Neuronal Response to Hearing Subject’s Own Names for Patients with Severe Motor and Intellectual Disabilities

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Neuronal Response to Hearing Subject's Own Names for Patients with Severe Motor and Intellectual Disabilities

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Abstract

Severe motor and intellectual disability (SMID) is a multiple disorder with severe physical disabilities and profound mental retardation. The evaluation of residual brain functions could contribute their developments and improve their rehabilitations in their early developmental stages. In order to assess brain function of such patients, we measured and analyzed EEG for patients with SMID in response to subject's own name (SON) as auditory stimulus, since SON studies have reported relationships with several kind of cognitive functions. Most of SON studies have been done in healthy subjects and several experimental designs were used for event-related potential (ERP) analysis. However, there were some concerns about the validity of previous experimental design for presenting SON, especially the repetition effects of control stimulus. Furthermore, ERP analysis is not appropriate for patients' assessment because of motor artifacts, rather than time-frequency analysis is suitable. In the present thesis, firstly we confirmed the reliability of experimental design by healthy subjects. After confirmed, a new suitable task was designed for the comparison with patients and healthy subjects. We showed two kinds of comparisons with healthy control subjects: group comparisons and individual investigations. Following paragraphs summarized the present experiments, results, and discussions.

To confirm the reliability of experimental design and consistency of the ERP components with

other reports, we investigated the EEG response to SON in healthy subjects. We prepared two control stimulus groups: repeated Unknown Name and single presented Unknown Name (various types of names were presented at once), to compare the SON in our experimental design. For analysis, we combined ERP and event-related (de)synchronization (ERS/ERD) methods. ERP was used to confirm the consistency with other reports, and ERS/ERD was performed for comparisons with further analysis of patients with SMID. Consisted with other reports, the results of the ERP analysis showed that SON elicited a late positive component (LPC) in parietal areas, including P300 and parietal positivity. Beta ERD was induced in response to the SON, while the other Unknown Name groups induced beta ERS. These SON responses were clearly different from both of the Unknown Name groups, and this result is indicative that the repetition of control stimulus did not affect the EEG response to SON.

Based on this investigation of experimental design, a new experimental task was adapted to the comparison with patients and normal. This new experimental task was also included SON. Patients were sorted by the clinical diagnostics as two patient groups. Using the experiment and measuring EEG, we analyzed responses to SON of each patient group and compared healthy subjects.

Before detail comparison with healthy subjects, we extracted several features of the response to hearing SON by discriminant analysis. As results from the discriminant analysis, alpha and beta evoked powers contributed to discriminate EEG responses to hearing SON. Then we compared these features with healthy and each patient group. In the comparison with patients' group, alpha evoked activity did not show any differences with healthy subjects, while beta showed statistical significances.

Considering varied clinical background, we performed individual analysis for each patient EEG data by inter-trial coherence (ITC). Each pattern of ITC in response to SON was compared with the averaged ITC of healthy subjects, to show how different their ITC responses from the normal control group. As results, ITC results showed that theta phase-locked activity increased in response to SON in four patients, and these tendencies were similar with healthy subjects' results. These results indicate that theta phase-locked activity in some patients with SMID was strongly associated with SON, as in healthy subjects.

From these present investigations, following conclusions were drawn. 1) Healthy subjects showed alpha suppression in response to SON and this alpha suppression was also observed in patients with SMID. Alpha suppression reflected long-term memory function, and it was evoked by hearing SON. We suggest that they remain long-term memory function for their own names as auditory stimulus. 2) Beta suppression was observed in healthy subjects by hearing their own names, though it was not appeared in patients. Beta suppression of healthy subjects indicated their self-referential cognitive function. Patients did not show this suppression and we suggested a possibility that they have lower self-recognition function by the present result. 3) Theta phase-locking was shown by all speech stimuli in healthy subjects as the response of auditory cortex to hearing speech stimuli, without regarding the difference between SON and other words. On the other hand, some patients showed higher theta phase-locking in response to SON than other words. We suggest that the stronger activation was occurred in auditory cortex of these patients with SMID in SON.

This thesis was the first investigation of EEG response to hearing their own names of patients with SMID and the present results will lead better evaluation of their brain function. Our study could contribute to the first step to evaluate the cognitive function of patients with SMID.

Contents

Chapter 1. General Introduction

1.1. Forward

Severe motor and intellectual disability (SMID) is a term used to describe a heterogeneous group of disorders that manifest as severe physical disabilities and profound mental retardation caused by some disturbance to the central nervous system (CNS). Patients with SMID have a markedly lower than normal intelligence quotient (IQ).

Recently, according to the development of clinical techniques, the survival rate of patients with SMID has been improved. At the same time, the need for educational and developmental system is increasing, specific to such patients. An appropriate educational system would support their longer lives and improve their quality of life. One big problem to establish the educational system for such patients is the extremely varied intellectual levels from the population of SMIDs. The variety of their intellectual levels is relied on brain residual function and their environment. Notably the residual function and compensation of brain function could have a deep connectivity to their intellectual function and development. It is necessary to know their residual function to help their education and select a suitable system depend on each patient. However, because we do not understand their remained functions correctly, sometimes we could overlook their developments easily. This attempt to evaluate brain function has been investigated, but most of these reports were not quantitative, only qualitative studies.

The aim of this thesis is to provide information to help evaluate the responses of SMID patients. Cognitive function and its development of them are difficult to assess by visual observation, while their motor function can be evaluate easily. In this thesis, we focused on their cognitive function level and attempted to know by objective approach. As a quantitative signal, we recorded brain activity using electroencephalography (EEG) and analyzed the EEG-cycle frequency. EEG measurement is non-invasive recording techniques and it is suitable for such patients who have multiple disorders.

As the test stimulus, calling own name (Subject's Own Name: SON) was selected because own names represent arguably among the most common, and perhaps the most semantically significant, words for most people. Own name recognition would be related to several cognitive function, thus we can use it to evaluate their residual cognitive function. We investigated the response to auditory SON as calling own name, because it is difficult for bedridden patients to sustain attention to visual stimulus, while the presentation of auditory stimulus is less stress. Several studies have presented auditory SON to comatose patients, and it indicated that SON can be used to bedridden status patients. Their cognitive residual function would be estimated by comparing EEG responses to hearing SON between normal and patients with SMID.

There are some problems need to solve before investigation of patients. The mechanism of healthy subjects when they hearing SON has been not revealed yet. Several studies have reported the Event-related potential evoked by SON, while their experimental designs have not fixed insufficiently. In regard to the number of stimulus presentation, control stimulus and SON was not comparable in some reports. The other concern is a statement of participants during a session, for example, some studies introduced active presentation in which participants are instructed to count their own names, to control the attention level. However, it is difficult to instruct such patients to response to a specific stimulus. Thus, passive presentation is more appropriate for assessment of patients with SMID. For oscillation changes caused by hearing SON, it is not investigated well, though these changes could show more information about EEG response and cognitive function.

In the present thesis, we examined three types of experiment. In Experiment 1, we confirmed the validity of experimental paradigm, including repeated control stimuli, to compare the EEG responses to SON. All participants in this section were only healthy subjects. Based on the results from Experiment 1, especially ERP components, we concluded that repetition control stimulus was not affected to EEG response within an experimental task. Then we measured EEG of persons with SMID using appropriate task for patients (Experiment 2 and 3) and focused on time-frequency changes. We analyzed the data by group comparisons: patient group vs. normal group (Experiment 2), and individual analysis (Experiment 3).

In the next section, we reviewed basic knowledge of EEG analysis and the background of patients with SMID. Furthermore, we introduced the related literatures about EEG response to hearing their own names, and proposed several kinds of cognitive function we can evaluate by this SON paradigm for the residual functions of patients with SMID.

1.2. Some basic notions

Basic Knowledge for EEG analysis

Event related Time-frequency Power changes. When some events occurred and were perceived, EEG oscillations will change according to events. Sometimes one oscillation synchronized, and sometimes de-synchronized by the event (Kalcher & Pfurtscheller, 1995; Pfurtscheller & Aranibar, 1977). Synchronization means that the power of an oscillation increased caused from a synchronization of neurons' activities. Alternatively, de-synchronization is the decrease of oscillation power by de-synchronized activities of neurons, but not by decreasing their activity (Mouraux & Iannetti, 2008).

To detect these oscillation synchronization/de-synchronization caused by events, Event-related Synchronization/De-synchronization (ERS/ERD) method has been developed (Kalcher & Pfurtscheller, 1995; Pfurtscheller & Aranibar, 1977). This method has been proposed to find which frequency bands were synchronized or de-synchronized from baseline in frequency domain. Originally it was used in only frequency information without time. Due to a necessity to know when the ERS/ERD changes occurred, time-frequency analysis has been introduced to analyze EEG (Pfurtscheller & Lopes da Silva, 1999). Using this time-frequency analysis, we can find when and which frequency synchronized or de-synchronized by stimulus comparing baseline.

Originally ERS/ERD was adapted to narrow frequency bands. To analyze wide frequency bands in time-frequency analysis, Makeig *et al*., have introduced Event-related spectral perturbation method (Makeig, 1993). It was based on the amplitude changes. Now ERS/ERD method is also used in wide frequency range. Cohen *et al*. have pointed out that both of them are commonly employed to detect the changes of oscillatory powers but the terminology is sometime ambiguous (Cohen & Gulbinaite, 2014).

Wavelet transform is one of common methods for EEG time-frequency analysis. Wavelet analysis uses “wavelet window” to retain temporal and frequency information as wavelet complex. This wavelet complex expresses amplitudes and phase of the EEG signal at the time and frequency.

Short time FFT (SFFT) is the other method for time-frequency analysis, but it has less frequency resolution than wavelet analysis (Farge, 1992). In this thesis, we used wavelet transform for time-frequency analysis.

Evoked and Induced activity. EEG signals can be classified two types of activity, evoked activity and induced activity (David, Kilner, & Friston, 2006; Catherine Tallon-Baudry & Bertrand, 1999). Evoked activity is phase-locked to the stimulus and induced activity is not phase-locked but it is event-related.

Evoked activity can be detected by averaging EEG wave across all trials because its latency is fixed at each trial. That is why evoked responses have a good time-resolution. Event related potential (ERP) is an easy and commonly used method to detect evoked response. By averaging EEG epochs aligned stimulus onset, characteristic ERP components are shown at the fixed latencies. Many ERP components have been discussed that what kind of cognitive pathway reflected in each ERP component. ERP components have good time resolution, while no precise frequency information. From time-frequency complex, we can extract evoked activity, while ERS contained both of evoked and induced power changes. Averaging epochs consisted from wavelet complex and calculating power, we can get time-frequency decomposition of evoked powers (Catherine Tallon-Baudry &

Bertrand, 1999). This evoked power is led from amplitude change. Inter-trial coherence (ITC) calculates the coherence of phase across trials in each frequency band to detect the phase-locking activity. This ITC method tell phase-locking even in small amplitudes since it calculate the distribution of phase (C Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996). Recently, many techniques are developed to detect phase information in EEG oscillatory changes to reveal cognitive process (Sauseng & Klimesch, 2008), and ITC is one of them.

Induced activity is a burst of one oscillation range whose latencies jitters from trial to trial (Catherine Tallon-Baudry & Bertrand, 1999). Because of the loose latencies from stimulus onset, induced activity will be canceled out when EEG waveforms were averaged across trials before calculating power. Single trial analysis contributes to find induced activity. In higher oscillation, induced activity has been focused on.

Patients with Severe Motor and Intellectual Disabilities

Severe Motor and Intellectual Disabilities (SMID) is defined as a heterogeneous group of disorders with severe physical disabilities and profound mental retardation in Japanese Child Welfare Act. Persons with SMID have an intelligence quotient (IQ) lower than 35, and their physical states are bedridden or sat but cannot rise from bed by themselves (Sasaki, 2013). Most of them have been suffered brain damages from prenatal or early childhood stages.

Recently, the mean age of population of patients with SMID in Japan is rising (Sasaki, 2011). This report has indicated that patients with SMID could survive longer, because of the advancement in clinical technology and the efforts to keep their health from clinical professionals. Moreover, many infants who damaged prenatal stage can be saved and grow up by novel clinical methods. This report provides a perspective that the population of survived patients with SMID will be increased.

In order to support lives of patients with SMID, it is important to evaluate their residual function and development of brain, not only to assess their physical health. Sometimes we misunderstand that patients, who have multiple disorders with physical function, should have lower intellectual levels and this intellectual function would not develop. However, no one can determine that such patients should not develop by their growth. We believe that there is a possibility that neural plasticity let their residual brain functional development compensate. For example, the previous study about children with early brain injury showed that their visual copying abilities were improved as the near levels as normal children by their developments of spatial integration skills (Akshoomoff, Feroleto, Doyle, & Stiles, 2002). If we can find and evaluate their residual function and development, we can provide patients with SMID suitable rehabilitations or education programs to improve their residual function. For the sake of appropriate rehabilitations, we have to find which function is residual and can be improved, because patients with SMID have multiple severe motor disabilities and mental retardation. That is why early evaluation for their brain function would lead an improvement of long lives of patients with SMID.

Many of studies about evaluation of such patients have been subjective approach. Observations from caregivers or medical doctors have been used for the research of their developmental assessment. However it was not sufficient to evaluate their residual function (Ohba & Era, 2002) because it was not objective. Subjective approach would be suspected of including personal feeling. To assess patients' function correctly, quantitative way would be more suitable, using physiological markers.

To evaluate their residual function, there are many measurement ways to reveal brain function. EEG, fMRI and NIRS are some of noninvasive ways to measure brain responses. Regarding to the state of patients, EEG measurement is the less stress and actual measurement method. For physiological markers, EEG has been used (Suzuki, Hayashi, & Akiyoshi, 2009), but most of investigations have introduced heart rate, NIRS and salivary amylase activity for persons with SMID (Hamamoto, Ogawa, & Mitsudome, 2003; Ohba & Era, 2002; Watanabe, Uchiyama, & Koike, 2006; M. Yamaguchi, Takeda, Onishi, Deguchi, & Higashi, 2006). These signals are not always sufficient to understand brain functions, though they allow us quantitative analysis. More EEG examining should be needed for assess of residual brain functions of patients with SMID.

Difference of the Concept between SMID and Profound Intellectual and Multiple Disabilities

SMID is a term from Japanese Child Welfare Act as we reviewed above. There are some kinds of terminations for such patients who have multiple disabilities, physical and intellectual. The taxonomy is not fixed and many definitions are used (Nakken & Vlaskamp, 2007). We reviewed one of the definitions, which is used widely international: Profound Intellectual and Multiple Disabilities (PIMD), to compare with the idea of SMID.

Profound Intellectual and Multiple Disabilities (PIMD) is a similar definition of patients with multiple disorders. The main concept of PIMD and SMID is very similar.IQ levels were lower than 20 whose patients with PIMD have and they have multiple disabilities, including visual, auditory and motor function.

In PIMD research fields, there are much research about alertness levels by external stimuli (Munde, Vlaskamp, Ruijssenaars, & Nakken, 2009), but most of them were estimation by observations from direct support persons. Some criteria were used for assessing their sensory perception by observation from recorded video, however, the reliability was decrease when it was used by someone who is familiar with the patient (Vlaskamp & Cuppen-Fonteine, 2007). As physiological signals, heart rate and electrodermal reactions have been utilized to assess their response to several sensory stimuli (Lima, Silva, Amaral, Magalhães, & de Sousa, 2013), whereas there are no reports assessing for patients with PIMD by brain responses directly or invasively in our knowledge. The situation about the less of examines of EEG response is similar with SMID and PIMD.

The notable difference between these terms is the idea of education and development for patients. There was different progress in education between PIMD and Japanese SMID. In 2007, Nakken and Vlaskamp pointed out that the educational system for students with PIMD sometimes participated with students who have no disabilities, regardless the variability of patients (Nakken & Vlaskamp, 2007). On the other hand, Japanese Welfare system has focused on education for patients with SMID, depending on their functional levels. For example, Katagiri *et al*. have reported an attempt of suitable education planning for patients with SMID from 1970s. Based on the appropriate education, the students with SMID have been estimated their development in each other (Katagiri *et al*., 1981). In this line, the educational concept and environment for SMID have been well developed. It originated the concept for patients with SMID to provide medical treat and education. This thesis used “SMID” as a term to describe such patients to follow this concept.

Previous Research about Brain Response to Subject's Own Name (SON)

To evaluate the residual function and development of patients with SMID, we focused on auditory stimulus. Most of these patients cannot read letters, and it is difficult to gaze at a visual stimulus for a while, because some patients cannot sit down and keep their body by themselves. Using auditory stimulus, we can certainly present stimulus by earphones. As test stimulus, we selected hearing their own names. Response to hearing Subject's Own Name (SON) is investigated by several reports measured EEG, and EEG responses to SON are related with some kind of cognitive functions as below. Some reports have investigated the brain responses to SON and they suggested the relationship with several cognitive functions. We will follow these reports and discussions.

SON and attention orientation process. SON have been discussed the role of capturing attention. In psychological investigation, it has been suggested that presenting SON as a visual text stimulus can orient attention strongly (Mack, Pappas, Silverman, & Gay, 2002).

Since Berlad and Pratt have reported the P300 amplitude in response to SON was larger than the other words speech stimuli (Berlad & Pratt, 1995), the attentional shift by SON has been examined by neuropsychological researches. Many other reports have confirmed that P300 was elicited by hearing SON (Folmer & D.Yingling, 1997; Holeckova *et al.*, 2008; Holeckova, Fischer, Giard, Delpuech, & Morlet, 2006; Müller & Kutas, 1996; Perrin *et al.*, 2005; Tateuchi, Itoh, & Nakada, 2012; Zhao, Wu, Zimmer, & Fu, 2011). P300 is one of positive ERP components and well investigated the meaning of elicitation (Friedman, Cycowicz, & Gaeta, 2001; Polich, 2007). Holeckova *et al*. have discussed that the elicited P300 in response to SON is "Novelty P300", which associated with automatic attention shift (Holeckova *et al*., 2006). This Novelty P300 has been proposed that it elicited by unexpected stimuli, in other words "novel" stimuli, and when the attention oriented to novel stimuli. This is the different from ordinary P300 (P3b), which is associated with working memory function (Friedman *et al*., 2001; Polich, 2007).

Some ERP studies of SON have also observed MMN, mismatch negativity (Holeckova *et al*., 2008, 2006; Tateuchi *et al*., 2012). This earlier ERP component (150 to 250 ms) than P300 elicitation has been discussed that it was a result from initiation of orienting response by external input, especially in auditory tasks (for example, Fishman, 2014; Garrido, Kilner, Stephan, & Friston, 2009; Näätänen, Paavilainen, Rinne, & Alho, 2007). MMN is a clue of the automatic attention shift, but it is elicited only when SON was presented infrequently in an experimental task (Tateuchi *et al*., 2012).

Oscillation power changes researches have shown that theta ERS was induced by SON (Fellinger *et al*., 2011). Since theta ERS is occurred in sustaining attention, the results could be considered that the attentional function was activated by hearing their own names. Frontal-midline theta, which is a famous increase of theta power, have suggested the relationship with attention function (Kubota *et al*., 2001; Missonnier *et al.*, 2006). In this line, hearing SON and orienting attention resulted in increasing theta powers.

Long-term memory function and hearing SON. Why SON can capture their attention? One of the reasons would be a relation with long-term memory. According to a report for 5-month-old infants, they showed significant response to SON, though such infants have not learned languages (Parise, Friederici, & Striano, 2010). It can be explained that their own names stored in their memory by hearing repeatedly. In this way, SON is presented as the most common and frequent word for each person and it can be memorized easily without high language skills.

Fellinger *et al*. shown theta ERS and alpha ERD, those suggested the relevance with long-term memory retrieval to SON and EEG responses (Fellinger *et al*., 2011). In long-term memory function, theta increase has been argued the relationship with memory retrieval (Bekkedal, Rossi, & Panksepp, 2011; Byrne, Becker, & Burgess, 2007; Khader & Rösler, 2011; Lee, Lee, Kim, & Jung, 2014; Mellem, Friedman, & Medvedev, 2013), and alpha suppression also has been reported with memory function tasks (Khader & Rösler, 2011; W. Klimesch, 1997; Wolfgang Klimesch, Sauseng, & Hanslmayr, 2007; Wolfgang Klimesch, 1996; Spitzer, Hanslmayr, & Opitz, 2008). If we stand to the position with the previous research from Fellinger *et al.*, we could reveal the residual memory function from EEG response of alpha suppression or theta synchronization by hearing SON.

Self-recognition process. Long-term memory cannot explain the difference of responses to "self" and "familiar" names, but they should not be same. We need to consider the concept of self or self-related cognition. The combine study of ERP and PET have revealed that p300 amplitude correlated with cerebral blood changes at right medial prefrontal cortex (MPFC), where have been discussed the relationship with self-referential or self-reflection (Perrin *et al*., 2005). fMRI studies also have suggested that MPFC is activated by self-referential or self-reflection function and self-knowledge (D'Argembeau & Salmon, 2000; D'Argembeau, 2013; Qin & Northoff, 2011; Tacikowski, Brechmann, & Nowicka, 2012). Tacikowski *et al*. showed that MPFC was activated when their own name was shown visually (Tacikowski *et al*., 2012).

However, only a few EEG research have shown the connectivity between the response to SON and self-related cognition function (Knyazev, 2013). Some ERP reports have described a difference with the response to SON and familiar names visually (Tacikowski, Cygan, & Nowicka, 2014; Zhao *et al*., 2011). P300 amplitude in SON showed significant difference with familiar names (Zhao *et al*., 2011) or famous names (Tacikowski *et al.*, 2014), but no differences between SON and closed-other names (Tacikowski *et al*., 2014). The specific EEG responses to SON remain unclear.

SON studies with comatose patients. Calling SON have been investigated to assess self-awareness of comatose, vegetative, locked-in syndrome and minimally conscious states (MCS) patients (Cavinato *et al*., 2011; Di *et al*., 2007; Fellinger *et al*., 2011; Fischer, Dailler, & Morlet, 2008; Fischer, Luaute, & Morlet, 2010; C Schnakers *et al*., 2008; Caroline Schnakers *et al*., 2009).

The most focused EEG marker was P300 component by ERP analysis in the reports for such patients. Fischer *et al*. have reported that some comatose patients showed novelty P300 by SON paradigm. In their experiment, they introduced SON as a novel stimulus and compared tone bursts as standard or deviant stimuli. They have proposed that novelty P300 elicitation suggested that patients had cognitive abilities to distinguish novelty of SON (Fischer *et al*., 2008). Schnakers *et al*. have also found P300 elicitation comparing the response of MCS and locked-in syndrome patients to SON and unfamiliar names with an instruction subjects to count how many SON was presented (C Schnakers *et al.*, 2008; Caroline Schnakers *et al.,* 2009). They also have shown that P300 elicited in response to SON under passive listening condition, while its amplitude was smaller than active listening condition. They suggested that P300 was a marker, which showed that patients preserved automatic speech processing function. Other research also have reported that MCS or partial vegetative patients showed P300 in response to SON under active counting task (Cavinato *et al*., 2011).

Vegetative and MCS patients were also investigated their response to SON by EEG time-frequency analysis (Fellinger *et al*., 2011). These patients showed theta power increase in response to SON with an instruction to count their own name because the patients might remain their memory function.

Problems Still Need to be Solved

Experimental paradigms for SON. As we reviewed above, many reports have explored brain response to SON. They have found similar responses, especially P300 elicitation in ERP analysis, while their experimental designs were not similar. Even if they have got common results, the meaning should be varied according to their experimental tasks. In this section, we discussed the differences and problems of previous experimental tasks for SON to analyze EEG.

One of the points is a difference between active or passive listening during an experimental task. Many investigations instructed subjects to count the number how many SON was presented in an experimental session (Cavinato *et al.*, 2011; Fellinger *et al*., 2011; Höller, Kronbichler, & Bergmann, 2011; C Schnakers *et al.*, 2008; Caroline Schnakers *et al*., 2009). With such an instruction, participants paid attention to auditory stimuli to distinguish the presented sound was target or not.

This instruction can keep their attention to sound stimuli and arousal levels of participants. However it is difficult to conclude the ERP components is resulting in response to SON, since SON is a “target” stimulus. It means that SON is replaceable to other auditory stimulus in the experiment as a target stimulus. We cannot reject a probability that the ERP components were elicited because of prediction to count the number of SON presenting. To subtract this prediction effects, Schnakes *et al.* have compared the EEG response with two kinds of instruction, count the number of SON and that of unfamiliar names (C Schnakers *et al.*, 2008; Caroline Schnakers *et al.*, 2009). In this way, SON effect can be extract, but it is necessary to confirm that the ability of speech processing was remained in patients. If participants did not have or lose the ability, they could not understand the instruction to count the number and such instructions would be meaningless. Other reports have explored the EEG response to SON in passive listening condition. They have not to tell participants to pay attention to sound. Moreover, they have presented something visual stimulus during experiments, for example, silent movie or video games (Holeckova *et al.*, 2006; Tateuchi *et al.*, 2012). These conditions have allowed them detect “automatic” response to hearing SON of participants, without any expectation. Passive listening to SON is more difficult to extract the characteristic response because it cannot control participants’ attention. It means that some trials participants were aware their own names, and other trials were not. Additionally we should consider that visual effects might be contaminated in whole recorded EEG. Nonetheless, this passive listening is suitable when we want to investigate the effect of SON regardless with the target effects.

The second point is whether control stimuli are truly comparable with SON or not. In an experimental design, tone bursts were used as standard and deviant stimuli, to compare with SON (Holeckova *et al*., 2006). It is suitable to determine whether participants can find SON as a novel stimulus, because artificial tone bursts were distinct from hearing SON. It indicates that SON is transposable other speech stimuli in order to show novelty recognition only. Several studies have introduced words or others' names to compare the response to SON (Berlad & Pratt, 1995; Fellinger *et al*., 2011; Folmer & D.Yingling, 1997; Höller *et al*., 2011; Müller & Kutas, 1996; Perrin *et al.*, 2005; Tateuchi *et al.*, 2012) in healthy subjects. These comparisons would be more reasonable because all of stimuli were auditory speech sound.

The third problem is repetition and frequency of stimulus presentations during a session. It has been discussed that repetition and habituation effects let brain responses to novel stimulus suppress (Friedman *et al.*, 2001; Polich, 2007; Rushby, Barry, & Doherty, 2005; S. Yamaguchi, Hale, D'Esposito, & Knight, 2004) or the effects let amplitudes of ERP components increase and decrease (Jiang, Zheng, & Li, 2013). Moreover, in a research about SON considering the multiple repetition effect, the response to unknown stimuli showed similar pattern with SON at the final phase, though it was different at initial phase in an experimental session (Tacikowski, Jednoróg, Marchewka, & Nowicka, 2011). This kind of habituation for control stimuli might increase familiarity with them and let difficult to find the differences between self-related stimuli and others. Frequency of presentation stimuli also has an important relevance with habituation effects. Tateuchi *et al.* have compared two conditions including SON in ERP investigation, one of them was frequent presentation of SON, the other one was infrequent presentation. In this comparison, infrequent SON presentation has showed positive component such as P300, though frequent SON presentation has never showed (Tateuchi *et al*., 2012).

Evaluation of Patients with SMID. As we reviewed above, few studies of such patients by EEG have been attempted, though the evaluation of remained cognitive brain function of patients with SMID is necessary. One of the reasons might be a difficulty to present stimuli to assess their cognitive function. Many assessment use visual stimuli paradigm but it is difficult for these patients to sustain focus on a screen for a while. Furthermore, they cannot respond corresponding to stimulus conditions. This problem limits experimental designs to only passive presentations. The third difficulty is low-frequency noise including EEG by their involuntary movements. This noise makes impossible to analyze ERP component because ERP analysis needs a broad frequency range, for example, from 0.1 to 30 Hz.

For the sake of overcoming these issues, following improvements were provided in the present thesis. 1) An auditory stimulus sequence was introduced as an experiment to measure EEG. Auditory stimulus can be presented by wearing earphones. Patients do not have to focus on a screen and this procedure let them be relaxed than presenting visual tasks. 2) The stimulus sequence was presented in passive condition. It means that participants were not instructed to respond to auditory stimulus. 3) To reject the concern to low-frequency noise, time-frequency analysis was performed to patients' EEG data. Most of patients' data included involuntary motion artifacts, we could not use a wide range filter to measure and off-line analysis. That is why we did not performed ERP analysis for patients. Instead of ERP, we introduced time-frequency analysis for EEG data of patients. By these solutions, the present thesis attempted to understand several aspects of the remained cognitive functions for patients with SMID.

Conclusion and the Aim of this Thesis

We investigated following points in the present thesis;

Experiment 1. **Confirm the experimental design in healthy subjects by the results from ERP components.** As we review and discuss above, we suspects that repetition stimuli within an experiment can influence to ERP components. We confirmed the repetition effect by improved paradigm including SON in healthy subjects. Furthermore, we tried to find some characteristics from time-frequency analysis because there are only a few reports about the response to SON by this analysis.

Experiment 2. **Measure EEG response from patients with SMID and analyze by group analysis.** In this section, we measured EEG of patients with SMID. We separated patients into two groups by their diagnosis and compared each patient group with healthy subject group. We designed new experiment which was suited for patients with SMID, considering with the results from Experiment 1. To reduce noise from patient data, we analyzed their evoked (phase-locked) activities.

Experiment 3. **Analyze patient's data individually.** Statement and diagnosis are different from each patient with SMID. We aimed to evaluate individually by analyzing their phase-locking activity from each EEG response to SON in this section.

We examined the EEG responses of patients with SMID and predicted that following features would appear; theta synchronization, alpha suppression and beta suppression, if some residual cognitive function were remained those related with hearing SON cognition. Our investigation will contribute to the EEG analysis in hearing SON paradigm, and understanding the EEG response of patients with SMID.

Chapter 2. Experiment 1

ERP and ERS/ERD Response to Subject’s Own Name comparing with repeated/non-repeated Unknown Names in Healthy Subjects

2.1. Abstract

Brain response to hearing Subject’s own name (SON) has been explored by event-related potential (ERP) studies and event-related (de)synchronization (ERD/ERS). To compare self-unrelated stimuli and one’s own name, the repetition effect of unrelated stimuli within the experiment is critical for ERP results. This section aimed to confirm if repetition of self-unrelated stimuli let decrease the differences of ERP or oscillation powers from SON.

We prepared two control groups to compare the SON in our experimental design, repeated Unknown Name (rUN) and single presented Unknown Name (sUN). sUN was consisted from various types of names and they were presented at once during a session. For analysis, we combined ERP and event-related (de)synchronization (ERS/ERD) methods to precisely detect and correct the EEG response.

The results of the ERP analysis showed that SON elicited a late positive component (LPC),

which reflected memory function. Beta ERD was induced in response to the SON, while the other Unknown Name groups induced beta ERS. The results from the SON, LPC and the beta ERD, were indicative of the recognition of their own name by memory retrieval. Parietal positivity suggests familiarity recognition, and beta ERD also supports this interpretation. These SON responses were clearly different from both of the Unknown Name groups, which are indicative that the Unknown Name groups played the role of correct control, rather than influencing repetition.

2.2. Materials and Methods

Participants

Seventeen right-handed volunteers, including one female (mean age 23.2 ± 1.96), without hearing impairments participated in our experiment. All of the participants were native Japanese speakers. Data from four participants were removed because they included too many artifacts (see below section, Data Analysis, for information about artifact removal). No participants reported any prior or current medical or neurological problems. The protocol was approved by the Kyushu University Ethics Committee.

EEG recording

EEGs were recorded across 19 channels with Ag/Cl scalp electrodes according to the International 10-20 system. The reference electrodes were placed on A1 and A2 and the ground was placed on Fpz. Electrode impedance was kept below 10 kΩ. EEGs were recorded using Nurofax mu (Nihoon Kohden, EEG-9100). The sampling rate was 500 Hz and an analog bandpass filter (0.016–120 Hz) was applied to EEGs.

Procedure

The stimulus set consisted of calling the SON and Unknown Names. All names were Japanese and

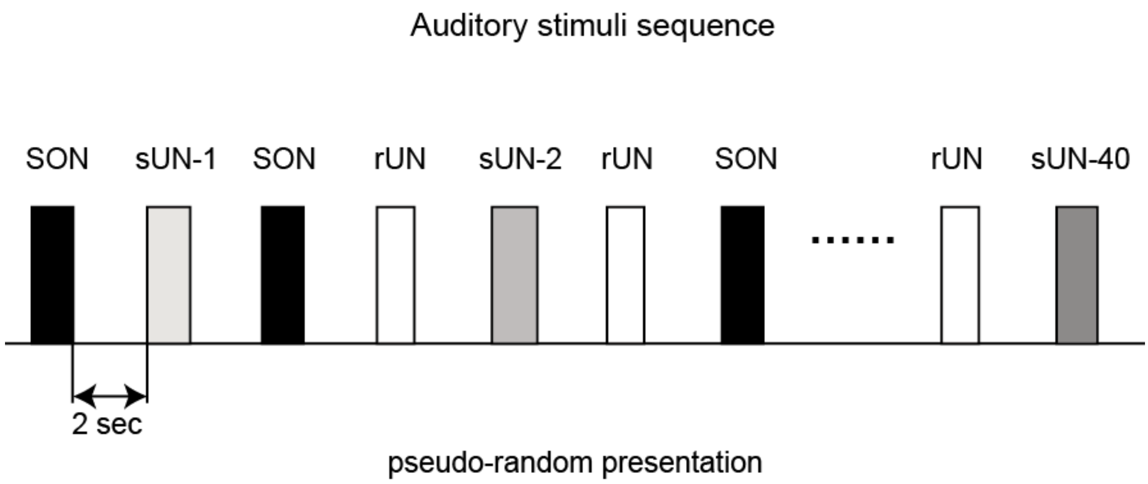


Figure 1. The auditory stimulus sequence of our experimental task. SON was repeated 40 times in a session. rUN was one unknown name and repeated as the same times as SON. sUN was consisted from 40 types of unknown names (sUN-1, sUN-2, … and sUN-40), and presented at once in a session. These auditory stimuli were presented in pseudo-random series.

given names. These sound stimuli were recorded in female voice, using CeVIO Creative Studio FREE (http://cevio.jp/index.php), free software for the creation of artificial speech sounds. Before the experiment, we removed some names from the Unknown Names group that were familiar to the participant (parents' names, grandparents' names, brothers' or sisters' names and close friends' names). We also removed some Unknown Names that started with the same first Japanese syllable of the SON (for example, if the SON was "Ta-ka-shi", we removed "Ta-ku-ya", "Ta-i-chi" and so on). All Unknown Names were selected from Japanese names.

Unknown Names stimuli were separated into two groups by repetition number in our experimental sequence. One of them was the repeated Unknown Name (rUN) group, which contained the same number of trials as the SON. The other was the single presented Unknown Name (sUN) group, consisting of various unknown names that were presented only once during the experiment. SON and rUN were presented 40 times interspersed with each other and 40 types of sUN were presented once in one sequence. These 120 stimuli were delivered in a pseudo-random series and the Inter-Stimulus Interval (ISI) was 2 sec (Fig. 1). This experimental sequence was presented by Psychophysics Toolbox Version 3, in Matlab ver. 7.5.0 (R2007b, The MathWorks, Natick, USA).

Each participant sat on a chair and listened to the presented sound stimuli through headphones in a shielded room. They were instructed to focus on a white fixation cross on a black screen during the experiment. The distance from participants to a screen was 1.5 m.

Data Analysis

The EEG data were filtered offline with a 0.1 Hz FIR high-pass filter. Epochs were rejected when they exceeded 100μV within -0.5 to 1 sec. This preprocessing was performed using the EEGlab toolbox (Delorme & Makeig, 2004), implemented in Matlab ver. 7.5.0 (R2007b, The MathWorks, Natick, USA).

For Event Related Potential analysis (ERP), we segmented epochs by stimulus onset and set the stimulus onset as 0 sec, and then averaged epochs in each participant. We applied 30Hz lowpass FIR filter again only for ERP data to reduce high frequency noise. The mean baseline amplitudes (-0.2 to 0 sec) were subtracted from each ERP. After this, we averaged the ERPs of all participants to create a grand average ERP for each channel.

For time-frequency analysis, we used the Morlet wavelet transform from the fieldtrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011) from 3 to 50 Hz. We set the parameters of the fieldtrip Morlet window lengths as 5 sec and the sliding window steps as 0.01 sec. Then we obtained the powers from the wavelet complex and averaged across trials in each participant. From the powers in each bin, we calculated Event related de-/Synchronization (ERD/ERS) (Pfurtscheller & Aranibar, 1977) in terms of a relative change from baseline (-0.2 to 0 sec).

Statistics

For ERP data, we conducted Kruskal-Wallis tests to compare late components across conditions (SON, rUN, sUN) of the mean amplitudes within 0.4 to 0.6 sec. Post-hoc testing was performed using the Steel-Dwass test. To compare the ERD/ERS, we conducted a Kruskal-Wallis test for the mean of beta (15–30Hz) ERS/ERD relative changes within 0.4 and 0.6 sec, and the Steel-Dwass test was performed as a post-hoc test. These durations of interest were selected following visual observations. The statistical tests were performed by JMP® 11 (SAS Institute Inc., Cary, NC, USA).

2.3. Results

ERP components

The grand average ERP showed different patterns in conditions (Fig. 2). ERP waveforms of all conditions showed negative waves in late latencies (about from 0.4 to 0.8 sec) at frontal sites (F3, Fz, F4). At parietal sites (P3, Pz, P4), late components (from 0.4 to 0.8 sec) showed their ERP differences clearly. At 0.4 to 0.8 sec, late positive ERPs were elicited in response to the SON. Conversely, a negative component was elicited in the sUN condition at the same latency. In the response to rUN, the ERP potential was midway between the SON and the sUN.

In statistical analysis, the Kruskal-Wallis test revealed a significant effect of condition on late component amplitudes at the mean of P3, P4 and Pz ($C^2_{(2, n = 36)} = 16{,}78$, $P < 0.001$) (Fig. 3b). Post-hoc analysis revealed a significant difference between SON vs. sUN ($P < 0.001$), and SON vs. rUN ($P = 0.032$). These results showed that the evoked response to SON was characteristic from other conditions, unknown names. The comparison of sUN vs. rUN also showed statistical significance ($P = 0.032$). It indicated that the evoked response to repeated unknown names and non-repeated ones showed different patterns, and suggested that repetition affected the ERP waveforms at late component.

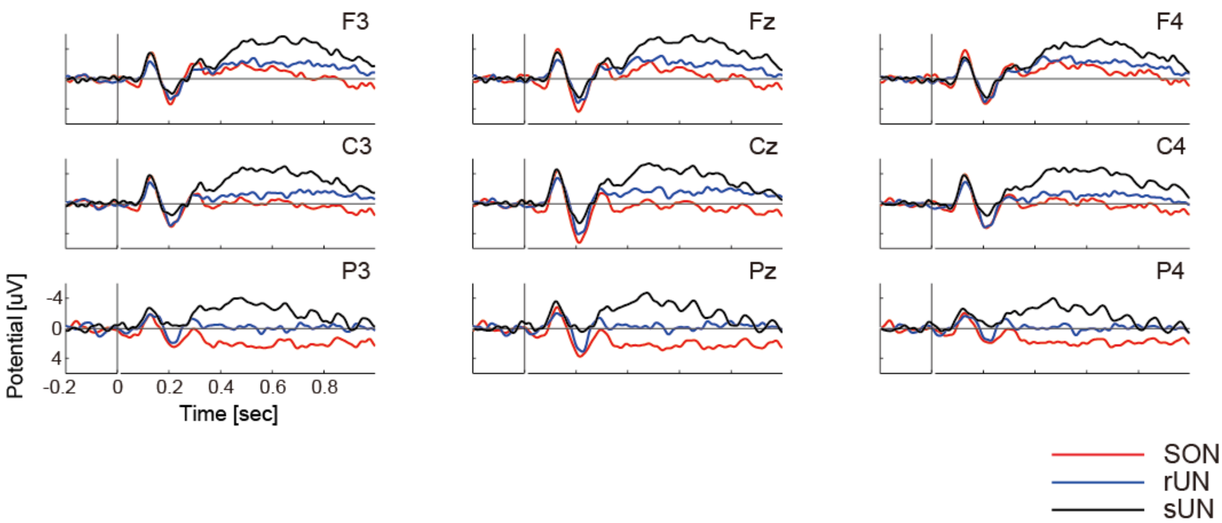
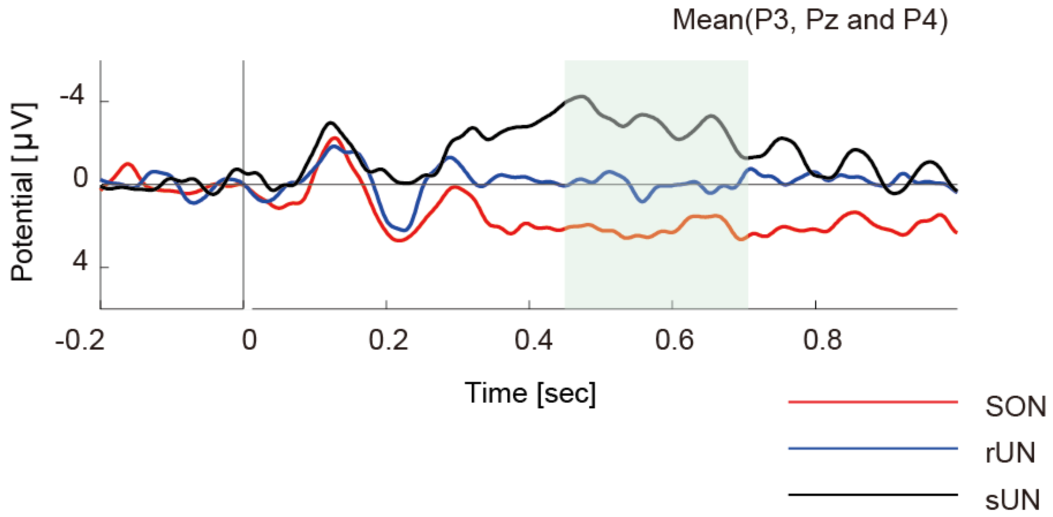


Figure 2. Grand averaged ERP at each channel corresponding to labels.

a)



b)

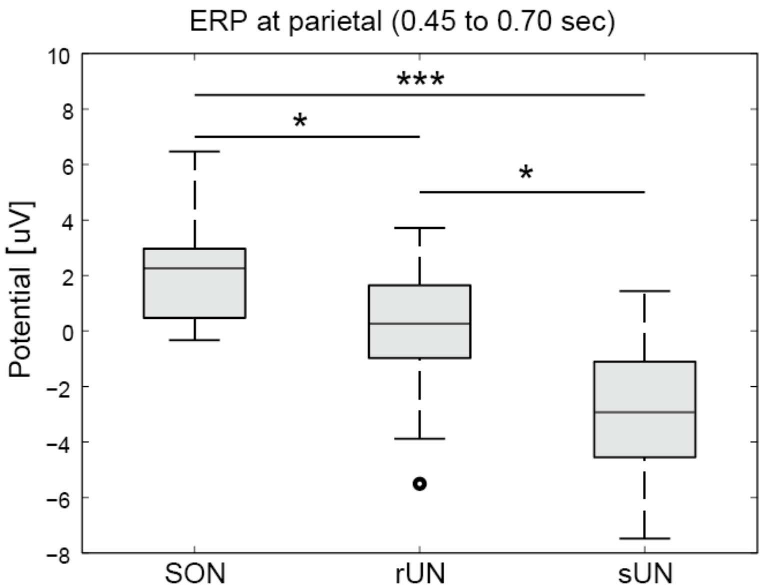


Figure 3. The mean ERP over parietal sites showed positive component in ERP a) The mean ERP waveforms over parietal sites (P3, P4 and Pz). The mean values of amplitudes at the shaded interval (0.45 to 0.7 sec) were performed statistical test as shown in b). Averaged ERP across 0.45 to 0.7 sec at parietal sites of each participant. Asterisks show statistically differences (* $P < 0.05$, *** $P < 0.001$).

Time-frequency analysis

We analyzed induced power changes by time-frequency analysis (Fig. 2). We selected C4 electrode since it was the most distinguishable the differences.

Theta ERS (4–8 Hz) was commonly found in each condition from 0 to 0.3 sec. Theta ERS did show any main effect ($C^2_{(2, n = 36)} = 1.04$, $P > 0.05$) from 0 to 0.2 sec and it was consisted with the visual inspection.

In alpha (8−13 Hz) and beta (15−30 Hz) bands, ERD was shown in response to SON at 0.4 to 0.6 sec, specifically. We did not find any main effect of relative alpha band (8−13 Hz) changes ($C^2_{(2, n = 36)} = 1.46$, $P > 0.05$) from 0.4 to 0.6 sec. This result is consistent from previous result in passive listening task (Fellinger *et al*., 2011; Höller *et al*., 2011).

From 15 to 30 Hz in the beta bands, we found ERD in the SON condition and ERS in sUN, particularly after 0.4 sec from stimulus onset (Fig. 4). Then we analyzed the statistical effects across condition in terms of beta power changes. The relative changes in the beta band power showed a statistical main effect across conditions from 0.4 to 0.6 sec ($C^2_{(2, n = 36)} = 15.29$, $P < 0.001$). We found that beta ERD was statistically significantly different in rUN ($Z = -2.51$, $P = 0.032$) and sUN ($Z = 3.44$, $P = 0.0017$) by post-hoc testing (Fig. 3b). The statistical result indicated that beta ERD was only shown in response to SON. In comparison with beta ERS for rUN and sUN, there were no

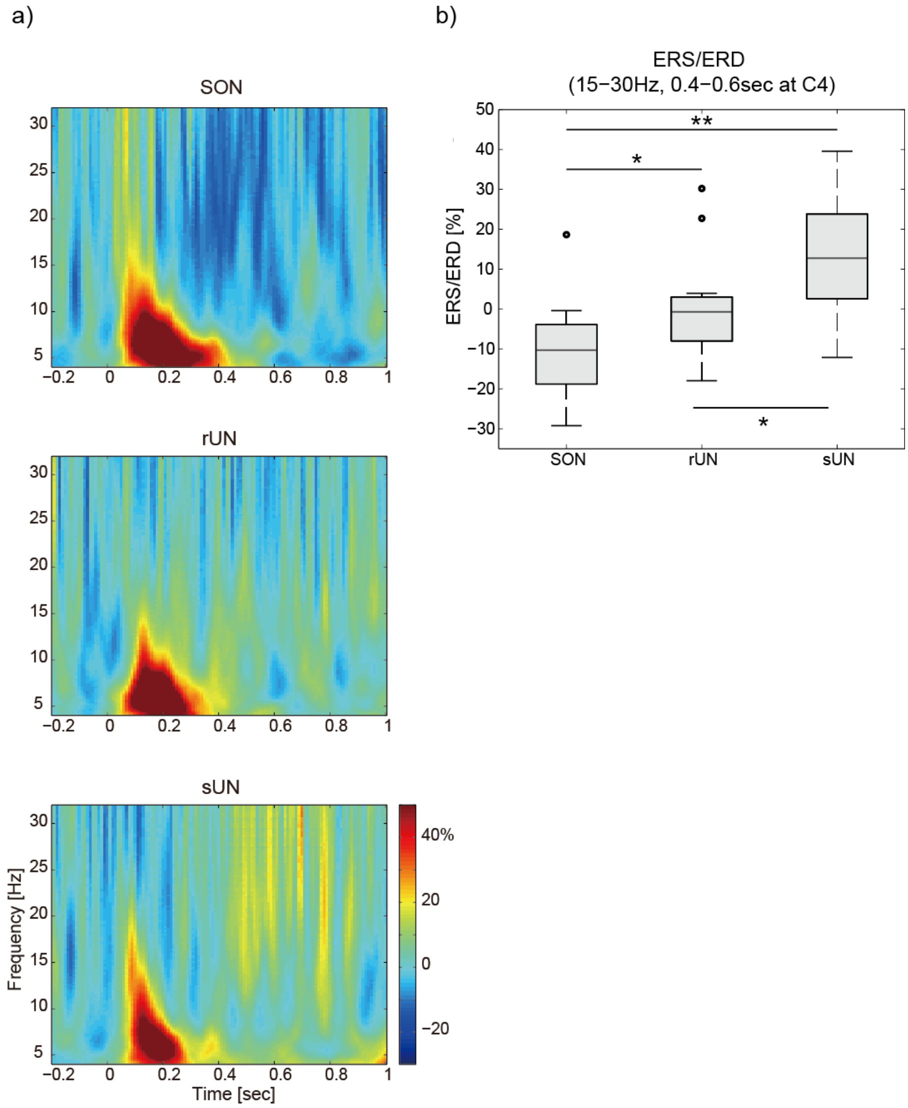


Figure 4. Time-frequency results showed beta ERD in SON

a) Time-frequency spectrogramp plot of ERS/ERD at C4, averaged across participants. Color bar shows the relative change from baseline. b) Averaged ERS/ERD across 0.4 to 0.6 sec at C4 of each participant. Asterisks show statistically significant differences (* $P < 0.05$, ** $P < 0.01$).

statistical differences ($Z = 2.15$, $P > 0.05$). This result suggested that the beta activities were robust by repetition effect.

2.4. Discussion

SON showed positive ERP (Fig. 3) waveform and beta ERD (Fig. 4) and rUN did not affect these significances (Figs. 3,4). These results showed characteristics of EEG responses to hearing SON and we suggest that repetition did not influence to the differences between unknown names and SON during our experimental session. Even though the ERP responses of rUN and sUN showed a possibility that repetition suppressed negative component of single presented stimuli, the ERP positivity or beta ERD of SON was too much large and repeating presentation did not disturb.

There are few investigations about oscillation changes by hearing SON to our knowledge. The present thesis found theta, alpha and beta power changes by the experiment. In this section, we discuss the meaning of these power changes to provide perspectives to apply similar experiments for patients with SMID in later chapters.

ERP Late Component

Our interest to the comparison with SON and rUN is whether repetition affected to the difference between these two conditions. Comparing with SON and rUN in ERP components, late positive waves were elicited by hearing SON at parietal sites, while rUN did not show (Figs. 2,3). This late positive waves were similar with late positive component (LPC) which have been reported the relationship with long-term memory process (Curran, 2004; Danker *et al.*, 2008; Finnigan, Humphreys, Dennis, & Geffen, 2002; Van Strien, Verkoeijen, Van der Meer, & Franken, 2007). Several papers demonstrated the LPC elicitation in old/new effect task if participants can detect the repetition of a target stimulus or not (Curran, 2004; Danker *et al.*, 2008; Finnigan *et al.*, 2002; Van Strien *et al.*, 2007). Though rUN repeated in a session, SON positivity was statistically larger than that of rUN (Fig. 3). This larger LPC showed that memory association with SON were very larger than repeated stimulus, even if it presented as the same number as SON.

The SON positivity was observed in parietal sites specifically (Fig. 2). We suspect that parietal positivity was included in LPC. Parietal positivity also has been discussed in terms of old/new recognition memory tasks. Other previous reports also indicate the relevance of parietal positivity to memory retrieval (Chen *et al.*, 2014; Curran, 2004).

Next we discuss the comparison of ERP components between rUN and sUN to show the repetition effect during a session. sUN showed larger negativity than rUN at almost all of channels, though SON and rUN did not show such negative component at parietal sites (Fig. 2). This negative component would be N400 and we suggest that the N400 elicitation in sUN was facilitated by the "new" stimulus (Finnigan *et al.*, 2002). sUN was presented only once and the novelty was clear for participants. N400 has been discussed with LPC in old/new effect papers (Danker *et al*., 2008; Finnigan *et al*., 2002; Van Strien *et al*., 2007), and it is consistent with the LPC elicitation by SON. The difference between rUN and sUN could be explained by the old/new effect studies. The repeated stimuli (rUN) were not “new”, rather than “old” stimuli, and we suggest their negativities were suppressed from this reason.

The negative component was observed in SON at frontal sites (Fig. 2). Other reports have shown FN400 facilitation by hearing SON (Tateuchi *et al*., 2012), while we did not find such clear and larger FN400 in SON (Fig. 2). It can be explained by the frequency of the stimulus presentation, because the report showed FN400 in infrequent SON presentation and did not find such FN400 in frequent SON presentation (Tateuchi *et al*., 2012). In our experiment, the frequency of SON presentation was one-third of whole stimuli, and that is, frequent presentation in the line of the report. Rather than FN400 of SON, sUN showed larger negativity as we discussed above (Fig. 2), maybe because of the balance of the new-recognition effects and frequent presentation.

Memory retrieval to hearing SON would be associated with familiarity recognition. The differences of ERP among conditions could be explained by familiarity recognition. Parietal positivity has been shown when the SON is spoken in a familiar voice (Holeckova *et al*., 2006). Holeckova *et al.* discussed that the familiarity invoked parietal positivity compared with when the

SON was spoken in an unfamiliar voice (Holeckova *et al*., 2006). In this line, the present observation of parietal positivity could be explained by the familiarity of one's own names compared with unknown names. Familiarity recognition can explain the waveforms in rUN. The familiarity of rUN should be lower than that of SON but higher than sUN, since it was presented repeatedly in the experimental task. It means that the differences of familiarity were linearity by the conditions. Considering with ERP, ERP waveforms of rUN were midway between SON and sUN. The linearity of ERP waveforms and familiarity levels were similar. In rUN condition, negative component (N400) was inhibited because the familiarity of rUN was increased during an experiment, but it did not exceed than that of SON, so rUN waveforms might not show positivity (parietal positivity). It might support our hypothesis that the present parietal positivity reflects the familiarity of participants' own names, because SON could cause recall of long term memory while Unknown Names could not. This late positivity seems to include a novelty P300 component. It has been reported that an auditory SON stimulus elicited a P300 in healthy participants (Holeckova *et al.,* 2008, 2006) and comatose patients (Fischer *et al*., 2008), or visual SON stimulus in healthy participants (Zhao *et al*., 2011). The P300 is known to be relevant to a top-down attentional shift to a distracter (Polich, 2007). In this experiment, the SON oriented attention as discussed in other reports (Fischer *et al*., 2008; Holeckova *et al*., 2008, 2006; Zhao *et al.*, 2011). In our measurements, the positive peaks was not clear because of the lower analog filter (see 2.2 Materials and Methods). Therefore, P300 and LPC was not clearly defined from the results.

Beta ERS/ERD

In ERS/ERD analysis, we observed ERD in the beta band in response to the SON, though sUN (or rUN) responses showed significant ERS (Fig. 3). To the best of our knowledge, there have been no reports that beta ERD is induced by SON. Several studies have reported that beta power suppression is shown by a familiar face stimulus rather than an unfamiliar one (Başar, Ozgören, Oniz, Schmiedt, & Başar-Eroğlu, 2007) and a self-referential judgment test (Mu & Han, 2010). Similarly, the beta ERD was indicative of the self-related stimulus. From our comparison of the responses to self-related (SON) and unfamiliar (Unknown Names, rUN or sUN) auditory stimulus groups, we found significant ERD in response to SON, and no differences between rUN and sUN. These results supported our notion that beta ERD reflected self-referential recognition. These results are suggestive of different cognitive processes, which are reflected in beta activity even by an auditory stimulus. In the present study we did not consider the differences between unfamiliar stimuli and self-related or familiar stimuli. More investigation is necessary for precise understanding of the association of the beta band and cognitive function for self- and unfamiliar stimuli.

The other aspect of beta ERD could be explained by the relevance of the beta band and the function for the maintenance of the "*status quo*". As reviewed by Engel *et al*., beta band ERS is associated with a continuation of the cognitive set and beta ERD is induced by novel events. They proposed that beta activity enhanced the maintenance of the status quo (Engel & Fries, 2010). Following this work, we suggest that the SON stimulus was interpreted differently from the others, even though all presented stimuli were grouped as "someone's name". Memory and/or self-recognition, those are triggered by hearing SON, would be factors to differentiate SON from others in an experiment.

Alpha ERD

Alpha ERD was observed in hearing SON, though there was no statistical significance. Previous study also have not find in statistical differences between the alpha responses of healthy subjects to SON and UNs in passive listening, while they have shown a significance in SON counting task (Fellinger *et al*., 2011). It can be explained that the counting reduced the variability of alpha relative changes to SON. Furthermore, the present alpha powers are including induced and evoked changes. Induced changes are not fixed by latency and have jitters (Catherine Tallon-Baudry & Bertrand, 1999). Our statistical test was used a fixed time window, so there is a possibility that such jitters let the results unclear.

Several studies about alpha oscillation have supported that alpha inhibition was related with long-term memory function (Burgess & Gruzelier, 2000; Wolfgang Klimesch *et al*., 2007; Park *et al.*, 2014). In this line, we suggest that long-term memory retrievals were caused by hearing SON, based on the alpha ERD (Fig. 4). The present results showed not only alpha but also beta ERD in SON as above. Some studies have discussed that inhibitions of both of alpha and beta powers were associated with long-term memory retrievals (Hanslmayr, Staudigl, & Fellner, 2012; Waldhauser, Johansson, & Hanslmayr, 2012). This is the one of evidences why we suggest that alpha ERD was occurred by SON even though there was no statistical difference.

Theta ERS

Our results showed that theta power increased at the nearly same time with N1 elicitation in all of stimuli: SON, rUN and sUN (Figs. 2,4). We suggest that our finding of theta increase was related with N1 component, which was evoked in all conditions commonly. N1 has been suggested that it reflects the activation of auditory cortex when hearing stimulus (Mayhew, Dirckx, Niazy, Iannetti, & Wise, 2010) and theta power increase has been observed with N1 component (Ponjavic-Conte, Dowdall, Hambrook, Luczak, & Tata, 2012). In the present results, theta increase would associate with N1 and indicated the auditory cortex responses to hearing speech stimulus. Therefore, theta

ERS was found commonly in the all conditions.

Fellinger *et al.* have showed theta increase by hearing SON in active counting task, as an indication of long-term memory (Fellinger *et al*., 2011). Certainly long-term memory function is one of the functional meanings of theta increase (Burgess & Gruzelier, 2000; Byrne *et al*., 2007; Doppelmayr, Klimesch, Schwaiger, Auinger, & Winkler, 1998; Khader & Rösler, 2011; Lee *et al.,* 2014; Mellem *et al*., 2013; Missonnier *et al*., 2006). However, they did not find differences in passive listening task (Fellinger *et al*., 2011) and the theta increase probably associated with target effect of counting task. Furthermore, the theta ERS which Fellingers' reported was sustained for about 0.4 sec and it was longer than the present results (about 0.2 sec). Considering this difference of experiment, we did not suggest the theta ERS reflect the long-term memory, rather than the association with N1 component of ERP.

Improvement points about experiment and analysis for the investigation about patients with SMID

In this section, we confirmed that repetition of control stimulus did not affect the response to SON, while there was a statistical difference in ERP components between single-presented stimuli group and repeated stimulus group. According to this suggestion, we edited the new experiment for patients with SMID, including repeated control stimuli in the next section.

For analysis of the later section, we decided to introduce evoked activity analysis. Induced activity is not fixed the latency and has many jitters, and these jitters would cause noise, especially for patients' data. In this section, we did not find any statistical differences in alpha band powers, while we observed the contrast in visual aspect. We suspected that no statistical significance was affected from the jitters from induced activities. From these reason, we focused on evoked activity.

Chapter 3. Experiment 2

Response to SON of Patients:

Alpha Suppression in Response to Hearing SON and Beta Abnormality of Patients with SMID

3.1. Abstracts

The aim of this chapter is to investigate EEG response to Subject's Own Name (SON) of patients with SMID, who have perinatal or childhood brain injury. We separated the patients as two groups by their diagnosis: Periventricular leukomalacia (PVL) and Cerebral hemorrhage (CH), for group comparison with healthy control group.

As control group, 11 normal subjects were measured EEG in response to hearing SON and Japanese words and calculated EEG evoked response by wavelet transform and we found alpha and beta powers showed different patterns between two conditions. Their evoked powers were separated to three frequency bands (Theta, Alpha, Beta) and three time widths (0–0.25, 0.25–0.5, 0.5–0.75 sec after stimulus onset). To find the feature of response to SON, these data were analyzed by discriminant analysis. We compared them with normal subjects and patients.

To discriminate the response to SON and words, we selected five indices, including information of

channel location, latency range and frequency band. These indexes contained alpha or beta bands. There was no evaluation index including theta power. In the comparison with normal subjects and patients, there were significant differences in beta responses to SON, while we did not found significance in alpha.

The similarity of alpha response to SON of patients with normal subjects, and we suggested that they remain long-term memory function to hearing SON. On the other hands, beta response to SON of patients were reflected the dissimilarity with healthy subjects, because of the probability that they have less self-recognition function.

3.2. Materials and methods

Subjects

In this experiment, healthy control and patient were examined. The patient group was consisted from PVL (Periventricular leukomalacia) and CH (Cerebral hemorrhage) patients. The PVL group included four patients (three males and one female) aged between 18 and 27 years and CH group included three patients (one male and two females) aged between 13 to 23 years. Patients' information is shown in Table 1. As healthy controls, 11 healthy, right-handed volunteers aged from

21 to 27 years old (mean age was 21.4 ± 1.10), including two females participated in this study. All subjects in this group reported no difficulty in hearing. The protocol was approved by the Kyushu University ethics committee.

EEG recording

EEGs were recorded using 19-channels with Ag scalp electrodes according to the International 10-20 system. The reference electrodes were placed on A1 and A2. The ground electrode was on the tip of the nose. Electrode impedance was kept below 10 kΩ. EEGs were recorded using Neurofax μ (Nihon Kohden, EEG-9100, Tokyo, Japan). The sampling rate of measured EEG was 500 Hz. A 0.08-300 Hz bandpass analog filter was applied online to EEG signals. The frequency of highpass filter was upper than that of Experiment 1 to reduce the noise from patients involuntary motor artifacts. It is not affected only to analyze time-frequency analysis without ERP investigations.

Table 1.

Status of SMID patients

	Age at time of measurement (years)	Age at injury	Sex	Cause of SMID	State of patient	Motor disabilities	IQ	Response to calling SON
S1	13	2 months	Female	CH by vitamin K deficiency	Bedridden	Cannot sit	< 10	Smile sometimes
S2	16	12 years	Female	CH by traffic accident	Bedridden	Cannot sit	< 10	Open mouth
S3	23	0	Male	PVL (widespread type), VLBWI	Can move with wheelchair	Cannot stand	< 10	A few words
S4	18	3 months	Male	CH by accidental trauma	Bedridden	Cannot sit	< 10	Smile sometimes
S5	27	0	Male	PVL (widespread type), VLBWI	Can move with wheelchair	Cannot stand	15	A few words
S6	18	0	Female	PVL (diffuse type), VLBWI	Bedridden	Cannot sit	< 10	Smile sometimes
S7	21	0	male	PVL (widespread type), VLBWI	Bedridden	Cannot sit	< 10	Smile sometimes

PVL (periventricular leukomalacia), CH (cerebral hemorrhage), VLBWI (very low birth weight infant)

Procedure

The subjects of normal group were required to sit on a comfortable chair and to listen to the presented sound stimuli through earphones. They were instructed to watch a silent movie and not to pay attention to the sound stimuli. This procedure aimed to simulate the attentional condition of SMID (Severe Motor and Intellectual Disabilities) patients, which is difficult to control. Patients lay on a reclining wheelchair instead of sitting on a chair and listened to the stimuli through the same earphones as the healthy subjects. The patients with SMID were not instructed to watch a silent movie.

The stimuli consist of three kinds of speech sounds: the Subject's own name (SON) and two control words. The mean duration of SON was 0.502 sec. The two control words were Japanese

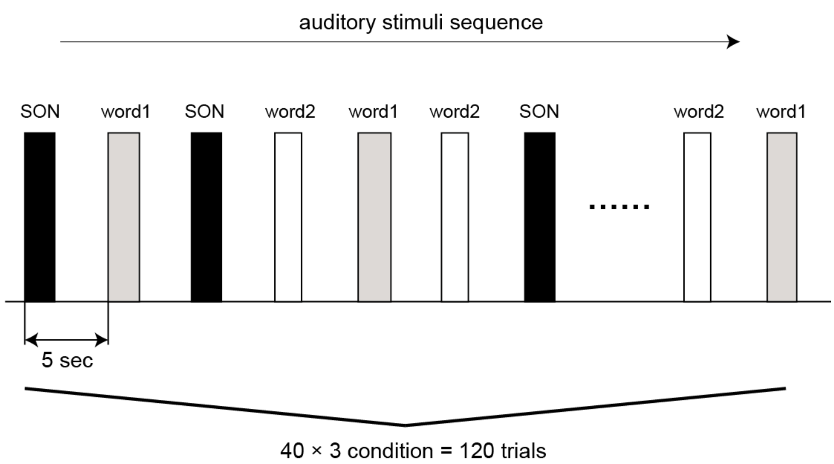


Figure 1. The auditory stimulus sequence of experimental task. SON was repeated 40 times in a session. Word 1 and word 2 were also presented 40 times each. Words (word 1 and 2) were consisted from the same number of Japanese mora. Stimulus Onset Asynchrony (SOA) was 5 sec. These auditory stimuli were presented in pseudo-random series.

general nouns with the same the number of Japanese mora as SON to let durations of words be as nearly equal as that of SON. The first Japanese mora of each word stimulus was different one. For example, if one of the words stimuli was “Ri-N-Go” (it means “apple” in Japanese), we did not use “Ri-Ka-I”, (it means “understanding” in Japanese) as the other word stimulus because they had common Japanese mora as a first syllable. These sound stimuli were recorded with artificial voice to simulate calling SON by unknown voice, using Softalk (http://www35.atwiki.jp/softalk/), and edited using STIM2 (Neuroscan Ltd., El Paso, USA) to set equal sound intensity levels (65 db).

Each stimulus was presented 40 times in one session and delivered in a pseudo-random series with for the presentation. Subjects were presented with two consecutive blocks of 120 stimuli (40 trials per each condition). Stimulus onset asynchrony was 5 sec. The presentation of these speech stimuli was controlled by STIM2 (Neuroscan Ltd., El Paso, USA).

Data analysis

The EEG data were filtered offline with a butterworth filter (6th order) of 0.1 and 50 Hz. The epochs that exceeded 150 μV within -0.25 to 0.8 sec were rejected. These preprocessing were performed by EEGlab toolbox (Delorme & Makeig, 2004) in Matlab ver. 7.5.0 (R2007b, The MathWorks, Natick, USA) . By outlier analysis using jackknife distances, one subjects was removed from normal subject group. This outlier analysis was performed by JMP® 11 (SAS Institute Inc., Cary, NC, USA)

To calculate evoked activity from EEG, we used time-frequency spectrograms from 3 to 50 Hz, which were computed using the continuous wavelet transform with complex Morlet wavelet by fieldtrip toolbox (http://www.ru.nl/ fcdonders/fieldtrip). We set the parameters of Morlet windows length as 5 sec and sliding window steps was 0.05 sec. The evoked activities were calculated by means of a time-frequency spectrograms over trials at each 0.05 sec bin (Catherine Tallon-Baudry & Bertrand, 1999) and mean of baseline (-0.25 to 0 sec.) were subtracted. Then calculated bins were segmented in each frequency band (Theta: 4–8Hz, Alpha: 8–13Hz, Beta: 15–30Hz) and time periods (0–0.25sec, 0.25–0.5sec, 0.5–0.75sec) at each channel.

Variable Selection

The preprocessed EEG power of normal group was analyzed by linear discrimination analysis to find variables which contribute to make a difference between the response to SON or control words. We adapted three frequency bands (Theta, Alpha, and Beta), latency intervals (0–0.25sec, 0.25–0.5sec, 0.5–0.75sec.) and 19 channels as variables and selected them by stepwise variable selection. After the analysis, we found five indexes which contributed to separate the response to SON from that to control words and their normalized scoring coefficients. The highest absolute normalized scoring coefficient was 3.79 and the lowest one was 0.804 within top five indexes (Table 2). We did all of above analysis by JMP® 11 (SAS Institute Inc., Cary, NC, USA).

Statistics

Paired t-test was adapted to compare powers between SON and words within normal subject group. The EEG power data of normal subjects which selected by discrimination analysis were performed by Multivariate ANOVA to test the significance between the response to SON and words. For comparison with the response to SON of normal subjects and patient group, we performed Mann-Whiteney test in each parameter. These analyses were done by JMP® 11 (SAS Institute Inc., Cary, NC, USA).

3.3. Results

Parameter Selection from Normal subjects data

The EEG spectrograms of evoked power were calculated from wavelet coefficients (Catherine Tallon-Baudry & Bertrand, 1999) for normal subject group (Fig. 2a). These spectrograms showed

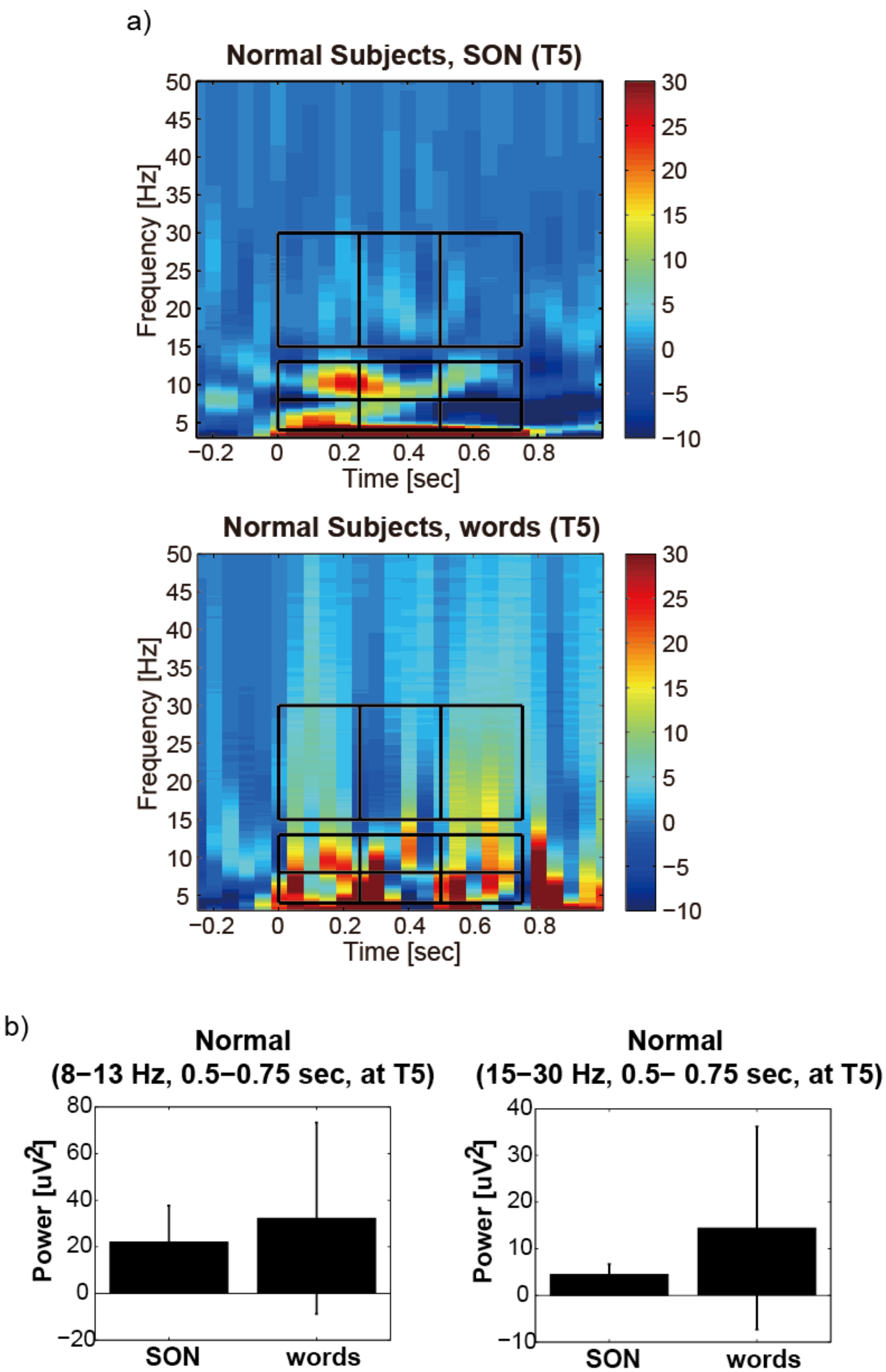


Figure 2 a) Averaged time-frequency power of evoked activity for normal group. Color bar shows the evoked power which calculated from wavelet coefficients (μV^2). Black lines show the frequency range (4–8, 8–13, 15–30 Hz) and time range (0–0.25, 0.25–0.5, 0.5–0.75 sec.) which were adapted to discriminant analysis. b) Evoked powers in response to SON or other speech words of normal subject group. Error bar shows each standard error.

different patterns in beta bands between two conditions. Especially at 0.5–0.75 sec beta and alpha power in SON was lower than words condition (Fig. 2b). There were no significant differences between SON and words in alpha (t = -0.54, P > 0.05), and beta (t = -1.11, P > 0.05).

For comparison with patients, it was necessary to select evaluation indexes including the information of time, frequency and channel location. These evaluation indexes were decided from normal subjects' data, because it was necessary to know that when and which frequency bands contributed to the common neuronal response to SON. The latency and frequency ranges of interest were decided from EEG spectrograms of healthy subjects (Fig. 2a). Considering the time-frequency changes and channel locations, we extracted five evaluation indexes by a multiple discriminant analysis (Willks-lamda F = 10.2, P = 0.0002). The error discrimination rate was 9.09 %. The absolute values of normalized scoring coefficient indicate the degree of contribution for classification. We focused on five indexes that have top five highest absolute values of scoring coefficient (Table 2). We show which channel, frequency band and latency range were included in these indexes as below.

For channels of the top five scoring coefficients, only T5 and T3 were selected to classify EEG powers by conditions. T5 and T3 are located at left lateral part. This result indicated that left lateral part related to classify the response to SON and words in healthy subjects. Beta band (15–30 Hz)

Table 2.

Selected parameters by Discrimination analysis (SON vs words) within normal subjects data and statistical results comparing Normal group and each patient group; PVL and CH.

Frequency	15–30 Hz	8–13Hz	15–30 Hz	15–30Hz	8–13Hz
Time	0.5–0.75sec	0.5–0.75sec	0–0.25sec	0.5–0.75sec	0–0.25sec
Channel	T5	T5	T5	T3	T5
Normalized scoring coefficient	3.79	-2.36	-1.55	-1.47	0.804

These data were sorted by absolute values of normalized scoring coefficients, which indicate higher contribution to discriminate two conditions.

was included in three evaluate indexes and alpha band (8–13 Hz) was selected in other indexes as interested frequency bands. The evaluation index with the highest absolute normalized scoring coefficient included beta band, and the second highest one was alpha band. For time ranges, 0–0.25 and 0.5–0.75 sec were selected as contributed latencies to separate the EEG powers of SON and words. The two indexes which have top two absolute normalized scoring coefficients showed 0.5–0.75 as time information. We focused on these evaluation indexes, as those can show the largest differences between SON and other speech stimuli, to investigate the response of patients.

Comparison with Normal and Patient groups

We focused on two evaluate indexes those have the top two highest absolute normalized scoring coefficients, to compare the response to SON between normal group and each patient group. Comparing with CH group and normal group in response to SON, alpha evoked power did not show statistical different (*P* = 0.350) (Fig. 3a) but the beta power was higher than that of normal group (*P* = 0.0127) (Fig. 3b). In comparison with PVL group and normal group in response to SON, alpha

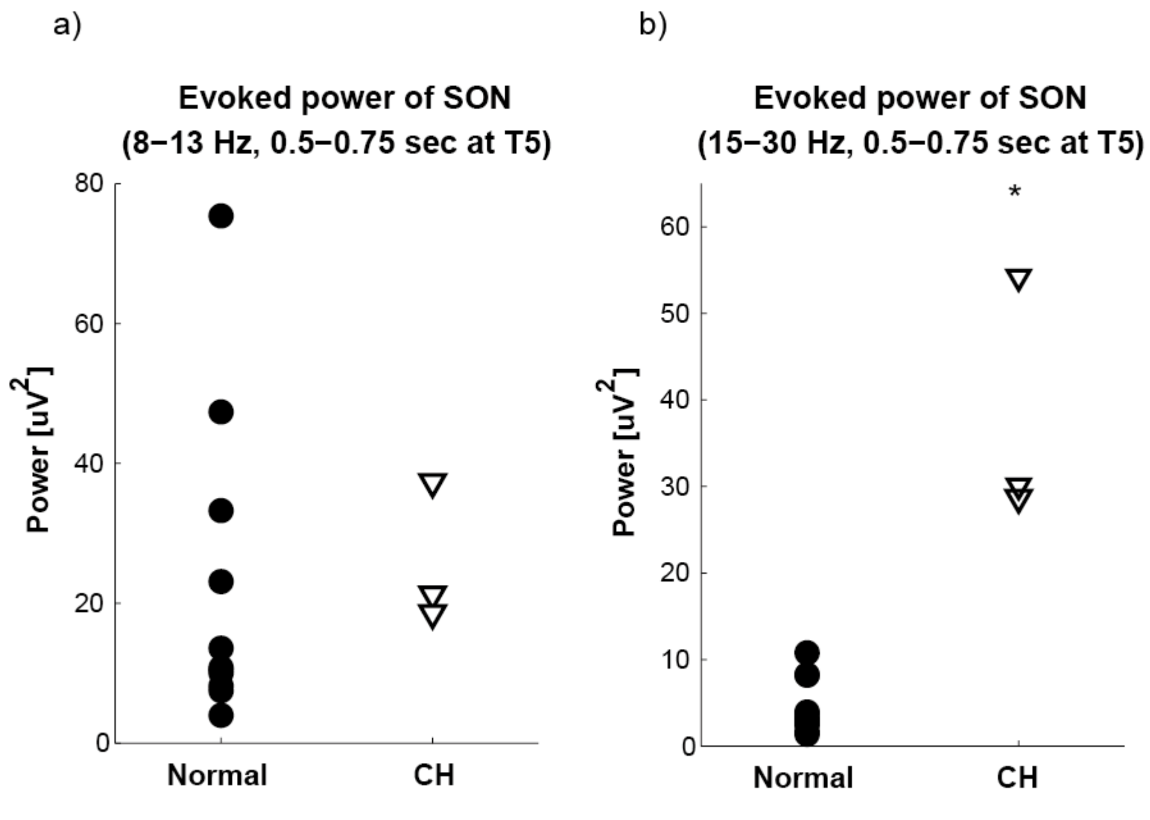


Figure 3 Evoked powers in response to SON of normal group and CH patients. Each dot shows evoked power of one subject. Plotted parameters were selected by top three absolute normalized scoring coefficients from Table 2. Asterisks show a statistical significant difference.

evoked power did not show statistical different (P = 0.472) (Fig. 4a) and the beta power was higher than that of normal group (Fig. 4b). This higher beta power showed marginal significance with normal group (P = 0.078).

3.4. Discussion

In the present chapter, we focused on PVL and CH patients as perinatal or childhood brain damages survivors and investigated their cognitive function using auditory Subject's Own Name (SON) by EEG time-frequency analysis. We found similarities in alpha band powers and differences in beta

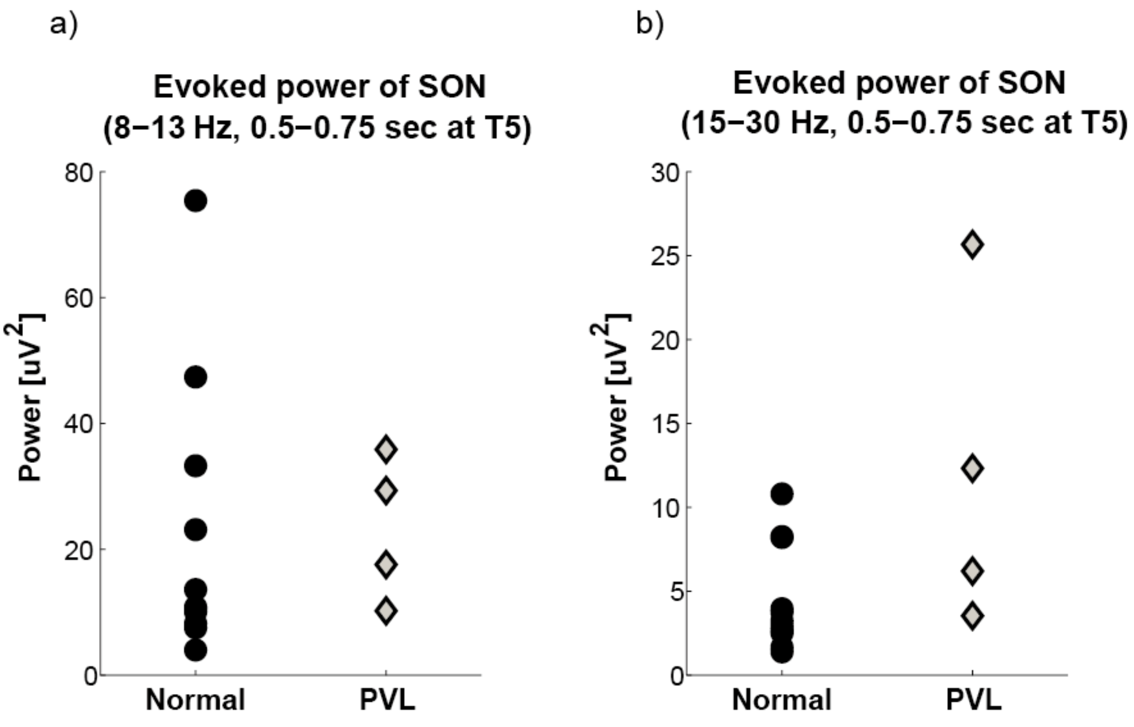


Figure 4 Evoked powers in response to SON of normal group and PVL patients. Each dot shows evoked power of one subject. Plotted parameters were selected by top three absolute normalized scoring coefficients from Table 2. Asterisks show a statistical significant difference.

band powers between normal subjects and patients, in response to SON. Alpha and beta oscillation have discussed their relationship with cognitive function, especially long-term memory (Hanslmayr *et al*., 2012; Khader & Rösler, 2011; Wolfgang Klimesch *et al*., 2007; Waldhauser *et al.*, 2012). We suggested that the patients have a similar cognitive process partially from our results as following discussion.

Before discuss the results, the difference from former chapter is mentioned here. In contrast with former chapter, we showed statistical significant in alpha powers in normal subjects. This difference from former results can be explained by following reasons. 1) We introduced evoked power analysis, which has less latency jitters in this chapter. This reducing of latency jitter might have contributed to increase the signal noise ratio. 2) We considered all channel locations (n=19) to show the difference with response to SON and control words by discriminant analysis, not only frequency bands and latency intervals. It increased the degree of freedom and let the significance clearer.

Response to SON of normal vs patients

To compare the cognitive function between normal subject group and each patient group, we focused on the power of each frequency band reflecting the results from the discriminant analysis (Table 2).

We mention incidentally that we did not find any different conclusions between CH-normal and PVL-normal comparisons. From our results, we found that alpha powers did not show any significant differences, though beta of each patient group showed statistically higher powers than normal group, in response to hearing SON. Here, we discuss the differences in cognitive function between normal group and each patient group from alpha and beta power changes.

There was no statistical difference in alpha power (8–13Hz, 0.5–0.75 sec at T5; see Table 2) in hearing SON between normal group and PVL group, and normal group and CH group (Fig. 3,4). Alpha evoked power in SON was smaller than words condition in averaged normal group at 0.5–0.75 sec after stimulus onset (Fig. 2), and indicated that alpha suppression also occurred in each patient group. This lower alpha power in SON within normal group was consistent with Fellingers' results for passive listening condition (Fellinger *et al.*, 2011). Out results were consistent with this report and supported their suggestion that the alpha suppression was a result from long-term memory retrieval by hearing SON (Wolfgang Klimesch *et al.,* 2007). A previous study reported that infants showed characterized ERP patterns by hearing SON, and the results indicated that infants memorized the syllable patterns to SON because it was the most presented word (Parise *et al.*, 2010). In this case, we suggested that the patients remained long-term memory function to retrieve the most frequently presented word: SON.

Alpha oscillations have also been discussed the relevance with attention process (Wolfgang Klimesch *et al.*, 2007), which suggested the alpha oscillation was inhibited by other functional process. Some ERP studies have demonstrated the orientation of attention by SON (Holeckova *et al.*, 2008, 2006; Tateuchi *et al.*, 2012). In the studies of alpha suppression and attention process, most of results were sustaining attention, not an orientation attention. Our experiment was passive listening without any instructions, and such sustaining attention process was not consisted with our results.

Meanwhile, beta powers of each patient group were higher than normal group (Fig. 3, 4), and the results indicated that abnormalities in cognitive function affected to the beta power. In patients with mild cognitive impairment, it has been reported that evoked beta activity increased in both of target and non-target stimuli, though healthy controls showed suppressed beta in response to target stimulus specifically, by visual oddball paradigm with mental counting instruction (Güntekin, Emek-Savaş, Kurt, Yener, & Başar, 2013). This report discussed that suppressed beta activity reflected cognitive load function, that is, results indicated that the patients did not remained the same levels with the cognitive load with normal subjects. This report supported our discussion that the higher beta powers showed the association with cognitive impairment. As more specific discussion of cognitive impairment, we focused on language skills. Higher evoked beta activity than normal group has been reported in autism children during language processing task (McFadden, Hepburn, Winterrowd, Schmidt, & Rojas, 2012). From this report, we suggested that higher beta powers of patients represented the abnormality of language skill.

Furthermore, we could consider the less functional levels of self-cognitive process, by discussing the result of beta and alpha power suppression. Many studies have shown the association between beta suppression and self-cognitive or process (Fellinger *et al*., 2011; Miyakoshi, Kanayama, Iidaka, & Ohira, 2010; Mu & Han, 2010, 2013). In the line of these reports, we suggest that patients have lower levels of self-cognitive function. Their less self-cognitive function could be explained by their language skills. According to a review of Morin, it is controversy whether language skill is involved to self-awareness or not, especially in higher self-awareness level (Morin, 2006) in psychological field. From our results, we could lead a hypothesis that, beta response abnormality would show the lower self-awareness levels than normal subjects, and their lower language skills and IQ levels supported this hypothesis. However, the investigation of language processing for PVL or CH in childhood was very few and more understandings about the relevance with self-awareness and language skills are necessary. To confirm this hypothesis, we need to evaluate their language skills in more detail. Furthermore, it is necessary to investigate their self-awareness levels, depending on the Theory-of-Mind (TOM) (Morin, 2006). There are some kind of stages of self-awareness; self-awareness, private self, meta-self-awareness, and so on. Precise investigations for such self-awareness levels in healthy subjects would help to understand the understanding for such patients' function of self-recognition.

Then we have to discuss time and channel locations those were common to the top two evaluation indexes (Table 2). In responses to SON of patient groups, beta powers at 0.5–0.75 sec were too much higher than normal group and we suggested that beta suppression was not occurred in this timing in patients. The latency differences with vegetative state, minimally conscious state patients and healthy subjects have been shown in response to SON for theta ERS (Fellinger *et al*., 2011). Considering this report, there is a probability that the latency of beta suppression of such patients is different with normal healthy subjects. The problem to show this latency differences is impossibility to use active response task for PVL or CH patients, who have injured their brain in early age. We analyzed evoked power to reduce the latency jitters and compared the same latency with normal group though we used passive listening task, which is difficult to control responses of subjects. To show their latency of beta power suppression in detail, we need to gather more patients who have similar clinical profiles and reduce the variable of latencies more from patients' data.

The selected electrodes were T5 and T3 and both of them were located on left temporal part. The auditory cortex have been reported that it located on temporal part and the function of auditory speech recognition localized at the left lobe (Tervaniemi & Hugdahl, 2003). To discriminate the response to hearing SON and words stimulus within normal group, left temporal part would play an important role. Moreover, some of PET and fMRI studies have showed that left anterior temporal lobe had a relevant to name retrieval (Grabowski *et al*., 2001; Tsukiura, Mochizuki-Kawai, & Fujii, 2006; Tsukiura, Suzuki, Shigemune, & Mochizuki-Kawai, 2008). The reason why T5 and T3 contribution to discriminate was larger than other channels could be explained that the type of speech stimulus; general noun or self-related proper noun.

Discriminant analysis results from normal subjects

The alpha and beta evoked activities contributed to discriminate the response to SON and words. It has been reported that alpha and beta had a relevance to language processing and recognition (Hirata *et al.*, 2007; Shahin, Picton, & Miller, 2009). In this line, the results were led by the language recognition function, and it supported the reliability of our discriminant analysis. In the report of Shahin *et al*., beta power decrease was observed in semantic decision task, and it is consistent with our results (Shahin *et al*., 2009), because SON and other words were semantically different.

Long-term memory function is very important to discuss the validity of discriminant analysis results, as we mentioned above. Memory retrieval to hearing SON could be activated, though we did not instruct to do anything during the experiment and the task was not related to long-term memory function. Recent investigations have reported that alpha/beta power suppression reflected a process of selective episodic-memory retrieval (Waldhauser *et al*., 2012). Considering this report, lower beta power in SON than other words stimuli would be associated with personal memory retrieval, while patient did not show beta suppression.

The top two indexes, those were selected by discriminant analysis, had a common time range, 0.5–0.75 sec (Table 2). This time range indicated just after the stimulus offset because mean duration of SON stimuli was 0.502 sec (See; 3.2 Material and Methods). We suggested that the responses after subjects understood the meanings of speech stimuli were more contributed to define the EEG patterns of SON and words (0.5–0.75 sec.) in normal subjects. The timing when alpha and beta power showed negative peak was consistent with other report which investigated the semantic evaluation by auditory speech stimuli. Such later suppression was discussed as an accompany with semantic evaluation (Shahin *et al*., 2009). We could expect that hearing SON let retrieve memories after subjects finished to catch the meaning of stimuli in normal subject group.

3.5. Conclusion and Improvement points

In the present chapter, we investigated the EEG response to hearing SON of patients with SMID by between-subjects analysis. To compare their responses with normal subjects, firstly we performed discriminate analysis and found five indexes. As results, we found that patients did not show significant different alpha powers by hearing SON with normal and suggested that such patients remain the long-term memory function for hearing their own name. Beta powers of patients showed dissimilar patterns with normal subjects and the results might be indicative of the less self-cognitive function. We could found some common results within patients group in this chapter.

Considering the variety of clinical profiles of patients, between-subject analysis is not appropriate. We need to analyze their EEG response individually. For individual analysis, it is important to reduce noise and increase signals in more, though we considered in this chapter carefully. In the next chapter, we compared two time-frequency methods: event-related spectral perturbation (ERSP) based on power changes, and inter-trial coherence (ITC) relied on phase-locked activity, to find a suitable methods for patients with SMID.

Chapter 4. Experiment 3

Phase-locked Theta Activity Evoked in Patients with SMID upon Hearing Own Names: Individual Analysis for Patients

4.1. Abstract

The present chapter attempted to analyze patients individually. It was necessary to consider signal and noise ratio more carefully for individual analysis than group analysis because the EEGs of patients have variances. To find an appropriate analysis method, we compared two kind of time-frequency analysis: event-related spectral perturbation (ERSP) and inter-trial coherence (ITC). ITC method is relied on phase changes, while ERSP detects event-related power changes based on amplitudes.

The former section suggested that alpha and beta EEG responses of healthy subjects were different depend on the speech stimulus condition (SON vs words). Based on this result, we compared the alpha and beta responses with healthy and patient groups. However, the theta activity of patients was not investigated yet. Thus we focused on theta activity.

The theta ITC of healthy subjects showed similar patterns in SON and words conditions, and post-hoc test for latency showed the significance at early latency. This suggested that the theta

responses were found commonly for speech stimulus. This result was consistent with that of former section, which did not find any differences in theta band.

On the other hand, some patients showed higher theta ITC to SON than words condition. This difference can be explained two kind of residual function: Auditory speech perception or selective attention. From the results of ERSP, we could not find any common patterns among patients' results.

4.2. Method

Subjects, EEG recordings and procedure

The measured EEG data and subjects were same as Experiment 2. The protocol was approved by the Kyushu University ethics committee.

Time-frequency analysis

Before time-frequency analysis, EEG data were preprocessed as follows: a 0.1–50 band-pass digital filter (Butterworth, 6th order) was applied to the data, and epochs containing amplitudes beyond two standard deviations (SD) were removed. The reference was an average of all channels, re-computed offline. S7 was rejected by this artifact removal step because of so much noise and artifacts. Time-frequency analysis was then performed on the remaining data.

Data analysis was conducted from EEG signals recorded from the Fz electrode, because the frontal regions have been well investigated in terms of EEG responses to SON (Fellinger *et al*., 2011; Höller *et al*., 2011) as well as responses measured through functional magnetic resonance imaging (D'Argembeau, 2013).

The Morlet wavelet transformation was used to compute spectral estimates of EEG responses (Mouraux & Iannetti, 2008). To measure event-related changes in the power spectrum, we employed ERSP analysis (Makeig, 1993) using the EEGlab package (Delorme & Makeig, 2004) implemented in Matlab (2007b; MathWorks, Natick, MA, USA). ERSPs measure average dynamic changes in the amplitude of a broadband EEG-frequency spectrum. ERSP was defined by

$$ERSP(f,t) = \frac{1}{n}\sum_{k=1}^{n}\left|F_k(f,t)\right|^2 \qquad (1)$$

where for *n* trials, $F_k(f,t)$ is the spectral estimate of trial *k* at frequency *f* and time *t*. The Morlet wavelet transformation was used to compute spectral estimates of single-trial EEG responses (Mouraux & Iannetti, 2008). The parameters "cycles" and "freqs" of the timefreq function were set to [3, 0.2] (the number of wavelet cycles was started at 3 and increased with frequency in increments of 0.2) and [0, 60] (analyzed frequency band, 0-60 Hz), respectively. For further investigation of coherence in the oscillation of interest, ITC was calculated, again using the EEGlab package (Delorme & Makeig, 2004), as described by Tallon-Baudry *et al*. (C Tallon-Baudry *et al*., 1996).

This measure indicates synchronization at a particular frequency and latency with time-locked EEG data across trials. ITC was defined by

$$ITC(f,t) = \frac{1}{n}\sum_{k=1}^{n}\frac{F_k(f,t)}{|F_k(f,t)|} \qquad (2)$$

where for n trials, $F_k(f,t)$ is the spectral estimate of trial k at frequency f and time t. The timefreq function was set to the same parameters as used for ERSP. As shown in Equation (2), the raw ITC represents an averaged vector across trials in each subject and each raw ITC is a complex value. Absolute values of ITCs were therefore plotted and analyzed by statistical methods in this report. In this paper, we termed the absolute ITC as "ITC" and the complex ITC as "raw ITC".

Statistics

Two-way analysis of variance (ANOVA) (condition × time) was conducted on the ITC of healthy subjects in each 200-ms step. Sidak's multiple comparison was then adopted as a post-hoc test within each condition to compare temporal effects between before onset (-200 to 0 ms) and other time points. These statistical tests were performed using GraphPad Prism for Windows version 6.00 (GraphPad Software, La Jolla, CA, USA).

We analyzed phase data to test for the statistical significance of ITCs for each SMID subject, because ITC values were calculated by averaging across trials for each subject. We calculated phase data from wavelet complexes and all phase bin data were performed by the common median multi-sample test for equal median directions, to test for non-parametric circular data, because we could not estimate the uniformity of the data distribution. We focused on the comparison with baseline and primary response, because we observed that the response to SON in healthy subjects at 0–200 ms showed statistical significance with before stimulus. We performed comparisons between SON response at 120–200 ms and before stimulus onset (-200–-120 ms) and confirmed that all healthy subjects showed statistically significant results from within-subject analysis in this interval individually ($P < 0.01$) (Table 2). The common median multi-sample test was performed using the Circstat toolbox (circ_cmtest.m), which is similar to the Mann–Whitney U test for linear data (Berens, 2009) implemented in Matlab (2007b; MathWorks, Natick, MA, USA). In our knowledge, there was no non-parametric test for phase data based on Wilcoxon signed-ranked test (Berens, 2009) . That is why we used this common median multi-sample test for within-subject analysis, even though the method is designed for between-subject analyses. Especially for patient data, it is not appropriate to use parametric test. The validity of this test for within-subject analysis is deeply connected to the independence of the data. Considering the technical problem of the mathematical aspects, it is very difficult that to show the independence of data because this method is non-parametric. We do not think that such a discussion of the mathematical theory underlying the statistics is suitable for inclusion in the present study. For within-subject statistics, showing independence is also very complex. In this statistical test, we consider that our data were not dependent, because the time intervals were not continuous as we show above (-200 to -120 vs. 120 to 200 ms). If the time intervals for comparison were continuous, such as -200 to 0 vs. 0 to 200 ms, they would not be independent.

4.3. Results

ERSP data averaged across healthy subjects are shown in Figure 1. The results showed increased high theta-band (6−8 Hz) power in the SON condition during 0−800 ms and decreased high alpha-band (10−13 Hz) in the SON condition during 200−400 ms. The theta increase in the SON condition differed significantly from that in the words condition ($P = 0.0010$) (Fig. 2a), but the alpha decrease did not (Fig. 2b).

Next we compared responses between healthy subjects and patients. The group of SMID patients was heterogeneous in terms of deficits and degree of damage, so we analyzed responses individually. Figure 3a shows the theta power of SMID patients for the time period between 0 and 800 ms. Three patients (S1, S4, and S6) showed higher theta ERSPs in the SON condition than in the words condition. The other three patients (S2, S3, and S5) showed decreases in theta ERSPs, differing from the results for the control group. The theta response of S3 to the words condition increased, while S2 and S5 showed decreases. In the alpha band, three patients (S3, S4, and S5) showed large decreases of ERSPs in the SON condition (Fig. 3b). The others (S1, S2, and S6) showed different alpha

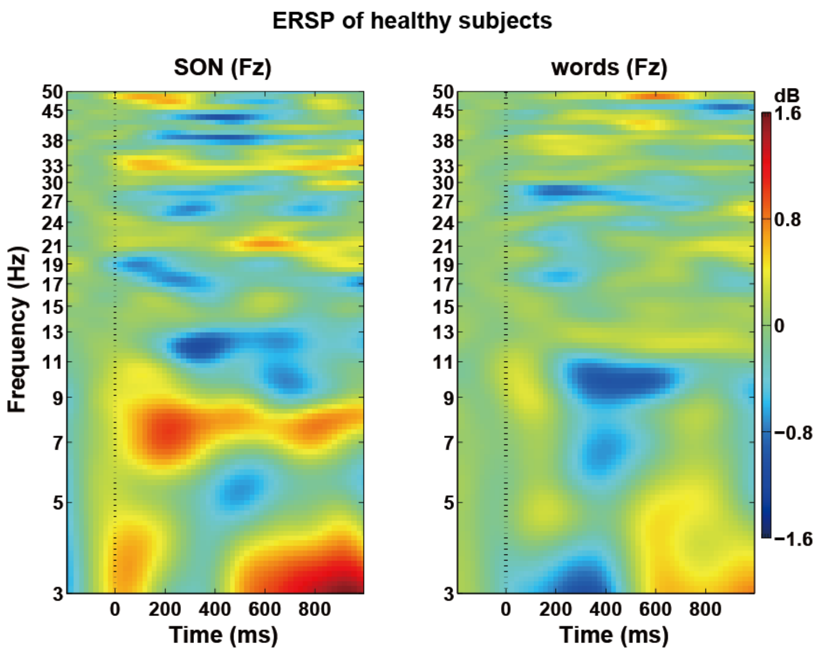


Figure 1. Averaged event-related spectrum perturbation associated with SON (left) and other words (right) across 11 healthy subjects at the Fz electrode. Color bar codes represent ERSP values.

responses in the SON condition, with S1 and S6 showing decreased alpha power and S2 showing an increase. Considering the combination of theta and alpha powers, only patient S4 showed the same pattern as healthy subjects in response to SON, with a theta increase and an alpha decrease. Based on these results, no common pattern was evident in EEG responses of SMID patients.

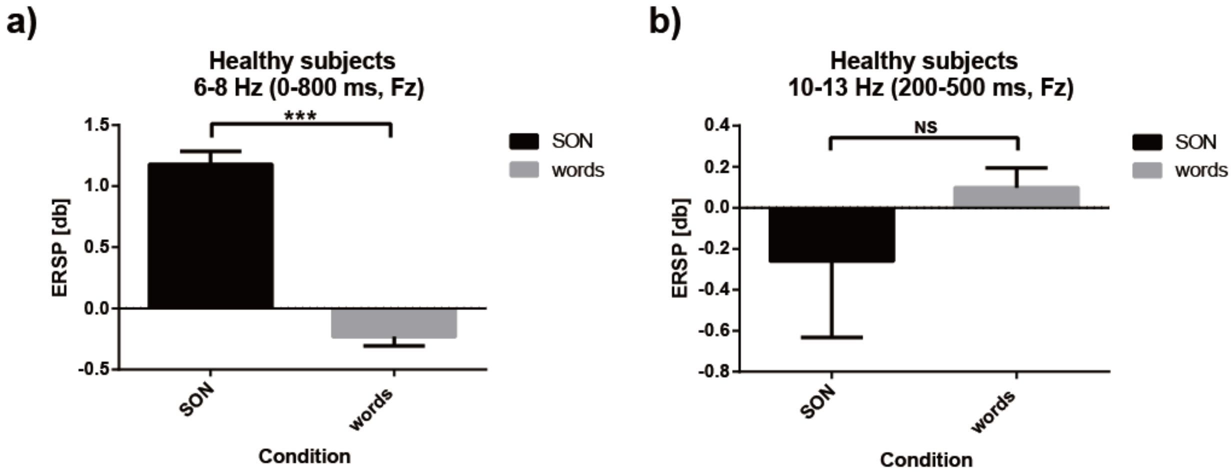


Figure 2. Mean and standard error bars of ERSPs. Channel location was Fz electrode and averaged across the 11 control subjects for (a) high theta (6-8 Hz) at 0-800 ms after stimulus onset and (b) high alpha (10-13 Hz) at 200-400 ms after stimulus onset. ***, $P < 0.001$; *NS*, not significant.

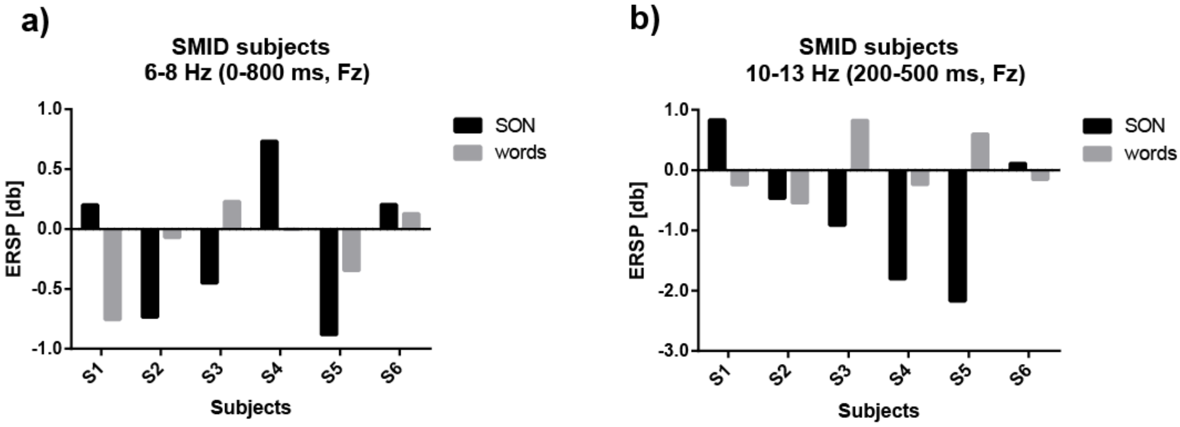


Figure 3. Mean of ERSPs for each SMID patient. Channel location was Fz for (a) high theta (6-8 Hz) at 0-800 ms after stimulus onset and (b) high alpha (10-13 Hz) at 200-400 ms after stimulus onset.

Figure 4 shows the averaged ITC for healthy subjects. Based on visual inspection, theta (4–8 Hz) ITCs occurring immediately after stimulus presentation (0–200 ms) were higher than those at other time points in both conditions. To test these differences, we conducted two-way ANOVA (2 conditions × 5 times) (Fig. 5). This revealed a main effect of condition ($F_{(1,20)} = 5.833$, $P = 0.0254$)

and time ($F_{(4,80)}$ = 13.16, P < 0.0001). Interaction (condition × time) was not significant ($F_{(4,80)}$ = 0.6657, P = 0.6177). Using Sidak's multiple comparison, SON responses at 0–200 ms were significantly higher than before stimulus onset at -200–0 ms (P = 0.0398), while other time points showed no significant difference (P > 0.05). The response to the words condition showed significance at 0–200 ms (P = 0.0002) and 200-400 ms (P = 0.0052) compared to before stimulus onset. Each patient has a unique profile and we cannot conclude that the population of patients with SMID was homogeneous as in the healthy subject group. For this reason, we did not conduct two-way ANOVA for patient data in the same way as for healthy subjects and instead performed individual analyses as below.

We plotted ITC for each patient to reveal individual theta phase-locked response to SON (Fig. 6). Three patients (S1, S2, and S4) showed patterns similar to those of healthy subjects, with higher ITC in the SON condition than in the words condition, especially at 0–200 ms after stimulus onset. S6 showed higher ITC in response to SON after 200 ms, although ITC responses to SON were less than to the words condition at baseline and primary response (0–200 ms). The other two patients showed ITCs that were lower in response to the SON condition than to the words condition, and the peak time point during the words condition was between 200 and 400 ms. To show the statistical difference of phase-locking activity individually, we conducted a multi-sample test for equal median directions for phase data in response to SON in each patient with SMID. We focused on the primary response to SON from stimulus onset to 200 ms because we observed that evoked response to SON at 0–200 ms was significantly higher than before stimulus onset in healthy subjects. Before analysis for patients, we confirmed that comparison between -200 to -120 ms and 120 to 200 ms showed statistically significant results in each healthy subject using the same test ($P < 0.01$), then performed analyses in the same manner for data from each patient. Within-subject analysis for each patient revealed that three patients (S2, S3, and S4) showed significant differences, and one patient (S1) showed a marginally significant difference ($P = 0.054$) (Table 1).

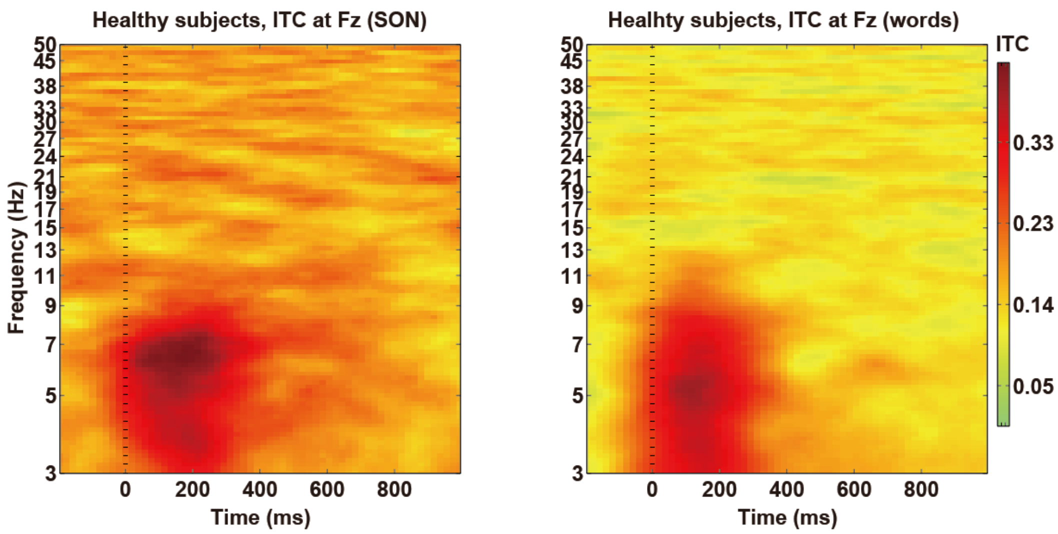


Figure 4. Averaged ITC at the Fz electrode for SON (left) and other words (right) across the 11 control subjects. Color bar codes represent ITC values.

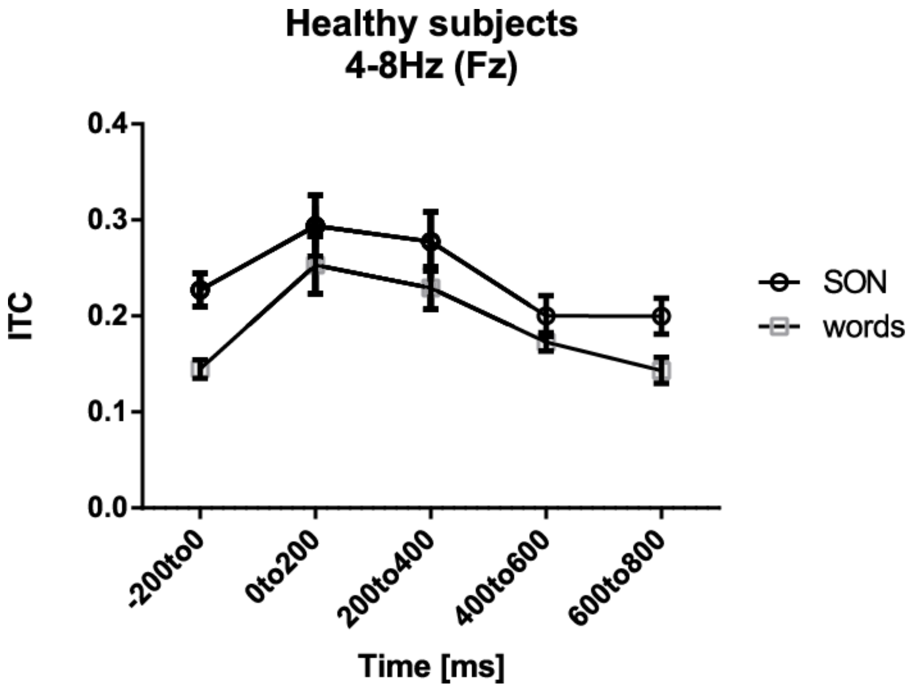


Figure 5. Averaged ITC at the Fz electrode for healthy subjects (mean ± standard error) in response to SON (black circles) and other words (gray squares) for theta (4-8 Hz). Two way ANOVA and post-hoc test were performed for results of healthy subject group. Filled symbols indicate a significant difference compared with before stimulus onset (-200 to 0 ms) within each condition.

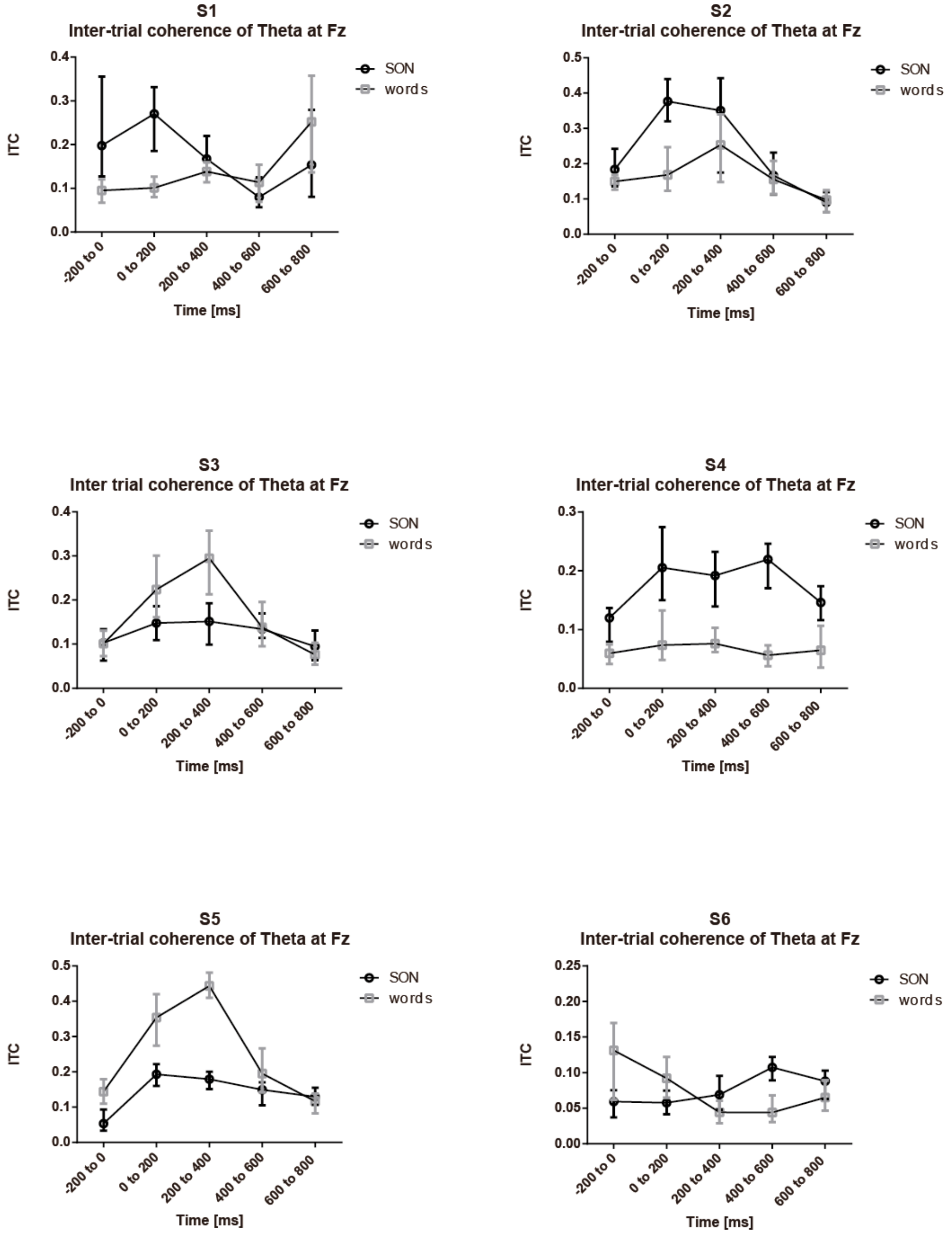


Figure 6. ITC for each patient with SMID. Each plot shows the median of theta (4–8 Hz) ITC within each 200 ms step intervals at the Fz electrode, in response to SON (black circles) and other words (gray squares). Error bars show the interquartile range. Numbers (S1 to S6) correspond to patients in Table 1 of Chapter 3.

Table 1.

Results of within-subject analysis for patients with SMID in response to SON

Subject	Test statistic value	*P*
S1	3.70	0.054
S2	22.3	<0.001
S3	60.5	<0.001
S4	36.5	<0.001
S5	1.90	0.17
S6	3.14	0.076

Each result was calculated using a common median multi-sample test from phase data, comparing before and after stimulus onset. Degrees of freedom (df) = 1 in each case.

4.4. Discussion

In this chapter, we tried to analyze EEG responses to SON of patients with SMID individually. We found that four patients showed higher theta phase-locked in hearing SON, though the average of healthy control subjects showed equally theta phase-locked in both of conditions. It means that SON of patients more activated their theta phase-locked activity than control words, and we suggest that SON evoked stronger response to auditory speech. We discuss the meaning of theta phase-locked responses of normal subjects. Then we compared the differences with patients and normal healthy group.

Theta Power and Phase-locked activity of normal healthy subjects

Results for the control group showed a theta-band ERSP increase in response to SON (Fig. 1). Theta-band ITCs of control subjects were higher in the SON condition than in the words condition (Fig. 5). This result indicates that phase-locked theta activity increased when subjects heard their own names, particularly immediately after stimulus onset. Because ERSP data consist of induced activity and evoked (phase-locked) activity (Catherine Tallon-Baudry & Bertrand, 1999), phase-locked theta activity could be indicated by the ERSP data occurring from 0 to 200 ms after onset (Fig. 1). The increase in theta ERSPs may contain a phase-locking effect.

The theta-band power increase in the SON condition can be explained in terms of the ability of the SON to function as a strong distracter. Studies have reported that phase-locked theta activity increased with sustained attention (Deiber *et al*., 2007; Sauseng, Klimesch, Gruber, & Birbaumer, 2008). Our results suggest that hearing SON results in a specific transition of attention that does not occur in response to other words. Comparing with the results of Experiment 1, we found a significant difference between SON and words (control stimuli). This theta power increase was different from which we observe in Chapter 2. The present theta power was sustained from 0 to 800 ms, while that of Experiment 1 was observed for 200 ms after stimulus onset. This difference of statistical results between the present chapter and Experiment 1 could be explained by the experimental designs. In the present chapter, we instructed the participants to pay attention to visual stimuli, not to auditory ones.

On the other hand, we did not tell the participants what they needed to focus on in the Experiment 1. The present instruction of the experiment might have triggered orientation of attention by hearing their own names (SON), from lower attention level to auditory. In Experiment 1, this kind of orientation attention was not clear because participants paid attention to all of auditory stimuli equally.

As a control data for patients, ITC responses of normal healthy subjects showed similar results in both of condition, SON and words. Both conditions showed theta phase-locking and it indicates that the similarity was mainly reflected to theta range. This result was consistent with the result from Experiment 2. The discriminant analysis of healthy subject data did not show the significance with theta ranges between conditions. ITC results of healthy subjects did not show the main effect in condition. It suggests that theta phase-locking occurred whenever they heard something speech stimuli in healthy subjects.

The meaning of phase-locking can be estimated from the latency and common appearance in both of condition. The latency of theta phase-locking was shown at early phase (0–200 ms). Main effect of time was also shown at this latency in each condition. It seems to be a primary response to auditory stimulus. Considering the result of Experiment 1 compared with N1 from ERP, the early theta phase-locking probably to be relevant with auditory cortex responses. The theta ITC increase has been observed with N1 component in auditory stimulus at frontal site (McMullan, Hambrook, & Tata, 2013). Many reports have suggested that theta phase-locking was occurred with the activation of by speech auditory stimulus (Howard & Poeppel, 2010, 2012; Luo & Poeppel, 2007). From these reports, we suggest that the responses from auditory cortex to speech stimuli affected to theta phase-locking. The other fMRI study, which have reported theta and BOLD activity have found as auditory cortex response, supports our results (Steinmann & Gutschalk, 2012). Furthermore, several studies about lexical semantic processing have shown the relationship with theta power (Bastiaansen, Linden, Keurs, Dijkstra, & Hagoort, 2005; Bastiaansen, Oostenveld, Jensen, & Hagoort, 2008; Hald, Bastiaansen, & Hagoort, 2006). In auditory lexical study, Shahin *et al*. have shown early evoked theta with lexical memory matching in auditory (Shahin *et al.*, 2009). The present theta-phase locked activity would be related with lexical semantic processing, not only just a responses to hearing voice speech stimuli.

Comparison between SMID patients and controls

We analyzed the EEG responses of patients with SMID individually. Firstly we investigated their responses by ERSP analysis and compared with healthy group, but we did not find any common features among patients (Fig. 3). For example, for three patients, changes in theta powers were similar to healthy subjects (i.e. showing an increase), but different patterns were shown in other three patients. We had expected that individual differences in patients to be marked because of their various clinical profiles.

Then we analyzed each patient's ITC response individually and compared the pattern with that of averaged healthy subjects. We were able to identify two specific patterns in patient theta-band changes using ITC analysis (Fig. 6). One pattern (four patients) showed higher ITC in response to SON, while the other pattern (two patients) showed higher ITC in response to words. Using ITC analysis, we showed that four patients had phase-locked theta activity after hearing SON (Fig. 6).

Three subjects (S1, S2 and S4) showed higher ITCs in response to SON, although changes in ITCs in the words condition were small. Thus we focused on the response to SON of patients. While ITC peak values differed, ITC peak latencies were almost the same as those for the healthy control group (0–200 ms; Figs. 5 and 6). These results suggest that phase-locked theta activity to SON was shown at the same latency as in healthy subjects.

We can estimate the auditory speech response to SON of each patient with SMID from theta ITC. The results suggest that these patients with SMID showed auditory cortex activity to SON as speech stimulus, in the context of theta phase-locking reflecting. Considering the reason why only SON activated the theta phase-locking, lexical semantic processing could be related, as we discussed above. In this line, some patients with SMID could understand their own name as something semantic. This hypothesis suggests that they can detect their own name because it was the most frequent auditory speech stimulus, though we cannot determine whether they know that as their "Own" names. Interestingly, these patients (S1, S2 and S4) have same cause of SMID, that was, CH. Though these three patients were bedridden states and have severe physical disabilities, we suggest that CH patients have better function of auditory speech perception and seem to have lexical semantic processing ability for hearing SON. Their age of insults were later than PVL patients and CH patients might have opportunity to learn their own names.

Finally, we need to focus on the two patients (S3 and S5) who showed ITC patterns opposite to those of the controls; namely, a theta decrease in response to SON (Figs. 5 and 6). One important difference between these patients and the others was the peak latencies of the responses. Peak ITCs in the words condition appeared 200–400 ms after the peak latencies of the other patients (0–200 ms). The mean duration of stimuli was 550.25 ms, indicating that the evoked theta activity in these two patients was elicited almost at the end of the stimulus. Phase-locked theta activity for these patients might not have represented the same components evident in other patients (evoked at 0–200 ms) in response to SON. One hypothesis to explain the difference is that rather than paying attention to familiar words (SON), these patients instead paid attention to unfamiliar words. Interestingly, these two patients had better motor function than the other patients and could move independently using their wheelchairs (see Chapter 3, Table 1). Some studies have reported that motor function is related to language processing (Bak & Hodges, 2004; Laureys, Perrin, & Brédart, 2007), and language processing in these patients may have developed differently than in the other patients. Considering that, there is a possibility that these two patients were strongly interested in unfamiliar word stimuli and showed different responses because of their unique development of language processing caused by differences in motor function compared with other patients. However, further investigation is needed to confirm this hypothesis.

Chapter 5. General conclusion

In the present thesis, we investigated the EEG responses to hearing SON of patients with SMID, aimed to evaluate their remained cognitive functions. The validity of experimental design is critical to show the reliability of such assessments for patients. Based on this idea, we focused on repetition influences of control stimulus and examined how the repetition affects the differences of EEG responses from that of SON. From the present results of ERP and beta ERD/ERS, we concluded that repetition of control stimulus did not decrease the differences of observed neuronal responses between SON and control. Then, we made a new experiment for patients with SMID and investigated their EEG responses to hearing SON. Comparing normal subject group and patient groups in response to SON, we did not find any significant differences in alpha relative power, though there was statistical difference in beta power. The individual analysis for patients showed that some patients indicated higher theta phase-locking in SON, while normal subject group showed theta phase-locking in all of speech stimuli. In this chapter, we discuss these results and comparisons, and the suggestion of remained brain function for the patients with SMID.

5.1. Repetition Effects and Experimental Design and ERP of healthy subjects

To make and show the reliability of the experimental design including SON, the most interested issue was how stimulus repetition influences to the response to hearing SON and other unknowns. As results, repetition of control stimulus did not affected to differences of ERP responses between that of SON and control. LPC component was observed in SON from 0.4 sec to 0.6 sec after stimulus onset at parietal sites. On the other hand, sUN (single-presented unknown name) evoked negative component, N400 and rUN (repeated unknown name) showed neutral potential at the same latency. From the comparison with SON and rUN, we confirmed that the ERP showed significant difference between SON and rUN conditions because of long-term memory retrieval. In oscillation power, we found differences in beta power between SON and rUN, and we conclude that there were also few repetition effects. We regarded these result as verifications of the reliability for the experimental sequence, which included repeated other speech stimuli, even though rUN showed significant differences with sUN and this result were indicative of repetition could differentiate the ERP components from a single-presented condition. In comparison with sUN and rUN, the repletion influenced the differences of ERP components. For SON investigations, its responses were too much larger and such repetition did not influenced.

5.2. Oscillation changes by SON in healthy Subjects

Relative oscillation changes of healthy subjects by SON showed several patterns: beta power suppression, alpha power suppression. Theta power increase was shown in all of speech stimuli in healthy subject group. These oscillation changes were observed in all of our experiments commonly. We summarized these relative oscillation changes in the present section.

Beta ERD in response to SON was significant larger from UNs, as results of Experiment 1. Beta ERD had relevance with the self-referential or familiarity recognition function and this result suggested that hearing SON activated self-referential recognition. In the response to hearing unknown names, sUN showed significant beta ERS, and rUN showed an inhibition of beta ERS. Nonetheless, rUN beta response remained significantly different from the beta ERD to SON. This kind of beta suppression by hearing SON was consistent with the results from Experiment 2. In Experiment 2, beta power suppression was found, other speech words stimuli evoked larger beta power, as results from discriminant analysis. The results from Experiment 2 supported the consistency of beta suppression in hearing SON and the relationship with self-referential function activated by SON.

Alpha suppression in SON was also observed in both of investigations with healthy subjects: Experiment 1 and 2. Though Experiment 1 did not show statistically differences, it was found in Experiment 2 in healthy subjects, comparing with SON and words conditions. Alpha ERD was known as the reflection to memory function, and in this case, we can consider the effects from long-term memory function. It indicates that long-term memory retrieval occurred by hearing SON. Recent investigations have reported that ERD in alpha and beta frequency range suggested the long-term memory retrieval (Waldhauser *et al*., 2012). This combination with beta ERD supported that alpha ERD was induced by SON, while it was not statistically significance in Experiment 1.

Theta synchronizations of healthy subjects were observed in speech stimuli commonly over our Experiments, 1 and 3. We did not get any parameters including theta band by discriminant analysis, and it suggested that there was no significant differences at theta power between SON and other words. The relationship with theta synchronization and ERP component, N1 can explain this phenomenon. In the present results, theta ERS was evoked at the near latency with N1 component. Other study has suggested the event-related phase resetting, which is related with ERP (Makeig *et al.*, 2002). N1 is reflected the activity in auditory cortex, and it means that observed theta synchronization indicated the activation for auditory cortex by all of speech stimuli. Furthermore, recent studies have shown that theta synchronization was evoked by speech auditory stimuli in auditory cortex. In this line, the common theta synchronizations were reflected the activity of auditory cortex in response to hearing speech stimuli. This explanation is consistent, considering with theta phase-locking was shown in SON and words stimuli.

5.3. Comparison with patients with SMID and healthy control subjects

For evaluations of residual brain function of patients with SMID, we tried to find similarity and dissimilarity of EEG response with those of healthy subjects. In the comparison with response to SON of patients with SMID and healthy subjects, alpha suppression in SON and theta phase-locking to SON were also observed in patients with SMID, not only healthy subjects. On the other hand, beta inhibition was not found in patients, rather than too much high beta evoked powers. These comparisons between patients and normal subjects are suggestive keys for residual brain functions of patients.

Auditory speech perception is basic and important function when we examine the response of patients to hearing SON. ITC of theta bands are reflected this auditory perception and it showed different patterns in patients with SMID individually. There are many reports about the theta phase-locking in response to hearing speech stimuli, and these reports also argued the relationship with theta phase-locking and auditory cortex activation. Based on these reports and considerations, the present results lead a suggestion: the auditory cortex automatic response to hearing SON as speech stimulus, of patients with SMID. Theta phase-locking for patients with SMID was indicated by ITC analysis in SON, while it was not shown in other speech stimuli, words condition. Even though without ERP analysis could not be performed because of much noise from patients, the theta phase-locking from ITC analysis is enough to show their response to speech stimuli. Several patients showed higher theta ITC in SON than other speech words and this result was indicative of higher auditory speech response was occurred by hearing their own names.

One of the most interested problems about the responses of patients, is whether they can determine their own names or not. As we discussed in results of healthy subjects, alpha inhibition was related with long-term memory. Alpha band response of patients with SMID was not statistically different from that of healthy subjects. This result indicated that their alpha band responses were similar with that of healthy subjects and was suggestive of their long-term memory retrieval by hearing SON. Our results supported the idea that patients with SMID could determine the patterns of syllables of their own names, and it suggested that their memory function is remained, probably.

In contrast, beta evoked activity was much more synchronized than that of healthy subjects in SON and these were statistical different. If beta activities reflected self-referential function as we discussed in beta ERD of healthy subjects, the present results suggested that self-recognition functions of patients with SMID were not developed as the same levels as healthy adult subjects. Self-recognition is higher level of consciousness and self-awareness. In this case, it is consisted if patients with SMID had a lower conscious and self-awareness levels than that of healthy subjects.

In the present study, we could evaluate some kind of residual function of patients with SMID; auditory cortex response, long-term memory and self-recognition function by presenting their own name. These results can be utilized to improve their rehabilitation and education. For example, we found that they remained long-term memory retrieval function in auditory. It raised a possibility that they could learn language from auditory aspects, even though they have been believed they cannot. The present thesis is the first step to assess their residual function and changes the environments for them who have multiple disorders.

5.4. Future Study

Investigate Familiarity and Self-related separately

Self (equal to oneself) and *familiar* (knowing or closed very much but not own) is considered as different, but we did not discriminate in the present thesis. Familiarity includes closed-others and famous but not self. There are no reports which revealed the difference by EEG analysis to our knowledge, though several fMRI studies have attempted. In this thesis we focused on EEG responses to their own name and compared with unknown names or other speech stimuli. It means that the results showed the contrast with *self* and *others,* but not *self* and *Familiar.* If we can detect the response to *self* and *familiar* separately, we can evaluate the residual function and development of patients with SMID in more detail. There are several reports about the response to self-related and familiarity. In fMRI investigation, it has shown that different brain regions were associated with each condition, familiar and self (Tacikowski *et al.*, 2014). In ERP paradigm of visual presentation for their own names by letters, self and familiar names were presented (Qin *et al*., 2012). However, the ERP components did not show different pattern in self and closed-other names (Qin *et al.*, 2012) in normal subjects.

The next interesting point is, whether patients with SMID understand the different between "Familiar and Unknowns" or, "Closed/Self or others (unrelated, general)". We did not find any clues to show patients with SMID recognized SON as "their OWN names". If we can determine that they can tell the difference of familiar/unfamiliar, the evaluation would be more precise. Furthermore, this kind of investigation will be supportive to reveal the brain response of normal subjects for basic neural science.

The necessity to more investigations of patients with SMID

Patients with SMID have varied physical and intellectual levels depend on each other. This makes the taxonomy of such patients difficult and that is why there are many classification terms to express people who have multiple disabilities (Nakken & Vlaskamp, 2007). As we discussed in the section of Experiment 3, it is necessary to evaluate them depend on their status and diagnosis. We showed some individual data of patients with SMID in this thesis. This is the step for individual evaluation of residual function quantitatively from brain response data. However, it is not enough to adapt the measurement methods for all of such patients.

To improve their evaluation by EEG response data, we need to gather more data from various types patients from SMID group. Much data enables us to find some patterns to classify them depend on the levels of development or function. For the sake of more data collection, it is necessary to overcome the noise from involuntary movements. Many of patients show involuntary movement and it makes their EEG noisy. In our experiments, we measured them who have less involuntary movement. The involuntary movements might occur when patients feel something irregular and stress. EEG measurement to assess them was included what let them feel stress. To collect much more data, supports from hospitals, families and caregivers will be essential.

For several patients who seem to have higher function than the average of patients with SMID, the more appropriate experimental task can be provided. In the population of patients, there are some kinds of levels depending on their language skills, though most of patients have lower ability than normal subjects. Now the present results provided some probabilities that they remained long-term memory function. Further studies will need to assess how and which kind of auditory speech stimulus they memorize. The results would be different by their levels of language skills, especially semantic cognitive function.

The present thesis could not show emotional effect by hearing their own names, though hearing their own name should be related the process of emotion. Nevertheless the process is not revealed well even in normal subjects, the emotional process and response is the most interested point to understand such patients with SMID. To show this issue, much more studies are needed about normal subjects by simple and reproducible method. This investigation will contribute to understand patients with SMID more, and support to communicate with them.

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