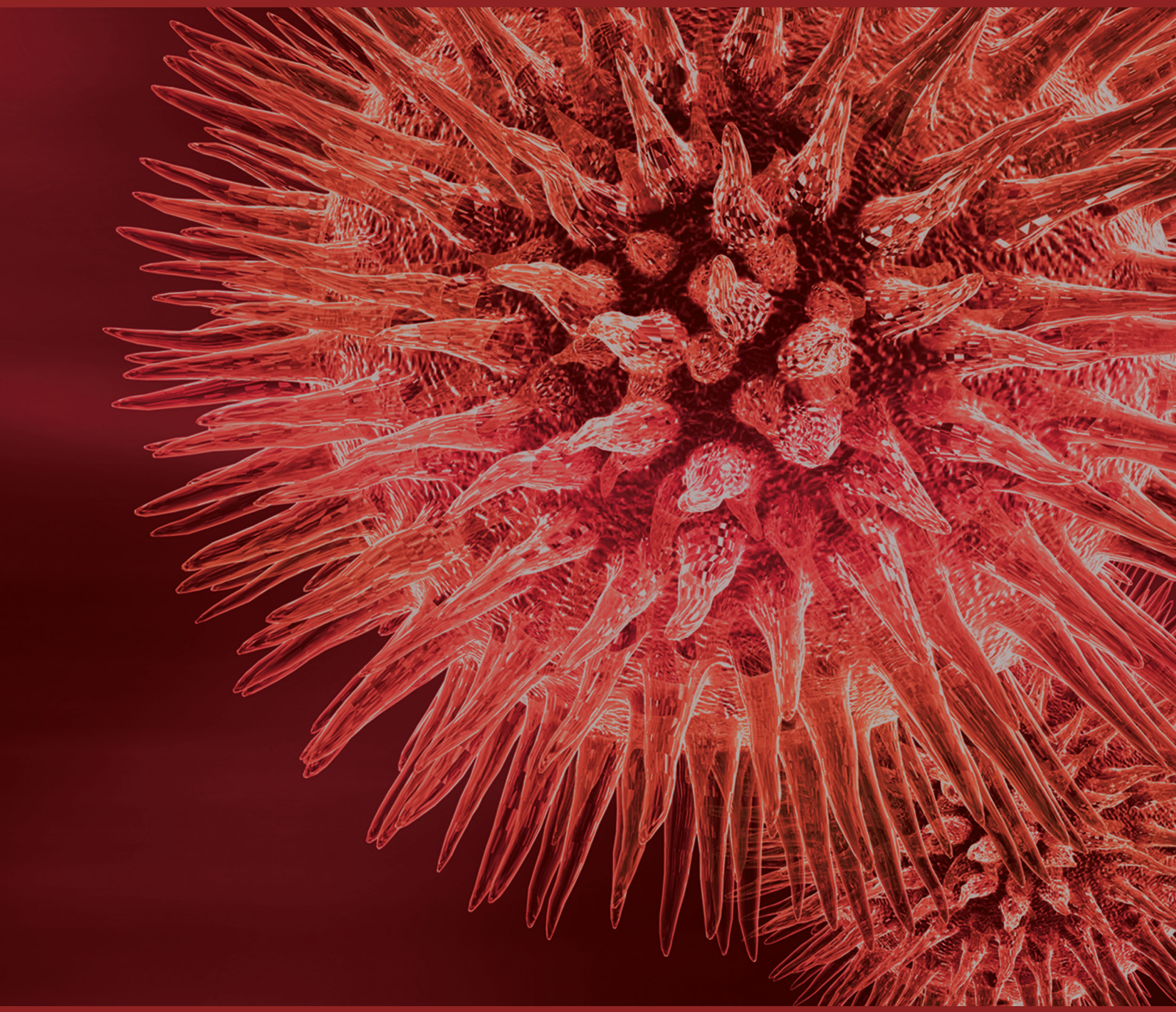
BioMed Research International

Chewing, Stress-Related Diseases, and Brain Function

Guest Editors: Kin-ya Kubo, Huayue Chen, Xiaolin Zhou, Jian-Hua Liu, and Olivier Darbin



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Editorial

Chewing, Stress-Related Diseases, and Brain Function

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While active mastication or chewing is primarily involved in food intake and digestion, it also promotes and preserves general health. Epidemiologic studies indicate that aged individuals with fewer teeth are more likely to develop cognitive dysfunction. Tooth loss is an epidemiologic risk factor for Alzheimer's disease. Abnormal mastication due to tooth loss or occlusal disharmony induces chronic stress, leading to pathologic changes in the hippocampus and deficits in learning and memory. Evidence suggests that chewing effectively sends various types of information to the brain. Chewing activates several brain regions that are essential for cognitive processing, including the hippocampus and prefrontal cortex. In addition, chewing gum before a meal can decrease food intake and help prevent obesity via neural pathways. In this special issue, several research groups report new findings regarding the importance of mastication.

Y. Ono et al. examined the effects of chewing on stress-induced long-term depression and anxiety-related behaviors in adult male rats. They found that chewing ameliorated the development of long-term depression in the hippocampal CA1 region. Chewing may activate the dopaminergic system in the ventral hippocampus to suppress stress-induced anxiogenic behaviors. This study demonstrates that chewing could be an active coping strategy for relieving stress-induced anxiety-like behaviors, which may be involved in the dopaminergic neuronal pathway.

R. A. F. Weijenberg and F. Lobbezoo explored the relationship between mastication, cognition, and pain. Active mastication might improve some measures of cognitive performance, such as working memory and subjective alertness. These effects can partially be explained by cerebral functional specialization. Stress and relief of stress can play an important role in the physiologic mechanisms underlying these effects. Oral habits such as bruxism might have the same effects relieving stress. Active chewing might relieve stress or pain, but long-term engagement in oral habits such as these increases the risk of fatigue, pain, and temporomandibular disorders.

K.-Y. Kubo et al. provide a concise review of the neuronal mechanisms that underlie the interactions between masticatory function and stress-coping behaviors in animals and humans. Chewing or biting as a stress-coping behavior attenuates stress-induced disorders, such as gastric ulcers, and cognitive and psychological impairment in rodents via suppression of stress-induced activation of the hypothalamic-pituitary-adrenal axis and autonomic nervous system. The histaminergic nervous system may also be involved in the chewing-induced attenuation of stress-induced cognitive deficits. In humans, many studies support an association between stress and sleep bruxism. Gum chewing during stress may affect the levels of various stress markers in the saliva and plasma and increase attention, self-rated alertness, and vigilance.

A. Allen and A. P. Smith report a pilot study investigating the effects of chewing gum on mode and cognitive performance both in the laboratory and naturalistic work

situations. Their findings revealed that chewing gum during the workday enhanced productivity and reduced cognitive problems. Thus, chewing gum can attenuate reductions in alertness and enhance worker performance.

T. Otsuka et al. describe a study using functional near-infrared spectroscopy to evaluate the effects of mandibular retrusive deviation on prefrontal cortex activation. Activation of the prefrontal cortex was significantly greater during clenching in the mandibular retrusive condition than during clenching in the control condition. This study demonstrates that functional near-infrared spectroscopy can be used to objectively evaluate the occlusal condition based on activity in the prefrontal cortex.

Y. Hirano and M. Onozuka present a systematic review of 151 published reports on the relationship between chewing and attention. More than half of the reports indicate that chewing has positive effects on attention, especially sustained attention. The effects seem to coincide with an improvement in mood and are influenced by time-on-task.

Y. Ono et al. focused on prefrontal brain activity based on functional near-infrared spectroscopy, a visual analogue scale, and the hemodynamic response. They found that increased hemodynamic responses in the prefrontal area reflect the top-down control of attention and/or self-regulation against uncomfortable somatosensory input, which is a potential marker of detecting the subjective of occlusal discomfort.

In summary, the papers in this special issue highlight several important research strategies for investigating relationship between chewing, stress-related disorders, and brain function. Findings from these studies will greatly contribute to our understanding of the physiologic mechanisms underlying stress-related disorders and chewing as a stress-coping behavior. As the editors of this special issue, we hope that the readers will find these articles interesting, informative, and inspiring.

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Review Article

Mastication as a Stress-Coping Behavior

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Exposure to chronic stress induces various physical and mental effects that may ultimately lead to disease. Stress-related disease has become a global health problem. Mastication (chewing) is an effective behavior for coping with stress, likely due to the alterations chewing causes in the activity of the hypothalamic-pituitary-adrenal axis and autonomic nervous system. Mastication under stressful conditions attenuates stress-induced increases in plasma corticosterone and catecholamines, as well as the expression of stress-related substances, such as neurotrophic factors and nitric oxide. Further, chewing reduces stress-induced changes in central nervous system morphology, especially in the hippocampus and hypothalamus. In rodents, chewing or biting on wooden sticks during exposure to various stressors reduces stress-induced gastric ulcer formation and attenuates spatial cognitive dysfunction, anxiety-like behavior, and bone loss. In humans, some studies demonstrate that chewing gum during exposure to stress decreases plasma and salivary cortisol levels and reduces mental stress, although other studies report no such effect. Here, we discuss the neuronal mechanisms that underline the interactions between masticatory function and stress-coping behaviors in animals and humans.

1. Introduction

Stress is a physiologic and psychologic response to environmental changes and noxious stimuli. Chronic stress negatively affects physical and mental health [1–3], ultimately leading to disease [4–8]. Stress-related diseases are prevalent worldwide. Stress activates the neuroendocrine system via the autonomic system and hypothalamic-pituitary-adrenal (HPA) axis, which leads to the release of corticosteroids and hormones [9, 10].

Chewing, swallowing, and speaking are important oral functions related to physical, mental, and social health [11–13]. In particular, masticatory ability influences nutritional status, overall health, and activities of daily living, especially in the elderly population [14, 15]. Chewing ability is frequently impaired in the elderly, and many older adults develop dental problems as a result of tooth loss, which compromises general health status and is an epidemiologic risk factor for Alzheimer's disease [16–20]. In animals, impairing mastication by removing teeth results in impaired spatial learning due to morphologic changes in the hippocampus [20]. Thus, chewing appears to have an important role in maintaining some aspects of cognitive function [20].

Chewing is also an effective stress-coping behavior. When exposed to an inescapable stressor, animals assume coping behaviors, such as chewing, that attenuate some elements of the stress response [21]. In humans, nail-biting, teeth-clenching, and biting on objects are considered outlets for emotional tension or stress. Animals provided the opportunity to chew or bite wooden sticks during immobilization or restraint stress exhibit decreases in stress-induced plasma corticosterone levels and attenuated HPA axis and autonomic nervous system responses to stress, which helps to prevent the stress-induced formation of gastric ulcers [4, 22–24], deficits in spatial learning ability [25, 26], and bone loss [27].

In humans, gum chewing is reported to relieve stress and improve task performance [28–30]. A recent functional magnetic resonance imaging study revealed that gum chewing during exposure to a loud noise inhibits the propagation of

stress-related information in the brain [31]. Data regarding the stress-attenuating benefits of gum chewing, however, are conflicting and difficult to replicate [32–34]. Here, we provide an overview of the mechanisms that underlie chewing as a stress-coping behavior in animals and humans.

2. Effects of Stress and Mastication

Mastication under stressful conditions prevents stress-induced ulcer formation in the stomach [4, 22–24], spatial cognitive deficits [25, 26], anxiety-like behavior [35], and osteoporosis [27]. Onishi et al. [36] reported that maternal chewing during prenatal stress prevents prenatal stress-induced learning deficits in the adult offspring. Several studies have demonstrated that chewing attenuates stress-induced functional and morphologic changes in the hippocampus [25, 36–40].

Spatial cognitive function is mainly controlled by the hippocampus. The hippocampus is sensitive to stress, as well as the aging process, and it is one of the first brain regions to be structurally and functionally modified by stress [41]. Stress-induced increases in corticosterone impair hippocampal-dependent learning and memory [42–44]. Recent reports indicate that chewing ameliorates stress-induced deficits in hippocampal-dependent spatial cognitive function. For example, Miyake et al. [25] reported that rodents given wooden sticks to chew on during immobilization stress exhibit attenuated stress-induced suppression of spatial memory and glucocorticoid receptor expression in the hippocampus. Chronic stress leads to the downregulation of corticosterone receptors and the inhibition of negative feedback from the hippocampus to the HPA axis [37]. Also in rats, active chewing during immobilization stress ameliorates the stress-induced impairment of N-methyl-D-aspartate receptor-mediated long-term potentiation [38], which may be due to chewing-induced activation of histamine H1 receptors [39]. In addition, aggressive mastication during stress prevents the stress-induced decrease in brain-derived neurotrophic factor mRNA and neurotrophin-3 mRNA in the hippocampus. Brain-derived neurotrophic factor plays an important role in long-term potentiation [45], neurogenesis [46], dendritogenesis [47], and activity-dependent neuroplasticity [48], consistent with the finding that chewing during stressful conditions ameliorates the stress-induced suppression of cell proliferation in the hippocampal dentate gyrus [40]. Cell proliferation in the hippocampal dentate gyrus strongly correlates with learning ability [49], and neurotrophin-3 influences the development of the hippocampus [50]. Nitric oxide levels are increased by restraint stress and, in rodents, biting suppresses the increases in the nitric oxide levels in the hypothalamus [51]. Analysis of blood flow in the amygdala and hypothalamus using laser Doppler flowmetry and O_2-selective electrodes in rats allowed to chew on sticks under restraint stress revealed recovery of stress-induced decreases in PO_2 levels [52]. Chewing may reduce nitric oxide by increasing PO_2 levels in the hypothalamus, thus altering hemoglobin-scavenging activity for nitric oxide. Previous animal studies indicated that the stress-coping effects of chewing are mediated by the autonomic nervous system and the HPA axis.

Additionally, exposure to stress is a precipitating factor for many illnesses, including mood disorders [53]. In humans, dysregulation of thyroid hormones [54] and glucocorticoids [55] has long been associated with mood disorders. Helmreich et al. [35] reported that chewing on a wooden dowel during tail-shock in rats prevented stress-induced anxiety-like behavior and attenuated stress-induced decreases in thyroid hormone. The effects of chewing on thyroid and glucocorticoid levels may account for the effects of chewing to reduce stress-induced anxiety.

Osteoporosis is a skeletal disease characterized by low bone mass and microstructural bone deterioration, with an increased risk of fracture [56]. A large body of evidence from animal and human studies indicates a link between chronic mild stress and bone loss [57–59]. We examined the effects of chewing during chronic stress on stress-induced bone loss. Chewing under chronic stress prevents the increase in plasma corticosterone and noradrenaline levels, which attenuates both the reduced bone formation and increased bone resorption, and improves the trabecular bone loss and microstructural bone deterioration induced by chronic mild stress [27].

Prenatal stress increases the risk for neurobiological and behavioral disturbances in adult offspring [60, 61]. Clinical studies demonstrated that pregnant mothers exposed to social, emotional, or hostile experiences have offspring with an increased susceptibility as adults to mental disorders, such as depression, schizophrenia, and cognitive deficits [62]. We examined whether allowing pregnant mice to chew on a wooden stick during stress decreased the stress-induced learning deficits of the adult offspring by measuring plasma corticosterone levels, spatial learning ability, and cell proliferation in the hippocampal dentate gyrus of the adult offspring [36]. Allowing mouse dams to chew on a wooden stick during exposure to prenatal stress attenuated the increase in prenatal stress-induced plasma corticosterone levels. Further, adult offspring of dams exposed to prenatal stress exhibited impaired learning and decreased cell proliferation in the dentate gyrus, which was attenuated by allowing the dams to chew on a wooden stick during exposure to prenatal stress. Maternal chewing during prenatal stress thus appears to be effective for preventing learning deficits in the adult offspring [36].

2.1. Mastication and the Autonomic Nervous System. Mastication during stressful conditions suppresses stress-induced activation of the autonomic nervous system, causing sympathetic nerve terminals to locally release catecholamines [4, 22, 63]. Aggressive biting during exposure to stress significantly attenuates stress-induced increases in dopamine metabolism [64] and noradrenaline turnover in the hypothalamus and limbic areas [4, 63]. Okada et al. [65] reported that restraint stress-induced increases in blood pressure and core temperature were significantly suppressed in rats allowed to chew on a stick compared with rats that were restrained but not given a stick to chew, consistent with other reports [66]. In addition,

chewing on a wooden stick during immobilization stress prevents poststress arrhythmias [67]. Interleukin- (IL-) 1α, IL-1β, and IL-6 have important roles in the thermoregulatory system [68] and allostasis [69]. IL-1β acts on the hypothalamus to enhance the secretion of corticotropin-releasing hormone [70, 71]. Stress induced by placing an animal in an open-field box leads to increased plasma IL-6 levels [72]. Therefore, biting induced inhibition of the stress-related increase in the core temperature might be due to the suppression of serum IL-1β and IL-6 levels. Cytokines such as IL-1α, IL-1β, and IL-6 are also involved in immunity. Some studies indicate that mastication-induced suppression of these cytokines prevents gastric ulcer formation [23, 24, 63, 64]. An animal study using micro-positron-emission tomography showed that chewing during immobilization stress suppresses the stress-induced increase in plasma corticosterone levels and glucose uptake in the paraventricular hypothalamic nucleus and anterior hypothalamic area, but not in the lateral hypothalamus [73].

2.2. Mastication and the HPA Axis. Mastication during stressful conditions suppresses activation of the HPA axis. In rats and mice, chewing or biting on wooden sticks under various stressors such as immobilization, restraint, cold exposure, and tail pinch attenuates the secretion of adrenocorticotropic hormone (ACTH) [38, 74, 75] and plasma corticosterone levels [23, 35, 38, 40, 63, 74, 76, 77]. Suppression of ACTH secretion may account for subsequent changes in physiologic stress markers in the paraventricular nucleus of the hypothalamus. Mastication under stress-inducing conditions suppresses the stress-activated expression of corticotropin-releasing factor, which controls ACTH secretion [78]; c-Fos, an indirect marker of neuron activity [79]; the phosphorylation of extracellular signal-regulated kinases 1/2 [80]; and the expression of nitric oxide synthase mRNA [81] and levels of nitric oxide [82], which is an important signaling molecule in corticotropin-releasing factor release [83] in the paraventricular nucleus of the hypothalamus. The negative feedback mechanism of the HPA axis reduces the secretion of glucocorticoids mainly by inhibiting the hypothalamic and hypophyseal activities and indirectly by binding to glucocorticoid receptors in the hippocampus [84]. Chewing ameliorates the stress-induced downregulation of glucocorticoid receptors, which suppresses negative feedback mechanisms [25]. In addition, biting on a wooden stick during chronic stress decreases neuronal nitric oxide synthase mRNA expression in the hypothalamus [81], which may be involved in the regulation of corticotropin-releasing factor secretion. Koizumi et al. [67] reported that chewing during immobilization stress prevents poststress arrhythmias in rats. Cardiovascular activity is controlled by the hypothalamus [85]. These effects of chewing on the HPA axis also ameliorate stress-induced cardiac imbalances and reduce susceptibility to stress-induced arrhythmias by inhibiting neuronal responses in the hypothalamus.

2.3. Neuronal Mechanisms That Underlie Stress Attenuation by Chewing. How does chewing during stress-inducing conditions suppress the autonomic nervous system and HPA axis? We suggest that stress-coping activities such as chewing engage the medial prefrontal cortex (mPFC) and the right central nucleus of amygdala neuronal activity asymmetrically [86]. The mPFC is critically involved in the regulation of stress-induced physiologic and behavioral responses [87–90]. Dopamine mainly controls the stress-related actions of the mPFC [91, 92]. Mice and rats exposed to an inescapable stress will chew on an inedible material, such as aluminum foil or cardboard, in the cage [76, 93]. Under inescapable stress conditions, chewing suppresses increases in plasma corticosterone [94]. Moreover, chewing also attenuates stress-related dopamine utilization preferentially within the mPFC [93]. Chewing-induced suppression of mPFC dopamine utilization is largely confined to the right hemisphere [93]. Together, these observations suggest a particularly important role for the right mPFC in stress-coping behavior. Chewing leads to an increase in fos-immunoreactivity that is selective for the right mPFC and a decrease in fos-immunoreactivity that is selective for the central nucleus of the right amygdala, a region that may regulate dopamine, both of which are implicated in regulating dopamine utilization in the mPFC, particularly under stress-inducing conditions [94–96]. In addition, chewing during stress-inducing conditions also attenuates the stress-induced release of noradrenaline in the amygdala [4, 22, 63]. Therefore chewing-induced changes in catecholamines in the mPFC and right central nucleus of the amygdala play an important role in stress-coping behavior.

A possible mechanism for chewing-induced alterations in hippocampus-related behavioral and morphologic changes is the brain histaminergic reaction. Chewing induces histamine H1 release in the hippocampus, and H1 receptor activation might recover stress-suppressed synaptic plasticity. The mesencephalic trigeminal nucleus receives proprioceptive sensory inputs via the trigeminal nerve from the masseter muscle spindle and the periodontal ligaments during mastication [97]. A subpopulation of the mesencephalic trigeminal nucleus neurons projects its fibers into the tuberomammillary nuclei (TMN) of the posterior hypothalamus in which histaminergic neuronal cell bodies are localized [98, 99]. Chewing increases the hypothalamic histamine concentration, thereby increasing satiety [100, 101], suggesting that chewing stimulates histaminergic neurons in the TMN. Axons of histaminergic neurons in the TMN project widely throughout the entire brain, including the hippocampus [102–105], and electrical stimulation of the TMN facilitates extracellular concentrations of histamine in the hippocampus [106]. Thus, a chewing-induced increase in the histamine level in the hippocampus might rescue long-term potentiation via the recovery of stress-attenuated N-methyl-D-aspartate receptors [39].

3. Human Studies

3.1. Sleep Bruxism and Stress. Sleep bruxism is a stereotypic movement disorder that is characterized by grinding or clenching the teeth during sleep and is generally associated with sleep arousal [107]. Sleep bruxism results in damage to the teeth, periodontal tissues, and masticatory muscles,

as well as cervical pain and temporomandibular disorders [108]. The onset of sleep bruxism peaks between 20 and 45 years of age, although it also occurs in children [107, 109, 110]. Sleep bruxism is common in females [111]. Although the complete etiology of sleep bruxism is not clear, some factors include occlusal interference [112], psychosocial stress [113–115], psychologic stress [113, 114, 116–118], smoking [113], striatal D2 receptor activation [119], and transient sleep arousal [120]. Some studies suggest that stress is a causal agent of sleep bruxism because sleep bruxism occurs more often after exhausting and stressful days [121]. In an epidemiologic study on British, German, and Italian populations, self-reported sleep bruxism was positively related to a highly stressful lifestyle [116] and significantly associated with severe stress at work [117]. An analysis of stress-coping strategies in patients with sleep bruxism compared to nonbruxing controls indicated that sleep bruxism patients utilize significantly fewer positive coping strategies such as escape [118, 122]. In contrast, other studies report no relationship between self-reported stress levels and the degree of sleep bruxism [123–125]. Overall, although the majority of studies suggest that sleep bruxism is associated with stress, the specific stress-factors that correlate with sleep bruxism remain unclear.

3.2. Chewing Gum and Stress. People chew gum for a variety of reasons, including modulation of psychologic states, for example, to facilitate concentration, relieve stress, and reduce sleepiness. Many studies have examined the effects of gum chewing on stress.

3.2.1. Chewing Gum and Stress Markers in Saliva. Analysis of stress markers in the saliva is a simple and useful method for determining stress levels in humans. In humans, gum chewing or bruxism-like activities under various stress conditions may influence the secretion volume of various stress markers in the saliva. Chewing leads to decreases in alpha-amylase activity (a sympathetic nervous system stress marker [126]), salivary cortisol levels (an endocrine system stress marker [28, 127]), and secretory immunoglobulin A (an immune system stress marker) [128, 129]. Bruxism-like activity during the presentation of a loud unpleasant sound prevents a stress-induced increase in salivary chromogranin A [130], a stress marker that reflects sympathetic activity [131]. Chewing and light teeth-clenching after stress loading lead to a rapid reduction of salivary cortisol levels [127]. Interestingly, a fast chewing rate [132] and a strong [133] chewing force induce a greater reduction in mental stress than a slow or weak force. Tasaka et al. [128] reported that chewing time affects the response of the endocrine system to mental stress, and continuous chewing for more than 10 min is effective for reducing stress, based on stress marker analysis in saliva. Contrary to these reports, however, chewing gum fails to attenuate salivary cortisol levels [33, 134]. The increase in the cortisol secretion is likely task-dependent. Also, these studies were performed at various times of day, and thus the conflicting results may be due to the diurnal alternations in cortisol secretion.

Pröschel and Raum [129] reported a positive association between chewing force and mean amplitude of the electromyogram of masticatory muscles. The mean electromyogram amplitude of the masticatory muscles during chewing increases with increased psychologic stress [135]. Psychosocial stress is associated with an increased chewing frequency and decreased appetite [136]. These findings suggest that chewing and bruxism-like activities are autonomic behaviors in response to stressful conditions, acting as stress-coping mechanisms. Niwa et al. [137] reported that chewing increases activity in the prefrontal cortex, which is involved in stress control, and leads to decreased stress markers in saliva [133].

3.2.2. Chewing Gum and Experimental or Naturally Occurring Stress. Several studies have demonstrated the benefits of chewing on stress, since Hollingworth [138] reported that masticatory movement reduced excessive muscular tension and energy. Soon after the report by Hollingworth, however, foot-tapping was reported to produce the same relaxing effects, suggesting that the stress-reducing effects were not specific to gum chewing [139]. Therefore, the benefits of gum chewing on stress remain a matter of debate. The effects of gum chewing on naturally occurring stress are consistently reported to be beneficial. For example, Zibell and Madansky [28] investigated whether chewing gum affects perceived levels of everyday stress among subjects who regularly chew gum or among subjects who do not usually chew gum. Stress levels and stress-specific emotions, such as feeling anxiety or tension, decreased after chewing gum, indicating that gum chewing reduces levels of anxiety and stress. Smith [29] performed a cross-sectional study of occupational stress in full-time workers and found that non-gum-chewers complained significantly more often of stress at work and home compared with gum chewers, and gum chewers had a lower incidence of high blood pressure. An intervention study revealed that chewing gum reduces occupational stress both at and outside of work, reducing fatigue, anxiety, and depression and leading to a more positive mood [29]. Chewing gum is also associated with perceptions of better performance [140]. Further, chewing gum is associated in a linear dose-response manner with levels of perceived stress at work and home, as well as anxiety and depression [141]. Similar findings were reported for university students [142]. Erbay et al. [143] examined whether chewing gum is a useful addition to traditional medical treatment of patients with mild to moderate depression and indicated that while chewing gum is not directly effective for elevating a depressed mood, it may reduce the symptoms originating from depression.

On the other hand, the effects of chewing on stress are also variable in studies of experimentally induced stress. Scholey et al. [30] investigated the effects of chewing gum on multitasking efficiency. Chewing gum significantly increases self-rated levels of alertness, decreases self-rated levels of anxiety and stress, reduces salivary cortisol levels, and enhances overall task performance. The effects were the same regardless of the gum flavor. The authors [30] speculated that their findings are linked to the increased heart rate [144, 145] and increased cerebral blood flow [146] associated with chewing.

Additional studies have reported a relationship between chewing under stress-inducing conditions and heart rate [147–151]. These findings suggest that an increase in cerebral blood flow [146, 152] and the related increase in glucose delivery [153] might act to reduce stress via an increase in the PFC glucose metabolism. Additionally, Kern et al. [154] demonstrated that an increase in glucose metabolism in the rostral mPFC is associated with a decrease in the salivary cortisol concentration following a stressful task. Numerous studies have reported an increase in cerebral activity after gum chewing [155–161] and demonstrated that the effect is specific to chewing gum and not just the chewing motion [162, 163]. Chewing gum ameliorates the effects of stress on mood, anxiety, and mental status [33, 134, 164]. One possibility is that the chewing-induced neural activation and psychologic and mental benefits improve task performance, which suppresses stress.

Notwithstanding the above reports, the effects of chewing gum on cognition and physiology are controversial. For example, the facilitative effects of chewing gum on memory [145, 153] have proved difficult to replicate [32], as has the accelerating effect of chewing gum on heart rate [32, 145]. The context-dependent memory effect demonstrated by Baker et al. [165] has not been replicated; thus the effects of chewing gum on context-dependent memory are conflicting [165–169]. In addition, Johnson et al. [33] detected no benefits of chewing on cortisol levels, state anxiety, or stress despite using a similar study design as Scholey et al. [30]. Torney et al. [34] also found no effect of chewing gum on mediating the level of stress experienced or on performance in a solvable anagram task. The anagram task used by Torney et al. [34] was only 5 min long, much shorter than the task used by Scholey et al. [30] (~20 min), suggesting that a greater period of chewing is needed to observe a reduction in stress [153].

Smith [134] examined whether gum chewing improves aspects of cognitive function and mood during exposure to a 75 dB stress-inducing noise. His findings revealed that chewing gum was associated with both more alertness and more positive mood. Reaction times were faster in subjects who were allowed to chew gum. Chewing gum also improved selective and sustained attention. Both heart rate and cortisol levels were higher during chewing, confirming that chewing gum has an alerting effect rather than a stress-reducing effect, consistent with another report [170]. Therefore, the findings regarding gum chewing are mixed, with some indicating that chewing gum is associated with significantly better alertness or vigilance [30, 33, 134, 148, 171, 172] and others indicating no benefit of chewing gum for attention, self-related alertness, and vigilance [173, 174]. The differences in these reports may derive from the duration of the study and time required for the task [174, 175].

Recently, the coping mechanism of chewing under noise stress conditions was examined using functional magnetic resonance imaging [31]. Gum chewing attenuated stress-induced activation of the bilateral superior temporal sulcus and left anterior insula [31]. Gum chewing reduced functional connections between the left anterior insula and the dorsal anterior cingulate cortex and inhibited the connectivity from the bilateral superior temporal sulcus to the left anterior insula [31]. Chewing gum under stress might act to attenuate the sensory processing of the stressor and inhibit the transmission of stress-related information in the brain [31].

4. Conclusions and Future Directions

Chewing or biting as a stress-coping behavior attenuates stress-induced diseases such as gastric ulcers and cognitive and psychologic impairments in rodents via suppression of stress-induced activation of the HPA axis and autonomic nervous reactions. The histaminergic nervous system may also be involved in the chewing-induced attenuation of stress-induced cognitive deficits. In humans, although the correlation between sleep bruxism and stress factors is controversial, many studies support an association between stress and sleep bruxism. Effects of chewing during stress are also conflicting. Gum chewing during stress may affect the levels of various stress markers in the saliva and plasma and increase attention, self-rated alertness, and vigilance.

Further studies are necessary to determine the possible causal relationship between sleep bruxism and stress factors. The amygdala and mPFC have a major role in stress-related behaviors and the mPFC also functions to regulate amygdala-mediated arousal in response to stress. Catecholamines such as 5-hydroxytryptamine dopamine and noradrenaline are involved in the corticolimbic circuitry, and gamma aminobutyric acid has a major role in amygdala functioning. Further studies focusing on the interactions between mastication and neuronal networks between the mPFC and amygdala and between the trigeminal nerve and cortical and limbic systems will help to clarify how mastication affects the expression of various stress-related markers. Studies using functional magnetic resonance imaging and functional near-infrared spectroscopy will be useful for analyzing brain activities in the mPFC and amygdala. More studies are necessary to clarify the benefits of gum chewing, by focusing on attention, alertness, vigilance, and others under task performance using functional magnetic resonance imaging and/or functional near-infrared spectroscopy in humans.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] B. S. McEwen, "Physiology and neurobiology of stress and adaptation: central role of the brain," *Physiological Reviews*, vol. 87, no. 3, pp. 873–904, 2007.

[2] B. S. McEwen and P. J. Gianaros, "Stress- and allostasis-induced brain plasticity," *Annual Review of Medicine*, vol. 62, pp. 431–445, 2011.

[3] S. E. Taylor, "Mechanisms linking early life stress to adult health outcomes," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 19, pp. 8507–8512, 2010.

[4] G. P. Chrousos and P. W. Gold, "The concepts of stress and stress system disorders: overview of physical and behavioral homeostasis," *The Journal of the American Medical Association*, vol. 267, no. 9, pp. 1244–1252, 1992.

[5] T. Tanaka, M. Yoshida, H. Yokoo, M. Tomita, and M. Tanaka, "Expression of aggression attenuates both stress-induced gastric ulcer formation and increases in noradrenaline release in the rat amygdala assessed by intracerebral microdialysis," *Pharmacology Biochemistry and Behavior*, vol. 59, no. 1, pp. 27–31, 1998.

[6] G. F. Koob, "Corticotropin-releasing factor, norepinephrine, and stress," *Biological Psychiatry*, vol. 46, no. 9, pp. 1167–1180, 1999.

[7] E. R. de Kloet, M. Joëls, and F. Holsboer, "Stress and the brain: from adaptation to disease," *Nature Reviews Neuroscience*, vol. 6, no. 6, pp. 463–475, 2005.

[8] C. Hammen, "Stress and depression," *Annual Review of Clinical Psychology*, vol. 1, pp. 293–319, 2005.

[9] I. J. Elenkov, R. L. Wilder, G. P. Chrousos, and E. S. Vizi, "The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system," *Pharmacological Reviews*, vol. 52, no. 4, pp. 595–638, 2000.

[10] J. I. Webster, L. Tonelli, and E. M. Sternberg, "Neuroendocrine regulation of immunity," *Annual Review of Immunology*, vol. 20, pp. 125–163, 2002.

[11] Y. Shimazaki, I. Soh, T. Saito et al., "Influence of dentition status on physical disability, mental impairment, and mortality in institutionalized elderly people," *Journal of Dental Research*, vol. 80, no. 1, pp. 340–345, 2001.

[12] K. Avlund, P. Holm-Pedersen, and M. Schroll, "Functional ability and oral health among older people: a longitudinal study from age 75 to 80," *Journal of the American Geriatrics Society*, vol. 49, no. 7, pp. 954–962, 2001.

[13] H. Nagai, H. Shibata, H. Haga et al., "Chewing ability in relation to physical health status," *Japanese Journal of Geriatrics*, vol. 27, no. 1, pp. 63–68, 1990.

[14] H. Miura, Y. Araki, and T. Umenai, "Chewing activity and activities of daily living in the elderly," *Journal of Oral Rehabilitation*, vol. 24, no. 6, pp. 457–460, 1997.

[15] H. Miura, Y. Arai, S. Sakano, A. Hamada, T. Umenai, and E. Isogai, "Subjective evaluation of chewing ability and self-rated general health status in elderly residents of Japan," *Asia-Pacific Journal of Public Health*, vol. 10, no. 1, pp. 43–45, 1998.

[16] A. Tada, T. Watanabe, H. Yokoe, N. Hanada, and H. Tanzawa, "Relationship between the number of remaining teeth and physical activity in community-dwelling elderly," *Archives of Gerontology and Geriatrics*, vol. 37, no. 2, pp. 109–117, 2003.

[17] U. Foerster, G. H. Gilbert, and R. P. Duncan, "Oral functional limitation among dentate adults," *Journal of Public Health Dentistry*, vol. 58, no. 3, pp. 202–209, 1998.

[18] H. Miura, M. Kariyasu, K. Yamasaki, Y. Arai, and Y. Sumi, "Relationship between general health status and the change in chewing ability: a longitudinal study of the frail elderly in Japan over a 3-year period," *Gerodontology.*, vol. 22, no. 4, pp. 200–205, 2005.

[19] G. R. Ribeiro, J. L. R. Costa, G. M. Bovi Ambrosano, and R. C. M. Rodrigues Garcia, "Oral health of the elderly with Alzheimer's disease," *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, vol. 114, no. 3, pp. 338–343, 2012.

[20] F. B. Teixeira, L. D. M. Pereira Fernandes, P. A. Tavares Noronha et al., "Masticatory deficiency as a risk factor for cognitive dysfunction," *International Journal of Medical Sciences*, vol. 11, no. 2, pp. 209–214, 2014.

[21] C. W. Berridge, R. A. España, and T. A. Stalnaker, "Stress and coping: lateralization of dopamine systems projecting to the prefrontal cortex," in *Brain Asymmetry*, K. Hugdahl and R. J. Davidson, Eds., pp. 69–104, MIT Press, Cambridge, Mass, USA, 2nd edition, 2002.

[22] M. Tanaka, "Emotional stress and characteristics of brain noradrenaline release in the rat," *Industrial Health*, vol. 37, no. 2, pp. 143–156, 1999.

[23] C. Sato, S. Sato, H. Takashina, H. Ishii, M. Onozuka, and K. Sasaguri, "Bruxism affects stress responses in stressed rats," *Clinical Oral Investigations*, vol. 14, no. 2, pp. 153–160, 2010.

[24] G. P. Vincent, W. P. Pare, J. E. D. Prenatt, and G. B. Glavin, "Aggression, body temperature, and stress ulcer," *Physiology and Behavior*, vol. 32, no. 2, pp. 265–268, 1984.

[25] S. Miyake, G. Yoshikawa, K. Yamada et al., "Chewing ameliorates stress-induced suppression of spatial memory by increasing glucocorticoid receptor expression in the hippocampus," *Brain Research*, vol. 1446, pp. 34–39, 2012.

[26] Y. Ono, T. Yamamoto, K.-Y. Kubo, and M. Onozuka, "Occlusion and brain function: mastication as a prevention of cognitive dysfunction," *Journal of Oral Rehabilitation*, vol. 37, no. 8, pp. 624–640, 2010.

[27] M. Furuzawa, H. Chen, S. Fujiwara, K. Yamada, and K.-Y. Kubo, "Chewing ameliorates chronic mild stress-induced bone loss in senescence-accelerated mouse (SAMP8), a murine model of senile osteoporosis," *Experimental Gerontology*, vol. 55, pp. 12–18, 2014.

[28] S. Zibell and E. Madansky, "Impact of gum chewing on stress levels: online self-perception research study," *Current Medical Research and Opinion*, vol. 25, no. 6, pp. 1491–1500, 2009.

[29] A. P. Smith, "Chewing gum, stress and health," *Stress and Health*, vol. 25, no. 5, pp. 445–451, 2009.

[30] A. Scholey, C. Haskell, B. Robertson, D. Kennedy, A. Milne, and M. Wetherell, "Chewing gum alleviates negative mood and reduces cortisol during acute laboratory psychological stress," *Physiology and Behavior*, vol. 97, no. 3-4, pp. 304–312, 2009.

[31] H. Yu, X. Chen, J. Liu, and X. Zhou, "Gum chewing inhibits the sensory processing and the propagation of stress-related information in a brain network," *PLoS ONE*, vol. 8, no. 4, Article ID e57111, 2013.

[32] O. Tucha, L. Mecklinger, K. Maier, M. Hammerl, and K. W. Lange, "Chewing gum differentially affects aspects of attention in healthy subjects," *Appetite*, vol. 42, no. 3, pp. 327–329, 2004.

[33] A. J. Johnson, R. Jenks, C. Miles, M. Albert, and M. Cox, "Chewing gum moderates multi-task induced shifts in stress, mood, and alertness. A re-examination," *Appetite*, vol. 56, no. 2, pp. 408–411, 2011.

[34] L. K. Torney, A. J. Johnson, and C. Miles, "Chewing gum and impasse-induced self-reported stress," *Appetite*, vol. 53, no. 3, pp. 414–417, 2009.

[35] D. L. Helmreich, D. Tylee, J. P. Christianson et al., "Active behavioral coping alters the behavioral but not the endocrine response to stress," *Psychoneuroendocrinology*, vol. 37, no. 12, pp. 1941–1948, 2012.

[36] M. Onishi, M. Iinuma, Y. Tamura, and K.-Y. Kubo, "Learning deficits and suppression of the cell proliferation in the hippocampal dentate gyrus of offspring are attenuated by maternal

chewing during prenatal stress," *Neuroscience Letters*, vol. 560, pp. 77–80, 2014.

[37] R. M. Sapolsky, L. C. Krey, and B. S. McEwen, "Stress down-regulates corticosterone receptors in a site-specific manner in the brain," *Endocrinology*, vol. 114, no. 1, pp. 287–292, 1984.

[38] Y. Ono, T. Kataoka, S. Miyake et al., "Chewing ameliorates stress-induced suppression of hippocampal long-term potentiation," *Neuroscience*, vol. 154, no. 4, pp. 1352–1359, 2008.

[39] Y. Ono, T. Kataoka, S. Miyake, K. Sasaguri, S. Sato, and M. Onozuka, "Chewing rescues stress-suppressed hippocampal long-term potentiation via activation of histamine H1 receptor," *Neuroscience Research*, vol. 64, no. 4, pp. 385–390, 2009.

[40] K.-Y. Kubo, K. Sasaguri, Y. Ono et al., "Chewing under restraint stress inhibits the stress-induced suppression of cell birth in the dentate gyrus of aged SAMP8 mice," *Neuroscience Letters*, vol. 466, no. 3, pp. 109–113, 2009.

[41] B. S. McEwen, "The neurobiology of stress: from serendipity to clinical relevance," *Brain Research*, vol. 886, no. 1-2, pp. 172–189, 2000.

[42] S. R. Bodnoff, A. G. Humphreys, J. C. Lehman, D. M. Diamond, G. M. Rose, and M. J. Meaney, "Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity, and hippocampal neuropathology in young and mid-aged rat," *Journal of Neuroscience*, vol. 15, no. 1, pp. 61–69, 1995.

[43] E. R. de Kloet, E. Vreugdenhil, M. S. Oitzl, and M. Joëls, "Brain corticosteroid receptor balance in health and disease," *Endocrine Reviews*, vol. 19, no. 3, pp. 269–301, 1998.

[44] J. J. Kim, E. Y. Song, and T. A. Kosten, "Stress effects in the hippocampus: synaptic plasticity and memory," *Stress*, vol. 9, no. 1, pp. 1–11, 2006.

[45] M. Korte, V. Staiger, O. Griesbeck, H. Thoenen, and T. Bonhoeffer, "The involvement of brain-derived neurotrophic factor in hippocampal long-term potentiation revealed by gene targeting experiments," *Journal of Physiology Paris*, vol. 90, no. 3-4, pp. 157–164, 1996.

[46] R. M. Lindsay, "Therapeutic potential of the neurotrophins and neurotrophin-CNTF combinations in peripheral neuropathies and motor neuron diseases," *Ciba Foundation Symposia*, no. 196, pp. 39–53, 1996.

[47] A. K. McAllister, D. C. Lo, and L. C. Katz, "Neurotrophins regulate dendritic growth in developing visual cortex," *Neuron*, vol. 15, no. 4, pp. 791–803, 1995.

[48] C. Gall and J. Lauterborn, "The dentate gyrus: a model system for studies of neurotrophin regulation," *Epilepsy Research, Supplement*, vol. 7, pp. 171–185, 1992.

[49] E. Gould, A. Beylin, P. Tanapat, A. Reeves, and T. J. Shors, "Learning enhances adult neurogenesis in the hippocampal formation," *Nature Neuroscience*, vol. 2, no. 3, pp. 260–265, 1999.

[50] W. J. Friedman, P. Ernfors, and H. Persson, "Transient and persistent expression of NT-3/HDNF mRNA in the rat brain during postnatal development," *The Journal of Neuroscience*, vol. 11, no. 6, pp. 1577–1584, 1991.

[51] S. Miyake, K. Sasaguri, N. Hori et al., "Biting reduces acute stress-induced oxidative stress in the rat hypothalamus," *Redox Report*, vol. 10, no. 1, pp. 19–24, 2005.

[52] S. Miyake, S. Wada-Takahashi, H. Honda et al., "Stress and chewing affect blood flow and oxygen levels in the rat brain," *Archives of Oral Biology*, vol. 57, no. 11, pp. 1491–1497, 2012.

[53] R.-P. Juster, B. S. McEwen, and S. J. Lupien, "Allostatic load biomarkers of chronic stress and impact on health and cognition," *Neuroscience and Biobehavioral Reviews*, vol. 35, no. 1, pp. 2–16, 2010.

[54] R. T. Joffe and S. T. H. Sokolov, "Thyroid hormones, the brain, and affective disorders," *Critical Reviews in Neurobiology*, vol. 8, no. 1-2, pp. 45–63, 1994.

[55] B. S. McEwen, "Glucocorticoids, depression, and mood disorders: structural remodeling in the brain," *Metabolism: Clinical and Experimental*, vol. 54, no. 5, pp. 20–23, 2005.

[56] National Institutes of Health, "Osteoporosis prevention, diagnosis, and therapy," *NIH Consensus Statements*, vol. 17, no. 1, pp. 1–45, 2000.

[57] G. Cizza, S. Primma, and G. Csako, "Depression as a risk factor for osteoporosis," *Trends in Endocrinology and Metabolism*, vol. 20, no. 8, pp. 367–373, 2009.

[58] P. Patterson-Buckendahl, R. Kvetnansky, K. Fukuhara, G. Cizza, and C. Cann, "Regulation of plasma osteocalcin by corticosterone and norepinephrine during restraint stress," *Bone*, vol. 17, no. 5, pp. 467–472, 1995.

[59] R. Yirmiya, I. Goshen, A. Bajayo et al., "Depression induces bone loss through stimulation of the sympathetic nervous system," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 45, pp. 16876–16881, 2006.

[60] C. Bustamante, P. Bilbao, W. Contreras et al., "Effects of prenatal stress and exercise on dentate granule cells maturation and spatial memory in adolescent mice," *International Journal of Developmental Neuroscience*, vol. 28, no. 7, pp. 605–609, 2010.

[61] V. Lemaire, M. Koehl, M. Le Moal, and D. N. Abrous, "Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 20, pp. 11032–11037, 2000.

[62] T. G. O'Connor, J. Heron, J. Golding, and V. Glover, "Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis," *Journal of Child Psychology and Psychiatry and Allied Disciplines*, vol. 44, no. 7, pp. 1025–1036, 2003.

[63] A. Tsuda, M. Tanaka, Y. Ida et al., "Expression of aggression attenuates stress-induced increases in rat brain noradrenaline turnover," *Brain Research*, vol. 474, no. 1, pp. 174–180, 1988.

[64] F. M. Gómez, M. T. Giralt, B. Sainz, A. Arrúe, M. Prieto, and P. García-Vallejo, "A possible attenuation of stress-induced increases in striatal dopamine metabolism by the expression of non-functional masticatory activity in the rat," *European Journal of Oral Sciences*, vol. 107, no. 6, pp. 461–467, 1999.

[65] S. Okada, N. Hori, K. Kimoto, M. Onozuka, S. Sato, and K. Sasaguri, "Effects of biting on elevation of blood pressure and other physiological responses to stress in rats: biting may reduce allostatic load," *Brain Research*, vol. 1185, no. 1, pp. 189–194, 2007.

[66] R. J. Irvine, J. White, and R. Chan, "The influence of restrains on blood pressure in the rat," *Journal of Pharmacological and Toxicological Methods*, vol. 38, no. 3, pp. 157–162, 1997.

[67] S. Koizumi, S. Minamisawa, K. Sasaguri, M. Onozuka, S. Sato, and Y. Ono, "Chewing reduces sympathetic nervous response to stress and prevents poststress arrhythmias in rats," *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 301, no. 4, pp. H1551–H1558, 2011.

[68] T. Oka, K. Oka, and T. Hori, "Mechanisms and mediators of psychological stress-induced rise in core temperature," *Psychosomatic Medicine*, vol. 63, no. 3, pp. 476–486, 2001.

[69] B. M. McEwen, "Stress, adaptation, and disease allostasis and allostatic load," *Annals of the New York Academy of Sciences*, vol. 840, pp. 33–44, 1998.

[70] F. Shintani, T. Nakaki, S. Kanba et al., "Involvement of interleukin-1 in immobilization stress-induced increase in plasma adrenocorticotropic hormone and in release of hypothalamic monoamines in the rat," *Journal of Neuroscience*, vol. 15, no. 3, pp. 1961–1970, 1995.

[71] R. Sapolsky, C. Rivier, G. Yamamoto, P. Plotsky, and W. Vale, "Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor," *Science*, vol. 238, no. 4826, pp. 522–524, 1987.

[72] D. Soszynski, W. Kozak, C. A. Conn, K. Rudolph, and M. J. Kluger, "Beta-adrenoceptor antagonists suppress elevation in body temperature and increase in plasma IL-6 in rats exposed to open field," *Neuroendocrinology*, vol. 63, no. 5, pp. 459–467, 1996.

[73] Y. Ono, H.-C. Lin, K.-Y. Tzen et al., "Active coping with stress suppresses glucose metabolism in the rat hypothalamus," *Stress*, vol. 15, no. 2, pp. 207–217, 2012.

[74] T. Lee, J. Saruta, K. Sasaguri, S. Sato, and K. Tsukinoki, "Allowing animals to bite reverses the effects of immobilization stress on hippocampal neurotrophin expression," *Brain Research*, vol. 1195, pp. 43–49, 2008.

[75] R. L. Conner, J. Vernikos-Danellis, and S. Levine, "Stress, fighting and neuroendocrine function," *Nature*, vol. 234, no. 5331, pp. 564–566, 1971.

[76] M. B. Hennessy and T. Foy, "Nonedible material elicits chewing and reduces the plasma corticosterone response during novelty exposure in mice," *Behavioral Neuroscience*, vol. 101, no. 2, pp. 237–245, 1987.

[77] K. Ayada, T. Tadano, and Y. Endo, "Gnawing behavior of a mouse in a narrow cylinder: a simple system for the study of muscle activity, fatigue, and stress," *Physiology & Behavior*, vol. 77, no. 1, pp. 161–166, 2002.

[78] N. Hori, N. Yuyama, and K. Tamura, "Biting suppresses stress-induced expression of corticotropin-releasing factor (CRF) in the rat hypothalamus," *Journal of Dental Research*, vol. 83, no. 2, pp. 124–128, 2004.

[79] M. Kaneko, N. Hori, N. Yuyama, K. Sasaguri, R. Slavicek, and S. Sato, "Biting suppresses Fos expression in various regions of the rat brain-further evidence that the masticatory organ functions to manage stress," *Stomatologie*, vol. 101, pp. 151–156, 2004.

[80] K. Sasaguri, M. Kikuchi, N. Hori, N. Yuyama, M. Onozuka, and S. Sato, "Suppression of stress immobilization-induced phosphorylation of ERK 1/2 by biting in the rat hypothalamic paraventricular nucleus," *Neuroscience Letters*, vol. 383, no. 1-2, pp. 160–164, 2005.

[81] N. Hori, M.-C. Lee, K. Sasaguri et al., "Suppression of stress-induced nNOS expression in the rat hypothalamus by biting," *Journal of Dental Research*, vol. 84, no. 7, pp. 624–628, 2005.

[82] S. Miyake, S.-S. Takahashi, F. Yoshino et al., "Nitric oxide levels in rat hypothalamus are increased by restraint stress and decreased by biting," *Redox Report*, vol. 13, no. 1, pp. 31–39, 2008.

[83] A. Costa, P. Trainer, M. Besser, and A. Grossman, "Nitric oxide modulates the release of corticotropin-releasing hormone from the rat hypothalamus in vitro," *Brain Research*, vol. 605, no. 2, pp. 187–192, 1993.

[84] J. P. Herman, P. D. Patel, H. Akil, and S. J. Watson, "Localization and regulation of glucocorticoid and mineralocorticoid receptor messenger RNAs in the hippocampal formation of the rat," *Molecular Endocrinology*, vol. 3, no. 11, pp. 1886–1894, 1989.

[85] C. Frank and S. Smith, "Stress and the heart: biobehavioral aspects of sudden cardiac death," *Psychosomatics*, vol. 31, no. 3, pp. 255–264, 1990.

[86] T. A. Stalnaker, R. A. España, and C. W. Berridge, "Coping behavior causes asymmetric changes in neuronal activation in the prefrontal cortex and amygdala," *Synapse*, vol. 63, no. 1, pp. 82–85, 2009.

[87] J. Amat, M. V. Baratta, E. Paul, S. T. Bland, L. R. Watkins, and S. F. Maier, "Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus," *Nature Neuroscience*, vol. 8, no. 3, pp. 365–371, 2005.

[88] A. F. T. Arnsten, "Catecholamine regulation of the prefrontal cortex," *Journal of Psychopharmacology*, vol. 11, no. 2, pp. 151–162, 1997.

[89] M. E. Jackson and B. Moghaddam, "Distinct patterns of plasticity in prefrontal cortex neurons that encode slow and fast responses to stress," *The European Journal of Neuroscience*, vol. 24, no. 6, pp. 1702–1710, 2006.

[90] R. M. Sullivan, "Hemispheric asymmetry in stress processing in rat prefrontal cortex and the role of mesocortical dopamine," *Stress*, vol. 7, no. 2, pp. 131–143, 2004.

[91] R. M. Sullivan and A. Gratton, "Relationships between stress-induced increases in medial prefrontal cortical dopamine and plasma corticosterone levels in rats: role of cerebral laterality," *Neuroscience*, vol. 83, no. 1, pp. 81–91, 1998.

[92] R. M. Sullivan and H. Szechtman, "Asymmetrical influence of mesocortical dopamine depletion on stress ulcer development and subcortical dopamine systems in rats: Implications for psychopathology," *Neuroscience*, vol. 65, no. 3, pp. 757–766, 1995.

[93] C. W. Berridge, E. Mitton, W. Clark, and R. H. Roth, "Engagement in a non-escape (displacement) behavior elicits a selective and lateralized suppression of frontal cortical dopaminergic utilization in stress," *Synapse*, vol. 32, no. 3, pp. 187–197, 1999.

[94] S. Ahn and A. G. Phillips, "Independent modulation of basal and feeding-evoked dopamine efflux in the nucleus accumbens and medial prefrontal cortex by the central and basolateral amygdalar nuclei in the rat," *Neuroscience*, vol. 116, no. 1, pp. 295–305, 2003.

[95] M. Davis, J. M. Hitchcock, M. B. Bowers, C. W. Berridge, K. R. Melia, and R. H. Roth, "Stress-induced activation of prefrontal cortex dopamine turnover: blockade by lesions of the amygdala," *Brain Research*, vol. 664, no. 1-2, pp. 207–210, 1994.

[96] L. E. Goldstein, A. M. Rasmusson, B. S. Bunney, and R. H. Roth, "Role of the amygdala in the coordination of behavioral, neuroendocrine, and prefrontal cortical monoamine responses to psychological stress in the rat," *The Journal of Neuroscience*, vol. 16, no. 15, pp. 4787–4798, 1996.

[97] E. S. Luschei, "Central projections of the mesencephalic nucleus of the fifth nerve: an autoradiographic study," *Journal of Comparative Neurology*, vol. 263, no. 1, pp. 137–145, 1987.

[98] H. Ericson, A. Blomqvist, and C. Kohler, "Brainstem afferents to the tuberomammillary nucleus in the rat brain with special reference to monoaminergic innervation," *Journal of Comparative Neurology*, vol. 281, no. 2, pp. 169–192, 1989.

[99] H. Ericson, A. Blomqvist, and C. Köhler, "Origin of neuronal inputs to the region of the tuberomammillary nucleus of the rat brain," *Journal of Comparative Neurology*, vol. 311, no. 1, pp. 45–64, 1991.

[100] T. Fujise, H. Yoshimatsu, M. Kurokawa et al., "Satiation and masticatory function modulated by brain histamine in rats," *Proceedings of the Society for Experimental Biology and Medicine*, vol. 217, no. 2, pp. 228–234, 1998.

[101] T. Sakata, H. Yoshimatsu, T. Masaki, and K. Tsuda, "Anti-obesity actions of mastication driven by histamine neurons in rats,"

Experimental Biology and Medicine, vol. 228, no. 10, pp. 1106–1110, 2003.

[102] C. Köhler, L. W. Swanson, L. Haglund, and W. J-Yen, "The cytoarchitecture, histochemistry and projections of the tuberomammillary nucleus in the rat," *Neuroscience*, vol. 16, no. 1, pp. 85–110, 1985.

[103] N. Inagaki, A. Yamatodani, M. Ando-Yamamoto, M. Tohyama, T. Watanabe, and H. Wada, "Organization of histaminergic fibers in the rat brain," *The Journal of Comparative Neurology*, vol. 273, no. 3, pp. 283–300, 1988.

[104] P. Panula, U. Pirvola, S. Auvinen, and M. S. Airaksinen, "Histamine-immunoreactive nerve fibers in the rat brain," *Neuroscience*, vol. 28, no. 3, pp. 585–610, 1989.

[105] R. E. Brown, D. R. Stevens, and H. L. Haas, "The physiology of brain histamine," *Progress in Neurobiology*, vol. 63, no. 6, pp. 637–672, 2001.

[106] T. Mochizuki, K. Okakura-Mochizuki, A. Horii, Y. Yamamoto, and A. Yamatodani, "Histaminergic modulation of hippocampal acetylcholine release in vivo," *Journal of Neurochemistry*, vol. 62, no. 6, pp. 2275–2282, 1994.

[107] American Academy of Sleep Medicine (AASM), *International Classification of Sleep Disorders*, American Academy of Sleep Medicine (AASM), Westchester, Ill, USA, 2nd edition, 2005.

[108] D. Manfredini, N. Landi, F. Fantoni, M. Segù, and M. Bosco, "Anxiety symptoms in clinically diagnosed bruxers," *Journal of Oral Rehabilitation*, vol. 32, no. 8, pp. 584–588, 2005.

[109] T. D. S. Barbosa, L. S. Miyakoda, R. D. L. Pocztaruk, C. P. Rocha, and M. B. D. Gavião, "Temporomandibular disorders and bruxism in childhood and adolescence: review of the literature," *International Journal of Pediatric Otorhinolaryngology*, vol. 72, no. 3, pp. 299–314, 2008.

[110] G. Bader and G. Lavigne, "Sleep bruxism; an overview of an oromandibular sleep movement disorder," *Sleep Medicine Reviews*, vol. 4, no. 1, pp. 27–43, 2000.

[111] M. Schmid-Schwap, M. Bristela, M. Kundi, and E. Piehslinger, "Sex-specific differences in patients with temporomandibular disorders," *Journal of Orofacial Pain*, vol. 27, no. 1, pp. 42–50, 2013.

[112] G. T. Clark, Y. Tsukiyama, K. Baba, and T. Watanabe, "Sixty-eight years of experimental occlusal interference studies: what have we learned?" *The Journal of Prosthetic Dentistry*, vol. 82, no. 6, pp. 704–713, 1999.

[113] J. Ahlberg, A. Savolainen, M. Rantala, H. Lindholm, and M. Könönen, "Reported bruxism and biopsychosocial symptoms: a longitudinal study," *Community Dentistry and Oral Epidemiology*, vol. 32, no. 4, pp. 307–311, 2004.

[114] A. Nakata, M. Takahashi, T. Ikeda, M. Hojou, and S. Araki, "Perceived psychosocial job stress and sleep bruxism among male and female workers," *Community Dentistry and Oral Epidemiology*, vol. 36, no. 3, pp. 201–209, 2008.

[115] D. Manfredini and F. Lobbezoo, "Role of psychosocial factors in the etiology of bruxism," *Journal of Orofacial Pain*, vol. 23, no. 2, pp. 153–166, 2009.

[116] M. M. Ohayon, K. K. Li, and C. Guilleminault, "Risk factors for sleep bruxism in the general population," *Chest*, vol. 119, no. 1, pp. 53–61, 2001.

[117] J. Ahlberg, M. Rantala, A. Savolainen et al., "Reported bruxism and stress experience," *Community Dentistry and Oral Epidemiology*, vol. 30, no. 6, pp. 405–408, 2002.

[118] M. Giraki, C. Schneider, R. Schäfer et al., "Correlation between stress, stress-coping and current sleep bruxism," *Head & Face Medicine*, vol. 6, no. 1, article 2, pp. 1–8, 2010.

[119] G. J. Lavigne, J.-P. Soucy, F. Lobbezoo, C. Manzini, P. J. Blanchet, and J. Y. Montplaisir, "Double-blind, crossover, placebo-controlled trial of bromocriptine in patients with sleep bruxism," *Clinical Neuropharmacology*, vol. 24, no. 3, pp. 145–149, 2001.

[120] T. Kato, J. Y. Montplaisir, F. Guitard, B. J. Sessle, J. P. Lund, and G. J. Lavigne, "Evidence that experimentally induced sleep bruxism is a consequence of transient arousal," *Journal of Dental Research*, vol. 82, no. 4, pp. 284–288, 2003.

[121] J. D. Rugh and W. K. Solberg, "Electromyographic studies of bruxist behavior before and during treatment," *Journal of the California Dental Association*, vol. 3, no. 9, pp. 56–59, 1975.

[122] C. Schneider, R. Schaefer, M. A. Ommerborn et al., "Maladaptive coping strategies in patients with bruxism compared to non-bruxing controls," *International Journal of Behavioral Medicine*, vol. 14, no. 4, pp. 257–261, 2007.

[123] C. J. Pierce, K. Chrisman, M. E. Bennett, and J. M. Close, "Stress, anticipatory stress, and psychologic measures related to sleep bruxism," *Journal of Orofacial Pain*, vol. 9, no. 1, pp. 51–56, 1995.

[124] T. Watanabe, K. Ichikawa, and G. T. Clark, "Bruxism levels and daily behaviors: 3 Weeks of measurement and correlation," *Journal of Orofacial Pain*, vol. 17, no. 1, pp. 65–73, 2003.

[125] A. M. da Silva, D. A. Oakley, K. W. Hemmings, H. N. Newman, and S. Watkins, "Psychosocial factors and tooth wear with a significant component of attrition," *The European Journal of Prosthodontics and Restorative Dentistry*, vol. 5, no. 2, pp. 51–55, 1997.

[126] N. Nakajo, S. Tomioka, S. Eguchi, K. Takaishi, G. Cho, and K. Sato, "Gum chewing may attenuate salivary alpha-amylase of psychological stress responses," *Journal of Japanese Dental Society of Anesthesiology*, vol. 35, no. 3, pp. 346–353, 2007 (Japanese).

[127] Y. Tahara, K. Sakurai, and T. Ando, "Influence of chewing and clenching on salivary cortisol levels as an indicator of stress," *Journal of Prosthodontics*, vol. 16, no. 2, pp. 129–135, 2007.

[128] A. Tasaka, K. Takeuchi, H. Sasaki et al., "Influence of chewing time on salivary stress markers," *Journal of Prosthodontic Research*, vol. 58, no. 1, pp. 48–54, 2014.

[129] P. A. Pröschel and J. Raum, "Preconditions for estimation of masticatory force from dynamic EMG and isometric bite force-activity relations of elevator muscles," *International Journal of Prosthodontics*, vol. 14, no. 6, pp. 563–569, 2001.

[130] M. Okamura, A. Yoshida, J. Saruta, K. Tsukinoki, K. Sasaguri, and S. Sato, "Effect of bruxism-like activity on the salivary chromogranin A as a stress marker," *Stomatologie*, vol. 105, no. 2, pp. 33–39, 2008.

[131] T. Kanno, N. Asada, H. Yanase et al., "Salivary secretion of highly concentrated chromogranin A in response to noradrenaline and acetylcholine in isolated and perfused rat submandibular glands," *Experimental Physiology*, vol. 84, no. 6, pp. 1073–1083, 1999.

[132] A. Tasaka, Y. Tahara, T. Sugiyama, and K. Sakurai, "Influence of chewing rate on salivary stress hormone levels," *The Journal of the Japan Prosthodontic Society*, vol. 52, no. 4, pp. 482–487, 2008.

[133] R. Soeda, A. Tasaka, and K. Sakurai, "Influence of chewing force on salivary stress markers as indicator of mental stress," *Journal of Oral Rehabilitation*, vol. 39, no. 4, pp. 261–269, 2012.

[134] A. P. Smith, "Effects of chewing gum on cognitive function, mood and physiology in stressed and non-stressed volunteers," *Nutritional Neuroscience*, vol. 13, no. 1, pp. 7–16, 2010.

[135] S. Ruf, F. Cecere, J. Kupfer, and H. Pancherz, "Stress-induced changes in the functional electromyographic activity of the masticatory muscles," *Acta Odontologica Scandinavica*, vol. 55, no. 1, pp. 44–48, 1997.

[136] K. Petrowski, G.-B. Wintermann, P. Joraschky, and S. Päßler, "Chewing after stress: psychosocial stress influences chewing frequency, chewing efficacy, and appetite," *Psychoneuroendocrinology*, vol. 48, pp. 64–76, 2014.

[137] M. Niwa, I. Hiramatsu, F. Nakata, C. Hamaya, N. Onogi, and K. Saito, "Functional significance of stress-relieving act of chewing and it effect on brain activation by stress," *Nihon Nouson Igakukai Zasshi*, vol. 54, no. 4, pp. 661–666, 2005 (Japanese).

[138] H. L. Hollingworth, "Chewing as a technique of relaxation," *Science*, vol. 90, no. 2339, pp. 385–387, 1939.

[139] G. L. Freeman, "Dr. Hollingworth on chewing as a technique of relaxation," *Psychological Review*, vol. 47, no. 6, pp. 491–493, 1940.

[140] A. P. Smith, K. Chaplin, and E. Wadsworth, "Chewing gum, occupational stress, work performance and wellbeing. An intervention study," *Appetite*, vol. 58, no. 3, pp. 1083–1086, 2012.

[141] A. Smith, "Effects of chewing gum on stress and health: a replication and investigation of dose-response," *Stress and Health*, vol. 29, no. 2, pp. 172–174, 2013.

[142] A. P. Smith and M. Woods, "Effects of chewing gum on the stress and work of university students," *Appetite*, vol. 58, no. 3, pp. 1037–1040, 2012.

[143] F. M. Erbay, N. Aydin, and T. Sati-Kirkan, "Chewing gum may be an effective complementary therapy in patients with mild to moderate depression," *Appetite*, vol. 65, pp. 31–34, 2013.

[144] M. Farella, M. Bakke, A. Michelotti, G. Marotta, and R. Martina, "Cardiovascular responses in humans to experimental chewing of gums of different consistencies," *Archives of Oral Biology*, vol. 44, no. 10, pp. 835–842, 1999.

[145] L. Wilkinson, A. Scholey, and K. Wesnes, "Chewing gum selectively improves aspects of memory in healthy volunteers," *Appetite*, vol. 38, no. 3, pp. 235–236, 2002.

[146] M. Sesay, A. Tanaka, Y. Ueno, P. Lecaroz, and D. G. de Beaufort, "Assessment of regional cerebral blood flow by xenon-enhanced computed tomography during mastication in humans," *The Keio Journal of Medicine*, vol. 49, no. 1, pp. A125–A128, 2000.

[147] D. Ekuni, T. Tomofuji, N. Takeuchi, and M. Morita, "Gum chewing modulates heart rate variability under noise stress," *Acta Odontologica Scandinavica*, vol. 70, no. 6, pp. 491–496, 2012.

[148] A. P. Allen, T. J. C. Jacob, and A. P. Smith, "Effects and after-effects of chewing gum on vigilance, heart rate, EEG and mood," *Physiology & Behavior*, vol. 133, pp. 244–251, 2014.

[149] Y. Shiba, E. Nitta, C. Hirono, M. Sugita, and Y. Iwasa, "Evaluation of mastication-induced change in sympatho-vagal balance through spectral analysis of heart rate variability," *Journal of Oral Rehabilitation*, vol. 29, no. 10, pp. 956–960, 2002.

[150] Y. Hasegawa, J. Sakagami, T. Ono, K. Hori, M. Zhang, and Y. Maeda, "Circulatory response and autonomic nervous activity during gum chewing," *European Journal of Oral Sciences*, vol. 117, no. 4, pp. 470–473, 2009.

[151] N. Kalezic, Y. Noborisaka, M. Nakata et al., "Cardiovascular and muscle activity during chewing in whiplash-associated disorders (WAD)," *Archives of Oral Biology*, vol. 55, no. 6, pp. 447–453, 2010.

[152] M. Onozuka, M. Fujita, K. Watanabe et al., "Mapping brain region activity during chewing: a functional magnetic resonance imaging study," *Journal of Dental Research*, vol. 81, no. 11, pp. 743–746, 2002.

[153] R. Stephens and R. J. Tunney, "Role of glucose in chewing gum-related facilitation of cognitive function," *Appetite*, vol. 43, no. 2, pp. 211–213, 2004.

[154] S. Kern, T. R. Oakes, C. K. Stone, E. M. McAuliff, C. Kirschbaum, and R. J. Davidson, "Glucose metabolic changes in the prefrontal cortex are associated with HPA axis response to a psychosocial stressor," *Psychoneuroendocrinology*, vol. 33, no. 4, pp. 517–529, 2008.

[155] M. Fang, J. C. Li, G. Lu, X. Y. Gong, and D. T. Yew, "A fMRI study of age-related differential cortical patterns during cued motor movement," *Brain Topography*, vol. 17, no. 3, pp. 127–137, 2005.

[156] Y. Hirano, T. Obata, K. Kashikura et al., "Effects of chewing in working memory processing," *Neuroscience Letters*, vol. 436, no. 2, pp. 189–192, 2008.

[157] T. Momose, J. Nishikawa, T. Watanabe et al., "Effect of mastication on regional cerebral blood flow in humans examined by positron-emission tomography with ^{15}O-labelled water and magnetic resonance imaging," *Archives of Oral Biology*, vol. 42, no. 1, pp. 57–61, 1997.

[158] T. Tamura, T. Kanayama, S. Yoshida, and T. Kawasaki, "Analysis of brain activity during clenching by fMRI," *Journal of Oral Rehabilitation*, vol. 29, no. 5, pp. 467–472, 2002.

[159] T. Tamura, T. Kanayama, S. Yoshida, and T. kawasaki, "Functional magnetic resonance imaging of human jaw movements," *Journal of Oral Rehabilitation*, vol. 30, no. 6, pp. 614–622, 2003.

[160] K. Kubota, T. Momose, A. Abe et al., "Nuclear medical PET-study in the causal relationship between mastication and brain function in human evolutionary and developmental processes," *Annals of Anatomy*, vol. 185, no. 6, pp. 565–569, 2003.

[161] H. Shinagawa, T. Ono, E. Honda et al., "Chewing-side preference is involved in differential cortical activation patterns during tongue movements after bilateral gum-chewing: a functional magnetic resonance imaging study," *Journal of Dental Research*, vol. 83, no. 10, pp. 762–766, 2004.

[162] K. Sakamoto, H. Nakata, and R. Kakigi, "The effect of mastication on human cognitive processing: a study using event-related potentials," *Clinical Neurophysiology*, vol. 120, no. 1, pp. 41–50, 2009.

[163] T. Takada and T. Miyamoto, "A fronto-parietal network for chewing of gum: a study on human subjects with functional magnetic resonance imaging," *Neuroscience Letters*, vol. 360, no. 3, pp. 137–140, 2004.

[164] A. Sasaki-Otomaru, Y. Sakuma, Y. Mochizuki, S. Ishida, Y. Kanoya, and C. Sato, "Effect of regular gum chewing on levels of anxiety, mood, and fatigue in healthy young adults," *Clinical Practice and Epidemiology in Mental Health*, vol. 7, pp. 133–139, 2011.

[165] J. R. Baker, J. B. Bezance, E. Zellaby, and J. P. Aggleton, "Chewing gum can produce context-dependent effects upon memory," *Appetite*, vol. 43, no. 2, pp. 207–210, 2004.

[166] A. J. Johnson and C. Miles, "Evidence against memorial facilitation and context-dependent memory effects through the chewing of gum," *Appetite*, vol. 48, no. 3, pp. 394–396, 2007.

[167] A. J. Johnson and C. Miles, "Chewing gum and context-dependent memory: the independent roles of chewing gum and mint flavour," *The British Journal of Psychology*, vol. 99, no. 2, pp. 293–306, 2008.

[168] C. Miles and A. J. Johnson, "Chewing gum and context-dependent memory effects: a re-examination," *Appetite*, vol. 48, no. 2, pp. 154–158, 2007.

[169] C. Miles, R. Charig, and H. Eva, "Chewing gum as context: effects in long-term memory," *Journal of Behavioral and Neuroscience Research*, vol. 6, pp. 1–5, 2008.

[170] G. Gray, C. Miles, N. Wilson, R. Jenks, M. Cox, and A. J. Johnson, "The contrasting physiological and subjective effects of chewing gum on social stress," *Appetite*, vol. 58, no. 2, pp. 554–558, 2012.

[171] K. Morgan, A. J. Johnson, and C. Miles, "Chewing gum moderates the vigilance decrement," *British Journal of Psychology*, vol. 105, no. 2, pp. 214–225, 2014.

[172] K. Sketchley-Kaye, R. Jenks, C. Miles, and A. J. Johnson, "Chewing gum modifies state anxiety and alertness under conditions of social stress," *Nutritional Neuroscience*, vol. 14, no. 6, pp. 237–242, 2011.

[173] M. Kohler, A. Pavy, and C. van den Heuvel, "The effects of chewing versus caffeine on alertness, cognitive performance and cardiac autonomic activity during sleep deprivation," *Journal of Sleep Research*, vol. 15, no. 4, pp. 358–368, 2006.

[174] L. Tucha, W. Simpson, L. Birrel et al., "Detrimental effects of gum chewing on vigilance in children with attention deficit hyperactivity disorder," *Appetite*, vol. 55, no. 3, pp. 679–684, 2010.

[175] L. Tucha and W. Simpson, "The role of time on task performance in modifying the effects of gum chewing on attention," *Appetite*, vol. 56, no. 2, pp. 299–301, 2011.

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Review Article

Chew the Pain Away: Oral Habits to Cope with Pain and Stress and to Stimulate Cognition

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The acute effects of chewing gum on cognitive performance, stress, and pain have been intensively studied in the last decade. The results have been contradicting, and replication studies proved challenging. Here, we review some of the recent findings of this topic and explore possible explanations for these discrepancies by incorporating knowledge derived from studies into oral habits and bruxism. Both stress and cerebral functional specialization (i.e., the involvement of specific brain structures in distinctive cognitive processes) are hypothesized to play a major role in the underlying physiological mechanisms of the diverse effects of chewing gum on cognition, stress, and pain.

1. Introduction

Mastication is essential for grinding our food into smaller particles [1]. During chewing, saliva is added to the particles to lubricate them and create a food bolus that can be swallowed [1]. Recently, reports have been published in the literature, stating that mastication might also serve other purposes, such as countering negative effects of stress [2] or aiding in cognitive function [3, 4]. It could be argued that the positive effects of mastication are similar to those of physical activity [5]. Although mastication is of course not the same as an intensive workout, it does have properties similar to exercise: it also increases heart rates [6, 7] and cerebral blood flow [8–10]. There are also direct cardiovascular improvements resulting from exercise [11]. Physical activity is a key element of an enriched environment, so while exercising, one is also experiencing an enriched environment [12], which has been shown to improve cognition [13]. Exercising can also attenuate the negative effects of stress [14]. Several studies have explored the relationship between mastication, cognition, stress, and pain. These studies will be discussed in more detail below. The aim of this review was to explore the relationship between mastication, cognition, and pain and to hypothesize on possible explanations.

2. Oral Habits

2.1. Gum Chewing. In two recent reviews [15, 16], the effects of chewing a piece of gum on cognition and stress in human volunteers are described. The outcomes of these reviews are summarized in Table 1. Although the papers have great overlap in the literature they included, the authors sometimes come to different conclusions. For example, while, in one paper, the authors emphasize that chewing gum cannot be seen as an aid for mental challenges [16], in the other paper, the authors conclude that chewing gum enhances alertness and that it might very well improve cognitive performance [15]. This discrepancy can partly be explained by the observation that Allen and Smith [15] are more lenient in their conclusions, as they view the majority vote as convincing, whereas Tucha and Koerts [16] focus on the contradictions and possible detrimental effects of chewing gum.

Nevertheless, both reviews agree that working memory is positively affected by chewing a piece of gum. It is interesting

Table 1: The outcomes of two reviews on the effects of mastication on cognition and stress in healthy volunteers.

Variable	Allen and Smith, 2011 [15]	Tucha and Koerts, 2012 [16]
Cognitive outcomes		
Academic performance		+
Alertness		
Subjective	+	
Attention		
Divided	0	0
Selective	±	±
Shifting		±
Sustained/vigilance	±	±
Executive functioning		0
Memory		
Context dependent	0	±
Recall	±	±
Recognition	−	
Working	+	+
Test performance		−
Speed	+	±
Spatial skill		±
Stress related outcomes		
Biomarkers (i.e., pupil dilation, heart rate)	±	
Acute, self-reported	0	
Chronic, self-reported	+	
Salivary cortisol	±	

The outcomes of two reviews on mastication, cognition, and stress. + = the authors report a positive effect; − = the authors report a negative effect; 0 = the authors report no effect; ± = the authors report contradicting results in the literature.

that both also agree in their conclusion that divided attention is unaffected. Some earlier papers mentioned that the distracting (novelty) effect of chewing gum while performing a task might have influenced test results, but the fact that divided attention is not affected argues against this.

As there are still many unexplained and contradictory findings, a final conclusion cannot yet be made on the acute effects of chewing a piece of gum on cognitive performance and stress. Underlying physiological mechanisms remain to be identified, and the time on task might be of influence, for example, how long participants chewed and whether they chewed only prior to examination or also during the test. It is possible that chewing gum has a transient positive effect, but only after cessation of chewing, since chewing while on task can have a negative effect [15, 16]. It would be interesting to see what effect other oral habits have on stress and cognition.

2.2. Bruxism. In a sample of children (7–17 years), with attention deficit hyperactivity disorder (ADHD), it was observed that levels of oral habits such as nail or pencil biting and bruxism were all elevated [17]. Bruxism is "a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible" [18]. The activity is involuntary and can occur during sleep (sleep bruxism) or during waking moments (awake bruxism) [19]. Nail biting is an oral habit that is commonly seen in the general population, and triggers for it are, amongst others, anxiety, stress [20], boredom, and frustration [21]. Anxiety, stress, boredom, and frustration are also the most common triggers for other (pathological) body-focused repetitive behaviors, such as skin picking and hair pulling [22]. The need that is being met by engaging in these self-damaging behaviors is thought to be "relief from negative affective states" [22].

Those suffering from their habits, for example, bruxers with complaints of pain or other temporomandibular disorders (TMD), usually seek the help from their dentist rather than a psychologist [23]. This is perhaps reflected in the current popular treatment options for bruxism: it is typically treated with oral splints, which is reflected in a publication bias with regard to bruxism therapies [23]. Behavioral therapies are the least popular therapies to be scientifically explored, while pharmaceutical approaches have been gaining popularity [23]. Current therapies seem to be focused on preventing damage, rather than finding and treating the cause [24]. This is most unfortunate, of course, as options for treatments are disregarded this way. Risk factors for bruxism were defined as peripheral, such as malocclusion, or central (pathophysiological or psychosocial) [25, 26]. It was concluded that peripheral causes are not likely to play a significant role in the etiology of bruxism [19, 25–27]. It can be argued that bruxism is a disorder from the central neurotransmitter system since the basal ganglia (part of the extrapyramidal system) and the thalamic pathways are implicated in the origin of bruxism, with a crucial role to play by the neurotransmitter dopamine [25]. Experienced stress plays a mediating role, at least in awake bruxism [28], while others argue that stress might even be the main cause for bruxism [27].

This latter theory is fitting with the observations that experienced daily life stress is related to daytime clenching [29] and that self-reported bruxers have higher anxiety levels and more often experience severe stress compared to healthy controls [30].

3. Mastication, Stress, and Pain

3.1. Mastication and Stress Relief. Chewing and clenching have been implied as a way to relieve stress and provide relaxation [31]. The chewing force needed to chew a piece of gum correlated to the amount of salivary cortisol reduction after performing a stressful task [32]. In restrained rats, the length of stress-induced bruxism activity correlated inversely to physiological parameters of stress, such as blood cortisol and adrenaline levels [33]. Whether this stress relieving effect is robust over prolonged periods of time is not yet clear. A longitudinal study examined the effect of regular gum chewing during 14 days (leisurely chewing a piece of gum for at least 5 minutes, twice per day) in young adults [34]. After these two

weeks, chewing gum was associated with decreased scores for anxiety, depression, fatigue, and confusion compared to a control group. This benefit of chewing was transient; however, as after 4 weeks (i.e., two weeks after stopping with the intervention), there was no longer a difference between the groups [34]. Another experiment showed a transient cerebral response to changes in the masticatory domain: using fMRI, it was shown that after being fitted with a new dental prosthesis, adaptive brain activation in the right and the left precentral and postcentral gyrus occurred during oromotor tasks like jaw clenching, but only in the first three months, even though the prosthesis was worn continuously [35].

3.1.1. Salivary Cortisol. Some comments with regard to cortisol assessments need to be made. There are two types of human cortisol that can be assessed: total cortisol and free cortisol. The latter can be sampled in blood, urine, or saliva [36]. Levine and colleagues [36] emphasize that despite current popularity of these "biomarkers of stress," the question remains unanswered whether these assessments reflect actual metabolic and cerebral functioning, namely, activity of the hypothalamic-pituitary-adrenal (HPA) axis, as the hypotheses on which these assessments rely are, in fact, still hypotheses [36]. Salivary cortisol assessments can provide some useful information, but the sampling technique is prone to false results, for example, due to pH changes after eating or drinking or due to contamination by blood from oral lesions [36]. Furthermore, only small correlations have been found between salivary cortisol and plasma free cortisol measurements (the latter being the gold standard) [36]. In another comprehensive review discussing salivary cortisol, it is shown that there is in fact little scientific support for the popularly assumed correlation between psychological stress and the endocrine response [37]. Hellhammer and colleagues [37] emphasize that although salivary cortisol can be used as a biomarker for perceived stress, this can only be done with great caution, and one must be aware that there will only be a moderate association with perceived, or task-induced, stress [37]. The salivary cortisol response is influenced by many factors, such as estrogens (gender, menstrual phase, and oral contraceptives), certain drugs, presence of chronic stress, long-term exercise [37], and overall physical fitness [11]. Sleep and the circadian rhythm also influence the HPA axis activity [38, 39] and finally one must keep in mind that cortisol levels also are not stable during the waking hours but exhibit ultradian oscillations [39]. Clearly, reports relying on salivary cortisol assessments have to be viewed with some caution.

3.2. Mastication and Pain. It is known that, in newborn babies, rhythmic oral motions, such as during breastfeeding or sucking on a pacifier, but also sweet taste such as that from breast milk, or glucose or sucrose solutions, are nonpharmacological approaches for pain relief [40]. Building on this knowledge, it was investigated whether sweet taste, chewing gum, or a combination of both could relieve pain in 7–12-year-old children, undergoing venipuncture or vaccination [41]. The authors did not find an overall effect of the intervention on pain responses. In boys, continuously chewing unsweetened gum reduced pain scores and ratings of unpleasantness. In girls, however, the opposite was observed: chewing sweetened gum reduced pain scores, but chewing unsweetened gum increased them [41]. It should be added that since the control group was also given chewing gum, prior to the procedure, it is possible that some carry-over effect of this chewing took place. On the other hand, the children chewed gum for only a brief period: the control group chewed for 1 minute, and the intervention group chewed for 2 minutes and during the short medical procedure. It is possible that the overall time was too brief to evoke a strong response to chewing.

In another experiment to investigate the effect of chewing on pain and possible underlying neural mechanisms, participants were submitted to nociceptive flexion reflex (NFR) protocol [42]. The NFR protocol encompasses a painful electrocutaneous stimulation of the lower leg, after which the muscle activity in the upper leg on the same side is measured [43]. Blood samples were taken and brain perfusion was assessed with near-infrared spectroscopy measuring (de)oxygenated hemoglobin [42]. The subjects chewed a piece of mint-flavored gum leisurely for 20 minutes. Assessments (applying the NFR and taking blood samples) were made at baseline, immediately after chewing and 30 minutes after chewing. Gum chewing decreased the NFR both immediately after and 30 minutes after chewing [42]. Serotonergic blood levels were increased after chewing, and significant cerebral perfusion was increased in the ventral part of prefrontal cortex (PFC) [42]. The authors conclude that chewing a piece of gum apparently has analgesic effects, with the PFC mediating this effect through serotonergic neurons of the dorsal raphe nucleus [42]. The same dorsal raphe nucleus is implicated in the origin of disordered eating [44], in a hypothesis that by changing the eating behavior (e.g., adhering to a food-restricted diet) one also changes the serotonergic pathways between the PFC and dorsal raphe nucleus and thus alters mood. This theory seems to fit with the other observations that stimulation through chewing might have beneficial effects on affect.

In an animal experimental study, rats were fed a soft diet for 11 days [45]. Subsequently, they were injected in one of the paws with complete Freund's adjuvant (CFA) to temporarily increase their sensitivity to pain (hyperalgesia). In the following 3–6 days, they were fed hard food (intervention) or continued on soft food (control). Then, a heat stimulus was separately applied to both paws, and the reaction time (withdrawal latency) was measured. The difference in reaction speed between the injected and the control paw was taken as a measure for the induced hyperalgesia. Rats on the hard diet showed less CFA-induced hyperalgesia. This protective effect of hard food was gone after injection with the opioid-antagonist naloxone [45]. Hard food was also protective against inflammation, as was shown by a decrease in activity in immunoreactive cells. Inhibiting sensory pathways, by cutting the inferior alveolar nerve or removing the primary somatosensory cortex, reduced but not completely reversed this effect [45]. The authors conclude that a protective effect from hard food might involve the opioid system, which is affected by sensory pathways, but perhaps also by other

neural pathways, such as the brainstem reticular formation [45].

A coupling of the endogenous opioid system and the stress response has been widely studied and is well established [46, 47]. For example, it was found that endogenous opioid systems attenuate the stress response in pregnancy [48]. Underlying mechanisms are being studied: the attenuating effect of suppression of kappa-opioid receptors on the stress response has been shown in a wide range of animal models [46], and endogenous opioids were found to negate the detrimental effects of stress hormones by protecting the endothelial function, a condition which is thought to underlie cardiovascular disease [49]. The locus coeruleus is thought to play a key role in the interaction of the opioid system and the stress response [47].

4. Discussion

The literature discussed above has shown that there currently is an interest in the relationship between mastication, cognition, stress, and pain. The acute effects of chewing gum on cognitive measures and biomarkers of stress, such as salivary cortisol, have not yet generated univocal results. However, a closer examination of cerebral functional specialization of cognitive functions might provide insight into the ambiguous results that are currently being reported.

4.1. Cerebral Functional Specialization. The subcortical basal ganglia are hypothesized to play a role in bruxism [25]. Interestingly, they are also involved in cognitive functions, such as the nondeclarative memory (also known as the procedural memory) [50]. Basal ganglia are also known to play a role in habit learning, most notably through feedback based learning (rewards and/or punishment) regardless of whether this learning is implicit or explicit [51]. This concurs with the finding that chewing a piece of gum can enhance working memory [52], which was assessed by having participants performing a routine that had to become habituated, and the finding that spatial memory (learning the route to an escape platform) was impaired in mice by removing the upper molar crowns [53].

The working memory enhancement of chewing gum would indicate a positive stimulus of chewing for the PFC and basal ganglia [54] and also for the medial temporal lobe and hippocampus for longer tasks [55]. Interestingly, short-term working memory function was not negatively impacted by physiological stress, but it was observed that task difficulty (which could be considered psychological stress) negatively influenced performance [56]. Participants showed elevated levels of activation in the PFC while maintaining their performance levels, a cerebral response which is thought to compensate for the distraction of the stressor [56]. If chewing reduces stress, this would facilitate the compensatory process and thus positively affect working memory performance. Both the hippocampus and the PFC are known for their sensitivity to stress [57], and a reduction of stress due to chewing would explain the positive effect of gum on the behavioral outcomes.

Declarative memory function (which can be subdivided into episodic/autobiographic and semantic memory) is involved in recall and recognition tasks [50]. This type of memory is localized throughout the brain, including the medial and temporal lobes [51], but key areas for recall memory are the frontal and parietal lobes and the cerebellum, while learning and storing new memories (i.e., reproduction and recognition) involve the hippocampus and the parahippocampal gyrus [50]. The fact that these kinds of memory are not enhanced by chewing a piece of gum is therefore perhaps not surprising, as they do not rely primarily on the basal ganglia. Most of the studies included in the two reviews discussed here [15, 16] did not use giving feedback (punishment or rewards) in their paradigm, and thus, they did not activate the basal ganglia [51]. Recently, Bos et al. showed that recall and recognition of newly learned words were improved in a stress condition (i.e., putting the hand in painfully cold water) [58]. This is also fitting with the current observations of the effects of chewing gum: if chewing indeed reduces stress, this would also negate any stress-induced enhancement of the long-term memory.

The lack or even detrimental effect of chewing on vigilance is most likely a negative effect on the vigilance network and the ascending reticular activating system (ARAS) [59]. The ARAS has also been suggested to play a role in sleep bruxism: minutes prior to the onset of sleep bruxism, arousal responses such as increased heart rate and muscle tone are observed in bruxers, which are indicators of ARAS activation [60]. It might be possible that active mastication reverses the same pathway and thus downregulates the ARAS, causing the negative effect on vigilance. Others reported that sleep bruxers do not perform better or worse than controls in neuropsychological tests for vigilance or motor response [61], which is fitting with the current observations.

5. Conclusion

Mastication, as other physical activities, can most likely relieve (acute) stress and even pain. Bruxers and nail biters might unknowingly draw upon this effect, in order to alleviate their commonly reported anxiety. Active mastication might improve some measures of cognitive performance, such as working memory [15, 16] or subjective alertness [15]. Bruxers have not been shown to display cognitive advantages over nonbruxers, with regard to vigilance [61]. This is perhaps not surprising, as chewing has not been shown to enhance vigilance either and, in fact, negatively effects it in children [62]. It would be interesting to see if bruxers outperform nonbruxers in other cognitive domains, such as spatial or working memory. Treatment for bruxism typically shows a dental focus, offering splints or other occlusal appliances. Counseling by a psychologist and a physical therapist in order to learn relaxation can be complementary to this [23].

Other populations that might benefit from these insights are persons at risk for cognitive decline or mental instability, such as older persons suffering from dementia and psychiatric patients. They might experience positive effects from oral and dental care and eating a diet that consists of hard, chewing-enhancing foods. Maintenance of masticatory

function should be endeavored for all clinical groups. However, the long-term use of chewing gum and engaging in other habits should not be encouraged, as this increases the risk for complaints of fatigue, tenderness, and even pain in the musculoskeletal structures of the masticatory system [63–67].

Highlights

(i) The heterogeneous effects of chewing gum on cognitive performance can partially be explained by cerebral functional specialization and the involvement of the basal ganglia.

(ii) Stress and relief of stress can play an important role in the physiological mechanisms underlying these effects.

(iii) Oral habits such as bruxism might draw upon the same effects for stress relief.

(iv) Active chewing might relieve stress or pain, but long-term engagement in oral habits increases the risk of fatigue, pain, or temporomandibular disorders.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] A. van der Bilt, "Assessment of mastication with implications for oral rehabilitation: a review," *Journal of Oral Rehabilitation*, vol. 38, no. 10, pp. 754–780, 2011.

[2] Y. Ono, T. Kataoka, S. Miyake et al., "Chewing ameliorates stress-induced suppression of hippocampal long-term potentiation," *Neuroscience*, vol. 154, no. 4, pp. 1352–1359, 2008.

[3] Y. Ono, T. Yamamoto, K.-Y. Kubo, and M. Onozuka, "Occlusion and brain function: mastication as a prevention of cognitive dysfunction," *Journal of Oral Rehabilitation*, vol. 37, no. 8, pp. 624–640, 2010.

[4] K.-Y. Kubo, Y. Ichihashi, C. Kurata et al., "Masticatory function and cognitive function," *Okajimas Folia Anatomica Japonica*, vol. 87, no. 3, pp. 135–140, 2010.

[5] R. A. F. Weijenberg, E. J. A. Scherder, and F. Lobbezoo, "Mastication for the mind-The relationship between mastication and cognition in ageing and dementia," *Neuroscience and Biobehavioral Reviews*, vol. 35, no. 3, pp. 483–497, 2011.

[6] E. Nitta, Y. Iwasa, M. Sugita, C. Hirono, and Y. Shiba, "Role of mastication and swallowing in the control of autonomic nervous activity for heart rate in different postures," *Journal of Oral Rehabilitation*, vol. 30, no. 12, pp. 1209–1215, 2003.

[7] Y. Shiba, E. Nitta, C. Hirono, M. Sugita, and Y. Iwasa, "Evaluation of mastication-induced change in sympatho-vagal balance through spectral analysis of heart rate variability," *Journal of Oral Rehabilitation*, vol. 29, no. 10, pp. 956–960, 2002.

[8] B. Kordass, C. Lucas, D. Huetzen et al., "Functional magnetic resonance imaging of brain activity during chewing and occlusion by natural teeth and occlusal splints," *Annals of Anatomy*, vol. 189, no. 4, pp. 371–376, 2007.

[9] T. Ono, Y. Hasegawa, K. Hori, T. Nokubi, and T. Hamasaki, "Task-induced activation and hemispheric dominance in cerebral circulation during gum chewing," *Journal of Neurology*, vol. 254, no. 10, pp. 1427–1432, 2007.

[10] Y. Hasegawa, T. Ono, J. Sakagami et al., "Influence of voluntary control of masticatory side and rhythm on cerebral hemodynamics," *Clinical Oral Investigations*, vol. 15, no. 1, pp. 113–118, 2011.

[11] M. Hamer, "Psychosocial stress and cardiovascular disease risk: the role of physical activity," *Psychosomatic Medicine*, vol. 74, no. 9, pp. 896–903, 2012.

[12] K. M. Volkers and E. J. A. Scherder, "Impoverished environment, cognition, aging and dementia," *Reviews in the Neurosciences*, vol. 22, no. 3, pp. 259–266, 2011.

[13] E. Kraft, "Cognitive function, physical activity, and aging: possible biological links and implications for multimodal interventions," *Aging, Neuropsychology, and Cognition*, vol. 19, no. 1-2, pp. 248–263, 2012.

[14] J. Tortosa-Martínez and A. Clow, "Does physical activity reduce risk for Alzheimer's disease through interaction with the stress neuroendocrine system?" *Stress*, vol. 15, no. 3, pp. 243–261, 2012.

[15] A. P. Allen and A. P. Smith, "A review of the evidence that chewing gum affects stress, alertness and cognition," *Journal of Behavioral and Neuroscience Research*, vol. 9, no. 1, pp. 7–23, 2011.

[16] L. K. Tucha and J. Koerts, "Gum chewing and cognition: an overview," *Neuroscience & Medicine*, vol. 3, no. 3, pp. 243–250, 2012.

[17] O. Sabuncuoglu, C. Orengul, A. Bikmazer, and S. Y. Kaynar, "Breastfeeding and parafunctional oral habits in children with and without attention-deficit/hyperactivity disorder," *Breastfeeding Medicine*, vol. 9, no. 5, pp. 244–250, 2014.

[18] F. Lobbezoo, J. Ahlberg, A. G. Glaros et al., "Bruxism defined and graded: an international consensus," *Journal of Oral Rehabilitation*, vol. 40, no. 1, pp. 2–4, 2013.

[19] F. Lobbezoo, J. Ahlberg, D. Manfredini, and E. Winocur, "Are bruxism and the bite causally related?" *Journal of Oral Rehabilitation*, vol. 39, no. 7, pp. 489–501, 2012.

[20] O. M. Tanaka, R. W. F. Vitral, G. Y. Tanaka, A. P. Guerrero, and E. S. Camargo, "Nailbiting, or onychophagia: a special habit," *American Journal of Orthodontics and Dentofacial Orthopedics*, vol. 134, no. 2, pp. 305–308, 2008.

[21] T. I. Williams, R. Rose, and S. Chisholm, "What is the function of nail biting: an analog assessment study," *Behaviour Research and Therapy*, vol. 45, no. 5, pp. 989–995, 2007.

[22] S. Roberts, K. O'Connor, and C. Bélanger, "Emotion regulation and other psychological models for body-focused repetitive behaviors," *Clinical Psychology Review*, vol. 33, no. 6, pp. 745–762, 2013.

[23] F. Lobbezoo, J. van der Zaag, M. K. A. van Selms, H. L. Hamburger, and M. Naeije, "Principles for the management of bruxism," *Journal of Oral Rehabilitation*, vol. 35, no. 7, pp. 509–523, 2008.

[24] J. L. de-la-Hoz, "Sleep bruxism: review and update for the restorative dentist," *Alpha Omegan*, vol. 106, no. 1-2, pp. 23–28, 2013.

[25] F. Lobbezoo and M. Naeije, "Bruxism is mainly regulated centrally, not peripherally," *Journal of Oral Rehabilitation*, vol. 28, no. 12, pp. 1085–1091, 2001.

[26] F. Lobbezoo, J. van der Zaag, and M. Naeije, "Bruxism: its multiple causes and its effects on dental implants—an updated

review," *Journal of Oral Rehabilitation*, vol. 33, no. 4, pp. 293–300, 2006.

[27] M. Wieckiewicz, A. Paradowska-Stolarz, and W. Wieckiewicz, "Psychosocial aspects of bruxism: the most paramount factor influencing teeth grinding," *BioMed Research International*, vol. 2014, Article ID 469187, 7 pages, 2014.

[28] D. Manfredini and F. Lobbezoo, "Role of psychosocial factors in the etiology of bruxism," *Journal of Orofacial Pain*, vol. 23, no. 2, pp. 153–166, 2009.

[29] M. K. A. Van Selms, F. Lobbezoo, D. J. Wicks, H. L. Hamburger, and M. Naeije, "Craniomandibular pain, oral parafunctions, and psychological stress in a longitudinal case study," *Journal of Oral Rehabilitation*, vol. 31, no. 8, pp. 738–745, 2004.

[30] J. Ahlberg, F. Lobbezoo, K. Ahlberg et al., "Self-reported bruxism mirrors anxiety and stress in adults," *Medicina Oral, Patologia Oral y Cirugia Bucal*, vol. 18, no. 1, pp. e7–e11, 2013.

[31] Y. Tahara, K. Sakurai, and T. Ando, "Influence of chewing and clenching on salivary cortisol levels as an indicator of stress," *Journal of Prosthodontics*, vol. 16, no. 2, pp. 129–135, 2007.

[32] R. Soeda, A. Tasaka, and K. Sakurai, "Influence of chewing force on salivary stress markers as indicator of mental stress," *Journal of Oral Rehabilitation*, vol. 39, no. 4, pp. 261–269, 2012.

[33] C. Sato, S. Sato, H. Takashina, H. Ishii, M. Onozuka, and K. Sasaguri, "Bruxism affects stress responses in stressed rats," *Clinical Oral Investigations*, vol. 14, no. 2, pp. 153–160, 2010.

[34] A. Sasaki-Otomaru, Y. Sakuma, Y. Mochizuki, S. Ishida, Y. Kanoya, and C. Sato, "Effect of regular gum chewing on levels of anxiety, mood, and fatigue in healthy young adults," *Clinical Practice and Epidemiology in Mental Health*, vol. 7, pp. 133–139, 2011.

[35] J. Luraschi, M. S. Korgaonkar, T. Whittle, M. Schimmel, F. Müller, and I. Klineberg, "Neuroplasticity in the adaptation to prosthodontic treatment," *Journal of Orofacial Pain*, vol. 27, no. 3, pp. 206–216, 2013.

[36] A. Levine, O. Zagoory-Sharon, R. Feldman, J. G. Lewis, and A. Weller, "Measuring cortisol in human psychobiological studies," *Physiology and Behavior*, vol. 90, no. 1, pp. 43–53, 2007.

[37] D. H. Hellhammer, S. Wüst, and B. M. Kudielka, "Salivary cortisol as a biomarker in stress research," *Psychoneuroendocrinology*, vol. 34, no. 2, pp. 163–171, 2009.

[38] E. Van Cauter, M. Balbo, and R. Leproult, "Impact of sleep and its disturbances on hypothalamo-pituitary-adrenal axis activity," *International Journal of Endocrinology*, vol. 2010, Article ID 759234, 16 pages, 2010.

[39] S. Postnova, R. Fulcher, H. A. Braun, and P. A. Robinson, "A minimal physiologically based model of the HPA axis under influence of the sleep-wake cycles," *Pharmacopsychiatry*, vol. 46, supplement 1, pp. S36–S43, 2013.

[40] R. Carbajal, S. Gréteau, C. Arnaud, and R. Guedj, "Pain in neonatology. Non-pharmacological treatment," *Archives de Pédiatrie*, 2014.

[41] M. D. Lewkowski, R. G. Barr, A. Sherrard, J. Lessard, A. R. Harris, and S. N. Young, "Effects of chewing gum on responses to routine painful procedures in children," *Physiology and Behavior*, vol. 79, no. 2, pp. 257–265, 2003.

[42] K. Kamiya, M. Fumoto, H. Kikuchi et al., "Prolonged gum chewing evokes activation of the ventral part of prefrontal cortex and suppression of nociceptive responses: involvement of the serotonergic system," *Journal of Medical and Dental Sciences*, vol. 57, no. 1, pp. 35–43, 2010.

[43] J. L. Rhudy and C. R. France, "Defining the nociceptive flexion reflex (NFR) threshold in human participants: a comparison of different scoring criteria," *Pain*, vol. 128, no. 3, pp. 244–253, 2007.

[44] I. Ioakimidis, M. Zandian, F. Ulbl, C. Bergh, M. Leon, and P. Södersten, "How eating affects mood," *Physiology and Behavior*, vol. 103, no. 3-4, pp. 290–294, 2011.

[45] A. Ogawa, T. Morimoto, J. W. Hu et al., "Hard-food mastication suppresses complete Freund's adjuvant-induced nociception," *Neuroscience*, vol. 120, no. 4, pp. 1081–1092, 2003.

[46] A. Van'T Veer and W. A. Carlezon Jr., "Role of kappa-opioid receptors in stress and anxiety-related behavior," *Psychopharmacology*, vol. 229, no. 3, pp. 435–452, 2013.

[47] E. J. Van Bockstaele, B. A. S. Reyes, and R. J. Valentino, "The locus coeruleus: a key nucleus where stress and opioids intersect to mediate vulnerability to opiate abuse," *Brain Research*, vol. 1314, pp. 162–174, 2010.

[48] P. J. Brunton and J. A. Russell, "Neuroendocrine control of maternal stress responses and fetal programming by stress in pregnancy," *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, vol. 35, no. 5, pp. 1178–1191, 2011.

[49] N. Toda and M. Nakanishi-Toda, "How mental stress affects endothelial function," *Pflugers Archiv European Journal of Physiology*, vol. 462, no. 6, pp. 779–794, 2011.

[50] M. H. M. Meeter, "Geheugen," in *Klinische Neuropsychologie*, R. Kessels, Ed., pp. 197–218, Uitgeverij Boom, Amsterdam, The Netherlands, 2013.

[51] K. Foerde and D. Shohamy, "The role of the basal ganglia in learning and memory: insight from Parkinson's disease," *Neurobiology of Learning and Memory*, vol. 96, no. 4, pp. 624–636, 2011.

[52] Y. Hirano, T. Obata, K. Kashikura et al., "Effects of chewing in working memory processing," *Neuroscience Letters*, vol. 436, no. 2, pp. 189–192, 2008.

[53] M. Onozuka, K. Watanabe, S. M. Mirbod et al., "Reduced mastication stimulates impairment of spatial memory and degeneration of hippocampal neurons in aged SAMP8 mice," *Brain Research*, vol. 826, no. 1, pp. 148–153, 1999.

[54] F. McNab and T. Klingberg, "Prefrontal cortex and basal ganglia control access to working memory," *Nature Neuroscience*, vol. 11, no. 1, pp. 103–107, 2008.

[55] N. K. R. Gudrun, "Ruimtelijke cognitie," in *Klinische Neuropsychologie*, R. Kessels, Ed., pp. 174–195, Uitgeverij Boom, Amsterdam, The Netherlands, 2013.

[56] A. J. Porcelli, D. Cruz, K. Wenberg, M. D. Patterson, B. B. Biswal, and B. Rypma, "The effects of acute stress on human prefrontal working memory systems," *Physiology & Behavior*, vol. 95, no. 3, pp. 282–289, 2008.

[57] B. S. McEwen, "Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators," *European Journal of Pharmacology*, vol. 583, no. 2-3, pp. 174–185, 2008.

[58] M. G. N. Bos, J. Schuijer, F. Lodestijn, T. Beckers, and M. Kindt, "Stress enhances reconsolidation of declarative memory," *Psychoneuroendocrinology*, vol. 46, pp. 102–113, 2014.

[59] D. H. E. Boelen, L. Fasotti, and J. M. Spikman, "Aandacht en executieve functies," in *Klinische Neuropsychologie*, R. Kessels, Ed., vol. 21, pp. 69–79, Uitgeverij Boom, Amsterdam, The Netherlands, 1992.

[60] G. J. Lavigne, N. Huynh, T. Kato et al., "Genesis of sleep bruxism: motor and autonomic-cardiac interactions," *Archives of Oral Biology*, vol. 52, no. 4, pp. 381–384, 2007.

[61] M. Major, P. H. Rompré, F. Guitard et al., "A controlled daytime challenge of motor performance and vigilance in sleep bruxers," *Journal of Dental Research*, vol. 78, no. 11, pp. 1754–1762, 1999.

[62] L. Tucha, W. Simpson, L. Evans et al., "Detrimental effects of gum chewing on vigilance in children with attention deficit hyperactivity disorder," *Appetite*, vol. 55, no. 3, pp. 679–684, 2010.

[63] P. Maillou, S. W. Cadden, and F. Lobbezoo, "The inhibitory effect of a chewing task on a human jaw reflex," *Muscle & Nerve*, vol. 41, no. 6, pp. 845–849, 2010.

[64] M. Koutris, F. Lobbezoo, M. Naeije et al., "Effects of intense chewing exercises on the masticatory sensory-motor system," *Journal of Dental Research*, vol. 88, no. 7, pp. 658–662, 2009.

[65] N. C. W. van der Kaaij, P. Maillou, J. J. van der Weijden, M. Naeije, and F. Lobbezoo, "Reproducible effects of subjectively assessed muscle fatigue on an inhibitory jaw reflex in humans," *Archives of Oral Biology*, vol. 54, no. 9, pp. 879–883, 2009.

[66] O. F. Molina, J. Dos Santos, M. Mazzetto, S. Nelson, T. Nowlin, and É. T. Mainieri, "Oral jaw behaviors in TMD and bruxism: a comparison study by severity of bruxism," *Cranio*, vol. 19, no. 2, pp. 114–121, 2001.

[67] E. Winocur, A. Gavish, T. Finkelshtein, M. Halachmi, and E. Gazit, "Oral habits among adolescent girls and their association with symptoms of temporomandibular disorders," *Journal of Oral Rehabilitation*, vol. 28, no. 7, pp. 624–629, 2001.

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Research Article

Prefrontal Hemodynamic Changes Associated with Subjective Sense of Occlusal Discomfort

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We used functional near-infrared spectroscopy to measure prefrontal brain activity accompanying the physical sensation of oral discomfort that arose when healthy young-adult volunteers performed a grinding motion with mild occlusal elevation (96 μm). We simultaneously evaluated various forms of occlusal discomfort using the visual analogue scale (VAS) and hemodynamic responses to identify the specific prefrontal activity that occurs with increased occlusal discomfort. The Oxy-Hb responses of selected channels in the bilateral frontopolar and dorsolateral prefrontal cortices increased in participants who reported increased severity of occlusal discomfort, while they decreased in those who reported no change or decreased occlusal discomfort during grinding. Moreover, the cumulative values of Oxy-Hb response in some of these channels were statistically significant predictive factors for the VAS scores. A generalized linear model analysis of Oxy-Hb signals in a group of participants who reported increased discomfort further indicated significant cerebral activation in the right frontopolar and dorsolateral prefrontal cortices that overlapped with the results of correlation analyses. Our results suggest that the increased hemodynamic responses in the prefrontal area reflect the top-down control of attention and/or self-regulation against the uncomfortable somatosensory input, which could be a possible marker to detect the subjective sense of occlusal discomfort.

1. Introduction

Dental outpatients often present with symptoms related to uncomfortable sensations such as pain or discomfort in the oromandibular area. Although objective findings that match the symptoms can be easily confirmed in the majority of cases, the evaluation of patients with vague complaints in the intraoral area such as occlusal discomfort without any identifiable organic cause (occlusal dysesthesia) has been a growing problem in recent years [1]. That dental therapy such as occlusal adjustment mostly does not relieve any discomfort in these patients raises the hypothesis that they develop a perception bias or a modified sensory processing network in their body image of the orofacial area. Because many cases of occlusal dysesthesia accompany psychiatric disorders such as somatoform disorders [1], it appears necessary to clarify how the emotional response toward occlusal discomfort is processed and represented in the higher cognitive areas of the brain. If the subjective symptom of occlusal discomfort can be quantified from the regional brain activity of the patient, the clinician can diagnose the occlusal dysesthesia based on the mismatch of the existing occlusal discomfort represented in the brain activity and the lack of objective findings in the oral area. This approach will enable clinicians to prevent unnecessary dental treatment to patients with occlusal dysesthesia and to allow patients to understand the actual disease behind

their occlusal problem. Thus, patients will be able to undergo appropriate treatment, which will improve their symptoms and quality of life.

We therefore studied regional brain activity corresponding to experimentally generated occlusal discomfort in participants without stomatognathic symptoms and determined the cortical areas in which the emotional response to modified and uncomfortable oral sensations is processed. Previous neuroimaging studies on occlusal discomfort have focused on comparing the basal brain activity between patients and control participants in a resting state [2, 3]. Although these studies are useful for extracting the basal brain activity specific to patients, it is hard to determine whether the extracted neuronal changes reflect the perceived discomfort *per se* or other "secondary" neuronal activity caused by their symptoms, such as stress responses and altered mood. We therefore used an "active" grinding paradigm in participants without stomatognathic symptoms to extract the regional brain activity that specifically responds to the elevation of perceived discomfort in participants. Considering that the ultimate goal of this study is to develop a monitoring system for occlusal discomfort in the clinical setting, we selected the prefrontal cortex, a top-down control center for somatosensory perception [3–5], as a region of interest for its accessibility.

We used functional near-infrared spectroscopy (fNIRS) to monitor prefrontal responses over other traditional brain imaging techniques for three reasons: first, fNIRS allows participants to take natural occlusal positions in a sitting position while undergoing a scan. Second, fNIRS has relatively better tolerance to body movement, given that the optodes are tightly attached to the head and that the head motion is restricted [6]. Third, the recent development of portable fNIRS systems makes it possible to continuously monitor hemodynamic responses in a real-world environment [7]. We also intended to reject pseudohemodynamic responses from changes in cutaneous and muscle blood flow during grinding motions, as well as motion artifacts from jaw movements, by subtracting hemodynamic signals during grinding with elevated occlusion from those during grinding with natural occlusion. To ensure that the subtraction could cancel out artifacts from muscle-related hemodynamic signals, the strength of masseter muscle activity during grinding motion with and without occlusal elevation was compared in a small group of participants. We gave a fixed height of occlusal elevation that evoked various intensities of discomfort among participants with individual occlusion to explore the spectrum of interactions of perceived discomfort on neural substrate activity.

2. Materials and Methods

2.1. Participants. Twenty-five participants aged from 21 to 49 years took part in the fNIRS experiment (14 males, 11 females, 28.9 ± 1.0 years) and six participants aged from 25 to 34 years took part in the electromyography (EMG) experiment (three males, three females, 29.5 ± 1.6 years). All were free of medical and psychiatric symptoms and had no perceived symptoms in their stomatognathic system.

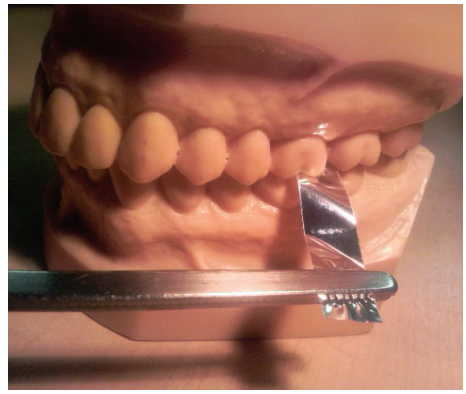

Figure 1: Simulation of occlusal discomfort using active grinding paradigm.

A clinician (GK or RH) interviewed all participants and assessed their stomatognathic function upon arrival to the lab and ensured that their individual occlusion was within the normal range. Written informed consent was obtained from each participant after a full explanation of the experiment was provided. The study followed the protocol for the use of human participants and was approved by the Ethics Committee of the Kanagawa Dental University Hospital.

2.2. Task Paradigm. Occlusal discomfort was simulated by grinding the teeth with stacked, tasteless, and odorless, metal strips (eight 12 μm strips stacked to 96 μm of thickness; Artus, Englewood, NJ) placed on the occlusal surface of the first molar of the habitual chewing side (Figure 1). The thickness of the metal strip was selected to be enough to cause obvious discomfort during grinding in most of the participants, but cause neither injury of the periodontal tissue nor tooth movement [8–10].

2.3. Data Acquisition. A single session of fNIRS measurement was performed using a block design, which consisted of alternating 30 s of grinding and 40 s of rest, repeated five times. We used the 22-channel fNIRS topography system ETG-7100 (Hitachi Medical Corporation, Tokyo, Japan), arranged into a 3 × 5 optical probe array positioned over the bilateral prefrontal cortices. The lowest optode row was aligned with the line connecting F7-F8 in the international 10–20 system. Interoptode distance was 3 cm for each source detector pair. Using a 3D digitizer (PATRIOT; Polhemus, Colchester, VT), the coordinates of all probe positions and the anatomical landmark positions (nasion, inion, auricles, and Cz) of each participant were obtained immediately after data collection.

Participants performed two sessions of fNIRS measurement in which they grinded their teeth with or without metal strips on their first molar. The experimenter pinched the tip of the metal strips using locking tweezers and applied them to the surface of the lower molar of a participant 10 s before each trial. Participants kept the metal strips in their mouth in the intercuspal position after they were applied to the tooth. Verbal instructions given at the beginning and

the end of the grinding period told the participants when to start and stop grinding, respectively. The metal strips were taken out of the mouth immediately after the grinding period each time. In trials without metal strips, the experimenter inserted only the tweezers into participants' mouths in the same way as in the trials with strips. The order of the two sessions was randomly assigned, and participants were asked to grind their teeth mildly and uniformly across trials and sessions. To ensure that participants could perform grinding with comparable muscle strength between sessions, another group of six participants who reported increased discomfort while grinding with strips compared with grinding without strips performed the same experimental tasks while EMG was recorded from the masseter (WEB-1000; Nihon Koden, Tokyo, Japan) on the grinding side without fNIRS recording.

At the end of each session, all participants evaluated the subjective severity of discomfort using a visual analog scale (VAS). The VAS varied from 0 (a state with no discomfort at all) to 100 (a state of intolerable discomfort). "Discomfort" was defined using the following six criteria: (i) the feeling of a "too-high" bite; (ii) jitteriness of the tongue, tooth, and oral cavity; (iii) difficulty in chewing; (iv) unstable intercuspal position (IP); (v) uneven contact of bilateral molar teeth; and (vi) tooth pain [11], each of which the participants were asked to evaluate. We subtracted VAS scores in the session when participants ground with metal strips from that without metal strips for each of these six criteria and used them as an index of subjective discomfort with elevated occlusion (hereinafter referred to as dVAS; ranges from −200 to 200) for further analysis.

2.4. Data Analysis. Changes in cerebral Oxy-Hb responses were averaged over five trials using a built-in function of the fNIRS system (ETG-7100 V3.13 K; Pre: 5.0 s, Recovery: 20.0 s, Post: 5.0 s). We used in-house developed software running on Matlab (Mathworks, Natick, MA, USA) for signal processing. To cancel out artifacts in Oxy-Hb responses related to jaw movement and muscle-originating hemodynamic responses, we subtracted Oxy-Hb responses during grinding with metal strips from those without metal strips (ΔOxy-Hb). Baseline correction was applied to the ΔOxy-Hb responses so that the value at the task onset was set to zero. The amplitude of the hemodynamic signal was further normalized by dividing the ΔOxy-Hb values by the standard deviation of those during the 5 s before task onset. These baseline-corrected and normalized ΔOxy-Hb responses were used for further analysis.

We performed four types of interparticipant analyses to determine the signatures of hemodynamic signals indicating the perceived severity of occlusal discomfort. First, participants were divided into four groups based on the total value of dVAS (tdVAS; Table 1) to examine the signal waveform. Cutoff values were set to mean + 1 standard deviation (1SD), mean, and mean − 1SD of tdVAS. As the number of participants who fell into the group with tdVAS less than mean − 1SD was small ($n = 2$) and the ΔOxy-Hb waveforms from this group were comparable to those from the neighboring group (tdVAS between mean and mean − 1SD; $n = 10$), these two groups were combined together for the schematic representation and statistical comparison of ΔOxy-Hb amplitudes between groups. However, we kept the highest tdVAS group (tdVAS more than mean + 1SD; $n = 3$) apart from the second highest tdVAS group (tdVAS between mean + 1SD and mean; $n = 10$), because the amplitudes of the ΔOxy-Hb responses in several channels demonstrated separated tendencies between the two groups (the statistical significance was confirmed in the analysis described in Section 2.4, also see Figure 2), indicating graded changes in the hemodynamic response depending on the severity of occlusal discomfort.

A two-way analysis of variance (ANOVA) test with repeated measures was adopted to investigate task-dependent ΔOxy-Hb responses and their interaction among groups. We calculated the mean amplitude of ΔOxy-Hb responses during 10–20 s and 20–30 s after starting grinding as the amplitudes of hemodynamic responses during the task period and those during 5–0 s before starting grinding as those during the rest period. The task period was divided into two parts to determine the time-dependent hemodynamic changes during the grinding activity. The rest period and the two task periods were set as the within-subject factor (time) and the three groups were set as the between-subject factor. The difference in the mean amplitudes of ΔOxy-Hb responses among groups was further determined using a post hoc multiple comparison with Bonferroni correction in the channels that showed a statistically significant interaction between the time and group. A Shapiro-Wilk test confirmed the normality of the data used in the analysis. We also processed and analyzed the ΔdeOxy-Hb responses in the same manner as we did with the ΔOxy-Hb responses to confirm the brain-derived temporal patterns of hemodynamic signals. However, we focused on the ΔOxy-Hb responses for the subsequent analysis because of the low signal-to-noise ratio of the ΔdeOxy-Hb responses.

Second, the correlation between the area under the curve of the ΔOxy-Hb responses during the grinding period (AUC) and tdVAS or individual dVAS scores was examined at each channel to further determine fNIRS channels that responded according to the perceived severity of occlusal discomfort. AUC was adopted to determine the cumulative metabolic activity that has been reported to correlate well with the cognitive load in the prefrontal cortex regardless of the individual differences in the time-course shape of the ΔOxy-Hb responses [6]. Either Pearson's correlation coefficient or Spearman's rank correlation coefficient was calculated depending on the result of the Shapiro-Wilk normality test.

Third, AUC and tdVAS were further used in a stepwise multiple-regression analysis to investigate whether a combination of AUC values from selected fNIRS channels would be a reliable predictor of tdVAS, the relative change in perceived discomfort.

Fourth, regional brain activities corresponding to the subtracted Oxy-Hb responses ΔOxy-Hb were identified using statistical parametric mapping (NIRS-SPM; [12]) with a generalized linear model (GLM). The NIRS-SPM converts the individual fNIRS channel positions into the MNI coordinates of the normalized brain and provides the interpolated activity map over the cortical surface from the T statistics calculated at discrete fNIRS channels. We took advantage

Table 1: Participant profiles and VAS scores.

Perceived discomfort	Age	Sex	Chewing side	dVAS						Total (tdVAS)
				Too high	Jitteriness	Difficulty in chewing	Unstable IP	Uneven contact	Tooth pain	
(a) NIRS experiment										
Severe	29	F	L	77	81	76	81	84	15	414
	27	M	R	32	66	53	40	100	54	345
	29	F	R	43	64	32	58	35	14	246
Moderate	39	F	L	34	35	36	37	56	22	220
	24	F	R	37	−8	38	46	45	15	173
	28	F	L	32	57	1	14	60	0	164
	34	F	R	24	16	15	37	36	36	164
	24	M	R	2	33	15	14	33	32	129
	26	M	R	31	19	9	33	36	0	128
	26	M	L	28	11	12	22	29	16	118
	25	F	L	33	3	25	26	27	0	114
	22	F	R	19	20	20	34	17	2	112
	33	M	R	26	16	14	29	20	0	105
Mild–none	31	M	R	23	16	21	18	17	−18	77
	31	M	R	23	0	0	24	22	0	69
	27	F	R	14	13	13	13	13	0	66
	24	M	R	4	4	5	5	3	4	25
	26	M	L	11	12	0	0	0	0	23
	26	M	L	6	0	6	0	0	0	12
	24	F	L	0	3	0	0	0	0	3
	29	M	R	−1	−2	−7	5	6	0	1
	24	M	R	0	0	0	0	−6	0	−6
	41	M	R	6	−11	−26	2	1	−1	−29
Comfortable	38	M	R	−33	−31	−29	−32	−41	−17	−183
	36	F	L	−49	−67	−70	−70	−49	−1	−306
Mean	**28.9**			**16.9**	**14.0**	**10.4**	**17.4**	**21.8**	**6.9**	**87.4**
SE	**1.0**			**4.9**	**6.2**	**5.6**	**5.8**	**6.6**	**3.2**	**29.4**
(b) EMG experiment										
	30	M	R	42	26	33	54	58	7	220
	28	F	L	24	24	23	23	24	6	124
	26	M	L	33	5	24	25	24	0	111
	34	F	R	15	3	6	11	16	21	72
	25	M	R	2	36	−1	−2	13	6	54
	34	F	L	5	10	0	3	12	0	30
Mean	**29.5**			**20.2**	**17.3**	**14.2**	**19.0**	**24.5**	**6.7**	**101.8**
SE	**1.6**			**6.4**	**5.4**	**5.9**	**8.2**	**7.0**	**3.1**	**27.6**

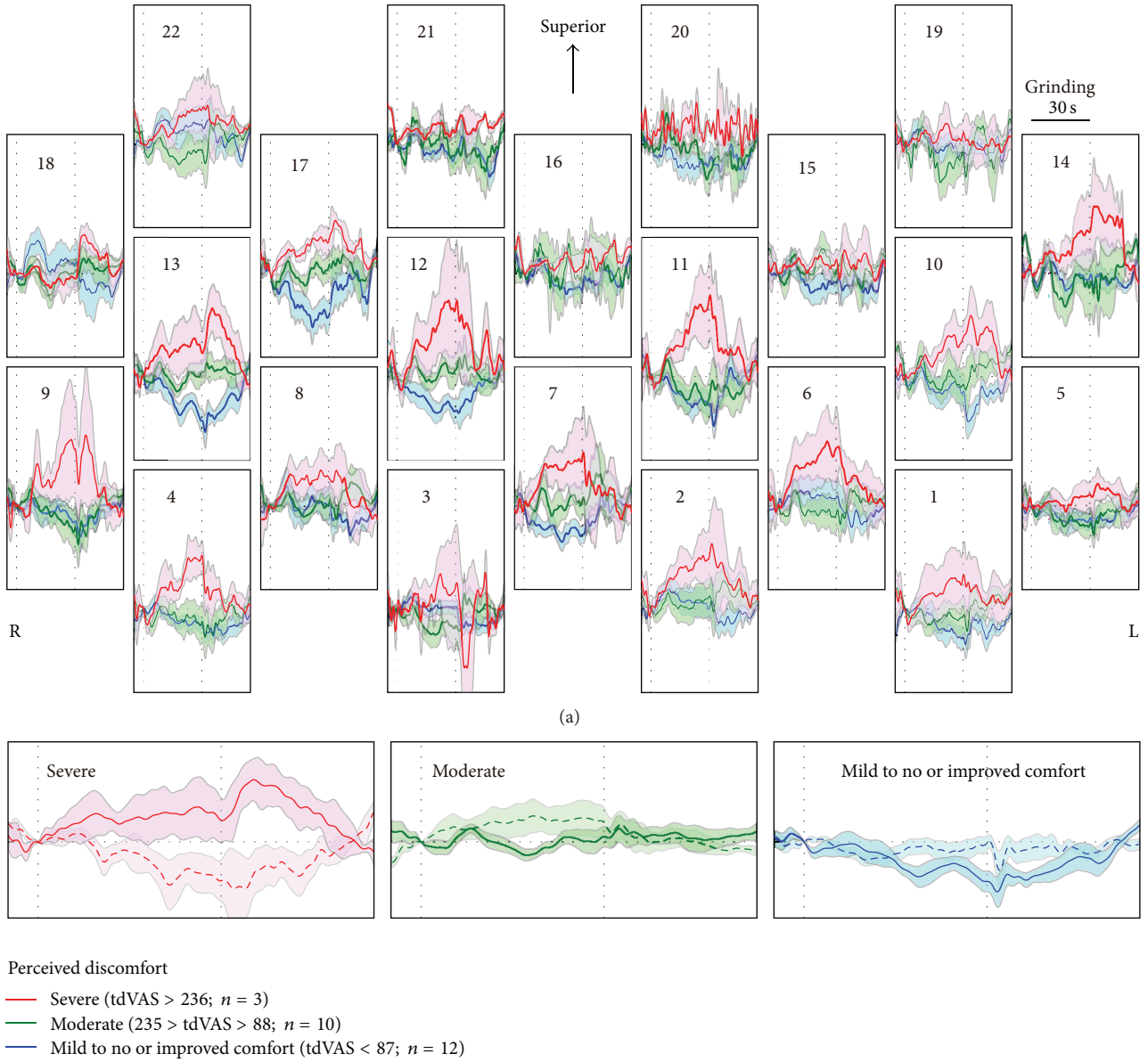

FIGURE 2: Comparison of the time-course of mean hemodynamic responses in participants with different severities of perceived discomfort. (a) Spatial distribution of the mean ΔOxy-Hb responses over the 22 channels located in the prefrontal area. The number and vertical lines in each subfigure show the corresponding channel number and the timing of grinding behavior. The shaded areas indicate the standard errors of the ΔOxy-Hb responses in the corresponding group. (b) Time-course changes of the mean ΔOxy-Hb (solid line) and the mean ΔdeOxy-Hb (dashed line) responses in participants with different severities of perceived discomfort in a representative channel (13). The shaded areas indicate the standard errors of the ΔOxy-Hb and ΔdeOxy-Hb responses in the corresponding group.

of the interpolated T-contrast maps in the normalized brain coordinates to extract the common cortical area among participants that responded to the perceived occlusal discomfort. The participants were divided into two groups who reported severe to moderate discomfort (tdVAS more than mean; $n = 13$) or mild to no discomfort (tdVAS less than mean; $n = 12$) in this NIRS-SPM analysis to increase statistical power. Discrete Cosine Transform-based detrending, which consists of a high-pass filter with a 128 s time constant, was applied to the ΔOxy-Hb responses. The temporal autocorrelation in the ΔOxy-Hb responses was further corrected by a precoloring method [12] using a Gaussian low-pass filter with a full width at half maximum of 1.5 s. Regression models were created using a hemodynamic response function [12] with a duration set at 30 s. The GLM parameters were estimated with the above preprocessed ΔOxy-Hb responses of each participant to obtain an interpolated beta-value map, which indicates the distribution of the task-dependent regional brain activity over the cortical surface covered by the optical probes. We

further collected the beta-value maps of the selected participants to estimate the common regional activity using the group analysis function [12]. The extracted task-dependent regional brain activity (T-contrast map) was superimposed onto the brain surface image implemented in the NIRS-SPM. The Brodmann areas corresponding to the activated region were further determined using xjview software (http://www.alivelearn.net/xjview8/).

EMG signals from the masseter were sampled at 500 Hz with a band-pass filter of 1.6 s to 1.6 ms time constant (which corresponds to 0.1–100 Hz). The data were imported and further processed in Matlab (Mathworks, Natick, MA, USA). Full-wave rectification and low-pass filtering with a 32 ms time constant (corresponding to 5 Hz) were applied to extract the ridge line of EMG activity. Muscle activities during the rest and grinding periods were extracted and averaged over trials for each participant. We further calculated the increase of the averaged muscle activities related to grinding by dividing those during grinding by those during rest. These grinding-related increases of muscle activities were compared between sessions with and without metal strips using a paired t-test.

All data are shown as mean ± standard error unless otherwise stated. We considered P values < 0.05 to be statistically significant.

3. Results

3.1. Grinding with Metal Strips Evoked Varying Intensity of Perceived Discomfort. Table 1 summarizes VAS scores of all participants with their profiles. Experimental occlusal elevation by metal strips led to increased perceived discomfort in most of the participants, although a few of them reported less discomfort or improved comfort while grinding metal strips. Among all participants who underwent the fNIRS or EMG experiments, the chief components of discomfort were uneven contact of the bilateral molar teeth (24.7% of total dVAS scores), unstable IP (19.7%), and "too-high" bite (19.4%), followed by jitteriness of the oral region (16.2%), difficulty in chewing (12.3%), and tooth pain (7.6%). The EMG experiment confirmed that the increase in masseter activity related to grinding was comparable between the two sessions (137 ± 14% and 115 ± 10% in grinding with and without metal strips, resp.; $P = 0.13$; Cohen's $d = 0.75$), indicating that participants could perform grinding with uniform strength regardless of the presence of metal strips.

3.2. Prefrontal Oxy-Hemoglobin Responses Indicate Region- and Perceived Discomfort-Specific Patterns. Figure 2(a) shows the complex interactions between perceived discomfort, region of interest, and mean amplitude of ΔOxy-Hb responses. Participants who reported severe discomfort (tdVAS > mean + 1SD, severe group) showed large and bell-shaped ΔOxy-Hb responses in most of the channels. Conversely, participants who reported a tdVAS of less than average, who perceived mild to no discomfort or improved comfort with grinding metal strips (mild to none group), showed suppressed ΔOxy-Hb responses in most of the channels. As expected, the ΔOxy-Hb responses of participants who reported moderate discomfort (moderate group) were mostly located between those from the severe group and the mild to none group, especially in the right hemisphere (channels 12, 13, and 17 in Figure 2(a)). The channels showing increased ΔOxy-Hb response were associated with decreased ΔdeOxy-Hb response (waveforms of a representative channel are shown in Figure 2(b)), which is a typical temporal pattern of cerebral hemodynamics [13].

There was a statistically significant interaction of the mean amplitudes of ΔOxy-Hb responses between time and group in channels 7 ($F[4, 44] = 3.38$, $P = 0.025$), 11 ($F[4, 44] = 2.91$, $P = 0.032$), 12 ($F[4, 44] = 3.87$, $P = 0.009$), 13 ($F[4, 44] = 3.84$, $P = 0.010$), and 17 ($F[4, 44] = 4.25$, $P = 0.006$), indicating different task-dependent hemodynamic responses among groups. The mean amplitudes of ΔdeOxy-Hb responses accordingly showed a statistically significant interaction between time and group at channel 13 ($F[4, 44] = 5.53$, $P = 0.001$). The post hoc multiple comparison with Bonferroni correction showed a statistically significant difference in the mean amplitudes of ΔOxy-Hb responses between the severe and mild to none groups in channels 7 ($t[13] = 3.01$, $P = 0.023$) and 13 ($t[13] = 3.20$, $P = 0.014$) during 10–20 s and in channels 7 ($t[13] = 3.15$, $P = 0.018$), 11 ($t[13] = 3.04$, $P = 0.020$), 12 ($t[13] = 3.00$, $P = 0.022$), 13 ($t[13] = 3.04$, $P = 0.020$), and 17 ($t[13] = 3.08$, $P = 0.018$) during 20–30 s after starting grinding, respectively ($P < 0.05$). The same multiple comparisons also indicated a statistically significant difference in the mean amplitudes of the ΔOxy-Hb and ΔdeOxy-Hb responses between the severe and moderate groups in channels 11 ($t[11] = 2.70$, $P = 0.040$) and 13 ($t[11] = 2.74$, $P = 0.039$) during 20–30 s after starting grinding, respectively. The longer participant continued grinding the more channels showed different mean amplitudes of ΔOxy-Hb response among groups. These results confirmed our hypothesis that prefrontal ΔOxy-Hb responses negatively correlate with perceived occlusal comfort during grinding.

3.3. AUC Values of Selected Channels Can Predict Severity of Perceived Discomfort. The correlation analysis of AUC and VAS scores at each individual channel revealed a significant positive relationship between the severity of perceived discomfort and hemodynamic responses in the prefrontal area (Figure 3). A significant correlation between AUC and tdVAS was found in channels corresponding to the right frontopolar (FPC) and dorsolateral prefrontal cortices (DLPFC), as well as the lateral transitional area of the left FPC and DLPFC. A similar relationship was obtained between AUC and dVAS for all individual discomfort criteria except tooth pain, for which a significant correlation was mostly found in the left FPC and DLPFC. Multiple-regression analysis further indicated that the AUCs of channels 1, 13, and 17 were significant predictors of tdVAS score (coefficient of determination $R^2 = 0.813$; $P < 0.001$), obeying the following equation:

$$\begin{aligned} \text{tdVAS} = {} & 0.21\text{AUC}(1) + 0.132\text{AUC}(17) \\ & - 0.11\text{AUC}(13) + 77.5, \end{aligned} \quad (1)$$

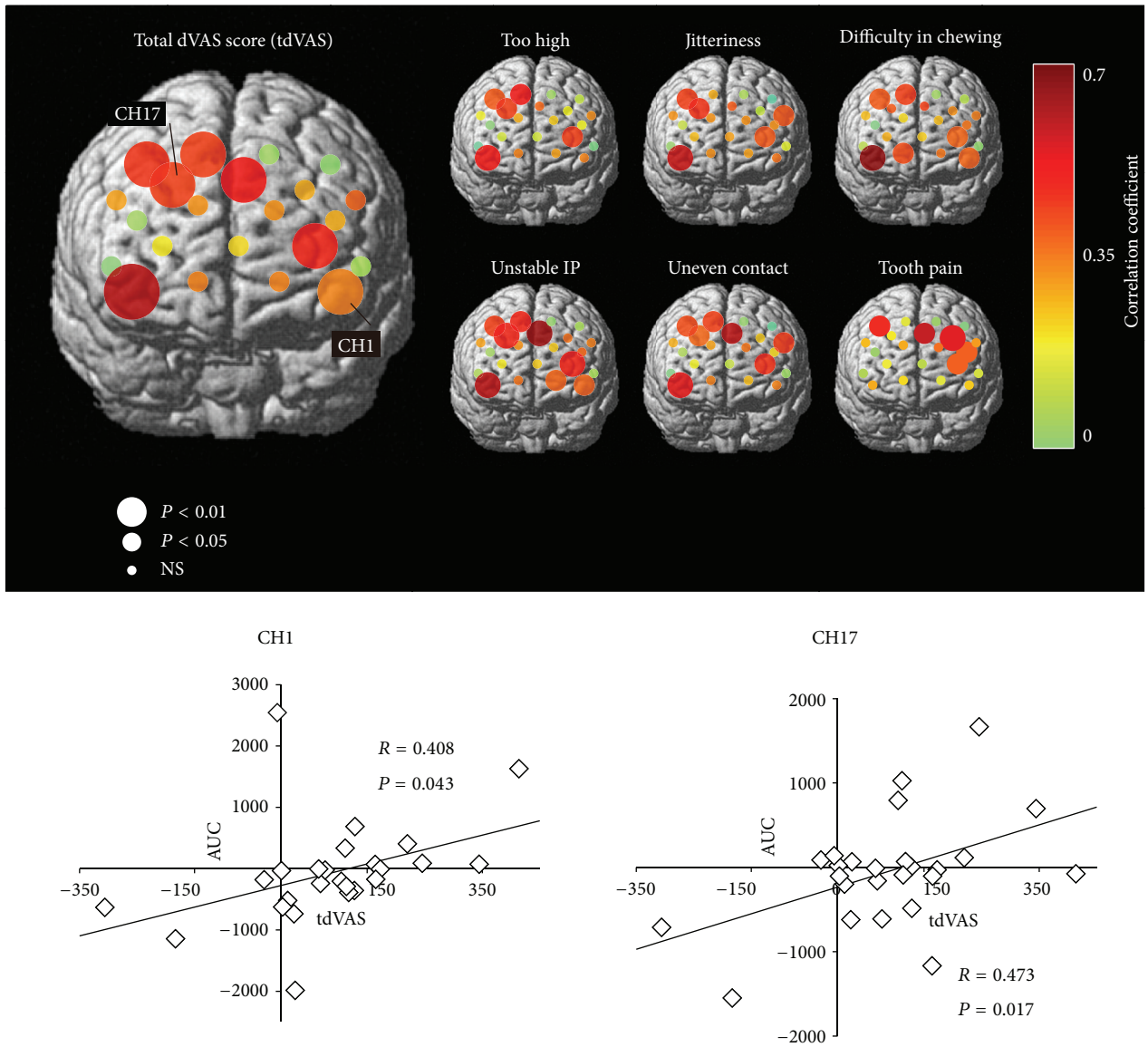

FIGURE 3: Results of channel-based correlation analysis between AUC and VAS scores. Upper panel: large, medium, and small circle diameters indicate P values of less than 0.01, less than 0.05, and equal to or more than 0.05 at the corresponding channel, respectively. The color scale indicates the correlation coefficient. Lower panel: correlated relationship between individual tdVAS scores and AUCs in representative channels. R indicates the correlation coefficient. Spearman's rank correlation coefficient was calculated at channels 3, 8, 9, 10, 13, 14, 15, and 16 because data were not normally distributed. Pearson's correlation test coefficient was calculated for the rest of the channels.

where AUC (CH) indicates the AUC value at channel CH. The standard partial regression coefficients were $\beta = 0.857$, 0.631, and −0.474 for channels 1 ($P < 0.001$), 17 ($P = 0.002$), and 13 ($P = 0.02$), respectively.

3.4. Occlusal Discomfort Associated with Regional Brain Activity in the Right FPC and DLPFC. The statistical analysis of ΔOxy-Hb responses from 13 participants who reported severe or moderate discomfort while grinding metal strips indicated localized regional brain activity in the transitional area of the right FPC and DLPFC (Brodmann areas 10 and 9; Figure 4). The localized activity was closely located around channel 17, whose AUC value showed a significant correlation with perceived severity of discomfort in the individual correlation analysis and was a significant explanatory variable in the multiple-regression analysis. We obtained similar right-lateralized regional brain activity in Brodmann areas 9 and 10 when the participants were further divided into two groups depending on their grinding side and analyzed separately (data not shown). No statistically significant regional brain activity was found in the analysis with the subgroup of participants whose tdVAS scores were less than average ($n = 12$; mild to no discomfort or improved comfort in grinding with metal strips).

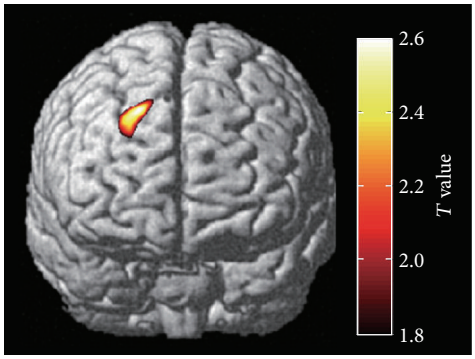

Figure 4: Results of statistical parametrical mapping of 13 participants who reported severe or moderate discomfort while grinding metal strips ($P < 0.05$; uncorrected). The highlighted area corresponds to Brodmann areas 9 and 10 (DLPFC and FPC) in the right hemisphere.

4. Discussion

We used fNIRS to measure prefrontal brain activity accompanying the occlusal discomfort that arose when participants performed grinding with mild occlusal elevation. Canceling out the artifacts related to jaw movement by using differential waveforms between grinding with and without occlusal elevation, we demonstrated a significant relationship between the severity of perceived discomfort and the cumulative hemodynamic responses in the right FPC and DLPFC. These results suggest that fNIRS responses in these prefrontal sites could be good predictors of occlusal discomfort.

Differential hemodynamic responses between two sessions with and without occlusal elevation showed event-related, Gaussian-like responses, confirming that motion artifacts related to the jaw opening and closing were successfully canceled out in most of the channels. The increased ΔOxy-Hb responses associated with decreased ΔdeOxy-Hb responses found in the channels that strongly responded to the grinding behavior in severe perceivers (Figure 2(b)) also show that the differential signals maintain the typical temporal pattern of cerebral hemodynamics. The comparable electromyographic activity between these sessions further suggests that the differential hemodynamic responses represent the sole change in neuronal activity related to somatosensory perception during grinding. Compared with a previously reported noise reduction technique that requires highly complex signal processing [14], our differential method is simple but effective enough to remove the motion- and muscle-originating artifacts in fNIRS signals measured over the forehead region.

Our sensor-level analyses and statistical parametrical mapping consistently showed that the activity in the right FPC and DLPFC correlated well with the severity of occlusal discomfort. Considering that these cortical areas have dense reciprocal connections between the limbic system [15] and respond depending on the cognitive load [6], these results suggest two possible roles of these prefrontal areas, attentional control and self-regulation, in the emotional processing of occlusal discomfort. The decreased hemodynamic activity during the task period in a subgroup of participants who perceived mild to no or improved comfort (Figure 2) may also support this idea because their attention and regulatory activity might be attenuated when they perceive less discomfort when grinding metal strips despite the expectation that they had during the rest period. Using ^{15}O-labelled water PET, Kulkarni et al. [16] compared the regional brain activity in two conditions in which participants were instructed to attend to either the location or the unpleasantness of noxious stimuli of the same intensity. While attention to the stimulus location resulted in the activation of the lateral pain system in the primary somatosensory and inferior parietal cortices, attention to the stimulus unpleasantness modified the neuronal responses to enhance the medial pain system, which includes the limbic system such as the amygdala and hypothalamus, the insula, and the FPC.

A PET study on chemically induced heat allodynia [5] further proposed the involvement of the DLPFC in perceiving "unusual" nociceptive stimulation. When compared with equally intense normal heat pain, heat allodynia involved relatively greater recruitment of the medial thalamic pathways, anterior cingulate cortex, orbitofrontal cortex, and DLPFC, which may convey greater affective reactions. Another intervention study using transcranial magnetic stimulation (TMS) demonstrated that induced activation of the right DLPFC improved response time on a cognitive discrimination task, suggesting enhanced attention and top-down control towards the task [17]. These previous findings demonstrate that increased activity in the FPC and DLPFC represents increased attention to afferent sensory information. Our results suggest that participants who reported high severity paid more attention to the elevated occlusion owing to the strong disturbance caused by modified somatosensory sensations from the oral cavity, resulting in enhanced activation in the prefrontal cortex.

Another important cognitive role of these prefrontal areas is to regulate emotional responses. Beauregard et al. [18] reported the activation of the FPC and the concurrent suppression of the limbic areas when participants voluntarily inhibited their emotion while watching highly arousing film clips. Activation of the DLPFC also works to weaken the perceived intensity and unpleasantness of painful thermal stimulation via dampening subcortical regions involved in pain processing pathways [3, 5]. In a repetitive TMS study that recruited 180 healthy volunteers, Graff-Guerrero et al. [4] demonstrated the selective effect of the right DLPFC activation on increasing pain tolerance. The increased FPC/DLPFC activity found in participants with severe perceived discomfort may represent an adaptive response to dampen the unpleasantness owing to the altered occlusion.

At this stage we are not able to conclude whether this increased prefrontal activity during uncomfortable grinding originates from attentional control or from self-regulatory responses to altered somatosensory feedback. Further study using the same experimental design in patients and in healthy volunteers while experimentally manipulating these

factors would contribute toward revealing the causal factor for the increased prefrontal activity in occlusal discomfort. If the distraction from the oral sensation during grinding attenuates prefrontal activity in healthy participants and if the correlation between perceived severity of discomfort and prefrontal activity was also preserved in patients, the prefrontal activity would likely represent the intensity of attention to the altered occlusion. In this case, the pathology might arise from an altered or reorganized body image in more primary somatosensory processing systems [19]. As most of the patients have a previous history of newly provided dental treatment such as restorations, dentures, and crowns to trigger their symptoms [1], the excessive attention and reinforcement of the altered occlusion might cause reorganization of the cortical sensory maps to convey unnecessarily detailed sensory information that is not normally available to consciousness [20], resulting in the awareness of occlusal discomfort. However, if prefrontal activity works to regulate emotional responses against the uncomfortable occlusion, the relationship may be distorted in patients owing to the lack of emotional regulatory response. Suppressed basal activity in the prefrontal cortex found in patients with orally localized somatoform pain disorder [2] raises the hypothesis that patients with unexplained occlusal discomfort might have some functional deficits in top-down control that usually ameliorates unpleasant somatosensory input and might therefore show low tolerance even to a slight modification of the occlusion. Concurrent measurement of the somatosensory and prefrontal cortices would further reveal the neuronal relationship between primary and higher centers of sensory perception in the pathophysiology of unexplained occlusal discomfort. Manipulating the emotional regulation in healthy participants while grinding metal strips would also contribute to test this hypothesis.

As a pilot study tackling the quantitative evaluation of the neuronal traits associated with occlusal discomfort, the current results have several limitations. First, we had no "pain only" group with which to compare prefrontal activity to differentiate the effect of pain and discomfort, because we included tooth pain as one of the factors of occlusal discomfort. Further research should be conducted to investigate whether the perception of occlusal discomfort and pain shares analogous neuronal mechanisms or not. Second, care should be taken to interpret the prefrontal activity, because the prefrontal cortex responds to variety of emotional and/or cognitive tasks [21], which suggests the possibility that the activity observed in the current study was a secondary emotional response such as negative emotion not specifically related to the occlusal discomfort. A whole-brain investigation including the limbic system and the somatosensory cortices using functional MRI with the same experimental paradigm would further confirm our current result that increased prefrontal activity reflects the perceived intensity of occlusal discomfort. Third, more investigation is required to confirm the conclusion of this study, because the number of participants who fell into the severe group was small. Further experiments would also benefit from the simultaneous measurement of EMG and fNIRS to allow the grinding force to be consistent between conditions and to avoid muscle artifacts in the fNIRS signals that might remain in the differential signals.

5. Conclusions

We demonstrated a positive relationship between the severity of occlusal discomfort and increasing neuronal responses in the right prefrontal cortex. Our active grinding method was capable of capturing the dynamics of the neuronal responses of occlusal discomfort in an event-related manner, which is also applicable to clinical examination. The comparison of the results obtained from symptom-free participants to those with patients would further elucidate the neuronal mechanism of unexplained occlusal discomfort.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Yumie Ono and Goh Kobayashi equally contributed to this paper.

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References

[1] E. S. Hara, Y. Matsuka, H. Minakuchi, G. T. Clark, and T. Kuboki, "Occlusal dysesthesia: a qualitative systematic review of the epidemiology, aetiology and management," *Journal of Oral Rehabilitation*, vol. 39, no. 8, pp. 630–638, 2012.

[2] H. Karibe, R. Arakawa, A. Tateno et al., "Regional cerebral blood flow in patients with orally localized somatoform pain disorder: a single photon emission computed tomography study," *Psychiatry and Clinical Neurosciences*, vol. 64, no. 5, pp. 476–482, 2010.

[3] K. Wiech, M. Ploner, and I. Tracey, "Neurocognitive aspects of pain perception," *Trends in Cognitive Sciences*, vol. 12, no. 8, pp. 306–313, 2008.

[4] A. Graff-Guerrero, J. González-Olvera, A. Fresán, D. Gómez-Martín, J. C. Méndez-Núñez, and F. Pellicer, "Repetitive transcranial magnetic stimulation of dorsolateral prefrontal cortex increases tolerance to human experimental pain," *Cognitive Brain Research*, vol. 25, no. 1, pp. 153–160, 2005.

[5] J. Lorenz, S. Minoshima, and K. L. Casey, "Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation," *Brain*, vol. 126, no. 5, pp. 1079–1091, 2003.

[6] Y. Ono, Y. Nomoto, S. Tanaka et al., "Frontotemporal oxyhemoglobin dynamics predict performance accuracy of dance simulation gameplay: temporal characteristics of top-down and bottom-up cortical activities," *NeuroImage*, vol. 85, pp. 461–470, 2014.

[7] Y. Hoshi, "Functional near-infrared optical imaging: utility and limitations in human brain mapping," *Psychophysiology*, vol. 40, no. 4, pp. 511–520, 2003.

[8] G. Tryde, O. Frydenberg, and N. Brill, "An assessment of the tactile sensibility in human teeth. An evaluation of a quantitative method," *Acta Odontologica Scandinavica*, vol. 20, pp. 233–256, 1962.

[9] M. J. G. M. Kloprogge, "Reflex control of the jaw muscles by stimuli from receptors in the periodontal membrane," *Journal of Oral Rehabilitation*, vol. 2, no. 3, pp. 259–272, 1975.

[10] M. Funakoshi and N. Amano, "Periodontal jaw muscle reflexes in the albino rat," *Journal of Dental Research*, vol. 53, no. 3, pp. 598–605, 1974.

[11] D. Ichikawa, "The effect of experimental occlusal interference on electroencephalograms by comparing psychophysiological response and masticatory muscle activity," *The Journal of the Japan Prosthodontic Society*, vol. 45, pp. 305–314, 2001.

[12] J. C. Ye, S. Tak, K. E. Jang, J. Jung, and J. Jang, "NIRS-SPM: statistical parametric mapping for near-infrared spectroscopy," *NeuroImage*, vol. 44, no. 2, pp. 428–447, 2009.

[13] F. Scholkmann, U. Gerber, M. Wolf, and U. Wolf, "End-tidal CO_2: an important parameter for a correct interpretation in functional brain studies using speech tasks," *NeuroImage*, vol. 66, pp. 71–79, 2013.

[14] N. Narita, K. Kamiya, K. Yamamura, S. Kawasaki, T. Matsumoto, and N. Tanaka, "Chewing-related prefrontal cortex activation while wearing partial denture prosthesis: pilot study," *Journal of Prosthodontic Research*, vol. 53, no. 3, pp. 126–135, 2009.

[15] A. F. T. Arnsten and K. Rubia, "Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 51, no. 4, pp. 356–367, 2012.

[16] B. Kulkarni, D. E. Bentley, R. Elliott et al., "Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems," *European Journal of Neuroscience*, vol. 21, no. 11, pp. 3133–3142, 2005.

[17] M.-A. Vanderhasselt, R. de Raedt, C. Baeken, L. Leyman, P. Clerinx, and H. D'haenen, "The influence of rTMS over the right dorsolateral prefrontal cortex on top-down attentional processes," *Brain Research*, vol. 1137, no. 1, pp. 111–116, 2007.

[18] M. Beauregard, J. Lévesque, and P. Bourgouin, "Neural correlates of conscious self-regulation of emotion," *The Journal of Neuroscience*, vol. 21, no. 18, Article ID RC165, 2001.

[19] C. Xerri, "Imprinting of idyosyncratic experience in cortical sensory maps: neural substrates of representational remodeling and correlative perceptual changes," *Behavioural Brain Research*, vol. 192, no. 1, pp. 26–41, 2008.

[20] W. Rief and A. J. Barsky, "Psychobiological perspectives on somatoform disorders," *Psychoneuroendocrinology*, vol. 30, no. 10, pp. 996–1002, 2005.

[21] S. M. Szczepanski and R. T. Knigh, "Insights into human behavior from lesions to the prefrontal cortex," *Neuron*, vol. 3, no. 5, pp. 1002–1018, 2014.

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Research Article

Chewing Prevents Stress-Induced Hippocampal LTD Formation and Anxiety-Related Behaviors: A Possible Role of the Dopaminergic System

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The present study examined the effects of chewing on stress-induced long-term depression (LTD) and anxiogenic behavior. Experiments were performed in adult male rats under three conditions: restraint stress condition, voluntary chewing condition during stress, and control condition without any treatments except handling. Chewing ameliorated LTD development in the hippocampal CA1 region. It also counteracted the stress-suppressed number of entries to the center region of the open field when they were tested immediately, 30 min, or 60 min after restraint. At the latter two poststress time periods, chewing during restraint significantly increased the number of times of open arm entries in the elevated plus maze, when compared with those without chewing. The *in vivo* microdialysis further revealed that extracellular dopamine concentration in the ventral hippocampus, which is involved in anxiety-related behavior, was significantly greater in chewing rats than in those without chewing from 30 to 105 min after stress exposure. Development of LTD and anxiolytic effects ameliorated by chewing were counteracted by administering the D1 dopamine receptor antagonist SCH23390, which suggested that chewing may activate the dopaminergic system in the ventral hippocampus to suppress stress-induced anxiogenic behavior.

1. Introduction

Chewing has been known as one of the active coping strategies to suppress stress. We have previously shown that chewing during stress exposure significantly attenuates neuronal responses to stress and the subsequent stress-related cognitive deficits in the hippocampus, such as impairment of spatial memory [1, 2]. Stress-induced changes in neuronal electrical properties in the hippocampus not only contribute to memory functions, but also mediate anxiety behavior [3, 4]; the hippocampus is a key region to express stress- and anxiety-related behaviors *via* its reciprocal connection with the amygdala and the prefrontal cortex [5]. In addition to its possible role in memory formation with counterpart phenomenon, long-term potentiation, hippocampal long-term depression (LTD) has been suggested to have a correlation with anxiety behavior [6]. Therefore, it is intriguing to investigate whether chewing under stressful conditions could interfere with stress-induced LTD and corresponding anxiety-like behavior. The present electrophysiological study evaluated the effects of spontaneous chewing during exposure to restraint stress on stress-related LTD development in the rat hippocampal CA1 region. We also used two measures of anxiety-like behaviors, exploration in a novel open field and an elevated plus maze, to determine time-course changes in stress-induced anxiety-like behavior in rats that were stressed with or without coping. We also incorporated *in vivo* microdialysis analysis to measure monoaminergic

signals in the hippocampus that relate to different anxiety-like behaviors found in rats depending on their coping styles [7]. Finally, we tested whether the pharmacological inhibition of the dopaminergic D1 receptor could counteract the effect of chewing in hippocampal LTD and in anxiety-like behavior. These results helped to determine the possible role of the dopaminergic signaling pathway in the mechanism of how chewing interacts with hippocampal synaptic plasticity to suppress stress-induced anxiety-like behavior.

2. Materials and Methods

2.1. Animals. Ten-week-old male Sprague-Dawley rats were maintained in a temperature-controlled room ($22 \pm 3^{\circ}$C) with a 12 h light/dark cycle (lights on at 7:00 a.m.). The rats had free access to water and food. All experiments were in accordance with the guidelines for Animal Experimentation of Kanagawa Dental University. All efforts were made to minimize the number of animals used and their suffering.

2.2. Stress Protocol and Drug Administration. To produce restraint stress, we tied a rat to a wooden board in a spread-eagle supine position for 30 min using leg fasteners as previously described [8]. Rats were randomly assigned to one of the three conditions of (1) stressed (ST), (2) stressed and chewing (SC), and (3) control (CT). Rats in group ST were restrained and left alone for the entire restraint period, and those in group SC were allowed to chew on a wooden stick (diameter, 5 mm) that was placed near the animal's mouth during restraint. Every rat in group SC responded to the wooden stick by chewing on it with a rapid and repetitive sequence of jaw opening and closing movements for at least two-thirds of the total restraint period. Rats in group CT were handled in the same manner as those in group ST and group SC but were returned to their home cage for 30 min instead of restraint. Some of the rats in group SC were administered intraperitoneal injections of 0.3 mg/kg SCH23390, a selective dopaminergic D1-receptor antagonist that penetrates the blood-brain barrier [9], which was dissolved in 0.9% saline 15 min prior to the stress protocol. All stress inducement and handling manipulations were performed between 9:00 a.m. and 11:00 a.m.

2.3. Electrophysiology. A total of 21 rats were used in the LTD experiment. Six rats were assigned to each group of CT, ST, and SC, respectively, and the remaining three rats were assigned to group SC+SCH23390. Immediately after the stress protocol, we anesthetized rats with 2-bromo-2-chloro-1,1,1-trifluoroethane (300 μL/100 g; Takeda Chemical Industries, Osaka, Japan), decapitated them, quickly removed their brains, and iced them in artificial cerebrospinal fluid (ACSF) containing 119 NaCl, 2.5 KCl, 26.2 $NaHCO_3$, 1 NaH_2PO_4, 1.3 $MgSO_4$, 2.5 $CaCl_2$, and 11 glucose (in mM, bubbled with 95% O_2–5% CO_2). We dissected the hippocampi, embedded them in agar blocks for slicing, cut transverse slices (450 μm thick) with a vibrating tissue slicer (Dosaka, Kyoto, Japan), and transferred them to a holding chamber at room temperature (25°C). We allowed the slices to recover for at least 60 min and then transferred them to an immersion-type recording chamber perfused at 1 mL/min with ACSF containing 0.1 mM picrotoxin (Sigma-Aldrich, Tokyo, Japan) at room temperature. To prevent epileptiform discharge of pyramidal neurons, we made a cut at the border between the CA1 and CA3 areas. A glass pipette filled with 3 M NaCl and positioned in the stratum radiatum of the CA1 area recorded the field excitatory postsynaptic potential (fEPSP). Bipolar stainless-steel electrodes (World Precision Instruments, Sarasota, FL, USA) placed in the stratum radiatum on opposite sides of the recording pipette stimulated the Schaffer collateral branches. We adjusted the intensity of fEPSP in the baseline period to around 50% of the maximal response and then recorded stable baseline fEPSP activity by applying a 40 μs voltage pulse at the determined intensity every 30 s for at least 10 min. LTD was induced by low-frequency stimulation (LFS) of 900 pluses at 1 Hz (15 min). All signals were filtered at 2 kHz using a low-pass Bessel filter and digitized at 5 kHz using a MultiClamp 700A interface running pCLAMP software (Axon Instruments, Union City, CA, USA). We measured initial slopes of the fEPSP and normalized them to the average of the values measured over the baseline period. The average slope size of the fEPSPs recorded between 30 and 40 min after the end of the LFS provided the basis for our statistical comparisons. We used a single slice from a single animal for subsequent analysis.

2.4. Open-Field Test (OFT) and Elevated Plus Maze Test (EPT). Eighty-nine and 87 rats were used in the OFT and EPT experiments, respectively. OFT and EPT were performed in a sound-isolated room to analyze anxiety-related behavior in a novel environment [10]. The open field consisted of a circular arena (150 cm in diameter) surrounded by walls 40 cm in height. A video camera (DCR-HC1000, Sony, Tokyo, Japan) was suspended from the ceiling above the arena to observe and record animal behavior. The field was constantly illuminated with an intense light (600 Lx at the floor of the arena). The animals in their home cage were brought into the experimental room at least 1 h before the beginning of the first trial of the day to acclimatize.

At the beginning of the OFT, the rat was placed at the center of the arena. The field was divided into two subdivisions of center (75 cm in diameter) and peripheral areas for scoring ambulatory activity. Rats were allowed to freely explore the arena for 5 min. The number of entrances into the subdivisions was recorded using a video tracking system (Top Scan, Clever Sys, Reston, VA, USA) as parameters for OFT. An entrance to a subdivision was counted if the center of gravity of the rat body passed through the border of the subdivision from outside to inside. After the completion of each trial, the animal was returned to the home cage and the field was cleaned with 30% ethanol.

The elevated plus maze had dimension of 1,100 mm in width and length. The corridors were 500 mm in length and 100 mm in width, and everything was raised 500 mm above the floor. Two facing corridors were closed by walls 450 mm in height (closed arms), and the rest remained open (open arms). The rat was initially placed at the center of the maze facing the open arm and was allowed to freely explore the maze for 5 min. The number of entrances to the open arm

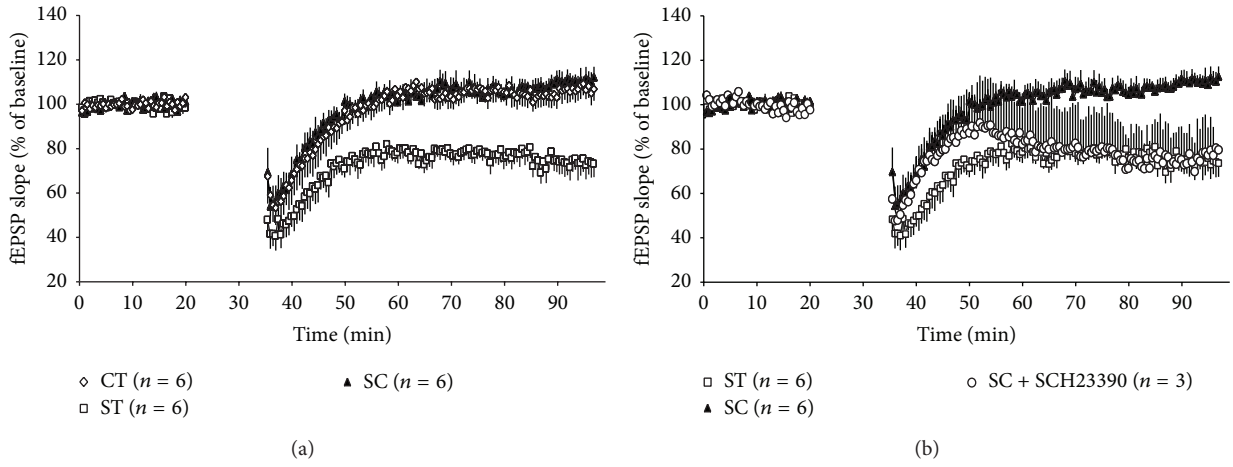


Figure 1: Effects of acute stress and SCH23390 on hippocampal CA1 LTD. (a) Time course of mean fEPSP slopes for different experimental groups. CT, ST, and SC refer to rats in the control, stressed, and stressed-with-chewing groups, respectively, without SCH23390 administration. LFS was applied during 20–35 min to induce LTD. (b) Time course of mean fEPSP slopes for SCH23390-treated SC groups (SC+SCH23390). Data from groups ST and SC were taken from (a) and superimposed for the comparison.

was measured for scoring anxiety behavior. The entrance to the open arm was counted if the center of gravity of the rat body passed through the border of the open arm from the center of the maze. After completion of each trial, the animal was returned to the home cage and the field was cleaned with 30% ethanol.

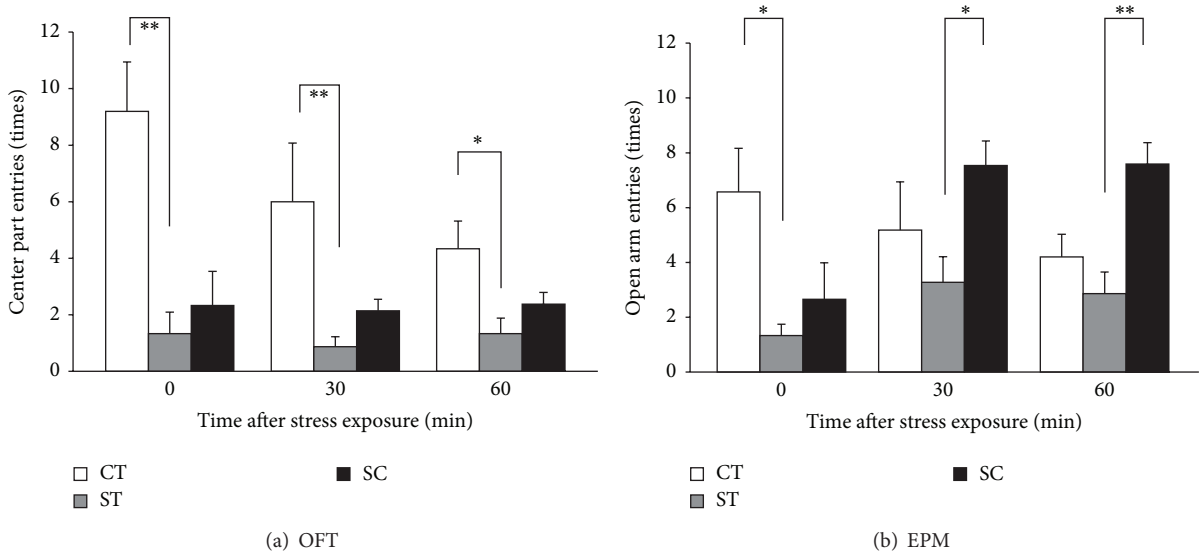
Rats were tested in either OFT or EPM at 0, 30, and 60 min after stress exposure. Fifty-one rats were administered SCH23390 and tested at 60 min after stress exposure.

2.5. Microdialysis. Concentrations of norepinephrine (NE), dopamine (DA), and serotonin (5-HT) were determined in the right ventral hippocampus (5.0 mm posterior, 5.0 mm lateral, and 3.0 mm inferior from the bregma) and were measured in an additional group of 15 rats. The ventral hippocampus was chosen because of its specific role in regulating anxiety-related behavior [11]. These rats were first implanted with a dialysis guide cannula with a dummy probe and divided into two subgroups that were treated in an identical fashion to the ST ($n = 7$) and SC ($n = 8$) groups after recovery of 4–6 days. Food and water were freely provided by the time of microdialysis measurement, and the rats were housed individually after probe implantation. On the day of stress exposure, a dialysis probe (A-I-8-02, Eicom, Kyoto, Japan) was inserted into the guide cannula instead of the dummy probe. The dialysis tube was directly connected to a high-performance liquid chromatography apparatus (Eicom, Kyoto, Japan) for online analysis of NE, DA, and 5-HT. A microperfusion pump perfused the hippocampus with normal Ringer's solution (147 mM NaCl, 4 mM KCl, 2.3 mM $CaCl_2$) through the dialysis tube at a flow rate of 1 mL/min. The dialysis sample was injected every 15 min *via* auto-injector (EAS-20, Eicom, Kyoto, Japan). The mobile phase consisted of 99% 0.1 M sodium phosphate-buffered solution, 1% methanol, 500 mg/L sodium 1-decanesulfonate, and 50 mg/L Na_2-EDTA. NE, DA, and 5-HT were separated on a 30 mm × 4.6 mm diameter Eicompack CAX column at 35°C. The working electrode (HTEC-500; Eicom, Kyoto, Japan) was composed of graphite, and the flow rate was set at 250 mL/min. Concentrations of NE, DA, and 5-HT were measured using known concentrations of the corresponding standard, which were quantified by means of the peak area ratio. All chemicals and drugs used as corresponding standards and the internal standard were purchased from Sigma (Tokyo, Japan). Chromatograms were obtained using the appropriate software (Power Chrom version 2; eDAQ Pty.).

2.6. Statistics. All values shown are mean ± S.E.M. Statistical analysis was conducted using IBM SPSS Statistics 21 (IBM, Armonk, NY, USA) and R [12]. We compared values using the one-way analysis of variance (ANOVA) test with post hoc Tukey's multiple comparisons or the Kruskal-Wallis test and the following pairwise comparisons depending on normality of the data. Because microdialysis data were repeated measures from animals in either condition of ST of SC, a two-way ANOVA with repeated measures and the post hoc multiple comparisons with Bonferroni correction were applied. We consider P values < 0.05 to be statistically significant, unless otherwise stated.

3. Results

3.1. Chewing Rescued Stress-Related LTD. In agreement with earlier findings [6, 13], LTD was not induced in control rats, but in stressed rats (Figure 1(a)). Chewing rescued stress-induced formation of LTD. The average slope size of fEPSPs was significantly suppressed in group ST (77.9 ± 3.3%) compared with group CT (105.2 ± 4.6%) and group SC (106.4 ± 4.8%; $F(2, 17) = 14.11$, $P < 0.001$). These results suggested an ameliorative effect of chewing on stress-related induction of LTD in the adult hippocampus. Administration of SCH23390 counteracted the effect of chewing in group SC. Blockage of dopaminergic neurotransmission during stress exposure and chewing decreased a late phase of fEPSP slope and induced LTD (Figure 1(b)).



(a) OFT (b) EPM

Figure 2: Effects of acute stress and chewing on poststress exploratory behavior in different durations after stress exposure. (a) The number of entries to the center region of the OFT. The number of animals used was n = (0 min: 5, 6, 6), (30 min: 5, 8, 7), and (60 min: 9, 9, 8) after stress exposure in the (CT, ST, and SC) groups, respectively. (b) Number of entries to the open arm of the EPM. The number of animals used was n = (0 min: 5, 6, 6), (30 min: 5, 8, 7), and (60 min: 9, 8, 8) after stress exposure in the (CT, ST, and SC) groups, respectively. Asterisks indicate statistically significant differences ($^{*}P < 0.05$, $^{**}P < 0.01$).

3.2. Chewing Rescued Anxiety Behavior and Facilitated Poststress Exploratory Activity. OFT results (Figure 2(a)) showed that restraint stress significantly reduced the number of entries to the center region in group ST (1.3 ± 0.8 times; $P < 0.017$), but not in group SC (2.3 ± 1.2 times), compared with group CT (9.2 ± 1.7 times; Kruskal-Wallis chi-squared = 8.90) immediately after stress. The suppressed number of entries to the center region in group ST lasted for at least 1 h (0.9 ± 0.4 and 1.3 ± 0.6 times at 30 and 60 min from stress exposure, resp., $P = 0.005$ and 0.026 in group ST, resp.). These results indicated acute restraint stress suppressed exploratory activity, which was counteracted by active coping with chewing.

The number of open arm entries in the EPM (Figure 2(b)) also demonstrated a stress-related decrease in the number of entries to the open arm in group ST (1.3 ± 0.4 times; $P = 0.02$) but not in group SC (2.7 ± 1.3 times), compared with group CT (6.6 ± 1.6 times; $F(2, 16) = 5.10$, $P = 0.022$) immediately after stress. However, the suppressed number of entries to the open arm recovered at 30 min after stress exposure. Interestingly, group SC rats exhibited more open arm entries after stress exposure compared with group ST at 30 min (7.8 ± 0.9 versus 3.3 ± 0.9 times; $P < 0.034$) and at 60 min (7.6 ± 0.8 versus 2.9 ± 0.8 times; $P = 0.006$) after stress. Note that the mean number of open arm entries in group SC was larger than in group CT in these two poststress timings, although they did not reach statistical significance. These results suggest an anxiolytic effect of chewing under stress.

3.3. Chewing Increased Poststress Hippocampal DA Concentrations. There was a statistically significant interaction between time and group in the time-course change of NE and DA concentrations in the ventral hippocampus, but not in 5-HT concentrations. The post hoc multiple comparisons found significant differences between groups ST and SC in NE concentrations at 195 and 225 min after stress exposure, respectively (Figure 3(a)), and those in DA concentrations from 30 to 105 min after stress exposure, respectively (Figure 3(b)). The time in which DA concentration significantly increased in group SC overlapped with the time in which rats from the same group exhibited significantly increased exploratory behavior in the EPM (30 and 60 min after stress exposure, resp.).

3.4. Antagonizing DA Transmission Inhibited the Anxiolytic Effect of Chewing. The synchronous increase in hippocampal DA concentrations and exploratory behavior further motivated us to investigate the role of dopaminergic transmission on the anxiolytic effect of chewing. As expected, systemic administration of SCH23390 suppressed the effect of chewing during exploratory activity at 60 min after stress exposure (Figure 4). There was no statistically significant difference among groups in the number of entries to the center region of the OFT and in those to the open arm in the EPM.

4. Discussion

The key finding of the present study is that active coping to restraint stress by chewing prevented stress-induced LTD in the adult male hippocampus, as well as poststress anxiety-like behavior. The development of the anxiolytic effect by chewing coincided with increased DA concentrations in the ventral hippocampus, which plays an important role in regulating anxiety-related behavior [11]. Pharmacological blockage of the dopaminergic D1-receptor counteracted the effect of chewing, both on LTD and on anxiety behaviors.

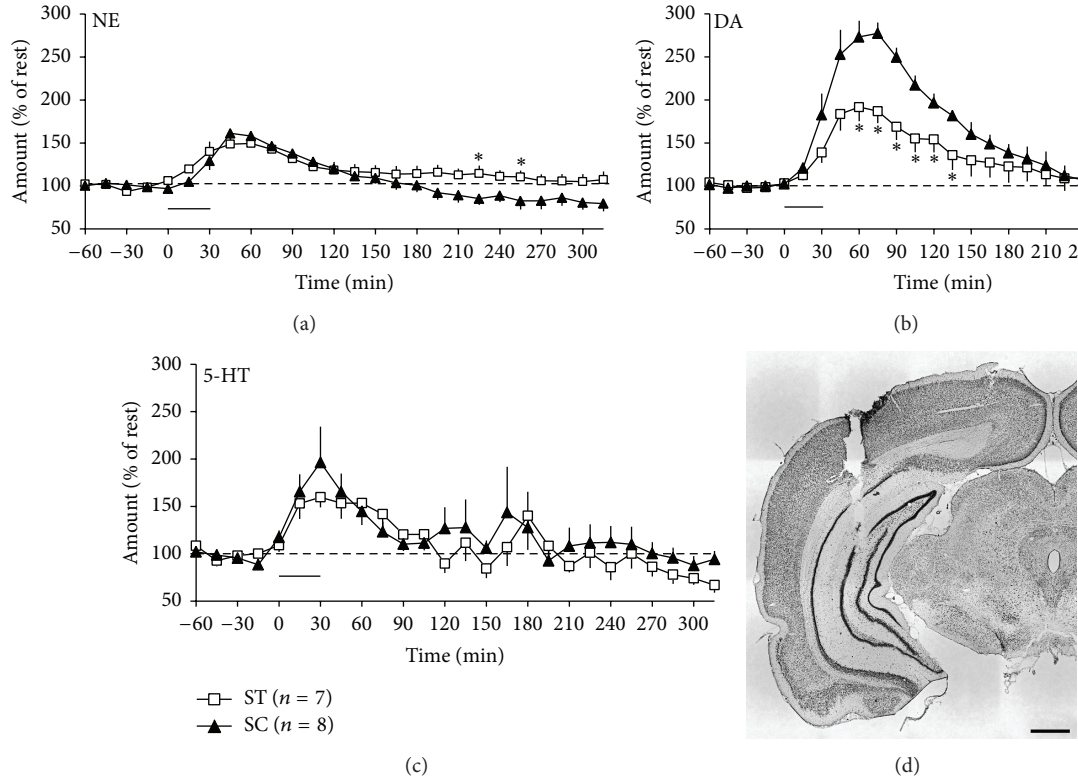


Figure 3: Effects of acute stress and chewing on concentration changes of norepinephrine (a), dopamine (b), and serotonin (c) in the ventral hippocampus. The thick horizontal bar indicates exposure to restraint stress. Asterisks indicate statistically significant differences ($P < 0.05$). (d) A representative brain slice showing the tract of microdialysis probe. Postmortem brain slices of all tested rats were Nissl stained to confirm the microdialysis tract in the ventral hippocampus and were analyzed using a light microscope. Scale bar equals 1 mm.

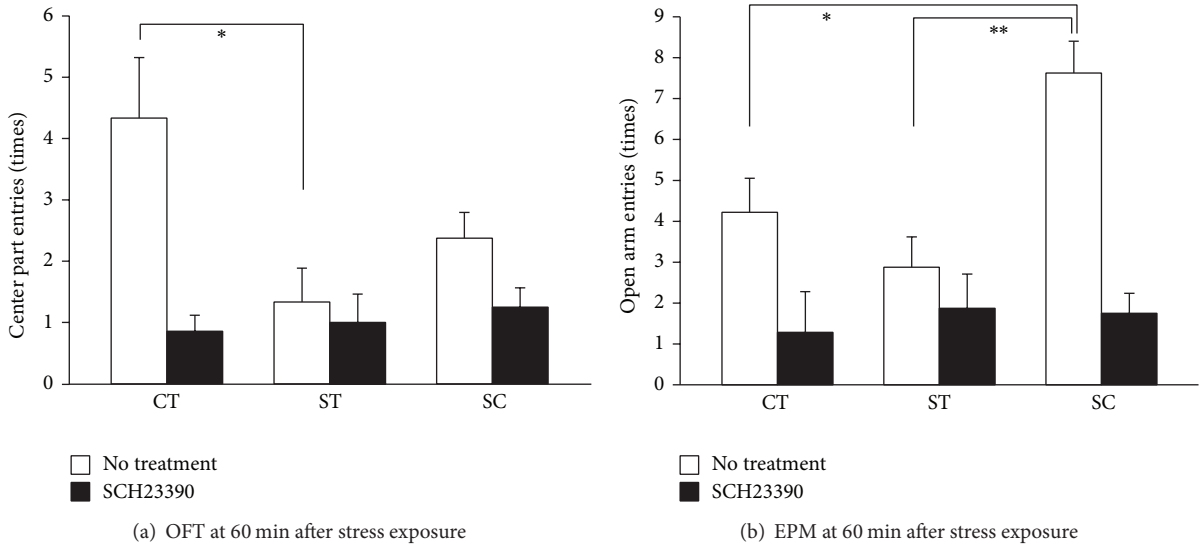


Figure 4: Effect of SCH23390 on exploratory behavior at 60 min after stress exposure. The number of animals administered SCH23390 (0.3 mg/kg i.p.) was $n = (9, 9, 8)$ in the OFT and (9, 8, 8) in the EPM for (CT, ST, and SC) groups, respectively. Data of "no treatment" were taken from Figure 2 and shown for comparison. Asterisks indicate statistically significant differences ($^{*}P < 0.05$, $^{**}P < 0.01$).

These results suggest an ameliorative effect of chewing on stress-induced anxiety-like behavior *via* activation of the hippocampal dopaminergic signaling pathway.

Yang et al. [14] reported that stress facilitates LTD induction in adult rats, which is mediated through the activation of glucocorticoid receptors to affect extrasynaptic NR2B-containing NMDARs to undergo the induction of LTD. The present results confirmed the effect of stress to induce hippocampal LTD in adult rats (Figure 1(a)). Mockett et al. [15] further demonstrated that dopamine D1/D5 receptor activation counteracts NMDAR-dependent LTD, which is also consistent with our results showing that blockade of D1-receptor activation impaired the effect of chewing in rats that normally chewed during stress exposure (Figure 1(b)). The present results suggest that both a reduction in glucocorticoid plasma concentration [16] and facilitation of neuronal DA concentrations in the hippocampus are essential to prevent hippocampal LTD development in rats that chewed during stress exposure.

Our previous studies in rats demonstrated that chewing relieves stress by suppressing stress responses in endocrine and autonomic nervous systems. Active chewing during stress exposure suppresses metabolic activity in the hypothalamus [16], the higher control center of systemic stress response, to prevent stress-related secretion of corticosterone and norepinephrine in plasma [8, 16, 17]. We have also previously found a possible involvement of histaminergic neuronal pathways to rescue stress-suppressed long-term potentiation in hippocampal neurons [18]. The current study further added a novel role of chewing in preventing stress-related anxiety behavior, possibly mediated by facilitating dopaminergic systems. The accumulating results suggest that chewing involves both direct hormonal effects and indirect neuronal mechanisms of the neural monoaminergic system to rescue NMDAR functions.

The dopaminergic system is essentially involved in rhythmic movement, including mastication [19, 20]. Reduced masticatory activity by molar extraction or powder-diet feeding reduces the response of hippocampal DA neurons, impairing hippocampal learning ability in the step-through passive avoidance test [21] and in the novel-object recognition test [22]. Results from the present study using microdialysis further demonstrated that active mastication facilitates DA release in the hippocampus (Figure 3). These results suggest a possible interaction between masticatory function and cognitive function in the hippocampus *via* modulation of DA responses. The late development of LTD in SCH23390-treated rats in group SC (Figure 1(b)) also supports the involvement of the DA pathway, because dopaminergic projection is essential for settlement of long-term plasticity in the hippocampus [23].

A limitation of this study was that we did not specifically block D1 receptors in the ventral hippocampus but used systemic administration of D1 receptor antagonists, which may act in different regions of the brain and affect exploratory behavior. These results were consistent with a previous report that systemic D1-antagonism reduces spatial exploration in a novel environment [9]. However, it would not affect the interpretation of the results that increased DA concentration in the ventral hippocampus by chewing is critical for preventing anxiety-like behavior, because intra-ventral hippocampal administration of SCH23390 itself has no modulatory effect on exploratory behavior and anxiety-like behavior [24, 25]. Further research is required to resolve the above methodological interference and confirm the results that we found in the current study.

5. Conclusions

Chewing during stress exposure could be an active coping strategy to relieve stress-induced anxiety-like behavior in rats. Behavioral examinations in various poststress time periods demonstrated a significant anxiolytic effect with chewing in stressed rats at 30 and 60 min after stress exposure, which corresponds with enhanced dopamine release in the ventral hippocampus. These results indicate possible involvement of the dopaminergic neuronal pathway in the stress-relieving mechanism of chewing.

Conflict of Interests

All authors declare no conflict of interests regarding the publication of this paper.

Acknowledgments

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References

[1] Y. Ono, T. Yamamoto, K.-Y. Kubo, and M. Onozuka, "Occlusion and brain function: mastication as a prevention of cognitive dysfunction," *Journal of Oral Rehabilitation*, vol. 37, no. 8, pp. 624–640, 2010.

[2] S. Miyake, G. Yoshikawa, K. Yamada et al., "Chewing ameliorates stress-induced suppression of spatial memory by increasing glucocorticoid receptor expression in the hippocampus," *Brain Research*, vol. 1446, pp. 34–39, 2012.

[3] J. J. Kim, M. R. Foy, and R. F. Thompson, "Behavioral stress modifies hippocampal plasticity through N-methyl-D-aspartate receptor activation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 10, pp. 4750–4753, 1996.

[4] W.-P. Ma, J. Cao, M. Tian et al., "Exposure to chronic constant light impairs spatial memory and influences long-term depression in rats," *Neuroscience Research*, vol. 59, no. 2, pp. 224–230, 2007.

[5] B. Leuner and T. J. Shors, "Stress, anxiety, and dendritic spines: what are the connections?" *Neuroscience*, vol. 251, pp. 108–119, 2013.

[6] K. Martinowich, R. J. Schloesser, Y. Lu et al., "Roles of p75 NTR, long-term depression, and cholinergic transmission in anxiety

and acute stress coping," *Biological Psychiatry*, vol. 71, no. 1, pp. 75–83, 2012.

[7] D. A. Zhukov and K. P. Vinogradova, "Learned helplessness or learned inactivity after inescapable stress? Interpretation depends on coping styles," *Integrative Physiological and Behavioral Science*, vol. 37, no. 1, pp. 35–43, 2002.

[8] Y. Ono, T. Kataoka, S. Miyake et al., "Chewing ameliorates stress-induced suppression of hippocampal long-term potentiation," *Neuroscience*, vol. 154, no. 4, pp. 1352–1359, 2008.

[9] B. Clausen, T. R. Schachtman, L. T. Mark, M. Reinholdt, and G. R. J. Christoffersen, "Impairments of exploration and memory after systemic or prelimbic D1-receptor antagonism in rats," *Behavioural Brain Research*, vol. 223, no. 2, pp. 241–254, 2011.

[10] V. Carola, F. D'Olimpio, E. Brunamonti, F. Mangia, and P. Renzi, "Evaluation of the elevated plus-maze and open-field tests for the assessment of anxiety-related behaviour in inbred mice," *Behavioural Brain Research*, vol. 134, no. 1-2, pp. 49–57, 2002.

[11] K. G. Kjelstrup, F. A. Tuvnes, H.-A. Steffenach, R. Murison, E. I. Moser, and M.-B. Moser, "Reduced fear expression after lesions of the ventral hippocampus," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 16, pp. 10825–10830, 2002.

[12] R Development Core Team, *R: A Language and Environment for Statistical Computing*, R Foundation for Statistical Computing, Vienna, Austria, 2011, http://www.R-project.org/.

[13] J. J. Wagner and B. E. Alger, "GABAergic and developmental influences on homosynaptic LTD and depotentiation in rat hippocampus," *Journal of Neuroscience*, vol. 15, no. 2, pp. 1577–1586, 1995.

[14] C.-H. Yang, C.-C. Huang, and K.-S. Hsu, "Behavioral stress enhances hippocampal CA1 long-term depression through the blockade of the glutamate uptake," *The Journal of Neuroscience*, vol. 25, no. 17, pp. 4288–4293, 2005.

[15] B. G. Mockett, D. Guévremont, J. M. Williams, and W. C. Abraham, "Dopamine D1/D5 receptor activation reverses NMDA receptor-dependent long-term depression in rat hippocampus," *Journal of Neuroscience*, vol. 27, no. 11, pp. 2918–2926, 2007.

[16] Y. Ono, H.-C. Lin, K.-Y. Tzen et al., "Active coping with stress suppresses glucose metabolism in the rat hypothalamus," *Stress*, vol. 15, no. 2, pp. 207–217, 2012.

[17] S. Koizumi, S. Minamisawa, K. Sasaguri, M. Onozuka, S. Sato, and Y. Ono, "Chewing reduces sympathetic nervous response to stress and prevents poststress arrhythmias in rats," *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 301, no. 4, pp. H1551–H1558, 2011.

[18] Y. Ono, T. Kataoka, S. Miyake, K. Sasaguri, S. Sato, and M. Onozuka, "Chewing rescues stress-suppressed hippocampal long-term potentiation via activation of histamine H1 receptor," *Neuroscience Research*, vol. 64, no. 4, pp. 385–390, 2009.

[19] S. H. Chandler and L. J. Goldberg, "Differentiation of the neural pathways mediating cortically induced and dopaminergic activation of the central pattern generator (CPG) for rhythmical jaw movements in the anesthetized guinea pig," *Brain Research*, vol. 323, no. 2, pp. 297–301, 1984.

[20] N. P. Lapointe, P. Rouleau, R.-V. Ung, and P. A. Guertin, "Specific role of dopamine D1 receptors in spinal network activation and rhythmic movement induction in vertebrates," *The Journal of Physiology*, vol. 587, part 7, pp. 1499–1511, 2009.

[21] S. Kushida, K. Kimoto, N. Hori et al., "Soft-diet feeding decreases dopamine release and impairs aversion learning in Alzheimer model rats," *Neuroscience Letters*, vol. 439, no. 2, pp. 208–211, 2008.

[22] M. Kawahata, Y. Ono, A. Ohno, S. Kawamoto, K. Kimoto, and M. Onozuka, "Loss of molars early in life develops behavioral lateralization and impairs hippocampus-dependent recognition memory," *BMC Neuroscience*, vol. 15, article 4, 2014.

[23] J. E. Lisman and A. A. Grace, "The hippocampal-VTA loop: controlling the entry of information into long-term memory," *Neuron*, vol. 46, no. 5, pp. 703–713, 2005.

[24] M. Nasehi, F. Kafi, and M.-R. Zarrindast, "Differential mechanisms of opioidergic and dopaminergic systems of the ventral hippocampus (CA_3) in anxiolytic-like behaviors induced by cholestasis in mice," *European Journal of Pharmacology*, vol. 714, no. 1–3, pp. 352–358, 2013.

[25] M. R. Zarrindast, N. Naghdi-Sedeh, M. Nasehi, H. Sahraei, F. Bahrami, and F. Asadi, "The effects of dopaminergic drugs in the ventral hippocampus of rats in the nicotine-induced anxiogenic-like response," *Neuroscience Letters*, vol. 475, no. 3, pp. 156–160, 2010.

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Research Article

Effects of Mandibular Retrusive Deviation on Prefrontal Cortex Activation: A Functional Near-Infrared Spectroscopy Study

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The objective of this study was to evaluate occlusal condition by assessing brain activity in the prefrontal cortex, which is associated with emotion. Functional near-infrared spectroscopy (fNIRS) was used to detect changes in cerebral blood flow in the prefrontal cortex of 12 healthy volunteers. The malocclusion model was a custom-made splint that forced the mandible into retrusion. A splint with no modification was used as a control. The cortical activation during clenching was compared between the retrusive position condition and the control condition. A visual analog scale score for discomfort was also obtained during clenching and used to evaluate the interaction between fNIRS data and psychiatric changes. Activation of the prefrontal cortex was significantly greater during clenching in the mandibular retrusive condition than during clenching in the control condition. Furthermore, Spearman rank-correlation coefficient revealed a parallel relation between prefrontal cortex activation and visual analog scale score for discomfort. These results indicate that fNIRS can be used to objectively evaluate the occlusal condition by evaluating activity in the prefrontal cortex.

1. Introduction

Some studies have reported that occlusal dysfunction affects the stress response via changes in brain activity and leads to nonoral health problems [1–6]. We have often seen the mandibular retrusive condition that is one form of malocclusal condition in dental practice. And that malocclusal condition is often caused by inappropriate dental treatment. Our previous functional magnetic resonance imaging (fMRI) studies have suggested that mandibular retrusion affects the emotional state of brain regions [1, 2]. In addition, prefrontal cortex (PFC) activity correlates with the severity of malocclusion. In this respect, measuring brain activity could provide an objective measure of occlusal dysfunction in humans.

Current methods used to measure brain activity in medical and clinical research include positron emission tomography, magnetoencephalography, fMRI, and functional near-infrared spectroscopy (fNIRS). These neuroimaging techniques have also been used in the field of dentistry to study the effects of various oral conditionson the brain [1, 2, 7, 8]. However, the results of these researches have yet to be translated into clinical dental applications, as the above-mentioned systems are often expensive and difficult to operate and fMRI and magnetoencephalography require the patient's head to be secured and the patient's posture to be limited. However, fNIRS is a noninvasive technique that measures brain activity via changes in cerebral blood flow (mainly in the cerebral cortex) by monitoring hemoglobin concentration using near-infrared light [9]. fNIRS devices

can be miniaturized to suit specific purposes, allowing brain activity to be assessed with the subject in any body position and without the subject having to remain perfectly still. Therefore, fNIRS is more suitable for clinical application than other neuroimaging methods. Several fNIRS studies have suggested that fNIRS of the prefrontal cortex (PFC) can evaluate the human emotional state for focus on prefrontal cortex (PFC) [10–12].

In the present study, we used fNIRS to objectively evaluate malocclusion. We used fNIRS to assess brain activity in the PFC during clenching in the presence of mandibular retrusive deviation, which is one form of malocclusion. The working hypothesis states that (1) the mandibular deviation affects the human emotional state and that (2) using fNIRS, we could evaluate the mandibular deviation objectively focusing on PFC activities.

2. Materials and Method

2.1. Subjects. Twelve healthy, right-handed volunteers (seven males and five females, mean age = 29.4 years, range 2.8 years) participated in this study. No subject had a history of neurological or psychiatric illness. All subjects had full dentition and healthy periodontal tissue. Written informed consent was obtained from each subject. The study was approved by the Ethics Committee of Kanagawa Dental University (approval number 251) and conformed to the STROBE guidelines for reporting observational studies (http://www.strobe-statement.org/).

2.2. fNIRS. In the present study, fNIRS (ETG7100, Hitachi Medical. Co., Kashiwa, Japan) was used to detect changes in cerebral blood flow. The probe had eight illuminators and seven detectors in a lattice pattern, resulting in 22 channels. The system used two different wavelengths (695 ± 20 nm and 830 ± 20 nm) and measured the level of oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) as well as their sum (total hemoglobin; total-Hb) at a time resolution of 0.1 s. Interoptode distance was 30 mm and the system was able to detect cerebral blood flow at a depth of approximately 20 mm from the scalp [13]. In this study, we used the change in oxy-Hb concentration as an indicator of the change in regional cerebral blood volume. Using a rat brain model, Hoshi et al. showed that that oxy-Hb is more sensitive to brain activity than deoxy-Hb [14].

The fNIRS probes were arranged according to the international 10/20 system used in electroencephalography. The fNIRS probes were standardized to the frontal region that covered the PFC. The lowest probe line was positioned along the Fp1-Fp2 line and the center probe was located at Fpz (Figure 1(a)).

To estimate the correspondence between channels and cortical topography, we employed a probabilistic estimation method [15], which registers fNIRS data to the Montreal Neurological Institute (MNI) standard brain space. fNIRS optode positions and several scalp landmarks were digitized using the 3D magnetic space digitizer (PATRIOT; Polhemus, Colchester, VT, USA). Using an anatomical database

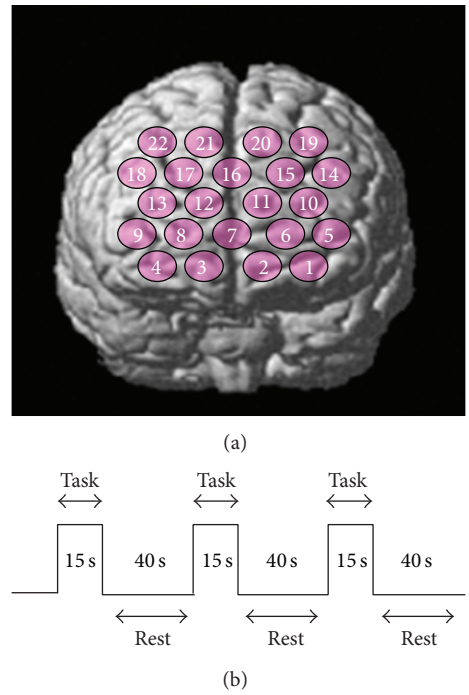

Figure 1: (a) The fNIRS probes were standardized to the frontal region that covered the prefrontal cortex. (b) Schematic illustration of block design.

[16], channel positions were then estimated in the standardized stereotaxic MNI 3D brain atlas (freeware available at http://www.jichi.ac.jp/brainlab/indexE.html). Based on the anatomical estimation, we selected channels that were located on anterior-dorsal region of the medial PFC (adMPFC). NIRS-SPM software (Bio Imaging & Signal Processing Lab, Daejeon, Korea; freeware available at http://bisp.kaist.ac.kr/NIRS-SPM.html) was also used. fNIRS data (oxy-Hb) were statistically analyzed based on a general linear model and P values were calculated. Areas activated in response to the clenching task were identified at uncorrected $P < 0.05$ [17].

2.3. Clenching Task. We made mandibular deviation model splints using the same procedure as described in our previous study [1]. Two maxillary splints were produced for each subject, starting with two 0.5 mm thick polyvinyl chloride sheets that were formed to the shape of the maxillary dentition. One of these formed sheets was the control splint. Self-curing dental resin was added to the anterior region of the other formed sheet, and while the resin was still malleable the sheet was fitted onto the subject's maxillary dentition using the chin-point technique, whereby the thumb and one finger were placed on the chin and used to guide the mandible backward and upward so that the mandibular anterior dentition pressed into the soft resin. The resin was allowed to harden, and this unit served as the maxillary splint that would force the subject's condyle into the rearmost position in the mandibular fossa during clenching. The mandibular shift produced by each splint was determined using the SAM condylar position measurement system (Great

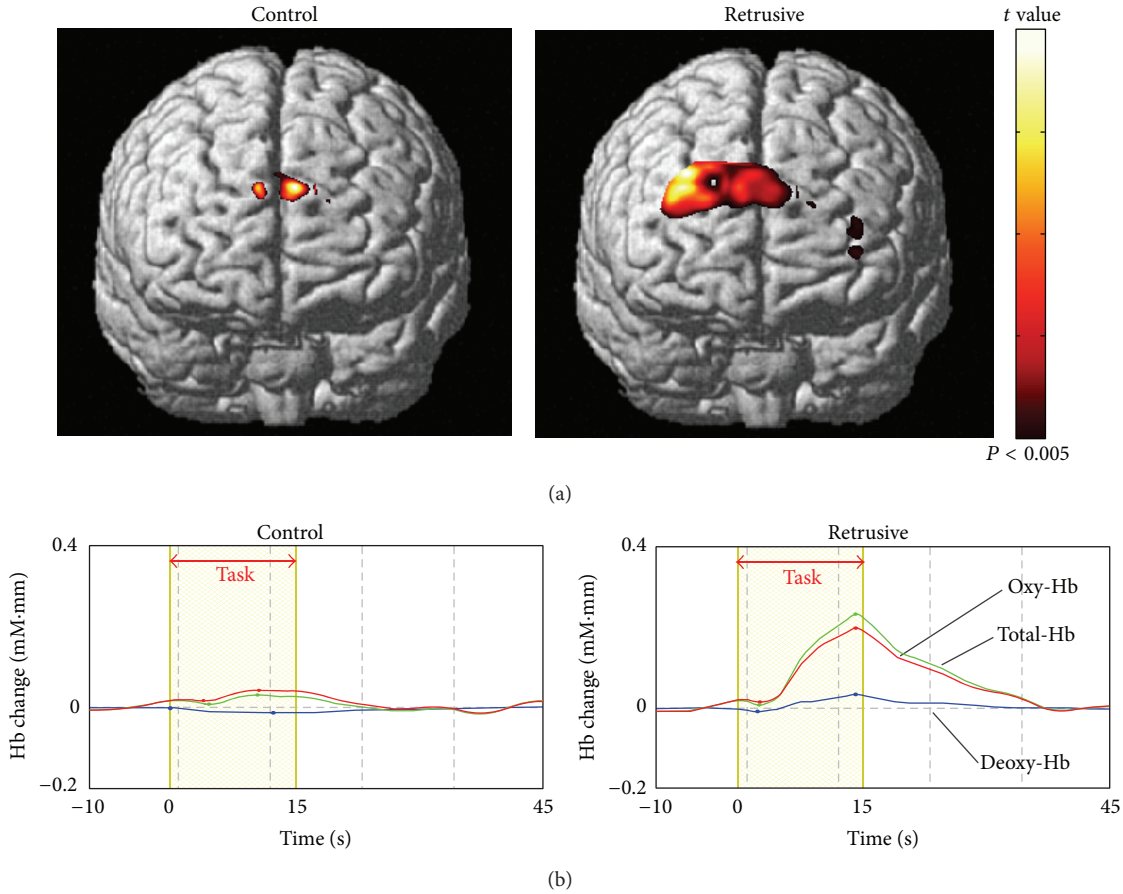

FIGURE 2: (a) Activation of the prefrontal cortex. Brain activation maps found by group analysis for each clenching task (n = 12 participants; $P < 0.005$, uncorrected). Color code denotes t value. (b) Time course of the change in hemoglobin in the prefrontal cortex of a representative participant. Task-related change in oxy-Hb (red), deoxy-Hb (blue), and total-Hb (green). Red arrow represents the clenching task.

Lakes Orthodontics, Ltd., Tonawanda, NY). To reduce measurement error, a single experienced technician tested each subject three times.

Each subject performed a maximum voluntary clenching (MVC) task with each splint (retrusion-forcing splint and control splint). With one of the splints in place, the subject performed a series of three cycles of clenching, each cycle consisting of 15 s MVC and 40 s rest (Figure 1(b)). A recovery and reset period of 20–30 min separated the two conditions (retrusion-forcing splint and control splint) for each subject to eliminate the influence of one task on the other.

2.4. Data Analysis. Cortical activation was evaluated using the task-related increase in oxy-Hb level. The oxy-Hb data were averaged across the three cycles of the MVC task. NIRS-SPM software (Bio Imaging & Signal Processing Lab) [17] was used to identify the task-related area. To remove the physiological noise, temporal smoothing using Gaussian Kernel and discrete cosine transform (DCT) were used. fNIRS data (oxy-Hb) were statistically analyzed based on a general linear model and P values were calculated. Areas activated in response to the clenching task were identified at uncorrected $P < 0.05$. This method identified the anterior-dorsal region of the medial PFC (adMPFC) as task-related area. Probabilistic estimation [15] was performed to confirm the brain area. Based on the anatomical estimation, we selected channels 7, 11, 12, and 16 located on the anterior-dorsal region of the medial PFC (adMPFC), which are our ROI in this study. The mean oxy-Hb level during each condition was calculated. Then, the average across channels 7, 11, 12, and 16 was calculated and compared across conditions using a paired t-test.

2.5. Visual Analog Scale (VAS). Each subject rated their subjective feeling of discomfort during the MVC task on a VAS ranging from 0 (no discomfort) to 10 (extreme discomfort). The VAS score was verbally expressed to an interviewer. A paired t-test was used to compare the VAS score across conditions, and statistical significance was set at $P < 0.05$. Spearman rank-correlation coefficient was calculated to evaluate the correlation between PFC activation and VAS score for the 12 subjects.

3. Results

Figure 2(a) shows the results of the NIRS-SPM spatial analysis for a typical subject. The adMPFC was activated during both control and retrusive position clenching. The activated area

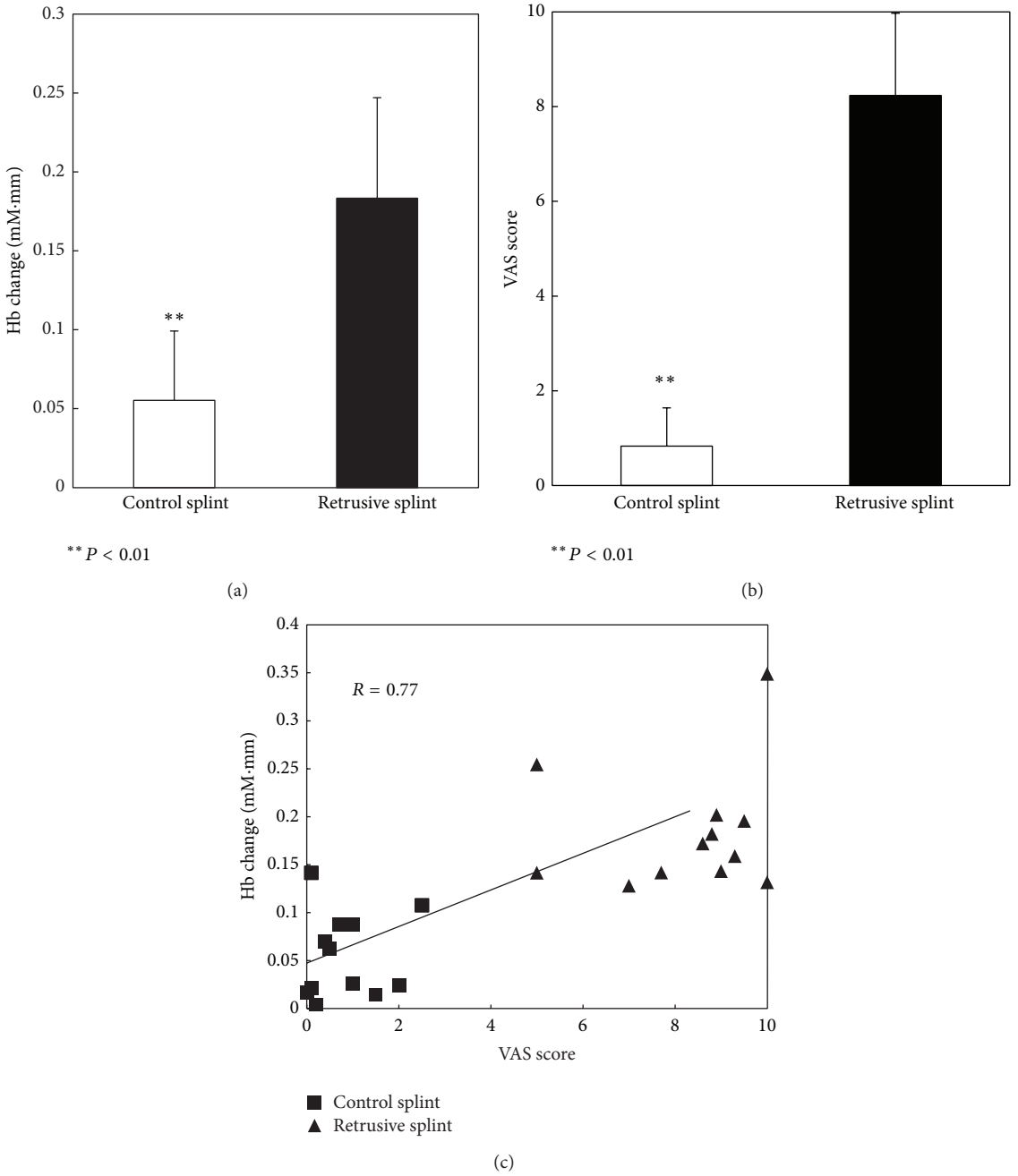

Figure 3: (a) Change in Oxy-Hb in the prefrontal cortex during the clenching task performed with the control splint and the retrusive splint. (b) Mean VAS score for discomfort. Error bars indicate SE. (c) The relation between the change in oxy-Hb in the prefrontal cortex and the VAS score for discomfort in the clenching task performed with the control splint and the retrusive splint.

was larger in retrusive position clenching than in control position clenching. Probabilistic estimation [15] indicated that channels 7, 11, 12, and 16 were located over Brodmann area 10, which corresponds to the anterior-dorsal region of the medial PFC (adMPFC; Table 1).

Figure 2(b) shows the time course of the change in oxy-Hb, deoxy-Hb, and total-Hb level. There was an increase in oxy-Hb and total-Hb in the PFC during both control and retrusive position clenching. The increase in oxy-Hb was greater in retrusive position clenching than in control position clenching. After clenching stopped, oxy-Hb gradually returned to baseline.

Figure 3(a) shows the change in oxy-Hb concentration in the adMPFC in control and retrusive position clenching. The comparison between control and retrusive position clenching revealed significantly greater activation during retrusive position clenching ($P < 0.01$). Figure 3(b) shows the VAS score for discomfort in control and retrusive position

Table 1: Channel location.

Channel	MNI coordinates (mm)			SD (mm)	Brodmann area
	X	*Y*	*Z*		
7	−8	73	11	9.5	10
11	−17	69	21	7.0	10
12	9	70	22	9.0	10
16	−7	64	33	8.0	9, 10

clenching. The comparison between control and retrusive position clenching revealed significantly larger VAS score for discomfort during retrusive position clenching ($P < 0.01$). Figure 3(c) shows the correlation between the change in oxy-Hb and the VAS score for discomfort. There was a statistically significant positive correlation between the change in oxy-Hb and the VAS score for discomfort ($R = 0.77$).

4. Discussion

To the best of our knowledge, this is the first study to investigate the relation between malocclusion and brain activation using fNIRS. Previous fMRI studies have suggested that PFC activation correlates with the severity of malocclusion [2]. In the present study, clenching with the malocclusion model (the mandibular retrusive condition) caused PFC activation. Hoshi et al. reported that pleasant or unpleasant emotions could be recognized from cerebral blood flow evaluated using fNIRS [11]. The PFC is closely associated with emotional stress and negative emotional reactions [10–12, 18] and is involved in various high-level cognitive functions [19–22]. Yasui et al. reported that oxy-Hb concentration, particularly in the adMPFC, reflected the level of mental stress and the activity of the autonomic nervous system [10]. In this study, there was a statistically significant positive correlation between prefrontal blood flow and VAS score for discomfort. This indicates that PFC activity in the present study probably played a role in the rating of unpleasantness.

In this study, we used fNIRS to observe the brain activation during clenching. fNIRS is affected by muscle activation. Therefore, the present results may be affected by temporal muscle activation. Narita et al. used principle component analysis to investigate PFC activation during gum chewing [23]. Principle component analysis enables the effects of muscle activation to be eliminated from the fNIRS signal. In this study, we did not use principle component analysis, and our results may therefore be affected by temporal muscle activation. However, in this study, we observed a tendency for an increase in oxy-Hb and a decrease in deoxy-Hb during the retrusive position condition. These results are consistent with previous fNIRS studies that showed an increase in oxy-Hb and a decrease in deoxy-Hb during brain activity [8, 13]. Therefore, we assume that the changes in hemoglobin observed using fNIRS in this study reflect brain activation.

Our previous studies suggested that fMRI was a useful diagnostic device for functional occlusion [1, 2]. However, an fMRI device requires a large, shielded room and has a high cost, so it is difficult to routinely use fMRI in the dental clinic. By contrast, the fNIRS device is relatively inexpensive compared to other neuroimaging methods. The spatial resolution is typically coarse, at 3 cm or more, but may improve with technical advancements, and the temporal resolution can be quite high. fNIRS has the particular advantage of being able to monitor a moving patient, which would be particularly suited to dental practice. The clinical significance of this study is applicable to dental practice the neuroimaging tool such as fNIRS.

5. Conclusion

The results of the present study suggest that fNIRS of the PFC could be used to objectively evaluate the occlusal condition. Because the fNIRS device is easier to control than other neuroimaging methods, it is more suitable for evaluating the occlusal condition in clinical settings. However, the exact link between malocclusion other than mandibular retrusion and activation of the PFC is unclear, because malocclusions vary widely and the sample size is not large enough to permit a definitive conclusion at the present time. Further research is required.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Takero Otsuka, Ryuichi Yamasaki, and Tateshi Shimazaki contributed equally to this work.

Acknowledgments

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References

[1] T. Otsuka, K. Watanabe, Y. Hirano et al., "Effects of mandibular deviation on brain activation during clenching: an fMRI preliminary study," *The Journal of Craniomandibular Practice*, vol. 27, no. 2, pp. 88–93, 2009.

[2] M. Greven, T. Otsuka, L. Zutz, B. Weber, C. Elger, and S. Sato, "The amount of TMJ displacement correlates with brain activity," *Cranio: Journal of Craniomandibular Practice*, vol. 29, no. 4, pp. 291–296, 2011.

[3] M. Onozuka, K. Watanabe, M. Fujita, K. Tonosaki, and S. Saito, "Evidence for involvement of glucocorticoid response in the hippocampal changes in aged molarless SAMP8 mice," *Behavioural Brain Research*, vol. 131, no. 1-2, pp. 125–129, 2002.

[4] E. Budtz-Jorgensen, "Occlusal dysfunction and stress. An experimental study in macaque monkeys," *Journal of Oral Rehabilitation*, vol. 8, no. 1, pp. 1–9, 1981.

[5] K.-Y. Kubo, Y. Yamada, M. Iinuma et al., "Occlusal disharmony induces spatial memory impairment and hippocampal neuron degeneration via stress in SAMP8 mice," *Neuroscience Letters*, vol. 414, no. 2, pp. 188–191, 2007.

[6] T. Yoshihara, Y. Matsumoto, and T. Ogura, "Occlusal disharmony affects plasma corticosterone and hypothalamic noradrenaline release in rats," *Journal of Dental Research*, vol. 80, no. 12, pp. 2089–2092, 2001.

[7] S. W. G. Derbyshire, A. K. P. Jones, M. Collins, C. Feinmann, and M. Harris, "Cerebral responses to pain in patients suffering acute post-dental extraction pain measured by positron emission tomography (PET)," *European Journal of Pain*, vol. 3, no. 2, pp. 103–113, 1999.

[8] T. Shimazaki, T. Otsuka, S. Akimoto, K. Y. Kubo, S. Sato, and K. Sasaguri, "Comparison of brain activation via tooth stimulation," *Journal of Dental Research*, vol. 91, no. 8, pp. 759–763, 2012.

[9] E. Watanabe, Y. Yamashita, A. Maki, Y. Ito, and H. Koizumi, "Non-invasive functional mapping with multi-channel near infra-red spectroscopic topography in humans," *Neuroscience Letters*, vol. 205, no. 1, pp. 41–44, 1996.

[10] H. Yasui, K. Takamoto, E. Hori et al., "Significant correlation between autonomic nervous activity and cerebral hemodynamics during thermotherapy on the neck," *Autonomic Neuroscience: Basic and Clinical*, vol. 156, no. 1-2, pp. 96–103, 2010.

[11] Y. Hoshi, J. Huang, S. Kohri et al., "Recognition of human emotions from cerebral blood flow changes in the frontal region: a study with event-related near-infrared spectroscopy," *Journal of Neuroimaging*, vol. 21, no. 2, pp. e94–e101, 2011.

[12] H. Doi, S. Nishitani, and K. Shinohara, "NIRS as a tool for assaying emotional function in the prefrontal cortex," *Frontiers in Human Neuroscience*, vol. 7, article 770, 2013.

[13] G. E. Strangman, Z. Li, and Q. Zhang, "Depth sensitivity and source-detector separations for near infrared spectroscopy based on the Colin27 brain template," *PLoS ONE*, vol. 8, no. 8, Article ID e66319, 2013.

[14] Y. Hoshi, N. Kobayashi, and M. Tamura, "Interpretation of near-infrared spectroscopy signals: a study with a newly developed perfused rat brain model," *Journal of Applied Physiology*, vol. 90, no. 5, pp. 1657–1662, 2001.

[15] A. K. Singh, M. Okamoto, H. Dan, V. Jurcak, and I. Dan, "Spatial registration of multichannel multi-subject fNIRS data to MNI space without MRI," *NeuroImage*, vol. 27, no. 4, pp. 842–851, 2005.

[16] M. Okamoto, H. Dan, K. Sakamoto et al., "Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10-20 system oriented for transcranial functional brain mapping," *NeuroImage*, vol. 21, no. 1, pp. 99–111, 2004.

[17] J. C. Ye, S. Tak, K. E. Jang, J. Jung, and J. Jang, "NIRS-SPM: statistical parametric mapping for near-infrared spectroscopy," *NeuroImage*, vol. 44, no. 2, pp. 428–447, 2009.

[18] S. Moratti, A. Keil, and M. Stolarova, "Motivated attention in emotional picture processing is reflected by activity modulation in cortical attention networks," *NeuroImage*, vol. 21, no. 3, pp. 954–964, 2004.

[19] B. Opitz, A. Mecklinger, and A. D. Friederici, "Functional asymmetry of human prefrontal cortex: encoding and retrieval of verbally and nonverbally coded information," *Learning and Memory*, vol. 7, no. 2, pp. 85–96, 2000.

[20] H. Barbas, "Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices," *Brain Research Bulletin*, vol. 52, no. 5, pp. 319–330, 2000.

[21] J. G. Craggs, D. D. Price, G. N. Verne, W. M. Perlstein, and M. M. Robinson, "Functional brain interactions that serve cognitive-affective processing during pain and placebo analgesia," *NeuroImage*, vol. 38, no. 4, pp. 720–729, 2007.

[22] S. Fallon, E. Shearman, H. Sershen, and A. Lajtha, "Food reward-induced neurotransmitter changes in cognitive brain regions," *Neurochemical Research*, vol. 32, no. 10, pp. 1772–1782, 2007.

[23] N. Narita, K. Kamiya, K. Yamamura, S. Kawasaki, T. Matsumoto, and N. Tanaka, "Chewing-related prefrontal cortex activation while wearing partial denture prosthesis: pilot study," *Journal of Prosthodontic Research*, vol. 53, no. 3, pp. 126–135, 2009.

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Review Article

Chewing and Attention: A Positive Effect on Sustained Attention

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Chewing is crushing food not only to aid swallowing and digestion, but also to help stress relief and regulate cognitive function, especially in attention. It is well known that chewing gum is used for sleepiness prevention during work, learning, and driving, suggesting a link between chewing and sustained attention. We hypothesized that chewing elevates attention and/or alertness, leading to improvements in cognitive performance. We carried out a systematic review of the PubMed database. We inspected the attributes of effects on attention in studies investigating the effects of chewing on attention or alertness conducted with pre-post design in healthy subjects, except elderly. We identified 151 references, 22 of which were included: 14 (64%) showed positive attributes of effects on attention, 1 (5%) showed negative attributes of effects on attention, 5 (23%) showed both positive and negative attributes of effects on attention, and 2 (9%) showed no significant attributes of effects on attention. Thus, positive attributes of effects of chewing on attention, especially on sustained attention, were shown in over half of the reports. These effects also appeared with improvement in mood and stress relief and were influenced by time-on-task effect. Further studies are needed, but chewing could be useful for modifying cognitive function.

1. Introduction

The most dominant function of chewing (or mastication) is thought to be crushing of food to aid swallowing and digestion. Besides this essential role, recent studies have mentioned a unique function that affects brain function. For example, bruxism, which is involuntary grinding of teeth typically during sleep, is thought to be caused by psychological stress [1, 2]. Furthermore, chewing gum is used for maintaining alertness and avoiding sleepiness while operating a vehicle or studying. Also, adverse oral health such as periodontitis [3] and tooth loss [4] may be a risk factor of cognitive decline in elderly. These findings support the concept that chewing is strongly associated with cognitive function such as learning and memory and keeping and increasing attention [5].

This relationship between chewing and cognitive functions was empirically estimated a long time ago. In 1939, Hollingworth [6] reported that chewing increased relaxation and the performance of cognitive function like number-checking and typing. This relaxation effect was investigated by means of electroencephalography (EEG), and regular gum chewing was shown to increase alpha power after chewing compared with control at almost all positions [7]. After that, additional EEG experiments were conducted under conditions of chewing gum with flavor or almost no taste and odor [8, 9]. The results showed that alpha and beta activity patterns were not consistent, although chewing flavored gum consistently increased beta activity and induced arousal effects. Thereafter, more than twenty studies investigated the effects of chewing on cognitive function using modern neuropsychological testing, the first one being carried out by Wilkinson et al. in 2002 [10]. They reported improvement of performance of episodic memory and spatial and numeric working memory in the chewing group.

However, no improvement was observed in attention. After that, Tucha et al. [11] presented controversial results in their replication study. They reported that chewing increased sustained attention, although no beneficial effect was found on memory, and there were aversive effects on alertness and flexibility. Since those studies, the issue concerning the existence and attributes of effects of chewing has remained a subject of discussion up to the present. Later on, several studies investigated the relationship between chewing and cognitive functions using functional magnetic resonance imaging (fMRI) and EEG [12–15] to elucidate the mechanisms of these effects. However, the reported effects of chewing on cognitive functions have been rather inconsistent and have still not been fully clarified. With regard to the results, we hypothesized that chewing affects attention and/or alertness, consequently leading to improvements of cognitive performance. Therefore, we reviewed the literature in respect to the effects of chewing on aspects of attention, and we discussed the existence and attributes of these effects.

2. Methods

2.1. Search Strategy. A systematic search strategy was used to identify appropriate publications. We conducted online search at the PubMed online database using the terms (chewing OR mastication) AND (attention OR alertness OR cognitive) NOT ("oral health" OR review OR elderly OR disorders) on August 5th, 2014, with no time span specified for publication date. A total of 151 hits came back.

2.2. Selection Criteria. Studies were included if they met the following criteria: (i) reported in an original paper, (ii) examined the effect of chewing in healthy children or adults, but not in the elderly, to rule out the possible influence of oral health and cognitive impairments, (iii) evaluated the efficacy of attention, including alertness, vigilance, executive control, and reaction time, compared with no gum chewing conditions, and (iv) written in English. After applying these selection criteria, 22 papers were included in the current review.

2.3. Variables of Interest. The following variables were examined for each article included in the review: (i) cognitive tests and psychological rating scales, if applicable, (ii) chewing objects, (iii) summary of results compared with nonchewing condition unless stated, and (iv) attributes of effects on attention.

3. Results and Discussion

The 22 articles were checked for cognitive tests and psychological rating scales, chewing objects, summary of results, and attributes of effects on attention (see Table 1). First, we focused on the most interesting variable, the attributes of effects on attention, categorizing them by the direction of effects. As shown in Table 1, more than half of the reports indicated positive attributes of effects on attention, with 14 (64%) showing positive (at least somewhat), 1 (5%) showing negative, 5 (23%) showing both positive and negative attributes of effects on attention, and 2 (9%) showing no significance. The appearance of reports presenting negative attributes showed a decreasing trend with recent experimental conditions. Next, we discussed the factors of mood and time-on-task effects on the results according to the summaries of results in order to understand the mechanisms.

With regard to mood, Smith [16] examined memory, intelligence test, alertness, and mood in a single study. He reported that alertness and hedonic tone in addition to intelligence test were improved, although memory showed no improvement. The following study by Smith [17] added improved selective and sustained attentions while the hedonic tone benefit had disappeared. Also, increased pretest alertness and hedonic tone and reduced posttest anxiety in mood were indicated, but without benefit for attention in another report by Smith [18]. He mentioned that two types of mechanisms were activated by chewing [16]. One was related to the mobilization of energetic resources, in particular facial muscles [19], and another was related to neurotransmitter function, specifically the 5-HT descending inhibitory pathway [20]. Scholey et al. [21] reported that chewing induced better performance on the test battery requiring memory and attention, with increased alertness and reduced state anxiety, stress, and saliva cortisol. They speculated that the mechanism of cognitive performance enhancement was secondarily induced by relief of mental stress [22], in addition to increased heart rate [10], cerebral blood flow [23], and brain activity [24] due to chewing. Thereafter, antistress effects were not replicated, but increased alertness was observed following the cognitive stressor test [25] and acute social stress test [26], which was suspected to be induced by greater cerebral activity following the chewing of gum [27]. Sakamoto et al. [14, 15] have reported the influences of chewing on the central nervous system by measuring reaction time (RT) and event-related potentials (ERPs). They suggested that chewing affects the state of arousal via the ascending reticular activating system, and this accelerates cognitive processing. More recently, Johnson et al. [28] found improvement in sustained attention covaried with subjective alertness, strongly supporting the hypothesis that chewing elevates attention and/or alertness, consequently leading to improvements in cognitive performance.

Another factor, the time-on-task effect in relation to the effect of chewing on attention, was discussed. Tucha and Simpson [29] proposed that time is an important factor in the psychodynamics of gum chewing. They put forward this new idea that it is one of the reasons for the difficulties in replicating the results of studies, in addition to the brand of gum, familiarity with gum, the experimental design, and statistical analysis. Tänzer et al. [30] examined the concentration performance in 8-9-year-old children using a 16-minute test. For the first 12 minutes, classes who did not chew gum performed better but were then overtaken by classes chewing gum, showing the interaction between chewing condition and time. After that, Allen and Smith [31] examined the time-on-task effect within each individual performance task, confirming this effect on vigilance reaction time. More recently, Morgan et al. [32] also reported that correct reaction

Table 1: Studies on the effects of chewing on attention.

Study	Cognitive tests and psychological rating scales	Chewing objects	Summary of results (compared with nonchewing condition unless stated)	Attributes of effects on attention
Wilkinson et al. (2002) [10]	15 tests on memory and attention	Sugar-free spearmint gum	Improvements of scores on episode and working memory and simple reaction time. Elevation of heart rate. No significant differences in attention.	Not significant
Tucha et al. (2004) [11]	12 tests on memory and attention	Sugar-free spearmint gum and sugar-free tasteless gum	Shortening of reaction time on sustained attention, prolongation of reaction time on alertness, and increase of number of errors on flexibility. No significant differences in memory and pulse rate.	Positive or negative depending on task
Stephens and Tunney (2004) [37]	8 tests on memory and attention	Sugar-free mint flavored gum	Improvements of scores on episode and working memory, attention, and processing speed. No significant differences in executive function.	Positive
Kohler et al. (2006) [36]	Psychomotor vigilance, tracking, and grammatical reasoning and alertness	Parafilm (sugar-free, tasteless)	Not significant or detrition of performance of speed and accuracy on simple and complex cognitive tasks except for a simple motor tracking task early during the period of sleep deprivation. No significant differences in alertness, heart rate, and root mean square of successive differences in R-R intervals.	Positive or negative depending on task and time
Sakamoto et al. (2009) [15]	Reaction time	Odorless and tasteless gum base	Shortening of reaction time and the peak latencies of event-related potentials (P300 and N100) in second and third session after chewing.	Positive
Smith (2009) [16]	Mood, alertness, intelligence test, and short term and working memory	Volunteer's preferred gum	Improvement of intelligence test. No significant difference in memory. Increased alertness at the end of the test session.	Positive
Scholey et al. (2009) [21]	4 tests including memory, attention, and mood	Volunteer's preferred gum	Overall better performance on the cognitive tasks. Increase of alertness and reduction of stress and salivary cortisol.	Positive
Smith (2009) [18]	5 tests on alertness and mood	Caffeinated gum or placebo gum	More positive mood after chewing and at the end of the study regardless of caffeine. Higher alertness after chewing. No significant difference in alertness without caffeine.	Not significant
Sakamoto et al. (2009) [14]	Reaction time	Odorless and tasteless gum base	Shortened reaction time at third trials after chewing. Increased contingent negative variation (CNV) at second and third trials after chewing. No significant differences in movement-related control potentials.	Positive
Tänzer et al. (2009) [30]	16-minute concentration test	Sugar-free fruit gum	Improvement of concentration performance with time in 8-9-year-olds.	Positive
Smith (2010) [17]	10 tests on memory, attention, and mood	Spearmint or fruit gum	Improvement of alertness and selective and sustained attention. Shortened reaction time; this effect became bigger as the task became more difficult. Increase of heart rate and saliva cortisol.	Positive
Tucha et al. (2010) [42]	Vigilance and sustained attention	Sugar-free spearmint gum	Deterioration of vigilance performance in both healthy children and children with ADHD (mean age 10.8 years). No significant difference in sustained attention.	Negative
Tucha and Simpson (2011) [29]	Sustained attention	Sugar-free spearmint gum	Detriment on sustained attention in earlier stages of 30-minute task and benefit on sustained attention at later stages.	Negative early to positive later within 30-min period
Johnson et al. (2011) [25]	4 tasks including memory and attention, mood, and alertness	Regular chewing gum	Increase of self-rated alertness and stress. No significant differences in task performance and saliva cortisol.	Positive

Table 1: Continued.

Study	Cognitive tests and psychological rating scales	Chewing objects	Summary of results (compared with nonchewing condition unless stated)	Attributes of effects on attention
Onyper et al. (2011) [41]	5 tasks including memory and attention	Spearmint or doublemint gum with or without sugar	Improvements of performance of several tasks in chewing for 5 minutes prior to testing. No significant differences in chewing throughout testing.	Positive in chewing prior to testing
Sketchley-Kaye et al. (2011) [26]	Acute stress task, mood, anxiety, and alertness	Regular chewing gum	Attenuation of state anxiety and increase of alertness under condition of acute social stress task. No significant differences in contentedness or calmness.	Positive
Allen and Smith (2012) [31]	4 tasks on attention and mood	Volunteer's preferred gum	Increased alertness, mood, and performance of attention test and shortened reaction time. Initial extended vigilance reaction times were shortened after trials.	Positive, but some tests showed negative effects initially
Allen and Smith (2012) [38]	4 tasks on attention and mood	Volunteer's preferred gum	Increased reported alertness for positive and neutral demand characteristics. Improved selective attention. Reduced performances of two attention tasks only at specific time of trials. Better response organization on categoric search task when demand characteristics and pretest attitudes to gum were both negative.	Positive, but some tests showed negative effects at specific time of trials
Hirano et al. (2013) [12]	Alerting and executive control	Odorless and tasteless gum base	Shortened reaction time. No significant differences in alerting and conflict effects. Higher activations in the anterior cingulate cortex and left frontal gyrus for the executive network and motor-related regions for both attentional networks	Positive
Johnson et al. (2013) [28]	Sustained attention, alertness, and mood	Cool Breeze gum	Improved attentional task performance. Higher alertness and mood. Shortened response times. No time-on-task effect.	Positive
Morgan et al. (2014) [32]	Short-term memory, vigilance, and mood	Sugar-free spearmint gum	Attenuated time-dependent decrement on both performance and subjective alertness. Shorter correct reaction time in the latter stage of the task.	Positive, especially in the latter stage of the task
Allen et al. (2014) [35]	Vigilance and mood	Gum base	Shortened reaction time and increased rate of hits. Heightened heart rate during chewing. Increased EEG beta power at F7 and T3 immediately after chewing.	Positive

times were significantly shorter in the latter stages of the task, in addition to the decline in both performance and subjective alertness in the chewing gum group. Johnson et al. [28] also reported the existence of time-on-task effect and initial impairment of attention. Tucha and Simpson [29] speculated that participants might be distracted by dual task interference [33] induced by gum chewing during early stages of cognitive tasks or that certain biological processes (e.g., increase of regional cerebral blood flow) have to add up or reach a certain threshold to facilitate cognitive processing. In this view, as a result of the study, the better performance of working memory task in chewing condition at the last stage could be explained [13].

The mechanisms of the beneficial effects of chewing on attention have been discussed for a long time, and they have been estimated as being derived from increases of cerebral blood flow and brain activity [12, 24, 27], cerebral blood flow [23, 34], cardiovascular system [10, 17, 35, 36], ascending reticular activating system [14, 15], glucose delivery [37], and flavors [11]. Recently, Hasegawa et al. [34] assumed that taste and odor can influence brain activation during chewing in sensory, cognitive, and motivational processes rather than in motor control, although some studies confirmed the beneficial effects on attention with tasteless and odorless gum base [12, 14, 15]. Allen and Smith [38] reported that a benefit for alertness was shown in persons with positive and neutral demand characteristics, but a positive effect on response organization was observed with demand characteristics [39] and the pretest attitude to gum. More recently, Yu et al. [40] demonstrated an fMRI study showing that gum chewing inhibited functional connectivity between the left anterior insular and the dorsal anterior cingulate cortex and functional connectivity from the superior temporal sulcus to the left anterior insula when activated by noise. They stated that gum chewing relieves stress by attenuating the sensory processing of external stressor and by inhibiting the propagation of stress-related information in the brain stress network. Allen et al. [35] reported that chewing can alter central and sympathetic nervous system activity associated with vigilance performance. The transient effect in their study was consistent with the short-lived effect of chewing gum on hits in the vigilance task.

In conclusion, many of the studies indicated that chewing exerts a positive effect on attention, and especially on sustained attention, in addition to improved mood and stress relief. Also, the effect seems to be influenced by time-on-task effect and do not last so long, such as 15–20 [41] or more than 30 minutes [29] after chewing, and then the mechanisms of the effects were not yet fully elucidated. Further studies are needed, but chewing could be useful as an easy method for modifying cognitive function on a daily basis and not be demanding physically and mentally.

Conflict of Interests

The authors declare that they have no conflict of interests regarding the publication of this paper.

References

[1] H. Abekura, M. Tsuboi, T. Okura, K. Kagawa, S. Sadamori, and Y. Akagawa, "Association between sleep bruxism and stress sensitivity in an experimental psychological stress task," *Biomedical Research*, vol. 32, no. 6, pp. 395–399, 2011.

[2] R. A. Hicks and P. Conti, "Nocturnal bruxism and self reports of stress-related symptoms," *Perceptual and Motor Skills*, vol. 72, no. 3, part 2, p. 1182, 1991.

[3] R. Stewart, R. J. Weyant, M. E. Garcia et al., "Adverse oral health and cognitive decline: the health, aging and body composition study," *Journal of the American Geriatrics Society*, vol. 61, no. 2, pp. 177–184, 2013.

[4] Y. Takata, T. Ansai, I. Soh et al., "Cognitive function and number of teeth in a community-dwelling elderly population without dementia," *Journal of Oral Rehabilitation*, vol. 36, no. 11, pp. 808–813, 2009.

[5] Y. Hirano and M. Onozuka, "Chewing and cognitive function," *Brain and Nerve*, vol. 66, no. 1, pp. 25–32, 2014.

[6] H. L. Hollingworth, "Chewing as a technique of relaxation," *Science*, vol. 90, no. 2339, pp. 385–387, 1939.

[7] Y. Masumoto, T. Morinushi, H. Kawasaki, and M. Takigawa, "Spectral analysis of changes in electroencephalographic activity after the chewing of gum," *Psychiatry and Clinical Neurosciences*, vol. 52, no. 6, pp. 587–592, 1998.

[8] Y. Masumoto, T. Morinushi, H. Kawasaki, T. Ogura, and M. Takigawa, "Effects of three principal constituents in chewing gum on electroencephalographic activity," *Psychiatry and Clinical Neurosciences*, vol. 53, no. 1, pp. 17–23, 1999.

[9] T. Morinushi, Y. Masumoto, H. Kawasaki, and M. Takigawa, "Effect on electroencephalogram of chewing flavored gum," *Psychiatry and Clinical Neurosciences*, vol. 54, no. 6, pp. 645–651, 2000.

[10] L. Wilkinson, A. Scholey, and K. Wesnes, "Chewing gum selectively improves aspects of memory in healthy volunteers," *Appetite*, vol. 38, no. 3, pp. 235–236, 2002.

[11] O. Tucha, L. Mecklinger, K. Maier, M. Hammerl, and K. W. Lange, "Chewing gum differentially affects aspects of attention in healthy subjects," *Appetite*, vol. 42, no. 3, pp. 327–329, 2004.

[12] Y. Hirano, T. Obata, H. Takahashi et al., "Effects of chewing on cognitive processing speed," *Brain and Cognition*, vol. 81, no. 3, pp. 376–381, 2013.

[13] Y. Hirano, T. Obata, K. Kashikura et al., "Effects of chewing in working memory processing," *Neuroscience Letters*, vol. 436, no. 2, pp. 189–192, 2008.

[14] K. Sakamoto, H. Nakata, Y. Honda, and R. Kakigi, "The effect of mastication on human motor preparation processing: a study with CNV and MRCP," *Neuroscience Research*, vol. 64, no. 3, pp. 259–266, 2009.

[15] K. Sakamoto, H. Nakata, and R. Kakigi, "The effect of mastication on human cognitive processing: a study using event-related potentials," *Clinical Neurophysiology*, vol. 120, no. 1, pp. 41–50, 2009.

[16] A. Smith, "Effects of chewing gum on mood, learning, memory and performance of an intelligence test," *Nutritional Neuroscience*, vol. 12, no. 2, pp. 81–88, 2009.

[17] A. Smith, "Effects of chewing gum on cognitive function, mood and physiology in stressed and non-stressed volunteers," *Nutritional Neuroscience*, vol. 13, no. 1, pp. 7–16, 2010.

[18] A. Smith, "Effects of caffeine in chewing gum on mood and attention," *Human Psychopharmacology*, vol. 24, no. 3, pp. 239–247, 2009.

[19] W. Waterink and A. van Boxtel, "Facial and jaw-elevator EMG activity in relation to changes in performance level during a sustained information processing task," *Biological Psychology*, vol. 37, no. 3, pp. 183–198, 1994.

[20] Y. Mohri, M. Fumoto, I. Sato-Suzuki, M. Umino, and H. Arita, "Prolonged rhythmic gum chewing suppresses nociceptive response via serotonergic descending inhibitory pathway in humans," *Pain*, vol. 118, no. 1-2, pp. 35–42, 2005.

[21] A. Scholey, C. Haskell, B. Robertson, D. Kennedy, A. Milne, and M. Wetherell, "Chewing gum alleviates negative mood and reduces cortisol during acute laboratory psychological stress," *Physiology & Behavior*, vol. 97, no. 3-4, pp. 304–312, 2009.

[22] L. E. Spieker, D. Hürlimann, F. Ruschitzka et al., "Mental stress induces prolonged endothelial dysfunction via endothelin—a receptors," *Circulation*, vol. 105, no. 24, pp. 2817–2820, 2002.

[23] T. Momose, J. Nishikawa, T. Watanabe et al., "Effect of mastication on regional cerebral blood flow in humans examined by positron-emission tomography with ^{15}O-labelled water and magnetic resonance imaging," *Archives of Oral Biology*, vol. 42, no. 1, pp. 57–61, 1997.

[24] M. Onozuka, M. Fujita, K. Watanabe et al., "Mapping brain region activity during chewing: a functional magnetic resonance imaging study," *Journal of Dental Research*, vol. 81, no. 11, pp. 743–746, 2002.

[25] A. J. Johnson, R. Jenks, C. Miles, M. Albert, and M. Cox, "Chewing gum moderates multi-task induced shifts in stress, mood, and alertness. A re-examination," *Appetite*, vol. 56, no. 2, pp. 408–411, 2011.

[26] K. Sketchley-Kaye, R. Jenks, C. Miles, and A. J. Johnson, "Chewing gum modifies state anxiety and alertness under conditions of social stress," *Nutritional Neuroscience*, vol. 14, no. 6, pp. 237–242, 2011.

[27] M. Fang, J. Li, G. Lu, X. Gong, and D. T. Yew, "A fMRI study of age-related differential cortical patterns during cued motor movement," *Brain Topography*, vol. 17, no. 3, pp. 127–137, 2005.

[28] A. J. Johnson, M. Muneem, and C. Miles, "Chewing gum benefits sustained attention in the absence of task degradation," *Nutritional Neuroscience*, vol. 16, no. 4, pp. 153–159, 2013.

[29] L. Tucha and W. Simpson, "The role of time on task performance in modifying the effects of gum chewing on attention," *Appetite*, vol. 56, no. 2, pp. 299–301, 2011.

[30] U. Tänzer, A. von Fintel, and T. Eikermann, "Chewing gum and concentration performance," *Psychological Reports*, vol. 105, no. 2, pp. 372–374, 2009.

[31] A. P. Allen and A. P. Smith, "Effects of chewing gum and time-on-task on alertness and attention," *Nutritional Neuroscience*, vol. 15, no. 4, pp. 176–185, 2012.

[32] K. Morgan, A. J. Johnson, and C. Miles, "Chewing gum moderates the vigilance decrement," *The British Journal of Psychology*, vol. 105, no. 2, pp. 214–225, 2014.

[33] K. Lambourne and P. Tomporowski, "The effect of exercise-induced arousal on cognitive task performance: a meta-regression analysis," *Brain Research*, vol. 1341, pp. 12–24, 2010.

[34] Y. Hasegawa, Y. Tachibana, J. Sakagami, M. Zhang, M. Urade, and T. Ono, "Flavor-enhanced modulation of cerebral blood flow during gum chewing," *PLoS ONE*, vol. 8, no. 6, Article ID e66313, 2013.

[35] A. P. Allen, T. J. C. Jacob, and A. P. Smith, "Effects and after-effects of chewing gum on vigilance, heart rate, EEG and mood," *Physiology & Behavior*, vol. 133, pp. 244–251, 2014.

[36] M. Kohler, A. Pavy, and C. van den Heuvel, "The effects of chewing versus caffeine on alertness, cognitive performance and cardiac autonomic activity during sleep deprivation," *Journal of Sleep Research*, vol. 15, no. 4, pp. 358–368, 2006.

[37] R. Stephens and R. J. Tunney, "Role of glucose in chewing gum-related facilitation of cognitive function," *Appetite*, vol. 43, no. 2, pp. 211–213, 2004.

[38] A. P. Allen and A. P. Smith, "Demand characteristics, pre-test attitudes and time-on-task trends in the effects of chewing gum on attention and reported mood in healthy volunteers," *Appetite*, vol. 59, no. 2, pp. 349–356, 2012.

[39] M. T. Orne, "On the social psychology of the psychological experiment: with particular reference to demand characteristics and their implications," *The American Psychologist*, vol. 17, no. 11, pp. 776–783, 1962.

[40] H. Yu, X. Chen, J. Liu, and X. Zhou, "Gum chewing inhibits the sensory processing and the propagation of stress-related information in a brain network," *PLoS ONE*, vol. 8, no. 4, Article ID e57111, 2013.

[41] S. V. Onyper, T. L. Carr, J. S. Farrar, and B. R. Floyd, "Cognitive advantages of chewing gum. Now you see them, now you don't," *Appetite*, vol. 57, no. 2, pp. 321–328, 2011.

[42] L. Tucha, W. Simpson, L. Evans et al., "Detrimental effects of gum chewing on vigilance in children with attention deficit hyperactivity disorder," *Appetite*, vol. 55, no. 3, pp. 679–684, 2010.

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Research Article

Chewing Gum: Cognitive Performance, Mood, Well-Being, and Associated Physiology

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Recent evidence has indicated that chewing gum can enhance attention, as well as promoting well-being and work performance. Four studies (two experiments and two intervention studies) examined the robustness of and mechanisms for these effects. Study 1 investigated the acute effect of gum on mood in the absence of task performance. Study 2 examined the effect of rate and force of chewing on mood and attention performance. Study 3 assessed the effects of chewing gum during one working day on well-being and performance, as well as postwork mood and cognitive performance. In Study 4, performance and well-being were reported throughout the workday and at the end of the day, and heart rate and cortisol were measured. Under experimental conditions, gum was associated with higher alertness regardless of whether performance tasks were completed and altered sustained attention. Rate of chewing and subjective force of chewing did not alter mood but had some limited effects on attention. Chewing gum during the workday was associated with higher productivity and fewer cognitive problems, raised cortisol levels in the morning, and did not affect heart rate. The results emphasise that chewing gum can attenuate reductions in alertness, suggesting that chewing gum enhances worker performance.

1. Introduction

Chewing gum can enhance alertness and sustained attention, although its effects upon stress may differ depending upon whether chronic or acute stress is examined; see reviews by Allen and Smith [1] and Hirano and Onozuka [2]. Chewing gum has enhanced sustained attention performance in previous research [3, 4], consistent with an alerting effect of chewing gum [4–6]. There is some evidence that this effect may be moderated by time-on-task, with the ameliorating effect of gum being greater following a long period of performance [6, 7]. Neuropsychological data further confirms an enhancement of sustained attention by gum. The event related potential P300, which is associated with vigilance, had a shortened latency following chewing gum [8], and frontal and temporal beta power were heightened by chewing gum following performance of a sustained attention task [9]. Quantitative EEG effects of chewing gum without cognitive performance seem to be moderated by flavour [10, 11], suggesting that alertness may be altered by chewing gum in the absence of cognitive performance. Quickening of reaction time on an adapted version of the attention network task [12] was associated with increased activity in motor regions for alerting and executive networks, as well as the anterior cingulate cortex and left frontal gyrus for the executive network [13]. Hirano et al. demonstrated this effect using gum without flavour or odour, suggesting that the motor activity of chewing may be a key factor in explaining these results; however, it remains unclear if a greater level of motor activity in chewing will heighten any associated effects. Although there is evidence that more vigorous chewing or greater resistance to chewing does not moderate chewing effects on memory [14, 15], the fact that chewing gum can enhance arousal which is depleted by attention tasks (e.g., by heightening heart rate and beta power during vigilance) [9] suggests that it is more plausible that more vigorous chewing could have a greater effect on attention.

Consistent with an alerting effect of chewing gum under laboratory conditions, chewing gum during the workday has also been shown to enhance self-reported productivity both in university staff [16] and in university students [17], consistent with an improvement in sustained attention. Although chewing gum has been associated with increased heart rate in experimental studies [9, 18] it remains unclear if sympathetic nervous system arousal may explain enhanced performance in an everyday working context.

People who chew gum habitually report less stress [19, 20], and chewing gum has reduced anxiety [21] and reported stress [22] induced by an acute social stressor, although other studies have not found a reduction on acute stress or anxiety [23, 24]. If chewing gum can reduce feelings of stress it may attenuate feelings of depression, a stress-related disorder. Strikingly, in a clinical sample of mild-moderately depressed patients, depression was reduced to a greater extent when gum was administered with antidepressant medication, compared to medication alone [25]. In a nonclinical sample, chewing gum for two weeks can reduce feelings of stress, anxiety, and depression in university staff [16], as well as reducing stress in university students [17]. In summary, it would appear that there is clearer evidence for an ameliorating effect of gum on chronic stress compared to acute stress [1]. Given this contrast between short- and long-term effects, it remains unclear if a shorter intervention (one day) can reduce feelings of stress, anxiety, and depression in a sample of working adults.

The current research aims to examine the effect of gum on well-being and cognitive performance by combining the study of chewing effects under controlled conditions with a more naturalistic examination of chewing gum during the workday. We firstly examined the acute effect of chewing gum on mood in the absence of cognitive performance (Study 1: Mood Effects in the Absence of Performance). Although previous research on mood effects of gum has examined chewing in the absence of cognitive performance, this has been in the context of sleep deprivation [26] or neurological testing, rather than under less demanding conditions. We then assessed the effects of intensity of chewing on mood and cognitive performance (Study 2: Rate of Chewing, Mood, and Cognition). To examine subjective and performance effects of chewing gum on an ongoing basis in a naturalistic setting we then tested the effects of chewing gum on well-being and performance during a single workday, to examine if effects observed over longer intervention periods are robust enough to be demonstrated within this time frame (Study 3: Working Day Intervention: Well-Being and Performance). The final study again examined a single workday intervention (Study 4: Working Day Intervention: Well-Being, Performance, and Physiology); underlying physiological mechanisms for effects on well-being and performance, which have previously been studied only under more acute testing conditions, were probed by examining changes in salivary cortisol and heart rate over the course of the working day while chewing gum.

2. Study 1: Mood Effects in the Absence of Performance

2.1. Methods. All studies described in this paper received ethical approval from Cardiff University's School of Psychology Ethics Committee and were conducted in accordance with the Declaration of Helsinki.

2.1.1. Participants. One hundred adults (81 females, 19 males; mean age = 21.1, SD = 3.6) were recruited. Participants were mostly students from the School of Psychology, Cardiff University. For all studies, people taking medication, who reported medical problems, who consumed more than 40 units of alcohol per week, or who smoked more than 10 cigarettes in the daytime and evening, were excluded from participation. Participants were recruited through a university notice board and an online experiment management system.

2.1.2. Materials

Chewing Gum. Wrigley's extra spearmint and Wrigley's gum base (synthetic rubber) were provided.

Mood Task. The mood task was presented on a desktop PC. Participants completed the tasks using a purpose-built response box with three large square buttons ("A" on the left, "B" on the right, and "Space" in the centre). Mood was measured using 18 bipolar visual analogue scales or VAS. Scores for alertness (maximum score = 400), hedonic tone (maximum score = 300), and anxiety (maximum score = 150) were derived from these scales. The component scales for alertness were drowsy/alert, strong/feeble, coordinated/clumsy, attentive/dreamy, lethargic/energetic, muzzy/clear headed, incompetent/proficient, and mentally slow/quick witted. The scales for hedonic tone were contented/discontented, happy/sad, antagonistic/friendly, interested/bored, self-centred/outward going, and withdrawn/sociable. The scales for anxiety were relaxed/excited, troubled/tranquil, and tense/calm. There was no time limit for this task. This mood scale has previously shown sensitivity to changes in mood in response to chewing gum [6].

2.1.3. Design. Participants were assigned at random to one of four conditions: chewing spearmint gum with replacement of gum (female = 20, male = 5), chewing gum without replacement (female = 22, male = 3), chewing gum base (female = 21, male = 4), and no chewing (female = 18, male = 6).

2.1.4. Procedure. Testing was scheduled for between 10.00 and 12.00. Participants filled in questionnaires assessing demographic information and habitual gum consumption on arrival. They were then provided with two pieces of spearmint gum or gum base if they were in a chewing condition and told to chew constantly throughout the procedure. Immediately after starting to chew gum they completed the initial mood assessment tasks. They were then requested to sit quietly and continue chewing. After 15 minutes, participants in a chewing condition were verbally reminded to continue chewing, and those in the replacement condition were reminded to replace the gum with two new pellets if the current gum had lost its flavour. Psychology textbooks and journals were available for participants to read, and participants could bring their own

reading material. After 25 minutes, the participants filled in the final mood assessment task.

2.1.5. Statistical Analysis. This analysis was conducted in two stages, with the first stage testing the effect of chewing gum per se, by comparing the no-gum control to the three gum conditions combined, using 2 × 2 mixed ANOVA, with the independent variables being time (initial and final assessment) and chewing (chewing versus no chewing). The second stage evaluated differences between all four gum conditions, using 2 × 4 mixed ANOVA, with the independent variable being time (as above) and gum condition (spearmint with replacement, spearmint gum without replacement, gum base, and no-gum control). The dependent variables were alertness, hedonic tone, and anxiety.

2.2. Results

2.2.1. The Effect of Time on Mood. Alertness fell significantly between the initial and final assessment, $F(1, 96) = 24.17$, $P < .001$, and *partial* $\eta^2 = .2$. Anxiety rose between the initial and final measurement, although this effect was only marginally significant, $F(1, 94) = 3.57$, $P = .06$, and *partial* $\eta^2 = .04$. Hedonic tone fell significantly over the course of the study, $F(1, 96) = 29.15$, $P < .001$, and *partial* $\eta^2 = .23$. Time had a significant effect on all components of hedonic tone, except self-centred/outward going.

2.2.2. The Effect of Chewing Gum on Mood. Averaging across gum conditions, alertness was higher in chewing gum conditions compared to the control, $F(1, 98) = 3.92$, $P = .05$, and *partial* $\eta^2 = .04$, but gum did not moderate the change in alertness between initial and final alertness, $F(1, 98) < .001$, $P = .99$, and *partial* $\eta^2 < .001$. Although alertness fell by slightly less in the gum with replacement condition, gum flavour and replacement did not significantly moderate changes in alertness between the initial and final assessment of mood, $F(3, 96) = .59$, $P = .62$, and *partial* $\eta^2 = .02$, nor did flavour and replacement have a significant main effect on alertness, $F(3, 96) = 1.61$, $P = .19$, and *partial* $\eta^2 = .05$ (see Figure 1(a)).

Comparing the no-gum control to all gum conditions, there was a trend for gum to increase hedonic tone, $F(1, 98) = 3.54$, $P = .06$, and *partial* $\eta^2 = .04$, although chewing gum did not moderate the difference between final and initial hedonic tone, $F(1, 98) = 1.68$, $P = .2$, and *partial* $\eta^2 = .02$. Although hedonic tone fell somewhat less in the gum with replacement condition, there was no significant effect of gum condition on change in hedonic tone, $F(3, 96) = 1.25$, $P = .3$, and *partial* $\eta^2 = .04$ or main effect of gum condition on hedonic tone, $F(3, 96) = 1.59$, $P = .2$, and *partial* $\eta^2 = .05$ (see Figure 1(b)).

Comparing the no-gum control to all gum conditions, gum did not have a main effect on anxiety, $F(1, 98) = .6$, $P = .44$, and *partial* $\eta^2 = .006$, and there was no interaction between chewing gum and time, $F(1, 98) = 3.54$, $P = .99$, and *partial* $\eta^2 < .001$. The gum conditions did not have a main effect on anxiety, $F(3, 96) = .37$, $P = .78$, and *partial* $\eta^2 = .01$, nor was there a significant effect of gum condition on change in anxiety over time, $F(3, 96) = .86$, $P = .47$, and *partial* $\eta^2 = .03$ (see Figure 1(c)).

2.3. Study 1 Discussion. Consistent with multiple studies examining chewing gum during cognitive performance, the results of Study 1 indicate that chewing gum may increase alertness in the absence of cognitive performance tasks. There was also a trend for hedonic tone to be increased by chewing gum. However, in the absence of cognitive performance tasks anxiety was not affected by chewing gum. The observed alerting effect was not dependent upon mint flavor; it may be the case that chewing plays a key role in such an alerting effect. It is thus of interest if the rate of chewing may moderate alerting effects of gum.

3. Study 2: Rate of Chewing, Mood, and Cognition

This experiment examined if rate of chewing could potentially moderate the effects of gum on attention and mood. Participants were filmed while chewing in order to establish the rate of chewing (pilot data indicated good interrater reliability for scoring of number of chews per minute).

3.1. Methods

3.1.1. Participants. Fifty-six adults (42 females, 14 males; mean age = 19.6, SD = 1.4) were recruited. Participants were mostly students from the School of Psychology, Cardiff University.

3.1.2. Materials

Chewing Gum. As a moderating effect of flavour was not observed in Study 1, participants were given a choice of flavours for this study, as well as Studies 3 and 4. The following chewing gums were available: Wrigley's spearmint, Wrigley's extra (flavours: spearmint, peppermint, cool breeze, and ice), and Wrigley's airwaves (flavours: cherry, green mint, black mint, menthol, and eucalyptus).

Cognitive Tasks

Selective Attention Tasks [27]

(i) Focused Attention Task. In this task target letters appeared as upper case A's and B's in the centre of the screen. Participants were required to identify as quickly and as accurately as possible if the target letter was an A or a B, by pressing A or B with the forefinger of the left or right hand, while ignoring any distracters presented elsewhere on the screen. Before each presentation of the target, three warning crosses were displayed for 500 ms. The middle cross was then replaced by the target, and the outer crosses were replaced by distracters (in the case of trials with distracters). The outer crosses were separated from the middle cross by 1.02° or 2.6°. The target letter was accompanied by nothing, letters which were the same as the target, letters which were different from the target, or asterisks.

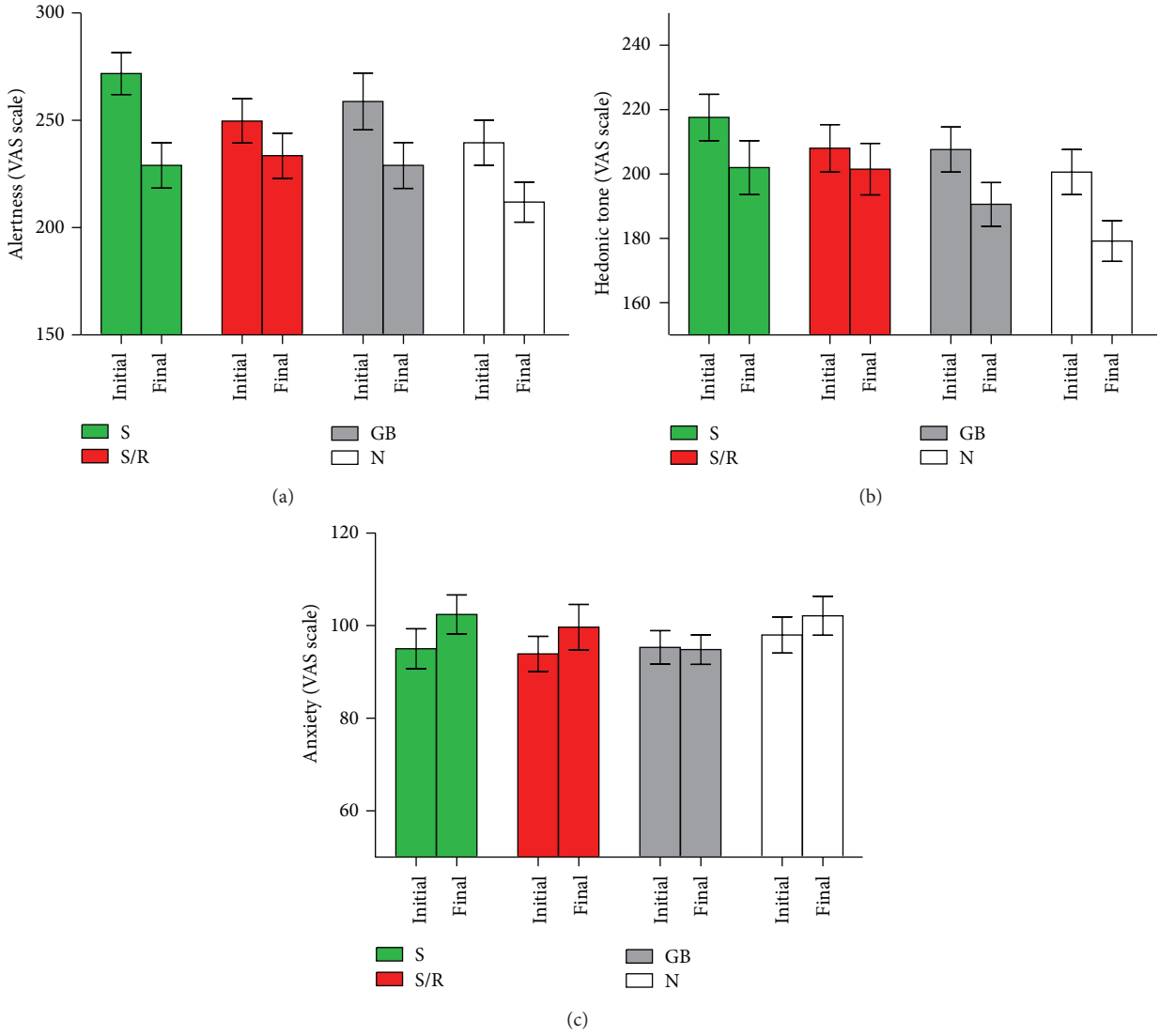

Figure 1: Chewing gum and initial and final mood (Study 1). (a) Alertness. (b) Hedonic tone. (c) Anxiety (S = spearmint gum without replacement, S/R = spearmint gum with replacement, GB = gum base, and N = no-gum control). Error bars represent standard error of the mean.

Mean reaction time, number of errors, and number of long responses (>800 ms) were measured. The threshold for long responses was based on previous research [28]. Breadth of attention was also assessed (the difference in reaction time and accuracy between targets with distracters presented near to the target versus targets with distracters at a further distance from the target). The difference in reaction time between conditions where the target changed from the previous trial and where it remained the same was used as a measure of speed of encoding of new information. Following 10 practice trials, participants completed three blocks of 64 trials. This test lasted approximately 5 minutes.

(ii) Categoric Search Task. This task was similar to the focused attention task previously outlined, including number of practice and experimental trials. However, in this task participants did not know where the target would appear. At the start of each trial, two crosses appeared 2.04° or 5.2° apart or further apart, located towards the left or right extremes of the display. The target then replaced one of these crosses. For half the trials the target was presented alone and for half it was accompanied by a distracter (a digit from 1 to 7).

Mean reaction time, accuracy, and long responses (>1000 ms) were recorded, as well as reaction time and accuracy with which new information was encoded. Differences in reaction time and accuracy for trials where the position of the target stimulus and response key were compatible versus where they were incompatible were used as a measure of response organisation. The effect of the stimulus appearing in a different location versus the same location as the previous trial was measured, as well as the effect of not knowing the location of the target. This task also lasted approximately 5 minutes.

Variable Fore-Period Simple Reaction Time Task [29]. In this task a box was displayed on the screen, followed by a square being presented in the middle of the box. The participant had to press the "Space" button as soon as the square was detected. The period of time elapsed before each appearance of the square varied. This task lasted 3 minutes.

Repeated Digits Vigilance Task [29]. Three-digit numbers were shown on the screen at the rate of 100 per minute. Each number was normally different from the preceding one, but for 8 occasions per minute the number presented was the same as that presented on the previous trial. Participants had to detect these repetitions and respond by hitting the "Space" button as quickly as possible. The number of hits (correctly detected repetitions), reaction time for hits, and number of false alarms were recorded. The task lasted 5 minutes.

3.1.3. Design. Each participant completed both the chewing gum and no-gum control conditions. Similar to previous studies, gum condition was included as a crossover variable to test if any effects of gum would carry over to a no-gum condition (for those who completed the gum condition first).

3.1.4. Procedure. Following informed consent and a familiarisation with the mood and attention tasks, participants completed the mood and attention tasks twice. Participants were instructed to chew two pieces of gum constantly at their own pace during one of these testing sessions and not to chew during the other testing session. Each set of the mood and attention tasks took approximately 25 minutes, and participants completed the second condition immediately after the first. Participants selected a packet of gum just before the chewing condition. They were filmed throughout the chewing session. In order to assess the rate of chewing during each task, notes were taken of when each computerised task began and ended. This timing of the tasks was matched to the footage of the participant completing the task, so that the rate of chewing during each specific task could be calculated. Participants indicated how hard they had been chewing on a scale of 1 (as softly as possible) to 11 (as hard as possible) immediately after the gum condition.

3.1.5. Analysis

Analysis of Footage. The footage was divided into the mood tasks, blocks for the selective attention tasks, and minutes for the simple reaction time task and repeated digits vigilance task, as well as gaps between tasks. Each piece of footage was rated twice, and the intraclass correlation (single measures) was .996, suggesting excellent test/retest reliability for the video rating. The mean of the two scores for each section of the footage was used as the final result.

Statistical Analysis. Mixed ANOVA was used to assess the effect of chewing gum (repeated measures: gum versus no-gum control), order of gum condition (independent measures: gum condition first versus gum condition second), and time-on-task. Time-on-task was entered as a repeated measures variable in the analysis of variables for which time-on-task data was available (i.e., alertness, hedonic tone, and anxiety, categoric search reaction time, focused attention reaction time, simple reaction time, repeated digits hit, false alarms, and reaction time). Time-on-task was defined as pre- versus posttest for reported mood (i.e., before and after the attention tasks) and blocks or minutes for cognitive tasks.

Multiple regressions with forced entry were used to test if the predictors were associated with changes in attention and mood between gum and no-gum conditions. The predictors were rate of chewing, speed of chewing and intensity (how hard gum was chewed), and prior amount of chewing (total count of times chewed; this did not apply for pretest mood, when chewing had just begun).

3.2. Results

3.2.1. Chewing Gum and Mood. There was a significant main effect of time and chewing gum on alertness; alertness fell between pre- and posttest assessments, $F(1, 54) = 57.13$, $P < .001$, and *partial* $\eta^2 = .51$, and chewing gum was associated with higher alertness, $F(1, 54) = 24.62$, $P < .001$, and *partial* $\eta^2 = .31$. There was also an interaction between gum condition and time, $F(1, 54) = 8.47$, $P = .005$, and *partial* $\eta^2 = .14$; alertness was higher in the gum condition posttest. There was a significant interaction between gum and order of gum condition, $F(1, 54) = 11.5$, $P = .001$, and *partial* $\eta^2 = .18$. Alertness was improved to a greater extent by chewing gum when it came first (see Figure 2(a)).

Hedonic tone fell significantly between pre- and posttest, $F(1, 54) = 62.45$, $P < .001$, and *partial* $\eta^2 = .54$, and hedonic tone was significantly higher in the gum condition, $F(1, 54) = 6.74$, $P = .01$, and *partial* $\eta^2 = .11$, but there was not a significant interaction between gum and time, $F(1, 54) = 2.32$, $P = .13$, and *partial* $\eta^2 = .04$. There was a significant interaction between gum and order of gum condition, $F(1, 54) = 14.43$, $P < .001$, and *partial* $\eta^2 = .21$. Hedonic tone was improved to a greater extent by chewing gum when it came first (see Figure 2(b)).

There was no significant effect of time on anxiety, $F(1, 54) = .09$, $P = .77$, and *partial* $\eta^2 = .002$, nor was there a significant main effect of chewing gum, $F(1, 54) = 2.75$, $P = .1$, and *partial* $\eta^2 = .05$. There was no interaction between gum and time, $F(1, 54) = 1.4$, $P = .24$, and *partial* $\eta^2 = .03$, and there was no interaction between gum and order of gum condition, $F(1, 54) = .76$, $P = .39$, and *partial* $\eta^2 = .01$ (see Figure 2(c)).

3.2.2. Chewing Gum, Time-on-Task, and Cognition. Chewing gum had a significant main effect on categoric search speed of encoding. There was a significant interaction between gum condition and time-on-task for repeated digits reaction time, $F(4, 216) = 4.22$, $P = .003$, and *partial* $\eta^2 = .07$ (see Figure 3(a)). Chewing gum lengthened reaction time during the fourth minute, $F(1, 54) = 13.91$, $P < .001$, and *partial* $\eta^2 = .21$, indicating a negative effect of chewing gum on performance at this time. There was also a main effect of time, $F(4, 216) = 20.53$, $P < .001$, and *partial* $\eta^2 = .28$, with reaction time lengthening over time, but there was not a main

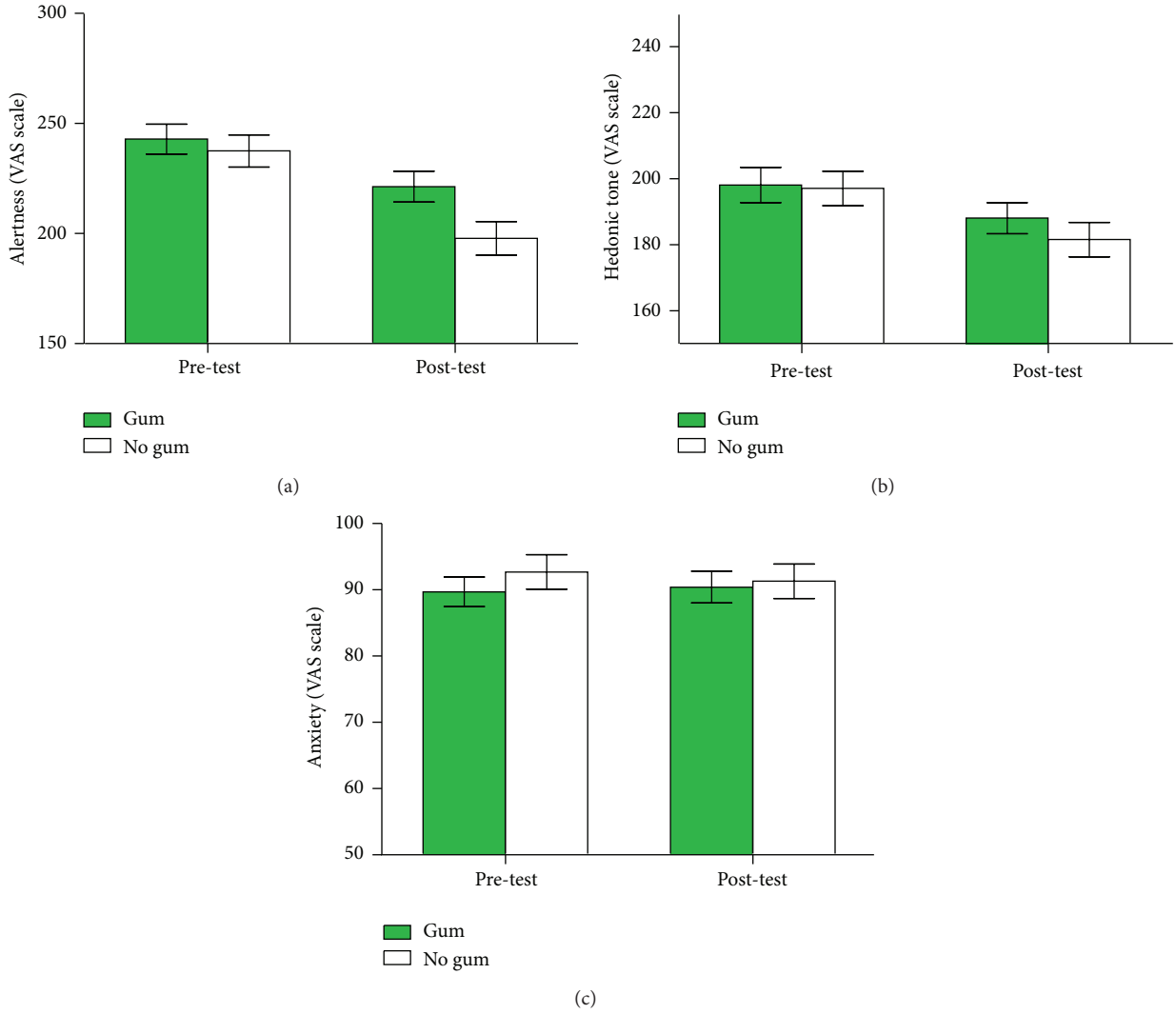

Figure 2: Chewing gum, pre- and posttest mood (Study 2). (a) Alertness. (b) Hedonic tone. (c) Anxiety. Error bars indicate standard error of the mean.

effect of chewing gum, $F(1, 54) = 1.04$, $P = .31$, and *partial* $\eta^2 = .02$. There was no significant interaction between gum and order of gum condition, $F(1, 54) = .04$, $P = .85$, and *partial* $\eta^2 = .001$.

There was a gum by time-on-task interaction for false alarms, $F(4, 216) = 2.25$, $P = .048$, and *partial* $\eta^2 = .05$; chewing gum reduced the number of false alarms during the final minute of the task, $F(1, 54) = 13.69$, $P = .001$, and *partial* $\eta^2 = .2$ (see Figure 3(b)), indicating a positive effect on performance during the final minute. There was a significant main effect of time-on-task, $F(4, 216) = 9.07$, $P < .001$, and *partial* $\eta^2 = .14$, with the number of false alarms falling during later minutes. There was, however, no main effect of chewing gum on false alarms, $F(1, 55) = 1.52$, $P = .22$, and *partial* $\eta^2 = .03$. There was an interaction between gum and order of gum condition $F(1, 54) = 6.7$, $P = .01$, and *partial* $\eta^2 = .11$. False alarms were heightened by gum when gum came before the no-gum control.

For vigilance hits, there was no significant main effect of chewing gum, $F(1, 54) = .91$, $P = .35$, and *partial* $\eta^2 = .02$ or interaction between gum and time-on-task, $F(4, 216) = .28$, $P = .89$, and *partial* $\eta^2 = .005$ (see Figure 3(c)). Again, there was a main effect of time-on-task, with percent hits falling during later minutes, $F(4, 216) = 31.27$, $P < .001$, and *partial* $\eta^2 = .37$. There was an interaction between gum and order of gum condition, $F(1, 54) = 16.5$, $P < .001$, and *partial* $\eta^2 = .23$. Hits were enhanced by chewing gum when it came before the no-gum control.

There was a gum × time interaction for categoric search reaction time, with gum shortening reaction time, but only during the first block, $F(2, 108) = 5.76$, $P = .004$, and *partial* $\eta^2 = .1$ (see Figure 3(d)). This was in the context of a strong main effect of time, $F(2, 108) = 5.92$, $P = .004$, and *partial* $\eta^2 = .1$, with reaction time significantly shortened during the second block, although there was not a main effect of gum, $F(1, 55) = .01$, $P = .95$, and *partial* $\eta^2 < .001$.

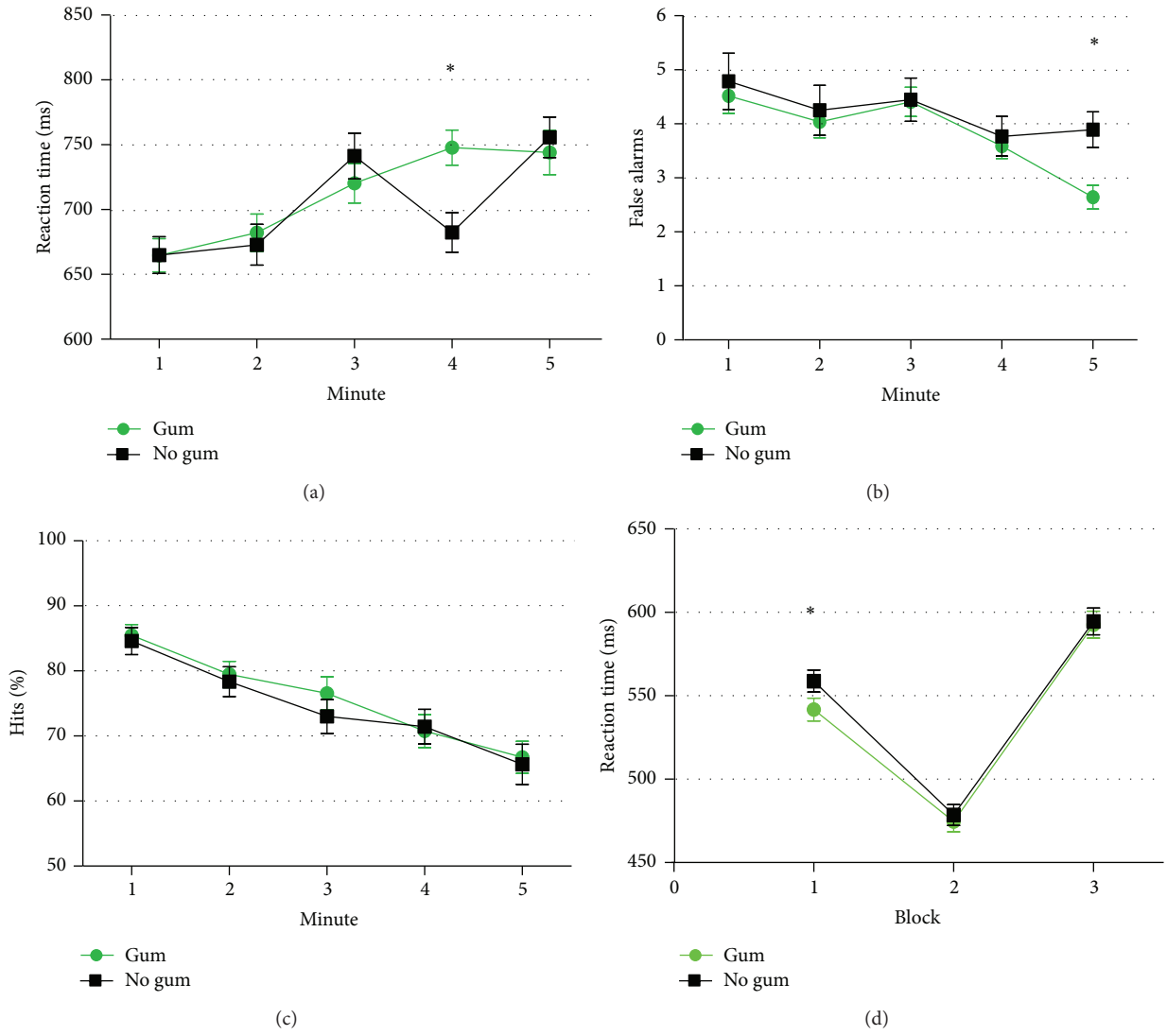

Figure 3: Time-on-task trends in chewing gum effects on (a) vigilance reaction time, (b) vigilance false alarms, (c) vigilance hits, and (d) categoric search reaction time (Study 2). Error bars represent standard error of the mean.

Gum had a significant main effect on focused attention speed of encoding, with slower encoding of information in the gum condition. There was a significant interaction between chewing gum and order of gum condition for focused attention mean reaction time, errors, speed of encoding, and simple reaction time. For simple reaction time, performance was improved by gum when it came after the control condition, while the opposite was true for focused attention. Results are summarised in Table 1.

3.2.3. Rate of Chewing, Mood, and Cognition. A faster rate of chewing was associated with lengthened simple reaction time (beta = .42, $P = .04$). Harder chewing was associated with faster encoding of new information on the categoric search task (beta = −.37, $P = .02$). Greater prior chewing was associated with a higher level of focused attention errors (beta = .32, $P = .04$). Rate of chewing, force of chewing, and prior chewing did not moderate mood or performance on the repeated digits vigilance task. Results are summarised in Table 2.

3.3. Study 2 Discussion. Consistent with previous research as well as Study 1, chewing gum was associated with higher alertness. This might be expected to improve sustained attention performance, although the results indicated lengthened reaction time as well as fewer false alarms as the vigilance task continued, suggesting negative and positive effects on sustained attention performance. Vigilance performance was not moderated by rate of chewing; however, although faster chewing was associated with lengthened simple reaction time, harder chewing was associated with faster encoding of new information on the categoric search task, and prior chewing was associated with more errors on the focused attention task. It thus may be useful for researchers to take some measure of how hard and fast participants are chewing in future research.

Table 1: Chewing gum, time-on-task, and attention.

	Gum	No gum	Results
Focused attention			
Mean reaction time (ms)	Block 1: M = 396.14 (5.89) Block 2: M = 395.2 (5.38) Block 3: M = 400.18 (5.31)	Block 1: M = 391.97 (5.85) Block 2: M = 397.55 (5.26) Block 3: M = 401.39 (5.23)	Gum: $F(1, 54) = .01$, $P = .94$, $\eta_p^2 < .001$ Time**: $F(2, 108) = 5.82$, $P = .004$, $\eta_p^2 = .1$ Gum × time: $F(1.802, 99.12) = 1.44$, $P = .24$, $\eta_p^2 = .03$ Gum × order: $F(1, 54) = 3.89$, $P = .054$, $\eta_p^2 = .06$
Total errors	10.18 (1.12)	10.15 (1.04)	Gum: $F(1, 54) = .003$, $P = .96$, $\eta_p^2 < .0001$ Gum × order††: $F(1, 54) = 5.37$, $P = .02$, $\eta_p^2 = .09$
Long responses	.27 (.09)	.45 (.21)	Gum: $F(1, 54) = .91$, $P = .35$, $\eta_p^2 = .02$ Gum × order: $F(1, 54) = 2.94$, $P = .09$, $\eta_p^2 < .05$
Breadth of attention[1]	18.99 (4.71)	25.83 (5.39)	Gum: $F(1, 54) = 1.03$, $P = .32$, $\eta_p^2 = .02$ Gum × order: $F(1, 54) = .78$, $P = .38$, $\eta_p^2 = .01$
Speed of encoding[2]	25.47 (2.77)	24.44 (2.61)	Gum: $F(1, 54) = .21$, $P = .64$, $\eta_p^2 = .004$ Gum × order††: $F(1, 54) = 12.15$, $P < .001$, $\eta_p^2 = .18$
Categoric search			
Total errors	11.16 (.8)	11.84 (.93)	Gum: $F(1, 54) = 1.45$, $P = .23$, $\eta_p^2 = .03$ Gum × order: $F(1, 54) = 2.51$, $P = .12$, $\eta_p^2 = .04$
Long responses	1.66 (.3)	1.87 (.36)	Gum: $F(1, 54) = .45$, $P = .5$ $\eta_p^2 = .008$ Gum × order: $F(1, 54) = .83$, $P = .37$, $\eta_p^2 = .02$
Response organisation[3]	27.51 (2.54)	26.88 (2.53)	Gum: $F(1, 54) = .05$, $P = .083$ $\eta_p^2 = .001$ Gum × order: $F(1, 54) = .07$, $P = .79$, $\eta_p^2 = .001$
Speed of encoding	17.69 (2.73)	4.77 (2.54)	Gum††: $F(1, 54) = 14.3$, $P < .001$, $\eta_p^2 = .21$ Gum × order: $F(1, 54) = .04$, $P = .84$, $\eta_p^2 = .001$
Spatial uncertainty[4]	105.92 (4.83)	116.26 (5.34)	Gum: $F(1, 54) = 3.28$, $P = .08$, $\eta_p^2 = .06$ Gum × order: $F(1, 54) = .043$, $P = .52$, $\eta_p^2 = .008$
Place repetition[5]	15.62 (2.56)	14 (2.92)	Gum: $F(1, 54) = .35$, $P = .56$, $\eta_p^2 = .006$ Gum × order: $F(1, 54) = .72$, $P = .4$, $\eta_p^2 = .01$
Simple reaction time	Block 1: M = 327.98 (6.39) Block 2: M = 336.58 (7.14) Block 3: M = 339.29 (6.68)	Block 1: M = 314.43 (7.32) Block 2: M = 331.02 (7.44) Block 3: M = 341.09 (8)	Gum: $F(1, 54) = 2.04$, $P = .16$, $\eta_p^2 = .04$ Time††: $F(2, 108) = 16.09$, $P < .001$, $\eta_p^2 = .23$ Gum × time: $F(2, 108) = 2.07$, $P = .13$, $\eta_p^2 = .04$ Gum × order***: $F(1, 54) = 22.08$, $P = .001$, $\eta_p^2 = .29$

Standard errors of the means are in parentheses. [1]Higher score = broader focus of attention. [2]Higher score = slower encoding of information. [3]Higher score = poorer organisation. [4]Higher score = greater uncertainty. [5]Higher score = greater effect of place repetition. **indicates $P < .01$, ††indicates $P < .001$, and ***indicates $P = .001$. Gum × gum order refers to interaction between gum condition and order in which gum condition appeared.

In order to further examine the effects of chewing gum on performance and reported feelings in a more naturalistic setting, the next studies examined chewing gum over the course of a working day.

4. Study 3: Working Day Intervention: Well-Being and Performance

This study examined the effects of chewing gum over a single workday on reported well-being and performance. We hypothesised that chewing gum would be associated with improved well-being and performance at work.

4.1. Method

4.1.1. Participants. One hundred and twenty-six adults (87 females, 39 males) were recruited. Mean age was 29 (SD = 6.7). Participants were full-time university staff; their occupations were administration/secretary (N = 36), researcher/lecturer (36), management (12), technician (10), applied psychologist (4), marketing (4), support worker (4), dentist (2), teacher (2), and other occupations indicated by one participant each (16).

4.1.2. Materials. Chewing gum was the same as used in Study 2.

Well-Being and Performance at Work. Self-report questionnaires were used to assess well-being and performance at work. The Hospital Anxiety and Depression Scale (HADS; [30]) was used; based on principal component analysis of survey data [31], we divided outcomes into inattention/hyperactivity (composed of the items "I feel restless as if I have to be the move," "I have lost interest in my appearance," and "I can enjoy a good book or radio or TV programme") as well as the anxiety and depression, based on the remaining

Table 2: Level of chewing and its effect on mood and cognition.

	Unstandardised B	SE B	Beta	Significance	R^2	Adjusted R^2
Mood						
Pretest alertness					.03	−.01
Constant	26.45	18.14		.15		
Rate of chewing	−.57	.62	−.13	.36		
Intensity	−1.04	2.65	−.06	.7		
Posttest alertness					.06	.01
Constant	20.74	13.08		.12		
Rate of chewing	−.9	.6	−.32	.14		
Prior chewing	.01	.02	.12	.61		
Intensity	2.19	2.53	.13	.39		
Pretest hedonic tone					.02	−.02
Constant	.56	9.77		.95		
Rate of chewing	−.25	.33	−.11	.45		
Intensity	1.44	1.43	.15	.32		
Posttest hedonic tone					.04	−.02
Constant	11.67	7.37		.12		
Rate of chewing	−.41	.34	−.26	.23		
Prior chewing	.004	.01	.11	.47		
Intensity	−.33	1.43	−.04	.82		
Pretest anxiety					.05	.01
Constant	−9.62	−.01		.11		
Rate of chewing	−.006	.2	−.01	.98		
Intensity	1.31	.85	.22	.13		
Posttest anxiety					.02	−.04
Constant	.2	4.07		.96		
Rate of chewing	−.09	.19	−.11	.62		
Prior chewing	−.001	.005	−.04	.86		
Intensity	.29	.79	.06	.71		
Focused attention						
Mean reaction time (ms)					.02	−.04
Constant	.8	8.93		.93		
Rate of chewing	.25	.29	.14	.39		
Prior chewing	−.003	.01	−.04	.81		
Intensity	−1.01	1.78	−.09	.57		
Total errors					.1	.05
Constant	−1.6	2.09		.45		
Rate of chewing	.02	.07	.04	.81		
Prior chewing*	.01	.003	.32	.04		
Intensity	−.15	.42	−.05	.72		
Number of long responses					.02	−.03
Constant	.1	.58		.86		
Rate of chewing	.01	.02	.04	.81		
Prior chewing	.001	.001	.12	.46		
Intensity	−.11	.12	−.15	.34		
Breadth of attention					.11	.06
Constant	−47.15	19.44		.02		
Rate of chewing	1.01	.63	.27	.09		
Prior chewing	−.02	.03	−.12	.46		
Intensity	4.3	3.87	.17	.27		

Table 2: Continued.

	Unstandardised B	SE B	Beta	Significance	R^2	Adjusted R^2
Speed of encoding					.03	−.03
Constant	−6.53	7.38		.38		
Rate of chewing	.13	.24	.09	.58		
Prior chewing	.003	.01	.04	.79		
Intensity	.69	1.47	.07	.64		
Categoric search						
Mean reaction time					.01	−.05
Constant	−1.86	12.14		.88		
Rate of chewing	.01	.44	.002	.99		
Prior chewing	.004	.02	.04	.83		
Intensity	−1.49	2.42	−.1	.54		
Total errors					.03	−.03
Constant	−2.12	1.72		.23		
Rate of chewing	−.01	.06	−.04	.83		
Prior chewing	−.001	.002	−.07	.72		
Intensity	.42	.34	.19	.23		
Long responses					.11	.06
Constant	1.84	.88		.04		
Rate of chewing	−.04	.03	−.22	.2		
Prior chewing	<.001	.001	.06	.73		
Intensity	−.26	.18	−.23	.14		
Response organization					.01	−.05
Constant	1.43	8.79		.87		
Rate of chewing	.21	.32	.12	.52		
Prior chewing	−.003	.01	−.05	.8		
Intensity	−.7	1.75	−.06	.69		
Speed of encoding					.11	.05
Constant	29.75	9.82		.004		
Rate of chewing	−.03	.36	−.02	.93		
Prior chewing	.02	.01	.21	.24		
Intensity*	−4.74	1.96	−.37	.02		
Spatial uncertainty					.05	−.004
Constant	−15.94	16.94		.35		
Rate of chewing	−.88	.61	−.25	.16		
Prior chewing	.01	.02	.09	.63		
Intensity	3.56	3.38	.16	.3		
Place repetition					.02	−.03
Constant	−2.41	8.23		.77		
Rate of chewing	−.1	.3	−.06	.73		
Prior chewing	.01	.01	.18	.35		
Intensity	.09	1.64	.009	.95		
Simple reaction time					.08	.03
Constant	−21.09	15.47		.18		
Rate of chewing*	.84	.49	.42	.04		
Prior chewing	.007	.02	.05	.7		
Intensity	.74	2.69	.04	.79		
Repeated digits vigilance						
Percent hits					.09	.04
Constant	1.41	1.79		.44		
Rate of chewing	−.11	.05	−.32	.06		
Prior chewing	<.001	.002	−.03	.86		
Intensity	.27	.33	.12	.42		

Table 2: Continued.

	Unstandardised B	SE B	Beta	Significance	R^2	Adjusted R^2
False alarms					.04	−.01
Constant	−.73	5.31		.89		
Rate of chewing	.17	.16	.17	.31		
Prior chewing	.002	.006	.06	.69		
Intensity	−1.11	.98	−.18	.26		
Reaction time					.06	.007
Constant	−17.49	24.72		.48		
Rate of chewing	−1.2	.75	−.27	.12		
Prior chewing	.02	.03	.12	.41		
Intensity	6.89	4.56	.23	.14		

*Indicates $P < .05$.

items from these original categories. The fatigue subscale from the profile of fatigue-related symptoms (PFRS; [32]) was used to assess fatigue, as well as a single-item question on how stressful participants found their job (as opposed to life in general). Single-item questions were also used to assess occupational performance; these questioned participants on cognitive failures and productivity/being behind with work (on scales from 0 to 4). These measures had all been used by Smith et al. [16].

4.1.3. Design. The study comprised a one-day intervention; participants were randomly assigned to a chewing condition (female = 39, male = 23) or nonchewing condition (female = 48, male = 16).

4.1.4. Procedure. During an initial study visit before the main testing day, participants completed a familiarisation with the tasks performed on the PC and completed a questionnaire concerning general levels of well-being and performance at work (these acted as baseline scores of well-being and performance). Participants also provided information about demographics, occupation, and habitual level of chewing gum. On the testing day, participants completed a full battery of the mood and attention tasks in the morning as baseline measures. They were required to chew gum (one full packet of 10 pieces) or avoid chewing gum over the course of the working day. Participants were informed that they could chew when they wished during the working day, although they were encouraged to chew when they felt stressed, and they were told to eat and drink as much as they usually would. They returned to the laboratory following work and completed the same well-being questionnaire as in the familiarisation, except this time pertaining to how they felt that workday. They then completed the full battery again, to assess the effects of gum chewing during the workday; no one chewed gum during this battery.

4.1.5. Statistical Analysis. Analyses of covariance were used, with chewing gum condition as the predictor, baseline scores as covariates, and well-being and performance as dependent variables.

4.2. Results. Chewing gum was associated with reduced occupational stress, $F(1, 119) = 3.83$, $P = .027$, and *partial* $\eta^2 = .03$, inattention/hyperactivity, $F(1, 118) = 3.0$, $P = .04$, and *partial* $\eta^2 = .03$, and fatigue, $F(1, 123) = 3.57$, $P = .03$, and *partial* $\eta^2 = .03$. Anxiety was slightly higher in the chewing gum group, as was depression, although these differences were nonsignificant (see Table 3). During the one-day intervention, chewing gum was significantly associated with reporting of fewer cognitive problems, $F(1, 122) = 7.18$, $P = .008$, and *partial* $\eta^2 = .06$ and lower levels of being behind with work, $F(1, 122) = 5.5$, $P = .02$, and *partial* $\eta^2 = .04$.

4.3. Study 3 Discussion. The results indicated that, similar to a previous intervention using the same measures but lasting for two weeks [16], chewing gum for a single working day was associated with lower job stress, fatigue, and inattention. The findings of improved reported performance, as well as the reduction in fatigue and inattention, chime with the findings of heightened alertness from Studies 1 and 2. However, after adjustment for baseline differences, anxiety and depression were not higher in the chewing gum condition. It is of interest if a physiological mechanism might underpin these findings. Consequently, in Study 4 heart rate and cortisol were measured to examine if these would also be altered by chewing gum over the course of a working day.

5. Study 4: Working Day Intervention: Well-Being, Performance, and Physiology

In this study we examined the effects of chewing gum on well-being and performance as well as heart rate and cortisol over the course of a working day. We hypothesised that chewing gum would reduce cortisol, consistent with a reduction in stress, and increase heart rate, consistent with findings of improved performance.

5.1. Methods

5.1.1. Participants. These were thirty full-time university staff (23 females, 7 males). Mean age was 30.4 (SD = 6.9). Their occupations were administration/secretary ($N = 12$),

Table 3: Well-being and performance at baseline and following one-day chewing gum intervention/no-gum control.

	Baseline		Intervention	
	Chewing gum	No gum	Chewing gum	No gum
Job stress	1.44 (.1)	1.48 (.07)	1.08 (.12)*	1.42 (.11)
Fatigue	2.39 (.12)	2.26 (.11)	2.18 (.14)*	2.33 (.12)
Anxiety	5.08 (.35)	4.63 (.29)	3.03 (.3)	2.61 (.29)
Depression	2.72 (.28)	2.12 (.24)	2.42 (.28)	1.97 (.23)
Inattention	2.17 (.17)	2.32 (.18)	2.05 (.2)*	2.52 (.21)
Behind with work	2.31 (.1)	2.48 (.11)	1.35 (.13)**	1.84 (.13)
Cognitive problems	1.97 (.12)	1.98 (.11)	1.01 (.11)†	1.39 (.12)

Standard errors of the means are in parentheses. Significant effects of gum intervention compared to no-gum, adjusting for baseline scores: * indicates $P < .05$, † indicates $P = .01$, and ** indicates $P < .01$.

researcher (9), and other occupations indicated by only one participant each (9).

5.1.2. Materials. Chewing gum as well as mood and well-being measures was the same as those used in Studies 2 and 3. Heart rate was measured using Polar s610 heart rate monitors with Spectra 360 gel. Saliva samples were collected using Sarstedt salivettes.

5.1.3. Design. Participants completed both chewing and no-gum control conditions in a crossover design.

5.1.4. Procedure. During a familiarisation day, participants spent a workday wearing a heart rate monitor, giving saliva samples and recording well-being and performance at the same time as they did during the main testing days. The main testing took place over two separate days. Chewing gum was consumed during one testing day and avoided during the other, control day. The testing days were at least one week apart, in order to avoid carryover effects. Participants came into the lab before work (between 8 a.m. and 9.30 a.m.) to collect heart rate monitors, salivettes, gum (in the gum condition), and questionnaires (if using hard copies).

Participants were requested to chew a full packet of gum during the intervention day. Participants were emailed online links or given hard copies of questionnaires, which were filled in at 10.00, 11.00, 12.00, 14.00, and 15.00. Participants were free to chew gum before filling in the first questionnaire at 10.00. Saliva samples were taken at the same time as the questionnaires. Heart rate was measured throughout the working day.

Participants were requested not to eat for one hour before the postwork session. After work, well-being and performance were assessed again. Participants were instructed to keep saliva samples refrigerated after being taken. Saliva samples were frozen in a −20 freezer on return to the laboratory.

5.1.5. Analysis

Physiological Analysis. Cortisol levels were measured in duplicate by radioimmunoassay adapted from Read et al. [33]. The limit of detection was .7 nmol/L, intra-assay coefficient of variation was 10.8%, 8.8%, and 5.3% at 3.3, 6.4, and 24.7 nmol/L, respectively, and interassay variation was 11.0%, 10.8%, and 10.7% at 2.5, 5.1, and 26.4 nmol/L. Heart rate data was visually examined for artefacts and these were removed.

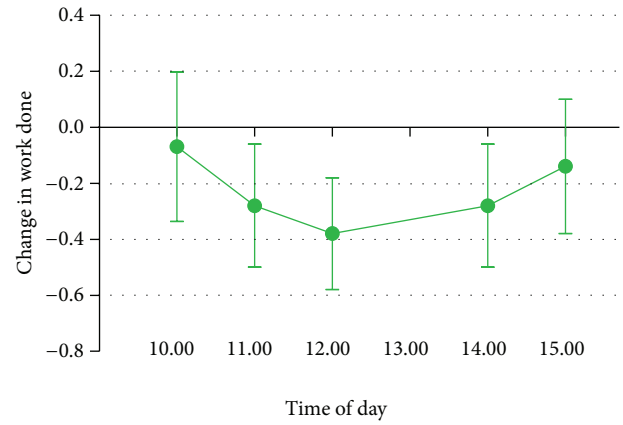

Figure 4: Change between gum conditions in work done (being behind with work) during working day (Study 4). Lower difference scores indicate higher productivity in the gum condition compared to no-gum control. Error bars represent standard error of the mean.

Statistical Analysis. The effects of gum (gum versus no gum) and time of day (10.00, 11.00, 12.00, 14.00, and 15.00) were analysed using repeated measures 2 × 5 ANOVA. The effect of gum as reported at the end of the day was analysed using repeated measures t-tests. As the testing days were separated by at least one week, order of gum condition was not entered into the analysis.

5.2. Results

5.2.1. Chewing Gum, Performance, and Well-Being. There was a trend for work done reported during the day to be higher in the gum condition, $F(1, 23) = 3.28$, $P = .08$, and *partial* $\eta^2 = .13$, with participants reporting being less behind with work (see Figure 4). There were no other effects of gum on well-being or performance during the workday (see Table 4). There were no significant interactions between gum condition and time of day for well-being and performance.

Table 4: Mean change between gum and control conditions in well-being and performance during the workday.

	10 a.m.	11 a.m.	12 noon	2 p.m.	3 p.m.	Results
Cognitive problems	−.03 (.13)	−.03 (.18)	−.27 (.2)	−.11 (.17)	−.41 (.22)	Gum: $F(1, 23) = 1.03$, $P = .32$, $\eta_p^2 = .04$ Time*: $F(2.68, 61.61) = 3.95$, $P = .02$, $\eta_p^2 = .15$ Gum × time: $F(4, 92) = .41$, $P = .8$, $\eta_p^2 = .02$
Job stress	0 (.25)	−.07 (.25)	−.17 (.17)	−.32 (.21)	−.24 (.18)	Gum: $F(1, 24) = .67$, $P = .42$, $\eta_p^2 = .03$ Time†: $F(2.82, 67.71) = 3.46$, $P = .01$, $\eta_p^2 = .13$ Gum × time: $F(2.01, 48.3) = .27$, $P = .77$, $\eta_p^2 = .01$
Fatigue	−.16 (.32)	−.24 (.36)	−.25 (.39)	−.9 (.4)	−.81 (.45)	Gum: $F(1, 25) = 2.99$, $P = .1$, $\eta_p^2 = .11$ Time: $F(2.08, 51.99) = 1.05$, $P = .36$, $\eta_p^2 = .04$ Gum × time: $F(4, 100) = .86$, $P = .49$, $\eta_p^2 = .03$
Anxiety	0 (.21)	0 (.16)	−.4 (.17)	−.07 (.1)	.07 (.16)	Gum: $F(1, 26) = .19$, $P = .67$, $\eta_p^2 = .007$ Time*: $F(4, 104) = 2.49$, $P = .047$, $\eta_p^2 = .09$ Gum × time: $F(2.74, 71.31) = .1.32$, $P = .28$, $\eta_p^2 = .05$
Depression	.13 (.14)	.18 (.13)	−.03 (.14)	.07 (.09)	.14 (.15)	Gum: $F(1, 22) = .01$, $P = .91$, $\eta_p^2 = .001$ Time: $F(2.2, 47.9) = 2.04$, $P = .14$, $\eta_p^2 = .09$ Gum × time: $F(4, 88) = 1.51$, $P = .21$, $\eta_p^2 = 06$

Standard errors of the means are in parentheses. *indicates $P < .05$; †indicates $P = .01$.

At the end of the workday, reporting of cognitive problems was lower in the gum condition than in the control. The gum intervention reduced anxiety and inattention/hyperactivity reported at the end of the day, although these effects were not significant. The effects of chewing gum reported at the end of the intervention conditions are summarised in Table 5.

5.2.2. Chewing Gum and Physiology

Heart Rate. Heart rate was higher during the gum condition for both regular chewers, $M = 1.6$ (change in beats per minute), SD = 8.8, and nonregular chewers, $M = .8$, SD = 5.9. There was a significant main effect of time of day, with heart rate at its lowest between 10 and 12, $F(4, 92) = 21.94$, $P < .001$, and *partial* $\eta^2 = .49$. However, there was no significant main effect of gum, $F(1, 23) = .87$, $P = .36$, and *partial* $\eta^2 = .04$, nor was there an interaction between gum and time, $F(4, 92) = .29$, $P = .88$, and *partial* $\eta^2 = .01$ (see Figure 5).

Cortisol. The interaction between gum condition and time of day was nonsignificant overall, $F(2.97, 65.3) = .82$, $P = .24$, and *partial* $\eta^2 = .04$ (Greenhouse-Geisser adjusted). However, salivary cortisol was higher in the gum condition for the first testing period at 10 a.m., $F(1, 25) = 332.46$, $P < .001$, and *partial* eta squared = .91 (see Figure 6).

5.3. Study 4 Discussion. Similar to Study 3, chewing gum was associated with reduced reporting of cognitive problems, along with a trend for being less behind with work, although we did not observe a positive effect on fatigue, inattention, or job stress in the current study, suggesting that over a one-day intervention the effect of chewing gum is more robust for performance than for well-being. There was some preliminary evidence that cortisol was increased in the morning, although heart rate was not significantly enhanced by chewing gum.

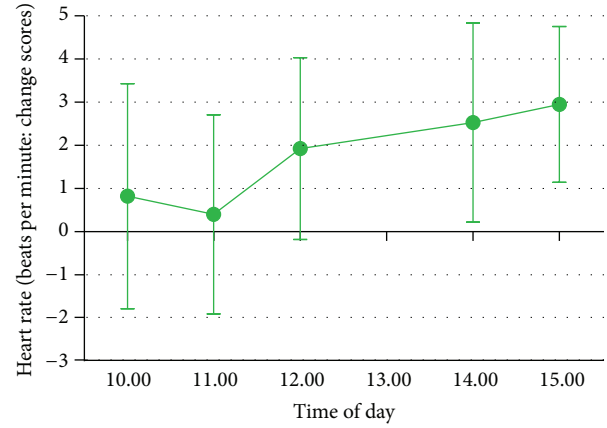

Figure 5: Change between gum conditions in heart rate over course of working day (Study 4). Higher difference scores indicate higher heart rate in the gum condition compared to no-gum control. Error bars represent standard error of the mean.

6. General Discussion

This research offers further evidence in support of an alerting effect of chewing gum, which was associated with heightened alertness both with and without cognitive performance. Although it is a possibility that those in chewing gum condition were coincidentally in a more alert state on entering the lab (which would be captured by a baseline mood measure) and that this carried over to the initial mood rating, there is previous evidence that chewing gum is associated with improved mood rated just after receiving gum [4, 34]. Chewing gum was also associated with reduced fatigue during a working day in Study 3 (Working Day Intervention: Stress

Table 5: Mean change between gum and control conditions in well-being and performance reported at the end of the workday.

Behind with work	−.13 (.21)	$t(29) = .54$, $P = .54$, Cohen's $d = .11$
Cognitive problems*	−.35 (.15)	$t(29) = -2.31$, $P = .03$, Cohen's $d = .42$
Job stress	−.12 (.12)	$t(29) = -.94$, $P = .35$, Cohen's $d = .17$
Fatigue	.02 (.11)	$t(29) = .21$, $P = .84$, Cohen's $d = .04$
Anxiety	−.49 (.36)	$t(29) = -1.38$, $P = .18$, Cohen's $d = .25$
Depression	.25 (.35)	$t(29) = .72$, $P = .48$, Cohen's $d = .13$
Inattention	−.37 (.25)	$t(29) = -1.48$, $P = .15$, Cohen's $d = .27$

*Indicates significant effect of gum intervention, $P < .05$. Negative score indicates lower score in gum condition. Standard errors of the mean are in parentheses.

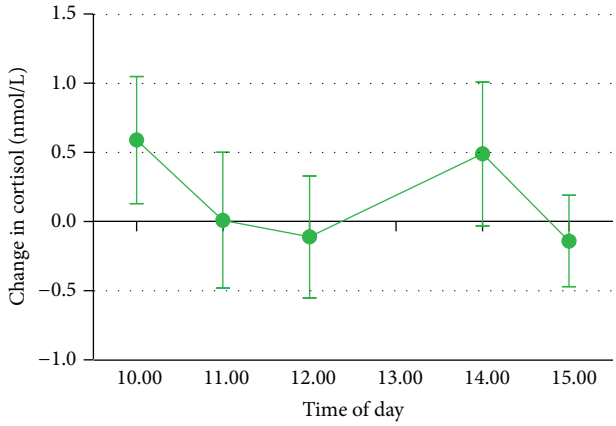

Figure 6: Change between gum conditions in cortisol over course of working day (Study 4). Error bars represent standard error of the mean.

and Performance), although this was not replicated within participants in Study 4 (Working Day Intervention: Stress, Performance, and Physiology). Neither rate of chewing nor flavour of gum moderated the alerting effect, suggesting the effect is not dependent upon mint flavour or intensity of chewing.

Under experimental conditions in Study 2, chewing gum had varying effects on sustained attention performance, with lengthened reaction time in the fourth minute but fewer false alarms during the final minute. This is consistent with previous evidence, which has suggested generally positive but sometimes mixed effects of gum on attention [2]. Although the reduction in false alarms suggests a positive performance effect and slowing in reaction time suggests a negative effect, both findings are consistent with the trade-off between speed and accuracy in vigilance performance. In the findings of Tucha et al. [35], chewing gum had a negative impact on the performance of a vigilance task for children with ADHD as well as normal children. They observed lengthened reaction time in the gum condition, similar to the present findings. However, children with ADHD made more omission errors (in the current research hits and consequently omission errors were not affected by gum) and neither group of children were affected in terms of commission errors (in contrast to the current research, which found a positive impact in terms of reduced false alarms later in the task). There is relatively limited research on chewing gum effects on sustained attention in children, but these findings suggest that children may respond in different ways to chewing gum and specifically that it may not have a beneficial effect in the context of ADHD. Faster chewing was associated with lengthened simple reaction times; a possible explanation for this is that of distraction, as suggested previously [36].

Chewing gum during the working day was associated with reduced cognitive problems and enhanced productivity in both Study 3 and Study 4, suggesting that the experimental findings on sustained attention may generalise to the working environment. Similar to the experimental work of Smith [4] as well as that of Gray et al. [22], there was some preliminary evidence that cortisol was enhanced following chewing gum. However, this was only the case during the initial stages of the day, suggesting that cortisol secretion is not increased throughout the day by chewing gum. The cortisol results also contrast with those of Scholey et al. [37], who observed a decrease in cortisol. This decrease in cortisol may be due to the fact that they used a different stressor compared to Gray et al., who used a psychosocial stress procedure, and Study 4 of the current research, which examined naturalistic cortisol changes over the working day. Although an increase in heart rate and improved vigilance have been observed experimentally following chewing gum [9], heart rate was not affected by chewing gum during the workday, suggesting sympathetic arousal may only be relevant for short-term effects of chewing gum. Previous research which indicated that chewing gum increased heart rate has also found that it improved sustained attention [9] and aspects of memory [18]; this could be an area of interest for further research.

Chewing gum reduced stress in Study 3, but not in Study 4, and in contrast to previous research, such as that of Smith et al. [16], chewing gum did not affect anxiety and depression. This may be due to the relatively brief duration of the chewing gum intervention compared to previous research, which typically employed two weeks of chewing gum. Within the depressed sample in Erbay et al. [25], chewing gum was clearly associated with alterations in gastrointestinal symptoms, suggesting that chewing gum may have a beneficial role in the brain-gut axis [38]; it may thus be of interest if chewing gum can ameliorate gastrointestinal symptoms in stress-related brain-gut axis disorders such as irritable bowel syndrome, although it should be noted that irritable bowel syndrome is associated with a prolonged cortisol response to acute stress [39], so chewing gum may not be beneficial in irritable bowel syndrome under stressful conditions if it increases cortisol.

There are a number of other different mechanisms which could explain the observed effects of chewing gum, such as facial muscle activation [4], as EMG has been shown to be maintained when sustained attention performance declines less [40]. However, as a greater rate of chewing would require greater activation of facial muscles, it seems unlikely that facial muscle activation is impacting on sustained attention in a dose-response manner given the current findings. Another mechanism could be altered central nervous system activity [9, 13, 41–43], perhaps due to a stimulation of regional blood flow or glucose delivery [44]. Allen et al. found enhanced beta activity with flavourless chewing gum; this is consistent with the finding from Study 1 that flavour did not appear to moderate any alerting effect of chewing gum. However, although Allen et al. observed increased heart rate under acute experimental conditions, the current results do not provide evidence for increased heart rate over the course of the working day. It should be borne in mind that, as chewing gum had a rapid effect on mood in Study 1, there should be a mechanism which is rapid-acting that could explain these effects.

Similar to a number of previous studies on the effects of chewing gum on cognition and mood [23, 37], we used predominantly female samples. There is previous survey evidence that females are more likely to chew gum than males [19], so it is likely that this is representative of broader consumption patterns.

Future research in this area could assess the psychophysiological effects of chewing gum in more depth; indices of heart rate variability and ambulatory blood pressure have been associated with work stress [45] and so may be informative of effects of chewing gum on stress. Given clearer effects of chewing gum during longer interventions it may be the case that cortisol secretion may be reduced along with occupational stress after two weeks of chewing gum. It would be useful to assess level of physical activity during the workday in future research; experimental conditions may be associated with a consistent level of physical activity, but activity levels may differ substantially between individuals' working days. This would lead to higher variability in heart rate, in which gum has been shown to increase under controlled, low-activity conditions [9, 18]. Physical activity can also impact upon cortisol levels [46, 47]; closer monitoring of physical activity requiring participants to avoid intense physical activity before and during a study could help to obtain more reliable results.

7. Conclusions

Chewing gum was associated with enhanced productivity and reduced cognitive errors at work, as well as heightened cortisol in the morning. However, rate of chewing, flavor, or cognitive performance did not moderate the enhancement of alertness and changes in sustained attention by chewing gum, suggesting that greater motor activity does not exaggerate these effects.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] A. P. Allen and A. Smith, "A review of the evidence that chewing gum affects stress, alertness and cognition," *Journal of Behavioral and Neuroscience Research*, vol. 9, no. 1, pp. 7–23, 2011.

[2] Y. Hirano and M. Onozuka, "Chewing and attention: a positive effect on sustained attention," *BioMed Research International*. In press.

[3] O. Tucha, L. Mecklinger, K. Maier, M. Hammerl, and K. W. Lange, "Chewing gum differentially affects aspects of attention in healthy subjects," *Appetite*, vol. 42, no. 3, pp. 327–329, 2004.

[4] A. Smith, "Effects of chewing gum on cognitive function, mood and physiology in stressed and non-stressed volunteers," *Nutritional Neuroscience*, vol. 13, no. 1, pp. 7–16, 2010.

[5] A. J. Johnson, M. Muneem, and C. Miles, "Chewing gum benefits sustained attention in the absence of task degradation," *Nutritional Neuroscience*, vol. 16, no. 4, pp. 153–159, 2013.

[6] A. P. Allen and A. P. Smith, "Effects of chewing gum and time-on-task on alertness and attention," *Nutritional Neuroscience*, vol. 15, no. 4, pp. 176–185, 2012.

[7] L. Tucha and W. Simpson, "The role of time on task performance in modifying the effects of gum chewing on attention," *Appetite*, vol. 56, no. 2, pp. 299–301, 2011.

[8] K. Sakamoto, H. Nakata, Y. Honda, and R. Kakigi, "The effect of mastication on human motor preparation processing: a study with CNV and MRCP," *Neuroscience Research*, vol. 64, no. 3, pp. 259–266, 2009.

[9] A. P. Allen, T. J. C. Jacob, and A. P. Smith, "Effects and after-effects of chewing gum on vigilance, heart rate, EEG and mood," *Physiology & Behavior*, vol. 133, pp. 244–251, 2014.

[10] Y. Masumoto, T. Morinushi, H. Kawasaki, T. Ogura, and M. Takigawa, "Effects of three principal constituents in chewing gum on electroencephalographic activity," *Psychiatry and Clinical Neurosciences*, vol. 53, no. 1, pp. 17–23, 1999.

[11] T. Morinushi, Y. Masumoto, H. Kawasaki, and M. Takigawa, "Effect on electroencephalogram of chewing flavored gum," *Psychiatry and Clinical Neurosciences*, vol. 54, no. 6, pp. 645–651, 2000.

[12] J. Fan, B. D. McCandliss, T. Sommer, A. Raz, and M. I. Posner, "Testing the efficiency and independence of attentional networks," *Journal of Cognitive Neuroscience*, vol. 14, no. 3, pp. 340–347, 2002.

[13] Y. Hirano, T. Obata, H. Takahashi et al., "Effects of chewing on cognitive processing speed," *Brain and Cognition*, vol. 81, no. 3, pp. 376–381, 2013.

[14] S. Rickman, A. Johnson, and C. Miles, "The impact of chewing gum resistance on immediate free recall," *British Journal of Psychology*, vol. 104, no. 3, pp. 339–346, 2013.

[15] M. D. Kozlov, R. W. Hughes, and D. M. Jones, "Gummed-up memory: chewing gum impairs short-term recall," *The Quarterly Journal of Experimental Psychology*, vol. 65, no. 3, pp. 501–513, 2012.

[16] A. P. Smith, K. Chaplin, and E. Wadsworth, "Chewing gum, occupational stress, work performance and wellbeing. An intervention study," *Appetite*, vol. 58, no. 3, pp. 1083–1086, 2012.

[17] A. P. Smith and M. Woods, "Effects of chewing gum on the stress and work of university students," *Appetite*, vol. 58, no. 3, pp. 1037–1040, 2012.

[18] L. Wilkinson, A. Scholey, and K. Wesnes, "Chewing gum selectively improves aspects of memory in healthy volunteers," *Appetite*, vol. 38, no. 3, pp. 235–236, 2002.

[19] A. P. Smith, "Chewing gum, stress and health," *Stress and Health*, vol. 25, no. 5, pp. 445–451, 2009.

[20] A. Smith, "Effects of chewing gum on stress and health: a replication and investigation of dose-response," *Stress and Health*, vol. 29, no. 2, pp. 172–174, 2013.

[21] K. Sketchley-Kaye, R. Jenks, C. Miles, and A. J. Johnson, "Chewing gum modifies state anxiety and alertness under conditions of social stress," *Nutritional Neuroscience*, vol. 14, no. 6, pp. 237–242, 2011.

[22] G. Gray, C. Miles, N. Wilson, R. Jenks, M. Cox, and A. J. Johnson, "The contrasting physiological and subjective effects of chewing gum on social stress," *Appetite*, vol. 58, no. 2, pp. 554–558, 2012.

[23] A. J. Johnson, R. Jenks, C. Miles, M. Albert, and M. Cox, "Chewing gum moderates multi-task induced shifts in stress, mood, and alertness. A re-examination," *Appetite*, vol. 56, no. 2, pp. 408–411, 2011.

[24] L. K. Torney, A. J. Johnson, and C. Miles, "Chewing gum and impasse-induced self-reported stress," *Appetite*, vol. 53, no. 3, pp. 414–417, 2009.

[25] F. M. Erbay, N. Aydin, and T. Sati-Kirkan, "Chewing gum may be an effective complementary therapy in patients with mild to moderate depression," *Appetite*, vol. 65, pp. 31–34, 2013.

[26] D. Hodoba, "Chewing can relieve sleepiness in a night of sleep deprivation," *Sleep Research Online*, vol. 2, no. 4, pp. 101–105, 1999.

[27] D. E. Broadbent, M. H. P. Broadbent, and J. L. Jones, "Performance correlates of self-reported cognitive failure and of obsessionality," *British Journal of Clinical Psychology*, vol. 25, no. 4, pp. 285–299, 1986.

[28] A. Smith, D. Sutherland, and G. Christopher, "Effects of repeated doses of caffeine on mood and performance of alert and fatigued volunteers," *Journal of Psychopharmacology*, vol. 19, no. 6, pp. 620–626, 2005.

[29] A. Smith, A. Kendrick, A. Maben, and J. Salmon, "Effects of breakfast and caffeine on cognitive performance, mood and cardiovascular functioning," *Appetite*, vol. 22, no. 1, pp. 39–55, 1994.

[30] A. S. Zigmond and R. P. Snaith, "The hospital anxiety and depression scale," *Acta Psychiatrica Scandinavica*, vol. 67, no. 6, pp. 361–370, 1983.

[31] A. P. Allen, *Chewing gum's effects on alertness, performance and stress [Ph.D. thesis]*, Cardiff University, 2013.

[32] C. Ray, W. R. C. Weir, S. Phillips, and S. Cullen, "Development of a measure of symptoms in chronic fatigue syndrome: the profile of fatigue-related symptoms(pfrs)," *Psychology & Health*, vol. 7, no. 1, pp. 27–43, 1992.

[33] G. F. Read, D. R. Fahmy, and R. F. Walker, "Determination of cortisol in human plasma by radioimmunoassay. Use of the 125I labelled radioligand," *Annals of Clinical Biochemistry*, vol. 14, no. 6, pp. 343–349, 1977.

[34] A. Smith, "Effects of caffeine in chewing gum on mood and attention," *Human Psychopharmacology: Clinical and Experimental*, vol. 24, no. 3, pp. 239–247, 2009.

[35] L. Tucha, W. Simpson, L. Evans et al., "Detrimental effects of gum chewing on vigilance in children with attention deficit hyperactivity disorder," *Appetite*, vol. 55, no. 3, pp. 679–684, 2010.

[36] S. V. Onyper, T. L. Carr, J. S. Farrar, and B. R. Floyd, "Cognitive advantages of chewing gum. Now you see them, now you don't," *Appetite*, vol. 57, no. 2, pp. 321–328, 2011.

[37] A. Scholey, C. Haskell, B. Robertson, D. Kennedy, A. Milne, and M. Wetherell, "Chewing gum alleviates negative mood and reduces cortisol during acute laboratory psychological stress," *Physiology & Behavior*, vol. 97, no. 3-4, pp. 304–312, 2009.

[38] J. F. Cryan and T. G. Dinan, "Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour," *Nature Reviews Neuroscience*, vol. 13, no. 10, pp. 701–712, 2012.

[39] P. J. Kennedy, J. F. Cryan, E. M. M. Quigley, T. G. Dinan, and G. Clarke, "A sustained hypothalamic-pituitary-adrenal axis response to acute psychosocial stress in irritable bowel syndrome," *Psychological Medicine*, vol. 44, no. 14, pp. 3123–3134, 2014.

[40] W. Waterink and A. van Boxtel, "Facial and jaw-elevator EMG activity in relation to changes in performance level during a sustained information processing task," *Biological Psychology*, vol. 37, no. 3, pp. 183–198, 1994.

[41] F. Li, H. Shen, B. Li, X. Zhou, and D. Hu, "Multiple neural networks involved in chewing gum: a functional MRI study using group-ICA," in *Advances in Cognitive Neurodynamics (II)*, pp. 399–405, Springer, Dordrecht, The Netherlands, 2011.

[42] H. Yu, X. Chen, J. Liu, and X. Zhou, "Chewing gum inhibits the sensory processing and the propagation of stress-related information in a brain network," *PLoS ONE*, vol. 8, no. 4, Article ID e57111, 2013.

[43] K. Kubo, H. Chen, and M. Onozuka, "The relationship between mastication and cognition," in *Senescence and Senescence-Related Disorders*, Z. Wang and H. Inuzuka, Eds., chapter 5, 2013.

[44] R. Stephens and R. J. Tunney, "Role of glucose in chewing gum-related facilitation of cognitive function," *Appetite*, vol. 43, no. 2, pp. 211–213, 2004.

[45] T. G. M. Vrijkotte, L. J. P. van Doornen, and E. J. C. de Geus, "Effects of work stress on ambulatory blood pressure, heart rate, and heart rate variability," *Hypertension*, vol. 35, no. 4, pp. 880–886, 2000.

[46] A. Viru, M. Viru, K. Karelson et al., "Adrenergic effects on adrenocortical cortisol response to incremental exercise to exhaustion," *European Journal of Applied Physiology*, vol. 100, no. 2, pp. 241–245, 2007.

[47] W. Kindermann, A. Schnabel, W. M. Schmitt, G. Biro, J. Cassens, and F. Weber, "Catecholamines, growth hormone, cortisol, insulin, and sex hormones in anaerobic and aerobic exercise," *European Journal of Applied Physiology and Occupational Physiology*, vol. 49, no. 3, pp. 389–399, 1982.