修士論文

Induction of speech fluency by using transcranial direct current electrical stimulation and delayed auditory feedback

経頭蓋直流電気刺激と遅延聴覚フィードバックを用いた

発話流暢性の導出

指導教員　橋本 龍一郎 准教授

首都大学東京人文科学研究科 人間科学専攻

言語科学教室　博士前期課程

矢田 康人

首都大学東京人文科学研究科
言語科学教室 博士前期課程
15864101　矢田 康人

Abstract

Stuttering is a speech fluency disorder characterized by word or part-word repetition, prolongation, and silent blocks. Past brain imaging studies have reported functional anomalies in speech-related regions such as overactivity of the right inferior frontal gyrus (IFG) and low activity of the bilateral superior temporal gyrus (STG) and structural abnormalities in these regions in people with stuttering (PWS). Moreover, it is also known that stuttering may be improved by delayed auditory feedback (DAF), suggesting that PWS may have abnormality in the auditory feedback function. However, the detailed mechanism of the occurrence of stuttering is still unknown, and imaging studies alone are unable to show the causal relationship between the occurrence of stuttering and the functional abnormality of speech-related regions. In addition, it is known that the improvement of stuttering due to changes in altered auditory feedback is greatly different among PWS. Based on previous literature on stuttering, in this study, we hypothesized that the cause of the stuttering is in the speech-related motor area and that abnormal function of the auditory cortex including auditory feedback is a secondary factor that exacerbates stuttering. We conducted a behavioral experiment to read aloud under the influence of transcranial direct current stimulation (tDCS) and DAF.

First, in Experiment 1, in order to investigate the causal relationship between speech-related area activity and speech disfluency of PWS, the bilateral IFG and STG were stimulated with tDCS, and reading-aloud task was carried out under the condition that the activity of these brain regions were changed. When the bilateral IFG and left STG were stimulated, a significant change in stuttering frequency was observed as compared with the non-stimulated (sham stimulation) condition. In particular, the degree of this change was the largest when we stimulated the right IFG. The stuttering frequency increased with anodic stimulation, and on the contrary, it decreased with cathodic stimulation. Moreover, only under conditions of the right IFG stimulations, a significant positive correlation was observed between the change of stuttering frequency and the severity of stuttering. These results demonstrated that the activity of the right IFG greatly affects speech disfluency of stuttering.

Next, in Experiment 2, in order to investigate the influence of auditory feedback on the speech disfluency of PWS, the reading-aloud task was performed under the condition that the auditory feedback was changed by the DAF. In this experiment, there was a

significant negative correlation between the exacerbation of speech disfluency by DAF and severity of stuttering. Moreover, in PWS whose level of speech disfluency in the reading-aloud task was in the normal range, the DAF rather increased speech disfluency. Regarding the speech speed, all stutterers showed a decrease in speech rate under the DAF conditions. These findings suggested that the influence of altered auditory feedback on the speech disfluency of PWS is related to the severity of stuttering, and that improvement of stuttering by DAF is not caused only by a decrease in speech rate. Based on the above results and reviewing previous literature, I propose that, in stuttering, the speech error occurs because there is abnormality in the motion prediction signal due to the altered activity of the speech-related regions. Furthermore, as a compensation for the abnormal prediction signal, the speech motor control system becomes heavily dependent on the auditory feedback in PWS. I further propose that there is a possibility that stuttering is caused mainly by activity abnormality in the speech-related motor area including the right IFG and that, as secondary factors, abnormalities in the auditory cortex and those of the auditory feedback make the stuttering more severe.

Contents

Chapter 1 Introduction

1.1 What is Stuttering

Stuttering is a fluency disorder of speech which prevents production of fluent utterance (Van Riper, 1982). As its core symptoms, the repetition of the beginning phonetic sound , prolongation , and block are defined. Secondary behaviors such as avoidance behaviors and escape behaviors developed from these speech symptoms are also included as symptoms of stuttering. Secondary behaviors are caused by fear of stuttering occurring and predictable anxiety, and they include clenching, paraphrasing, replacement, insertion of words, concomitant movement at utterance, and cancellation of utterance may also arise (Guitar, 2006). The percentage of people with stuttering (PWS) in the total population (prevalence) is said to be about 1% (Andrews et al., 1982), and 60% of them occur by 3 years and 95% by 4 years (Andrews et al., 1983) . The incidence rate is as high as about 5%, out of which 50 to 80% are supposed to be normalized spontaneously (Yairi & Ambrose., 1999; 2013). Although there is not much difference in prevalance incidence among males and females (Mansson, 2000), females have a higher percentage of normalization without intervention (Yairi & Ambrose, 2013), and the proportion of men increases as age increases. It is said that the ratio of adults to stuttering men and women is 3 or 5: 1 (Guitar, 2006). A type of stuttering that develops in early childhood is called developmental stuttering and accounts for about 90% of the total stuttering. The remaining 10% is called acquired stuttering, in which those who are caused by neurological diseases and brain damage are called neurogenic stuttering, and those caused by mental stress are called psychogenic stuttering. Acquired stuttering

has characteristics that are different from developmental stuttering (Guitar, 2006). Since stuttering generally refers to developmental stuttering, stuttering is treated as developmental stuttering in this study as well.

Although genetic factors and environmental factors are considered as causes of developmental stuttering (Andrews et al., 1991), it is explained not by a single factor but by multiple factors such as genetic and environmental factors interacting with each other (Kidd, 1984). Researches on causes of stuttering has been accumulating for about 100 years from the 1900's to the present day, but it has not been sufficiently elucidated at this stage.

Denes & Pinson described the communication process of verbal expression as a "speech chain" (Denes & Pinson, 1993), and showed that words are transformed into speech sounds through linguistic, physiological and acoustic levels (Figure 1.1). In this concept, stuttering is considered to be a problem at the physiological level of this hierarchy. In other words, while there may be few linguistic and acoustic impairments seen in aphasia and dysarthria, physiological changes related to speech control such as motor commands from the brain to vocal organs and motor processing in utterance play major roles. In speech control, not only feedforward motor control but also feedback control which processes sensory information of his/her own voice via auditory/somatosensory feedback is important, and it is suggested that any problems with the feedback mechanism of motor control adversely affect stuttering (Max et al., 2004). The idea that stuttering is caused by auditory feedback processing is also supported by epidemiological findings that deaf people have a low incidence of stuttering (Bloodstein

& Ratner, 2008; Montgomery & Fitch, 1988). According to Montgomery & Fitch 's report, it is reported that the prevalence in stuttering in children who do not hear early in school age is 0.12%, it is also quite low compared with 5% incidence of stuttering and 1% prevalence rate. Therefore, there is a possibility that there may be some problems in the auditory function and feedback processing of PWS. In this research, we examine the effect of speech- motor-control and auditory feedback for the fluency of utterance and the mechanism of stuttering.

1.2 Functional and structural features of the stutters brain

The development of brain functional imaging such as Positron Emission Tomography (PET), functional Magnetic Resonanse Imaging (fMRI) with high spatial resolution, and magnetoencephalography (MEG) with high temporal resolution have revealed brain activity at the time of utterance and structural specificity in stuttering persons. Using these methods, characteristic hypotheses such as the immature theory of left hemisphere superiority, the hearing monitor disorder theory of self utterance, and the hyperactivity theory of the right hemisphere had been examined in the past. But unlike conventional imaging studies of the present day, the sample size was small and because the conditions of the targeted PWSs were heterogeneous, a unified view has not been obtained. In recent years, however, meta analysis research using the technique called activation likelihood estimation (ALE) was conducted on the brain functions of PWS, and as a result, the following three findings in particular were deemed as high reproducible: (1) over-activity of motor-related areas including primary motor cortex, supplementary

motor cortex, cingulate gyrus, and cerebellar vermis (Vermis III), (2) under-activity of bilateral auditory cortex, (3) right hemisphere dominant activity of Rolandic operculum and the insula. In addition, structural alterations of PWS's brain have been reported due to the progress of computational anatomy in recent years. In particular, many studies report increased cortical white matter volume and gray matter volume reduction, and structural abnormalities of nerve fibers that connect between speech related areas.

In this section, we overview the functional features such as hyper-activation of the motor-related regions and the hypo-activity of the auditory cortex and the structural abnormality of the cortex and the nerve fiber, all of which were replicated in many previous studies(Figure 1.2).

1.2.1 Functional features

One of the most replicable findings concerning the brain function of a stuttering person is that the activity level of the right hemisphere is enhanced when stuttering occurs. It is noteworthy that the level of activity in regions of the right hemisphere homologous to the motor speech areas (Fox et al, 1996; Fox et al, 2000; Braun et al, 1997; De Nil et al 2000). One of these areas is called the right inferior frontal cortex (Fox, 2003). The inferior frontal gyrus area is considered to be an area for planning the phoneme structure during utterance (Kent, 1997). In addition, activities in the right insula increase during stuttering (Fox, 2003). In the left hemisphere, the insula is thought to function as a connecting node between the Wernicke's area and Broca's area, which is considered to play an important role in monitoring of the word's phonological representation and

speaker’s own utterance (Ingham Et al., 2003).

There are mainly two interpretations about excessive activity of the right cerebral hemisphere at the time of stuttering. One hypothesis is that the primary utterance / language region is formed in the right cerebral hemisphere during the prenatal period (Geshwind & Galaburda, 1985). Since the organization of the right cerebral hemisphere is not generally suitable for rapid processing of signals required for speech, stuttering may appear as the loads of language processing increase at the stages of language development (Kent, 1984). The second hypothesis is that a child with stuttering first tries to recruit the region of the left cerebral hemisphere for utterance, but the neural network for speech does not function properly due to some factors. In such cases, it is thought that the child's brain begins to utilize the right cerebral hemisphere in compensation to obtain a fluent utterance. The similar problems are observed in a person with aphasia in which patients utilize the right cerebral hemisphere to compensate for the function of the injured site of the left hemisphere (Sommer et al., 2002; Weiller et al., 1995).

For the second hypothesis, there are several supporting evidence. Braun and colleagues showed a negative correlation between activity in the sensory region of the right cerebral hemisphere and stuttering (Braun et al, 1997). In other words, the more dysfluent the utterance, the more active activity of this area. Furthermore, Neumann and colleagues revealed that subjects with moderate stuttering showed larger activation in the right cerebral hemisphere than subjects with severe stuttering. This suggests that the activity of the right cerebral hemisphere compensates for the dysfunction of the left cerebral hemisphere. In other words, moderate PWS may activate the right cerebral

hemisphere in compensation to alleviate the symptoms of stuttering.

Both hypotheses may be correct. That is, some people may develop processing capabilities of language into the right cerebral hemisphere before the development of stuttering, whereas the other people may develop processing capabilities in the right cerebral hemisphere as a compensatory response only after the onset of stuttering. Furthermore, there is a possibility that some people will simultaneously process speech and language on both hemispheres. Regardless of these possibilities, it is likely that its efficiency is worse than normal process and that stuttering may occur as compensation to inefficient process of speech and language processing.

While many studies have shown that over-activity of the right cerebral hemisphere in PWS, lack of activity of the left superior temporal lobe where the auditory cortex and the Wernicke field are located has also been reported (Fox et al., 1996; Fox et al., 2000; Braun et al., 1997; De Nil et al., 2003). This finding suggests that stuttering may not use auditory feedback to monitor and control utterances during stuttering. Furthermore, based on a number of studies including the one showing that fluency of speech was induced by changing the way the PWS listen to their own utterances, and the one showing that PWS have difficulty in carrying out the listening tasks (Barasch et al., 2000; Molt, 1997), the possibility that the auditory processing is not functioning normally during the stuttering is likely.

In addition, the Wernicke's area is considered to be an important area for storing phonological representations of words (Caplan, 1987; Paulesu et al., 1993). Therefore, the activity in this area plays an important role in phonological planning of utterance. If

this activity is lacking during stuttering, it is possible that a series of functional impairments such as phonetic selection, voice planning, and exercise execution may ensue.

1.2.2 Structural features

The brains of PWS may have different characteristics not only functionally but also structurally from those of people who do not stutter (PWNS). Foundas et al. examined the morphology of the surrounding sites of Broca's and Wernicke's areas of adult stutterers with structural MRI (Foundas et al., 2001). The study has shown that the volume of the planum temporale (PT) that is considered to be involved in higher-order auditory processing is larger in the left cerebral hemisphere than in the right cerebral hemisphere PWNS and that the volume of the PT in the stuttering person is either bilaterally symmetric or right hemisphere dominant. In addition, atypical structural patterns were also observed with high frequency, including the abnormal sulcal-gyral patterns around the sylvian fissure. Furthermore, in a study conducted by the same group (Foundas et al., 2004), it was shown that PWS with an asymmetry of PT structure in the right cerebral hemisphere is more severe in stuttering and the effect of induced fluency by delayed auditory feedback is greater than PWNS.

In addition, Beal et al. examined the developmental change of the cortical thickness of the left Broca's area using the MRI images of 116 males including 55 stuttering persons from 6 to 48 years old (Beal et al, 2013). In this study, from the childhood to adulthood, the cortical thickness decreased with the development of white matter, but PWS showed

a sharp decrease in the lower left frontal opercular part than PWNS. On the other hand, developmental changes in other regions of interest were not significantly different between PWS and PWNS.

Furthermore, unlike the conventional method that analyzed only a part of the brain regions predetermined based on the hypothesis, in recent years, an analytical method to automatically investigate the morphological abnormality of the brain, covering the whole area of the brain using high resolution structure MRI images including Voxel-Based Morphometry (VBM) has been applied to various mental diseases and neurological disorders (Ashburner & Friston, 2000). Janke et al carried out a study using VBM for adult stutterers and reported increase in white matter volume in the right hemisphere around the site corresponding to the face and oral cavity in the superior temporal gyrus, inferior frontal gyrus, and precentral gyrus (Jancke et al, 2004). In addition, asymmetry of the temporal lobe volume was also observed, similar to the result of Foundas et al. 's region of interest (ROI) study (Foundas et al., 2001).

Diffusion Tensor Imaging (DTI) is a method for analyzing the micro-structure of white matter in the brain. This is a technique for quantifying the degree of freedom of the diffusion direction of water molecules in a living body. With this technique, white matter microstructure such as axon and myelin sheath can be evaluated. The stuttering study using DTI was performed for the first time by Sommer et al. in 2002 (Sommer et al., 2002). In this study, anomalies in the white matter microstructure of PWS were highly localized to the motor cortex and somatosensory field of the left cerebral hemisphere. In addition, a significant decrease in FA value, which is an indicator of

white matter integrity, was observed in the Rolandic operculum of the left hemisphere.

In addition, in the study by Cai et al. (Cai et al., 2014), analysis of the brain connection pattern was performed with a specific focus on the speech production system in the brain. The study showed that, as compared with PWNS, the coupling of activities in the speech production network of the stuttering person was overall reduced. In addition, as a result of comparing the FA value for each voxel, a significant decrease in FA value was observed in the major white matter tracts such as the superior longitudinal fasciculous and the cingulate bundle of the right cerebral hemisphere. Furthermore, DTI research for children has been reported. Chang et al. analyzed DTI data of children aged 3 to 10 years and compared the FA values between the stuttering group and the non-stuttering group (Chang & Angstadt, 2015). As a result, significant decrease in FA value was observed in white matter tracts connecting auditory and motor areas, corpus callosum, cortex and subcortical connections.

1.3 The auditory feedback processing

1.3.1 Speech fluency and auditory feedback processing

Two types of motor control are involved in speech production: feedback control using sensory information resulting from execution of motor command and feedforward control (Kawato et al., 1987). In feedback control, speech motion is monitored. In addition to the afferent feedback information coming as an auditory sensation, it is necessary to internally predict the feedback signal and calculate the error of feedback and prediction. In our brain, we have a system called forward model that can calculate the

returning sensation signals as a result of motor command (Wolpert & Kawato, 1998). Such prediction signal is compared with the actual sensory feedback. In the feedback error learning schema, by refining the internal model (inverse model) of motion using the error signal, the system adjusts so that the motor command can be corrected and appropriate motion commands are generated. Therefore, the sensory feedback information in the learning period of motor learning is important in order to be able to generate a correct feedforward motion command.

The correction of speech utterance through feedback can be explained separately in the speech acquisition phase (infant period) and its later phase. In the speech acquisition phase, we learn the correspondence between the speech motion and the auditory feedback that comes back as a result of speech motion by performing random articulation movement called babbling to acquire correct speech motion. Even after learning speech, by changing articulatory organs or auditory feedback, modification and correction of speech motion, including Lombard effect (the intensity of the voice rises under noise) (Lombard, 1911), pitch shift (the pitch of voice changes in the opposite direction to voice perturbation) (Hain et al., 2000), perturbation (when the movement of the articulatory organs is restricted, the speaker gradually pronounces the correct sound) (Guenther 1994), may occur. More specifically, when an error between the internal prediction signal and the actual auditory feedback occurs, it is considered that correction of the motion command has been realized by sending the error signal as the error to the brain region of the motor system (Guenther 1994; Hickok et al., 2011).

However, since feedback control is real-time motion correction using information

obtained by sensory feedback, signal transmission involves noise and delay. In addition, it is known that the feedforward controller is utilized through feedback error learning in motor control in general. Therefore, the motor speech system also is able to control quickly and accurately without depending on feedback. It is difficult to achieve quick control by feedback system, so it is considered that the control of speech motion is mainly performed by automated motion control of feedforward system. Therefore, it is considered that feedback control is hardly used in speech motion except when the auditory feedback is altered to a large extent (Lombard effect, pitch shift, perturbation) due to some factors such that the error from prediction is noticeable and it is necessary to correct the motion. So, in the utterance after learning the speech, the forward control is heavily weighted, whereas the feedback control is supposed to be supplementary (Civier et al., 2010; Guenther et al., 2006; Kawahara, 2003).

1.3.2 Auditory feedback processing of stuttering person

Previous studies have suggested that PWS have problems with auditory feedback processing. It is known that the fluency of utterances of is improved by changing auditory feedback, for example, delaying their own voice called Delayed Auditory Feedback (DAF). When this method is applied, it has been known for a long time that a PWNS's utterance becomes dysfluent while a stuttering is improved in PWS (Kalinowski et al., 1999; Lee, 1950). The similar phenomenon has also been confirmed by masking own voice by masking noise (MAF: Masking Auditory Feedback) and voice frequency modulation (FAF: Frequency Altered Feedback) (Howell et al., 1987;

Kalinowski et al., 1996; Lincoln et al., 2006).

The mechanism of stuttering has been studied using a computational framework called Directions Into Velocities of Articulators (DIVA) model (Guenther et al., 2006; Civier et al., 2010) (Fig 1.3). In the DIVA model, it is proposed that the speech motion is performed by integrating a feedforward system and a feedback system with appropriate weights between the two systems. According to the study by Guenther et al., it is suggested that stuttering persons have problems with the generation of the motor command of the feedforward system, and that stuttering symptoms will occur in order to execute speech motion with larger weight on auditory feedback. Guenther and colleagues simulated stuttering using DIVA, showed that by increasing the weight on the auditory feedback, repetition and enlargement of the pronunciation of the pronunciation sound actually appears in the model. They suggested that, because articulation control based on auditory feedback is not in time, a speech error occurs, and then the speech motion is reset by the error. It has been suggested that the symptoms of stuttering are caused by performing the speech production again after the reset of speech motion.

To summarize stuttering in the DIVA model, auditory feedback does not function properly for PWS at the time of execution of speech motor command.

1.4 Noninvasive brain stimulation methods

With the development of brain function imaging method in recent years, many findings regarding altered brain activity in persons with stuttering at the time of speech production have been obtained. The functional brain imaging method is a technique to

visualize the activity in the brain in a non-invasive way (Sakakibara, 2009). Among them, fMRI is the most widely used. This is a device that can detect changes in the blood flow of the brain using the change in the magnetic field due to changes in the ratio of oxygenated hemoglobin to deoxygenated hemoglobin. It is known that the blood flow in the brain is changed by the electrical activity of neurons, and the amounts of oxygenated hemoglobin and deoxygenated hemoglobin change according to changes in blood flow (BOLD effect). As the oxygenated hemoglobin increases in the relative ratio, the local magnetic field increases accordingly, so it is possible to detect changes in blood flow by capturing changes in MR signals.

Although functional brain imaging including fMRI can measure brain activity non-invasively, but it also has its own problems. One is that function imaging can only capture the correlation between a function and the activity of a certain region of the brain. Consider when measuring the brain activity at the time of executing the task requiring the function *A* with fMRI. Even if activity is observed in the region α, it does not necessarily mean that the function *A* requires activation of the region α. In addition, according to Sakakibara (2009), fMRI can detect changes in blood flow, but it is a secondary physiological change associated with neuronal activity. He claimed as follows: "In the region where an increase in oxygenated hemoglobin is observed, oxygen consumption will also increase, but it is only an assumption and it is not understood what it is actually." Furthermore, Yokoyama (2010) points out problems with the “subtraction method”, which is the basic data analysis method of functional imaging techniques including fMRI. According to Yokoyama, the subtraction method is based on the

functional localization hypothesis, that is, when it is desired to obtain brain activity related to the cognitive process *A*, we can get the activity data related only to the cognitive process *A* by subtracting brain activity which is obtained when subjects perform tasks that require cognitive process *B* only from brain activity which is obtained when subjects perform tasks that require cognitive processes both *A* and *B*. Regarding this problem, Yokoyama points out that we need to recognize that in results of statistical analysis where the subtraction method was performed, it is often the case that activities in "silent" regions may be active, but activation is subtracted out by the control task. And he also claimed: "We have arbitrarily determined statistical thresholds and have identified only activities that are beyond that threshold, so we should pay attention to regions whose activities are not visible."

Noninvasive brain stimulation method is a technique to complement the problems of these functional brain imaging. Noninvasive brain stimulation method is a method to temporarily change brain function noninvasively by inducing magnetic energy or weak current to the brain. Representative examples include transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS). By using these noninvasive brain stimulation methods to change the activity of a specific part of the brain and see the influence on a certain function, it becomes possible to show the causal relation between a specific brain activity and a certain function.

1.4.1 Transcranial magnetic stimulation (TMS)

TMS is a method of electrically stimulating the brain by inducing eddy currents in part of the brain right under the stimulation coil. Clinical studies using TMS have rapidly increased in their number since the first successful demonstration of inducing contraction of finger muscles by stimulation of the human motor cortex (Barker et al., 1985). Unlike the transcranial electric stimulation method, local electrical stimulation is possible because magnetic energy is used as a medium of electric stimulation, and the spatial resolution of stimulation is considered to be about 5 mm.

Since the electrically stimulated brain region is forcibly activated by external energy, its function is often temporarily blocked. This effect is called “virtual lesion”. Using this virtual lesion method, it may be possible to test the prerequisite condition that is assumed between the brain region of interest and the function. In addition, by providing information complementing the brain function imaging, it may be possible to examine a causal relationship between the brain region and the function. Furthermore, it also brings insight into the timing of the stimulated brain region involved in task execution, because TMS can stimulate at a specific timing during task execution. In this regard, TMS provides information complementing the functional brain imaging such as fMRI, which depends on the cerebral blood flow metabolism signal with a long time constant.

1.4.2 Transcranial direct current electrical stimulation method (tDCS)

Transcranial direct current electrical stimulation method (tDCS) is a method of stimulating the brain by applying very weak DC from on the skull. In humans, effects

on improvement of depression symptoms, rehabilitation of motor disorder, improvement of memory ability, to name a few, are known. According to previous animal studies, tDCS is thought to shift the resting membrane potential in the positive direction by anodic stimulation and hyperpolarization by cathodic stimulation. It is an important feature of tDCS that polarity-specific action can be derived.

Most of the current tDCS protocols use electro current of about 2 mA, and by using electrodes (about 5 x 7 cm) with sufficiently large contact area with the scalp, it is little need to concern about serious adverse events such as skin burn (Fregni et al., 2015).

Although the full physiological mechanism of action of tDCS has not been elucidated yet, the changes in the membrane potentials of the target neurons are shown by stimulation in the animal model. In humans as well, the inhibition of sodium ion channel and calcium ion channel attenuates elevation of cortical excitability induced by to anodal stimulation. So there is a possibility that modulation of the membrane potential of neurons by stimulation may serve as one of the main physiological factors underlying the effect of tDCS (Filmer et al., 2014).

There are many non-invasive brain stimulation methods including the aforementioned TMS, but, among them, tDCS has an advantage of allowing us to manipulate either enhancement or suppression of the activity of a specific brain region depending on the polarity of electric stimulation. It is expected to be used for basic research and therapeutic research of neurological diseases in which brain function is different from normal.

1.5 Purpose of the experiments and outline of the manuscript

1.5.1 Purpose and hypothesis

Based on Section 1.2 and Section 1.3, here we make two hypotheses about the brain mechanism of stuttering. First, the main cause of the occurrence of stuttering may be functional abnormality of the motor-related field (Hypothesis I). Second, the functional anomaly of the auditory area may be a secondary or modulating factor, which exacerbates the non-fluency of speech (Hypothesis II). The reasons behind the hypotheses are as follows: First, hyperactivities of motor related areas such as primary motor cortex and supplementary motor area have been reported in many imaging studies (Belyk et al., 2015), especially in the right hemisphere. In addition, it is considered that problems with speech-motor-control are a factor that causes symptoms of stuttering, because stuttering shows problems of articulation movement such as repetition and block. Since the reduction in the activity of the auditory cortex at the time of stuttering has also been shown in many previous studies, the activity of auditory cortex is considered to have some influence on stuttering. Especially, some PWS improved stuttering by DAF (Kalinowski et al., 1996), while fluent speakers are disturbed in fluent speech (Lee, 1950), and in the DIVA model, by relying more on the auditory feedback, the repetition and prolongation of the head phoneme, which are core stuttering symptoms, have been observed in the model (Civier et al., 2010). Therefore, it is inferred that the speech dysfluency of stuttering and the auditory feedback function are related. However, the effect of DAF is not observed in all PWS. And it is considered that feedback control is hardly used in normal speech production. Therefore, the problem of auditory functions including auditory feedback may be a secondary factor of severe stuttering. And,

though conventional functional imaging studies have shown the correlation between anomalous activities of motor related areas and auditory cortex and stuttering, they have not been able to clarify the causal relation. Therefore, in this study, we examined the hypotheses I and II with the aim of clarifying the causal relation between the activity of motor related areas and auditory cortex and speech fluency.

tDCS can temporarily increase or decrease cortical excitability. By using this method, it is conceivable that we can investigate the causal relation between stuttering and activity in both areas by changing the activity of speech motor related area and auditory cortex and capturing the change of stuttering symptom accompanying it.

However, it is difficult to investigate the relation between the non-fluency of utterance and auditory feedback only by observing the utterance at the time of stimulation. Therefore, in this study, we added a reading aloud experiment under the DAF condition on the same subjects and examined this relation. By conducting two experiments, it is considered that the following two points can be clarified. First of all, we can examine whether abnormalities in activity in motor related areas and auditory cortex are causes of stuttering, or compensatory due to other factors. When fluency of utterance changes with activity in one of the regions-of-interest change due to stimulus, activity abnormality in that area is considered to be a factor causing stuttering. In addition, if speech fluency is not changed when the auditory cortex is stimulated, it can be inferred that the decrease in activity in the auditory cortex may not be the cause of stuttering. Furthermore, by examining the relationship between speech fluency change by DAF and the severity of stuttering during the baseline (i.e., under normal auditory feedback), we can also

investigate whether auditory feedback is a factor that modulates the degree of stuttering.

1.5.2 Outline of the manuscript

My thesis consists of four chapters. In the first chapter, the functional and structural characteristics of the brain of PWS were overviewed. Particularly, we stressed the possibility that there are problems with the processing mechanism of auditory feedback and the motor control related to utterance as the major causes of stuttering. And we suggested the potentials of non-invasive brain stimulation method in addition to conventional functional brain imaging method as promising research tools for studying brain mechanisms underlying stuttering. Based on these previous findings, we conducted two experiments in this study. Chapters 2 and 3 explain two experiments conducted in this research.

In Experiment 1, a behavioral experiment was carried out, in which participants with developmental stuttering read aloud written verbal vignettes while applying tDCS to specific locations in the speech areas. Next, as Experiment 2, we carried out a behavioral experiment in which participants read aloud under the DAF condition. In chapter 4, we discuss how auditory feedback processing and motor control related to utterance contribute to stuttering symptoms based on findings of the two experiments.

Chapter 2. Experiment 1: Examination of changes in speech fluency for stutters by application of tDCS

2.1 Purpose

In the previous functional imaging studies, the following three findings were

particularly repeatedly observed PWS: (i) over-activity of speech motor control areas including motor cortex, supplementary motor cortex, basal ganglia, and cerebellum, (ii) reduction of the auditory area activity, and (iii) lack of functional dominance of the left hemisphere during the production of speech. On the other hand, it is not clear which observation is the cause of stuttering symptoms and which observation is compensatory to the cause of the stuttering. In order to address this question, we conducted an experiment in which changes in speech fluency were examined in PWS by applying tDCS to brain areas that were shown to be involved in speech motor control and auditory feedback processing.

2.2 Method

2.2.1 Participants

15 PWS (average age: 23.4, standard deviation: 2.44 years old, 5 females, 1 left handed) participated in this experiment. They were recruited from self help groups of PWS (Wisuta Kanto, Tokyo). All of the participants had normal audiovisual and vocal ability.

Before the experiment, I gave them explanations of the experiment in verbal and written form, and gained a consent in a written form from every participant. All participants were examined for speech dysfluency symptoms, and stuttering severity was rated by a speech therapist (YY) based on Standardized test for stuttering. The experiment was approved by the Ethics Review Committee of the Graduate School of Humanities and Sciences, Tokyo Metropolitan University.

2.2.2 Issues and experimental equipment

Materials used for the reading aloud task include several famous fairy tales ("Ants and the Grasshopper", "Jack and the Beanstalk" "The Little Prince"). A vignette used in one trial consisted of 100 to 125 clauses. The vignette was presented to a reading board set in front of the participants. During the reading voice of each participant reading aloud was recorded using a microphone (RadioShack Dynamic Microphone) that is connected to a PC (FUJITSU LIFEBOOK SH54/G) implemented with a recording software (Audacity2.1.2, Carnegie Mellon University , USA).

As the stimulator, the DC-STIMULATOR PLUS (Neuro Conn, Germany) was used. The size of the stimulation electrode was 7 cm x 5 cm. Before the experiment, the electrodes were soaked in water mixed with conductive gel. The pair of anode and cathode electrodes was positioned to a stimulation site and contralateral forehead. The stimulus site was one of the 4 speech-related regions: (i) left inferior frontal cortex (Broca's area), (ii) right inferior frontal cortex, (iii) left superior temporal cortex (Wernicke's area), and (iv) right superior temporal cortex. The position was determined based on expansion 10-20 method, the position is 1/3 from F7 and F8 to FC5 and FC6, TP7 and TP8 to C5 and 1/3 position to C6.

The stimulation intensity was set at 2 mA. In active stimulation, DC was applied for 210 seconds starting from 10 seconds before the presentation of the vignette to the completion of the task. In the sham stimulation, weak current was delivered only for 60 seconds starting from 10 seconds before the presentation of the vignette. Both active

stimulation and sham stimulation were set to reach a steady value of 2 mA over 10 seconds. In the sham stimulation condition, the stimulation was continued for 1 mA for 30 seconds, the current value was gradually decreased over 5 seconds, and the stimulation was stopped.

In this study, we used a study mode of DC stimulator plus, and conducted experiments in a double-blind method in which both the experimenter and participant are blind to information of whether the session is active stimulation or sham stimulation. In this mode, the experimenter can switch the active / sham stimulation condition by entering a 5-digit code which represented either active or sham stimulation. Only the supervisor knew which code was the actual stimulation condition or the sham stimulation condition, and he gave the 5-digit numbers to the experimenter before the experiment.

2.2.3 Experimental procedure

Participants sat on a chair and participated in the experiment. For identifying the location of stimulations, we first measured the distance between the inion and the nasion, and then identified and marked the position of the CZ, and measured the head circumference and covered the electrode cap matching the size of the head based on CZ. Thereafter, F7, F8, FC5, FC6, TP7, TP8, C5, C6 were marked based on the extended 10-20 method. Then, we covered the rubber electrode with a sponge soaked in water containing a conductive gel, attached one of the electrodes to the stimulation region and the other to the forehead part of the contralateral hemisphere, fixed the electrode with a rubber band, and put a swimming cap on a subject to further fixate the positions of the

electrodes. Finally, we checked the impedance, and the maximal electrical resistance ensured for safety was set to 40 kΩ.

After placing the electrodes, we started the experiment. The subject read aloud the sentences presented on the board when the experimenter prompted the subject 20 seconds after the start of stimulation. At the time of reading aloud, we instructed the participants to pay attention to their own voice volume and speed and keep these parameters natural in everyday conversation. Stimulation was continued even after the reading ended until the prescribed time had ended for 20-30s.

2.2.4 Experiment Design

A experimental procedure in a single block is shown in Figure 2.1. Each participant partook in the experiment for 2 days, in which one day was entirely either for anodic or for cathodic stimulation. In addition to the active stimulation blocks, the participant underwent one sham stimulation block. Because there were four stimulation sites (left and right inferior frontal gyrus (left IFG and right IFG) and left and right superior temporal gyrus (left STG and right STG)), there were 5 experimental blocks in total for each day. The order of anodic and cathodic stimulation was counterbalanced between participants. The site of the sham stimulation was one of the four regions-of-interest, and the choice of the site was counterbalanced between participants. Each block took about 8 minutes including time for electrode attachment and detachment. Therefore, the experiment time was about 40 minutes for 5 blocks in total in each day.

2.3 Evaluation of utterance

The stuttering core symptom appearance rate was calculated by counting the number of occurrences of repeating, prolongation , and blocking of the pronunciation of speech, all of which are the core symptoms of stuttering based on the Standardized test for stuttering. We counted the occurrences for each block of audio data recorded. Evaluation of the utterance was conducted twice in two days by an experimenter (YY) who is a licensed speech therapist. The intraclass correlation coefficient were 0.90 in the two evaluations.

2.4 Data processing

For the calculation of stuttering frequency using the sound data recorded at the time of measurement, the stuttering frequency at the sham stimulation condition was subtracted from the stuttering frequency at the active stimulation conditions (anodal and cathodal stimulations), and change of the stuttering frequency by the active stimulation of tDCS was calculated. Possible correlation between the amount of change and the severity score of stuttering based on the Standardized test for stuttering was analyzed. First, in order to determine the factors affecting the stuttering frequency, we performed a two-way analysis of variance (ANOVA) with the factors of the target region (bilateral inferior frontal gyrus, bilateral superior temporal gyrus) and of stimulation condition (anodal stimulation, cathodal stimulation, sham stimulation) using a statistical analysis software (GraphPad Prism 7, GraphPad, San Diego, USA). Next, for each active stimulation condition, one-way ANOVA was performed with the factor of the stimulation region to investigate the influence of the polarity of stimulation (anodal and casodal

stimulations) on each target region. Post-hoc tests were conducted for factors that showed significant main effects or interaction. Furthermore, in order to investigate the influence of each active stimulus on the stuttering frequency for each target region, a series of paired t tests were performed between active stimulation condition and sham stimulation condition as to each of the 8 conditions (polarity: 2 conditions x stimulation region: 4 regions). Moreover, we also calculated Person's correlation coefficient between the effect of stimulation and the severity of stuttering that was assessed using either the reading-task or the total scores of the Standardized test for stuttering. In both cases, the statistical significance level was set at $p < 0.05$.

2.5 Results

2.5.1 Change of stuttering frequency by tDCS

The frequency of stuttering in each condition of all subjects is shown in Fig 2.2. Of the 15 subjects, 11 people participated in the experiment for 2 days, the remaining 4 people participated only for 1 day. As a result of two-way ANOVA with the factors of the target region and of stimulation condition, the main effects of target region and stimulation condition were significant in the change of stuttering frequency $F(1, 10) = 6.443$, $p < 0.05$, $F(3, 30) = 2.955$, $p < 0.05$. In addition, the interaction was significant $F(3, 30) = 23.01$, $p < 0.01$ (Figure 2.3).

As a result of an ANOVA with the factor of target region, the effect of the factor was significant for both anodal stimulation and cathodal stimulation ($F(2.001, 24.02) = 22.62$, $p < 0.01$ for anodal stimulation; $F(1.544, 18.53) = 15.14$, $p < 0.05$ for cathodal

stimulation.) In addition, as a result of multiple comparisons, significant difference was confirmed between left IFG and right IFG, right IFG and left STG, right IFG and right STG in both stimulation conditions (Fig 2.4).

As a result of a series of paired t tests between sham stimulation and active stimulation for each target region, significant difference between anodal and sham stimulation conditions was observed in right IFG and left STG, (t (12) = 3.846, p <0.01, for right IFG; t (12) = 2.32, p <0.05 for left STG). Similarly, the significant effect of the cathodal stimulation was confirmed in the bilateral IFG (t (12) = 2.714, p <0.05 for right IFG; t (12) = 5.349, p <0.05 for left IFG (Figure 2.5)).

2.5.2 Correlation between the effect of tDCS and severity of stuttering

The severity scores of stuttering in the reading-task of the Standardized test for stuttering had the average score of 2.6 points and the standard deviation of 1.12 points. When we classified the participants along the severity of stuttering, we found that 3 of them fell into the normal range, 4 into the range of "very mild" level of stuttering, 4 into the range of "mild" level, and 4 into the range of "moderate" level. In addition, the severity of the total scores of the Standardized test for stuttering had the average score of 3.06 and the standard deviation of 1.03 points. Based on the total score, 6 of the participant fell into the range of "very mild" level of stuttering, 3 into the range of "mild" level, 5 into the range of "moderate" level, and 1 into the range of "severe" level.

When we calculated the Person's correlation coefficient between the effect of stimulation and the severity of stuttering that was assessed using either reading-aloud task

or total scores of the Standardized test for stuttering, we observed a significant positive correlation between both of severity scores and the effect of anodal stimulation in right IFG($r = 0.51$, $p < 0.05$ for reading-aloud task; $r = 0.60$, $p < 0.05$ for total scores (Figure 2.6)).

2.6 Discussion

In this experiment, we examined the effect of modulation of cortical activity on stuttering by applying either the anodic or cathodic stimulation to the cerebral cortex areas related to speech dysfluency of stuttering by tDCS.

In this study, interaction between the factor of target region and of stimulation condition was observed in the change of stuttering frequency. This means that the activity of each target region has a different effect on the speech dysfluency of stuttering, which means that the magnitude of the influence differs between regions. In addition, as a result of ANOVA with the factor of target region for each active stimulation condition and post-hoc comparisons, significant difference was confirmed in the following pairs: left IFG and right IFG, right IFG and left STG, right IFG and right STG under both anodic and cathodic stimulation conditions. That is, the change in activity of right IFG has the greatest influence on stuttering frequency in both anodic and cathodic stimulations. This finding is consistent with the Hypothesis I that the main factor of the occurrence of stuttering is the functional and structural abnormality of motor-related areas. Furthermore, regarding the stuttering frequency, we compared between sham stimulation condition and active stimulation condition for each stimulus region. As a result, significant difference was observed in right IFG and left STG in anodal stimulation

condition, and in bilateral IFG in cathodal stimulation condition. This means that changes in activity of left and right IFG and left STG changed stuttering frequency. In other words, the activities of these three regions significantly contribute to the occurrence of stuttering. In the right IFG, the stuttering frequency increased at anodal stimulation and the stuttering frequency decreased at cathodal stimulation. This result also seems to support the hypothesis I. On the other hand, in the left IFG, the frequency of stuttering decreased at cathodal stimulation, but there was no significant change at anodal stimulation. In the left STG, the stuttering frequency decreased when anodal stimulation, but there was no significant change at cathodal stimulation. Although the previous research suggested that the activity of the left STG is related to stuttering (Fox et al., 1996; Fox et al., 2000; Braun et al., 1997; De Nil et al., 2003), the results suggested that the reduction of activity in this area may not necessarily a factor causing speech dysfluency. This finding supports the Hypothesis II. Furthermore, there was a significant positive correlation between the effect of anodal stimulation in the right IFG on reading fluency and the severity of stuttering. This result suggests that the stuttering frequency is more susceptible to the increase in the activity of the right IFG as the stuttering becomes more severe.

Chapter 3. Experiment 2: Delayed Experiment on Auditory Feedback for Stutters

3.1 Purpose

As stated in Chapter 1, it is known that the fluency of utterances of PWS is improved by DAF in which feedback of speakers' own voices are delayed for 50 ms to

200 ms delay. However, this effect is not found in all PWS, and therefore may depend on the severity of stuttering and sex, individual anatomical differences in the brain, and other factors. In addition to differences among individuals, but effects of DAF may be also dependent on whether speech is generated under the spontaneous talking condition or reading. In order to address a factor that may affect the individual difference in DAF effect, the overt reading task under DAF condition is performed and examined whether factors of the stuttering severity and speaker's sex influence the effect of DAF on the utterance fluency of PWS.

3.2 Method

3.2.1 Participants

15 PWS (average age: 23.4, standard deviation: 2.44 years old, 5 females, 1 left handed) participated in this experiment. They were recruited from self-help groups of PWS (Wisuta Kanto, Tokyo). All of the participants had normal audiovisual and vocal ability.

Before the experiment, I gave them explanations of the experiment in verbal and written form, and gained a consent in a written form from every participant. All participants were examined for speech dysfluency symptoms, and stuttering severity was rated by a speech therapist (YY) based on the Standardized test for stuttering. The experiment was approved by the Ethics Review Committee of the Graduate School of Humanities and Sciences, Tokyo Metropolitan University.

3.2.2 Materials

Experimental 2 was conducted before Experimental 1. We used the fairy tale "The North Wind and the Sun" as the material for the overt reading task. The sentences were presented on the reading board that was positioned in front of the participant. The voices of the participants were recorded from the microphone (RadioShack Dynamic Microphone) and caused a delay of 200 ms through the effector (LEXICON MX 300). The speech signal was further synthesized with pink noise (90 db SPL) using a mixer (MACKIE 802 VLZ 4) in order to mask their own voice without delay that may be heard through air conduction sound. The final modified speech was presented to the participant through the earphone (JVC HP-RX 500) (Figure 3.1). The voices of the participants were digitized and recorded using voice recording software (Audacity2.1.2, Carnegie Mellon University, USA).

3.2.3 Procedure

Participants sat on the chair and participated in the experiment. The experimenter first attached the earphone and checked the sound pressure of the pink noise and the delay of the voice. We checked the delay of the voice by pronouncing the sentence of the 10 phrases aloud. The participants were instructed to pay attention to their own voice while reading aloud the sentences. After the instruction, participants wore earmuffs (Bilsom Leightning L3) and started reading aloud when the assignment was presented on the reading board.

3.2.4 Experiment Design

The experiment was conducted twice with the same task in order to eliminate the difference in effect due to the presence or absence of experience of DAF. The experimental time per test was about 10 minutes including confirmation of DAF .

3.3 Evaluation of utterance

Using the recorded voice data, the occurrence rate of non-fluency and the speech rate were calculated. When speaking under DAF condition, it is known that stuttering of sound, distortion of articulation, unnatural change of speech speed, and other forms of dysfluency occur in PWNS. Therefore, in this experiment, in evaluating the utterance, in addition to the core symptoms of stuttering (repetition of headphones, stretching, blocking), distortion of articulation and unnatural change of speech rate are classified as dysfluency. The rate of fluency was the ratio of the number of dysfluency to the number of phrases in total. In addition to the rate of dysfluency, speech speed was calculated by first identifying the reading time excluding the part where stuttering symptoms appeared using voice analysis software "Praat" and then dividing the total number of mora included in the sentence stimuli by the reading time.

3.4 Data processing

For the calculation of speech dysfluency frequency using the sound data recorded at the time of measurement, the speech dysfluency frequency at the sham stimulation condition(normal condition) in the Experiment 1 was subtracted from the speech dysfluency frequency in DAF condition, and the change of the speech dysfluency

frequency by DAF effect was calculated. This amount of change and the severity score of stuttering based on the Standardized test for stuttering were analyzed. First, in order to investigate whether there is an effect on speech fluency by DAF, a series of paired-t tests were performed between DAF condition and normal condition using a statistical analysis software (GraphPad Prism 7, GraphPad, San Diego, USA). Next, a t-test was conducted between male and female for the amount of change of the speech dysfluency frequency to examine the effect of sex on the DAF effect.

Moreover, we also calculated the Person's correlation coefficient between the change of speech dysfluency and the severity of stuttering that was assessed using either the reading-task or the total scores of the Standardized test for stuttering. Furthermore a paired-t test was conducted between sham stimulation condition and DAF condition for the speech ratio to examine the DAF effect on the speed of reading. In both cases, the statistical significance level was set at $p < 0.05$.

3.5 Results

As a result of comparison of speech dysfluency frequency under the DAF condition and that under the normal condition, no significant difference was found (t (14) =0.723, p=0.49) (Figure 3.2). Next, we compared differences in change of speech dysfluency frequency by DAF between male and female, and found no significant difference (t (13) = 0.861, p=0.41) (Figure 3.3). However, as the result of correlation analysis between the change of speech dysfluency and the severity of stuttering that was assessed using either the reading task or the total scores of the Standardized test for stuttering, there was

a significant negative correlation in both cases (r = -0.71, p <0.01, r = -0.71, p <0.01) (Figure 3.4).

As for the speech rate, a significant difference was found as a result of comparison between the DAF and normal conditions (t (14) = 5.934, p <0.01) (Figure 3.5). Subsequently, the speech rate in the DAF condition was subtracted by that in the normal condition to calculate the change of the speech rate, and the correlation analysis was performed between the change of the speech rate and that of the speech dysfluency. As a result, no significant correlation was found (r = 0.04, p =0.88) (Figure 3.6).

3.6 Discussion

In this experiment, we examined the influence of auditory feedback on the speech dysfluency PWS by conducting the reading aloud task under the DAF condition for PWS. Contrary to previous studies（Lincoln et al., 2006）, there was no significant difference in the frequency of speech dysfluency between DAF condition and normal condition. In this study, however, we observed subjects with clearly reduced frequency of speech dysfluency and subjects with clearly increased frequency of speech dysfluency in DAF condition. Therefore, when we compare the frequency of speech dysfluency of each of two conditions on average, the degree of change in the frequency of speech dysfluency by DAF may be canceled out. In this sense, there is a possibility that difference between the two conditions was not significant because of the heterogeneity regarding the effect of DAF among PWS. For the gender comparison, no significant difference was found between male and female. This result did not support the results of previous studies

(Fukawa et al., 1988). In this experiment, however, since the difference in the sample sizes between men and women is large and the severity is not controlled, our negative observation need to be confirmed in the future studies using the larger number of participants. In the correlation analysis with the severity score of stuttering, there was a significant negative correlation with the both severity scores. This result was consistent with the results of previous studies (Foundas et al., 2004). Particularly for subjects whose severity of stuttering in the reading aloud tasks was in the normal range, the frequency of speech dysfluency tended to increase, which suggests that the more severe the stuttering, the more positive the influence of auditory feedback. Moreover, it is conceivable that this result also suggests the possibility that there are PWS whose auditory feedback function is normal, and their symptoms tend to be mild. Changes of auditory feedback by DAF are known to alter activation of the auditory cortex (Hashimoto and Sakai, 2003; Sakai et al,. 2009; Takaso 2010), and it is thought that this result is more consistent with the hypothesis II that functional and structural abnormalities in auditory cortex are secondarily exacerbating speech dysfluency.

As for the speech rate, a significant decrease was observed in the DAF condition as compared with the normal condition. This is consistent with previous studies (Bloodstein & Ratner 2008; Kalinowski et al., 1996). No significant correlation was found between the change of the speech rate and that of speech dysfluency. This seems to indicate that the factor of speech dysfluency change is not only the decrease of speech rate. In other words, it is suggested that improving speech fluency of stuttering by DAF is not only by influence of declining speech rate.

Chapter 4. Overall consideration

4.1 A summary of experiments

In this research, we modulated the cortical activity of bilateral IFG and STG by tDCS in the reading aloud tasks and examined the influence of the activity of these areas on the occurrence of stuttering (Experiment 1). In addition, we performed the reading aloud experiment under DAF conditions and examined how the speech fluency of the PWS changes due to changes in auditory feedback (Experiment 2). First, in Experiment 1, significant differences in stuttering frequency were observed when the left and right IFG and left STG were stimulated by active stimulation among the four regions of the cerebral cortex that are related to stuttering. Therefore, it has been shown that the activities of the three regions influence the speech dysfluency of stuttering. Especially when the right IFG was stimulated, the change in stuttering frequency was the greatest, and increasing the activity with anodal stimulation exacerbated the stuttering frequency, on the other hand, suppressing the activity with cathodal stimulation reduced the stuttering frequency. In addition, correlation with the severity of stuttering was shown only in right IFG. From these results, it is suggested that increased activity of right IFG may be one of the major causes of stuttering. On the other hand, with respect to the left IFG and the left STG, the change in the stuttering frequency was observed only in stimulating by either anodal stimulation or cathodal stimulation.

Experiment 2 showed that DAF has an influence on speech dysfluency and speech speed of PWS. Furthermore, it was found that amelioration of speech dysfluency by DAF

was more clearly observed as the stuttering is more severe, and that speech dysfluency may increase with DAF in some mild stutterers. In addition, it was suggested that improvement of speech fluency of stutters by DAF is not simply the effect of reducing the speech speed. From these observations, the following conclusions may be drawn.

First of all, among the speech-related motor cortex and auditory cortex in which the relation with stuttering is indicated in the previous studies, the area that greatly influences the occurrence of stuttering is the motor speech areas, particularly the one in the right hemisphere. In this study, the stuttering frequency was modulated due to the activation modulation of the left and right IFGs (motor speech area) and the left STG (the auditory area). However, only the right IFG showed changes in both polarities, and only the right IFG showed correlation with the severity of stuttering. Therefore, it is inferred that although the change in the activity in other areas at the time of the stuttering have significant impact on the occurrence of stuttering, its influence is relatively minor and may be secondary to the stimulation to the right IFG. So, the greatest factor of speech dysfluency of stuttering may be activity abnormal activity of motor speech areas in right hemisphere including right IFG.

It is also suggested that abnormalities in the auditory feedback function are not found in all PWS, and may also be factors for exacerbating speech dysfluency of stuttering. In the Experiment 1, the effect of stimulation to the auditory cortex on the stuttering frequency was not large, and the effect was recognized only by anodal stimulation. However, in Experiment 2, a negative correlation was found between the severity of stuttering and the change of speech dysfluency due to DAF. Furthermore, in

the cases of mild stuttering, speech dysfluency was rather exacerbated by DAF. If an abnormality in the auditory feedback function is a factor common to PWS, such a difference should not occur in the effect by the DAF in mild PWS. Therefore, abnormal auditory feedback may not be cause of the occurrence of stuttering, but may be a secondary factor that could make the symptom more severe. It is considered that the direction of impact by DAF (exacerbation or amelioration) and the magnitude of impact are dependent on the severity of stuttering.

Based on the two considerations that the cause of the stuttering is abnormal in the motor speech area of the right hemisphere (i.e., the right IFG) and that the problem of auditory field abnormality and auditory feedback could be factors of exacerbating symptoms of stuttering, we advance comprehensive understanding of the relationship between the function of the motor speech area and auditory cortex and stuttering, and the strategy of speech motor control of PWS while incorporating findings and model research obtained from function brain imaging research.

4.2 Relationship between stuttering and speech-related areas

4.2.1 Relationship between stuttering and speech-related motor areas

From the results of this study, it was shown that the stuttering frequency changes with the right IFG activity. This suggests that the activity abnormality of the motor speech area including IFG may cause stuttering. Then, is it the right IFG that stimulated in this experiment, which is the cause of the stuttering occurrence? In this study, right IFG was selected as the stimulation region, but in brain imaging research, overactivity in

occurrence of stuttering was reported in a wide range of speech-related motor areas such as motor area, supplementary motor area, basal ganglia, cerebellum, and insula. The basal ganglia forms a loop with the cerebral cortex (Figure.4.1), and it is known that the motor fields - the basal ganglia loop is greatly involved in the speech motion. In addition, it is reported that in PWS, dopamine secretion in the basal ganglia is excessive in stuttering (Wu et al., 1997) and a study showing that the activity of the basal ganglia is different between PWS and PWNS (Giraud et al, 2008; Watkin et al., 2008). Moreover, Giraud et al (2008) reported that there is a positive correlation between the frequency of stuttering and the activity of the basal ganglia, and this abnormal activity is improved by speech therapy. Therefore, the following two possibilities are considered for the change of stuttering frequency by stimulating right IFG in this study. ① Changes in activities of the right IFG directly affected stuttering frequency. ② Indirectly changing the function of the basal ganglia by stimulating the right IFG affected stuttering frequency. In this study, however, it is not possible to directly measure the activation of right IFG and areas in the basal ganglia, so it is unknown how activations in the motor speech areas are actually modulated. Therefore, we are unable to draw conclusions regarding whether cortical activity in the motor speech areas induced the change of stuttering frequency when we stimulated the right IFG.

4.2.2 Relationship between stuttering and auditory cortex activities and auditory feedback

Experiment 1 showed that the activity of the left auditory cortex affects stuttering frequency, but its effect was small. Experiment 2 also showed that the speech dysfluency of PWS was modulated by DAF and there was a significant correlation between the change of speech fluency and the severity of the stuttering. The left auditory area is thought to play crucial roles in speech prediction and auditory feedback matching (Tourville et al., 2008), and our results suggested that auditory feedback relates to stuttering. In addition, in this study, when a mild PWS read aloud under the DAF condition, their speech dysfluency tended to exacerbate. Based on the correlation between the change in speech dysfluency frequency caused by DAF and the severity of stuttering, this result may suggest that an abnormality of auditory feedback may not be found in all PWS. Rather, such abnormal auditory feedback may be considered as one of the multiple factors that exacerbate stuttering. In brain imaging studies, however, reduction of activity of the auditory cortex has been consistently observed in all previous studies (Belyk et al., 2015; Brown et al., 2005; Budde et al., 2014). So, how does an abnormality in auditory feedback in stuttering affect stuttering, and what is the relationship between reduced functionality of the auditory cortex and stuttering?

As we mentioned in Chapter 1, the findings that PWS perform speech movement depending on auditory feedback has been shown by brain imaging research (De Nil et al., 2001), behavioral research (Fukawa et al., 1998) , and computational modeling studies (Civier et al., 2010; Guenther et al., 2006). From the results of these studies, it is suggested that PWS have not fully developed feedforward control, which is a strategy of automatic motion control, and as a result, they perform motor control by relying more on

auditory feedback. Consistently, in the DIVA model, it is proposed that since the PWS cannot successfully control their speech using the feedforward system, the load for auditory feedback is increased (Civier et al., 2010). They suggested that it is difficult to realize quick speech motion by feedback system control, and speech error is likely to occur in speech motion depending on auditory feedback, as a result, speech dysfluency occurs.

Regarding the reduction in activity of the auditory cortex when PWS utter, first, as described in Chapter 1, it is considered that error is signaled by outputting an inhibitory motion prediction signal for speech motion related area for afferent auditory feedback during speech. Therefore, when auditory feedback can be correctly predicted and the error is small, then the activation of the brain region involved in the comparison becomes small. On the contrary, when the error signal is large, the activation becomes large (Tourville et al., 2008). Brown et al. suggested that the reduction in auditory cortex activity during speech in stuttering is due to the strong suppression of auditory feedback by the prediction signal. They also argued that the accuracy of the predicted signal is worse because the intensity of the prediction signal is strong in PWS. Furthermore, it is known that the precision of this motor prediction is also influenced by the effects of dopamine (Wintere & Weinberger, 2004). Based on the results of our study and the findings of these previous studies, it may be possible that the reduced activity in the auditory cortex, which was shown in previous studies, is not the cause of the stuttering, but the secondary factor involved in the increasing of activity of the speech-related motor areas.

In Experiment 2, it was shown that DAF reduces the speech speed. This is consistent with the previous studies (Guitar, 2006). Based on Fitts' law that motion speed and accuracy are in a trade - off relationship in motion control, it is expected that the accuracy of speech motion will be improved by slowing the speech speed. Previous studies have shown that most PWS improve speech fluency by DAF (Lincoln et al., 2006). Based on Fitts' law, it is thought that by decreasing the speech speed by DAF, it is possible to improve the accuracy of the prediction signal and lead to improvement of speech fluency.

However, we observed no correlation between the declining of speech speed and the change of speech fluency by DAF. Also, the reduction of speech speed was recognized even in mild PWS who showed increase in speech dysfluency by DAF. Therefore, we suggest that there are other factors that improve the speech fluency of PWS by DAF. Regarding the observation that speech dysfluency was exacerbated in mild PWS, it is conceivable that the abnormality of auditory feedback was small, and the auditory feedback was temporally disturbed under the DAF condition. Under such condition, the error signal from motion prediction became large and therefore speech became more dysfluent as was the case in PWNS. According to previous studies (Foundas et al., 2001; 2004), the effect of promoting speech fluency by DAF is greater for those who have the different asymmetry of left and right PT volumes from PWNS than those those who have the similar asymmetry as PWNS (left hemisphere dominance). Therefore, the difference in degree of abnormality of auditory feedback in the PWNS and the difference in accuracy of information matching in the left auditory area may be caused

by this structural difference. However, because the detailed mechanism in which non-PWS's speech become dysfluent by DAF has not been clarified yet, it is difficult to speculate further in this research alone.

4.2.3 Hypothetical mechanism of stuttering

In this study, in Experiment 1, the stuttering frequency increased when we raised the activity of speech-related motor field that is thought to output the motion prediction signal by tDCS, and the stuttering frequency decreased when we reduced activity of the same area. In this study, assuming that the intensity of the signal is proportional to the level of brain activity and its accuracy becomes worse by the release of dopamine, it is possible that when stimulating the right IFG with anodal stimulus and raising the activity of that area, the activity of that area and the basal ganglia changes, and the strength of the motor prediction signal becomes stronger, and as a result the precision worsens, leading to the increase in the stuttering frequency. Also, as mentioned above, reduction in auditory cortex activity is thought to be due to the prediction signal. Based on the results and discussions of Experiments 1 and those of Experiment 2, the following hypotheses about the mechanism of stuttering were considered from the viewpoint of the abnormality in the activity of the speech-related motor field and the auditory feedback function.

First, the PWS has a structural abnormality in the white matter tract, which is considered to constitute a feedforward route (Cai et al., 2014; Chang & Angstadt, 2015), and such connection failure occurs between speech-related regions in the brain. As a result, the intensity of the motion prediction signal from the speech-related motion field

increases. Therefore, this signal suffers from strong noise, and accuracy deteriorates. In addition, by excessive secretion of dopamine due to hyperactivity of basal ganglia, the accuracy of this signal worsens. As a result, the degree of reliance on auditory feedback in speech motion control increases and the precision of the collation decreases, so that the error signal between motion prediction and auditory feedback increases. According to the DIVA model, as this error becomes larger, speech motion resettings occur more frequently, which results in speech dysfluency in stuttering (Fig 4.2). In addition, it is possible that the precision of comparison between feedforward and feedback signals and the dependence on auditory feedback, which are assumed to be performed in the left auditory cortex, are altered among the PWS. Furthermore, due to some factors including structural abnormality of PT, stuttering becomes severe if the accuracy of the original verification is bad or the reliance on auditory feedback is higher. In conclusion, due to the reduction in the accuracy of the motion prediction in the speech motion caused by the overactivity of the speech-related motor field and the decline in the accuracy of the verbal motion strategy and the motion estimation and feedback information depending on auditory feedback, speech dysfluency is caused in stuttering.

4.3 Limitations of this study

There are several limitations in this study that need to be noted. First, in this study, because the bilateral IFG and STG are used as the stimulation regions, and the change of brain activity by tDCS is not directly measured, it is not clear that how influence on activities of other speech-related motor areas including the basal ganglia are influenced

by the stimulation. Also, since the size of the electrodes used is relatively large, the localization of the stimulation is limited. Furthermore, regarding the relationship between the effect of tDCS and DAF and the severity of stuttering, the sample size at each severity level is relatively small, and therefore it is necessary to examine in larger sample size. In future studies, by conducting experiments targeting PWNS in the same way as this study, and by comparing with the results of this tDCS study and combining imaging methods, it will be possible to clarify in more detail the causal relation between speech dysfluency and the activity of the speech related areas and the influence of auditory feedback on speech fluency.

Conclusion

In this study, in order to examine the mechanism in the brain of stuttering, we conducted a reading-aloud experiment under two conditions on the PWS. One condition is to change the activation of speech-related regions that are supposed to be related to stuttering with tDCS. Another condition is DAF. The results showed that the activity of the right IFG had a great influence on the occurrence of stuttering, and that the influence of DAF on the speech dysfluency of stuttering was different depending on the severity of stuttering. From the results of this study, we suggest that the speech dysfluency of stuttering may be partly caused by the following two factors (i) the precision of the motion prediction signal speech motion becomes worse due to overactivity of the speech-related motor areas and (ii) the weighting to the auditory feedback information increases. To conclude, we infer that the occurrence of stuttering is caused by overactivation of speech-

related motor area including right IFG, and the abnormality of auditory system may be a secondary factor or a modulating factor that exacerbates stuttering.

Figures and Tables

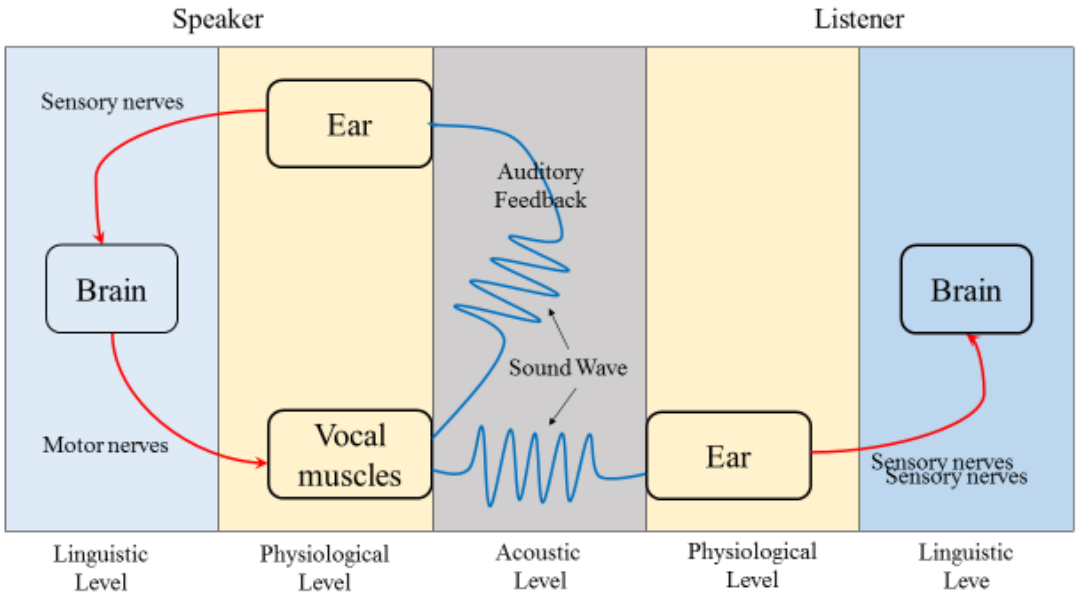


Figure 1.1. Conceptual diagram of "Speech Chain"

This shows that words are transformed into speech sounds through linguistic, physiological and acoustic levels.

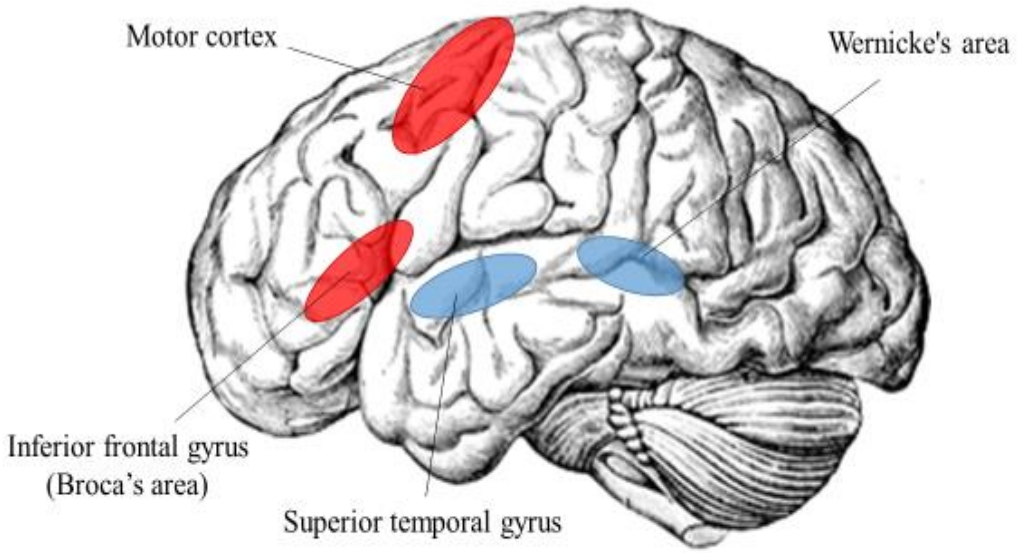


Figure 1.2. Speech-related areas which were commonly suggested to be related to stuttering in previous brain function imaging studies.

The lateral view of the left hemisphere of the human brain. Colored regions show inferior frontal gyrus, motor cortex, Wernicke's area, superior temporal gyrus. The areas painted in red are the areas where over activity has been reported, and the areas painted in blue are the areas where activity decline has been reported.

Source: http://www.pngall.com/brain-png

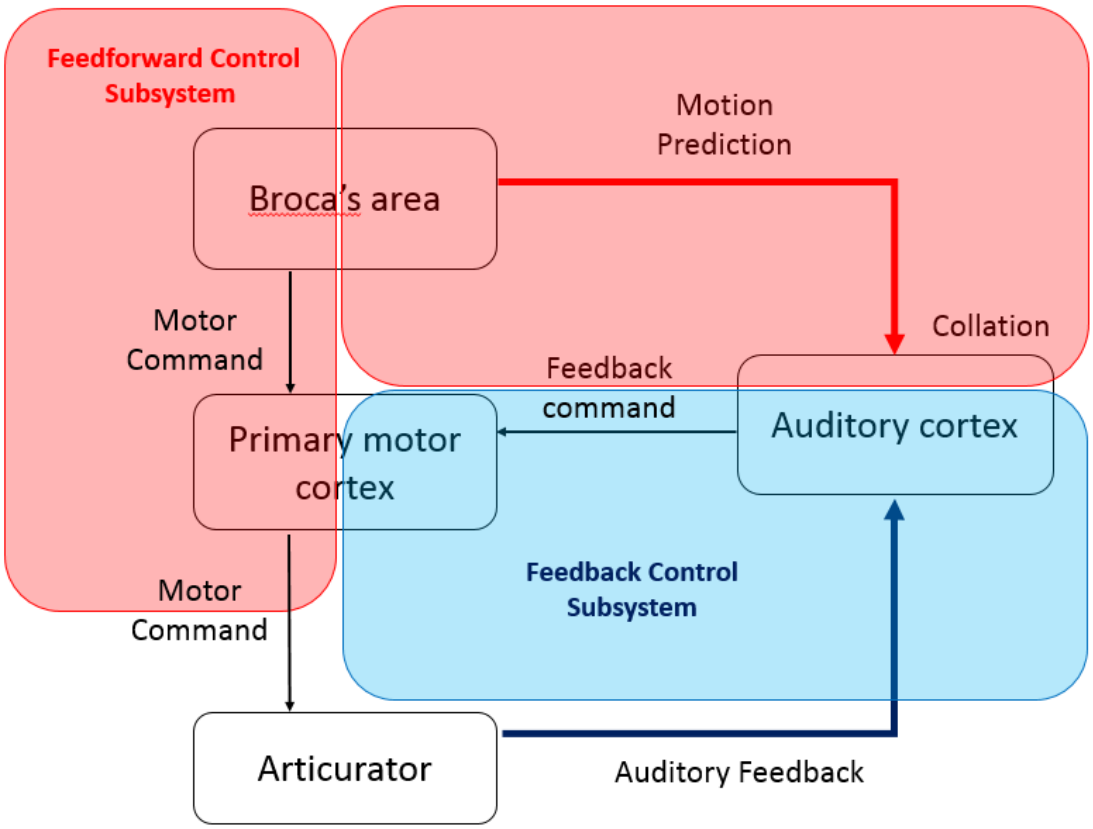


Figure 1.3. Schematic views of DIVA model

In this model, speech production system is composed of two control subsystems: Feedforward Control Subsystem and Feedback Control Subsystem.

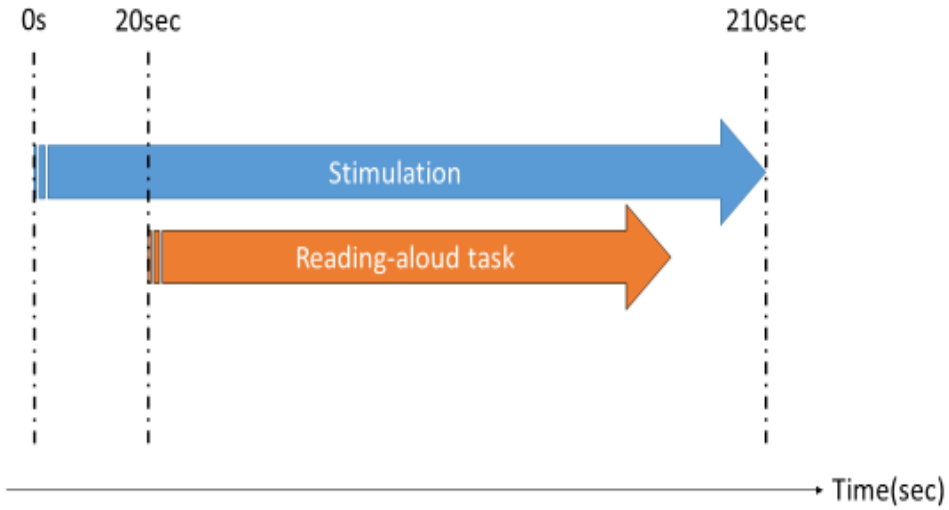


Figure 2.1. The experimental procedure in a single block

The two arrows represent the stimulation period by the tDCS and the execution period of the reading-aloud task, respectively. The stimulation by tDCS is performed from 20 seconds before the start of the reading and continues until 210 seconds elapse since the start of the stimulation even after the reading is finished.

	Anodeal Stimulation					Cathodal Stimulation				
	LIFG	RIFG	LSTG	RSTG	Sham stimulation	LIFG	RIFG	LSTG	RSTG	Sham stimulation
Subject 1	10.5	14.5	5.8	6.7	8.2	4.0	1.8	5.0	3.8	6.6
Subject 2	16.0	17.5	12.8	15	15.1	15.7	11.8	16.1	14.4	14.2
Subject 3	5.6	12.7	8.3	8.3	7.7	5.5	4.1	7.2	8.6	8.3
Subject 4	5.0	6.7	3.7	4.0	4.5	3.1	2.0	4.2	5.2	4
Subject 5	11.2	11.8	9.7	9.0	10.2	10.5	9.1	10.0	10.5	12
Subject 6	8.5	10.6	7.1	8.4	8.3	8.8	7.5	10.4	8	9
Subject 7	7.6	13.7	3.3	4.5	10.8	3.8	0.8	13.2	5.5	11.6
Subject 8	6.4	8.0	5.3	5.5	6.0	5.2	5.0	6.5	5.4	6.7
Subject 9	15.4	25.6	14.5	16.7	16.1	13.1	12.2	19.5	16	15.8
Subject 10	1.8	5.6	5	1.7	8.7	3.6	2.4	6.6	5	6.7
Subject 11	4.0	6.9	5	3.5	3.2	3.0	1.8	5.3	4.2	3.8
Subject 12						6.2	3.8	4.8	5.6	6.2
Subject 13	0.8	3.0	0.0	0.0	0.0					
Subject 14						26.0	21.5	28.3	24.5	25.9
Subject 15	0.0	3.0	0.0	0.0	0.8					

Figure 2.2. The frequency of stuttering in each condition of all subjects

The left side shows the stuttering frequency (%) under the anodal stimulation condition and the right side shows the stuttering frequency (%) under the cathodal stimulation condition.

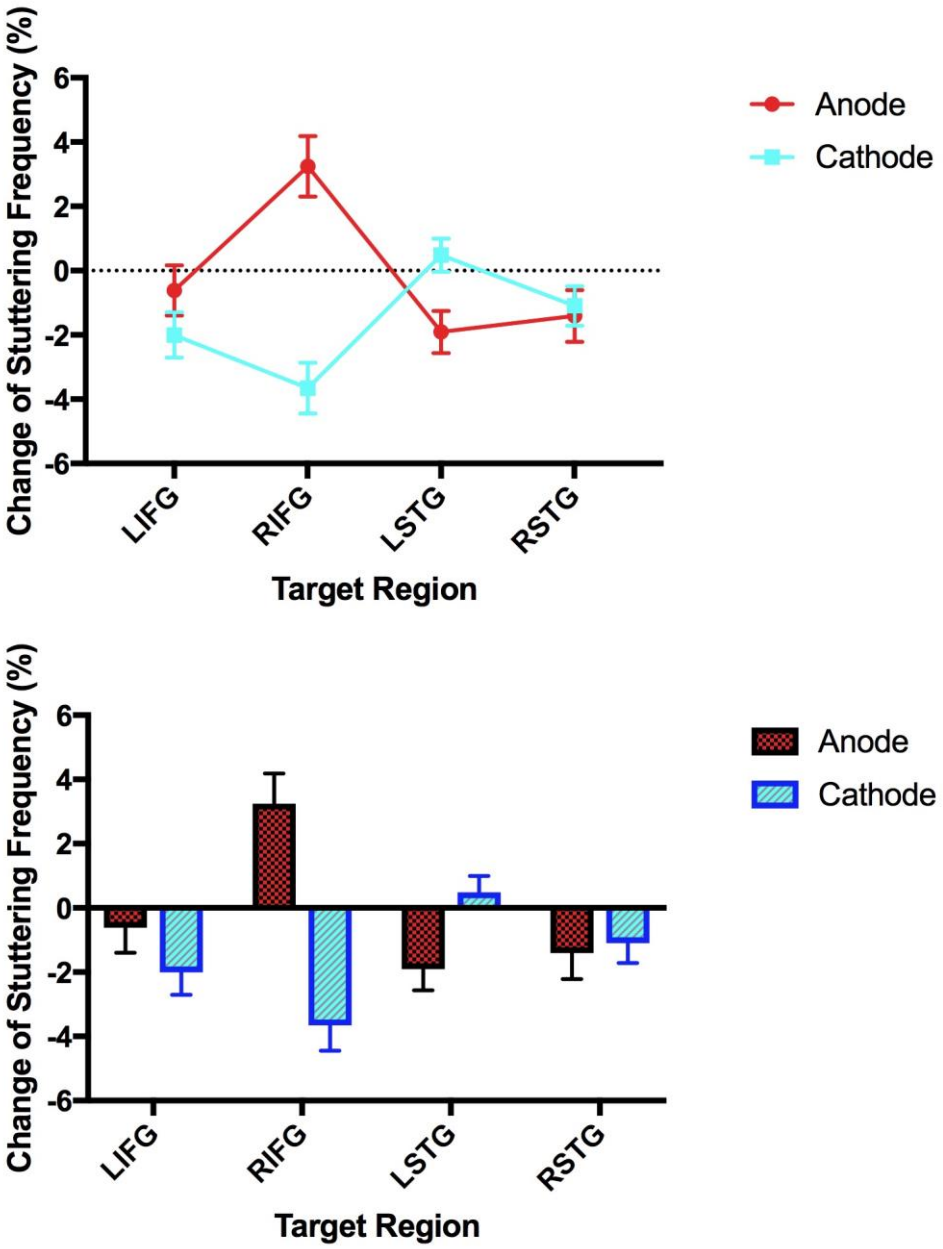


Figure 2.3 Comparison of effects of Anode stimulation and Cathode stimulation in each region

Error bars represent standard error (SE).

n＝11.

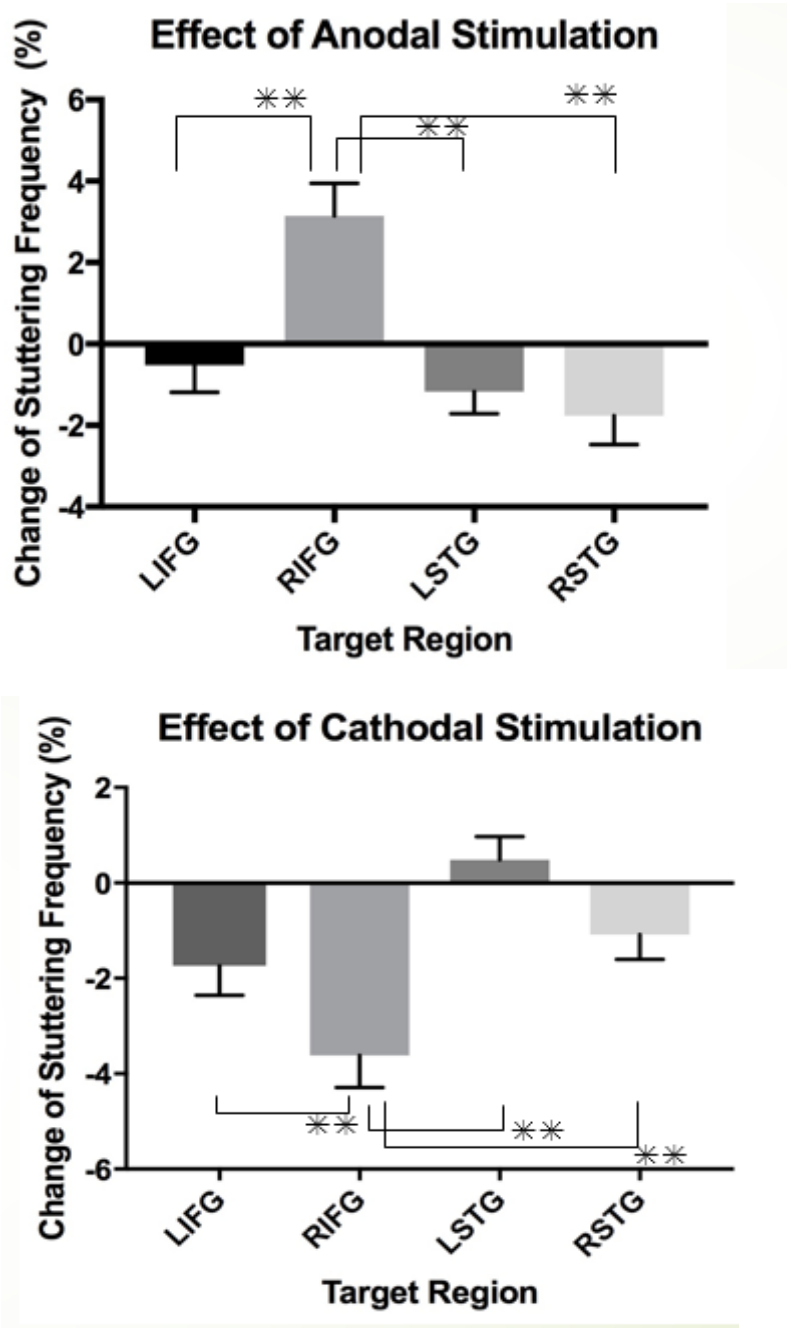


Figure 2.4 Comparison of the effect on the same stimulus between the regions

Significant difference was confirmed between left IFG and right IFG, right IFG and left STG, right IFG and right STG in both stimulation conditions ($p<0.01$).

Error bars represent standard error (SE).

n=13.

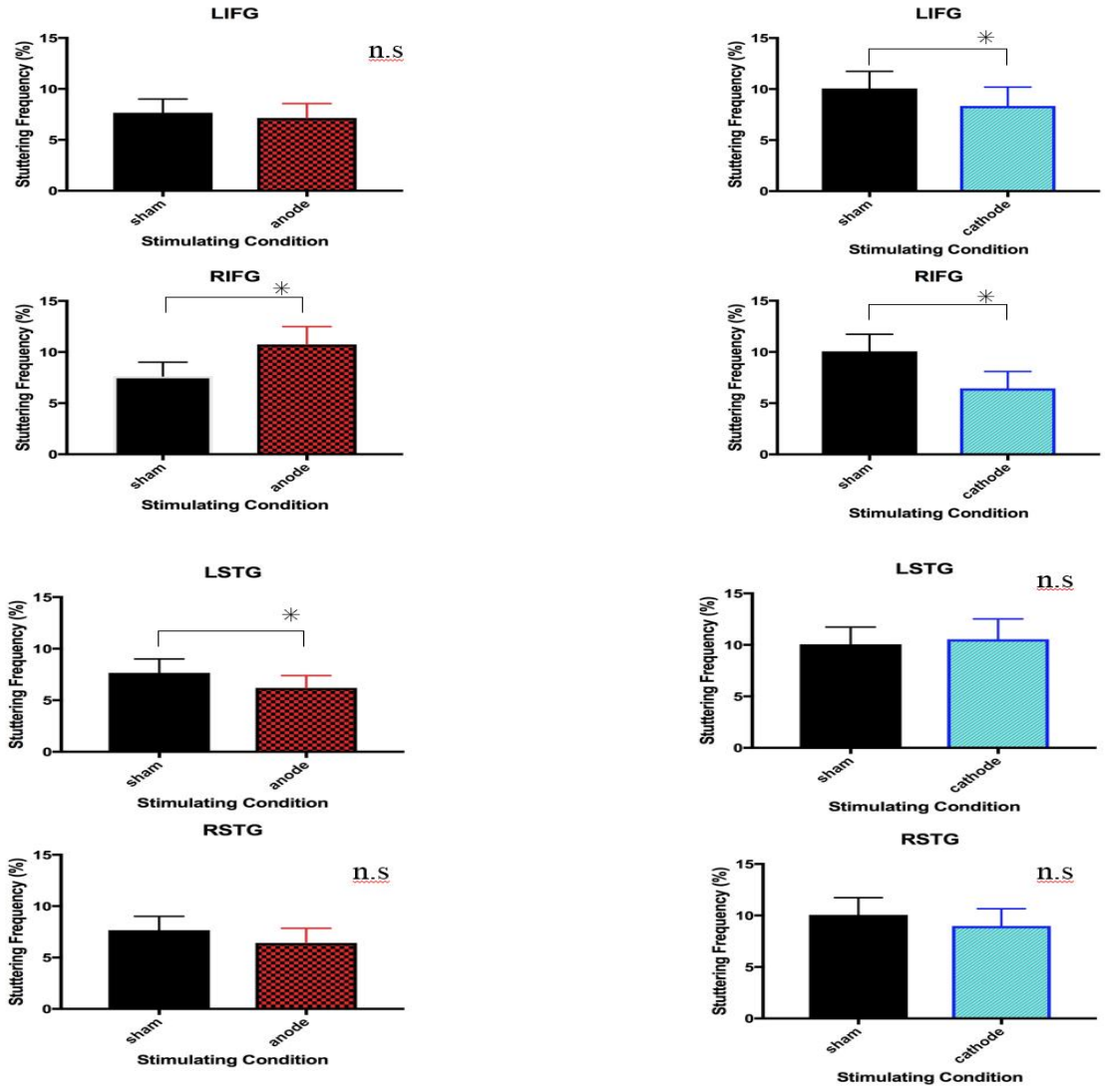
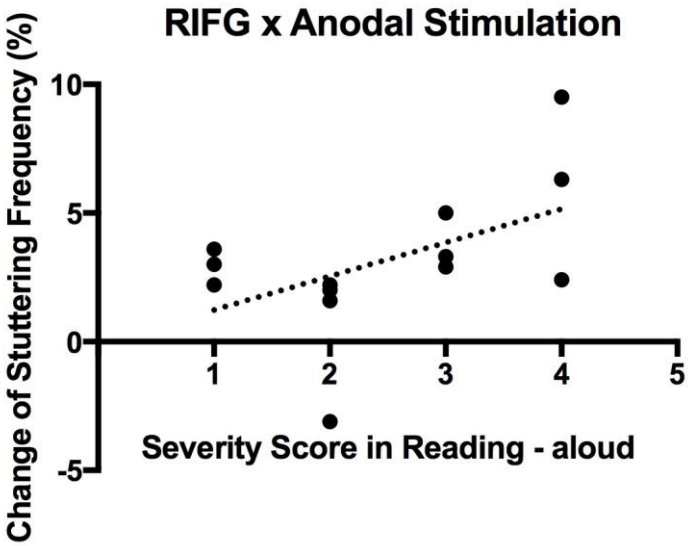


Figure 2.5 Comparison of stuttering frequency of active stimulation condition and sham stimulation condition in each region

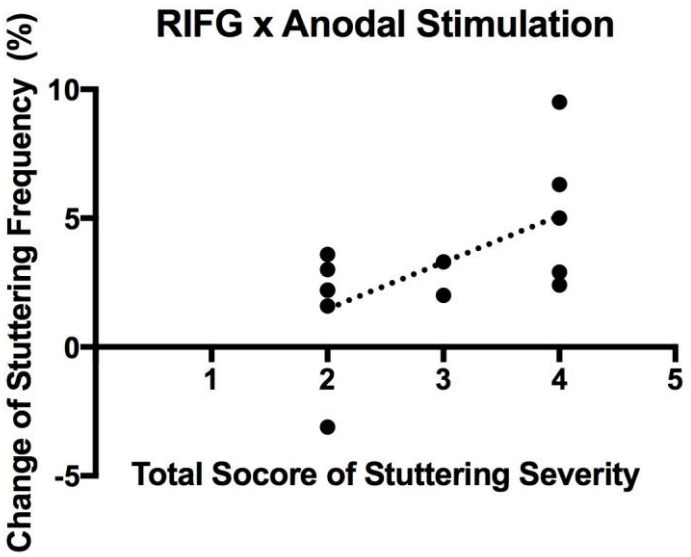
Significant difference between anodal and sham stimulation conditions was observed in right IFG and left STG, and the significant effect of the cathodal stimulation was confirmed in the bilateral IFG (p<0.01).

Error bars represent standard error (SE).

n=13.



r = 0.51*



r = 0.60*

Figure 2.6. Correlation between the effect of tDCS and severity of stuttering

n=13

$p < 0.05$

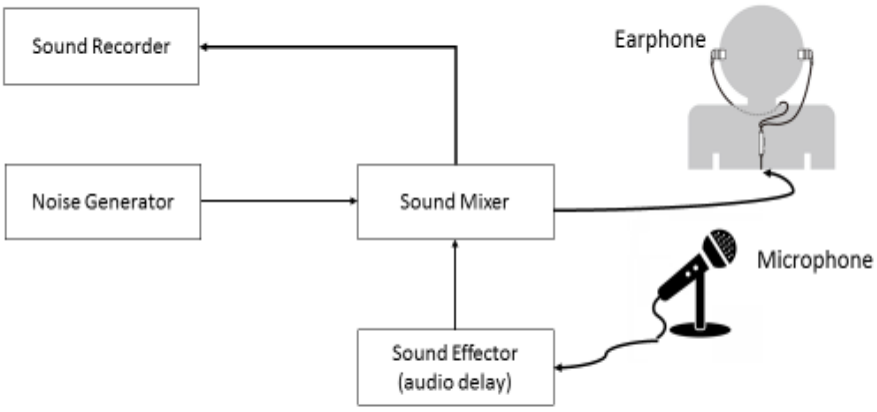


Figure 3.1 Delayed auditory feedback system

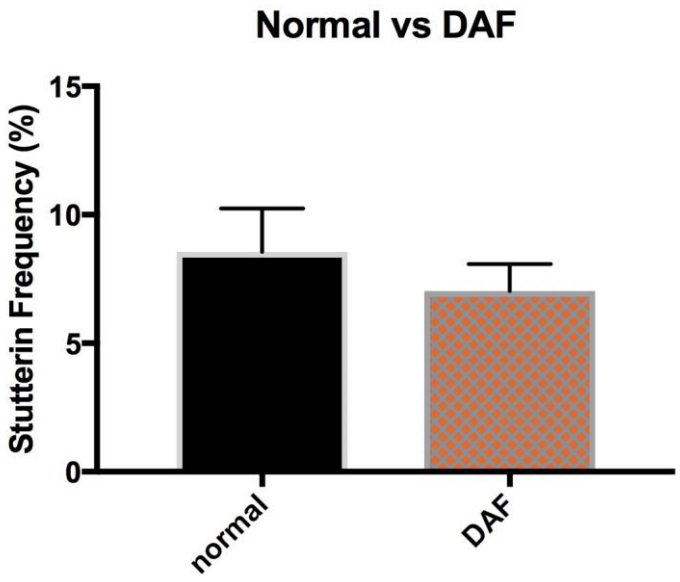
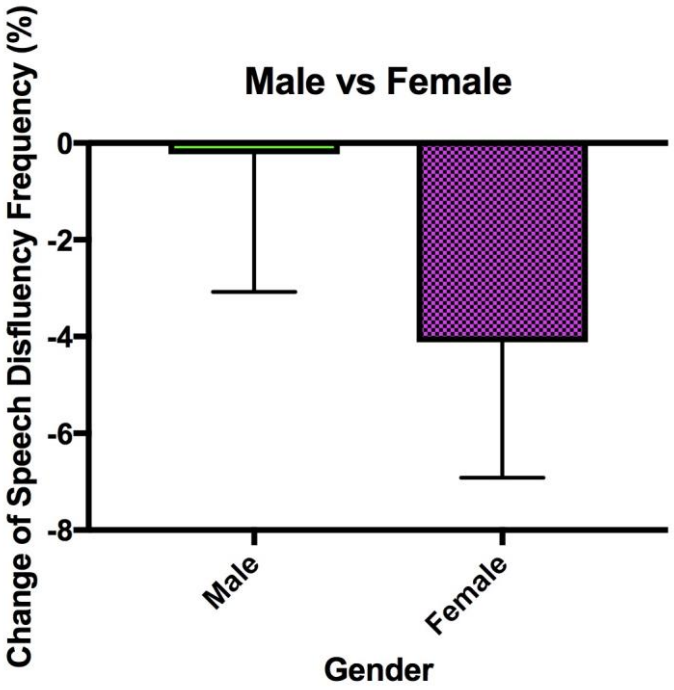


Figure.3.2. Comparison of speech dysfluency in DAF condition and Normal condition

No significant difference was found.

Error bars represent standard error (SE).

n=15.



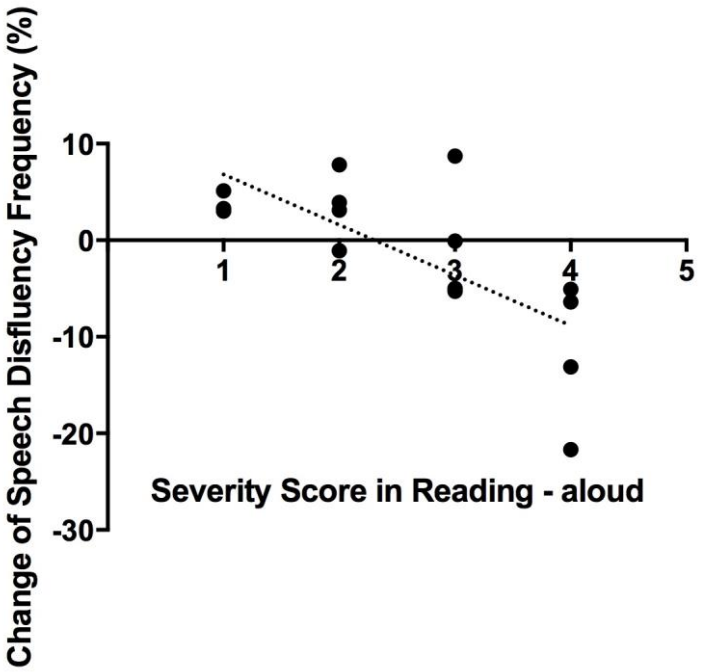
n.s.

Figure 3.3. The difference between male and female

No significant difference was found.

Error bars represent standard error (SE).

Male: n=10, Female: n=5.



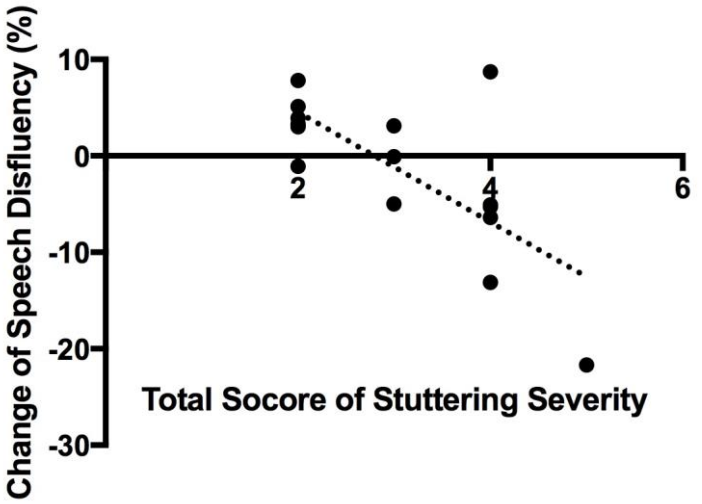


Figure 3.4. Correlation between the effect of DAF and severity of stuttering

n=13

$p < 0.01$

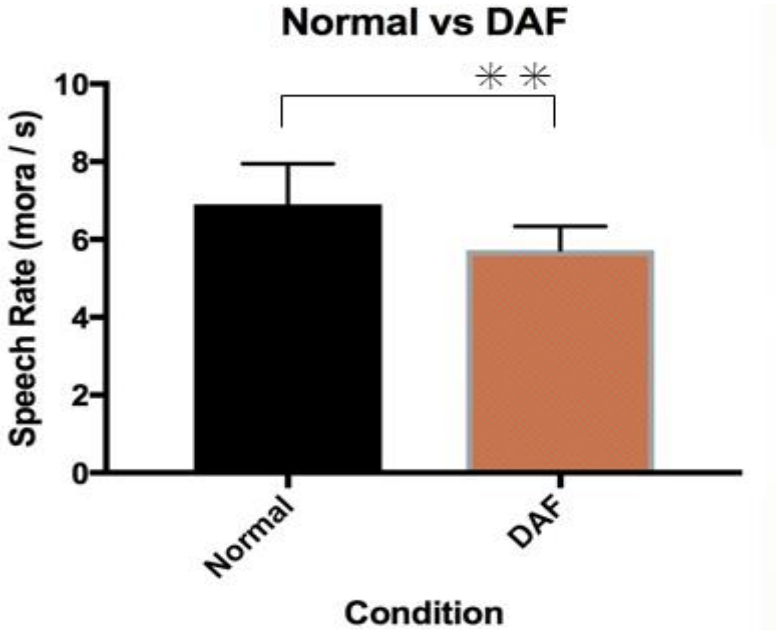
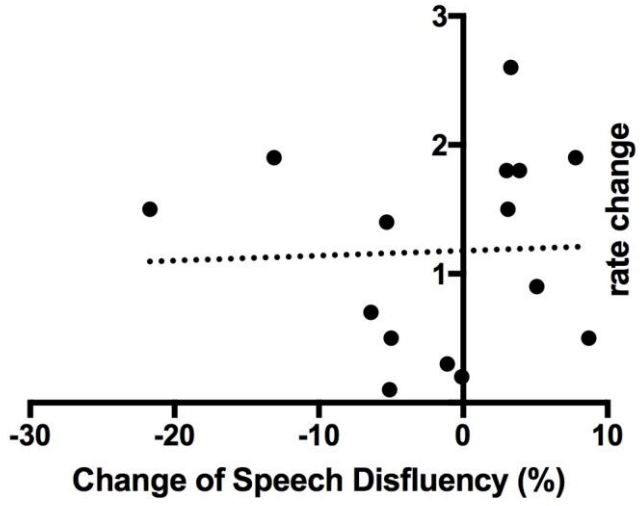


Figure 3.5 Comparison of speech rate in DAF condition and normal condition

Error bars represent standard error (SE).

n=15.

p<0.01



r = 0.04

Figure 3.6. Rrelation between the effect of DAF and speech rate

n=15

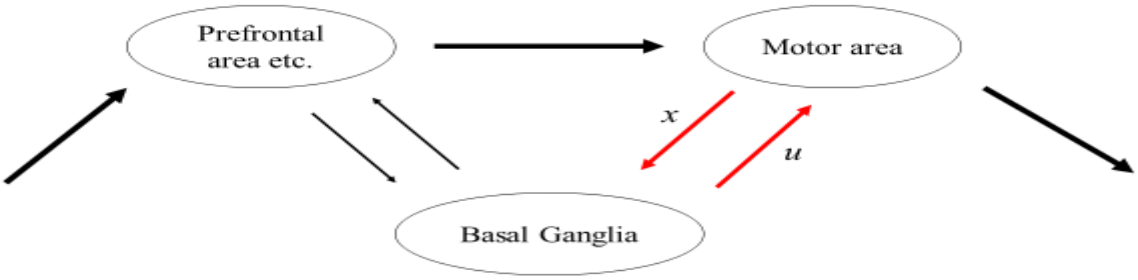


Figure 4.1 The roop with Basal Ganglia and cerebral cortex

In the basal ganglia, we think that there is a function to correct the error by feedback control (u) corresponding to the fluctuation of the trajectory (x) generated in the motor field.

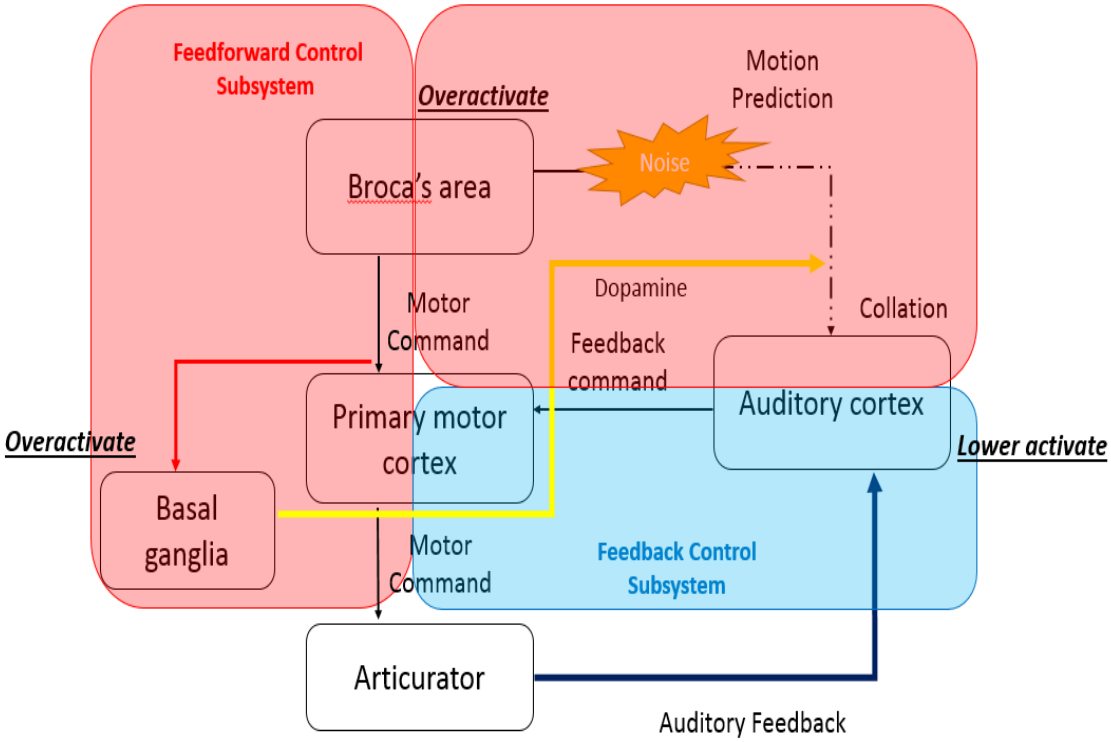


Figure4.2 Hypothetical model of stuttering

References

Andrews, G., Hoddinott, S., Craig, A., Howie, P., Feyer, A.-M., & Neilson, M. (1983). StutteringA Review of Research Findings and Theories circa 1982. *Journal of Speech and Hearing Disorders*, *48*(3), 226–246.

Andrews, G., Howie, P. M., Dozsa, M., & Guitar, B. E. (1982). StutteringSpeech Pattern Characteristics Under Fluency-Inducing Conditions. *Journal of Speech, Language, and Hearing Research*, *25*(2), 208–216.

Andrews, G., Morris-Yates, A., Howie, P., & Martin, N. (1991). Genetic factors in stuttering confirmed. *Archives of General Psychiatry*. Retrieved from http://psycnet.apa.org/psycinfo/1992-13326-001

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—the methods. *Neuroimage*, *11*(6), 805–821.

Barasch, C. T., Guitar, B., McCauley, R. J., & Absher, R. G. (2000). Disfluency and time perception. *Journal of Speech, Language, and Hearing Research*, *43*(6), 1429–1439.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *The Lancet*, *325*(8437), 1106–1107.

Beal, D. S., Gracco, V. L., Brettschneider, J., Kroll, R. M., & Luc, F. (2013). A voxel-based morphometry (VBM) analysis of regional grey and white matter volume abnormalities within the speech production network of children who stutter. *Cortex*, *49*(8), 2151–2161.

Bloodstein, O., & Bernstein Ratner, N. (2008). A handbook on stuttering New York:

Thomson Delmar Learning.

Braun, A. R., Varga, M., Stager, S., Schulz, G., Selbie, S., Maisog, J. M., … Ludlow, C. L. (1997). Altered patterns of cerebral activity during speech and language production in developmental stuttering. An H2 (15) O positron emission tomography study. *Brain*, *120*(5), 761–784.

Brown, S., Ingham, R. J., Ingham, J. C., Laird, A. R., & Fox, P. T. (2005). Stuttered and fluent speech production: an ALE meta-analysis of functional neuroimaging studies. *Human Brain Mapping*, *25*(1), 105–117.

Budde, K. S., Barron, D. S., & Fox, P. T. (2014). Stuttering, induced fluency, and natural fluency: A hierarchical series of activation likelihood estimation meta-analyses. *Brain and Language*, *139*, 99–107.

Cai, S., Tourville, J. A., Beal, D. S., Perkell, J. S., Guenther, F. H., & Ghosh, S. S. (2014). Diffusion imaging of cerebral white matter in persons who stutter: evidence for network-level anomalies. *Frontiers in Human Neuroscience*, *8*, 54.

Caplan, D. (1987). *Neurolinguistics and linguistic aphasiology: An introduction*. Cambridge University Press. Retrieved from https://books.google.co.jp/books?hl=ja&lr=lang_en|lang_ja&id=E3XrTCsU7bkC&oi=fnd&pg=PR9&dq=Caplan+1987&ots=zeTWUNWcH_&sig=9gbOzTIl6c7aKf22D9KeqwtaVtw

Chang, S.-E., Zhu, D. C., Choo, A. L., & Angstadt, M. (2015). White matter neuroanatomical differences in young children who stutter. *Brain*, *138*(3), 694–711.

Civier, O., Tasko, S. M., & Guenther, F. H. (2010). Overreliance on auditory feedback may

lead to sound/syllable repetitions: simulations of stuttering and fluency-inducing conditions with a neural model of speech production. *Journal of Fluency Disorders*, *35*(3), 246–279.

Conture, E. G., McCall, G. N., & Brewer, D. W. (1977). Laryngeal behavior during stuttering. *Journal of Speech, Language, and Hearing Research*, *20*(4), 661–668.

Denes, P. B., & Pinson, E. (1993). *The speech chain*. Macmillan.

Filmer, H. L., Dux, P. E., & Mattingley, J. B. (2014). Applications of transcranial direct current stimulation for understanding brain function. *Trends in Neurosciences*, *37*(12), 742–753.

Foundas, A. L., Bollich, A. M., Corey, D. M., Hurley, M., & Heilman, K. M. (2001). Anomalous anatomy of speech–language areas in adults with persistent developmental stuttering. *Neurology*, *57*(2), 207–215.

Foundas, A. L., Bollich, A. M., Feldman, J., Corey, D. M., Hurley, M., Lemen, L. C., & Heilman, K. M. (2004). Aberrant auditory processing and atypical planum temporale in developmental stuttering. *Neurology*, *63*(9), 1640–1646.

Foundas, A. L., Corey, D. M., Angeles, V., Bollich, A. M., Crabtree–Hartman, E., & Heilman, K. M. (2003). Atypical cerebral laterality in adults with persistent developmental stuttering. *Neurology*, *61*(10), 1378–1385.

Fox, P. T. (2004). Brain imaging in stuttering: where next? *Journal of Fluency Disorders*, *28*(4), 265–272.

Fox, P. T., Ingham, R. J., Ingham, J. C., Hirsch, T. B., Downs, J. H., Martin, C., … Lancaster, J. L. (1996). A PET study of the neural systems of stuttering. Retrieved

from http://www.nature.com/nature/journal/v382/n6587/abs/382158a0.html

Fox, P. T., Ingham, R. J., Ingham, J. C., Zamarripa, F., Xiong, J.-H., & Lancaster, J. L. (2000). Brain correlates of stuttering and syllable production. *Brain*, *123*(10), 1985–2004.

Freeman, F. J., & Ushijima, T. (1978). Laryngeal muscle activity during stuttering. *Journal of Speech, Language, and Hearing Research*, *21*(3), 538–562.

Fregni, F., Nitsche, M. A., Loo, C. K., Brunoni, A. R., Marangolo, P., Leite, J., … others. (2015). Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): review and recommendations from an expert panel. *Clinical Research and Regulatory Affairs*, *32*(1), 22–35.

Fukawa, T., Yoshioka, H., Ozawa, E., & Yoshida, S. (1988). Difference of susceptibility to delayed auditory feedback between stutterers and nonstutterers. *Journal of Speech, Language, and Hearing Research*, *31*(3), 475–479.

Geschwind, N., & Galaburda, A. M. (1985). Cerebral lateralization: Biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. *Archives of Neurology*, *42*(5), 428–459.

Giraud, A.-L., Neumann, K., Bachoud-Levi, A.-C., von Gudenberg, A. W., Euler, H. A., Lanfermann, H., & Preibisch, C. (2008). Severity of dysfluency correlates with basal ganglia activity in persistent developmental stuttering. *Brain and Language*, *104*(2), 190–199.

Guenther, F. H. (1994). A neural network model of speech acquisition and motor equivalent speech production. *Biological Cybernetics*, *72*(1), 43–53.

Guenther, F. H., Ghosh, S. S., & Tourville, J. A. (2006). Neural modeling and imaging of the cortical interactions underlying syllable production. *Brain and Language*, *96*(3), 280–301.

Guenther, F. H., Hampson, M., & Johnson, D. (1998). A theoretical investigation of reference frames for the planning of speech movements. *Psychological Review*, *105*(4), 611.

Guitar, B. (2013). *Stuttering: An Integrated Approach to Its Nature and Treatment*. Lippincott Williams & Wilkins.

Hain, T. C., Burnett, T. A., Kiran, S., Larson, C. R., Singh, S., & Kenney, M. K. (2000). Instructing subjects to make a voluntary response reveals the presence of two components to the audio-vocal reflex. *Experimental Brain Research*, *130*(2), 133–141.

Healey, E. C., Trautman, L. S., & Susca, M. (2004). Clinical applications of a multidimensional approach for the assessment and treatment of stuttering. *Contemporary Issues in Communication Science and Disorders*, *31*, 40–48.

Hickok, G., Houde, J., & Rong, F. (2011). Sensorimotor integration in speech processing: computational basis and neural organization. *Neuron*, *69*(3), 407–422.

Howell, P., El-Yaniv, N., & Powell, D. J. (1987). Factors affecting fluency in stutterers when speaking under altered auditory feedback. In *Speech motor dynamics in stuttering* (pp. 361–369). Springer. Retrieved from http://link.springer.com/chapter/10.1007/978-3-7091-6969-8_28

Ingham, J. C. (2003). Evidence-based treatment of stuttering: I. Definition and application.

Journal of Fluency Disorders, *28*(3), 197–207.

Jäncke, L., Hänggi, J., & Steinmetz, H. (2004). Morphological brain differences between adult stutterers and non-stutterers. *BMC Neurology*, *4*(1), 1.

Kalinowski, J., Stuart, A., Sark, S., & Armson, J. (1996). Stuttering amelioration at various auditory feedback delays and speech rates. *International Journal of Language & Communication Disorders*, *31*(3), 259–269.

Lee, B. S. (1950). Effects of delayed speech feedback. *The Journal of the Acoustical Society of America*, *22*(6), 824–826.

Lincoln, M., Packman, A., & Onslow, M. (2006). Altered auditory feedback and the treatment of stuttering: A review. *Journal of Fluency Disorders*, *31*(2), 71–89.

Luc, F., Kroll, R. M., & Houle, S. (2001). Functional neuroimaging of cerebellar activation during single word reading and verb generation in stuttering and nonstuttering adults. *Neuroscience Letters*, *302*(2), 77–80.

Mansson, H. (2000). Childhood stuttering: Incidence and development. *Journal of Fluency Disorders*, *25*(1), 47–57.

Max, L., Guenther, F. H., Gracco, V. L., Ghosh, S. S., & Wallace, M. E. (2004). Unstable or insufficiently activated internal models and feedback-biased motor control as sources of dysfluency: A theoretical model of stuttering. *Contemporary Issues in Communication Science and Disorders*, *31*(Spring), 105–122.

Molt, L. F., & Guilford, A. M. (1979). Auditory processing and anxiety in stutterers. *Journal of Fluency Disorders*, *4*(4), 255–267.

Montgomery, B. M., & Fitch, J. L. (1988). The prevalence of stuttering in the

hearing-impaired school age population. *Journal of Speech and Hearing Disorders*, *53*(2), 131–135.

Neilson, M. D., & Neilson, P. D. (1987). Speech motor control and stuttering: A computational model of adaptive sensory-motor processing. *Speech Communication*, *6*(4), 325–333.

Paulesu, E., Frith, C. D., Frackowiak, R. S., & others. (1993). The neural correlates of the verbal component of working memory. *Nature*, *362*(6418), 342–345.

Sommer, M., Koch, M. A., Paulus, W., Weiller, C., & Büchel, C. (2002). Disconnection of speech-relevant brain areas in persistent developmental stuttering. *The Lancet*, *360*(9330), 380–383.

Tourville, J. A., Reilly, K. J., & Guenther, F. H. (2008). Neural mechanisms underlying auditory feedback control of speech. *Neuroimage*, *39*(3), 1429–1443.

Van Riper, C. (1982). *The nature of stuttering*. Prentice Hall.

Watkins, K. E., Smith, S. M., Davis, S., & Howell, P. (2008). Structural and functional abnormalities of the motor system in developmental stuttering. *Brain*, *131*(1), 50–59.

Weber-Fox, C., Wray, A. H., & Arnold, H. (2013). Early childhood stuttering and electrophysiological indices of language processing. *Journal of Fluency Disorders*, *38*(2), 206–221.

Weiller, C., Isensee, C., Rijntjes, M., Huber, W., Müller, S., Bier, D., … Diener, H. C. (1995). Recovery from Wernicke's aphasia: a positron emission tomographic study. *Annals of Neurology*, *37*(6), 723–732.

Winterer, G., & Weinberger, D. R. (2004). Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. *Trends in Neurosciences*, *27*(11), 683–690.

Wolpert, D. M., & Kawato, M. (1998). Multiple paired forward and inverse models for motor control. *Neural Networks*, *11*(7), 1317–1329.

Wu, J. C., Maguire, G., Riley, G., Lee, A., Keator, D., Tang, C., … Najafi, A. (1997). Increased dopamine activity associated with stuttering. *Neuroreport*, *8*(3), 767–770.

Yairi, E. (1983). The Onset of Stuttering in Two-and Three-Year-Old ChildrenA Preliminary Report. *Journal of Speech and Hearing Disorders*, *48*(2), 171–177.

Yairi, E., & Ambrose, N. (2013). Epidemiology of stuttering: 21st century advances. *Journal of Fluency Disorders*, *38*(2), 66–87.

Yairi, E., & Ambrose, N. G. (1999). Early Childhood Stuttering IPersistency and Recovery Rates. *Journal of Speech, Language, and Hearing Research*, *42*(5), 1097–1112.

榊原洋一. (2009). 「脳科学」 の壁: 脳機能イメージングで何が分かったのか. 講談社.

横山. (2010). 脳からの言語研究入門—最新の知見から研究方法まで. 東京: ひつじ書房.

河原英紀. (2003). 聴覚フィードバックの発声への影響: ヒトは自分の話声を聞いているのか?(< 小特集> 発話と知覚の相互作用). 日本音響学会誌, *59*(11), 670–675.

Acknowledgments

In writing the master's thesis, Associate Professor Ryuichiro Hashimoto of the Graduate School of Humanities and Sciences, Tokyo Metropolitan University, gave me polite guidance for two years. I thank you from the bottom of my heart. Also, Associate Professor Fumiataka Homae and Assistant Professor Yutaka Fuchino are very grateful for their various advices on the meeting. In carrying out the experiment, Mr. Kengo Matsuhashi of undergraduate student in Tokyo Metropolitan University helped, and many stutterers cooperated. I appreciate very much. In addition, I got various advice from Daichi Iimura about experiment method. Thank you once again. Finally, I thank my family for supporting my student life.