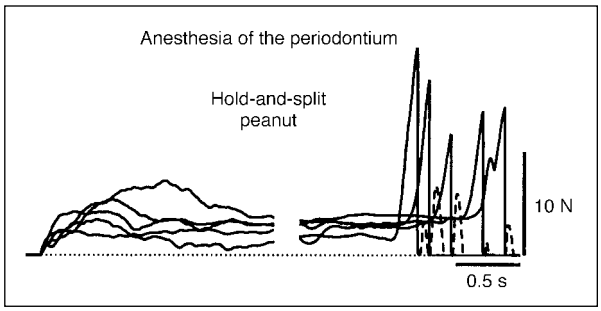
Periodontal Afferent Signals

For the monitoring of tooth loading and the control of oral motor behaviors like biting and chewing, we rely on sensory signals from a variety of sense organs, including the periodontal ligament mechanoreceptors. These nerve endings provide information about tooth loads and are located among, and intimately related to, the collagen fibers in the periodontal ligaments that attach the root of the tooth to the alveolar bone. This relationship may explain the adaptation characteristics of these mechanoreceptors[1] and the influence of biomechanical changes within the ligament such as occur in advanced periodontitis.[2] The basic force-encoding properties of human periodontal mechanoreceptors have been presented along with a discussion about their functional role in the control of human biting behavior (for a more comprehensive review, see Trulsson and Johansson.[3])

Signals from single periodontal ligament afferents in the inferior alveolar nerve were recorded via neurographic techniques in awake human subjects while forces were applied to the surfaces of a nylon cube cemented to the tooth under investigation, most often an incisor.[4,5] It was found that all human periodontal afferents continuously discharge during sustained tooth loads, ie, they are slowly adapting.[3] In addition, periodontal afferents were found to exhibit receptive fields broadly tuned for the direction of tooth loading.[5] Typically, the afferents respond to forces applied to the tooth in 2 to 4 of 6 directions tested (lingual, labial, mesial, distal, upward, downward). These receptive field properties agree with those observed in the cat,[6,7] but are in contrast to those in the dog which appear to have narrower receptive fields.[8] It was also demonstrated that about half of the human periodontal afferents respond to loading of a group of adjacent teeth, typically 2 to 4.[9] Each afferent exhibits the highest response rates to stimulation of 1 particular tooth, with a gradual and rather sharp decline in responsivity to loads applied to the adjacent teeth. Mechanical coupling between neighboring teeth (via interdental contacts and trans-septal collagen fibers) generates the multiple-tooth receptive fields instead of the branching of single afferents to more than 1 tooth.[9]

To study the encoding of intensity of tooth loads by human periodontal afferents, ramp-and-hold-shaped force profiles of different amplitudes were delivered to the tooth in its most responsive direction (Fig 1a).[10] The relationship between the amplitude of the steady state (hold) force and the steady state discharge rate was analyzed (Fig 1b). A majority of the





Figs 2a and 2b Examples of force profiles (5 superimposed trials) obtained during the hold-and-split task with peanuts during normal periodontal sensibility, and during anesthesia of the periodontium, respectively. Note the considerably higher and more variable hold forces produced by the subjects during the periodontal anesthesia.

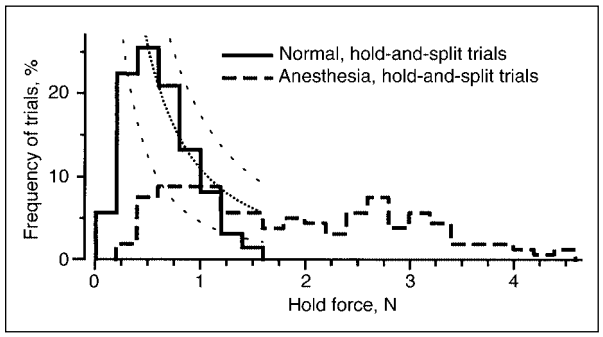


Fig 2c Frequency distribution of hold forces spontaneously adopted by the subjects; solid and dashed line histograms refer to trials with normal sensibility and trials with anesthesia of the periodontium, respectively. Superimposed curves represent the sensitivity to changes in tooth load of human periodontal afferents. The 3 dotted curves refer to the mean ± one standard deviation of the first force differential averaged across the 19 periodontal afferents in Fig 1b. (After Trulsson and Johansson.[11])

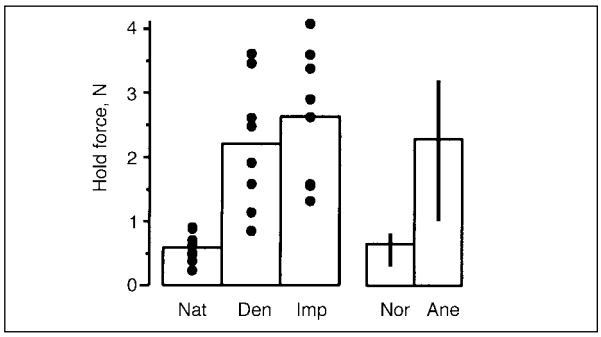


Fig 2d Left bar charts show mean hold forces employed by subjects in the natural (Nat), denture (Den) and implant (Imp) groups. Average values for individual subjects are indicated by filled circles (n = 20). Right bar charts represent the mean hold force by subjects during normal conditions (Nor) and during periodontal anesthesia (Ane). Vertical lines indicate the range of average values for individual subjects. (After Trulsson and Gunne.[12])

afferents (15/19) showed a marked, curved (hyperbolic) relationship between the steady state discharge rate and the amplitude of the hold force (Fig 1b).[10] The afferents showed the highest sensitivity to changes in static force at force levels below about 1 N. The sensitivity gradually decreased at higher forces. Moreover, for these "hyperbolic" afferents, the sensitivity to changes in force (dynamic sensitivity) decreased in parallel with the static sensitivity as the force increased. A minority of the human afferents studied (4/19) exhibited nearly linear stimulus-response relationships (Fig 1b). These afferents efficiently encoded force also at higher force levels.

Because of their overall high sensitivity to low forces (< 1 N), it was hypothesized that periodontal afferents from the front teeth are particularly suited for conveying information about the contact state between food and the dentition during initial contact and holding maneuvers.[11] To test this hypothesis, a common oral behavior was selected for study, specifically, holding and biting through a piece of food with the front teeth.[11] During this hold-and-split task (Fig 2a), the time-varying forces were recorded while subjects bit on either half a peanut or a piece of biscuit. The forces at which the food split (peanuts 18.4 ± 4.7 N; biscuit 9.1 ± 3.0 N; mean ± SD) was larger, by an order of magnitude, than the forces exerted while the subjects just held the food between the incisors (0.62 ± 0.32 N).

The following observations indicate that subjects use periodontal afferent information to specify the level of force during the hold phase of a hold-and-split task. First, the distribution of hold forces is skewed to coincide with the range over which periodontal afferents are most sensitive to changes in force (Fig 2c). That is, subjects choose

to use hold forces great enough to achieve a stable clasp, but they automatically avoid higher forces that compromise the sensitivity of most afferents to force changes. Second, during anesthesia of the periodontal tissues, the hold forces are considerably greater and show greater variability, both during individual trials and between trials (Fig 2c; also compare the force profiles in Figs 2a and 2b).[11] Finally, high hold force levels are observed for patients lacking periodontal ligament receptors, ie, patients treated with dental prostheses supported only by the oral mucosa or by osseointegrated implants.[12] Indeed, the averaged hold forces produced by patients lacking these receptors are remarkably similar to those generated by dentate subjects with periodontal anesthesia (Fig 2d). Furthermore, in anesthetized subjects, and in patients lacking periodontal receptors, the morsel frequently escaped from the incisal edges during the biting task, indicating an impaired spatial control of the jaw-action vector.[11,12] Thus, when periodontal afferent information is lacking, patients show a marked disturbance in the control of precisely directed, low biting forces, suggesting that the periodontal receptors play an important role in the specification of the level, direction, and point of attack of forces used to hold and manipulate food between the teeth.

Osseoperception

Amputation of a limb or extraction of a tooth may lead to the loss of a large number of exteroceptors that normally play an important role in motor control. In turn, this may reduce tactile function to a great extent (for a review, see Jacobs and van Steenberghe.[13]) Even after rehabilitation with a prosthetic limb or an osseointegrated implant, tactile function remains impaired, which may present the further risk of overloading the prosthesis or implant.[14] A better understanding of tactile function is therefore of primary importance for evaluating the physiological integration of osseointegrated implants in the human body.

Notwithstanding the above, patients seem to achieve quite good function after rehabilitation with a bone-anchored prosthesis. Some of these patients even note a special sensory awareness, which has been denoted as osseoperception.[15] Osseoperception is defined as a perception of external stimuli transmitted via a bone-anchored prosthesis through the bone by activation of receptors located in the periprosthesis environment, the periosteum, the skin, the muscles, and/or the joints.[14] In the human trigeminal system, it has been observed that during psychophysical threshold determinations, patients still perceive mechanical stimuli exerted on osseointegrated implants in the jaw bone.[16,17]

This observation prompts a discussion of what receptor group(s) is (are) responsible for the osseoperception phenomenon (for a review of potential receptor groups, see Sakada.[18]) Recent histological studies indicate that there might be some reinnervation around osseointegrated implants, but further research is needed to find out whether this reinnervation ever plays a real functional role.[19] Evaluation of the functional role of the remaining receptors could be carried out by invasive microelectrode recordings, or noninvasive neurological or psychophysical approaches. Animal neurophysiological data suggest that intraosseous receptors are involved in the osseoperception phenomenon.[20] However, this could not be confirmed in humans.[21] Trigeminal somatosensory evoked potentials (TSEPs) have been used to noninvasively evaluate the osseoperception phenomenon in the masticatory system. In a recent study, it was demonstrated that after tooth extraction and implant placement, stimulation of the implant still elicits a detectable TSEP with a positive wave having a peak latency between 18 ms and 25 ms, often preceded by a negative wave with a latency around 12 to 17 ms.[22] The fact that eliciting a motor response at the lip yielded a wave with a latency around 8 to 11 ms indicates that the aforementioned waves represent a sensory response to implant stimulation. It seems that this response is not derived from the peri-implant mucosa, since anesthesia of the latter does not affect the TSEP signal.

Another possible way of obtaining reliable information on the characteristics of the receptors that may be involved in the osseoperception phenomenon in humans is psychophysical threshold determination. Psychophysical methods include a number of well-defined tests, which may help to determine the threshold level of receptors in human subjects. The tests allow one to relate the physiological functions of receptors to the subjective responses of the patients. Given that psychophysical tests are simple and noninvasive, they might be recommended for the clinical assessment of osseoperception and for following-up the physiological integration of osseointegrated implants in the human body.

It has been established in several psychophysical studies that oral tactile function is influenced by tooth position and dental status (for a review, see

Jacobs and van Steenberghe.[13]) It is reduced when periodontal ligament receptors are reduced in number or eliminated (eg, by anesthesia, periodontitis, or tooth extraction). The clinical consequence is that a patient's ability to detect occlusal inaccuracies is decreased in partially dentate or edentulous patients. Indeed, the active detection threshold (ie, the threshold during functional loading) is 7 to 8 times higher for dentures as compared to teeth.[16] For the passive detection of forces, thresholds for dentures are increased 75 times.[17] When implants are present, the active thresholds are only 3 to 5 times higher as compared to teeth; the passive thresholds are only 50 times higher. Discrepancies between active and passive thresholds can be explained by the fact that several receptor groups may respond to active testing, while the passive method selectively activates periodontal ligament receptors. The fact that the latter are eliminated after extraction may explain the reduced tactile function in edentulous patients.

Even with a reduced tactile function, patients with osseointegrated implants still perceive mechanical stimuli after pushing against an implant. This suggests the involvement of osseoperception by activation of periosteal or other receptors in the immediate environment of the implant. This could imply that the feedback pathway to the sensory cortex is partly restored with a hypothetical representation of the implant to allow more natural functioning and to avoid overloading.

Orofacial Pain and Jaw Function

Experimental Models

Pain in the orofacial region is a very common health problem in modern society[23] and can be considered one of the important reasons for people to seek consultation and treatment in the dental office. Clinically, orofacial pain frequently seems to be associated with disturbances in somatosensory and jaw-motor function in addition to changes in mood, behavior, and psychosocial function. Below, recent results from human models of experimental pain, which have been used to address the question of how a standardized, nociceptive stimulus influences aspects of somatosensory and motor function in the orofacial region, will be reviewed briefly. For more complete reviews, see Svensson and Jensen,[24] Stohler,[25] and Sessle.[26]

Intuitively, the most logical approach for studying effects of pain on human function is to examine patients who suffer from pain. Unfortunately, this is associated with several confounding factors, eg, variability in perceived pain intensity, quality, and location; differences in pain duration and time patterns; influence of current or previous interventions; and psychological factors. There is also the important question of whether pain and the observed phenomenon merely coexist or actually have a cause-and-effect relationship. This is particularly true when the data are derived from cross-sectional studies. Therefore, human models of experimental pain may serve as indicators of cause-and-effect relationships, because pain can be induced in healthy volunteers and subsequent changes in the somatosensory or jaw motor function are likely to be consequences of the nociceptive input. Obviously, there are limitations regarding the intensity and duration of an experimental nociceptive stimulus, and the results obtained should be viewed as suggestive rather than conclusive. Human models of experimental pain may, nonetheless, be able to bridge the wealth of information derived from basic animal research to well-designed clinical trials in distinct populations of patients.

Injection of small amounts of sterile, hypertonic saline (4% to 6%) has for a long time been used in human experimental muscle pain research.[27] Hypertonic saline is a nonspecific stimulus, in that non-nociceptive afferents may be activated concomitantly with nociceptive group III and IV afferents.[28] Intramuscular administration of hypertonic saline, however, evokes robust neuronal activity in convergent spinal dorsal horn neurons and in neurons encoding nociceptive information in the thalamus. Furthermore, the dominant sensation in conscious humans is a deep aching pain.[29,30] This strongly suggests that hypertonic saline is a potent chemical stimulus for activation of muscle nociceptors, but other algesic substances with more specific receptor mechanisms need to be considered in future studies.

Kellgren[27] originally described the quality and intensity of saline-induced pain in the craniofacial muscles. Following an injection of 0.1 mL 6% saline into the masseter muscle, a deep aching pain developed after a short delay and increased to a peak after 1 to 2 minutes. About 5 minutes after the injection, the pain had disappeared. More recently, the manual bolus injection technique has been refined so that a computer-controlled syringe-pump can maintain a continuous slow infusion of hypertonic saline.[29,30] This technique allows longer periods (up to 15 to 20 minutes) of relatively constant pain in the craniofacial muscles. Furthermore, this type of tonic experimental pain seems to have quali-

ties similar to clinical pain[31] and allows sufficient time for detailed study of the somatosensory and jaw-motor effects of the pain.[30,32]

Referral and Spread of Orofacial Pain

Injections and infusions of hypertonic saline into the central part of the masseter muscle have generally supported the classical referral patterns of pain to the teeth, temporomandibular joint, and temple.[33] Clinically, it is important to recognize this widespread nature of jaw-muscle pain, although there can be large inter-individual variability in the areas from which pain is perceived. In the trigeminal region, it is notable that muscle pain can be referred to the teeth and vice versa. It has also been shown that teeth exposed to a previous painful event under general anesthesia may be the site of referral when other trigeminal structures are stimulated more than a week later.[34] This suggests that nociceptive activity may facilitate neurons in the trigeminal brainstem sensory nuclear complex, and that a central hyperexcitability can persist for an extended period of time. Indeed, these features have been shown to occur in animal studies.[35,36] In line with the occurrence of hyperexcitability, recent studies have documented increased areas of referred pain following injection of hypertonic saline into patients with fibromyalgia or chronic whiplash syndrome (by comparison with control subjects).[37,38] Recent data from the trigeminal region also suggest that patients with myofascial temporomandibular disorders experience larger areas of perceived pain when the masseter muscle is injected with hypertonic saline, but not when a leg muscle is injected.[39]

The referral of muscle pain is dependent on the perceived intensity of the painful stimulus, the duration of the stimulus, and the afferent inputs from the area of referred pain.[40] The self-reported painful area also increases as a function of time, which illustrates the radiating or spreading nature of jaw-muscle pain.[30] Furthermore, there seem to be gender differences in that women report larger areas of pain following an injection into the masseter muscle than do men.[41] The issue of gender differences in nociceptive transmission and processing has recently attracted much attention and is being pursued in several research laboratories.[42]

Orofacial Pain and Jaw Motor Activity

The causal relationship between muscle function and pain has been discussed for several decades. The early hypotheses focused on a vicious cycle where muscle hyperactivity caused pain, which in turn caused more muscle hyperactivity. More recently, this concept has been critically examined and rejected due to lack of scientific evidence.[43] Instead, it has been suggested that motor function may be adapted by nociceptive inputs–mainly through the control of a central pattern generator and sets of interneurons in the brainstem. The hypothesis has been proposed that nociceptive afferent activity may have a net inhibitory action on the alpha-motoneuron pool during agonist function and a net facilitatory action during antagonist function: the pain-adaptation hypothesis.[43] Experimental models of muscle pain have been used to test this hypothesis in humans and will be discussed briefly below.

Two independent studies in human volunteers have recently demonstrated that painful injections of hypertonic saline are not associated with consistent changes in the electromyographic (EMG) activity of the jaw-closing muscles with the jaw at rest.[44,45] This seems to be in contrast with the finding of robust increases in EMG activity following injection of the inflammatory substance mustard oil into deep craniofacial tissues of anesthetized rats.[46,47] However, the EMG activity in the rats was increased both in the jaw-closing muscles and the jaw-opening muscles, which could represent a splinting reaction to limit further movements of the jaw.

Jaw muscle pain induced by tonic infusion of hypertonic saline into the human masseter muscle has, moreover, been shown to reduce the maximum voluntary occlusal force and the maximum EMG activity of jaw-closing muscles.[48] Experimental jaw muscle pain also reduces the EMG activity of the jaw-closing muscles in their agonist phase during mastication, and increases the EMG activity in the antagonist phase in accordance with the prediction from the pain-adaptation hypothesis.[32] While these studies address the behavior of whole muscles or muscle groups either by recording of surface EMG, kinematics or force, it is less clear how single motor units behave in the presence of muscle pain.

A recent study demonstrated that experimental jaw muscle pain may cause a decreased firing rate in active masseter motor units without a change of recruitment threshold at low levels of isometric clenching.[49] The volunteers in that study were all able to maintain a constant isometric contraction during pain without an increase in the variability of the measured bite force. Due to technical limitations in the identification of the shape and waveform of single motor units, these results are representative only for the activity of low- and

moderate-threshold single motor units. Nevertheless, the result implies that an increased inhibitory drive, induced by activation of nociceptive muscle group III and IV afferents, has a uniform effect on the active units. Consistent with this are findings of decreased activity of the digastric motoneuron pool during experimental jaw muscle pain in decerebrate rabbits.[50] These studies are both in accordance with the pain-adaptation model. Thus, studies on single motor units may be used to examine in detail jaw motor function during pain. So far, the human experimental data have not contradicted the pain-adaptation hypothesis, but continued research is needed to fully understand the clinical implications, and in particular, the transition from acute effects to chronic effects. At this stage, 1 clinical implication seems to be that management of pain is likely to resolve changes in jaw motor function.

Psychological Factors Influence Sensory and Reflex Functions

It has long been recognized that the sensations which we feel are dependent, to a greater or lesser extent, on our state of mind. However, it is now also clear that not only can sensory signals be interpreted in different ways once they reach the conscious parts of the brain, but that signals coming down from brain centers can influence incoming sensory signals before they reach consciousness.

From an experimental point of view, the most obvious examples of this are the phenomena known as stress-induced analgesia. This term is used most commonly in the context of animal experiments in which either behavioral or reflex responses to nociceptive stimuli are reduced when animals are subjected to stressful conditioning procedures (for general review, see Amit and Galina[51]; for specific orofacial examples, see Vassel et al[52]). When used in that context, the term analgesia is not strictly correct—behavioral and reflex responses can give only an idea of what is happening in sensory systems. The correct term should really be stress-induced antinociception, although this is rarely used. Such semantics are less problematic when studying similar phenomena in humans. Although such studies often involve physiological measurements–such as of nociceptive reflexes—many also use psychophysical measurements of pain and thus permit the use of the term analgesia when pain is reduced. Indeed, the fact that both reflexes and sensations are reduced by stress is 1 persuasive line of evidence for believing that the effects are mediated by signals coming down from the brain to lower centers to affect the afferent signals before they ascend to the brain.

In human beings, the principal evidence that psychological factors can modify sensory pathways at the lower centers of the nervous system comes from studies showing that segmental reflexes are modulated by the state of mind of the experimental subject. Most studies of this type have been concerned with spinal segments of the body—notably with the modulation of flexion withdrawal reflexes in the limbs.[53–57] The reflex in question in these studies involved excitation in a muscle (usually the biceps femoris), and the result of most psychological manipulations—be they changes in attention level or induced stress—was to reduce these excitatory reflexes. By contrast, the predominant exteroceptive reflexes in human muscles innervated by the trigeminal nerve are the inhibitory ones seen in the jaw-elevator muscles (for a recent review, see Orchardson and Cadden[58]). Recent studies have shown that these reflexes are also reduced by similar psychological factors (see below).

The most clear-cut effects of psychological factors on human jaw reflexes have resulted from studies of the monophasic reflex inhibition of voluntary EMG activity in the masseter muscle, which occurs around 40 ms after electrical stimulation of the hairy skin of the lip.[59,60] The psychological manipulation that has produced the strongest suppression of this reflex is induced anxiety.[61] This was achieved in a fashion previously used by Willer and his colleagues when studying human flexion withdrawal reflexes.[55,57] In brief, just before receiving a set of reflex-inducing stimuli to the lip, the subjects were warned that at some point during the application of the stimuli they would also receive a very painful burst of stimuli to the sural nerve in the retromalleolar fossa (which they had previously experienced at the beginning of the experimental session). Each time that stress was induced in this fashion, the inhibitory reflex was reduced in magnitude. In fact, such a result was obtained in all 15 subjects in that study, regardless of whether or not the sural stimulus was actually delivered. In other words, it was the threat of the stimulus rather than the stimulus itself that had this effect.

However, such effects are produced not only by relatively drastic stress-inducing procedures. Milder means of diverting attention are also effective, eg, getting subjects to concentrate on a visual signal or asking them to undertake difficult mental

arithmetic tasks (such as the 17-times table).[62] Although the effects of these procedures were less than those resulting from induced stress, they occurred consistently: Concentrating on a visual signal reduced the reflex in 9 out of 11 subjects while the arithmetic task reduced it in 10 out of 10 subjects.

One possible explanation for these reductions in the size of an inhibitory reflex might have been that when the subjects were being stressed or undertaking attentional tasks, they may have produced increased levels of muscle activity which were more difficult for the afferent input from the lip stimulus to inhibit. However, this appeared not to be the case. In all the experiments with induced stress or mental arithmetic as the condition, the subjects also used a visual feedback signal in order to maintain a stable level of EMG activity in the masseter (around 10% of maximum)—so in theory there was no reason to believe that the voluntary drive to the motoneurons would have altered. Indeed, the results were essentially the same in subjects whose baseline EMG activity went down a little as in subjects whose baseline EMG activity went up a little.[62]

This reflex evoked by stimulation of the lip is ideal for studies of this type: The stimuli are easy to control and apply repeatedly and the monophasic nature of the inhibitory response permits relatively simple quantitative analysis. However, from the point of view of everyday function, reflexes triggered by stimulation of the lip are likely to be less relevant than those evoked by mechanical stimulation within the mouth. For this reason, subsequent studies focused on the effects of psychological factors on the more complex reflex responses evoked by such intra-oral stimuli. Although the results of these studies were less clear-cut, it seems that psychological factors do have similar effects on these reflexes as on the responses to lip stimulation. Most notably, it has been shown that, at least in some individuals, the reflexes evoked by tapping on a tooth are modified while the subjects undertake mental arithmetic tasks.[63]

Figure 3 shows the methods and results from an experiment on the effects of mental arithmetic on the reflex responses to tooth tapping. Such responses consist typically of 4 waves in the rectified post-stimulus electromyogram (Figs 3b and 3c). These are often labeled the Q, R, S, and T waves as it has been argued that their morphology is similar to part of an electrocardiogram.[64] The Q, R, S, and T waves have been shown to represent reflex inhibition, excitation, inhibition, and excitation, respectively.[64] The most common effect of the mental arithmetic task is shown in Fig 3b, namely an increase in the EMG level around the interface between successive inhibitory and excitatory waves (either Q-R and/or S-T). These effects were weak and at first it was not clear whether such small changes were really induced by the psychological state or whether they were just random fluctuations in the EMG response. In order to overcome this, a technique was employed to estimate—in pairs of individual EMG responses—the statistical probability of differences between the 2 responses being due to chance alone.[65] On this basis, it was found that changes like those shown in Fig 3b and in many other subjects could be accounted to the conditioning procedure (the mental arithmetic task). Only rarely was a different effect seen, although in a majority of cases, the psychological factor made no significant difference to the reflex responses.

The use of visual feedback in these experiments again insured that the effects of conditioning must have been occurring at a pre-motoneuronal level, ie, on the central terminals of trigeminal primary afferents or on interneurons. However, given that the effects were concentrated around the interfaces between inhibitory and excitatory responses, it was possible that they could have been due either to inhibition of the inhibitory responses (disinhibition) or facilitation of the excitatory waves or both. Although it can be argued that both do occur,[66] disinhibition seems to be far more important, as evidenced by the fact that similar effects were produced by reducing the tap stimulus intensity (Fig 3c), which can be regarded as the equivalent of producing an inhibition.

Theoretical Implications of Psychological Factors, Including Those Relating to Orofacial Pain

From a theoretical point of view, the fact that attentional factors, most notably stress, can modulate human jaw reflexes needs to be taken into account when considering other factors which have been reported to produce such effects. For example, it has been shown that homotopic[67] or heterotopic[68–70] noxious stimuli can depress inhibitory jaw reflexes, sometimes very powerfully. Given the potentially stressful and attention-altering nature of the noxious stimuli in these studies (eg, intramuscular infusions of hypertonic saline, painful thermal stimulation of a limb, painful muscle ischemia), one could imagine that some of the effects might have been secondary to psychological factors. However,

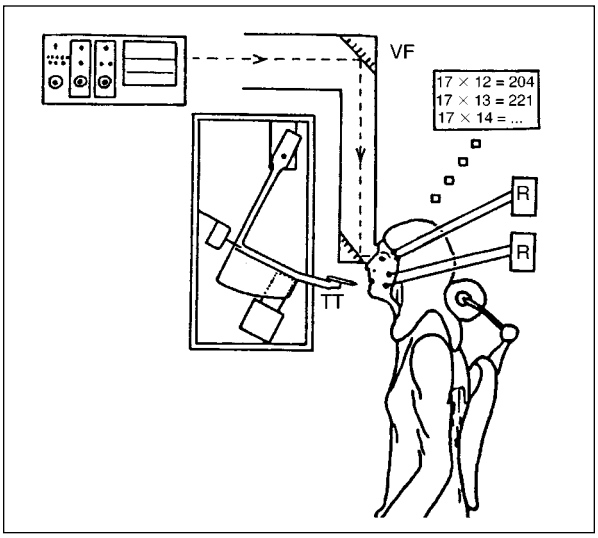


Fig 3a The experimental set-up in studies investigating the effects of an attentional task on the reflex responses to tooth tap. EMG recordings (R) were made from the active masseter and anterior temporal muscles while tooth tap (TT) stimuli were applied to an upper central incisor tooth using a pendulum system. The subject was provided with visual feedback (VF) of the EMG activity via a periscope to assist in maintaining a stable level of muscle activity. The reflexes evoked by the tap stimuli were compared under control conditions and when the subjects undertook a mental exercise ("17-times table").

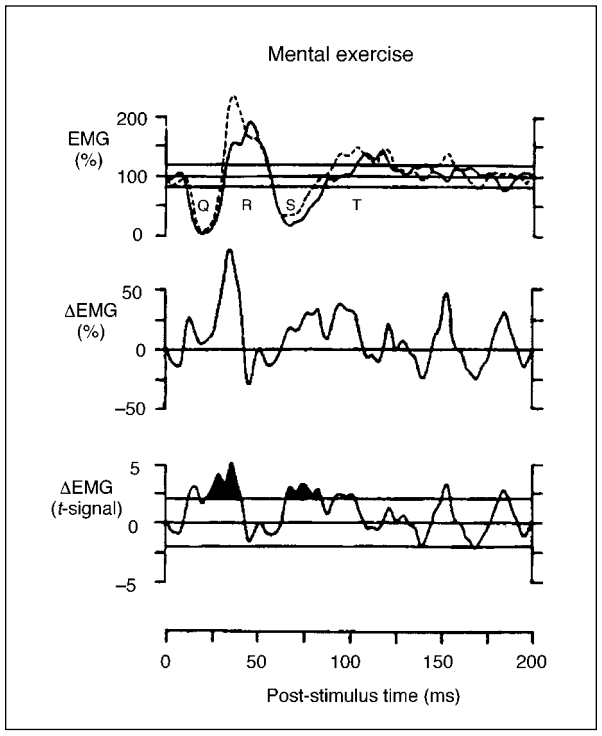


Fig 3b Top row: individual examples of EMG responses (Q, R, S, and T waves; see text) to the application of the tooth tap stimuli. The solid line record shows the control responses while the broken line represents those occurring during mental exercise. Middle row: the differences between corresponding digital points on the conditioned and control records shown above. Bottom row: the *t*-values of the data in the middle row (obtained by dividing each point by its own SEM value); central horizontal line is the zero level while the outer horizontal lines are the 95% confidence limits according to the *t*-distribution for n = 36 (number of sweeps contributing to the average). Shaded areas represent significant changes ($P < .05$) in the EMG signal during conditioning.

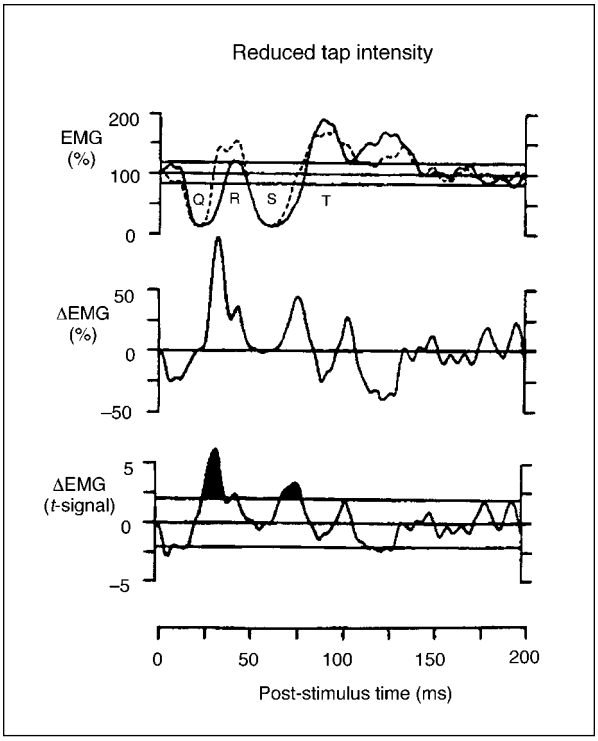


Fig 3c Same as Fig 3b, but in this case the "conditioning" was a reduction in the tap intensity rather than the mental arithmetic task. Note that in both b and c, the main effects were increases in the EMG activity around the Q-R and S-T interfaces.[66]

for a number of reasons, it is most unlikely that these effects of the noxious stimuli would be entirely related to psychological changes: *(1)* near identical homotopic and heterotopic noxious stimuli produce different effects on the reflexes,[67] although they might be expected to produce similar psychological effects; *(2)* there is a clear dissociation between the levels of pain (and presumably stress) produced by the heterotopic noxious stimuli and the effects they have on the reflexes[71]; and *(3)* there are subtle but demonstrable differences in the effects of heterotopic stimuli and psychological manipulations on the responses to tooth tap.[66] More direct mechanisms are also likely to play a role in the effects of noxious conditioning stimuli, eg, the effects of the heterotopic stimuli might be ascribed to the phenomena known as Diffuse Noxious Inhibitory Controls or DNIC (for review see Le Bars et al[72]).

The knowledge that psychological factors can modify jaw reflexes has consequences for other studies of such reflexes, particularly when these studies involve the repeated monitoring of the reflexes on separate occasions. One can envisage that in the course of such longitudinal studies, the subject may become more or less stressed by the laboratory setting and/or the experimental procedures and as a result, their reflexes might be altered. Such alterations could be wrongly attributed to some other factor, such as the therapy being received by a patient for the alleviation of some craniomandibular disorder. Indeed, from a clinical perspective, it is possible that these findings may also be pertinent to reported changes in jaw reflexes in patients with disorders such as myogenous craniomandibular dysfunction (CMD), bruxism, or tension headache[73,74] (for a review, see De Laat et al[75]). The most frequently reported of these changes is a reduction in, or absence of, the long-latency inhibitory jaw reflex—one of the responses which are modulated by psychological factors. Given that patients with myogenous CMD may have greater levels of psychological distress than symptom-free subjects,[76] it seems possible that this could contribute to their suppressed reflexes. The suppression of an inhibitory reflex could in turn, by increasing the use of these muscles, be a predisposing factor for the myogenic pain suffered by the patients. Although such a hypothesis must remain speculative, it does underline the importance of gaining a better understanding of factors which cause physiological changes in jaw reflexes before interpreting changes which occur in pathophysiological conditions.

Overview and Future Perspectives

The human jaw system consists of a mandible which is the only "limb" to cross the anatomic sagittal plane. It articulates with the skull base by means of 2 parallel joints. This feature implies that the human trigeminal neuromotor system involves homonymous bilateral reflexes. Since high forces can be exerted by the jaw-closing muscles versus the rather weak jaw-opening muscles, they must be balanced by a fast cybernetic modulation. Indeed, during biting through brittle food at an opening of 2 cm with a constant closing force of 100 N, the teeth in 1 jaw might be expected to collide with their antagonists at a speed of around 4.5 meters per second. However this does not happen. The actual speed is 0.4 m/s or less, due not to neural control but to the force-velocity properties of the jaw-closing muscles.[77] Appenteng et al[78] also found arguments in favor of a presynaptic change at the jaw-closing muscle motoneuron level. They assumed that the large difference in output between the strong jaw-closing muscles and their antagonists requires inhibition of excitatory transmission to the former to guard against uncontrolled activity. Reflexes in the trigeminal system and the role of periodontal afferent inputs are essential for many other aspects of jaw function as described above.

Periodontal mechanoreceptors, especially those in the ligament, have a tactile and reflex function. The tactile function seems more or less related to periodontal ligament mechanoreceptors, depending on the degree of mouth opening (for review, see Jacobs and van Steenberghe.[13]) The active threshold level for the interocclusal detection of small objects such as strips is very much dependent on the activity of periodontal mechanoreceptors, while for larger interocclusal distances, muscle and articular receptors seem to take over.[13] During functional mouth openings, such as during food comminution, periodontal mechanoreceptors play a prominent role.[11] The perspectives offered by recent discoveries of endosseous or periosteal mechanoreceptive function are fascinating. Indeed, thanks to the availability of endosseous implants, which are connected to the external environment by means of a transepidermal abutment, one can, after eliminating the eventual contribution of the soft tissue seal, determine the effect of loading the implant on the tactile perception (so-called osseoperception).[15] A load transferred by means of an intraosseous implant results in an increase of pressure throughout the bone and thus deformation of either intra-osseous or subperiosteal mechano-

receptors occurs. Therefore, the location of the receptors involved remains unresolved.

Further, this review has briefly described the use of human experimental pain models to gain further insight into the mechanisms that regulate the complex interaction between somatosensory and jaw motor functions. The strength of the current day accumulated knowledge on the influence of orofacial pain on trigeminal motor and sensory function comes from its experimental basis rather than being extrapolated from clinical observations. But besides the observed neurophysiological adaptations due to an acute or chronic pain sensation,[49] psychological factors also play a role: Both sensory afferent inputs and reflexes are reduced by stressful situations. Logically, stress can be related to pain sensations,[55] which bridges the research on sensory and reflex functions of the trigeminal system with the rapidly expanding literature on orofacial pain. It should be underlined that not only stress but any diversion can dramatically influence jaw reflexes.[61–63] It is a well-known observation that attention and psychological factors can even influence the gain of a stretch reflex,[79] although one would assume that its monosynaptic nature would make it less susceptible to such modulation and produce a fairly linear input-output relationship. Hardly exploited in this perspective are the observations of Passatore et al,[80] which demonstrated the influences of sympathetic nervous system activation on the jaw-closing muscle stretch reflex (it exceeds that of limb muscles). It is not yet clear whether these modulations are clinically relevant. A major goal and challenge for future research is to integrate the information from animal studies, human experimental pain research, and clinical trials.

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