

Review Article

Effect of Mastication on Human Brain ActivityKiwako Sakamoto^{1,2)}, Hiroki Nakata^{1,2)}, Masato Yumoto²⁾, Ryusuke Kakigi¹⁾

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Abstract

Mastication is a complicated movement generated from a neural population in the brainstem and a neural network involving several brain regions. Recently, attention has been focused on the relationship between mastication and age-related decline in human cognitive function, but the neural mechanisms underlying this association remain unknown. In this article, we review research on the effect of mastication based on data obtained using event-related potentials (ERPs), including the P300 component and contingent negative variation (CNV), motor-related cortical potentials (MRCPs), and reaction time (RT) as behavioral data. The peak latency of P300 and RT clearly shortened with the repetition of sessions in Mastication, but not in Control, Jaw Movement, or Finger Tapping. The mean amplitude of CNV differed between the Mastication and Control conditions with the repetition of sessions. By contrast, there was no significant difference in the amplitude of MRCP between Mastication and Control in any of the sessions. These results suggest that mastication is associated with cognitive processing rather than movement-related processing in the human brain. We believe that non-invasive recording methods, such as electroencephalography (EEG), magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), functional magnetic resonance imaging (fMRI), and near-infrared spectroscopy (NIRS), will supply valuable evidence in support of a positive relationship between mastication and cognition.

KEY WORDS: chewing, P300, ERP, CNV, MRCP**Introduction**

While the precise relationship between age-related decline in human cognitive function and mastication remains unknown, several studies have obtained data on the effect of mastication on brain activity from elderly subjects. Miura *et al.* (2003)¹⁾ showed that subjects aged over 65 with dementia had significantly fewer teeth, smaller occlusal area, and weaker bite force than normal elderly subjects, suggesting that masticatory function in the elderly is associated with cognitive status. Weyant and colleagues (2004)²⁾ also reported a significant association between limitations of oral function and depression. These reports may suggest the potential involvement of masticatory function in human cognitive processing.

Mastication consists of the activities of the lower jaw and masticatory muscles concerned with rhythmic and voluntary movement. The motor command for this sequential rhythmic movement is generated by a neural population in the central pattern generator (CPG) of the brainstem^{3,4)}. Recent neuroimaging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) in humans have found that several regions of the brain are activated during mastication, including the primary somatosensory cortex (SI), primary motor cortex (MI), supplementary motor area (SMA), premotor area (PM), prefrontal cortex (PFC), insula, posterior parietal cortex (PPC), thalamus, striatum, and cerebellum⁵⁻¹⁰⁾. These studies

suggest that mastication is a complicated movement generated from a neural population in the brainstem and a neural network involving several brain regions. However, these results must be interpreted with care, as the relationship between increases in cerebral blood flow during mastication and cognitive function is unclear. That is, whether or not mastication truly affects the brain activity associated with cognitive processing must be clarified.

Some studies have reported an effect of mastication on psychological tests relating to arousal¹¹⁻¹³⁾, energy expenditure and heart rate^{14,15)}, choice reaction time (RT)¹⁶⁾, and working memory¹⁷⁻²⁰⁾. Several neurophysiological studies have also tried to clarify the effect by recording background electroencephalography (EEG) activity^{11,21,22)}; however, evidence has shown no significant change in memory^{23,24)} or background EEG^{25,26)} after gum-chewing. Consequently, objective methods and indices are needed to investigate the effect of mastication in detail.

The P300 component

The present review article introduces two studies which evaluated the effect of mastication on the central nervous system (CNS) using event-related potentials (ERPs) obtained by time-locked averaging EEG.

The first study demonstrated the effect of mastication on P300 (P3b) in human ERPs. P300 or P3b is one of the most widely studied components with a parietal distribution on the scalp and has been linked to the cognitive processes of context updating, context closure, and event-categorization²⁷⁻²⁹. P300 occurs 300–600 ms after a target stimulus in oddball paradigms, wherein two stimuli are presented in a random series with one of the two, that to which the subject is instructed to respond, occurring relatively infrequently³⁰. The amplitude of P300 is proportional to the amount of attentional resources devoted to a given task³¹⁻³³, whereas the latency is considered a measure of stimulus classification speed or stimulus evaluation time³⁴ and is generally unrelated to response selection processes^{35,36}.

Sakamoto *et al.* (2009)³⁷ investigated the effect of mastication on the peak amplitude and latency of P300. The experiment consisted of two conditions, Mastication and Control, each performed on a different day. The Mastication condition comprised four sessions of recordings at different times: Pre, Post 1, Post 2, and Post 3. In each session, the subjects performed an auditory oddball paradigm for approximately five minutes. After one session, the subjects were asked to chew gum for five minutes at a relaxed self-pace. In total, there were three gum-chewing intervals. The Control condition included the same four sessions, but the subjects were instructed to relax without chewing gum in each interval. For Mastication, a special odorless and tasteless gum base was prepared (CAT21 Chewing Pellet; NAMITEC Co., LTD., Osaka-city, Japan). This gum was made of polyvinyl acetate, wax, and polyisobutylene, based on the Japan Food Hygiene Law. The probability of auditory stimulation for target (2000 Hz) and standard tones (1000 Hz) was 20% and 80%, respectively, in a random series, and the interstimulus interval was 2 sec. The subjects had to respond by pushing a button with their right thumb as quickly as possible only after the presentation of a target stimulus. The authors also performed an additional experiment consisting of two conditions, Jaw Movement and Finger Tapping. In Jaw Movement, the subjects were asked to open and close their jaw at their own pace during each interval and not to bite, to avoid the effect of tactile afferent information. In Finger Tapping, the subjects were instructed to tap their right index finger at their own relaxed pace during each interval. Tasks involving repetitive muscle activity or movement of other body parts would be needed to clarify whether the modulation of ERP waveforms was specific to mastication. In addition, gum-chewing is a fairly complex behavior, involving rhythmic movements of the jaw muscles, tactile sensations of several organs in the oral cavity, tongue movement, and secretion of saliva. Each of these components may contribute differently to brain activity.

Figure 1 shows the mean RT for each condition. The RT for Mastication shortened with repeated sessions, whereas the RTs for Control, Jaw Movement, and Finger Tapping lengthened with repeated sessions. *Figure 2* shows the grand-averaged ERP waveforms after target stimuli in the Mastication and Control conditions. Peak latency of P300 was clearly shorter in Post 3 than in Pre and Post 1 in Mastication, but not in the Control. In the Jaw Movement and Finger Tapping conditions, no such shortening of the peak latency of P300 was observed.

In the Jaw Movement condition, rhythmic jaw movement was found to exert no effect on RT or P300, indicating that mastication with an object in the mouth is more important than rhythmic jaw

movement alone; therefore, a number of factors elicited by gum-chewing might affect the CNS. In their study using fMRI, Takada and Miyamoto (2004)⁹ found that the neurons in the frontal and parietal cortices were more strongly activated during gum-chewing than during sham gum-chewing. These authors suggested that this fronto-parietal network contributes to higher cognitive information processing. In the Finger Tapping condition, the subjects tapped their right index finger, but no significant effects on RT or P300 were noted. This task, involving repetitive muscle activity or movement of other body parts, clarified that the modulation of ERP waveforms was specific to mastication.

RT, defined as the time from stimulus onset to the response, including components such as stimulus evaluation and response selection, is an important measure in understanding sensorimotor performance in humans^{38,39}. Therefore, the modulation of RT in Mastication indicates the sequential processing from stimulus input to response output to be sped up by the effect of mastication. On the other hand, RTs in Control, Jaw Movement, and Finger Tapping were clearly or significantly longer in Post 3 than in Pre (*Figure 1*). Many studies have demonstrated relationships between RT and the components of ERPs, such as P300, during discrimination tasks. The latency of P300 has been considered a measure of stimulus classification speed or stimulus evaluation

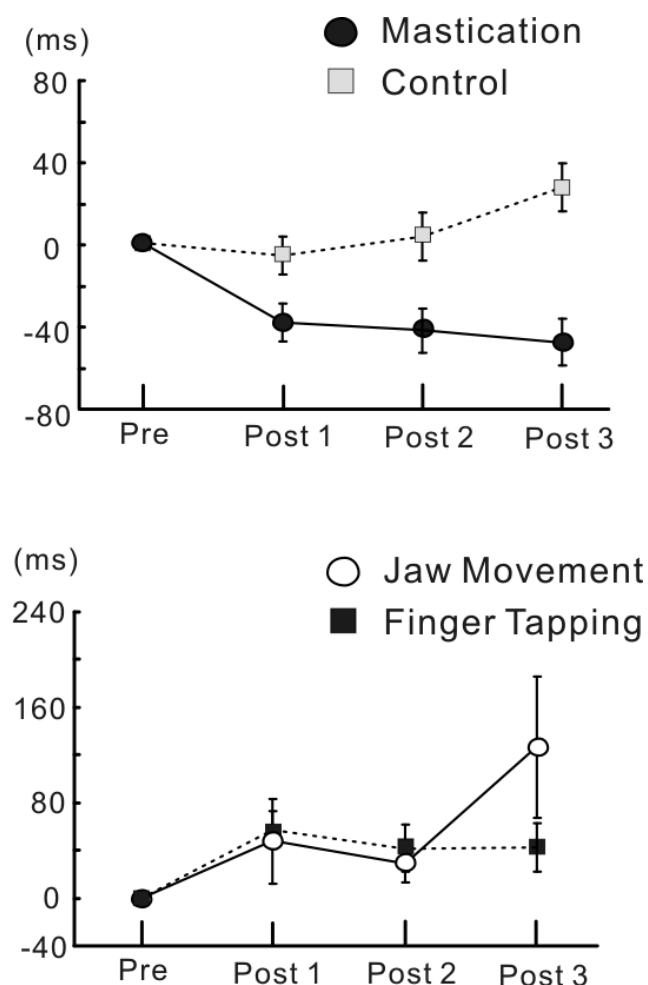


Fig. 1. Upper figures: Mean reaction time (RT) for the Mastication and Control conditions. The values shown are differences between the pre and post conditions. The value for Pre is set at 0 ms. Lower figures: Mean RT in the Jaw Movement and Finger Tapping conditions.

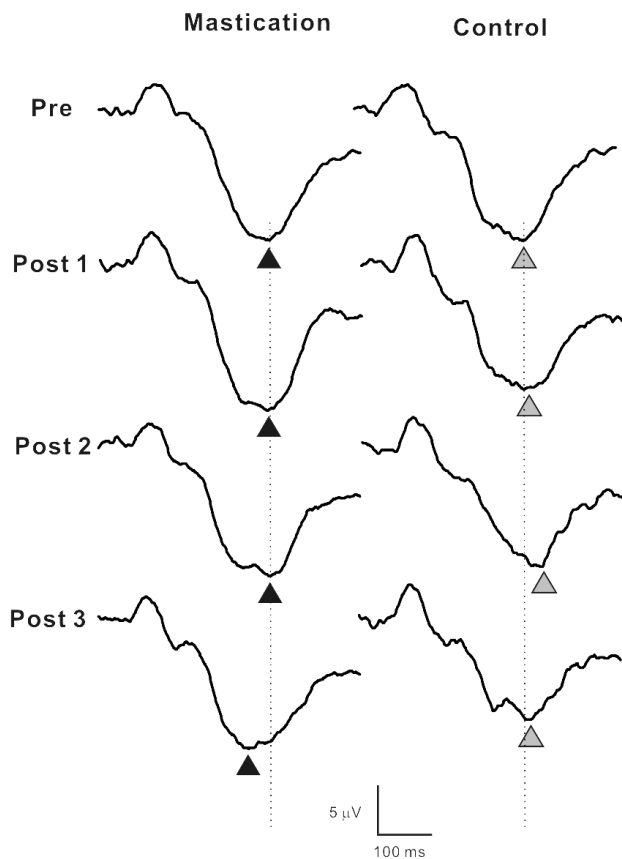


Fig. 2. Grand-averaged waveforms of P300 at Pz for the Mastication and Control conditions. Figures on the left show the waveforms in Mastication, with black triangles indicating the peak latency of P300. The dotted-line indicates the peak latency of P300 in Pre. Of note, the peak clearly occurs earlier in Post 3 than in Pre. Figures on the right show the waveforms in Control, with gray triangles indicating the peak latency of P300. Again the dotted-line indicates the peak latency of P300 in Pre. The peak is almost identical among sessions or slightly longer in the Post sessions than in Pre. Adopted from Sakamoto *et al.* (2009)³⁷.

time^{34,40}). In the Mastication condition, the peak latency of P300 was significantly shorter in Post 3 than in Pre and Post 1 (**Figure 2**), indicating that, as with RT, the latency of P300 can be affected by mastication. That is, mastication influences the speed of the stimulus evaluation in human cognitive processing.

As mentioned above, many studies have reported the effect of mastication in tests in fields such as psychology, working memory, and background EEG, but the mechanisms of the effect are still unclear. This effect was also observed in ERP waveforms, and several possible explanations have been suggested.

The first, mentioned already, is the effect of mastication with an object in the mouth. The second is that mastication influences arousal. It is well established that the level of arousal is affected by the neural activity of the brainstem, as clarified by Moruzzi and Magoun (1949)⁴¹ who electrically stimulated the mesencephalic reticular formation of cats when EEGs signified a sleep-like state. On the onset of stimulation, there was a rapid and dramatic change of the EEG reflecting the awake brain^{41,42}. Based on these authors' previous findings, the reticular formation in the brainstem and the neural pathways basic to the cortical arousal response became known as the ascending reticular activating system (ARAS). The ARAS has two pathways, dorsal and ventral; the dorsal pathway

activates the cortex via the thalamus, while the ventral pathway does so via the hypothalamus and basal forebrain. It is assumed that the ARAS is affected by mastication, because rhythmic mastication is generated by a CPG in the brainstem^{3,4,43}. Many studies have reported that the CPG is driven not only by mastication, but also by cyclic movements such as stepping, walking, and pedaling⁴⁴⁻⁴⁶. ERP-based studies have found that, after such exercise, the peak latency and/or amplitude of P300 is changed^{40,47-52}. Magnie and colleagues (2000)⁵⁰ and Yagi and colleagues (1999)⁴⁹ suggested that the arousal level has an important influence on ERP waveforms. While this seems unlikely, since neither Jaw Movement without gum nor Finger Tapping affected RT or P300, these movements are not usually performed in daily life, as opposed to gum-chewing, walking, and pedaling, despite the rhythmic nature of these latter activities. Thus, it may be that Jaw Movement without gum and Finger Tapping did not drive the CPG.

A third explanation is the effect of motor-related activities elicited by mastication. Repetitive electrical stimulation of a certain area of the cerebral cortex induces rhythmic jaw movements in many species, including monkeys^{53,54}, cats⁵⁵⁻⁵⁷, guinea pigs⁵⁸⁻⁶⁰, and rabbits^{61,62}. Such rhythmic jaw movements with coordinated rhythmic movements of the tongue and facial organs as well as the secretion of saliva are known collectively as fictive mastication, and the cortical regions involved are termed the 'cortical masticatory area (CMA)'^{3,43}. At present, the descending input from the CMA is considered the major source generating and activating the masticatory CPG³. The CMA includes several cortical regions, such as the face MI, the face SI, the area immediately lateral to the face MI, and a deep area at the inner surface of the frontal operculum⁵⁴. Recent neuroimaging studies have also found a neural network involving the SMI, SMA, PM, PFC, insula, PPC, thalamus, striatum, and cerebellum⁵⁻¹⁰. However, this hypothesis may be questioned, because Jaw Movement without gum did not affect RT or P300 [you must use "or" with a negative verb (did not affect)].

A fourth explanation is the effect of serotonergic (5-HT) neurons. Jacobs and Fornal (1993)⁶³ reported that the activity of 5-HT neurons was enhanced by voluntary rhythmic movement, such as mastication, locomotion, and respiration, which was modeled in animals⁶⁴. In addition, recent studies in humans have demonstrated a close relationship between the 5-HT activity induced by rhythmic movement and the effect on background EEG and the nociceptive flexion reflex^{65,66}. Indeed, since this study did not assess the level of 5-HT activity, further studies might be needed to clarify this hypothesis.

Of course, there is the possibility that more than one of the above explanations applies.

CNV and MRCPs

Sakamoto and colleagues (2009)⁶⁷ focused on contingent negative variation (CNV) and movement-related cortical potentials (MRCPs), which have been widely studied and are considered to be linked to the cognitive and motor preparation processes. CNV is an ERP, and its amplitude increases during the time interval between a first warning stimulus (S1) and second imperative stimulus (S2). CNV has been associated with both motor preparation and cognitive processes including expectancy, motivation, attention and arousal⁶⁸⁻⁷⁰. CNV consists of at least

two components, an early frontocentral dominant component (early-CNV) and a late centroparietal dominant component (late-CNV). In contrast, MRCPs are recorded preceding self-initiated voluntary movement and reflect movement preparation, not involving cognitive processing for imperative stimulus⁷¹). These potentials begin with a slow rising negativity, called the Bereitschaftspotential (BP), and progress to a steeper, later negativity starting about 500 ms before the movement onset, called the negativity slope (NS)⁷. These previous findings indicate that CNV and MRCPs have similar waveforms and features concerning motor preparation but differing brain activities. Therefore, comparing the effect of mastication between CNV and MRCPs is useful in investigating the effect of mastication on the human brain in detail, and this comparison provides four possible hypotheses regarding the effect of mastication on brain activity.

The first is that mastication affects both CNV and MRCPs. If this hypothesis holds true, mastication should affect both motor preparation and cognitive processes. The second is that the effect occurs on CNV, not MRCPs, indicating that cognitive processing rather than motor preparation processing is influenced. The third hypothesis describes just the opposite: that mastication affects MRCPs, not CNV. In this case, it is likely that motor preparation processing is more critical than cognitive processing. The fourth is that mastication affects neither CNV nor MRCPs.

In the CNV study, the subjects performed a warning stimulus (S1) – imperative stimulus (S2) paradigm. S1 and S2 were auditory pure tones of 1 kHz and 2 kHz, respectively. The subjects had to respond by pushing a button with their right thumb as quickly as possible after the presentation of an S2 stimulus. A pair of S1 and S2 stimuli was given to the subjects with an interval of 2 sec, and the S1-S1 interval was 10 sec. This experiment consisted of two conditions, Mastication and Control. The Mastication condition comprised four sessions of recordings at different times: Pre, Post 1, Post 2, and Post 3. In each session, the subjects performed an S1-S2 paradigm for approximately five minutes. After one session, the subjects were asked to chew gum for five

minutes at their own constant rate. In total, there were three gum-chewing intervals. The Control condition also included the same four sessions of a S1-S2 paradigm (Pre, Post 1, Post 2, and Post 3), but the subjects were instructed to relax without chewing gum for five minutes in each interval. In the MRCP study, the subjects performed brisk extension movements with the middle finger of their right hand. Each movement was repeated voluntarily at irregular self-paced intervals exceeding 6 sec. One session comprised 70 epochs of movement. This experiment also consisted of two conditions, Mastication and Control. The procedure was the same as for CNV.

Figure 3 shows the mean RT in the CNV study, with a significant difference noted in Post 3 between Mastication and Control, but not in Pre, Post 1, or Post 2. **Figure 4** shows the grand-averaged CNV at each session in Mastication and Control [this is an incorrect use of “respectively”. Please understand]. In Mastication, the amplitudes of CNV gradually increased with repetitive sessions (Post 1, Post 2, and Post 3), compared to Pre. On the other hand, in Control, the amplitudes were almost the same or gradually decreased with repetitive sessions. **Figure 5** shows the grand-averaged MRCPs for each session in Mastication and Control. It is apparent that the waveforms did not change with repetitive sessions in Mastication or Condition. In the CNV study, the mean amplitudes of CNV, including early- and late-components, differed between the Mastication and Control conditions, particularly at Post 2 and Post 3. In contrast, in the MRCP study, no significant difference was noted in the amplitude of BP and NS between Mastication and Control in any session. As mentioned above, a comparison for the effect of mastication between CNV and MRCPs provided four possibilities for the effect of mastication on brain activity, and these results indicated that mastication influenced cognitive processing rather than motor preparation processing in the human brain.

Many previous studies have shown that several brain regions are related to generators of CNV. Previous intracranial recordings of CNV demonstrated a role for the PFC, orbitofrontal cortex,

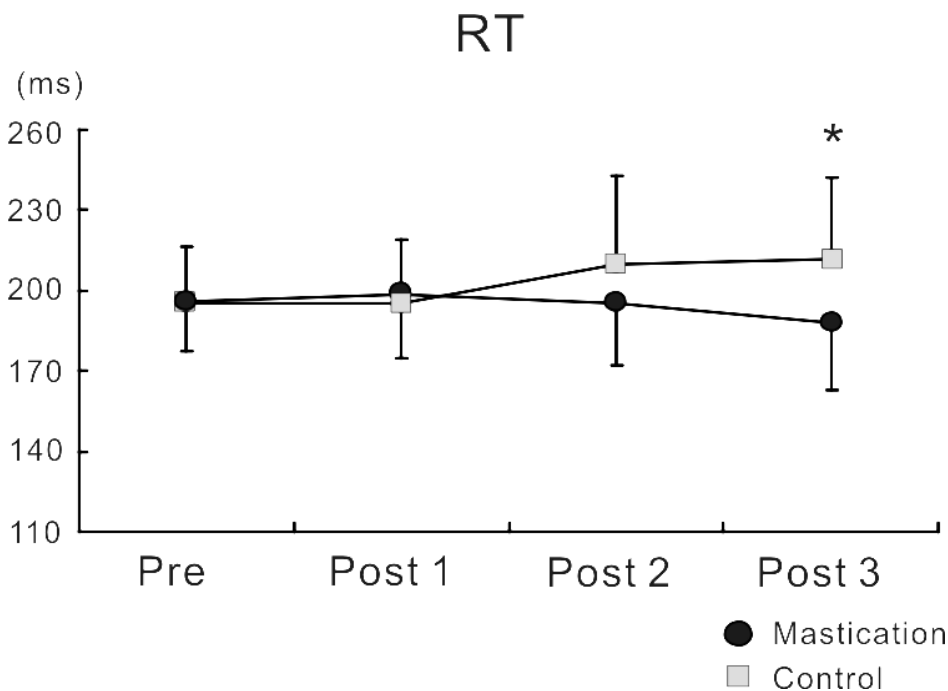


Fig. 3. Mean RT in each condition in CNV study across all subjects. * $p < 0.05$, showing a significant difference between Mastication and Control. Adopted from Sakamoto *et al.* (2009)⁶⁷.

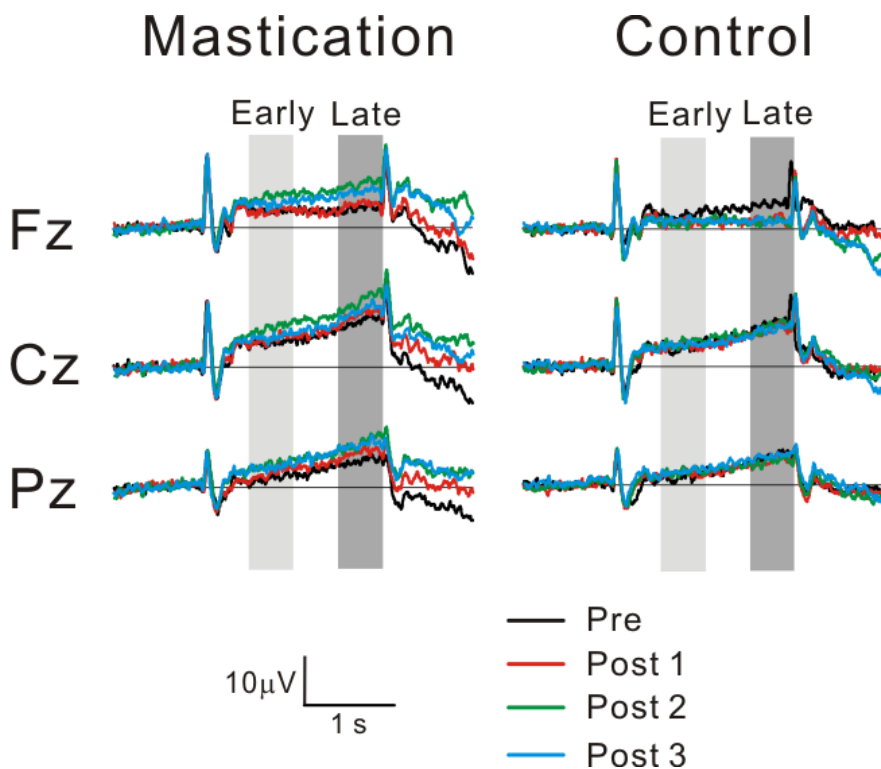


Fig. 4. Grand-averaged CNV waveforms of each session. Black, red, green, and blue lines indicate waveforms of Pre, Post 1, Post 2, and Post 3, respectively. Thin and thick gray zones indicate early- and late-CNV, respectively. Early = early-CNV; Late = late-CNV

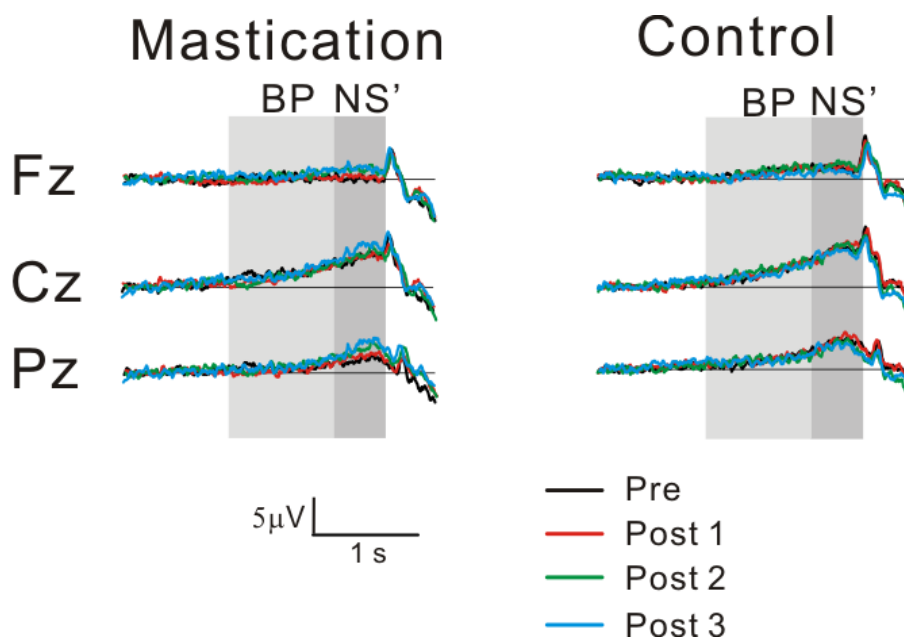


Fig. 5. Grand-averaged MRCP waveforms of each session. Black, red, green, and blue lines indicate waveforms of Pre, Post 1, Post 2, and Post 3, respectively. Thin and thick gray zones indicate BP and NS, respectively. BP = Bereitschaftspotential; NS = negative slope

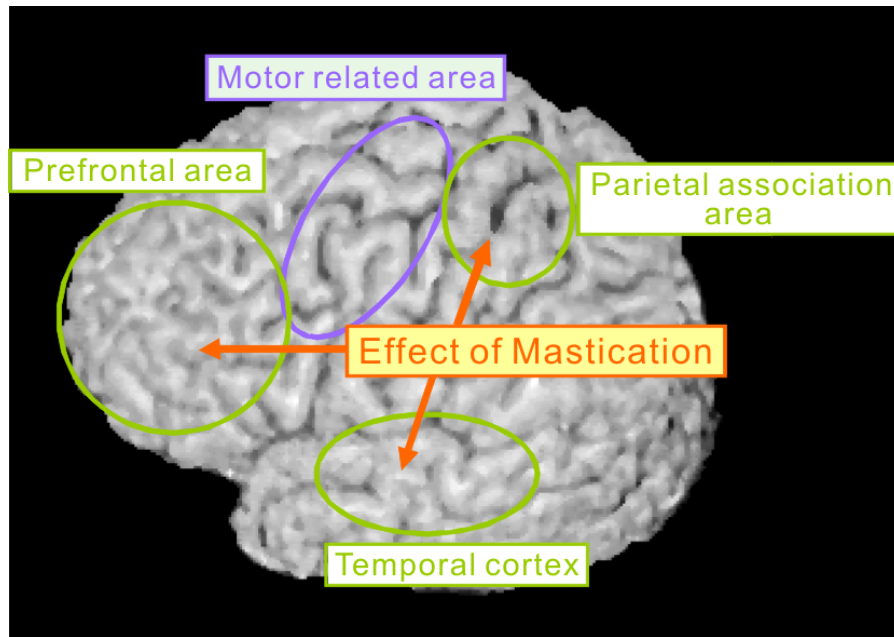


Fig. 6. A model of brain regions related to the effect of mastication, based on two studies using P300, CNV, and MRCPs. Effects should be noted in the prefrontal area, temporal cortex, and parietal association area, but not in the motor-related area.

SMA, PM, MI, SI, cingulate gyrus, temporal area, parietooccipital lobes, insula, and subcortical structures, including the basal ganglia and thalamus⁷²⁻⁷⁷). Moreover, the generation of CNV involves the ascending ARAS from the brain stem and midbrain, which is strongly related to arousal levels⁷⁸). In the present study, we were unable to conclude precisely which brain regions were affected by mastication, but generator mechanisms for CNV were more strongly activated during the mastication task.

In contrast to CNV, MRCPs were not affected by mastication in any session, even though CNV and MRCPs have similar waveforms and features, possibly due to a difference in generators. The generation of MRCPs mainly involves movement-related regions. That is, BP and NS' are generated from the pre-SMA, SMA, PM, MI, SI, anterior cingulate cortex (ACC), and subcortical structures including the basal ganglia and thalamus, as shown by intracranial recordings^{70,72-75,79}). Taking these studies into consideration, generation of CNV requires a broader cortico-subcortical network than MRCPs. Clinical studies in several patients with lesions in the cerebellum found that BP was completely absent while CNV remained normal⁷²). In patients with Parkinson's disease, Ikeda and colleagues reported that BP remained normal but CNV was diminished⁷³). In addition, in a CNV paradigm without a motor task in response to an imperative stimulus (S2), well-pronounced negativity was recorded prior to S2^{69,80}). These previous studies indicated that CNV clearly differs from MRCPs⁸¹), although it shares some cortical generators with MRCPs and contains BP-like features. Thus, the effect of mastication is suggested to be associated with cognitive processing rather than movement-related processing. **Figure 6** indicates a model of brain regions related to the effect of mastication, based on the results from studies of P300, CNV, and MRCPs.

Conclusion

Recently, several non-invasive recording methods have been used to measure human brain activity. Among these are methods based on neurophysiology, including EEG, magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS), and methods based on neuroimaging, including fMRI and near-infrared spectroscopy (NIRS). These methods should be utilized in attempts to clarify the effect of mastication on the human brain in detail. Combining recording methods such as these would be useful in evaluating human brain activities in several respects. In addition, studies of P300, CNV, and MRCPs suggest that the effect of mastication is linked to human cognitive function. In the near future, the relationship between age-related decline in cognitive function and mastication should be resolved. We believe that non-invasive recording methods can supply valuable evidence supporting a positive relationship between mastication and cognition.

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