On fNIRS-based Study of Human Cognitive Function Related to Taste

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(Degree)
博士（工学）

(Date of Degree)
2014-03-25

(Date of Publication)
2015-03-01

(Resource Type)
doctoral thesis

(Report Number)
甲第6105号

(URL)
https://hdl.handle.net/20.500.14094/D1006105

Doctoral Dissertation

On fNIRS-based Study of Human Cognitive Function Related to Taste

fNIRS を用いた人間の味覚認知に関する研究

By

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January 2014

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Abstract

Gustation serves an important role in human as one specific and basic function of oral cavity (Liu, 2002), which is closely related to brain function. The information and sensation gained by receptors is not only to modulate food intake but also affect high cognitive process of human brain (Kato, 2007).

Some traditional neurobiology, neurophysiology and neuro-anatomy studies, based on electrophysiological, clinical and anatomical researches, have accumulated a lot of knowledge and theories about taste organ, anatomic constitution of taste pathways, transduction of taste signal and classification of tastants. However, because such traditional techniques are invasive and can't be applied directly to human, the knowledge of how the central nervous system is organized to process information of taste is relatively poor concomitantly. Recently, with the rapid development of functional imaging techniques, the issue about the sensory function of human brain has attracted many researchers' attention. Nevertheless, compared with other sensory functions, such as vision, audition and olfaction, studies on gustatory cognitive processing remain scarce. The representation of gustatory neural circuits is still in its infancy.

Functional near-infrared spectroscopy (fNIRS), as an emerging noninvasive neuroimaging technique, is widely used to monitor the brain activation and can reveal hemodynamic and metabolic changes (Ferrari et al., 2012). In the almost 35 year since Jobsis firstly applied NIRS to monitor changes in tissue oxygenation (Jobsis, 1977), this

technology has developed remarkably. Compared to other neuroimaging methods, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI) or magneto encephalography (MEG), fNIRS has many advantages. As we all known, the experiments, using fMRI or another brain imaging technologies, requires the subject being scanned stays completely still so that it can capture a clear image. It makes the subject feel stressful physiologically and/or physically. On the contrary, fNIRS only requires compact experimental equipment and is less restrictive of subject's movement, allowing the brain function to be monitored under more natural conditions (Coyle et al., 2004; Hoshi et al., 2001). So far, this technique has been widely used for some brain research of sensory, motor and other high cognitive process. In order to answer the question on central organization of taste, some researches have been already conduced on gustation, but the results are not identical.

It is known that fNIRS can measure activity of surface cortex, but can't reach the deeper gustatory areas such as insula which is located deep inside the brain. Among the regions which fNIRS can measure, the lateral prefrontal cortex (PFC) was suggested to be related to taste and other food-related activities (Kringelbach et al., 2004). This finding evoked research interest in the fields associated with feeding behaviors, such as obesity and eating disorders (Wagner et al., 2006; Kato, 2007).

Inspired by these previous findings, we investigated the following questions: (a) whether fNIRS can be used to research on taste-related brain function; (b) whether PFC is involved in taste processing; (c) and, if true, show where is responding to taste in the human brain. To answer these questions, based on the event-related design, we selected fNIRS to monitor activation of human lateral PFC during taste processing. The primary aim of this study is to find the region of interest (ROI) which is related to taste, and

make further understanding on the central organization of taste, especially for clarifying the mechanism of taste preference. We hope the investigation would further contribute to the understanding of higher cognitive processing on gustatory system and to provide some theoretical evidence for studying on taste disease, such as dyspepsia and disorder.

In this study, firstly, we used fNIRS to monitor the activation of prefrontal lobe on human brain in sweet solution with different concentration. Based on event-related design, the experiments were performed with 16 volunteers by sweet taste stimulus. It was confirmed that fNIRS provided an alternative way for studying taste-related brain function under more natural conditions, and the PFC is involved in sweet taste processing. In addition, the activated channels induced by the higher concentration were more than those of lower concentration. These findings are in line with previous studies.

Then, we compared the representation of a pleasant and an aversive taste using fNIRS, so as to obtain further understanding of the taste preference mechanism. The pleasant stimulus used was sweet taste (10% sucrose), and the unpleasant stimulus was sour taste (1% critic acid). The experiments were also performed with 16 healthy volunteers using the OEG-16 fNIRS sensor. A general linear model was used to analyze the collected fNIRS data. For the concentration change of oxygenated hemoglobin, we found significant deactivation was induced by sweetness and sourness in parts of the frontopolar area, orbitofrontal area and dorsolateral prefrontal cortex in bilateral hemisphere of human brain. And the right PFC showed different levels of activation between sweetness and sourness. In addition, brain activity was more sensitive to sourness than sweetness.

Finally, we investigated brain activation responses to aversive tastes (bitterness and sourness) using electroencephalogram (EEG) and hemoencepalogram (NIR-HEG)

simultaneously so as to clarify the intrinsic food preference mechanism. A conventional delayed response task based on contingent negative variation (CNV) paradigm was adopted to extract real brain response components from spontaneous background signals. Results showed excessive evoked EEG potentials in both bitter and sour responses, but not in purified water. Therefore we suggested that these potentials would be only attributed to sour and bitter stimuli. As these potentials appeared before P3, we considered that they are unconscious electro-physiological early markers for attention. We also identified CNV in a late stage for sour stimulus and suggested it is related to taste prejudice. In addition, NIR-HEG responses showed significant changes for every stimulus and, in particular, sourness gave larger rise than bitterness. In spite of limitation to timing accuracy of taste presentations, the early markers found in this study could be fundamentals for investigating individual food preference.

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Chapter 1

Introduction

Recently, the prevalence of taste diseases, which caused by aging society and the changes of the diet structure, such as anorexia nervosa, dyspepsia and taste disorder, appears to be increasing. Although these diseases are not life-threatening diseases directly, they have a strong impact on our quality of life. For this reason, the interest in understanding gustatory processing is growing, not only for basic science, but also for applications. So far, many researchers have done a lot of works about gustatory sensation and some knowledge of taste cognitive processing has been accumulated. But compared with some other sensory such as olfaction, vision and audition, relatively little is known of how the human brain process taste. And the results are also on disputed.

This chapter will provide an introduction of the human taste-related brain function, followed by an overview of the sense of taste. And then, the motivation and structure of this dissertation will be presented.

1.1 Human Taste-Related Brain Function

Actually, the research on human taste-related brain function has been a topic of both clinical and academic speculation for a long time. Gustation serves an important role in human as one specific and basic function of oral cavity (Liu, 2002), and it plays a central role in food intake. The gustatory sensation and information provides a

passageway for energy and nutrient balance. Information conveyed via the gustatory system aids in identifying edible and nutritious foods sources, enables us to avoid poisonous substances, as well as drives the hedonic evaluation of potential nutrition, which can take place prior to during, or after ingestion (Ohla et al., 2012). Therefore, gustation serves a vital function that calls for efficient coupling of perception and behavior in order to allow a fast behavioral response (Liu, 2002; Drewnowski, 1997; Ohla et al., 2012). For its importance, there is currently an increasing interest in the cognitive neuroscience of taste-related brain function associated with daily feeding behaviors. It is not only for academic explorations, but also for application (Ohla et al., 2012). To date, a lot of theory and knowledge about the sense of taste have been accumulated, which we will talk about specifically in the next session.

1.2 Related Work

Some traditional neurophysiology and neuro-anatomy studies have accumulated a lot of knowledge and theories about taste organ, anatomic constitution of taste pathways, transduction of taste signal and classification of tastants. Most of them depended on autopsy, head injured patients and animal experiments. However, since the traditional technique are harmful and cannot be applied to human, the accumulated knowledge and in particular to taste-related brain function is far from complete. More recently, with the advent of modern neuroimaging techniques, a wider range of taste-related brain function can be monitored more objectively and effectively. And the findings recast our understanding about the central organization of taste. Hereby, we would like to give a review focus on the taste-related brain function.

1.2.1 Research perspective for gustatory processing

For the complexity of taste-related brain function, a number of investigators have attempted to study it on some aspects summarized as follows.

1.2.1.1 Basic taste quality

Although the subjective feeling of taste varies, in generally, the sensation of taste can be categorized into five basic taste qualities: sweetness, sourness, saltiness, bitterness, and possibly umami. The basic tastes give the brain information which is always utilized in the ultimate decision of ingestion or rejection of a potential food. The Sensation of umami tells the body that protein-rich food is being ingested; sweet taste indicates carbohydrate intake and salty taste give us information that is important for the balance between minerals or electrolytes and water. The taste of bitter and sour likely developed as warning signals. Many toxic plants taste bitter, and a strong bitter taste can induce vomiting (Gazzaniga et al., 2009).

In the fields of biochemistry and molecular and cell biology, the signal transduction have been explored for these basic tastes. Nonetheless, the questions how the brain processes the taste encoding and taste information are still unanswered. In 1994, Japanese researchers, Kinomura, *et al.* used positron emission tomography (PET) to study the functional anatomy of salt taste perception in human brain and found that discrimination of 0.18% saline from pure water was associated with significantly increased regional cerebral blood flow (rCBF) values in the thalamus, the insular cortex, the anterior cingulate gyrus, the parahippocampal gyrus, the lingual gyrus, the caudate nucleus, and the temporal gyri (Kinomura et al., 1994). To our knowledge, this is also the first time to investigate the taste-related brain mapping for human. Afterwards,

several researches studied on taste perception for the basic taste quality. They selected sucrose, sugar, quinine, citric acidic, sodium chloride and other substance as taste stimuli, and found the activation evoked by these basic tastes mainly includes insula and neighboring operculum, the orbitofrontal cortex limbic system and amygdala (O` Doherty et al., 2002; Zald DH et al., 2002; Small DM et al., 1997 a, 1997 b).

1.2.1.2 Pleasant and aversive tastes

According to the emotion evoked by the taste, the basic five tastes can be classified as aversive/ unpleasant and appetitive/ pleasant taste. The emotions derived from tastants refer to food modulation, balance of nutrition, harm avoidance and other human behavior. These taste-related emotions play important roles in human survival. Specifically, among these five basic tastes, sweetness is often regarded as a pleasurable sensation, while sourness serves as an aversive taste (Miller, 2011; Chen et al; 2011). The investigation for brain activation evoked by these two classes is not only to understand the location of gustatory system, but also help us to further access the mechanism of taste preference and emotion. Zald *et al*. (2002) attempted to investigate the neural correlates of tasting concentrated quinine and sugar solution and found pleasant and unpleasant gustatory stimuli activate the right posterior orbitofrontal cortex (OFC), and the left inferior frontal pole/anterior OFC demonstrates valence-specific responses to aversive gustatory stimuli (Zald et al., 2002). A recent functional magnetic resonance (fMRI) study investigated the brain activation to pleasant and unpleasant tastes and further to investigate whether the regions activated by these two tastes show topological separation (O`Doherty et al., 2002).

1.2.1.3 Taste-related brain function and physiological status of subject

The taste-related brain function is closely related to the feeding behavior, and the physiological status of subject, such as in hungry or satiety condition, may affect the brain function during the gustatory processing. For instance, there are some evidences showing that neurons in the secondary taste cortex region have been found to be modulated by the motivational state of the animal, responding to the sight or taste of food when the animal is hungry and not responding when the animal is satiated (Rolls et al., 1989; Mora et al., 1979). For human, Small *et al.* performed successive PET scans on volunteers as they ate chocolate to beyond satiety, while non-specific effects of satiety (such as feelings of fullness and autonomic changes) were also present and probably contributed to the modulation of brain activity. As the subjects became satiated, their desire for more chocolate dropped (Small et al., 2001). Several studies indicated the same stimulus may activate different cerebral regions in the different physiological status of subject.

1.2.1.4 Lateralization of brain activation to gustatory processing

The lateralized activation pattern of is of interest on the taste processing. Although it is well known that the primary gustatory afferents from the tongue project to the ipsilateral nucleus of the solitary tract (Goto et al., 1983; Jyoichi et al., 1985; Najakajima et al., 1983), the laterality of the gustatory pathway has been controversial. In some brain lesions studies, they performed the experiments on the patients, who showed impairment of gustation on the tongue on the ipsilateral side of the vascular lesion in the unilateral midbrain, and suggested ipsilateral projection from the nucleus of the solitary tract to the thalamus (Shikama et al., 1996; Uesaka et al., 1998). On the other hand,

Fujikane and others reported the central gustatory pathways in humans ascend contralaterally from the solitary nucleus to the ventroposteromedial nucleus of the thalamus (Fujikane et al., 1998; Lee et al., 1998; Onoda et al., 1999). And there are some studied showed the gustatory pathway from the tongue to the gustatory cortex is bilaterally (Aglioti et al., 1999, 2000). There may be also lateralization differences in the taste encoding for specific tastes. Anyway, although these neuroimaging and lesion studies have research on the laterality of gustation, the lateralized effects in the brain processing of specific tastes remain mysterious.

1.2.1.5 Taste cognitive processing for memory or expectation

In addition to the aspects presented above, there are some researcher investigated the taste higher cognitive processing in human brain based on the taste memory and expectation. In such studies, the investigators recorded the brain activation when the subject was inquired to imagine or recall one taste instead of tasting. For instance, Levy *et al.* (1999) recorded the brain activation while the subjects were required to taste the stimuli in their imagination and results showed the activated regions is in consisted with the general gustatory pathway (Levy et al., 1999). Similarly, Okamoto *et al.*(2006) have done a series researches on PFC activity for taste encoding based on different experimental tasks and designs, and almost of the results illustrated the lateral PFC is recruited of intentional taste encoding (Okamoto et al., 2006a, 2006b). Such researches not only reveal the taste cognitive mechanisms related to memory encode and expectation, but also provide more information for the neural mechanism of taste system.

1.2.2 Neural mechanisms of taste transformation

1.2.2.1 Functional brain mapping of taste sensory system

Up to now, although the common gustatory areas have been well known, the cortical localizations for taste sensory system are still controversial. To summary, there are three types of cortices which are believed to be involved in sensory information processing: primary, secondary, and association system (Okamoto et al., 2007).The primary cortex, located around the insular and operculum areas, is the part of the human brain cortex that firstly receives neural signals from peripheral sensory organs (Pritchard, 1991, 1999; Kinomura et al., 1994; Small et al., 1999; Barry et al., 2001). This gustatory sensory information is then project to the orbitofrontal cortex (OFC) which is located in human prefrontal cortex (PFC), and it has been regarded as the secondary gustatory area (Zald et al., 2000, 1998; Kringelbach et al., 2004). The association cortices receive neural inputs from multiple sensory areas and process multi-modal information. The cognitive processing of sensory information often involves association cortices in addition to sensory cortices (Small et al., 2004; Kobayashi et al., 2004; Kringelbach et al., 2004).

Generally, for taste, the anatomical location main includes the OFC, the anterior insula, the frontal operculum, anterior cingulate cortex, and some areas in association cortices, but the precise location has not been fixed. In fact, cortex location of taste is remains in disputed (Okamoto et al., 2007).

1.2.2.2 Cerebral regions in taste activity

As presented above, the gustatory system includes the primary, secondary areas and other associated cortex. In this session, we summarized the previous findings and have review about the anatomical location of these gustatory areas in detail.

Insula and Operculum

Brain functions studies indicated there is a close relationship between the taste and the insula and operculum. The dorsal insula and neighboring operculum are frequently described as primary gustatory cortex on the basis of anatomical, electrophysiological, and lesion evidence (Norgren, 1990). Furthermore, a number of neural imaging studies attempted to investigate functions of insula and neighboring operculum in gustatory system and most of them support their role in gustatory processing (Small et al. 1997b, 1999; Zald et al. 1998a; Faurion et al. 1999; Francis et al. 1999; Frey and Petrides 1999; Kinomura et al. 1994). To summary, so far, the main interest of investigators for this region is its specific mechanism. They wondered whether there is any different activation response to different tastants or whether it shows any hemispheric difference.

Orbitofrontal cortex and prefrontal cortex

From the insula and operculum, the gustatory information is conveyed to the OFC, which is a part of the PFC region in frontal lobes in human brain. The OFC is involved in the cognitive processing of decision making. For taste, The OFC is regarded as the secondary gustatory area. Studies indicated that some neurons in the OFC respond to gustatory stimuli. Rolls and colleagues refer to the caudolateral OFC as secondary gustatory cortex based on single-cell recordings and its afferents from the insula (Baylis et al. 1995; Rolls et al. 1990). The posterior OFC foci lie close to (although slightly medial to) a region in humans that shares similar anatomical features to this caudolateral gustatory region in monkeys (Small et al. 1999). This likely represents an earlier stage of processing than the anterior areas showing responses to tastes. Indeed, the anterior regions largely lack direct gustatory and amygdala projections but likely receive

information from these areas secondary to more posterior OFC areas (Carmichael and Price 1996; Zald and Kim 2001).

Furthermore, in addition to OFC, the role of PFC in taste process has gradually attract the investigator`s attention. It is well known that the PFC is involved in various higher cognitive functions such as planning, reasoning, and language comprehension, and these cognitive abilities change dramatically as a function of age throughout childhood and adolescence (Diamond 2002; Davidson and others 2006; Huizinga and others 2006). Understanding the mechanisms through which these changes occur is of crucial importance for many fields of research including cognitive neuroscience, psychology, psychiatry, and neurology, among others (Goldman-Rakic 1987; Casey and others2000; Hutten locher 2003; Munakata and others 2004). Regarding the feeding behavior, recently, Okamoto et al. and another researchers have done series studies for investigating the taste-related cognitive function in these areas and found it indeed was involved in higher cognitive processing in taste condition (Kringlbach, 2004; Okamoto et al., 2006a, 2006b). The PFC appears to play an important role in processing the pleasantness and reward value of eating food.

Limbic system and Amygdala

The limbic system is a complex set of brain structures, located just under the cerebrum on both sides of the thalamus. This system includes the hippocampus, the hypothalamus, the amygdala, the basal ganglia, the cingulate gyrus and several others nearby areas. It appears to be primarily for our emotional lives and other our higher mental functions. The limbic system is involved in the detection and expression of emotional responses, and is important for learning, memory and olfaction (Ward, 2010). Behavioral,

ethological and electrophysiological studies in a number of mammalian species indicated that the gustatory system possess relatively direct projections to the amygdala. A similar activation was also found in human (Zald and Pardo, 1997). In 1998, Zald *et al*. further examined activation of limbic system response to taste and found increased activation in the right amygdala, left anterior orbitofrontal cortex, medial thalamus, pregenual and dorsal anterior cingulate and the right hippocampus, and highlighted the role of the pregenual cingulate in negative emotional processing.

1.2.3 Brain imaging techniques

In this part, we will review the developed non- or less- invasive brain imaging techniques for exploring the gustatory processing and their findings in human taste mechanisms.

During the past two decades, the human brain has been explored by new non-invasive techniques of functional brain imaging, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and near infrared spectroscopy (NIRS).These new methods extended the research on human high cognitive processes and make us further understanding about brain function.

In 1881, Angelo Mosso found PET makes it possible to visualize activated brain regions based on the phenomenon that neural activity is accompanied by an increase in local cerebral blood flow (CBF). This is the first time to demonstrate the correlation between energy demand and the CBF. Since then, PET, as a medical and research tool, is used heavily in clinical oncology and normal brain mapping to examine links between specific psychological processes or brain activity. Regarding taste sensory system, Kinomura, *et al.* (1994), using PET, reported that several regions including the thalamus, anterior cingulated cortex, and insula were increased in the gustatory discrimination task

compared to the control task (Kinomura et al., 1994). Further, Small, *et al.* reported a PET study for evaluating differential processing of olfactory, gustatory and combined stimuli as indicated by comparison of evoked CBF changes during different conditions. Ogawa, *et al.* (1990) reported blood oxygen level dependent (BOLD) contrast *in vivo* preparation firstly, and it became the fundamental evidence for using fMRI to brain imaging (Ogawa et al., 1990a, 1990b). Neural activation is associated with a localized increase in CBF, which supplies excessive oxyhemoglobin and, in consequence, increases MRI signal intensity (Kobayashi, 2006). In typical fMRI studies, the stimulation paradigm includes ON and OFF blocks. In ON blocks, gustatory stimulation such as a tastant solution is applied to the tongue, and in OFF blocks no stimulus or water is applied. A similar conclusion that passive gustatory stimulation activates the insula/operculum has been reached in gustatory studies using fMRI in humans (Faurion et al., 1999; Francis et al., 1999; Barry et al., 2001; Kobayashi et al., 2004; Kringelbach et al., 2004; Kikuchi et al., 2005; Ogawa et al., 2005). In the case of fMRI studies, as subjects must lie on their back in MRI scanners, methods of delivering taste solutions are restricted and it is also stressful for subjects.

In principle, PET and fMRI are superior to the other imaging techniques in their spatial resolution so that they have been considered to be the most suitable brain imaging techniques for exploring the localization of human brain functions (Raichle, 2000).

fNIRS measured the changes in the concentration of oxygenated (OxyHb) and deoxygenated hemoglobin (DeoxyHb) in the tissue (Cope and Delpy, 1988) and it reflects the temporal change of cerebral blood volume (CBV). So far, it has been widely used to research brain and sensory function through hemodynamic responses associated

with neuron behavior. Several reports describe the potential of NIRS method in measuring the brain activity respond to motor, visual, auditory, cognitive, emotion and other stimuli (Hoshi and Tamura, 1993; Nakajima et al., 1994; Villringer et al., 1993). And more recently, Okamoto and her colleagues used fNIRS to investigate the cortical substrates of taste memory, which is an important part of episodic memory and found the activation of the lateral prefrontal cortex response to taste encoding (Okamoto et al., 2011). Although this method offers low spatial resolution, the previous studies indicated that the fNIRS is more suitable for investigating the brain function with its higher temporal resolution and compact construction. To our knowledge, to this date, there are a few fNIRS studies for investigating gustatory brain function and the fNIRS study of gestation is just in its early stage.

1.2.4 Summary

Taken together, although a number of information about taste have been accumulated based on the experimental evidences, the study of the gustatory system, is at a much earlier stage of development than are studies of other sensory system, especially for audition and vision. The reasons are fairly obvious. In addition to the clinical specialist, the study on gustatory system is of limited interest compared to the amount of research aimed at visual studies to investigators. Furthermore, manipulation of the stimulus is difficult and limited to a few variations (Uttal, 2010). With the development of non- or less-invasive brain imaging techniques, more and more investigators have paid attention to this field. As just discussed, it is clear that the taste sensory is encoded by an interactive complex of many different brain regions, and taste plays an important role in our feeding behavior even to other higher cognitive function. The research for investigating neural mechanism of taste is not only for basic science, but also for

clinical application.

1.3 Focus of the Dissertation

Inspired by these previous findings, we investigated the following questions: (a) whether fNIRS can be used to research on taste-related brain function; (b) whether PFC is involved in taste processing; (c) and, if true, show where is responding to taste in the human brain. To answer these questions, based on the event-related design, we selected fNIRS to monitor activation of human lateral PFC during taste processing. The primary aim of this study is to find the region of interest (ROI) which is related to taste, and make further understanding on the central organization of taste. We hope the investigation would further contribute to the understanding of higher cognitive processing on gustatory system and to provide some theoretical evidence for studying on taste dyspepsia and disorder.

1.4 Dissertation Overview

In this dissertation, we attempted to investigate the representation of taste in human prefrontal lobe, in particular, to compare the representation of a pleasant and an aversive taste using EEG and fNIRS, so as to obtain further understanding of the central organization of taste. This paper is organized as follows (Figure 1-1)

Chapter 2 illustrated the background theories and knowledge about brain function and gustatory system. It began by a description of the structure and function of neuron. It then introduced the human brain cortex and works up to brain imaging techniques. Finally, it considered how the brain represents taste information.

Chapter 3 used fNIRS, a non-invasive neuroimaging technique, to monitor the

activation of prefrontal lobe on human brain during sweet taste processing. The primary aim of this chapter was to find ROIs which is related to sweetness, and make further understanding of the central organization of taste. Based on event-related design, the experiments were performed with 16 volunteers by sweet taste stimulus.

Chapter 4 investigated the representation of taste in human PFC, in particular, to compare the representation of a pleasant and an aversive taste using fNIRS, so as to obtain further understanding of the taste preference mechanism. The pleasant stimulus used was sweet taste (10% sucrose), and the unpleasant stimulus was sour taste (1% critic acid). Based on event-related design, the experiments were performed with 16 healthy volunteers using an fNIRS sensor of OEG-16. A general linear model was used to analyze the collected data.

Chapter 5 investigated brain neurophysiological responses to unpleasant gustatory stimuli using EEG and near-infrared hemoencepalogram (NIR-HEG) simultaneously to clarify the intrinsic food preference mechanism. A conventional delayed response task based on Go/Nogo paradigm was adopted to extract real brain response components from spontaneous background signals.

Chapter 6 made some general discussions on the representation of pleasant and unpleasant taste in human brain, and finally concludes the whole dissertation.

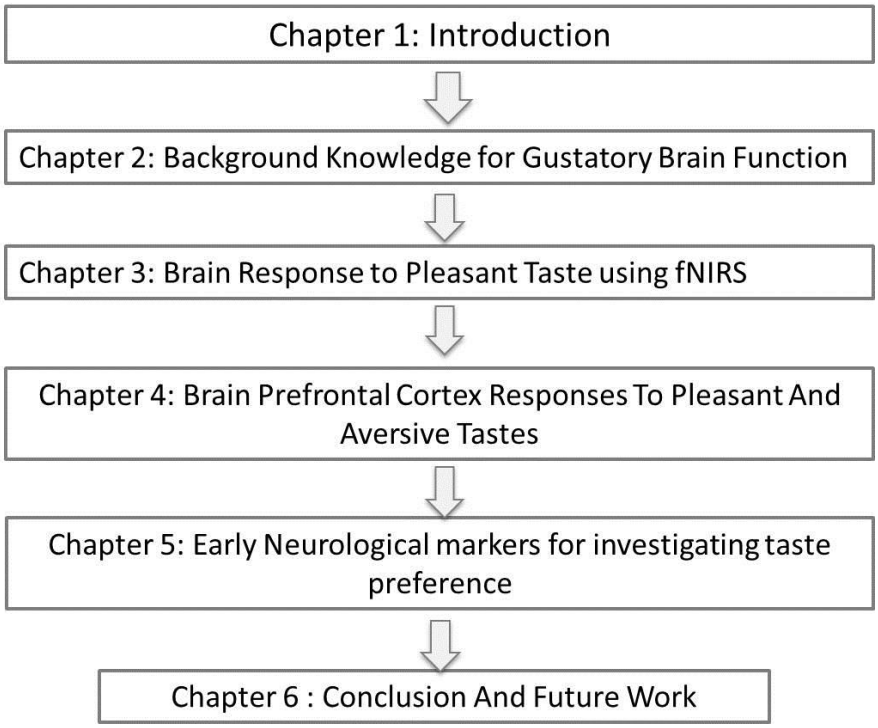


Figure 1-1 Structure of this dissertation

Chapter 2

Brain Function and Gustatory System

As presented in chapter 1, feeding is crucial physiological behavior for supplying the energy. The information and sensation provided by the gustatory pathway not only does food nourish the body, but also provides nourishment for the soul. Taste function and brain function appear to be closely related. Before the discussion of the higher cognitive processing mechanism of taste, we should first cover the basic theories and knowledge about brain function and gustatory system, which will help the reader to better understand the higher cognitive processing of taste.

This chapter would introduce some basic theories and knowledge about brain function and gustatory system. It began by a description of the structure and function of neuron. It then introduced the human brain cortex and works up to brain imaging techniques. Finally, it considered how the brain represents taste information.

2.1 Neuron and Its Function

2.2.1 Structure and function of the neuron

There are 100 billion neurons in the human brain approximately, which are in charge of processing and transmitting information through electrochemical signals. All neurons

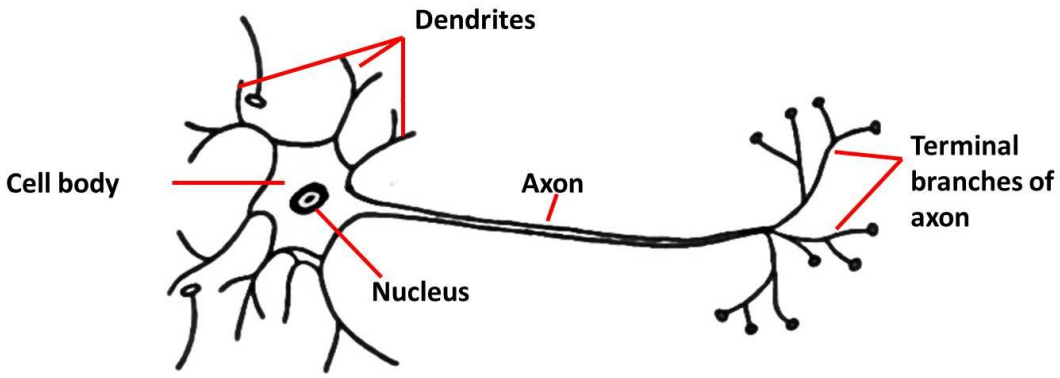


Figure 2-1 A typical neuron. The cell body contains the cellular machinery for the production of proteins and other cellular macromolecules. Like other cells, the neuron contains a nucleus and other intracellular organelles. Extending form the cell body is various processes, dendrites and axon.
[Modified from http://www.appsychology.com/Book/Biological/neuroscience.htm]

have the same structure basically. A typical neuron process there components: a cell body (often called the soma), dendrites and an axon (Figure 2-1). As with most cells, the cell body contains the nucleus and other organelles. The nucleus contains the genetic code, and this is involved in protein synthesis. Extending from the cell body is various processes, dendrites and axon. Each neuron includes many dendrites but only a single axon. Dendrites are usually large treelike processes that receive information from other neurons in close proximity. In contrast, the axon passes messages away from the cell body to other neurons. The electrochemical signals enable communication between neurons via synapse. The two neurons forming the synapse are referred to as presynaptic and postsynaptic, reflecting the direction of information flow (from axon to dendrite). When a pre synaptic neuron is active, an electrical current (an action potential) is propagated down the length of the axon (Ward, 2010; Gazzaniga et al., 2009).

2.1.2 Electrical signaling and the action potential

Each neuron is surrounded by a cell membrane that acts as a barrier to the passage of certain chemicals. Within the membrane, certain protein molecules act as gatekeepers and allow particular electrochemical in an out under certain conditions. These signals are generated and propagated by charge-carrying ions including sodium (Na^+), potassium (K^+), chloride (Cl^-), and calcium (Ca^{2+}).The balance between these ions on the inside and outside of the membrane is such that there is normally a resting potential of -70mV across the membrane (the inside being negative relative to the outside) (Ward, 2010). There are several stimuli that can activate a neuron leading to electrical activity, including pressure, stretch, chemical transmitters, and changes of the electric potential across the cell membrane (Joe and Ray, 2000). Stimuli cause specific ion-channels within the cell membrane to open, leading to a flow of ions through the cell membrane, changing the membrane potential.

2.1.3 Neural activity and cerebral blood flow（CBF）

In human, most of non- or less- brain imaging methods are used to access the relationship between the neural activity and the CBF. Neurovascular coupling is a term for the interaction between neuronal (electrical) activity, cortical blood circulation and oxygen consumption in brain tissue. Brain activation is accompanied by a complex sequence of cellular, metabolic, and vascular processes (Brain N et al., 2008). Although the requirement for postsynaptic activation in the generation of vascular processes is still under debated and investigation, the basic mechanism of the cellular, metabolic and vascular can be described as Figure 2-2 showed. Various cellular processes of neurons require energy in the form of adenosine triphosphate (ATP). ATP is synthesized first by

glycolysis, which is anaerobic and produces a small amount of ATP, and then by oxidative glucose metabolism, which requires oxygen and produces a large amount of ATP. Cerebral metabolism thus depends on a constant supply of both glucose and oxygen. A continuous supply of these two energy substrates is maintained by CBF, which delivers glucose and oxygen to neural tissue through the complex web of blood vessels in the brain's vascular system. Accordingly, during neural activity, increases in oxygen and glucose consumption are followed by an increase in CBF. Whereas the fractional increases in CBF and glucose consumption are similar in magnitude, oxygen consumption increases much less than CBF, leading to a net increase in the amount of oxygen present in the blood and tissue. This oversupply of oxygen due to the mismatch between CBF and oxygen consumption is the basis of BOLD fMRI, which detects alterations in levels of deoxygenated hemoglobin and cerebral blood volume (Brian et al., 2008). In a word, it is clear from the existing data that the neural activation and CBF are closely related.

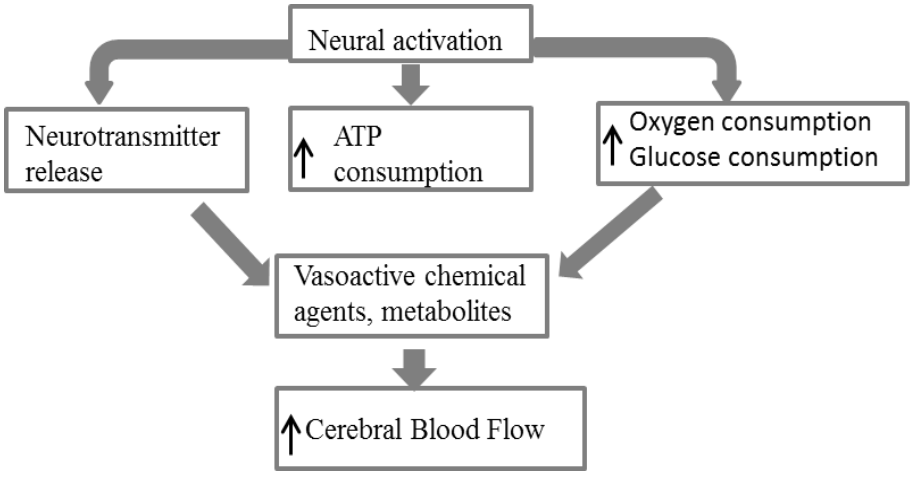


Figure 2-2 The relationship between neural activtiy and CBF

[Modified from Brain N. Pasley and Ralph D. Freeman (2008), scholarpeida 3(3):5340. http://www.scholarpedia.org/article/Neurovascular_coupling]

2.2 Human Brain Cortex and Function

2.2.1 A gross organization of the brain

The nervous system is the organ system, which controls every part of our daily life for producing, controlling and guiding our acts, thoughts and response to the world. It includes two major division, the central nervous system (CNS) and peripheral nervous system (PNS). The PNS is made of nerves which directly connect to the skin, muscles, blood vessels and other organs of the body not encased in bone. Meanwhile, the CNS is made of the brain and the spinal cord. The information from the environment gathered by sensory nerves is send to the spinal cord and then to the brain, which is the organ responsible for guiding and controlling behavior.

For neuroscientists, the first change to identify gross neuroanatomy is to how to view brain. Recently, the development of the neuroimaging techniques made it possible to view the live brain and therefore, more and more knowledge of brain has been accumulated. In generally speaking, the brain mainly consists of hindbrain, midbrain and forebrain. The hindbrain includes medulla, pons and cerebellum. It is an important part for controlling a number of body function and process. The midbrain region tectum and tegmentum, which serves as a relay center for auditory, visual and motor system information. The forebrain consists of the hypothalamus, thalamus, limbic system and the cerebrum/cortex. It is the largest section and the most highly developed part of brain. The increased complexity of this part allows the enormous flexibility in human behaviors and solving skill. To this date a great many of studies reported that the structures most identified with the higher cognitive function are found in the forebrain, and foremost among these is the cerebral cortex (Dennis Rains, 2001).

2.2.2 Cerebral cortex and functions

Neurons are organized within the brain to form white matter and gray matter. Gray matter consists of neuronal cell bodies. White matter consists of axons and support cells (glia). The brain consists of highly convoluted folded sheet of gray matter, the cerebral cortex, which makes the brain more efficient. In detail, the cerebral cortex consists of two folded sheets of gray matter organized into two hemispheres (left and right). The surface of the cortex has become increasingly more convoluted with evolutionary development. Having a folded structure permits a high surface area to volume ration and thereby permits efficient packaging. The raised surfaces of the cortex are termed gyri (or gyrus in the singular). The dips or folds are called sulci (or sulcus in the singular) (Dennis Rains, 2001, Ward, 2010).

The thickness of the cerebral cortex varies from 1 to 4.5 mm, with an average of 2.5 mm (Brodmann, 1909; von Economo, 1929; Zilles, 1990). Traditionally, the cerebral cortex is organized into different layers with different cell types. Each of the layers has different densities. Most of the cortex is the neocortex, which has six layers with each

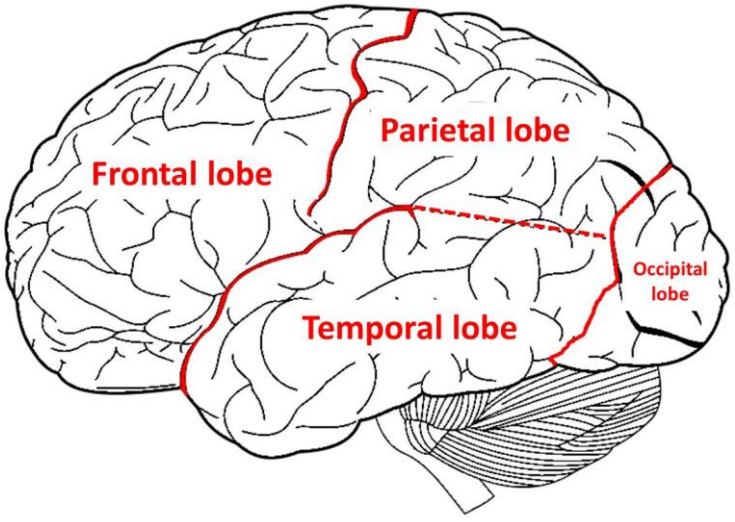


Figure 2-3 The cerebral cortex

area of them having characteristic patterns. Other cortical regions with fewer than six layers are known as the mesocortex and the allocortex (Ward, 2010).

Each cerebral hemisphere is divided into four sections by sulci (or fissures) and gyri, called the frontal lobe, parietal lobe, temporal lobe, and occipital lobe (Figure 2-3). These lobes have been associated with more complex functions varying including auditory perception, emotion, memory, reasoning and other function. The dividing line between the lobes is sometimes prominent, but in other cases the boundary cannot readily be observed (e.g. between temporal and occipital lobes) (Ward, 2010). In addition, in a medial section, you can find the other regions of the cortex such as the cingulate cortex. Finally, the insula (an island of cortex) lies under the temporal lobe.

Specifically, the frontal lobe is located at the front of each cerebral hemisphere. It plays a crucial role in human higher cognitive processes associated with expressive language, motor skills, reasoning, and higher level cognition, and significantly determines our daily capabilities, social interactions and judgment and decision. Indeed, existing date showed that the changes appeared in memory, attention, socialization, sexual habit and other cognition as a result of the front lobe damage.

Posterior to the frontal lobe is the parietal lobe which is located in the middle section of the brain. This part is usually concerned with processing tactile sensory information such as pressure, touch, temperature, pain and how you perceive thing visually. The somatosensory cortex is mainly located in the parietal lobe and is essential to the processes input from systems in the body. Damage to the parietal lobe can result in loss of perception of bodily sensation, problems with verbal memory and language.

The temporal lobe is located below the lateral fissure and on the bottom section of the brain. This part plays an important role in processing and analyzing the auditory

information. It is mainly regarded as the location of the primary auditory cortex for interpreting sounds and the heard language. The temporal lobe contains the hippocampus and plays a key role in the formation of explicit long-term memory modulated by the amygdala (Smith and Kosslyn, 2007). Damaging the temporal lobe can lead to problems with auditory perception, language and speech perception, and memory.

The part behind the parietal and temporal lobes is the occipital lobe. It is located at the back of the brain and is main responsible for interpreting visual stimuli and information. As we all known, the primary visual cortex is located in the occipital lobe. It is certainly no surprise that damage affecting this lobe can lead to visual problems such as it is difficultly to recognize object and identify color, even to cause some trouble of recognizing words.

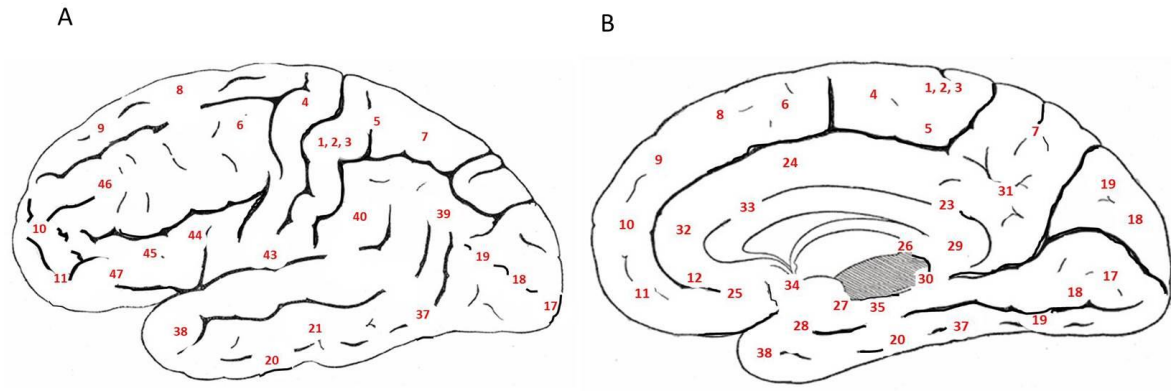


Figure 2-4 The Brodmann areas of the brain on the lateral and medial surface [Modified from Wikipedia http://en.wikipedia.org/wiki/Brodmann_area].

Ward (2010) has summarized that there are three different ways in which regions of cerebral cortex may be divided and, hence, labeled (Ward 2010):

1. Regions divided by the pattern of gyri and sulci. The same pattern of gyri and sulci

is found in everyone (although the precise shape and size varies greatly). As such, it is possible to label different regions of the brain accordingly.

2. Regions divided by cytoarchitecture. One of the most influential ways of dividing up the cerebral is in term of Brodmann's areas (Figure 2-4). Brodmann divided the cortex up into approximately 52 areas (Labeled from BA1 to BA52), based on the relative distribution of cell types across cortical layers. Areas are labeled in a circular spiral starting from the middlem, like the numbering system of Parisian suburbs. Over the years, the map has been modified.

3. Regions divided by function. This method tends only to be used for primary sensory and motor areas. For example, Brodmann area 17 and 6 are also termed the primary visual cortex and the primary motor cortex, respectively. Higher cortical regions are harder (if not impossible) to ascribe unique functions to.

2.2.3 The role of the prefrontal lobe (PFC)

In this study, we focused on the prefrontal cortex, which is located in the very front of the frontal lobe in brain. There are different ways to subdivide the PFC starting from Brodmann area. Within the PFC, the most basic anatomical division subdivided the PFC in to three parts: the lateral surface, the medical surface and the orbitofrontal surface. The lateral surface of the prefrontal cortex lies anterior to the premotor cortex (Brodmann's area 6) and the frontal eye fields (in Brodmann's area8). This surface lays closet to the skull. The medial surface of the PFC lies between the two hemispheres and to the front of the corpus collosum and the anterior cingulate cortex. The orbital surface of the PFC lies above the orbits of the eyes and the nasal cavity. This is also called the ventromedial prefrontal or orbitofrontal cortex. These areas refer to the Brodmann's areas is showed in Table 2-1(Ward, 2010).

The function of the PFC is as fascination as it is elusive. In general, this brain region has been implicated in planning complex cognitive behavior, personality expression, decision making, and moderating social behavior (Yang and Raine, 2009). The basic activity of this brain region is considered to be orchestration of thoughts and actions in accordance with internal goals (Miller et al., 2002). The most typical psychological term for functions carried out by PFC is executive. Executive function relates to abilities to differentiate among conflicting thoughts, determine good and bad, better and best, same and different, future consequences of current activities, working toward a defined goal, prediction of outcomes, expectation based on actions, and social control (the ability to suppress urges that, if not suppressed, could lead to socially unacceptable outcomes) (Alvarez et al., 2006; Goldman-Rakic, 1988; Price, 1999). Many have indicated an

Table 2-1 The prefrontal lobe refer to Brodmann areas

Brodmann's areas	Other names	Possible functions (left hemisphere)	Possible functions (right hemisphere)
45, 47, 44	Ventrolateral prefrontal cortex (VLPFC)	Retrieval and maintenance of sematic and/or linguistic information (Area 44+45 on the left also called Broca's area)	Retrieval and maintenance of visual and/ or spatial information
46, 9, 8, 11	Dorsolateral prefrontal cortex (DLPFC)	Selecting a possible range of responses, and suppressing inappropriate ones; manipulating the contents of working memory	Monitoring and checking of information held in mind, particularly in conditions of uncertainty; vigilance and sustained attention
10	Anterior prefrontal cortex; frontal pole; rostral prefrontal cortex	Multi-tasking; maintaining future intentions/goals whilst currently performing other tasks or sub-goals.	
24(dorsal) 32(dorsal)	Anterior cingulate cortex (dorsal)	Monitoring in situations of response conflict an error detection	

[From Ward J: the student`s guide to cognitive neuroscience, 2nd edition, 2010)

integral link between a person`s personality and functions of the prefrontal cortex (DeYoung et al., 2010).

2.3 Brain Imaging Techniques

2.3.1 Types of brain imaging techniques

For centuries, the structure of the brain has been investigated based on the dead head and much has been learned by this approach. Recently, neuroanatomy has been revolutionized and the brain can be examined in living individuals by a number of accepted and safe brain imaging techniques which have been developed, like fMRI, PET, MEG, and EEG as we referred to in Chapter 1, These methods allow us to monitor the human brain activity or access the problems of brain without invasive neurosurgery. As a result, many insights have focused on about the sensory function on human brain. Here, we briefly introduce them and then focused on the fNIRS we used in this study in next.

Computed tomography (CT) was developed by Godfrey Hounsfieds and Allan Cormach in 1997. The goal of CT is to builds up an image of a slice brain based on the differential absorption of X-rays. For the first time, CT scans noninvasively revealed the gross organization of gray and white matter, and the position of the ventricles in the living brain (Bear et al., 2006). However, this method does not resolve the human brain structure well. While still used widely, CT is gradually being replaced by a newer imaging method, called MRI (Bear et al., 2006). The fMRI, using MRI technology, measures brain activity by detecting the changes in blood oxygenation and flow associated with neural activity. When a brain area is in use, blood flow to that region also increases. Compared to CT, fMRI does not use ionizing radiation, and provides a

much better spatial resolution. It also provides better discrimination between white matter and gray matter (Ward, 2010). Nowadays, this method is usually used to investigate the brain area for specific function in a particular mental and cognitive process. Meanwhile, the other brain imaging techniques now in widespread use is PET. It uses a radioactive tracer to generate a map of functional processes in the brain. PET shows worse temporal and spatial resolution over fMRI, but less noisy than fMRI. In

Table 2-2 A Comparison among brain imaging techniques

Technique	**Target**	**TR**	**SR**	**Merits**	**Demerits**
MEG	Neural electric activity	1 ms	5 mm, 3D	High Temporal resolution	Difficulty in measuring some regions
EEG	Neural electric activity	1 ms	10-15 mm, 3D	Low cost, high exp.Flexibility	Low Spatial resolution
PET	HR, metabolic response	10-45 s	4 mm, 3D	Quantitative measurement	High cost, invasiveness
fMRI	Hemodynamic Response	0.5-5 s	1-5 mm, 3D	Structural data availability	High cost, low exp. flexibility
fNIRS	Hemodynamic Response	0.1-1 s	10-30 mm,2D	Low cost, high exp. Flexibility	Measurement limited to the lateral cortex surface

Commonly used neuroimaging techniques are summarized and listed (Okamoto and Dan, 2007). TR, temporal resolution; SR, spatial resolution; HR, hemodynamic response; 3D, 3-dimentional; 2D, 2-dimentional; exp., experimental.

addition, EEG is frequently used in the experiment for investigating brain electrical activity. It records from electrodes placed on the scalp. MEG is a neuroimaging technique for mapping brain activity. It is used to measure the magnetic fields produced by electrical currents occurring naturally in the brain by extremely sensitive devices known as SQUIDs (superconducting quantum interference devices) (Wikipedia). More recently, NIRS, a new neuroimaging method, is used to measure brain activity through

hemodynamic response associated with neuron behavior. It works by shining light in the near infrared part of the spectrum (700-900nm) through the skull and detecting how much the remerging light is attenuated. How much the light is attenuated depends on the blood oxygenation and thus NIRS can provide an indirect measure of brain activity (Demitri, 2007). The development of these non- or less- invasive neuroimaging techniques has allowed brain mapping of higher cognitive functions to process rapidly. The advantages and disadvantages of them are summarized in Table 2-2. Among these development techniques, we focused on fNIRS, and we introduced its basic theory more specifically in next.

2.3.2 Functional near- infrared spectroscopy (fNIRS)

2.3.2.1 Acquisition principle of NIRS measurement

fNIRS is a new technique for non-invasive monitoring of issue oxygenation and its kinetics. Up to this date, it has been used solely in research for the global hemodynamic change of brain and for rough regional activation after stimulating the brain physiologically (Watanabe et al., 1996). In this session, acquisition principle of biological information for NIRS measurement is explained as follows. In optics, the he Beer-Lambert law allows the transformation from raw optical density data to concentration changes. According to Beer-Lambert law (Figure 2-5), assuming that the incident light to a solution in a certain density is I_0, and the light that got through the solution is I, A is the absorbance, the relationship between A and the two intensities is usually written as Equation 2.1 shown (Spectratech Inc., 2009, Deoly et al., 1988; Eda, 2009)

$$A = -\ln\left(\frac{I}{I_0}\right) = \varepsilon c d \quad (2.1)$$

where, ε is the extinction coefficient, c is the concentration of solution and the d is the

distance. That is, if ε in a specific wavelength was obtained beforehand, c can be obtained by measuring I_0, I, and *d*.

The Equation 2.2 represents the modified Beer-Lambert Law by extending the Beer-Lambert Law, which describes an optical attenuation in a highly scattering medium.

$$\Delta A = -\ln(\Delta I / I_0) = \varepsilon \Delta c \langle d \rangle + \Delta s \qquad (2.2)$$

Here, ΔA is the change of absorbance. ΔI means a change in amount of transmissive light, Δc for concentration change, *d* for average length of light path, and Δs for effect

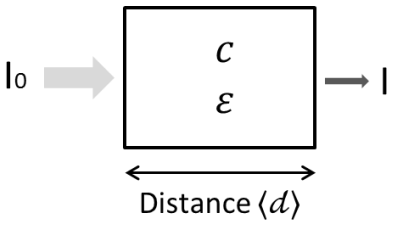


Figure 2-5 Beer-Lambert Law

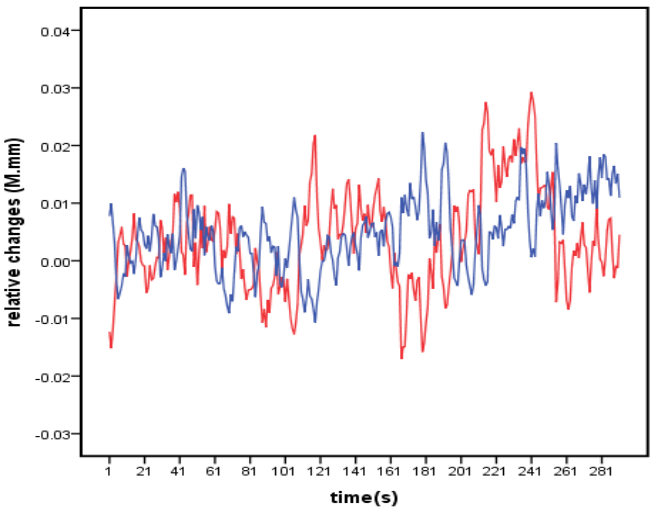


Figure 2-6 An fNIRS data example from a channel. The red line represents the concentration change of oxyHb, while the blue line represents concentration change of DeoxyHb.

change by scattering. Assuming that the oxyhemoglobin (OxyHb) and deoxyhemoglobin (DeoxyHb) are the major two choromophores, and the incident light to live body in a specific wavelength is I_0 (λ), change in amount of the light that returned ex vivo by being effected by in-vivo absorption and scattering is ΔI (λ), the measured optical density changes are then described as Equation 2.3 (Spectratech Inc., 2009; Eda, 2009)

$$\Delta A(\lambda) = (\varepsilon \text{ oxy } (\lambda)\Delta \text{Coxy} + \varepsilon \text{ deoxy } (\lambda)\ \Delta \text{Cdeoxy})\ \langle d \rangle\ + \Delta s \quad (2.3)$$

From this expression, we can get the concentration change of OxyHb (ΔCoxy) DeoxyHb (ΔCdeoxy) (Figure 2-6). Then the concentration change of total hemoglobin (ΔCtotal) is calculated as a sum of ΔCoxy and ΔCdeoxy.

2.3.2.2The advantages and disadvantages of fNIRS

Compared to the other brain imaging techniques such as fMRI and PET, fNIRS as a new neuroimaging technique that is completely noninvasive and does not require strict motion restriction is desirable (Coyle et al., 2004; Hoshi et al., 2001). It enables brain studies on subjects who are difficult to examine with PET and fMRI physiologically and/or physically (Hoshi, 2003). One of other advantages of fNIRS is that before the measurement steps, no or a minimum of sample preparation operations are needed. In addition it is much faster, thereby lowering costs. More cost saving are achieved. To summary, several advantages of using fNIRS were delineated: lower costs, faster analyses, litter of no operator involvement, environmental benefits, improved precision and possible automation.

This is not to say that fNIRS is be-all and end-all. As we all known, the distance between the emitter and detector is 3cm, the spatial resolution is lower than fMRI.

Further, many metals and inorganic species in general do not have appreciable absorbance in the near infrared region; this limits the use of fNIRS for application. That means that fNIRS can measure activity of surface cortex, but can't reach the deeper gustatory areas such as insula which is located deep inside the brain (Kringelbach et al., 2004). In addition, there are maybe some noisy induced by the sensor.

2.4 Gustatory System

2.4.1 Neural pathway of Gustation to brain

The sense of taste is a chemosensory system intimately associated with ingestion and rejection of potential foodstuffs (Dethier, 1993). Sensory transduction in the gustatory system begins when a food molecule, or tastant, stimulated a receptor in a taste cell and causes the receptor to depolarize (Gazzaniga et al., 2009). The taste cells are located in taste buds (see in Figure 2-7). The mouth contains roughly 10,000 taste buds. They are located on papillae and Most are found in the surface of tongue, though they are also found, to a lesser degree, on the oral mucosa of the palate and epiglottis.

Taste qualities are the logical subdivision of the sensory modalities. In general, gustatory neurobiologists agree that the basic tastes usually include salty, sour, bitter, sweet, and possibly umami, although human experience many tastes subjectively. Each cell is sensitive to one of five basic tastes, and each of the basic taste sensation has a different form of chemical signal transduction. In the signal transduction for salty taste, the salt molecule (NaCI) breaks down to Na+ and CI- , and the Na+ ion is conducted into an ion channel in the cell, thus depolarizing the cell. Other signal transduction pathways, such as sweet carbohydrate tastant, are more complex, involving receptor binding that does not lead directly to depolarization, but rather initiated cascades of

chemical “messengers” that eventually lead to cellular depolarization (Gazzaniga et al., 2009).

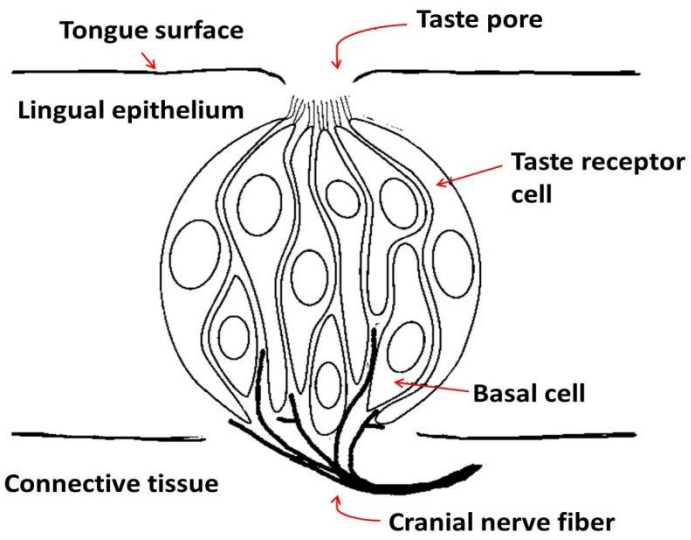


Figure 2-7 Schematic drawing of a taste bud. Each cell is sensitive to one of five basic tastes [Modified from http://commons.wikimedia.org/wiki/File:Taste_bud.svg]

Once a taste cell has been depolarized, gustatory sensory information on the nerve fibers from taste buds travels from the tongue via the three cranial nerves: VIIth (facial) cranial nerve carries information from the anterior two-thirds of the tongue; IXth (glossopharyngeal) from the posterior third of the tongue; Xth (vagus) nerve from the taste buds on the surface of the epiglottis (Kabayashi, 2006). Information from the primary neurons in all three nerves respectively is relayed to rostral and lateral regions of the nucleus of the solitary tract in the medulla (Figure 2-8) (Beckstead and Norgren,1979). From here, nerves pass to the ventral posterior complex of thalamus and then the gustatory signal is send to the gustatory area of the cerebral cortex.

2.4.2 The gustatory cortex and its function

The neural pathway of gustation is introduced above. Here, we would refer to the gustatory cortex more specifically.

The taste information from the thalamus then projects to several regions of the

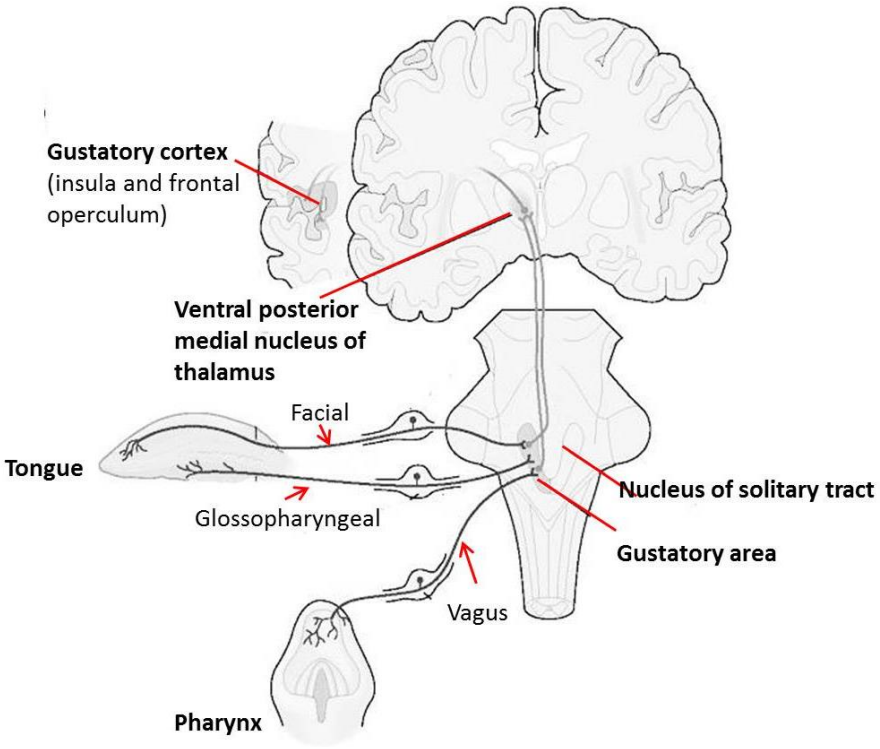


Figure 2-8 Diagram of taste pathway. Signals from the taste buds travel via different nerves to gustatory areas of the nucleus of the solitary tract which relays information to the thalamus; the thalamus projects to the gustatory cortex.
[Modified from Barrett KE, Barman SM, Brooks H: Gonong`s Review of Medical Physiology, 23rd edition. http://www.accessmedicine.com]

neocortex which includes the gustatory cortex. The research on localization of the gustatory cortex has been performs. It mainly includes the primary and the secondary gustatory areas. The primary gustatory cortex is a brain structure responsible for the perception of taste. It consists of two substructures: the anterior insula on the insular

lobe, and the frontal operculum on the inferior frontal gyrus of the frontal lobe (Marieb et al, 2008). Because of its composition the primary gustatory cortex is sometimes referred to in literature as the AI/FO (Anterior Insula/Frontal Operculum) (Pritchard et al., 1999). By using the neuroimaging techniques, many studies have been done to observe the associated structure and function of the primary gustatory area. It has been elucidated that neurons in the AI/FO respond to several stimuli, such as sweetness, saltiness, bitterness, and sourness, while they also code the intensity of the taste stimulus (Scott et al., 1986; Ogawa et al., 1988; Kabayashi and Masayuki, 2006). Regarding the secondary gustatory area, from the AI/FO, the gustatory information is conveyed to the orbitofrontal cortex which is regarded as secondary gustatory area (Carmichael and Price, 1994; Rolls et al., 1988, 1990). The gustatory neurons in the orbitofrontal cortex may play an important role in food identification and selection (Kobayashi, 2006).

2.4.3 Using experimental designs

In previous studies, two authorized models generally utilized in cognitive experiments especially using fMRI are a block design model and an event-related design model (Chee et al., 2003). A separate issue as to the choice of experimental design is how the different stimuli will be ordered. Broadly speaking, there are two choices. First, stimuli that belong together in one condition could be grouped together. This is termed a block design. Second, different stimuli or conditions could be interspersed with each other. This is termed an event-related design. In an event-related design the different intermingled conditions are subsequently separated out for the purpose of analysis (Ward, 2010). A comparison of these two design models is exhibited in Figure 2-9.

The choice of design is determined by the nature of the task and whether the date

comes from PET or fMRI. In the early days, the initial experimental construct, known as block design, was utilized in the PET experiment, because of averaging the response of many closely spaced, successive trails over a short interval of time (i.e. 15-50s). The

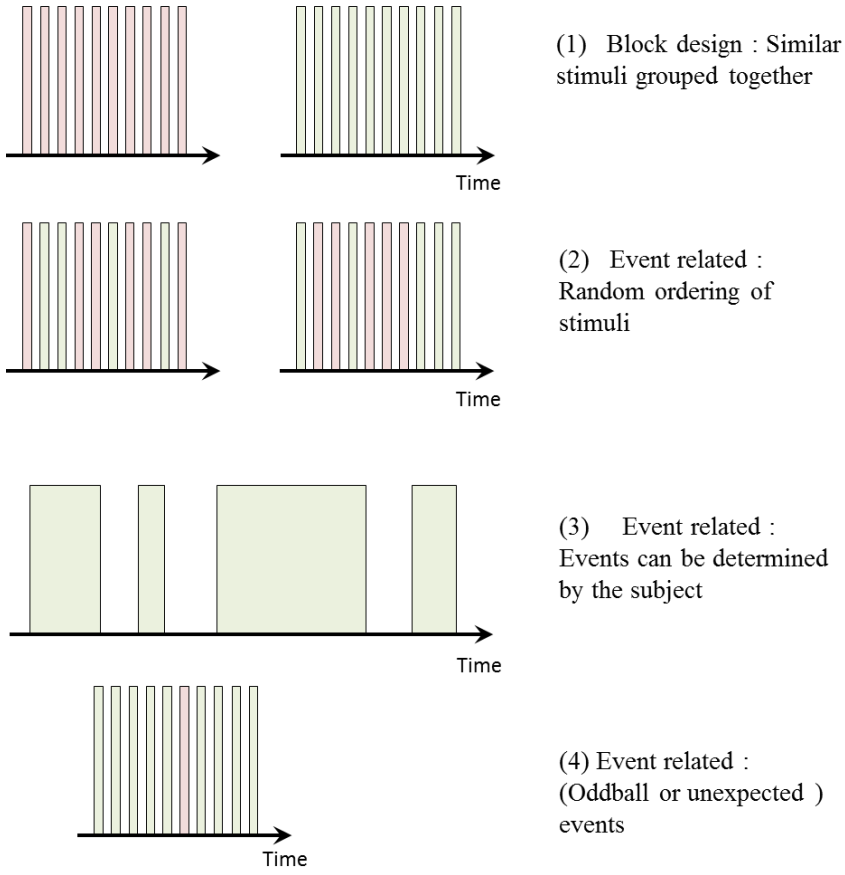


Figure 2-9 A comparison of block design versus event-related design. The purple and green bars could represent different types of stimuli, condition or task. [From Ward J: the student`s guide to cognitive neuroscience, 2nd edition, 2010)

advantage of block design has more power than event-related design. The experiments using the block design are simpler to implement because careful randomization and spacing of different stimulus categories is not required (Donaldson and Buchner, 2001). It is more able to detect significant but small effect (Josephs and Henson, 1999). However, in a block design, two or more conditions are alternated in blocks in some

order, and this makes the type of stimulus within each block very predictable, which will interfere with experiment result as a consequence (Wikipedia). In fMRI one has a choice of event-related design or block design. The advantage of event-related design over block design is that it enables much wider range of experimental designs and is more closely related to the typical design structure of most cognitive psychology experiments. It permits a randomized presentation of stimuli that theoretically reduce confounds arising from stimulus predictability (Ward, 2014). Many researches usually utilized the block design to do the fMRI experiments for investigating the taste-related brain function so far. And some previous studies suggested that when some taste rewards are predictable, brain regions recruited during expectation are, in part, dissociable from areas responding to reward receipt (O'Doherty et al., 2002).

2.5 Summary and Key Points of This Chapter

In this chapter, we firstly show you the neuron and its functions. The neuron is the basic cell type that supports cognition. By axons sending signals to other cells and dendrites receiving signals, a densely interconnected network for connections is formed. Surrounding each of the neuron, a cell membrane acts as a barrier to the passage of certain chemicals. Within the membrane, certain protein molecule acts as gatekeeper for allowing particular electrochemical goes in and comes out.

As been known for long time, accompanying with almost all neural activity responses to stimulus, a local increase in cortical blood flow appears in the brain. This hemodynamic response is the basis of many neuroimaging methods. The basic mechanism of the cellular, metabolic and vascular has been investigated. However, the requirement for postsynaptic activation in the generation of vascular processes is still

under debated and investigation. . It would be of significant value to be able to interpret clinical data from neuroimaging method in terms of neuronal function.

The brain, belonging to the CNS, is the most complex organ in the human body. It can do some amazing thing by producing our thought, action, memory, feeling and experience of the world. Furthermore, the cerebral cortex, making the brain more efficient, consisted of the frontal lobe, parietal lobe, occipital lobe, and temporal lobe. These lobes are associated with more complex function including auditory perception, emotion, memory, and reasoning. Among these, the function of the PFC is gradually attracting attention.

With the rapid development of functional imaging techniques, such as fMRI, PET, MEG, and EEG, many insights have focused on about the sensory function on human brain. These brain imaging techniques allow viewing activity or problems within the human brain, without invasive neurosurgery. Among these non- and less- invasive neuroimaging techniques, fNIRS, a new technique for non-invasive monitoring of issue oxygenation and its kinetics, has attracted more and more attention. In this chapter, we showed basic principle of fNIRS for biological information and discussed its advantages and disadvantage.

The gustatory system is the sensory system for the sense of taste. The gustatory system allows humans to distinguish between safe and harmful food. Sensory transduction in the gustatory system begins when a food molecule, or tastant, stimulates a receptor in a taste cells and causes the receptor to depolarize. Once a taste cell has been depolarized, it sends a signal to the gustatory nucleus in the medulla, which in turn synapses on the ventral posterior medial nucleus of the thalamus. Finally, the VPM synapses with the primary gustatory cortex located in the insula and operculum. Primary

gustatory cortex is connected to secondary processing areas of orbitofrontal cortex. Each taste cell is thought to respond to only one type of tastant. The complex range of tastes that experience, however, must result from the integration of information conveyed from the taste cells and processed in areas like the orbitofrontal cortex.

Two authorized models generally utilized in cognitive experiments especially using fMRI are a block design model and an event-related design model.

Chapter 3

Prefrontal Cortex Activity Reponses to Pleasant Taste

fNIRS, as a non-invasive neuroimaging technique, was used to monitor the activation of prefrontal lobe on human brain during sweet taste processing. The primary aim of the present study was to find the ROI which is related to sweetness, and make further understanding of the central organization of taste. Based on event-related design, the experiments were performed with 16 volunteers by sweet taste stimulus.

This chapter is organized as follows: we introduce the background firstly. Section 2 presents the stimuli, experimental procedure and data analysis in detail. The results of present study are shown in Section 3, followed by discussion about the results in Section 4. Finally, some conclusions are drawn in Section 5.

3.1 Background

As Chapter 1 presented, recently, the prevalence of taste diseases which caused by aging society and the changes of the diet structure, such as anorexia nervosa, dyspepsia and taste disorder, appears to be increasing (Kato, 2007; Parrott and Greenwood, 2007). Although these diseases are not life-threatening diseases directly, they have a strong impact on our quality of life (Liu, 2002; Drewnowski, 1997). For its importance, the interest in understanding gustatory processing is gradually growing, not only for basic science, but also for applications. So far, the molecular biology and receptors underlying

the logic of taste was unravelled, and some knowledge and theory about high cognitive processes for taste have been accumulated. However, owing to the complexity of human brain and limitation of device, by now, most questions about the central organization of taste are still largely unanswered.

With the development of modern neuroimaging techniques such as PET, fMRI and fNIRS, a wider range of brain and gustatory researches have been accommodated. Among these less- or non-invasive neuroimaging techniques, we focused on fNIRS, which is widely used to monitor the brain activation and measures changes in the hemoglobin oxygenation state in human brain (Jobsis, 1977; Gagnon et al., 2012). Compared to other neuroimaging methods, fNIRS as a new neuroimaging technique that is completely noninvasive and does not require strict motion restriction is desirable (Coyle et al., 2004; Hoshi et al., 2001). Meanwhile, it is low cost. It enables brain studies on subjects who are difficult to examine with PET and fMRI physiologically and/or physically (Hoshi, 2003).

The PFC, located in the very front of the brain, is in charge of abstract thinking and thought analysis and is also responsible for regulating behavior. Since the PFC regulated so many behavior and thought-processing pathways, it is gradually drawing the researchers' attention. Recently, some cognitive process and sensory evaluation studies, using PET, MRI and another neuroimaging technique, have accumulated some knowledge and theories about visual and auditory modalities for PFC functions. Subsequently, the question whether the PFC is also involved in taste cognitive processing is widely assumed. Related to this question, previous studies found that the lateral prefrontal cortex is closely related to taste and other food-related activities (Rolls et al., 1989; Kringelbach et al., 2004; Okamoto et al., 2006a, 2006b). Although some

works have been done to examine the lateral PFC functions with taste, the results are not identical.

As mentioned above, in present research, we used fNIRS to monitor human PFC function during taste processing to find the ROI which is related to pleasant taste, and make further understanding of the central organization of taste. We also hope our findings will be helpful for studying on some taste disease which caused by aging and diet.

3. 2 Materials and Methods

3.2.1 Subjects

16 healthy right-handed subjects took part in the study. The average age of the subjects was 26.3 (range from 20 to 44 year). Subjects refrained from eating for at least 2 hours prior to running the experiment. Before the present experiment, the subjects were told about the experiment and a pilot study was done. All subjects gave informed consent approved by the Human Ethics Committee of Health Promotion and Education Graduate School of Human Development and Environment in Kobe University.

3.2.2 Stimuli

In this experiment, we made the 5% and 10% solution of sucrose dissolved in purified water. And this sweetened solution with different solution was used as tastant, which is a signal of energy supply and usually brings a pleasurable sensation. Purified water (tasteless) was selected as a control condition to minimize the artificial noise from somatosensory effects, swallowing effects and other brain function. Samples were served at room temperature.

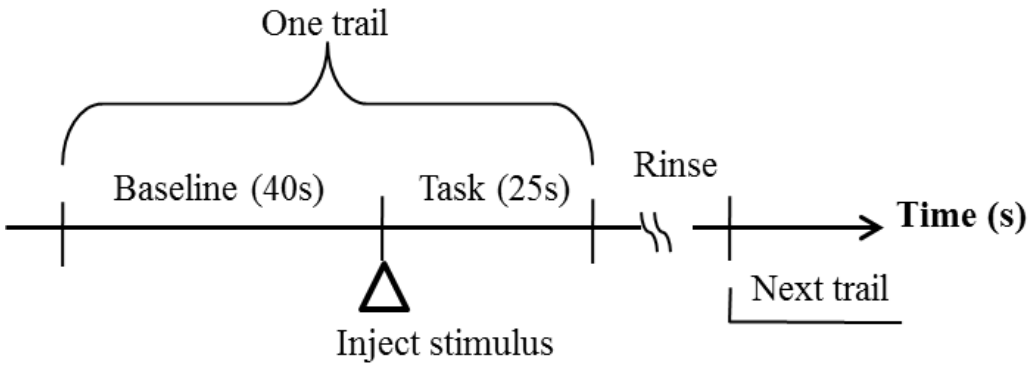


Figure 3-1Experimental protocol

3.2.3 Experimental procedure

During the fNIRS recording session, the subjects were seated in a comfortable chair in a quiet room. The event-related design was adopted for detecting hemodynamic response to gustatory stimuli. Figure 3-1 presented the schematic diagram of the protocol. The subjects were required to try to relax as possible for 40 seconds as baseline. Then stimulus, in quantities of 8 ml, was manually injected in to the subject's mouth via a syringe connected to a tube. And the subject was asked to hold the stimulus in mouth and taste for 25 seconds, which was defined as task. Finally, they spitted it out and rinsed his/her mouth with purified water to prevent adaptation. In this study, they tasted the purified water, 5% solution of sucrose and 10% solution of sucrose in order. Throughout the whole process, the subject kept closing eyes.

After the fNIRS sessions, the intensity of tastants was rated by the subjects as a subjective evaluation on the dislike-like.

3.2.4 fNIRS measurement and data analysis

While the subject performed the tests, we recorded activity in the lateral PFC using a multichannel fNIRS sensor of OEG-16 (Spectratech Inc., Tokyo, Japan). In this case, both 770nm and 840 nm wavelengths were used to measure ΔoxyHb and ΔdeoxyHb

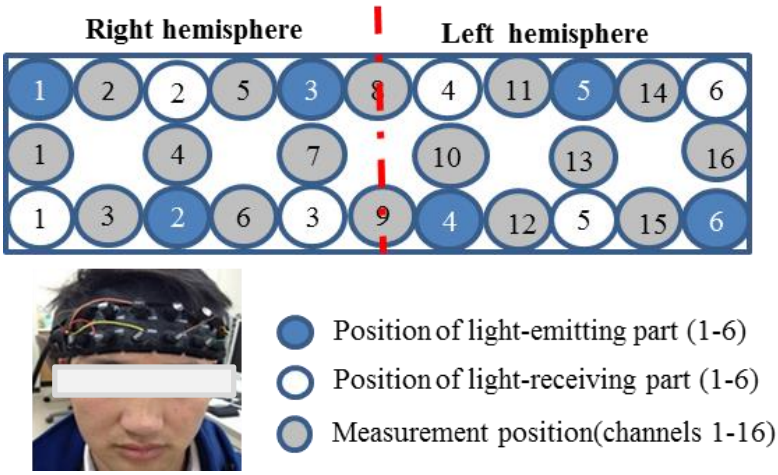


Figure 3-2 Experimental condition of fNIRS

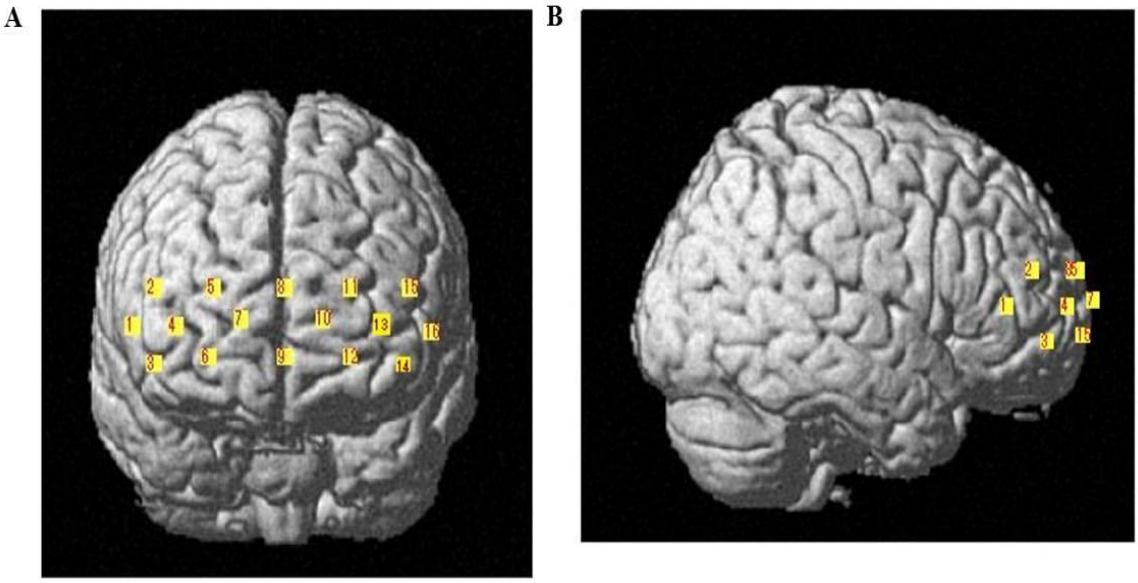


Figure 3-3 Channels' estimated cortical location. A is from frontal view, while B is from right lateral view.

(Delpy et al.,1988). Subsequently, the total hemoglobin signal (ΔtotalHb) was calculated as a sum of ΔoxyHb and ΔdeoxyHb. The signal bandwidth of oxyHb and deoxyHb is 0.76 Hz. as illustrated in Figure 3-2, in present study two arrays of six emitters and six detectors were paced ate alternate points and 16 measurement points

Table 3-1 Probabilistic estimation of channels' cortical location in MNI coordination and corresponding anatomical label

Ch	MNI coordinate				
	Position			SD	Anatomical label
	x	y	z		BA
Ch1	53	39	7	5.97	45 - pars triangularis Broca's area
					46 - Dorsolateral prefrontal cortex
Ch 2	46	48	20	6.24	46- Dorsolateral prefrontal cortex
					45 - pars triangularis Broca's area
Ch 3	46	54	-5	5.11	46 - Dorsolateral prefrontal cortex
Ch 4	38	60	8	5.07	10 - Frontopolar area
					46 - Dorsolateral prefrontal cortex
					11 - Orbitofrontal area
Ch 5	25	65	20	5.75	10 - Frontopolar area
					46 - Dorsolateral prefrontal cortex
Ch 6	27	68	-3	4.50	11 - Orbitofrontal area
Ch 7	15	70	9	5.03	10 - Frontopolar area
					11 - Orbitofrontal area
Ch 8	3	66	20	7.07	10 - Frontopolar area
Ch 9	3	68	-3	5.54	10 - Frontopolar area
					11 - Orbitofrontal area
Ch 10	-13	70	9	4.91	10 - Frontopolar area
					11 - Orbitofrontal area
Ch 11	-24	65	20	5.83	10 - Frontopolar area
					46 - Dorsolateral prefrontal cortex
Ch 12	-23	70	-3	4.64	11 - Orbitofrontal area
Ch 13	-35	55	22	5.12	10 - Frontopolar area
					11 - Orbitofrontal area
					46 - Dorsolateral prefrontal cortex
Ch 14	-44	49	20	6.46	45 - pars triangularis Broca's area
					46 - Dorsolateral prefrontal cortex
Ch 15	-43	55	-5	4.95	10 - Frontopolar area
					46 - Dorsolateral prefrontal cortex
Ch 16	-51	40	6	6.31	45 - pars triangularis Broca's area
					46 - Dorsolateral prefrontal cortex

were available (Emitter-Detector distance was 3 cm). In order to have a reliable cerebral structural correlation, the center of the probe matrix was placed on the Fz of the international 10-20 system. Since we conducted the experiment with the OEG-16 without any supplementary tool such as a 3D digitizer, it is difficult to identify the activated foci of human brain. To resolve this problem, we referred to the spatial registration of fNIRS device ETG4000 3×11 (manufactured by Hitachi), which contained the channels of spectratech OEG-16 system. The probabilistic for each channel are listed in Table 3-1 as the standard MNI coordinates produced by Montreal Neurological Institute in Canada (Figure 3-3).

Regarding the data analysis, since data from the detectors were too noisy for analysis, data was firstly filtered with moving average (data points: 5) to eliminated physiological noise. Baseline correction was performed using linear fitting. Following this, activation of baseline and task for each trail was averaged. To determine the significantly activated channels, we compared the baselines and tasks to examine whether the channel is activated by stimulus at first. Cognitive subtraction was used to compare purified water with sweetened solution so as to identify the true activities evoked by sweet taste backwardly. Statistical analyses were conducted using PAWS version 18.0 (SPSS Inc.).

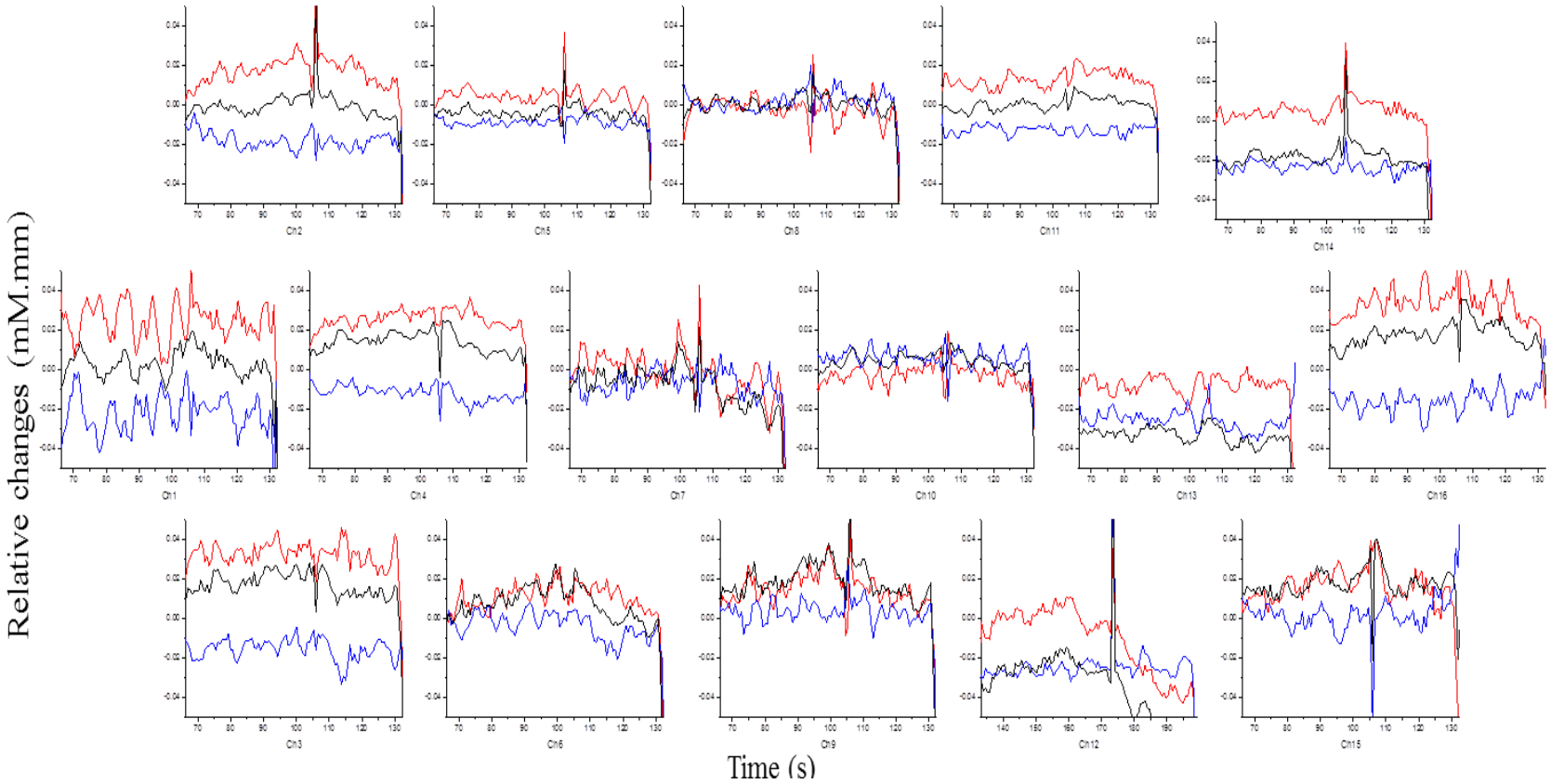


Figure 3-4 Grand average (16 subjects) concentration changes of oxyHb, deoxyHb and totalHb during 5% sweetened solution of sucrose. (Hemoglobin concentration changes are exhibited in colors lines: ΔoxyHb, red; ΔdeoxyHb, blue; ΔtotalHb, black).

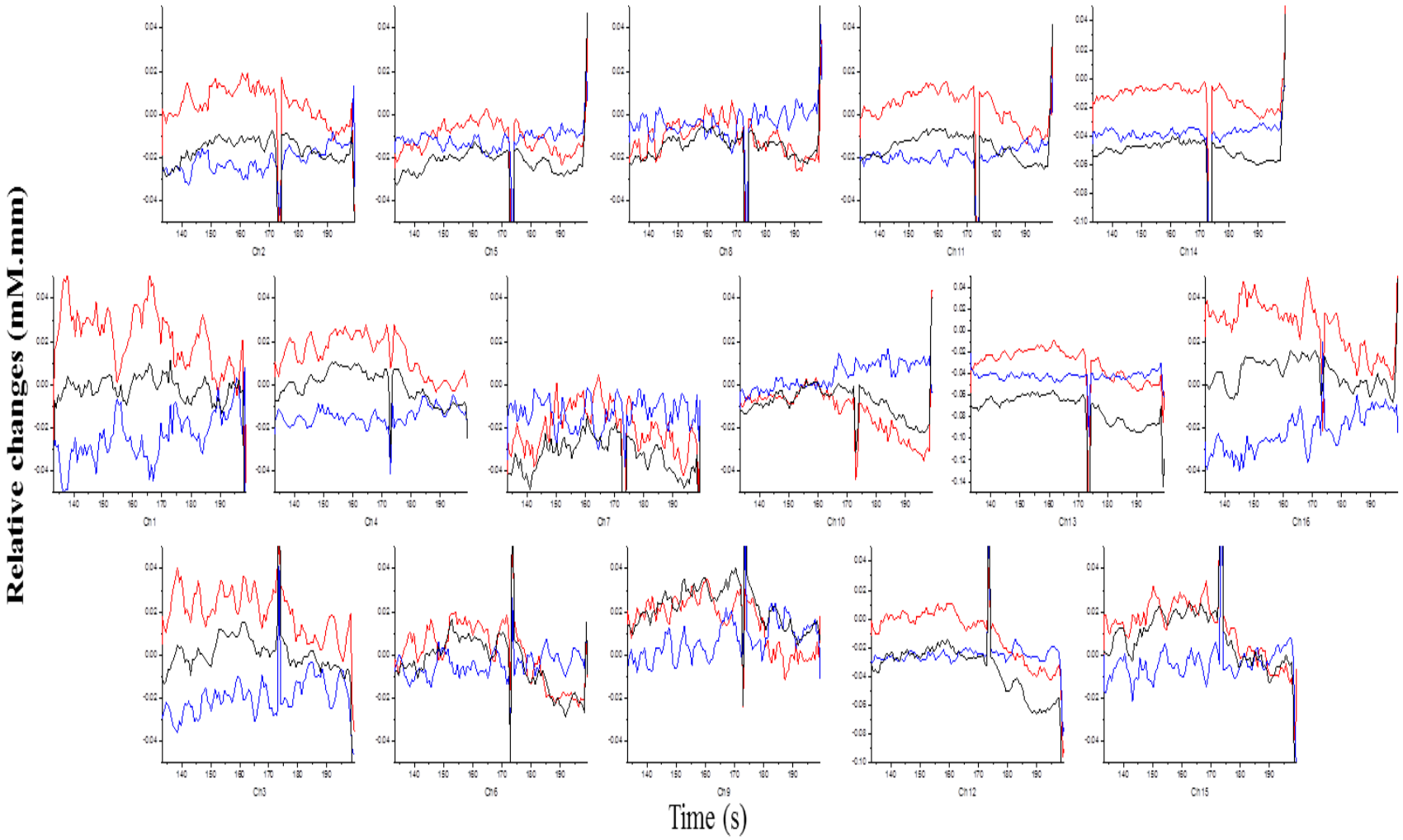


Figure 3-5Grand average (16 subjects) concentration changes of oxyHb, deoxyHb and totalHb during 10% sweetened solution of sucrose. (Hemoglobin concentration changes are exhibited in colors lines: ΔoxyHb, red; ΔdeoxyHb, blue; ΔtotalHb, black).

3.3 Result

The signal changes in ΔoxyHb, ΔdeoxyHb and ΔtotalHb for each channel during tasting 5% sweetened solution were exhibited in Figure 3-4 and it seemed to almost nothing change. On the other hand, Figure 3-5 presented the concentration changes of oxyHb, deoxyHb and totalHb in the 10% sweet solution processing and it showed a relative decrease of oxyHb, accompanied by a deoxyHb increase in most channels. In addition, the totalHb response pattern seemed to be similar to the oxyHb.

For statistical analysis, Analysis of variance (ANOVA) on the data was performed separately for ΔoxyHb, ΔdeoxyHb and ΔtotalHb. With the help of ANOVA, from the global data of 16 subjects, the results were obtained as following. The brain responses to sweet solution with different concentrations were seen in different anatomical area in PFC. Furthermore, the activated channels induced by the higher concentration were more than that induced by the lower concentration in present study. Specifically, for ΔoxyHb, the results of statistical analysis revealed no significant effect of PFC except Ch7 in the lower concentration condition, which is closed to frontopolar area and orbitofrontal area. While the in the higher concentration condition the following nine channels revealed significance located in bilateral pars triangularis Broca's area (Ch1and Ch16), dorsolateral PFC (Ch3, Ch4, Ch11, Ch13 and Ch16), frontopolar area (Ch4,Ch10,Ch11, Ch13), and the orbitofrontal area (Ch4, Ch6, Ch10, Ch12 and Ch13). For ΔdeoxyHb, two channels (Ch4 and Ch6) showed significance for lower concentration solution referred to frontopolar area, dorsolateral PFC and orbitofrontal area in the left hemisphere, while significance could be found in bilateral dorsolateral PFC, pars triangularis Broca's area (Ch2, Ch3, Ch5, and Ch16) for the higher one. For

ΔtotalHb, Ch7 also showed a significant change for the lower concentration, and six channels (Ch4, Ch6, Ch12, Ch13, Ch15, and Ch16) showed significant changes for the higher one. In addition, the individual analysis showed that the activated areas of brain are different among all of the subjects under the sweet stimuli processing.

3. 4 Discussion

Some traditional neurophysiology and neuro-anatomy studies have accumulated a lot of knowledge and theories about taste organ, anatomic constitution of taste pathways, transduction of taste signal and classification of tastants. Most of them depended on autopsy, head injured patients and animal experiments. The accumulated knowledge, in particular to taste-related brain function, is far from complete. With the advent of modern neuroimaging techniques, a wider range of taste-related brain function can be monitored more objectively and effectively. Some studies have shown that the neuron activity is closely related to cell energy metabolism. While the functional area of human brain is stimulated and activated under some task condition, regional brain activation is accompanied by increases in rCBF and the regional cerebral oxygen metabolic rate ($rCMRO_2$). It is widely accepted that the degree of the increases in rCBF exceeds that of the increase in $rCMRO_2$ (Fox and Raichle, 1986), which results in a decrease in deoxyHb in venous blood. The fNIRS can measures the concentration changes of oxyHb, deoxyHb and totalHb and to reveal the brain activation. Owing its strengths and advantages, fNIRS provide an alternative way to monitor taste-related brain function. The present study gave evidence that the fNIRS can be used to monitor the human prefrontal cortex activity which is respond to sweet taste.

In previous studies, two authorized models utilized in cognitive experiments using

fMRI are a block design model and an event-related design model. The experiments using the block design are simpler to implement because careful randomization and spacing of different stimulus categories is not required (Donaldson and Buchner, 2001). However, in a block design, two or more conditions are alternated in blocks in some order, and this makes the type of stimulus within each block very predictable, which will interfere with experiment result as a consequence. Relatively, the latter event-related design is more complex and less selected for fMRI studies. It permits a randomized presentation of stimuli that theoretically reduce confounds arising from stimulus predictability. So far, many researches usually utilized the block design to do the fMRI experiments for investigating the taste-related brain function. And some previous studies suggested that when some taste rewards are predictable, brain regions recruited during expectation are, in part, dissociable from areas responding to reward receipt (O'Doherty et al., 2002). Therefore, in present study, the experiment performed on event-related design so that the interference arising from stimulus predictability could be avoided effectively.

To date, the issue of cortex localization of taste cognitive processing is still on dispute. In nonhuman primate, behavioral, ethological and electrophysiological evidence suggested that the sense of taste is conveyed via nucleus of the solitary tract, thalamus, projected to the primary gustatory cortex (anterior insula/frontal operculum), and then further processed in the second gustatory cortex which is sometimes referred to orbitofrontal cortex in frontal lobe (Zald et al., 2002). Furthermore, in humans, some experiments for investigating gustatory neural circuitry also have been done among human and all most of them supported the issue above and indicated these areas presented above are activated by taste stimuli (Barry et al., 2001; Kinomura et al., 1994;

Pritchard et al., 1999; Zatorre and Jones-Gotman, 2000).Especially relevant to sweet taste, servered as a signal of energy regulation (Swithers and Davidson, 2008) and usually bringing a pleasurable sensation, some evidences suggested glucose ingestion could improve cognition (Riby et al., 2004, 2008) and also have benificial effects on attentional control (Scholey et al., 2009; Gagnon et al., 2010). Furthermore, considering its importance, few studies have used EEG, PET, fMRI or another neurophysiology and neuroimanging techniques to examine brain acitvation pattern associated with sweet taste. For instance, evidences for EEG suggests that clear right frontcentral activation and caudolateral orbitofrontal cortex was specifically observed for sweet taste (Franken et al., 2011), while other fMRI or PET studies found increased rCBF values in the thalamus, the insular cortex, the anterior cingulate gyms, the parahippocampal gyrus, the lingual gyrus, the caudate nucleus, and the temporal gyri, especially in the left or bilateral hemisphere (Kringelbach et al., 2004; Kinomura et al., 1994). To summary, these studies reported above suggested that sweet taste processing acutely influenced the cerebral activity. However, the mechanisms for sweet gustatory system are still uncompleted. Hence, our study used fNIRS, a new noninvasive neuroimaging technique, to investigate the sweet taste cognitive mechanism and results suggested the bilateral prefrontal cortex was activated in taste system. To exact, parts of pars triangularis Broca's area, dorsolateral PFC, frontopolar area, and the orbitofrontal area was acutely influenced when the participants were in the sweet taste condition. Significant activation in orbitofrontal cortex with subjective pleasantness is consistent with an important role for the orbitofrontal cortex in human emotion and motivation. The more regions reported here is similar to some previous findings but also shows some differences for different experimental designs or tasks (Kringelbach et al., 2004; Okamoto et al., 2006a,

2006b). Admittedly, this study has some limitations and more evidence is required to clarify this issue. A future NIRS study may overcome the influences induced by subjects' number, taste concentration, persons' physical self (Ganchrow and Erickson, 1970; Funakoshi and Ninomiya, 1977) or another factors, to further assesse questions about taste cortical activation on human brain.

3.5 Summary

Taken together, fNIRS, a noninvasive neuroimaging technique, created potential for studying a wider variety of taste-related brain function under more natural conditions. The present study demonstrated that the LPFC is involved in representing the subjective pleasantness of tastants, which may be important in influencing whether a food is selected as a goal of action. We also hope the investigation will further contribute to the understanding of sweet taste cognitive mechanisms and even to provide some theoretical evidence for studying on taste dyspepsia and disorder.

Chapter 4

Prefrontal Cortex Activity Reponses to Pleasant and Aversive Tastes

The aim of the study was to investigate the representation of taste in human PFC, in particular, to compare the representation of a pleasant and an aversive taste using fNIRS, so as to obtain further understanding of the taste preference mechanism. The pleasant stimulus used was sweet taste (10% sucrose), and the unpleasant stimulus was sour taste (1% critic acid). Based on event-related design, the experiments were performed with 16 healthy volunteers using the OEG-16 fNIRS sensor. A general linear model was used to analyze the collected data.

4.1 Background

As we presented before, gustation serves an important role in human as one specific and basic function of oral cavity (Liu, 2002). The sense of taste is one of the chemosensory systems, which allows human sense the chemical environment. And it is closely related to brain function. The information and sensation gained by receptors is not only to modulate food intake but also affect high cognitive process of human brain (Kato, 2007). For its importance, brain activity during taste cognitive processing associated with daily feeding behaviors has recently attracted increasing attention. In the past several years, the study of taste sensation and perception has been energized by the discovery that taste and other food-related activities occur in the PFC (Kringelbach et al., 2004), which

is involved in various higher cognitive functions such as planning, reasoning and language comprehension (Miller and Cohen, 2001). This finding has recast our understanding of neural communication in gustatory system. Correspondingly, Okamoto et al have done a series researches on PFC activity for taste encoding based on different experimental tasks and designs, and almost of the results illustrated the lateral PFC is recruited of intentional taste encoding (Okamoto et al., 2006a, 2006b). Similarly, the acute effects of glucose ingestion on prefrontal brain activation during the execution of a divided attention task have exhibited in fasting non-diabetic older adults (Gagnon et al., 2012). Several neuroimaging and neurophysiological studies have provided supporting evidence for the above finding (Bembich et al., 2010). Thus, the PFC seems to be also responsible for taste cognitive processing. However, although taste-related brain function can be inferred by accumulating establish fundamental evidences, compared with other sensory functions, such as vision, audition and olfaction, studies on gustatory cognitive processing, in particular to PFC, remain scarce. The representation of gustatory neural circuits is still in its infancy.

Inspired by these previous studies and based on our previous researches which were talked about in chapter 3, in this research, we further investigated whether similar hemodynamic changes were also detected in PFC when tasting pleasant and unpleasant tastes. Although the subjective feeling of taste varies, in generally, the sensation of taste can be categorized into five basic taste qualities: sweetness, sourness, saltiness, bitterness, and possibly umami. Meanwhile, as taste sense both harmful and beneficial things, all basic tastes are classified as either aversive and appetitive, depending on the effect the things they sense have on our bodies, such as salty, sweet and umami drives us toward essential nutrients, whereas bitter and sour alerts us to potentially harmful

substance. Thus, emotion induced by taste refers to food modulation, balance of nutrition and harm avoidance, and they all play important roles in human survival. Among these five basic tastes, sweetness is often regarded as a pleasurable sensation, while sourness serves as an aversive taste. Because the prefrontal cortex plays an importance role in many higher cognitive functions (Miller and Cohen, 2001), we speculated that pleasant and aversive taste processing would activate some parts of the PFC at first. And, if true, show where is responding to these tastes in human brain. The primary aim of this study was to use fNIRS to obtain correlations between prefrontal cortex activity and the subjective emotion-effects produced by sweet and acidic tastes based on ERD.

We used fNIRS to monitor the brain activation and reveal hemodynamic and metabolic changes (Ferrari and Quaresima, 2012). In the almost 35 year since Jobsis firstly applied NIRS to monitor changes in tissue oxygenation (Jobsis, 1977), this technology has developed remarkably. Compared to other neuroimaging methods, such as PET, fMRI or MEG, fNIRS has many advantages. The experiments, using fMRI or another brain imaging technologies, requires the subject being scanned stays completely still so that it can capture a clear image. It makes the subject feel stressful physiologically and/or physically. On the contrary, fNIRS only requires compact experimental equipment and is less restrictive of subject's movement, allowing the brain function to be monitored under more natural conditions (Coyle et al., 2004; Hoshi et al., 2001). So far, this technique has been widely used for some brain research of sensory, motor and other high cognitive process.

4.2 Materials and Methods

4.2.1 Participants

A total of 16 healthy volunteers (8 males and 8 females), aged 26.31±5.462 years (mean ± SD), participated in the experiment.All of them are right-handed and none had a history of mental and neurological disease. The volunteers werenot allowed to eat 2 hours before the experiment but were allowed to drink normally.This study was approved by the Human Ethics Committee of Health Promotion and Education, Graduate School of Human Development and Environment in Kobe University.

4.2.2 Stimuli

Ssweetened solution (10% sucrose) and acidic solution (1% citricacid) were chosen as taste stimuli. In our previous works, the pre-experiment had been done by sweet and acidic solution with different concentration, and we found, most of the subjects were activated by these two stimuli (10% sucrose and 1% citricacid) strongly. In addition, to determine the brain cortex areas specifically activated by these stimuli, purified water (tasteless) was used as reference to minimize noise induced by oral motor and other brain function in the subsequent analysis. All samples are served at room temperature.

4.2.3 Experimental procedure

The experiment was performed using ERD. Figure 4-1 shows the schematic diagram of the protocol. A single session comprised of a baseline and a task. During the experiment, as a baseline condition, we asked the subject to sit on a chair in a quiet room and try to relax with eyes closed for 40 seconds. Following this, stimulus, in quantities of 8 ml, was manually injected into the subject’s mouth via a hand-held syringe connected to a tube. The subject was asked to hold the stimulus in the mouth for 25 seconds (include the injection time) and then spit it out. After the task, the subject rinsed off his/her

mouth with purified water to prevent adaptation. Then they continued to run the same process with the two stimuli. In this experimetn, purified water was firstly injected and

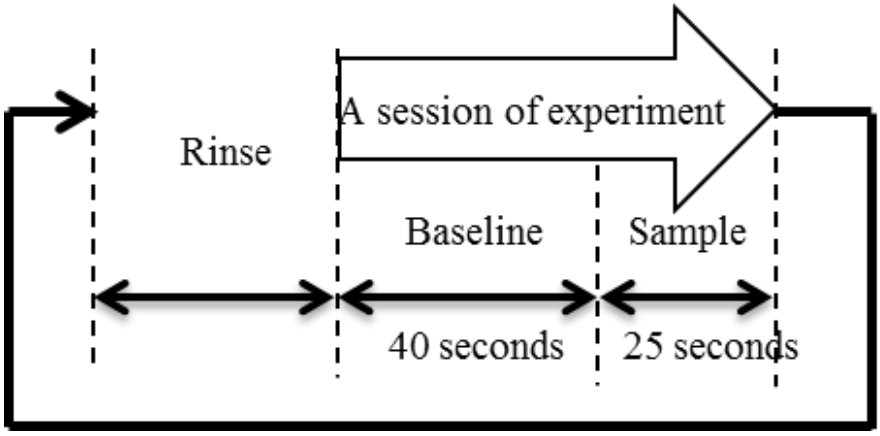


Figure 4-1 The schematic diagram of experimental design

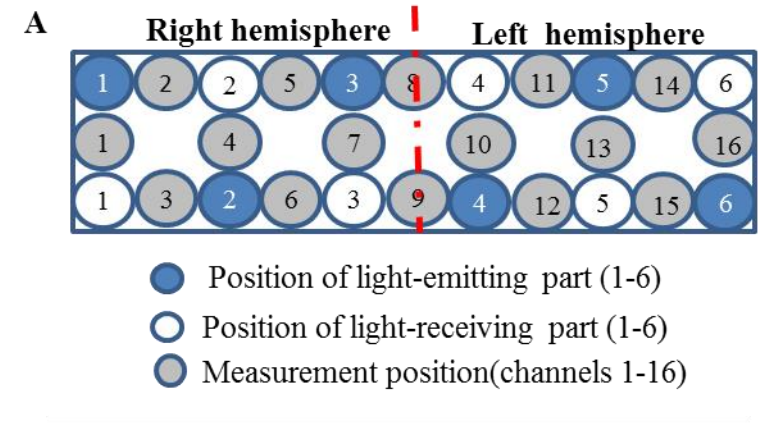
followed by sweet solution and acidic solution. Some pilot studies were done so that subjects knew about experiment and it was beneficial for us to seek some ROIs of gustatory system effectively.

The subjective ratings of the pleasantness of the stimuli were also measured just after the fNIRS recording session using a rating scale ranging from +2 = very like/ pleasant, 0 = neutral, -2 = very dislike/ unpleasant.

4.2.4 fNIRS measurement

We used a multichannel fNIRS instrument (Spectratech OEG-16 from Spectratech Inc., Tokyo, Japan) to cover the prefrontal lobe and monitor the subject's brain activity during the taste processing. The system operated at two different wavelengths of 770 nm and 840 nm, emitting an average power of 3.6 mW/mm^{-2}. The time resolution is 0.65 seconds, and the depth of brain tissue which can be measured from the surface is 3 cm in this case. Up to now, there has not been any positional standard for fNIRS, thus, we placed OEG-16 over the frontal lobe using Fp1 and Fp2 of the international 10-20

system as reference points for placement, as showed in Figure 4-2.



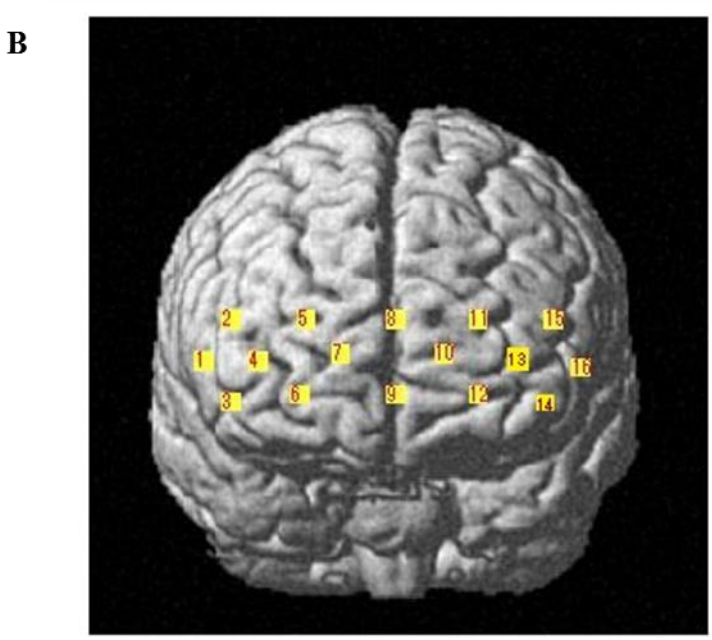


Figure 4-2 A. Schematic illustration of the multi-channel array (Spectratech OEG-16 system, 16 channels). B. fNIRS channels' estimated cortical location in MNI space

4.2.5 fNIRS data acquisition and analysis

Using the modified Beer-Lambert Law (MBLL) for highly scattering medium (Delpy et al., 1988; Eda, 2009), the optical data was transferred into the oxygenated hemoglobin (oxyHb), deoxygenated hemoglobin (deoxyHb), and total hemoglobin (totalHb) concentration changes as ΔoxyHb, ΔdeoxyHb, and ΔtotalHb respectively in mM.mm

unit, as the following equation:

$$\Delta A_{\lambda} = \varepsilon_{\lambda} \Delta c \langle d \rangle + \Delta s \qquad (1)$$

Here, ΔA_{λ} means the change of absorbance at a given wavelength, ε_{λ} for concentration change, $\langle d \rangle$for average length of light path, and Δs for effect change by scattering. Considering multiple measurement at two wavelengths in this case, we can rewrite equation (1) as follows:

$$\Delta A_{\lambda 840} = \left(\varepsilon_{\mathrm{oxy}\lambda 840} \Delta c_{\mathrm{oxy}} + \varepsilon_{\mathrm{deoxy}\lambda 840} \Delta c_{\mathrm{deoxy}}\right) \langle d \rangle + \Delta s \qquad (2)$$

$$\Delta A_{\lambda 770} = \left(\varepsilon_{\mathrm{oxy}\lambda 770} \Delta c_{\mathrm{oxy}} + \varepsilon_{\mathrm{deoxy}\lambda 770} \Delta c_{\mathrm{deoxy}}\right) \langle d \rangle + \Delta s \qquad (3)$$

From (2) and (3), we can obtain Δc_{oxy} and $\Delta c_{\mathrm{deoxy}}$. Then the total hemoglobin signal (ΔCtotalHb) is calculated as a sum of Δc_{oxy} and $\Delta c_{\mathrm{deoxy}}$ as following

$$\Delta c_{\mathrm{totalHb}} = \Delta c_{\mathrm{oxy}} + \Delta c_{\mathrm{deoxy}} \qquad (4)$$

Our analyses focused on oxyHb, which is most sensitive to change in regional cerebral blood flow, and provided the strongest correlation with the blood oxygen level dependent signal among the three fNIRS parameters (Hoshi et al., 2001). Afterwards, moving average filter was applied to remove global influence (e.g. changes in heart rate or respiratory influences), and we made the data point as 5 and one repeat time. All sessions in all channels were used for statistical processing.

For each channel in each of the 3 conditions (purified water sweetened and acidic solution), a baseline was calculated as the mean value of ΔoxyHb in 40s, while a task was calculated as the mean value of ΔoxyHb over 25s after injecting stimulus. To identify the significantly activated channels, we performed ANOVA comparing the different stimulus in different condition respectively (i.e. baseline1 vs. task1, task1 vs. task 2) (To enable the analysis, the thresholds for significance in the result were then set at $p<0.05$ (Bonferroni)). Our analysis is summarized as follows: firstly, we compared

the baseline with task values respectively (i.e. baseline1 vs. task1) to get the channels

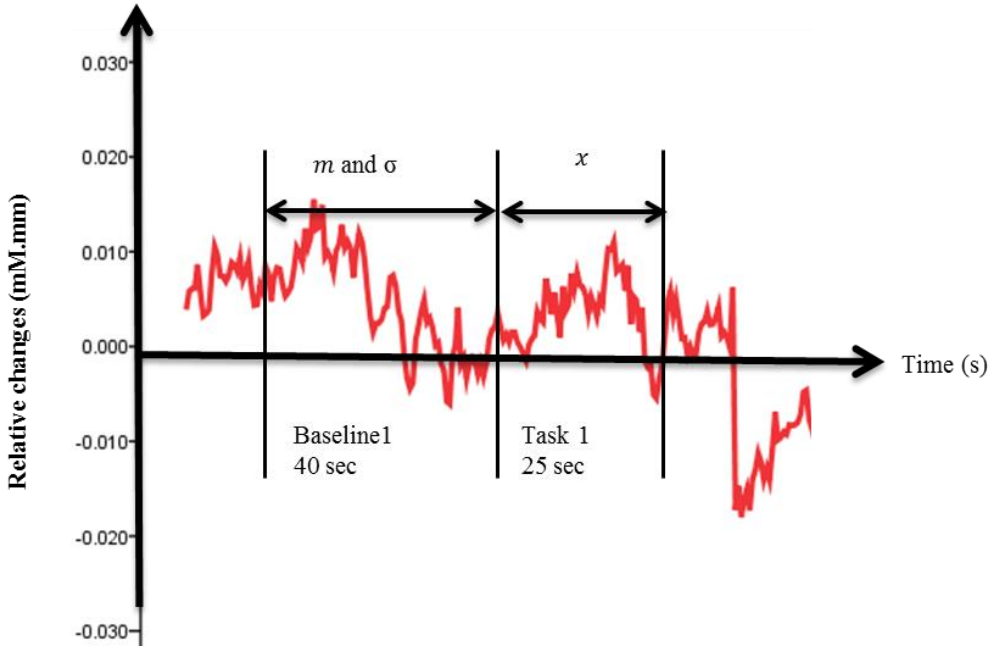


Figure 4-3 Normalized changes for fNIRS data in task condition.

which are significantly influenced by stimulus. Then, because the baselines of three stimuli showed different level from each other, we calculated the Z-score of each task value as it is normalized before they can be used for comparison among themselves. The equation is shown as:

$$z = \frac{x - m}{\sigma} \qquad (5)$$

Here, m represents the mean value of the baseline, σ is the standard deviation of the baseline, and x is the value of the tasks for 25seconds (Figure 4-3). By using the z-scores, we could then compare the task values to find out whether there is any difference among the three tastes. Specifically, based on the channels which were activated by stimuli firstly, if they show different level between tasteless (purified water) and tastes (sweetness and sourness), we identified the activities in these channels are

truly evoked by sweetness and sourness. In other word, these regions are involved in the sweet and/or sour taste processing. We also compared neural responses to sweetness and sourness to find out whether there is any anatomical separation between these two taste senses. Statistical analyses were conducted using SPSS version 18.0 (SPSS Inc.).

Since we conducted the experiment with the OEG-16 without any supplementary tool such as a 3D digitizer, it is difficult to identify the activated foci of human brain. To resolve this problem, we referred to the spatial registration of fNIRS device the ETG4000 3×11 (manufactured by Hitachi), which contained the channels of OEG-16. From there, we obtained Channel localizations of OEG-16 on human brain. The channels covered inferior frontal gyrus, middle fontal gyrus, superior frontal gyrus and the lateral orbitofrontal gyrus (Figure4-2B).

4.3 Results

4.3.1 Pleasantness ratings

The average pleasantness rating for the sweetened solution condition was +1.13±0.5 (mean ± SE), whereas -0.69 ± 0.94 for the acidic solution condition (paired t = 5.68, df=15, $p<0.001$), which matched the subjects' self-reported that the sweetened solution made them pleasant and the acidic solution is unpleasant.

4.3.2 Prefrontal cortical responses

Figure 4-4 and 4-5 represented the activation of prefrontal lobe cortex when tasting the sweet solution and acidic solution and most of channels showed a relative decrease of oxyHb. According to ANOVA, we observed different PFC areas across different tasks. In the purified water condition, a significant activation from baseline to task in oxyHb was observed in almost all channels. In sweetened solution condition, the regions in

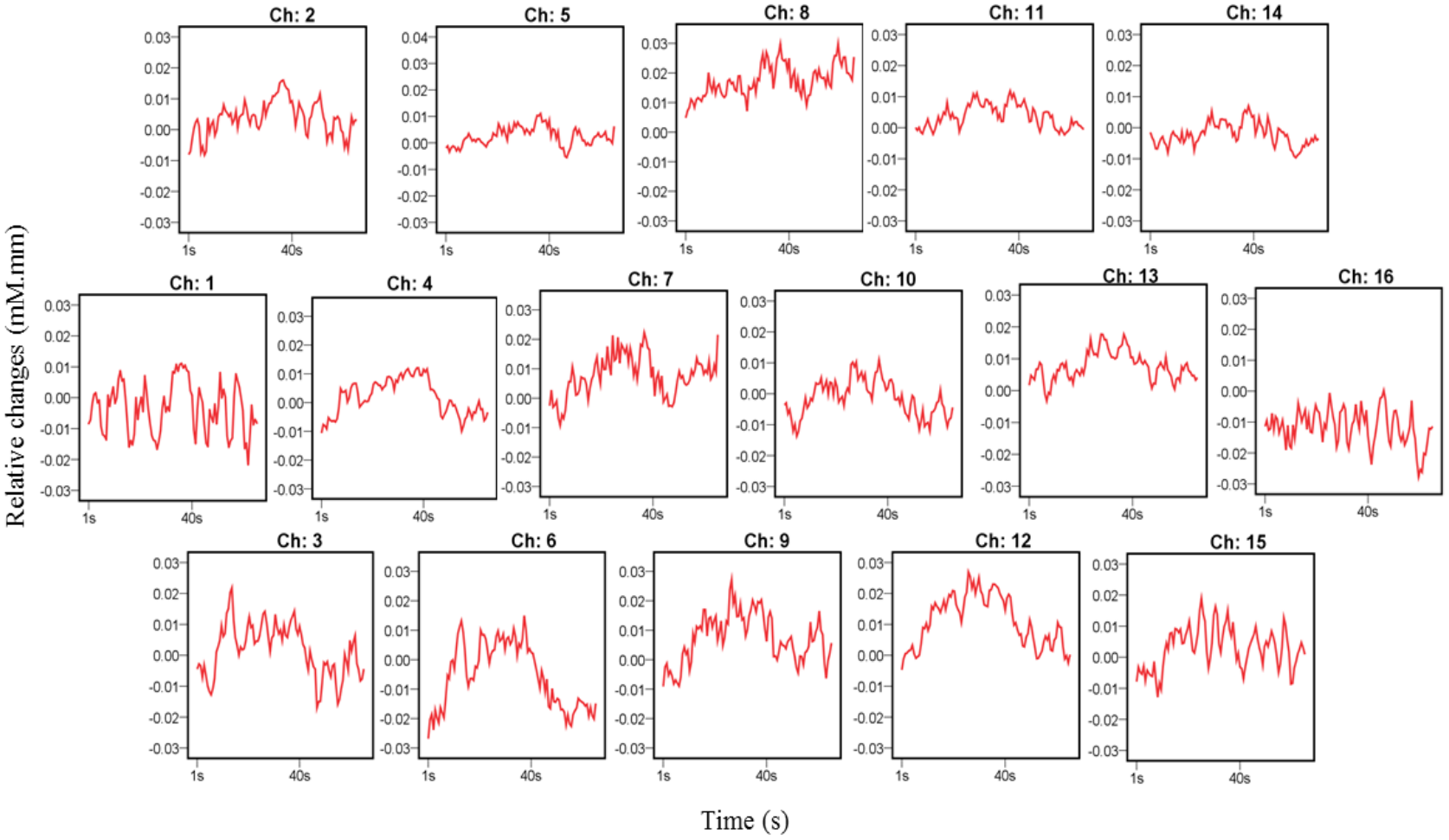


Figure 4-4 Grand average concentration changes of oxyHb for 16 subjects during the sweet taste processing.

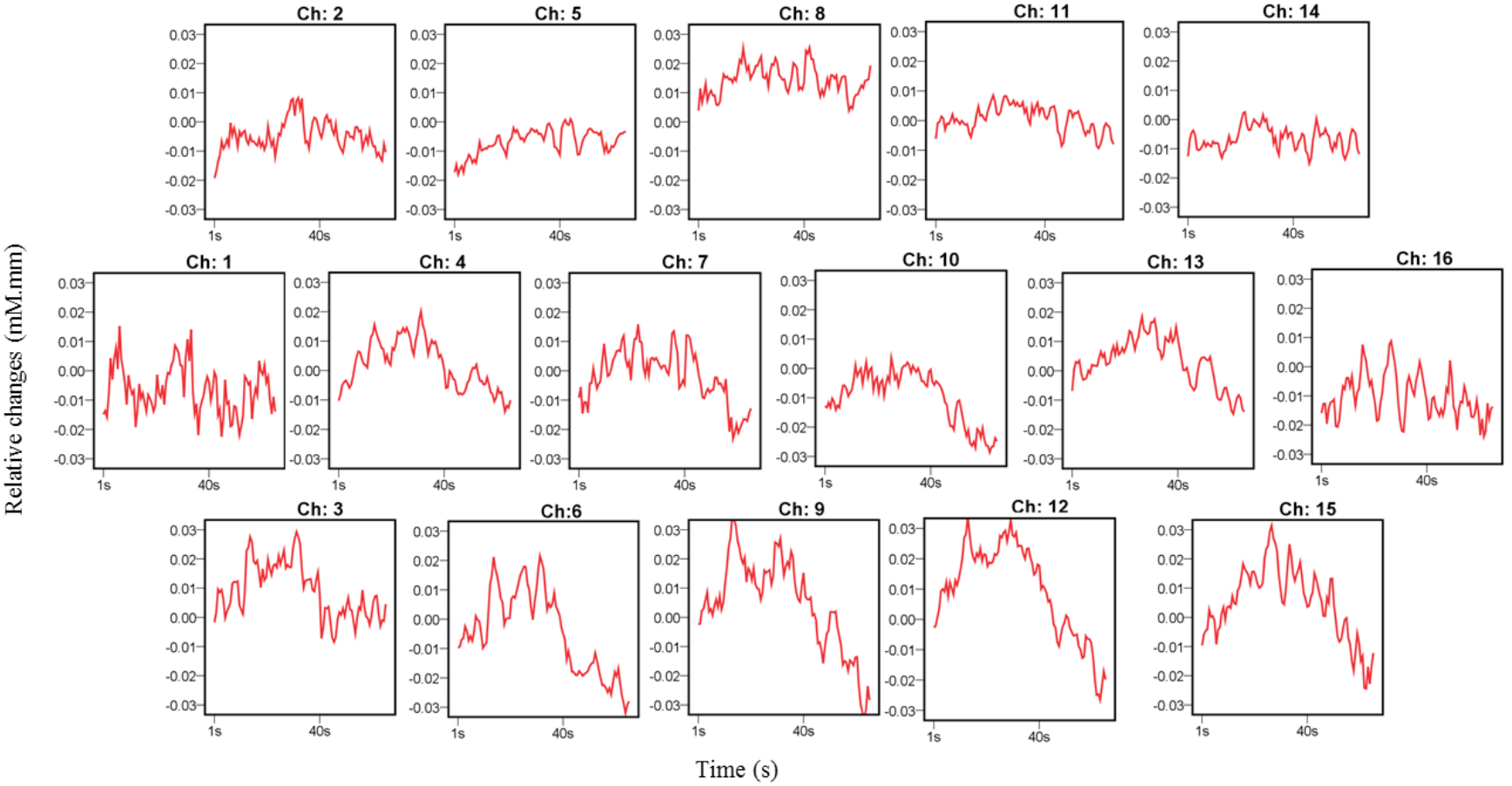


Figure 4-5 Grand average concentration changes of oxyHb for 16 subjects during the acidic taste processing.

bilateral prefrontal cortex (ch3, 4, 6, 10, 11, 12 and 14) exhibited significant activation during sweetness stimulating condition. Although these channels were activated by sweet taste and in some sense related to sweet gustatory system, they also would be responses to sensory, motor or proprioceptive in origin. To elicit the cerebral activity by sweetness, then, comparing tasteless (purified water) and sweetness, the main activated signals appeared at five channels (ch3, 4, 6, 11 and 12) (Figure4-6). The MNI coordinates estimated for these channels were close to the reported location of

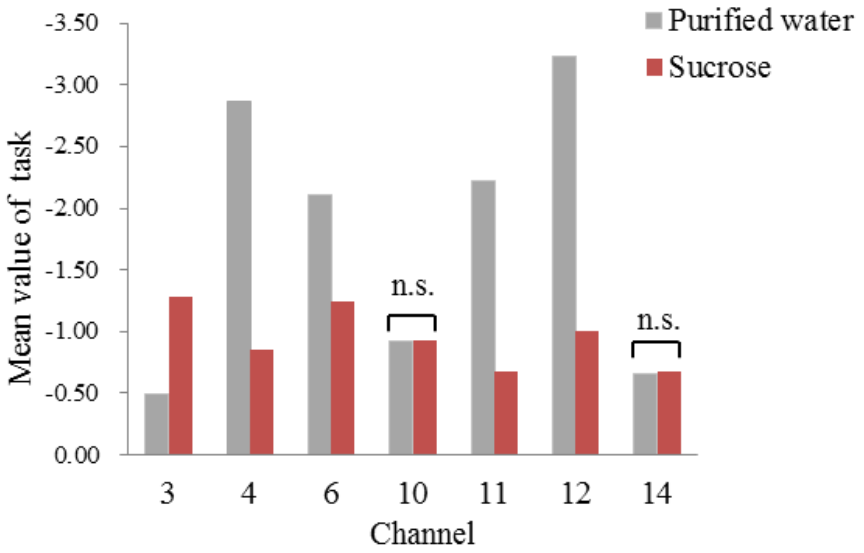


Figure 4-6 Contrast 1 (Sucrose vs. Purified water). Normalized activation levels (z-score) for the channels, acutely activated in purified water and sweetened solution, were compared. n.s.: not significant.

frontopolar area, orbitofrontal area and dorsolateral prefrontal cortex (Table 4-1）. Similarly, the contrast, tasteless and sourness, revealed significant activation in eight channels: ch3, 4, 5, 6, 9, 10, 11 and 13 (Figure4-7), which were in parts of the dorsolateral prefrontal cortex, the frontopolar area, and the orbitofrontal area (Table 4-2). Furthermore, Figure4-8 and table 4-3 showed that parts of the frontopolar area and

orbitofrontal area of human brain especially in the right hemisphere (ch3, 4, and 6) were significantly activated by sweet and sour taste but showed different level between them simultaneously. In addition, the results showed sourness is more sensitively activated than sweetness.

Table 4-1 The activated channels related to sweetness

ROI	Ch	MNI-space correspondence				Cortical areas	
		x	y	z	SD	BA	
Right PFC	3	46	54	-5	5.11	46	Dorsolateral prefrontal cortex
	4	38	60	8	5.07	10	Frontopolar area
						46	Dorsolateral prefrontal cortex
						11	Orbitofrontal area
	6	27	68	-3	4.5	11	Orbitofrontal area
Left PFC	11	-24	65	20	5.83	10	Frontopolar area
						46	Dorsolateral prefrontal cortex
	12	-23	68	-3	4.64	11	Orbitofrontal area

BA, Brodmann area; PFC, prefrontal cortex.

4.4 Discussion

The results from this study showed that the fNIRS (OEG-16) could be used to measure the taste-related brain function. Relatively to our primary aim, comparing purified water to sweetened and acidic solution respectively, the group analysis showed the ROI (tasteless-sweetness) included the regions of one part of the frontopolar area, orbitofrontal area and dorsolateral prefrontal cortex, while the ROI (tasteless-sourness) overlapped the area activated by sweetness (ch3, 4, 6 and 11) and also showed some another foci (ch5, 9, 10 and 13). We conclude that, in some sense, these regions in the prefrontal cortex of human brain are involved in the perception of sweetness and sourness in taste system. Previous neuro-imaging studies of the representation of taste in

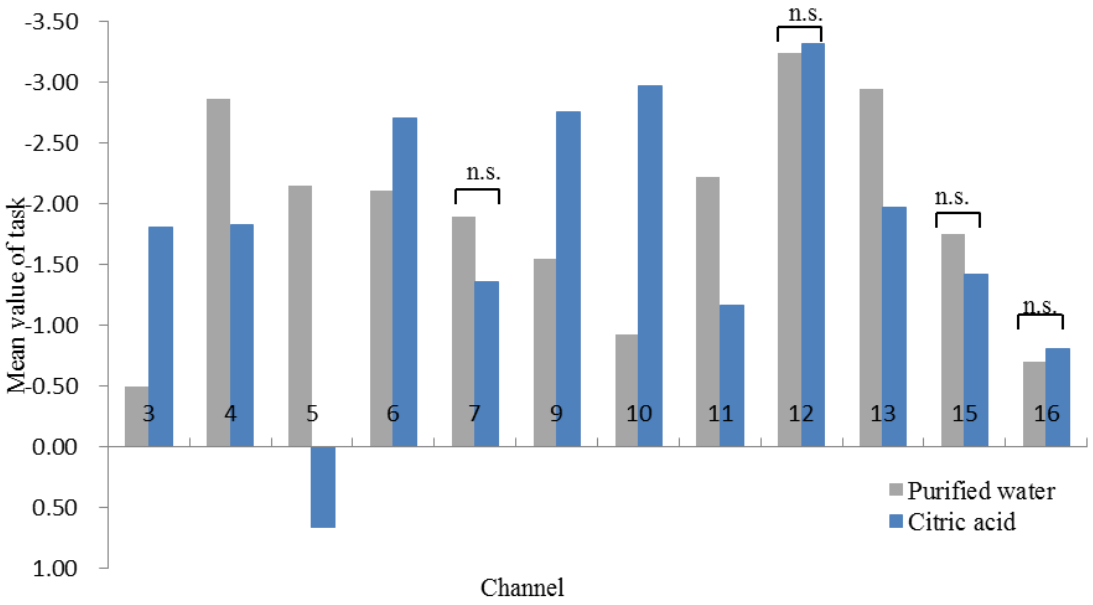


Figure 4-7 Contrast 2 (Citric acid vs. Purified water). Normalized activated levels (Z-score) for the channels, activated in purified water and acidic solution significantly, were compared. n.s.: not significant.

human brain have found cortical areas reacted to taste such as the frontal operculum/insula and the orbitofrontal cortex (Small et al., 1997, 1999; Zald et al., 1988). Furthermore, many neuroimaging studies have shown right-hemispheric dominance is involved in both taste perception (Zatorre and Jones-Gotman, 1999; Barry et al., 2001) and recognition (Small et al., 1997) of gustatory stimuli, while some studies have shown bilateral or left-lateral areas of human brain are concerned with the quality of taste (Kinomura et al., 1994; Pritchard et al., 1999). Our finding supported that the lateral PFC, especially the right hemisphere, are acutely influence by the pleasant and aversive tastes.

Another novel finding of this study is that the difference between sweet and acidic taste appeared in parts of the dorsolateral prefrontal cortex (ch3 and 4), frontopolar area (ch4) and the orbitofrontal area (ch6) in the right hemisphere. This provides new evidence to support the issue that human prefrontal area is involved in the

discrimination of taste qualities.

Furthermore, as the results presented above, aversive stimulus was activated in more regions among the PFC than the pleasant. This may be derived from taste quality and intensity. In a PET studies, they found the aversive taste (saline solution) was slightly more perceptually intense than pleasant taste(chocolate) in the right amygdala, left orbitofrontal cortex and pregenual cingulate (Zald et al., 1998). In our case, Sourness is indeed an aversive taste while sweetness is pleasant for our subjects. Furthermore, the sourness made subjects stronger feelings. It is likely the similar neural mechanism is related to taste quality and intensity in our study.

Table 4-2 The activated channels related to sourness

ROI	Ch	MNI-space correspondence				Cortical areas	
		x	y	z	SD	BA	
Right PFC	3	46	54	-5	5.11	46	Dorsolateral prefrontal cortex
						10	Frontopolar area
	4	38	60	8	5.07	46	Dorsolateral prefrontal cortex
						11	Orbitofrontal area
	5	25	65	20	5.75	10	Frontopolar area
						46	Dorsolateral prefrontal cortex
Anterior PFC	6	27	68	-3	4.5	11	Orbitofrontal area
	9	3	68	-3	5.54	10	Frontopolar area
						11	Orbitofrontal area
	10	-13	70	9	4.91	10	Frontopolar area
						11	Orbitofrontal area
Left PFC	11	-24	65	20	5.83	10	Frontopolar area
						46	Dorsolateral prefrontal cortex
	13	-35	55	22	5.12	10	Frontopolar area
						11	Orbitofrontal area
						46	Dorsolateral prefrontal cortex

BA, Brodmann area; PFC, prefrontal cortex.

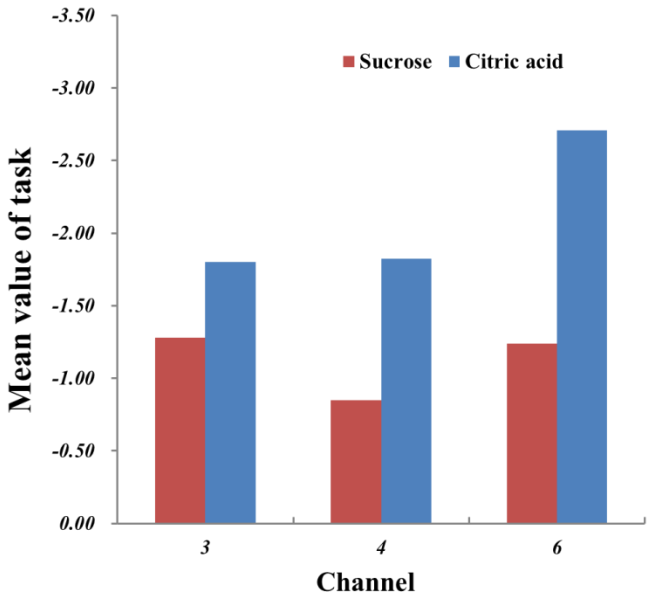


Figure 4-8 Contrast 3 (Sucrose vs. Citric acid). The channels which were truly evoked by sweet and sour tastes were used to compare, and all of them showed different levels significantly.

Table 4-3 The areas related to discrimination of taste quality.

ROI	Ch	MNI-space correspondence				Cortical areas	
		x	y	z	SD	BA	
Right PFC	3	46	54	-5	5.11	46	Dorsolateral prefrontal cortex
						10	Frontopolar area
	4	38	60	8	5.07	46	Dorsolateral prefrontal cortex
						11	Orbitofrontal area
	6	27	68	-3	4.5	11	Orbitofrontal area

BA, Brodmann area; PFC, prefrontal cortex.

In addition, as the result presented above, most parts of the PFC showed a relative decrease of oxyHb during the sweet and acidic taste processing. Why does oxyHb in PFC tend to be decrease during pleasant and aversive taste? Task-induced decreases of oxyHb or rCBF in PFC have been reported by previous studies using video-game-like

tasks (Matsuda and Hiraki, 2006). Regarding to taste, the decrease in neuronal response to a food as the monkey is fed to satiety is partly specific to the food eaten, and this mechanism reflects the preference of the monkeys for the foods (Kringelbach et al., 1994; Rolls et al., 1989). Although each of these studies differed in various tasks and designs, deactivation in dorsal PFC was commonly observed. Some possible factors are applicable to such phenomenon such as attention demand (Mazoyer et al., 2002; Shulman et al., 1997) and "vascular steal" (Wade, 2002). Especially relevant to present study, possible explanation relates to passive hemodynamic changes is attention demand or taste preference rather than vascular steal. Even if our experimenter told subjects no to think of anything during the testing, it is also probable that some unconscious attention demand was required for these pleasant and aversive tastes.

The present findings in humans are consistent with some earlier findings but at the same time there were also some difference in our study. That would be due to the following factors. Firstly, in this case, the Bonferroni correction was performed to set an upper bound on the family wise error rate. Actually, this method is usually used for some data analysis in neuropsychology study and strongly controls the probability of making one or more false detection among all the simultaneously channels. However, such correction may be too strict, and therefore, the ROIs obtained in this case are just the most related foci's of sweet and sour taste. In other word, it is possible that the truly activated channels were overlooked. Secondly, because the taste-related brain function is closely related to the feeding behavior, the physiological status of subject, such as in hungry or satiety condition, may affect the brain function during the gustatory processing. There are some evidences showing that neurons in the secondary taste cortex region have been found to be modulated by the motivational state of the animal,

responding to the sight or taste of food when the animal is hungry and not responding when the animal is satiated (Rolls et al., 1989; Mora et al., 1979). Here, the volunteers did not consume any food the 2 hours before the experiment, so that the activated regions we found were little different from some previous studies. Furthermore, in the neuropsychology and brain function mapping studies, two major types of experimental designs utilized in cognitive experiments using some neuroimaging techniques are block and event-related designs (Chee et al., 2003). In present study, we utilized event-related design, which may be more appropriate for exploring higher cognitive functions (Friston et al., 1999), and injected sweet solution before acidic solution. This experimental paradigm perhaps influenced the regions of interest we found and may explain the activated intensity of sweetness and sourness (Carmichael and Price, 1995, 1996). In addition, there were 16 subjects (Chinese and Japanese) participated in this experiment. As this study is our first time using OEG-16 as a monitor tool for brain cortex functions during the sweet and sour taste processing, it was still in a very early stage and comes with a few limitations. More experiments are required to evaluate this method and further investigate questions about taste preference mechanism.

4.5 Summary

The present study used fNIRS to investigate the prefrontal cortex activity during pleasant and aversive tastes and deactivation was observed in parts of frontopolar area, orbitofrontal area and dorsolateral prefrontal cortex. We hope the investigation will further contribute to the understanding mechanism of taste preference, and to provide some theoretical evidence for studying on taste disease such as dyspepsia and disorder.

Chapter 5

Early Neurological Markers for Investigating Taste Preference

In last chapter, we reported the PFC function associated with taste preference. To further clarify the intrinsic food preference mechanism, we investigated neurophysiological responses to unpleasant gustatory stimuli using EEG and NIR-HEG at the same time. A conventional delayed response task paradigm was performed in the experiment.

The chapter is organized as follows. Section 3.2 presents the stimuli, experimental procedure and data analysis in detail. The results of present study are shown in Section 3.3, followed by discussion about the results in Section 3.4. Section 3.5 summarizes the whole chapter.

5.1 Background

ERPs are a measure of neural activity (derived from the EEG), recorded from scalp electrodes) that can be recorded noninvasively from humans while they perform cognitive tasks (see Ba-shore and van der Molen, 1991 for a review). The first successfully recorded ERP for taste, one of our basic senses, was published nearly half a century ago (Ohla et al., 2012). Since then, numerous studies have been concerned with the cognitive processes related to gustatory system. Some have examined the effects of

glucose ingestion on ERP and found glucose ingestion acutely influenced ERP components (Smith et al., 2009; Riby et al., 2008). Moreover, Riby et al. studied neurocognitive correlates of glucose effects using ERPs and showed that the P3b component had a smaller amplitude, shorter latency and duration when participants were in the glucose condition (Riby et al., 2008). So far, many researchers have done a lot of works about gustatory sensation and some knowledge of taste cognitive processing has been accumulated. However, early sensory ERP deflection to taste have been rarely described (reviewed in Ohla et al., 2012), and the results are also on disputed. To our knowledge, especially, relatively little is known of the neural mechanisms for taste preference. The primary aim of the current study was to expend the previous research by examining the effect of the aversive taste on cognitive performance to get further understanding about the intrinsic food preference mechanism. In this study, critic acid and caffeine severed as aversive taste. One important consideration for the utility of critic acid and caffeine as stimuli is the role they play in cognitive facilitation. Caffeine is one of the most widely used stimulant worldwide and is generally thought to provide benefits such as enhanced mental alertness, energy and a sense of well-being (Koppelstaetter et al., 2008), while the citric acid exists in a variety of fruits and vegetables and it is a key player in our body's ability to create energy (Kozawa and Fukuda, 2009). Furthermore, according to a study in the Journal of Clinical Biochemistry and Nutrition, these two aversive tastes may reduce physical fatigue and lessen physiological stress. Considering their importance, although they make people feel uncomfortable or unpleasant, it is significant to investigate the cognitive processes related to aversive taste. We hope the finding in this study will be effective for investigating the children's dietary bias.

We investigated neurophysiological responses to unpleasant gustatory stimuli based on S1-S2 contingent negative variation (CNV) paradigm, to clarify the intrinsic food preference mechanism. The CNV was one of the first ERP components to be described and it is a slow negative-going ERP elicited by a warning stimulus that requires anticipation of a target stimulus (Picton and Hillyard, 1988; Walter et al., 1964). After discovery of the CNV, Loveless and Sanford (1975) and Weerts and Lang (1973) suggested that the component is quantifiable in to two distinct subcomponents: an "early" CNV and a "late" CNV (Loveless and Sanford, 1975; Weerts and Lang, 1973). the presence of the early CNV is generally thought to be a cortical reflection of controlled, rather than automatic, psychological processes in response to an S1 that requires anticipation of a subsequent S2 (Picton and Hillyard, 1988; Shiffrin and Schneider, 1977), while the late CNV is measured just prior to the onset of the target stimulus, and reflects the additional contribution of cortical resources required for motor response preparation (Damen & Brunia, 1994; Brunia & Damen, 1988). To date, there are many researches which describe what stimulus characteristics can affect characteristics of the CNV. For example, attention and expectancy, intensity, modality, duration, stimulus rate, probability, stimulus relevance, and pitch discrimination can affect the CNV component (Frost et al., 1988; Tecce, 1972). However, there also exists some debate regarding which cognitive processing is the CNV associated. Considerable evidence suggested that the early component of the CNV of the ERP, thought to reflect anticipated cognitive effort, is sensitive to effortful process that contributes to the manifestation of prejudice (Chiu et al., 2004). Since several patterns of cognitive processes that are measurable by the early and late CNV may be related to the expression of the prejudice, in present study, we expected the S1-S2 CNV paradigm

would be adapted to quantify the cognitive processing during taste processing for investigating neural mechanisms of taste preference.

Meanwhile, NIR-HEG is a relatively new HEG neurofeedback system. It covers the human prefrontal lobe and can measure changes in the local oxygenation level of the blood. By far, this device is the simplest neurofeedback system available, which providing you succinct, real-time feedback pf your brain function. In addition, in macaque monkeys, the cortical processing of gustatory information takes place in the insula/ operculum (Rolls and Scott, 2003; Rolls et al., 1988). Correspondingly, the orbitofrontal cortex (OFC) receives projections from the insula/ operculum and has been associated with the reward value of tastes (Rolls et al., 1989). Furthermore, similar results have been found in human, and increasing researches suggested that the LPFC is closely related to taste and other food-related activities (Kringebach et al., 2004; Okamoto et al, 2006a). The importance of LPFC in taste processing is gradually drawing attention (Kringebach et al., 2004). To date, some studies examined LPFC functions with taste and indicated the LPFC is involved in the taste processing. However, to our knowledge, only preliminary steps have been taken to the direct investigation of the underlying neural mechanisms of taste, especially for food preference.

5.2 Materials and Methods

5.2.1 Participants

5 right handed volunteers from Kobe University participated in the experiments (three female and two male). They were between 25 and 50 years of age. Prior to the recording session, all participants completed a health questionnaire and none of them had any past

or current psychiatric and neurological diseases and self-reported taste disturbance. Participants were instructed to fast for two hours but drink normally before running experiment. This study was approved by the Human Ethics Committee of Health Promotion and Education Graduate School of Human Development and Environment in Kobe University. Subjects gave written informed consent prior to the experiment.

5.2.2 Stimuli

In present study, we selected the sour solution (1% citric acid) and bitter solution (0.01% caffeine) as tastants. The choice of these solutions was based on our previous experiments where stimuli with different concentrations had been employed. Meanwhile, purified water was selected as a control condition to minimize the artificial noise from somatosensory effects, swallowing effects and other brain function.

5.2.3 Experimental procedure and data acquisition

Before the testing session, each subject received detailed instructions regarding the experiment. They were instructed to minimize body and brain movement as possible and asked to remain relaxed throughout the experiment. In order to ensure subjects understood the task requirements, pre-experiments were given to practice.

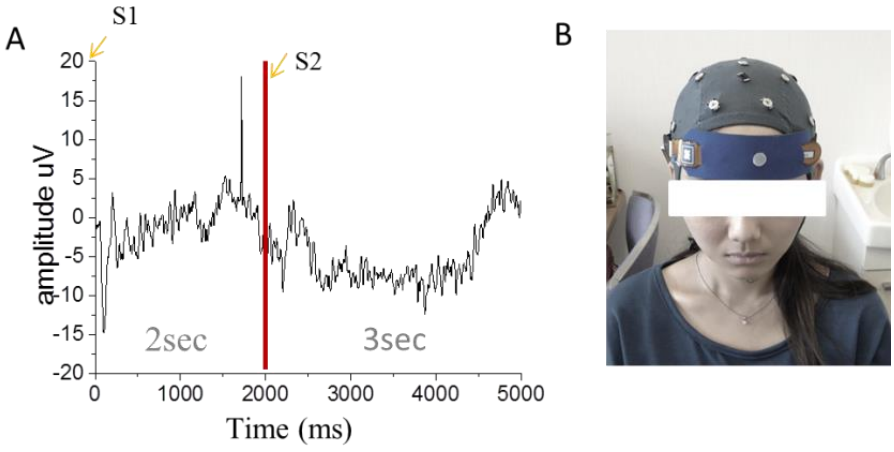


Figure 5-1The experimental protocol and Instruments. A, one trail of the experimental protocol. B, experimental conditions of EEG and NIR-HEG.

During the EEG and NIR-HEG recording session, the subjects were seated in a comfortable chair in a quiet room (Figure 5-1). A conventional delayed response task paradigm was adopted for detecting neurological signs responding to gustatory stimuli. Figure 5-1 showed the experimental protocol as one trail. S1 is a warning signal using a click, and S2 seconds later we used another click as imperative signal to order the experimenter inject the stimulus. The subject tastes the stimulus for 3 seconds. Stimulus was manually injected into the subject's mouth via a hand-held syringe connected to a tube in quantities of 0.2 ml each time. Each stimulus was presented 30 times repeatedly and continuously.

The ERPs were recorded using NeXus-32 and Bio Trace+ Software. Electrodes were placed at standard positions according to the International 10-20 EEG system, while the NIR-HEG covered the prefrontal lobe. In each condition (purified water, sour solution

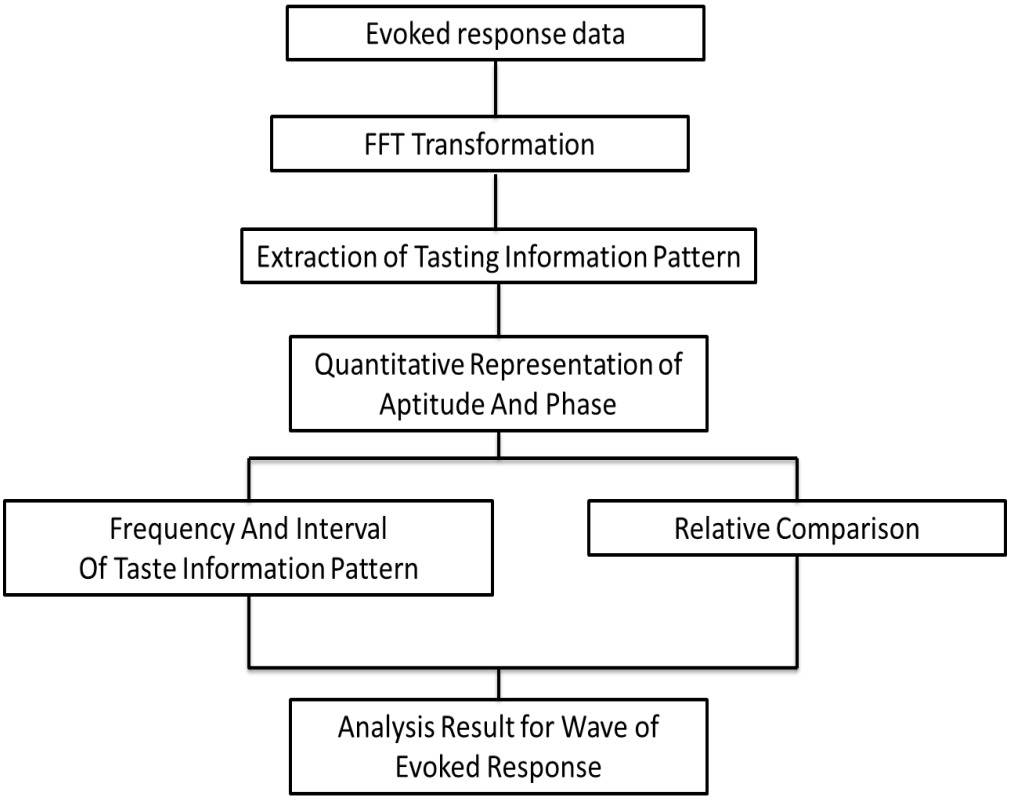


Figure 5-2 The schematic analysis

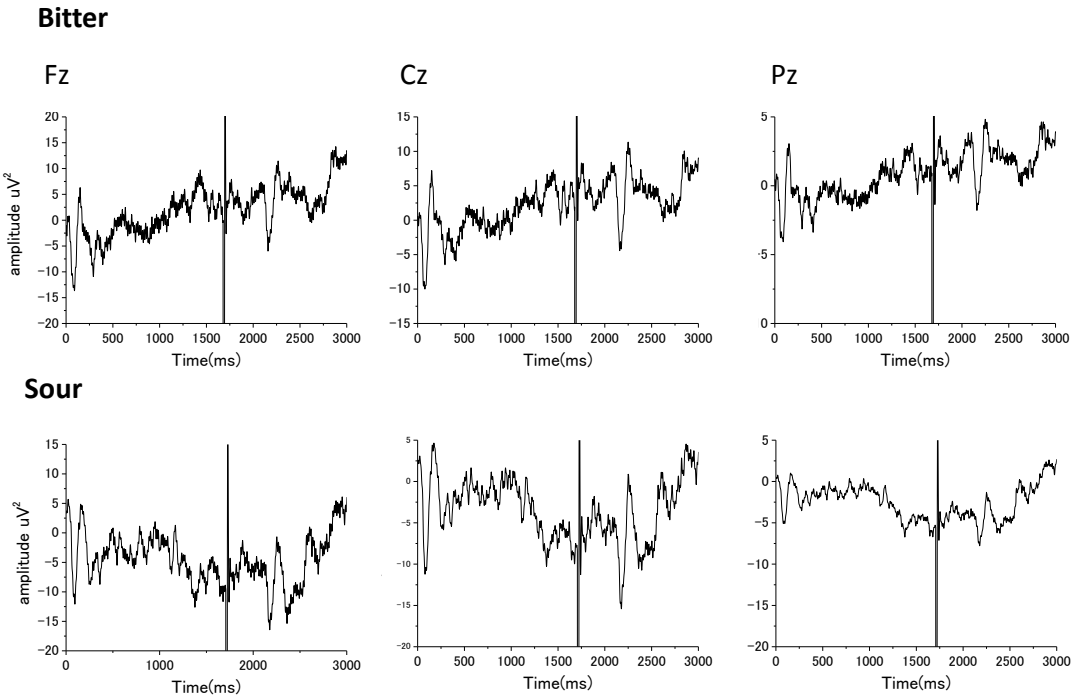


Figure 5-3 ERPs to bitter and sour tastes in Fz, Pz and Cz postion

and bitter solution), the EEG was recorded for 2.5 min, and signs (5s) were extracted as an average value of 30 times. Data was filtered offline between 0.05Hz and 45Hz. Figure 5-2 exhibited the schematic analysis for data.

The intensity of the tastants was rated by the subjects as a subjective evaluation on the dislike-like scale after the EEG session.

5.3 Result

5.3.1 EEG data

The ERPs were recorded from Fz, Pz and Cz exhibited in Figure 5-3. Previous research indicated that the P3 component is centered on the parietal and central scalp regions while the CNV appears most prominently at the vertex and is bilaterally symmetrical (Tecce, 1972). Therefore, our analysis focused on the Cz electrodes. Conversely, the ERP components have been shown to be centred on the central scalp. Figure 5-4

summarized the ERP data response to taste stimulus for the Cz position. After averaging the gustatory ERPs recorded, two positive peaks (P1, P2) and two negative peaks (N1, N2) were observed on the bitter and sour condition. To confirm these gustatory ERPs were truly evoked by bitterness and sourness, we also examined the potentials evoked by purified water and compared it with the components evoked by citric acid and caffeine. These peaks, P1, P2, N1, N2, were not found on the purified water condition obviously. The amplitudes of these responses ranged between 5 and 15 μV, and the sour taste elicited responses of greater amplitude than bitterness. In present study, we also identified a CNV component in a late stage for the sour and corresponding clear P3 (Figure 5-4C).

5.3.2 NIR-HEG data

Meanwhile, in present study, we had a try to use NIR-HEG to monitor the activation of human prefrontal cortex, which plays an important role in human higher cognitive processing. The individual signal changes in hemoglobin during tasting bitter and sour solutions were exhibited in Figure5-5 and Figure 5-6. Figure5-5 showed the responses to bitter stimulus for two subjects. Although they showed different responses individually, in generally, both of them showed a relative decrease of hemoglobin during tasting bitter solution. On the other hand, there was a relative increase in sour solution processing exhibited in Figure 5-6. In addition, the responses of sourness from NIR-HEG also showed more sensitive than that induced by bitterness. For statistical analysis, significances between purified water, bitter and sour solutions respectively could be found in present study.

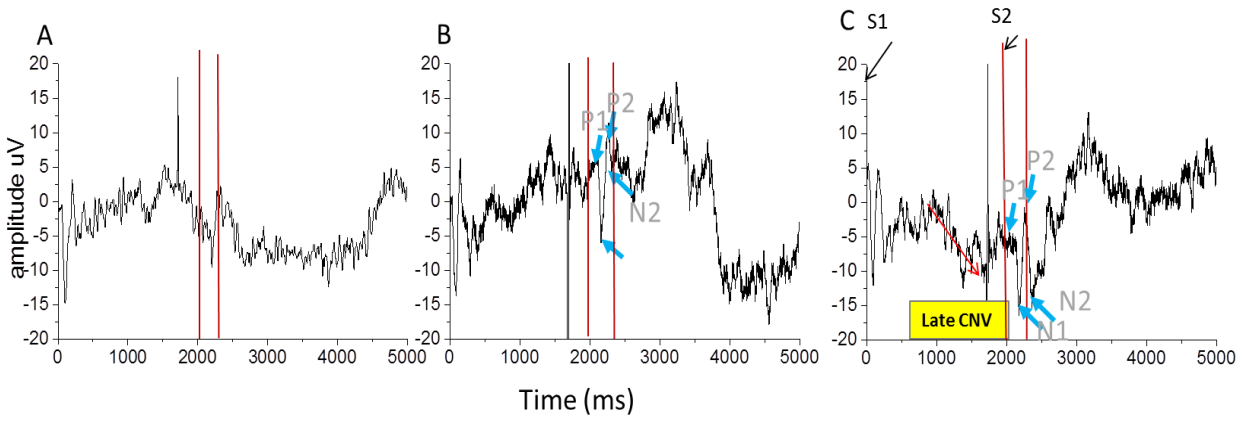


Figure 5-4 ERPs to taste stimuli in Cz. A represents the evoked potential response to water, B for bitter taste and C for Sour taste

5.4 Discussion

The primary aim of the current study was to expend the previous research by examining the effect of the aversive taste on cognitive performance for investigating taste preference. The results showed some electrophysiological early markers appeared during tasting citric acid and caffeine, and we suggested that these components we found would be only attributed to sour and bitter tastes. As these potentials appeared before P3, we considered they would be unconscious electrophysiological early markers for attention. The early sensory ERP deflections to taste found in present study were in agreement with previous researches, which reported P1, P2 and N2 were observed for salt, glucose and electric taste (Mizoguchi et al., 2002; Wada, 2005; Ohla et al., 2010). In addition, this study showed the sour taste gave larger rise than bitter taste. It may be due to the quality and intensity/concentration of tastants, which have been suggested to affect amplitude increase of the evoked potential (Ohla et al., 2010).

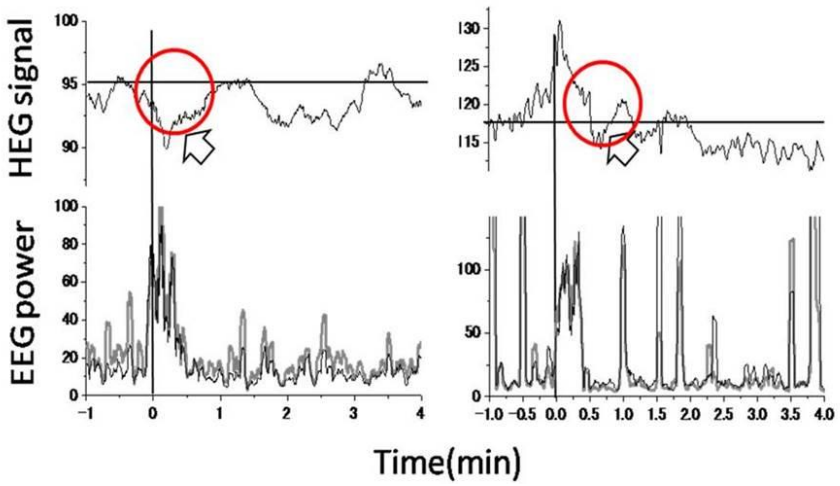


Figure 5-5 HEG and EEG responses to bitter stimulus (Experiments were performed with two participants). All participants decreased their HEG signals

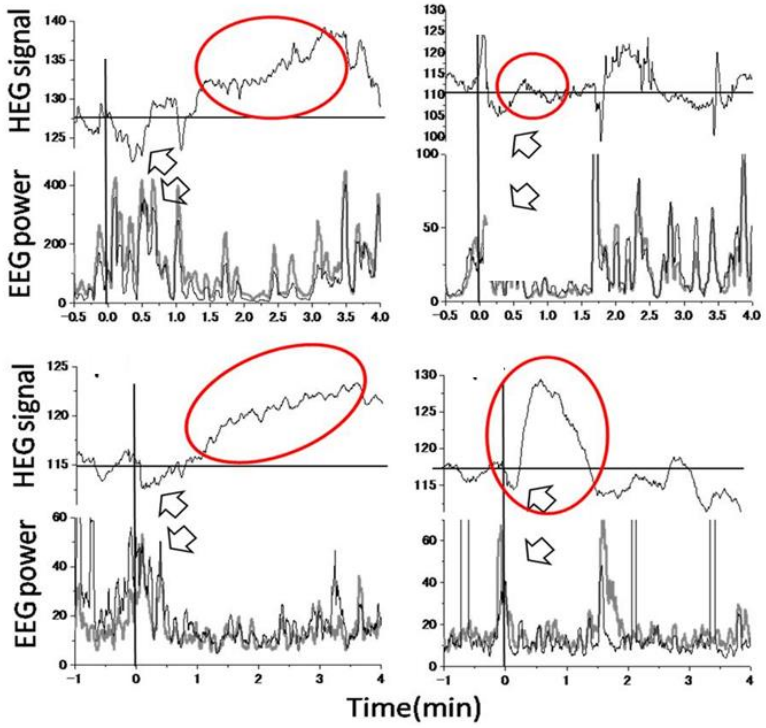


Figure 5-6 HEG and EEG responses to sour stimulus (Experiments were performed with four participants). All participants increased their HEG signals

In this study, the effects of aversive taste on the CNV wave were assessed in order to explore the utility of the CNV as a marker of activity of taste preference. In line with the expectations, we identified CNV in a late stage for the sour and corresponding clear P3

(Figure 5-4.C). Between S1 and S2, two waves can be observed, the early and the late CNV wave (Loveless and Sanford, 1975; Weerts and Lang, 1973). In this study, the late CNV wave was investigated in sour solution condition. The late CNV is measured just prior to the onset of the target stimulus, and reflects the additional contribution of cortical resources required for motor response preparation (Chiu et al., 2004, Brunia and Damen, 1988). Especially relevant to present study, the late CNV was suggested to be related to the prejudice for sour taste, which matched the subjects' self-reported that sourness made them feel more unpleasant.

Tasted reward areas are located in different OFC region. For example, Roll *et al.* (1988) studies on the responsiveness of neurons in the fontal operculum gustatory cortex and found the firing rates of neurons in OFC are modulated by hunger and satiety. It suggested the OFC region represent the gustatory reward value (Rolls et al., 1988). O` Doherty *et al. (*2001), using fMRI, showed the individual differences for areas activated glucose and salt and the group analysis indicated the inferior medial OFC responds to changes in pleasantness associated with eating (O` Doherty et al., 2001). There are also another studies researching on the LPFC function with taste based on different task and design. Anyway, these physiological studies have focused on a variety of issues, but all of them reported that the OFC contains a significant cortical taste projection area. We believed the PFC plays a critical role in modulating taste information processing, and the experiment here indicated the prefrontal cortex was involved in sour and bitter taste cognitive processing, which was consistent with previous findings. In future work, we will do more investigation to get more specific information of human prefrontal work about gustatory system.

In present study, we used sour solution (1% citric acid) and bitter solution (0.01%

caffeine) as gustatory stimuli. Future work will be needed to examine whether the amplitudes and latencies of the gustatory ERPs peaks are dependent on the taste qualities (such as sweet, salt and umami) or the concentration. Furthermore, it must be admitted that our studies was performed on 5 participants and there is a possibility that the ERPs amplitude is under the level of statistical significance. We will extend our experiments among more subjects to explore this possibility in the future.

5.5 Summary

Taken together, in this chapter, we reported an EEG study to investigate taste preference using aversive stimuli. The early markers before P3 were related to sour and bitter taste and we considered they would be unconscious electrophysiological early markers for attention. Especially, the CNV appeared to be a biomarker for taste preference. Furthermore, this study gave further evidence supported that the prefrontal cortex was involved in taste cognitive processes. Since this study was a pilot, we will extend such investigation to further more participants having various food preferences.

Chapter 6

Conclusion

This dissertation addressed the problem of human prefrontal cortex activity response to pleasant and aversive tastes. The primary aim of this study was to find ROIs where were related to these two tastes, and make further understanding on the central organization of taste. The present findings in humans are consistent with some earlier findings but at the same time there were also some difference in our study. Since the study on the brain function of taste is just in the early stage, we will extend such investigation to further access the problem of taste preference mechanism.

6.1 Conclusion

The results obtained in this dissertation could be summarized as follows:

Chapter 1 presented background and the motivation for this research, defined its objective and exhibited the overview of this dissertation. Regarding the literature reviews, we focused on the previous research perspective for gustatory system, neural mechanisms of taste transformation and the research tools of brain imaging techniques.

Chapter 2 illustrated the background theory and knowledge about brain function and gustatory system. It began by a description of the structure and functions of neuron, then introduced the human brain cortex and worked up to brain imaging techniques. Finally, it considers how the brain represents taste information.

Chapter 3 used fNIRS to monitor the activation of prefrontal lobe on human brain

during sweet taste processing. The primary aim of this chapter was to find the ROI which is related to sweetness, and make further understanding of the central organization of taste. Based on event-related design, the experiments were performed with 16 volunteers by sweet taste stimulus. It was confirmed that the PFC is involved in sweet taste processing and fNIRS provided an alternative way for studying taste-related brain function under more natural conditions. This study might be effective for detecting the accession area in the cortex of sweet taste and helpful for studying on human feeding and taste disease like taste dyspepsia or disorder.

Chapter 4 investigated the representation of taste in human PFC, in particular, to compare the representation of a pleasant and an aversive taste using fNIRS, so as to obtain further understanding of the taste preference mechanism. The pleasant stimulus used was sweet taste (10% sucrose), and the unpleasant stimulus was sour taste (1% critic acid). Based on event-related design, the experiments were performed with 16 healthy volunteers using the OEG-16 fNIRS sensor. A general linear model was used to analyze the collected data. For the concentration change of oxygenated hemoglobin, we found significant deactivation was induced by sweetness and sourness in parts of the frontopolar area, orbitofrontal area and dorsolateral prefrontal cortex in bilateral hemisphere of human brain. And the right PFC showed different levels of activation between sweetness and sourness. In addition, brain activities were more sensitive to sourness than sweetness. Finally, we confirmed that the PFC was involved in sweet and sour taste processing, and fNIRS provided an alternative way for studying taste-related brain function under more natural conditions.

Chapter 5 investigated brain activation responses to aversive tastes (bitterness and sourness) using EEG and NIR-HEG simultaneously to clarify the intrinsic food

preference mechanism. A conventional delayed response task based on Go/Nogo paradigm was adopted to extract real brain response components from spontaneous background signals. Results showed excessive evoked EEG potentials in both bitter and sour responses, but not in purified water which was a control condition. Therefore we suggested that these potentials would be only attributed to gustatory stimuli. As these potentials appeared before P3, we considered that they are unconscious electro-physiological early markers for attention. We also identified CNV in a late stage for sour stimulus and corresponding clear P3. In addition, NIR-HEG responses showed a rise for every stimulus and, in particular, sourness gave larger rise than bitterness. In spite of limitation to timing accuracy of taste presentations, the early markers found in this study could be fundamentals for investigating individual food preference.

In this dissertation, the taste preference mechanisms were studied step by step. In chapter 3,the PFC activation for sweet tastes using fNIRS, and then experiment was extended to monitor the PFC activity to pleasant and aversive tastes and compared the activations for these two tastes subsequently, which was discussed in chapter 4. Based on the founding from chapter 3 and 4, the brain neurophysiological activation for taste was discussed in chapter 5.

6.2 Future Work

In studies of food preferences of children, we frequently meet a case that some children exhibit the ability of exhibiting no preferences for any food even including aversive tastes. Elucidation of the mechanism how children gain this ability is a key to overcoming the food preference issues in the development science field. There are some psychological explanations for the ability, including a hypothesis that strong mental

capacity regulates negative emotional valence against aversive tastes, however, few papers have reported neurophysiological aspects for such child's ability. Therefore, for further works, to examine the brain activation to pleasant and aversive tastes can be applied to the children.

In addition, According to recent neural studies on emotion, the strong mental capacity can be attributed to a function of the prefrontal cortex which regulates activity of the deep brain networks (DBNs) including a subcortical emotional network known as the Yakovlev circuit. Recently, we made a questionnaire survey about taste preference and science of coherence (SOC). The results showed the people with higher SOC can more control themselves to eat the food which the dislike, which who with lower SOC cannot eat the food they dislike. In the next, the prefrontal activation will be further investigated to access the problem of taste preference mechanism.

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Publications

The dissertation is based on the research that was previously reported in the following publications.

Hu CH, Kato Y and Luo ZW (2013a) An fNIRS Research on Prefrontal Cortex Activity Response to Sweet Taste. In: The57th Annual Conference of the Institute of System, Control and Informatics Engineers (SCI 2013).

Hu CH, Kato Y and Luo ZW (2013b) An fNIRS Research on Prefrontal Cortex Activity Response to Taste: Sweetness and Sourness. In: The 13th European Congress of Psychology (ECP 2013)

Hu CH, Kato Y, Katagiri Y and Luo ZW (2013c) Early neurological markers for unconscious detection of bitter and sour taste for investigating taste preferences. In: The First Aizu Conference on Biomedical Informatics and Technology (ACBIT 2013).

Hu CH, Kato Y, Katagiri Y and Luo ZW (2013d) Neurophysiological study of taste preference mechanism. In: the 15th Annual Congress of the Academy of Human Informatics.

Hu CH, Kato Y, Katagiri Y and Luo ZW (2013e) An fNIRS study of taste cortical areas in human brain: sweetness and sourness. In: 2013 IEEE/SICE International Symposium on System Integration (SII2013).

Hu CH, Kato Y and Luo ZW (2013f) An fNIRS Research on Prefrontal Cortex Activity Response to Pleasant Taste. In: Journal of Behavioral and Brain Science. Vol. 3, pp. 617-623.

Hu CH, Kato Y and Luo ZW (2014 a) Activation of human prefrontal cortex to pleasant and aversive taste using functional near-infrared spectroscopy. In: Food and Nutrition. Vol.5, pp. 236-244.

Hu CH, Kato Y, Katagiri Y and Luo ZW (2014 b) Brain Response to Aversive Taste for Investigating Taste Preference. In: Journal of Behavioral and Brain Science. Vol. 4, pp. 43-48.

Acknowledgements

First and foremost, I would like to express my deep and sincere gratitude to my advisor Professor Zhiwei Luo for his constant encouragement and patient guidance. He led my research into a new level. Without his consistent and illuminating instruction, my research will not reach its present form. I was extremely grateful to him for providing me the chances that attending international conferences. Since absorbing the knowledge from other researchers around the world, I got a whole bunch of new ideas about my research. It was really inspired me a lot.

Next, I much thank Prof. Uehara and Prof. Matoba for the effort in reviewing the dissertation. Without their help, this dissertation would not be so logically structured and accurately written.

At the same time, I want to show my sincere thanks to Prof. Kato, We did the experiment together. She provided me many useful advices about my Psychology experiments and helped me get out of the dilemma using her delicate understanding on psychology experiments. During my academic writing process, she pointed out some weakness in my paper kindly. Because of this, my paper can be improved step by step.

I am also grateful to Prof. Nagano, Prof. Togashi and Prof. Katagiri for all their supports. They gave me plenty of instructions and ideas in the seminars, and I have learned so much from him.

During my experiment, I gained many supports from my experimenters. I really appreciate the efforts which come from my volunteers, especially Mr. Lv and Mr. Cao.

Without them, my experiments cannot be worked out smoothly. It is my pleasure to thank my colleagues in CS11 laboratory. I am grateful to masters and undergraduate students for their delicious coffee and beautiful study environment as well as the organization of laboratory events.

Finally, I would like to thank my family and dear friends for their generous supporting. I will give my best wishes to my parents for their mental and finance support in three years. I will thank my brother, because of his patient enlightening when I was disappointed. There have been so many friends, past and present. I thank you all for sharing yourselves with me and I am deeply grateful.

Doctor Thesis, Kobe University

“On fNIRS-based Study of Human Cognitive Function Related Taste”, 103 pages

Submitted on January, 21st, 2014

The date of publication is printed in cover of repository version published in Kobe University Repository Kernel.

Chenghong Hu