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Feed-forward-related neural activity for vocalization:

A magnetoencephalographic study

(脳磁図を用いた feed-forward 機能に関する

脳内ネットワークの研究)

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[Introduction] The feed-forward function was described as an automatic neural process to control an action before actual movement. The feed-forward function involves a sensorimotor integration process, which can be affected by the external environment, stimuli, and internal state of brain activity at the moment of action. Brain activity associated with the feed-forward function has studied. However, neural activity regarding the sensory-motor integration for the feed-forward function remains unclear. Recently, the functional connectivity in the neural activity in the brain has been assessed based on the advantages of analytical techniques. We considered that analysis of neural connectivity might provide information regarding the interrelationship between sensory and motor control related to the feed-forward process. Controlling the vocal strength in the presence of environmental noise is known as a unique example of motor adjustment by the feed-forward function. We speak loudly in a noisy environment from the first word of speech. The vocal strength is adjusted to the environmental noise condition before the vocalization by the feed-forward function.

[Objective] The objective of the present study was to detect brain activity related to the feed-forward function from the viewpoint of the brain network. Since we focused on neural activity for the feed-forward function, we used an MEG system, which has the advantage of analyzing neural activity with a high temporal resolution.

[Methods] Nine healthy volunteers participated in the study. The MEG signals were recorded in a magnetically shielded room with an MEG system before vocalization under auditory conditions of environmental noise. The four auditory conditions included 42 dB of background noise, and 60, 80, and 100 dB of white noise. On the screen placed in front of the subjects, simple Japanese word was presented. Three seconds after the onset of the environmental noise, a word was presented on the screen for 5 seconds. The environmental noise stopped 2 seconds after the end of the word presentation. Therefore, one trial for a word took 10 seconds. In a trial without artificial environmental noise, a word was solely presented for 5 seconds, 3 seconds after the onset of the trial. Participants were instructed to read the word (Vo sequence). When no word was presented on the

screen, the participant was instructed just to watch the screen for 5 seconds (no vocalization, NV sequence). Eight conditions of trial, with or without reading under the 4 auditory conditions, were repeated 5 times. The MEG signals for 300 ms before the onset of vocalization in the Vo sequence were assessed. In the NV sequence, MEG signals of 300 ms in the middle of 5-second intervals were assessed for analysis. Functional connectivity was analyzed as synchrony between cortical areas, which is expressed as coherence value. Coherence analysis reveals a value with stable phase relations receives a maximum value of 1, whereas coherence with highly random phase relations is 0. Five vocalization-related cortices selected; truncanal area in the primary motor area (M1), premotor area (PM), supplementary motor area (SMA), posterior inferior frontal area (pIF), and posterior part of superior temporal area (pST) in each hemisphere. The left pST and pIF area corresponded to the conventional Wernicke's and Broca's areas, respectively. To assess effects of environmental noise on the vocalization performance, standardized vocal strength in the conditions with environmental noise relative to the condition without additional noise was calculated. The standardized vocal strength was compared among environmental noise conditions using a one-way repeated measures analysis of variance (ANOVA). Coherence values in six frequency bands (mean, 15, 30, 45, 60, 75, 90 Hz) were separately calculated among stimulus conditions. The correlation coefficients between the coherence values and vocal strength, and those values between the coherence values and environmental noise were calculated by Pearson's test.

[Results] The vocal strength of the participants significantly increased with an increase in the intensity of environmental noise. Coherence between M1 and pIF in the frontal cortex without vocalization and auditory pST in the temporal area before vocalization was negatively correlated with the level of environmental noise and vocal strength, respectively.

[Discussion] The present results revealed the brain areas in which neural activities changed relating to the vocal strength or environmental noise. Important findings in the present study are as follows: 1) the coherence value of the brain activity in the vocalization-related cortices before vocalization was related to the vocal strength, 2) brain areas, in which coherence was related to the vocal strength, included the left pST, which was not a movement-related but an auditory-related area, and 3) a coherence value change associated with environmental noise was observed between the right M1 and pIF, which were not auditory-related but motor-related areas. We considered that the change in brain activities in the pST before vocalization and the M1 and pIF during noise conditions in the NV sequences were related to sensory and motor integration for the feed-forward function.

脳磁図を用いた feed-forward 機能に関する脳内ネットワークの研究

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【背景】 Feed-forward 機能は、実際に運動が出力される前段階において、その運動をコントロールする神経のプロセスとされている。この feed-forward 機能は、知覚と運動を統合するプロセスを有しており、これは運動が出力される時の外的な環境や刺激、脳の内的な活動状態によって影響を受ける。Feed-forward 機能に関する脳活動が調査されており、動作直前の運動関連領域での知覚情報の処理について報告されている。しかし、feed-forward 機能における知覚と運動の統合プロセスに関する神経活動は、明らかにされていない。近年、解析技術の向上により、脳内の神経活動について、皮質間の機能的な連関の測定が可能となった。私たちは、神経の連関について解析することにより、まだ特定されていない feed-forward 機能の知覚と運動の相互関係についての知見を得ることが可能であると考えた。Feed-forward 機能による運動コントロールの一例として、雑音のある環境での声の大きさの調節が知られており、雑音の大きい環境では、発声の最初の文字から大きく話す。これは、feed-forward 機能によって、発声する前段階から、周囲の雑音の状況に合わせて発声音量が調節されたためである。

【目的】本研究は、雑音呈示下での発声を行い、脳内ネットワークの視点から、時間分解能に優れた脳磁図 (MEG) を用いて feed-forward 機能に関連する脳活動を特定することで、運動が出力される前段階に行われる知覚と運動の統合プロセスである、feed-forward 機能に関連する神経活動を明らかにすることを目的とした。

【方法】9名の健常ボランティアを対象に、様々な大きさの背景雑音が呈示されている条件下において、発声直前の脳磁場活動を、全頭型 MEG システムを用いて計測した。聴覚条件は4種類であり、42 dB の環境雑音と 60, 80, 100 dB のホワイトノイズとした。被験者は前方のスクリーンに呈示された単語を声に出して音読するよう指示を受けた。全ての単語はひらがなであり、最初の文字の発音を【あ】で統一した。背景雑音が呈示され始めた3秒後に単語が5秒間呈示され、単語の呈示が終了した2秒後に背景雑音を停止したため、1試行は、10秒間とした。人工的な背景雑音を伴わない試行では、伴う試行と同様に開始3秒後に5秒間単語が呈示された。被験者は、普段話すような自然な強さと速さで単語を読むように指示され (発声条件)、スクリーンに何も示されない時は、5秒間眺めるように指示された (非発声条件)。発声の有無と4種類の聴覚刺激による、計8条件をそれぞれ5試行ずつランダムに実施した。発声は、被験者の側方に設置した高感度マイクにて記録した。発声条件では、発声開始直前の300ms間の脳磁場活動を解析に使用した。非発声条件では、聴覚刺激が呈示されている5秒間の間中の300ms間の脳磁場活動を使用した。脳の機能的な連関は皮質間の同期として解析され、これは coherence 値として表された。Coherence 解

析では、一定した位相の関係性は最大値の 1 を示し、ランダムな位相の関係性は 0 として示された。先行研究に基づいて選択された 5 つの発声関連皮質を解析の対象とした；両半球の一次運動野 (M1)、運動前野 (PM)、補足運動野 (SMA)、後下前頭領域 (pIF)、上側頭領域後部 (pST)。左半球の pST と pIF は、それぞれ Wernicke's area と Broca's area に該当する。発声における背景雑音の影響を評価するために、追加の人工的な雑音がない状態の発声音量に対して、背景雑音の各条件における発声音量の変化率を算出することで、標準化された発声音量を算出した。標準化された発声音量は一元配置分散分析 (ANOVA) を用いて比較した。各条件下における 6 つの周波数帯域 (平均が 15, 30, 45, 60, 75, 90 Hz) での coherence 値をそれぞれ算出した。Coherence 値と発声音量, coherence 値と背景雑音の音量との間の相関関係について、Pearson の相関係数にて解析した。

【結果】被験者の発声音量は、背景雑音が大きくなるにしたがって有意に増加した。非発声条件では、前頭領域の M1 と pIF 間の連関において、coherence 値と背景雑音の大きさに有意な負の相関が認められ、発声条件では、側頭領域の pST を含む連関において、coherence 値と発声音量に有意な負の相関が認められた。

【考察】本研究結果は、発声音量や背景雑音の大きさに関連して神経活動が変化する脳領域を明らかにした。本研究における重要な発見は、1) 発声直前における、発声関連皮質の脳活動の coherence 値が、発声音量と関連していた、2) coherence 値が発声音量と関連していた脳領域に左 pST が含まれており、これは運動関連領域ではなく聴覚関連領域である、3) 背景雑音の大きさに関連した coherence 値の変化が、右 M1 と pIF にて認められ、これらは聴覚関連領域ではなく運動関連領域である。発声直前の pST における脳活動の変化と、非発声条件における雑音呈示下での M1 と pIF の脳活動の変化が、feed-forward 機能の知覚と運動の統合に関連していることが示唆された。

1. Introduction

When humans intend to perform an action, motor and sensory brain activities are controlled before the action (Wolpert & Miall, 1996). The feed-forward function was described as an automatic neural processes to control an action before actual movement, and the processes included an internal forward model used in the current state of the motor system and motor command to predict the next state (Wolpert & Miall, 1996). The feed-forward function involves a sensorimotor integration process, which can be affected by the external environment, stimuli, and internal state of brain activity at the moment of action (Perkell et al., 2007). The feed-forward process, as well as feed-back process, contributed to update and correct the motor programs with information on the external environment before and during actual movement to reach a goal of action (Medendorp, 2011).

Brain activity associated with the feed-forward function was studied using functional magnetic resonance imaging (fMRI) (Christensen et al., 2007), near-infrared spectroscopy (NIRS) (Sato, Fukuda, Oishi, & Fujii, 2012) and electro-corticography (ECoG) (Sun et al., 2015). The results in the previous studies suggested neurons in motor-associated cortices encoded sensory information before movements. An abnormal feed-forward function was also suggested in studies on the limbs and body movement of elderly persons with dementia and patients with schizophrenia and other neurological and psychological disorders, resulting in the complete loss of motor preparation and execution (Olafsdottir, Yoshida, Zatsiorsky, &

Latash, 2007; Mathalon & Ford, 2008; Bunday & Bronstein, 2009; Jo et al., 2016; Elliott et al., 2010). Studies relevant to feed-forward function using a magnetoencephalography (MEG) have been carried out (Walla, Mayer, Deecke & Thurner, 2004; Mersov, Cheyne, Jobst & De Nil, 2017), and they reported that the premotor and motor cortices were responsible to created fluency of speech through feed-forward process. However, neural activity regarding the sensory-motor integration for the feed-forward function remains unclear.

Recently, the inter-regional relationship and functional connectivity in the neural activity in the brain have been assessed based on the advantages of analytical techniques (Sakkalis, 2011). The importance of neural activities among cortices, the brain network, has been emphasized in various brain functions (Stam & van Straaten, 2012). From the viewpoint of the brain network, inter-cortical connectivity has been investigated during and before motor performance (Wolpert & Miall, 1996; Muthuraman et al., 2014; O'Neill et al., 2017) and motor imagery (Obayashi, Uemura, & Hoshiyama, 2016). We considered that analysis of neural connectivity may provide information regarding the interrelationship between sensory and motor control related to the feed-forward process, which has not been elucidated.

Controlling the vocal strength in the presence of environmental noise is known as a unique example of motor adjustment by the feed-forward function (Tartter, Gomes, & Litwin, 1993; Zollinger & Brumm, 2011). We speak loudly in a noisy environment from the first word of speech. The vocal strength is adjusted to the environmental

noise condition before the vocalization by the feed-forward function. The objective of the present study was to detect brain activity related to the feed-forward function from the viewpoint of the brain network, using an experimental setting for vocalization under conditions with environmental noise. We recorded brain activity before a motor performance, vocalization, whereby the intensity might be adjusted based on the intensity of environmental noise. Since we focused on neural activity for the feed-forward function, we used an MEG system, which has the advantage of analyzing neural activity noninvasively with a high temporal resolution (Lounasmaa, Hämäläinen, Hari, & Salmelin, 1996).

Therefore, we investigated changes in inter-cortical connectivity before vocalization in healthy subjects by changing the intensity of environmental noise using an MEG system in the present study. We reported the feed-forward-related neural activity obtained in our preliminary but challenging study in the present paper.

The efference copy and corollary discharge have been associated during the feed-forward processes (Crapse & Sommer, 2008). Since we considered that we could not clearly distinguish and extract these phenomena in the feed-forward processes, we used the term “feed-forward” to describe the neural process focused on in the present study.

2. Material and methods

2.1. Subjects

Nine healthy volunteers (5 males and 4 females, mean age: 23.6 ± 1.07 years) participated in the study. All subjects were right-handed based on the Edinburgh Inventory (Oldfield, 1971), and they had no history of neurological/psychological disorder. The present study was approved by the Ethical Committee of the Faculty of Medicine, Nagoya University.

2.2. Experimental procedure

The MEG signals were recorded in a magnetically shielded room with a whole-head MEG system (PQ-1160C, Ricoh Co., Japan) with a liquid helium recycler (HCS-MEG1, FTI, Japan). The MEG system included 160-channel axial-type first-order gradiometers with a 50-mm-long baseline detection coil. The gradiometers were arranged in a uniformly distributed array on a helmet-type dewar. Fiducial points for MEG were the nasion and both pre-auricular points, and the surface of the scalp of each subject was digitally traced using a 3-dimensional digitizer (SR system-R, Ricoh Co., Japan). The fiducial points and trace of the scalp surface were used to obtain the Montreal Neurological Institute (MNI) stereotactic coordinate for each subject, and pseudo-individual anatomy was created from standard brain anatomy, the International Consortium for Brain Mapping (ICBM) 152 non-linear atlases (Fonov, Evans, McKinstry, Almlie, & Collins, 2009), using the software Brainstorm (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011). The number of vertices of the cortical surface was 15,002 in the present study on the standard brain. Further anatomical

and MEG signal analyses were performed of the pseudo-individual brain. Using a pair of electrodes placed on the right hand and foot, electrocardiograms (ECG) were recorded. The MEG signals were continuously recorded with an initial bandpass filter of 0.3-2,000 Hz and a notch filter of 60 Hz at a sampling rate of 5,000 Hz.

Brain activity before vocalization was recorded by an MEG system under auditory conditions of environmental noise. Four conditions of artificial environmental noise involved white noise, and the noise was provided through elastic silicon tubes (3.5 mm diameter) connected to a pair of tube earphones in the participant's ears. A pair of canal-type acoustic microphones (DEH17K, Diamond Antenna Co., Tokyo, Japan) was connected to the other side of the elastic tubes outside the magnetically shielded room. The background noise through earphones was 42 dB in the magnetically shielded room. Artificial white noise was added to the background noise, and the intensity of the noise was adjusted to 60, 80, and 100-dB earphone levels. Although the background noise did not include a specific sound but a white-noise-like sound heard through the earphones, it was different in frequency structure from the artificial noise added. Therefore, the four auditory conditions included 42 dB of background noise, and 60, 80, and 100 dB of white noise. On the center of the screen placed 45 cm in front of the subjects, one of twenty simple Japanese words in white text on a black background was presented at the center of the screen (5 x 10 cm, 6.3 x 12.5-degree visual field). Each word comprised 2 or 3 Japanese syllabaries, hiragana (12 and 8 words for 2 and 3 syllabaries, respectively). Pronunciation of the

initial syllabary in all words was [a] in Japanese; e.g., a word [a-i] which means “love” in Japanese. All participants in a trial, environmental noise was presented for 10 seconds. Three seconds after the onset of the environmental noise, a word was presented on the screen for 5 seconds. Therefore, the environmental noise stopped 2 seconds after the end of the word presentation. One trial for a word with an auditory condition took 10 seconds. In a trial without artificial environmental noise, a word was solely presented for 5 seconds at same timing in a trial with environmental noise, 3 seconds after the onset of the trial (Fig. 1). An interval of 5 seconds was given between trials. Participants were instructed to read the word with natural intensity and speed of voice (Vo sequence) under the auditory conditions. When no word was presented on the screen, the participant was instructed just to watch the center of the screen for 5 seconds (no vocalization, NV sequence). Eight conditions of trial, with or without reading under the 4 auditory conditions, were repeated 5 times. Forty trials were randomly ordered for each participant, and same word stimuli were not presented for each participant.

Vocalization was recorded with a high-sensitivity microphone (KM184, Neumann), placed 80 cm lateral to the subject. The voice was simultaneously recorded as a sonography with the MEG signals with a similar bandpass filter of 0.3-2,000 Hz and a notch filter of 60 Hz at a sampling rate of 5,000 Hz.

2.3. Data analysis

Prior to the analysis, the ECG and eye-blink artifacts were detected in the preparation process in Brainstorm. The ECG and eye-link or eye-movement artifacts were detected and the Signal-Space Projection (SSP) with Independent Component Analysis (ICA) methods (Tesche et al., 1995; Uusitalo & Ilmoniemi, 1997) were applied following an offline bandpass filter of 3-150 Hz. The MEG signals for 300 ms before the onset of vocalization under each condition in the Vo sequence were assessed to conduct further analysis. In the NV sequence, MEG signals of 300 ms in the middle of 5-second intervals were assessed for analysis.

Functional connectivity was analyzed as synchrony between cortical areas, which is expressed as cortico-cortical coherence. We obtained the coherence value using the code within Brainstorm, in which coherence analysis is calculated based on an algorithm of minimum norm estimation (MNE) (Hämäläinen & Ilmoniemi, 1984). Coherence analysis reveals the consistency over time of the phase difference between two signals as a function of the frequency, and a value with stable phase relations receives a maximum value of 1, whereas coherence with highly random phase relations is 0 (Bardouille & Boe, 2012).

From the results in the MNE analysis, mean cortical current signals were estimated in five vocalization-related cortices selected based on the previous studies (Gunji, Kakigi, & Hoshiyama, 2000; Haggard & Whitford, 2004; Crapse & Sommer, 2008; Reznik, Ossmy, & Mukamel, 2015; Wang et al., 2014); truncal area in the primary motor area (M1), premotor area (PM), supplementary motor area (SMA),

posterior inferior frontal area (pIF), and posterior part of superior temporal area (pST) in each hemisphere. The left pST and pIF area corresponded to the conventional Wernicke's and Broca's areas, respectively. Details of the cortical areas selected are shown in Table 1 and Fig. 1. Coherence values were calculated between the current signals in two cortical areas.

2.4. Statistical analysis

To assess effects of environmental noise on the vocalization performance, standardized vocal strength in the conditions with environmental noise relative to the condition at background noise without additional artificial noise was calculated. The standardized vocal strength was compared among environmental noise conditions using a one-way (environmental noise) repeated measures analysis of variance (ANOVA). Standardized vocal strength was analyzed by ANOVA followed by Tukey-Kramer's test for multiple comparisons. Coherence values in six frequency bands, 7.5-22.5 (mean, 15 Hz), 22.6-37.5 (30 Hz), 37.6-52.5 (45 Hz), 52.6-67.5 (60 Hz), 67.6-82.5 (75 Hz), and 82.6-97.5 (90 Hz), were separately calculated among stimulus conditions. The correlation coefficients and p values between the coherence values and vocal strength, and those values between the coherence values and environmental noise were calculated by Pearson's test. A p-value of less than 0.01 was considered significant.

3. Results

3.1. Data preparation following data acquisition

All participants successfully performed the present task without error of vocalization. The vocal strength was measured from the baseline to the peak of sonography (Fig. 2). Duration of the vocalization recorded by sonography varied among trials, since word presented was different among trials. We did not measure the duration of sonography, but larger vocal strength in Fig. 2 showed longer duration of sonography. The vocal strength of the participants significantly increased with an increase in the intensity of environmental noise ($F(8, 16) = 6.79, p = 0.0073$, ANOVA) (Fig. 3). Since vocal strength varied among participants, each value was standardized by dividing the value by that at the condition with background noise of 42 dB to use for correlation analysis with coherence value.

As shown in the right half of Fig. 1, current waveforms were estimated via MNE in the cortical areas selected. We calculated coherence values for all combination among 5 cortical areas selected in each hemisphere in 6 frequency bands separately. Therefore, 20 coherence values were obtained at a frequency band for each trial in a participant. Coherence values varied among participants, and each value was standardized by dividing the value by that at the condition with background noise of 42 dB to use for correlation analysis with coherence value. In Vo sequence, correlations between coherence value and strength of environmental noise and between coherence and vocalization strength were calculated at each frequency band.

In NV sequence, correlation between coherence value and strength of environmental noise was assessed at each frequency band.

3.2. Correlation between inter regional connectivity and vocalization strength

Among coherence values obtained 20 combinations of cortical areas at each frequency, a significant negative correlation between coherence values and vocal strength among the conditions was obtained in Vo sequences between the right M1 and SMA at 15 Hz, the left PM and pST at 45 Hz, the left PM and pIF at 15 Hz, and the right PM and pIF at 90 Hz (Table 2). In Vo sequence, there was no coherence value which correlated with strength of environmental noise.

3.3. Correlation between inter regional connectivity and strength of environmental noise

Coherence value and strength of environmental noise were negatively correlated only between the right M1 and pIF at 60 Hz in NV sequences (Table 2).

4. Discussion

The present results revealed the brain areas in which neural activities changed relating to the vocal strength or environmental noise. Important findings in the present study are as follows: 1) the coherence value of the brain activity in the vocalization-related cortices before vocalization was related to the vocal strength, 2)

brain areas, in which coherence was related to the vocal strength, included the left pST, which was not a movement-related but an auditory-related area, and 3) a coherence value change associated with environmental noise was observed between the right M1 and pIF, which were not auditory-related but motor-related areas. We considered that the change in brain activities in the pST before vocalization and the M1 and pIF during noise conditions in the NV sequences were related to sensory and motor integration for the feed-forward function.

It was not surprising that the coherence values changed before vocalization among motor-related cortices with the vocal strength. Gunji et al., (2000) reported that the truncal motor area was activated before vocalization. The truncal area, including areas for respiratory muscles, should be responsible for vocal strength. Involvements of neural activity in the M1, SMA, PM, and pIF areas being negatively correlated with the vocal strength suggested that these areas contributed to the decision on the vocal strength during the pre-movement period for vocalization. The pST, which was basically an auditory-related area, also involved brain areas in which the coherence value was negatively correlated with the vocal strength. As shown in Fig. 3, environmental noise and vocal strength were significantly correlated with each other. There remained a possibility that the pST involvement was due to the auditory induced change in pST during Vo sequences. However, no correlation was noted between the coherence value and environmental noise in auditory-related areas but one was observed between the right M1 and pIF areas during NV sequences.

Therefore, the involvement of the pST area was not solely due to the auditory evoked effect, but was caused in association with vocalization. Similarly, the change in coherence between the M1 and pIF areas, which were motor-related areas, during NV sequences suggested that the information on the environmental noise was processed in these areas under the condition without motor performance. We considered that the present results suggest the brain areas in which auditory and motor processes are integrated. The pST, M1, PM, and pIF areas could also be candidates of the brain areas for the feed-forward process from the viewpoint of neural connectivity.

There was no brain area showing a significant correlation between the coherence value and environmental noise during the Vo sequence. We considered that the mixture of vocalization-related brain activities did not show a significant correlation of the coherence value with environmental noise.

The cortical areas, which showed significant changes in the coherence value in the present study in the Vo sequence, were also reported as the areas contributing to motor control during the pre-movement period. Reznik et al. (2015) reported that the SMA and M1 contributed to modification of the neural activity in the pST area during the perception of self-generated sounds, which could be produced with the feed-forward function, or efference copy and corollary discharge (Crapse & Sommer, 2008). The SMA and PM cortices were related to the feed-forward function, especially the adjustment of brain signals (Haggard & Whitford, 2004), and Wang et al. (2014)

reported that the activity of the inferior frontal gyrus including Broca's area, pIF in the present study, 300 ms before vocalization was related to the efference copy. These results of previous studies support the present results.

The r values of Pearson's correlation analysis were all negative between coherence values and the vocal strength or amount of environmental noise in the present study. The negative value of coherence in the present study indicated desynchronization of the activity between the brain areas. In the previous study, desynchronization of the beta frequency band between 15 and 30 Hz around the primary motor area was correlated with the muscle force (van Wijk, Beek, & Daffertshofer, 2012). Since the vocal strength was dependent on the muscle force of trunkal respiratory muscles, a decrease of coherence values with an increase in vocal strength might be in agreement with the results of a previous study (van Wijk et al., 2012). We could not determine the role of brain activity with a frequency higher than the beta band, which was negatively correlated with a vocal strength and level of environmental noise in the present study. However, a previous study suggested that a high gamma band between 70-150 Hz was related to the efference copy in the frontal and temporal regions (Kingyon et al., 2016). Desynchronization among motor-related areas in the present study might be in line with this previous study (Kingyon et al., 2016).

We analyzed neural connectivity based on coherence values in each hemisphere. There was no consistent laterality or dominance based on the present

results. Vocalization-related brain activities before vocalization of a simple syllable showed bilateral function (Gunji et al., 2000), and sensory motor integration for speech production was processed in the plana temporale on both sides, which was in pST in the present study (Simmonds, Leech, Collins, Redjep, & Wise, 2014). Ylinen et al. (2015), in their study of evoked magnetic fields, concluded that the auditory-motor circuit for forward prediction during speech production differed between hemispheres, and they did not act in dominant and non-dominant manners but showed hemisphere-specific roles. Since we used the initial syllable of a word in the present experiment, the present results might contribute to speech production, but there was no dominant side showing a significant change in coherence. The hemispheric sharing of roles for the feed-forward function should differ among tasks of vocalization, and further studies are needed to gain an overview of brain activity in both hemispheres.

As described above, we analyzed neural connectivity within each hemisphere among selected cortical areas. The involvement of other brain areas and interhemispheric interaction for the feed-forward function should be investigated in further studies, with increasing the number of participant. In an intrinsic brain function, such as feed-forward function, the mixture of brain activity for the perceptual control, learning or habituation of performance could not be excluded, since participants were aware of the environmental noise in the present study. Experimental design, including number of trials, should be also considered.

Destruction of the feed-forward function was suggested in neurological and psychological disorders (Olafsdottir et al., 2007; Mathalon & Ford, 2008; Bunday & Bronstein, 2009; Jo et al., 2016; Elliott et al., 2010). Function among the brain areas relating the feed-forward function could be abnormal in the patients. The feed-forward function was considered to be an intrinsic and automatic function, which could be visualized by analysis of neural connectivity. Studies of the pathological condition of the feed-forward function in patients are needed in further studies to determine critical connections for the function.

5. Conclusions

We carried out the present study to clarify neural activity associated with the feed-forward function, referring to sensory-motor integration processed before motor performance. In the present study, activity in motor-related areas in the frontal cortex without vocalization and auditory-sensory-related areas in the temporal area before vocalization was negatively correlated with the level of environmental noise and vocal strength, respectively. We considered that the present findings were, at least partially, relevant to the feed-forward function for vocalization.

Conflicts of interest

The authors declare no conflicts of interest.

References

- Bardouille, T., & Boe, S. (2012). State-related changes in MEG functional connectivity reveal the task-positive sensorimotor network. *PLoS One*, 7(10), e48682. doi: 10.1371/journal.pone.0048682.
- Bunday, K. L., & Bronstein, A. M. (2009). Locomotor adaptation and aftereffects in patients with reduced somatosensory input due to peripheral neuropathy. *J Neurophysiol*, 102(6), 3119-3128.
- Crapse, T. B., & Sommer, M. A. (2008). Corollary discharge across the animal kingdom. *Nat Rev Neurosci*. 9(8), 587-600. doi: 10.1038/nrn2457.
- Christensen, M. S., Lundbye-Jensen, J., Geertsen, S. S., Petersen, T. H., Paulson, O. B., & Nielsen, J. B. (2007). Premotor cortex modulates somatosensory cortex during voluntary movements without proprioceptive feedback. *Nat Neurosci*, 10(4):417-419.
- Elliott, D., Hansen, S., Grierson, L. E., Lyons, J., Bennett, S. J., & Hayes, S. J. (2010). Goal-directed aiming: two components but multiple processes. *Psychol Bull*, 136(6), 1023-1044.
- Fonov, V. S., Evans, A. C., McKinstry, R. C., Almli, C. R., & Collins, D. L. (2009).

- Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *NeuroImage*, 47 (Supp 1): S102.
- Gunji, A., Kakigi, R., & Hoshiyama, M. (2000). Spatiotemporal source analysis of vocalization-associated magnetic fields. *Brain Res Cogn Brain Res*, 9(2), 157-163.
- Haggard, P., & Whitford, B. (2004). Supplementary motor area provides an efferent signal for sensory suppression. *Brain Res Cogn Brain Res*, 19(1), 52-58.
- Hämäläinen, M., & Ilmoniemi, R. J. (1984). Interpreting measured magnetic fields of the brain: estimates of current distributions. *Technical Report*, TKK-F-A559, Helsinki University of Technology.
- Jo, H. J., Maenza, C., Good, D. C., Huang, X., Park, J., Sainburg, R. L., & Latash, M. L. (2016). Effects of unilateral stroke on multi-finger synergies and their feed-forward adjustments. *Neuroscience*, 5(319), 194-205.
- Kingyon, J., Behroozmand, R., Kelley, R., Oya, H., Kawasaki, H., Narayanan, N. S., & Greenlee, J. D. (2016). Corrigendum to "High-gamma band fronto-temporal coherence as a measure of functional connectivity in speech motor control". *Neuroscience*, 29, 335:242. doi: 10.1016/j.neuroscience.2016.07.019.
- Lounasmaa, O. V., Hämäläinen, M., Hari, R., & Salmelin, R. (1996). Information

processing in the human brain: magnetoencephalographic approach. *Proc Natl Acad Sci U S A*, 20;93(17), 8809-8815.

Mathalon, D. H., & Ford, J. M. (2008). Corollary discharge dysfunction in schizophrenia: evidence for an elemental deficit. *Clin EEG Neurosci*, 39(2), 82-86.

Medendorp, W. P. (2011). Spatial constancy mechanisms in motor control. *Philos Trans R Soc Lond B Biol Sci*, 27;366(1564), 476-491.

Mersov, A., Cheyne D., Jobst, C., & De Nil, L. (2017). A preliminary study on the neural oscillatory characteristics of motor preparation prior to dysfluent and fluent utterances in adults who stutter. *J Fluency Disord*, 17, S0094-730X(16)30067-5. doi: 10.1016/j.jfludis.2017.05.003.

Muthuraman, M., Hellriegel, H., Hoogenboom, N., Anwar, A. R., Mideksa, K. G., Krause, H., Schnitzler, A., Deuschl, G., & Raethjen, J. (2014). Beamformer source analysis and connectivity on concurrent EEG and MEG data during voluntary movements. *PLoS One*, 11;9(3):e91441. doi: 10.1371/journal.pone.0091441.

Obayashi, Y., Uemura, J. I., & Hoshiyama, M. (2016). Functional inter-cortical connectivity among motor-related cortices during motor imagery: A

magnetoencephalographic study. *Somatosens Mot Res*, 34(1), 1-8. doi: 10.1080/08990220.2016.1257985.

Olafsdottir, H., Yoshida, N., Zatsiorsky, V. M., & Latash, M. L. (2007). Elderly show decreased adjustments of motor synergies in preparation to action. *Clin Biomech (Bristol, Avon)*, 22(1), 44-51.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 9(1), 97-113.

O'Neill, G. C., Tewarie, P. K., Colclough, G. L., Gascoyne, L. E., Hunt, B. A., Morris, P. G., Woolrich, M. W., & Brookes, M. J. (2017). Measurement of dynamic task related functional networks using MEG. *Neuroimage*, 1(146), 667-678. doi: 10.1016/j.neuroimage.2016.08.061.

Perkell, J. S., Denny, M., Lane, H., Guenther, F., Matthies, M. L., Tiede, M., Vick, J., Zandipour, M., & Burton, E. (2007). Effects of masking noise on vowel and sibilant contrasts in normal-hearing speakers and postlingually deafened cochlear implant users. *J Acoust Soc Am*, 121(1), 505-518.

Reznik, D., Ossmy, O., & Mukamel, R. (2015). Enhanced auditory evoked activity to self-generated sounds is mediated by primary and supplementary motor cortices. *J Neurosci*, 4;35(5), 2173-2180. doi: 10.1523/JNEUROSCI.3723-14.

- Sakkalis, V. (2011). Review of advanced techniques for the estimation of brain connectivity measured with EEG/MEG. *Comput Biol Med*, 41(12), 1110-1117. doi: 10.1016/j.compbiomed.2011.06.020.
- Sato, Y., Fukuda, M., Oishi, M., & Fujii, Y. (2012). Movement-related cortical activation with voluntary pinch task: simultaneous monitoring of near-infrared spectroscopy signals and movement-related cortical potentials. *J Biomed Opt*, 17(7), 076011. doi: 10.1117/1.JBO.17.7.076011.
- Simmonds, A. J., Leech, R., Collins, C., Redjep, O., & Wise, R. J. (2014). Sensory-motor integration during speech production localizes to both left and right plana temporale. *J Neurosci*, 24;34(39), 12963-12972. doi: 10.1523/JNEUROSCI.0336-14.
- Stam, C. J., & van Straaten, E. C. (2012). The organization of physiological brain networks. *Clin Neurophysiol*, 123(6), 1067-1087. doi: 10.1016/j.clinph.2012.01.011.
- Sun, H., Blakely, T. M., Darvas, F., Wander, J. D., Johnson, L. A., Su, D. K., Miller, K. J., Fetz, E. E., & Ojeman, J. G. (2015). Sequential activation of premotor, primary somatosensory and primary motor areas in humans during cued finger movement. *Clin Neurophysiol*, 126(11), 2150-2161. doi: 10.1016/j.clinph.2015.01.005.

- Tadel, F., Baillet, S., Mosher, J. C., Pantazis, D., & Leahy, R. M. (2011). Brainstorm: A User-Friendly Application for MEG/EEG Analysis. *Comput Intellig Neurosci*, ID 879716, 1-13.
- Tartter, V. C., Gomes, H., & Litwin, E. (1993). Some acoustic effects of listening to noise on speech production. *J Acoust Soc Am*, 94(4), 2437-2440.
- Tesche, C. D., Uusitalo, M. A., Ilmoniemi, R. J., Huutilainen, M., Kajola, M., & Salonen, O. (1995). Signal-space projections of MEG data characterize both distributed and well-localized neuronal sources. *Electroencephalogr Clin Neurophysiol*, 95, 189-200.
- Uusitalo, M. A., & Ilmoniemi, R. J. (1997). Signal-space projection method for separating MEG or EEG into components. *Med Biol Eng Comput*, 35, 135-140.
- van Wijk, B. C., Beek, P. J., & Daffertshofer, A. (2012). Differential modulations of ipsilateral and contralateral beta (de)synchronization during unimanual force production. *Eur J Neurosci*, 36(1), 2088-2097. doi: 10.1111/j.1460-9568.2012.08122.x.
- Walla, P., Mayer, D., Deecke, L., & Thurner, S. (2004). The lack of focused anticipation of verbal information in stutterers: a magnetoencephalographic study. *Neuroimage*, 22(3), 1321-1327.

- Wang, J., Mathalon, D. H., Roach, B. J., Reilly, J., Keedy, S. K., Sweeney, J. A., & Ford, J. M. (2014). Action planning and predictive coding when speaking. *Neuroimage*, 1(91), 91-98. doi: 10.1016/j.neuroimage.2014.01.003.
- Wolpert, D. M., & Miall, R. C. (1996). Forward Models for Physiological Motor Control. *Neural Netw*, 9(8), 1265-1279.
- Ylinen, S., Nora, A., Leminen, A., Hakala, T., Huutilainen, M., Shtyrov, Y., Mäkelä, J. P., & Service, E. (2015). Two distinct auditory-motor circuits for monitoring speech production as revealed by content-specific suppression of auditory cortex. *Cereb Cortex*, 25(6), 1576-1586. doi: 10.1093/cercor/bht351.
- Zollinger, S. A., & Brumm, H. (2011). The Lombard effect. *Curr Biol*, 23;21(16), R614-615. doi: 10.1016/j.cub.2011.06.003.

Table 1. Cortical areas analyzed: truncal area in the primary motor area (M1), premotor cortex (PM), supplementary motor area (SMA), posterior inferior frontal area (pIF), and posterior part of the superior temporal area (pST). The areas are shown in Fig. 1.

Regions	Size of area (cm ²)	
	Left	Right
M1	10.00	9.13
PM	4.98	4.94
SMA	7.34	7.49
pIF	15.71	15.63
pST	13.51	13.50

Table 2. Correlation coefficient (r) and p-value in Pearson's correlation test for each the correlation between coherence value and vocal strength and the amount of environmental noise. Abbreviations are the same as in Table 1.

Frequency band (mean, Hz)	Sequence	Side	Cortical regions	r	p
Correlation between coherence value and vocalization strength					
15	Vocalization	Right	M1 - SMA	-0.652	0.00001
15	Vocalization	Left	PM - pIF	-0.445	0.0073
45	Vocalization	Left	PM - pST	-0.492	0.0058
90	Vocalizaion	Right	PM - pIF	-0.435	0.0062
Correlation between coherence value and environmental noise					
60	No vocalization	Right	M1 - pIF	-0.433	0.0069

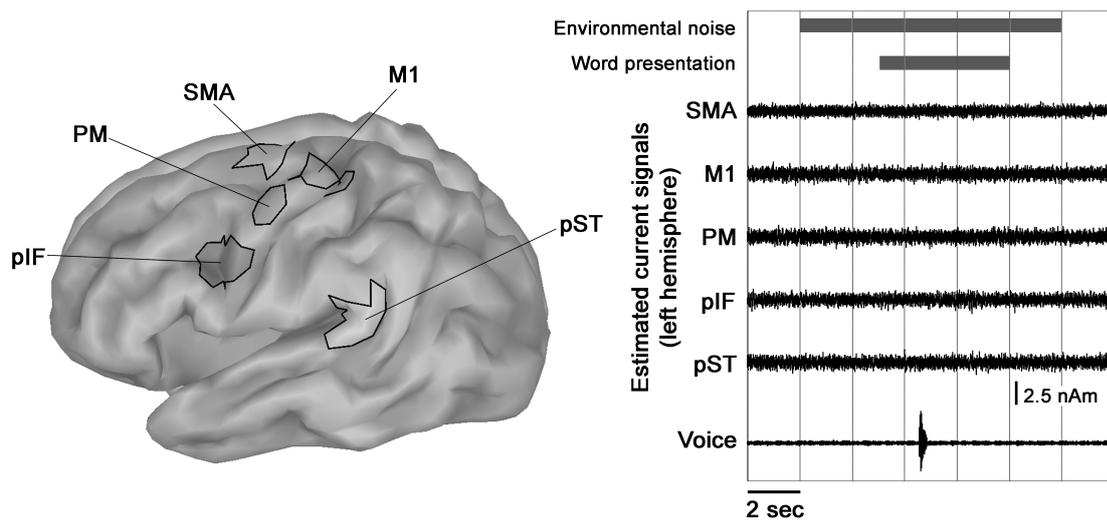


Fig. 1: Left: Brain areas selected in the left hemisphere. Truncal area in the primary motor area (M1), premotor area (PM), supplementary motor area (SMA), posterior inferior frontal area (pIF), and posterior part of the superior temporal area (pST). The areas in the right hemisphere were similarly selected. Right: Current signals estimated in each cortical areas in the left hemisphere and voice of the participant recorded as a sonography during a trial with vocalization (voice). Timings of environmental noise and word presentation are shown horizontal bars.

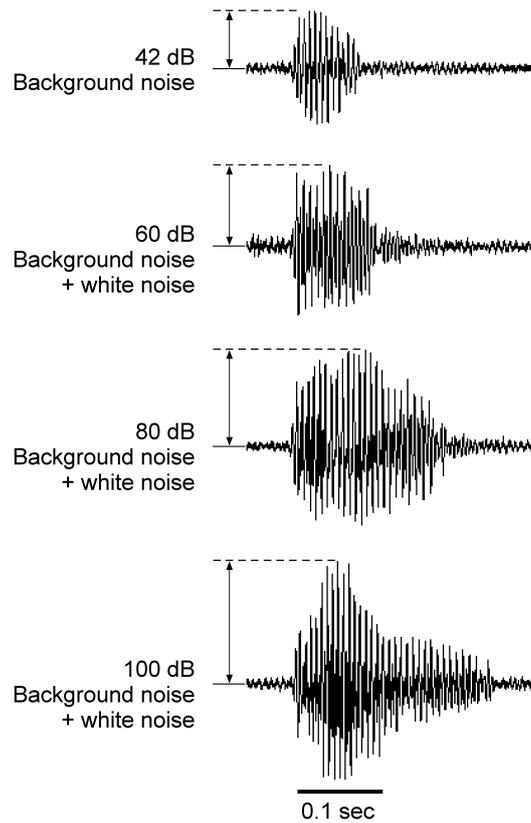


Fig. 2: Participant's vocalization recorded as sonography in representative trials. The vocal strength was measured from the baseline to the peak of sonography indicated by arrows. The vocal strength increased as the intensity of environmental noise increased. Duration of the vocalization varied among trials, since word presented was different among trials, although it seems longer for larger strength of vocalization.

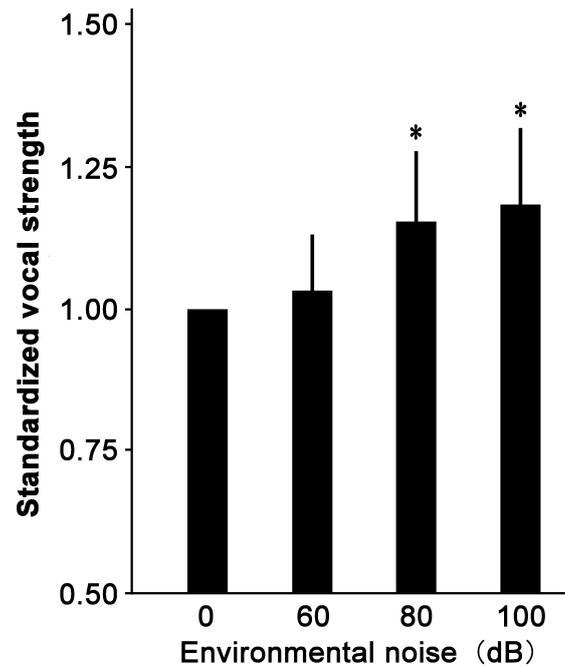


Fig. 3: Standardized vocal strength

Standardized vocal strength relative to the condition without additional noise (0) to background noise (42 dB) among conditions with environmental noise, compared with the background noise. Vocal strength increased with increasing environmental noise ($p = 0.0073$, ANOVA) and vocalization under the condition with noise at 80 and 100 dB was significantly louder than with noise under 0 and 60-dB conditions. * $p < 0.001$, Tukey-Kramer's test.