Cortical Mechanism of Oral Sensation in Human

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Abstract

Somatosensory information from peripheral sensory neurons innervating the oral region is projected into the thalamus via the trigeminothalamic tract and from there to the primary somatosensory cortex. Representation of oral sensation in the human primary somatosensory cortex has been demonstrated by invasive technique (direct cortical stimulation and intracranial recording of somatosensory-evoked potentials) and non-invasive neuroimaging. The present review describes the projection pathway of the human trigeminothalamic tract and the cortical somatotopic organization of the dent-oral structure-representing area in the primary somatosensory cortex, and gives a brief introduction to non-invasive neuroimaging.

Introduction

Somatosensory information from the orofacial area is received by peripheral sensory neurons (trigeminal neurons) and projected into the thalamus via the trigeminothalamic tract from where it is projected into the primary somatosensory cortex. Representation of oral sensation in the human primary somatosensory cortex has been demonstrated by invasive direct cortical stimulation and intracranial recording of somatosensory-evoked potentials (1-5). The foot-, hand- and trunk-, as well as orofacial- and intraoral-representing areas in the primary somatosensory cortex receive input from peripheral sensory neurons. The primary somatosensory cortex includes area 3b, known as the "somatosensory homunculus". Cortical representation of oral sensation in human is widely distributed over the primary somatosensory cortex, and this distribution is located more laterally and inferiorly than that for any other body area (1, 2). The relatively large area occupied by the oral region-representing region of the primary somatosensory cortex in comparison with those for the rest of the human body suggests great importance for oral function in human.

In obtaining a detailed organizational map of the

sensory cortex, use of invasive procedures such as direct cortical stimulation, intracranial recording and intraoperative electrocorticography, all of which require surgical procedures, is problematic in human due to ethical considerations. However, a variety of other neuroimaging tools have recently been developed which offer the possibility of non-invasive study of human brain function, including positron emission tomography, functional magnetic resonance (MR) imaging, electroencephalography (EEG) and magnetoencephalography (MEG). These revolutionary and non-invasive neuroimaging tools have allowed us to clarify the locations and distribution of those areas representing oral structures (including tooth-pulp, gum, buccal mucosa, tongue, lip and palate) in the sensory cortex in human. Thus, these tools have enabled us to re-think the classical homunculus by adding these orofacial areas to it. In the present review, I describe in detail the cortical somatosensory mechanisms for oral structures in human.

Neuroimaging tools

Recently, a variety of non-invasive neuroimaging tools have been developed (Fig.1). These allow noninvasive study of human cortical functions, in-

Fig. 1. Spatial and temporal resolution with neuroimaging of human brain. CT, computed tomography; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography.

cluding sensory, motor, cognitive and behavioral functions, as well as their integration mechanisms. These neuroimaging tools for the human brain can be classified into three modalities. Positron emission tomography and functional MR imaging record information on cerebral blood flow, oxygen consumption and metabolic activity. Positron emission tomography and functional MR imaging can determine localized brain activity with high spatial resolution. However, their temporal resolution is not sufficient to clarify the sequence of temporal activation of the cortical activation area (Fig. 1). EEG and MEG can clarify information processes in cortical neurons with high temporal resolution by allowing recording of cortical potentials from the scalp with EEG or magnetic fields with MEG (Fig. 1). MR imaging provides detailed spatial information on the anatomical structure of the human brain. However, MR imaging cannot analyze brain function due to low temporal resolution (Fig. 1). When we compare these imaging modalities, both MEG and EEG recordings reflect the direct function of the brain and provide high temporal sub-millisecond resolution of activity. MEG, in particular, records magnetic fields produced by cor-

tical neurons from the scalp surface. In addition, used in combination with brain MR imaging, MEG enables pinpoint 3-dimensional localization of dynamic sources reflecting cortical neuron activity with respect to anatomical structures with high spatial resolution to the millimeter. Thus, only MEG can provide spatial (anatomical) and temporal information about where in the brain elevated levels of neurophysiological activity are present and when this activity occurs in relation to the onset of a stimulus (6, 7).

Somatosensory stimulation to record cortical activity

To record cortical somatosensory response and/or determine the oral-representing area in the somatosensory cortex non-invasively in human, somatosensory stimulation is necessary. However, electrical stimulation of the orofacial area may cause contamination of cortical responses such as somatosensory-evoked potentials or fields by electrical artifacts because the magnetic sensor (superconducting quantum interference device; SQUID) for MEG or scalp Ag-AgCl electrodes for EEG recordings are in contiguity with the oral region. Problems may arise with data acquisition when taking magnetic or electrical recordings or performing functional-MR imaging due to head movement caused by tactile stimulation. Therefore, the device for stimulation needs to be fixed and/or attached to the stimulation site(s) to avoid such "movement artifacts". In addition, the oral mucosa is exposed to a moist environment by saliva, which interferes with site-specific electrical stimulation by current leak. Electrical stimulation of the tongue may induce an electrical taste (8-10). Therefore, there are difficulties in applying somatosensory stimulation. To avoid these difficulties, a number of somatosensory electrical or tactile stimulation devices have been developed which are suitable for application to the oral area (Table 1) for non-invasive neuroimaging. With electrical stimulation, the size of the electrode must be kept to the minimum to avoid contamination of data obtained by neuroimaging tools by electrical arti-

Table 1. Various oral somatosensory stimulation modalities of human non-invasive neuroimaging

Modality	Device	stimulation site	tool	Refs.
Electrical stimulation				
	Custom-made device			
	Electrodes embedded in impression material	Tongue	MEG	(11)
	Electrodes fixed on clip	Lower lip	MEG	(12)
	Electrodes fixed on clip	Lower lip, gingiva and tongue	MEG	(13)
	Electrodes fixed on clip	Lips	MEG	(14)
	Electrodes attached to teeth by plastic splint	Dental pulp (non-painful)	MEG	(15)
	Electrodes attached to teeth by glue	Dental pulp (painful)	fMRI	(16)
	Electrodes embedded in plastic splint	palate	MEG	(60)
Tactile stimulation				
	Air-pressure driven pneumatic device			
	Balloon diaphragm	Lips, tongue	MEG	(29)
	Balloon diaphragm	Lips	MEG	(30)
	Balloon diaphragm	Lips	MEG	(65)
	Air puff device			
	Air puff (high-speed controlled)	Lips	EEG	(20)
	Piezo-driven device			
	Modified Braille cells	Lips, buccal, tongue	MEG	(10)
	Hand stimulation			
	Stimulation by experimenter	Lips, periodontium, tongue	fMRI	(61)

facts. To prevent problems arising from a moist environment and allow site-specific electrical stimulation in the oral region, these electrodes are (Table 1) 1) embedded into dental impression materials for tongue stimulation (11), 2) fixed onto a clip (clip electrodes) to stimulate lips, gingiva and tongue (12-14), 3) attached to the tooth surface by a plastic splint to apply non-painful stimulation (15), 4) attached to the tooth surface by glue for painful stimulation (16), and 5) embedded into a plastic splint to stimulate palatal mucosa. For tactile stimulation of the oral region, air-pressure driven pneumatic device(s) employing a balloon diaphragm have been used for lip and tongue stimulation. This type of tactile stimulator(s) allows recording of cortical neuronal activities induced by pure tactile sensation from a moist environment. However, air-pressure driven pneumatic tactile stimulation device(s) are unable to record/detect/estimate temporal cortical activation sequences following stimulation (10, 17-19). With high temporal non-invasive neuroimaging such as MEG and EEG (Table 1), this was due to the relative weakness and/or indistinct onset of the tac-

tile stimulus, which resulted in insufficient synchronization of the respective neural population (19). Therefore, to record/detect temporal cortical activation sequences following stimulation by EEG and/or MEG, high-speed controlled stimulators allowing distinct onset of the tactile stimulus have been developed (see below). Hashimoto et al (1988) (20) have developed and used fast-rising air puffs generated by a high-speed air control system. Such air puffs have evoked a larger cortical response than electrical stimulation with neither stimulus nor muscle artifacts, unlike with electrical stimuli. Recently, Tamura et al (2008) have developed (10) a piezo-actuator tactile stimulation device. This was modified from Braille cells for the visually impaired, and consists of a piezoelectric element to which a direct current is applied (0.7 mm/0.4 ms with 0.18 N in force and 1 ms in duration) to produce tactile stimulation of the area targeted (10). The piezo-actuator tactile stimulator produces electrical noise. However, this noise can be easily separated from the EEG and/or MEG recordings, since the noise is generated by direct current and the duration is short.

Both these tools, air puffs and the piezo-actuator tactile stimulator, allow recording of short latency cortical somatosensory responses reflecting cortical activation by direct cortical projection of trigeminal neurons from the moistened oral region with high temporal resolution, enabling us to precisely determine the functional topography of those areas representing whole intraoral structures.

Bilateral cortical representation of trigeminally innervated orofacial area

Bilateral sensation of the tongue following unilateral direct cortical stimulation in human has been reported (1, 2). Clinical findings have confirmed that unilateral cortical infarctions in the primary somatosensory and motor cortex, while causing serious impairment of upper limb function on the contralateral side, do not impair bite force or jaw-closing function (21). In addition, the unilateral somatosensory cortex of the facial area can be resected without serious facial sensory deficits (2, 22). In monkey studies (23-26), neurons in the ipsilateral thalamic ventral posteromedial nucleus innervated by the ipsilateral trigeminal nuclei projected to the ipsilateral somatosensory cortex (26). It was found that 40% of the ventral posteromedial nucleus of the thalamus was devoted to representation of ipsilateral intraoral structures and that ipsilateral representation occupied 40% of the trigeminal representation area of area 3b (26). The proportion of neurons in monkey area 3b with a contralateral receptive field was 52%, that for ipsilateral was 31%, and that for bilateral was 17% (27). In human MEG studies, bilateral somatosensory-evoked magnetic field responses in the primary somatosensory cortex following orofacial trigeminal nerve-innervated area stimulation have been described (11, 14, 28-30). However, the exact pathway of the ascending trigeminothalamic tracts to the ipsilateral cortical representation area of the orofacial and intraoral region is not yet fully understood. Hoshiyama et al (1996) proposed three possible projection pathways as follows: 1) projection from contralateral cortical activity via the corpus callosum, 2) direct ipsilateral

projection via uncrossed ascending fibers, and 3) projection to both hemispheres from the thalamus. Initial cortical responses have been identified at around 10-15 ms following stimulation of the orofacial area (5, 20, 31). In a human EEG study, bilateral initial cortical responses of somatosensory-evoked potentials with a peak latency of around 15 ms in both hemispheres have been reported following lip tactile stimulation, with no significant differences in their latencies (20). In addition, in an MEG study (10), bilateral equivalent current dipoles generating early components in the magnetic wave form with a peak latency of around 15 ms following intraoral stimulation have been located in the bilateral primary somatosensory cortex. These contralateral and ipsilateral equivalent current dipoles have been localized symmetrically in the cortices with the same orientation (10). No significant inter-hemispheric differences were observed in the initial peak latencies for bilateral magnetic wave forms following intraoral stimulation, indicating that ipsilateral projection from contralateral cortical activity via the corpus callosum is unlikely. If ipsilateral responses were caused by spread through the corpus callosum, then the ipsilateral peak latency for the earliest components in the magnetic wave form would be slower than the contralateral peak latency (30). However, no such difference was observed. In addition, the moment (the strength of cortical activities reflecting amplitude in excitatory postsynaptic potentials after stimulation) of equivalent current dipoles generating earliest components in the magnetic wave in the contralateral hemisphere was larger than that in the ipsilateral hemisphere (10). These reports suggest that sensory afferents innervating the intraoral region project to both contralateral and ipsilateral primary somatosensory cortices via the trigeminothalamic tract, and that the contralateral ascending pathway for projection is predominant.

Cortical representation of human dental pulp

Electrophysiological findings indicate that the function and innervation of the sensory nerve in dental pulp are the same in both human and animal.

Both these structural and functional similarities provide a basis for comparison of sensation and nerve fiber responses in human dental pulp. Peripheral nerve fibers are classified based on their diameter and conduction velocity. These include A-alpha, A-beta, A-gamma, A-delta, B, and C fibers. In human dental pulp, it has been reported that there are two types of sensory nerve fiber: myelinated A-delta fibers and unmyelinated C fibers. In contrast, it was not clear as to whether A-alpha and A-beta fibers exist in human dental pulp, whereas A-beta fiber is present in animal dental pulp. A-beta, A-delta and C fibers are known to be present in dental pulp in experimental animals (32-35). In general, A-delta nociceptors mediate 'first' (i.e., rapid, acute and sharp) pain and C nociceptors mediate 'second' (i.e., delayed, more diffuse and dull) pain evoked by noxious stimulation (36-39). In contrast, most, but not all, A-beta fibers detect innocuous stimulation when applied to skin, muscle and joints, and are not involved in mediation of pain.

Cortical projection of intra-dental nociceptive neurons in human

The response characteristics of pulpal nerve fibers and their modality of pulpal sensation in human indicate that A-delta and C fibers are responsible for the pain sensitivity of dentin. It has been proposed that pain is the only conscious sensation elicited by physiological stimulation of dental pulp in human (40, 41). However, intra-dental A-beta fibers are also present in human (see below).

In a human EEG study, it has been demonstrated that cortical potentials evoked by painful electrical dental pulp stimulation via pairs of electrodes implanted into dentin had a first peak latency of 84 ms, suggesting activation of the secondary somatosensory cortex by intradental A-delta neurons (42). In a human MEG study, it has been reported that the current source at the peak latency (100 ms) of the somatosensory evoked magnetic fields following electrical noxious dental pulp stimulation was located at the upper bank of the anterior Sylvian fissure, corresponding to activation of the anterior end of the

secondary somatosensory cortex (43). More recently, a functional MR imaging study in human (16) has demonstrated that the bilateral primary somatosensory cortex was activated during electrically induced painful stimulation of the tooth pulp, whereas painful mechanical stimulation to the hand activated the contralateral primary somatosensory cortex only. These results are consistent with the most recent MEG results showing that sensory afferents innervating the intraoral region project to both the contralateral and ipsilateral primary somatosensory cortices (see above) (10). In addition, the secondary somatosensory cortex, insular region and anterior cingulate have bilaterally been activated by painful tooth pulp stimulation. Tooth pain also induces strong activation of the anterior and medial parts of the insular region. The most powerful activations were observed in the secondary somatosensory cortex. In activation of the secondary somatosensory cortex, the center of gravity of activation during painful tooth pulp stimulation was reported to be localized laterally and anteriorly, whereas painful mechanical stimulation to the hand resulted in medial and posterior activation of the secondary somatosensory cortex. In addition, the secondary somatosensory cortex is responsible for coding the intensity of an applied dental pulp stimulus. These results are in line with the general characteristics of the cortical pain perception mechanism, i.e., the insular region, anterior cingulate gyrus, primary somatosensory and secondary somatosensory cortices participate in pain perception from the body, including peripheral areas innervated by the trigeminal nerve (44-52). Thus, sensory information from intra-dental nociceptors is processed in these cortical areas in the human brain.

Cortical projection of intra-dental "non"-nociceptive neurons in human

It has been reported that non-painful sensation of dental pulp can be evoked by low electrical stimulation. Non-painful sensation, i.e. prepain, induced by low-intensity electrical stimulation is thought to result from activation of the lowest threshold A-

fibers, some of which can be classified as A-beta fibers according to their conduction velocities (35). The existence of large myelinated nerve fibers in the dental pulp has been anatomically and functionally identified in anesthetized animals (33, 53-56).

A human magnetoencephalographic study (15) has investigated early neuronal cortical responses to dental pulp stimulation resulting in activation of the primary somatosensory cortex. In this study, following non-painful dental pulp stimulation through intact enamel by a pair of specialized silver electrodes on the occlusal surface of the right intact maxillary first premolar under rubber dam isolation, bilateral prominent magnetic fields were demonstrated in the parietotemporal area with peak latencies of 27 ms, indicating that dental pulp afferents projected to the primary somatosensory cortex with short latencies (with A-beta conduction velocity). The equivalent current dipoles of this early component following dental pulp stimulation were identified along the inferior-most part of the posterior wall of the central sulcus, corresponding to the primary somatosensory cortex. The location of somatosensory representation of dental pulp in the primary somatosensory cortex was more anterior and inferior to that of the hand. In animals (cat and monkey), the dental pulp representation area in the primary somatosensory cortex plays an important role in sensory discrimination and recognition of localization and intensity of stimuli applied to dental pulp (57-59). Therefore, tooth pulp A-beta afferents projecting to the primary somatosensory cortex in human may also play an important role in oral function.

Somatotopic organization of oral region-representing area: lip, tongue, palatal and buccal mucosa area in primary somatosensory cortex

Using a variety of invasive (such as electrocortical) and non-invasive techniques (such as EEG, functional MR imaging and MEG), a lot of reports describe the oral structure-representing area in the primary somatosensory cortex, including the lip (3, 5, 10, 12-14, 20, 29-31), tongue (4, 5, 10, 13, 28, 29), buccal mucosa (10), hard palate (5, 60), teeth (dental pulp)

(15, 16) and gingiva (13). The results of these studies indicate that the cortical representation area of oral sensation in human is widely distributed over the postcentral gyrus and that it is located in the primary somatosensory cortex more laterally and inferiorly than that of any other body area. It has been reported that, along with the postcentral gyrus (i.e., the posterior banks of the central sulcus), the tongue-representing areas in the primary somatosensory cortex are located inferiorly and laterally to those for the lips (13, 61). An MEG (13) and a functional MR imaging (61) study have reported the following pattern of somatotopic organization from top to bottom along central sulcus: index finger, lips, teeth (periodontal sensation) and tongue. In intracranial recordings (5), the following pattern of organization from top to bottom along the sulcus has been reported: index finger, lips, tongue and palate. More recently, Tamura et al (2008) (10) reported the functional topographic organization of intraoral structure representation in the primary somatosensory cortex. Since the recording procedure in Kubo et al (2008) (15) and Bessho et al (2007) (60) was the same as that in Tamura et al (2008) (10), we can incorporate their estimated coordinates on the Z-axis of the dental pulp- (15) and palate- (60) representing areas into those of the intraoral structures-representing area described by Tamura et al (2008) (10). Taken together, their results for the locations of whole intraoral structure-representing areas showed the following pattern of somatotopic organization from top to bottom along the central sulcus: index finger, upper or lower lip, dental pulp, anterior or posterior tongue, hard palate and superior or inferior buccal mucosa. All the results described above show consistency with each other and with the classical "sensory homunculus" (5, 10, 13, 61, 61).

Conclusion: wide distribution of oral-representing area of primary somatosensory cortex

Tamura et al (2008) (10) determined extent of distribution of the intraoral region in the contralateral primary somatosensory cortex. The distribution of the sensorimotor cortex devoted to a particular

structure is directly related to its innervation density (62). The intraoral-representing area has been reported to occupy approximately 30% of the entire primary somatosensory cortex (10), as expected by the high neuronal innervation densities in the oral region. However, locations elicited by sensory stimulation of two sites within the same oral structure (such as the anterior and posterior areas of the tongue) were not significantly separated in their representing areas in the primary somatosensory cortex (10). In monkey studies, neurons in the primary somatosensory cortex have bimaxillary receptive fields covering the upper and lower lips (63, 64). The existence of neurons with composite receptive fields covering more than one oral structure might allow detection or manipulation of objects in the oral vestibule or oral cavity proper by information integration in the primary somatosensory cortex. In addition, although Miyamoto et al (2005) (61) describes the representation area of lips, periodontal membrane and tongue in human showing consistency with the classical "sensory homunculus" (1, 2), this somatotopic representation becomes unclear in the middle and caudal portions of the postcentral gyrus. These findings support the theory that input from oral structures converges hierarchically across the primary somatosensory cortex, indicating that somatosensory information can be integrated as it is conveyed caudally in the primary somatosensory cortex (61). Therefore, large amounts of peripheral sensory information from the oral cavity are processed in the primary somatosensory cortex as cortical representation. This information is also integrated in the primary somatosensory cortex as necessary to provide neural substrates for oral stereognosis to drive orofacial functions such as articulation, mastication and oral object exploration. The bilateral projection pathway of trigeminal sensory information to the cortex has been suggested to prevent serious loss of sensory function after cortical dysfunction such as infarction in the primary somatosensory cortex (2, 22), indicating the importance of oral function.

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