Abstract: Orthodontic tooth movement is accompanied by inflammatory responses in the periodontal ligament. Chemical mediators such as interleukin-1β have key roles in nociception around teeth. Such nociceptive inputs to the periodontal ligament continue for several days and potentially induce plastic changes in higher brain regions, including the cerebral cortex. This review summarizes research on orthodontic treatment-induced modulation of neural activities in the central nervous system. Furthermore, we describe our recent findings on the spatiotemporal effects of orthodontic treatment in the somatosensory and insular cortices.

Keywords: central nervous system; experimental tooth movement; pain; periodontal ligament; inflammation.

Introduction
The main aims of orthodontic treatment include improvement of oral functions, such as mastication and speech, and dental aesthetics. The principal method of orthodontics is application of continuous mechanical force to teeth, which induces inflammation in the periodontal ligament (PDL) and remodels alveolar bone (1,2). Orthodontic tooth movement frequently induces pain (3,4), and clinical studies have shown that orthodontic treatment-induced pain begins 24-48 h after treatment and resolves within 5 days (5-7).

PDL inflammation induces hyperalgesia
The PDL has a critical role in regulating occlusal force associated with muscle spindles in jaw-closing muscles (8,9). Somatosensation in the PDL is mediated by multiple receptors, including Ruffini endings (10), Merkel cells (11), and free nerve endings of Aδ- and C-fibers (10). Ruffini endings and Merkel cells process mechanosensation, while free nerve endings process nociception and itch.

Experimental tooth movement (ETM) induces inflammation in the PDL, which facilitates release of proinflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor α from macrophages and endothelial cells (2,12-14). These cytokines activate osteoclasts, thereby promoting osteoclast differentiation and facilitating their bone-remodeling function (1,7,15-17). In addition to inducing inflammation and bone remodeling, these two proinflammatory cytokines mediate inflammatory hyperalgesia by generating cyclooxygenase-2 (COX-2) in endothelial cells, immune cells, and fibroblasts (18-22). Activation of COX-2 by IL-1β promotes release of prostaglandins (18,23), which sensitize nociceptors on C-fibers (24), decrease the nociception threshold, and increase membrane excitability, a phenomenon referred to as hyperalgesia (24-26). Tumor necrosis factor α is also a mediator that induces mechanical hyperalgesia by producing IL-1β and...
cytokine-induced neutrophil chemoattractant-1 (23,26).

In addition to the prostaglandin-mediating sensitization of nociceptors, algogenic substances such as bradykinin, histamine, and serotonin are produced by PDL inflammation and facilitate nociception (7,27). An increase in nociceptive fibers involving calcitonin gene-related peptide (CGRP) and galanin, which originate from the trigeminal ganglion (10) and send nociceptive information principally to the trigeminal spinal subnucleus interpolaris (Vi) and caudalis (Vc) (28,29), is also likely involved in ETM-induced hyperalgesia (30-34).

Ascending pathways mediating PDL nociception
Fos and extracellular signal-regulated protein (ERK) are typical activity-dependent markers that have been used to explore brain regions responding to continuous mechanical pressure on the teeth. ETM increases Fos expression and/or ERK phosphorylation in rat Vi/Vc neurons receiving primary afferents from the trigeminal nerve (35-39). Fos upregulation by ETM is also observed in the higher brain, including the parabrachial nucleus (36-38,40), periaqueductal gray matter (37,38), central amygdala, and the paraventricular nucleus of the hypothalamus and thalamus (41). These immunohistochemical findings indicate that orthodontic treatment of teeth facilitates nociception-related regions in the central nervous system.

Upregulation of Fos expression begins from several hours to 1 day after ETM (35,38,40,41) and continues for approximately 3 days (42). This time course may explain the temporal profile of pain induced by orthodontic treatment.

Cortical responses to PDL stimulation
The topographical organization of somatosensation in response to PDL stimulation has been well documented in the primary somatosensory cortex (S1) of the cat (43-45) and rabbit (46). These studies described the somatotopic organization of the orofacial region in the anterior coronal gyrus (area 3b) of S1. The lip- and PDL-responding areas are caudal to the tongue- and palate-responding areas, and the areas of the maxillary oral structures, including the lip and PDL, are dorsally adjacent to those of the mandibular structures (43). In addition, these reports describe both contralateral and bilateral representation in S1. PDL-responding neurons in S1 are classified as slowly adapting and rapidly adapting neurons and exhibit direction selectivity during tooth loading (44,46).

In contrast to the PDL-responding area in S1, little information is available regarding the response to PDL stimulation in other cortical areas. Yamamoto et al. (47) reported that in the rat a subset of neurons in the insular cortex (IC) responds to mechanical stimulation of oral structures. In agreement with this study, a functional magnetic resonance imaging (fMRI) study of humans reported activation of the IC and supplementary motor cortex during vibratory stimulation of teeth (48). Taken together, these studies suggest that the IC is another possible PDL-related cortical region. Recent optical imaging studies support this hypothesis. Horinuki et al. (17) reported that, in addition to S1, the cortical area caudally adjacent to the middle cerebral artery responds to electrical stimulation of maxillary and mandibular incisor and molar PDL. These anatomical findings indicate that the area corresponds to the secondary somatosensory cortex (S2) and oral region of the IC (IOR), as reported by Nakamura et al. (49). S2/IOR receives varied somatosensory information from oral regions, including PDL sensation, gustation (50-52), and nociception (49,53,54). Interestingly, electrical stimulation of S2/IOR induces rhythmic jaw movement (55,56). This convergence of orofacial sensory information in S2/IOR may contribute to integration of oral function, e.g., it may improve palatability by adding the sensation of texture to taste.

It has been unclear how S2/IOR is excited by PDL stimulation. S2/IOR receives excitatory inputs from the thalamic nucleus and amygdala (57). This suggests that S2/IOR contributes to PDL sensation, in parallel to the S1, and that information processed in S1 and S2/IOR may be mutually integrated, as previously suggested (58). The anatomical finding of dense projections from S2/IOR to S1 supports this hypothesis (59).

The somatotopic organization of incisor and molar PDLs in the S2/IOR remains controversial: the maximally activated areas overlap, but the initial responses are segregated (17). Projections from the thalamus may be somatotopically distributed, while cortico-cortical projections may be intermingled in the S2/IOR. Such profiles might explain the clinical discrepancy of accurate identification of a tooth with fast pain and poor identification of a tooth with slow pain (60,61).

Plastic changes in cortical responses to PDL stimulation
Disturbance of sensory inputs may induce plastic changes in the cerebral cortex. A typical example is ocular dominance plasticity in the primary visual cortex (V1), where competitive inputs from the left and right eyes converge (62-64). Disturbance of the balance between the left and right eyes, due to short-term monocular deprivation
during childhood, changes the physiological properties of V1 neurons so that they respond only to the open eye, and these changes persist into adulthood. This type of plastic change is principally mediated by shrinkage of thalamocortical projections from the closed eye into V1.

Enhancement of the maximum response to electrical PDL stimulation implies that there are plastic changes in S2/IOR (Fig. 1); however, in models that receive ETM, the initial response shows little change (17,65). This suggests that ETM alters the patterns of cortico-cortical connections but not thalamocortical projections. It is also notable that ETM during adolescence induces temporal change in the excitation in S2/IOR; enhancement of cortical response recovered within 1 week. Clinical studies indicate that orthodontic treatment induces pain for a few days but that this pain disappears within 1 week in most patients (7,15). Thus, ETM models reflect clinical pathophysiology and further suggest that orthodontic treatment does not induce continuous plastic changes in the cerebral cortex.

**Functional aspects of facilitation of cortical responses by ETM**

In addition to the ascending pathway, ETM treatment modulates neuromodulatory systems, including the brainstem adrenergic (37) and serotonergic systems (38,66), which are involved in the descending pain modulatory system. ETM might activate these neuromodulatory systems via the cerebral cortex. Indeed, an anatomical study found that the IC projects to the locus coeruleus (67). In this context, ETM-induced facilitation of the cortical excitation may have a role in descending inhibition.

Spreading of excitatory areas in the S1 and S2/IOR in response to PDL stimulation may indicate enlargement of the field in response to stimulation. This spread of excitatory areas may therefore be part of the mechanism for radiation of pain. These hypotheses provide a reasonable explanation for the clinical finding that patients undergoing orthodontic treatment often feel pain both from the PDL and from other oral structures during mandibular and maxillary tooth movement.

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**Conflict of interest**

The authors have no conflict of interest to declare.

**References**


