ORIGINAL ARTICLE

Increased activity in frontopolar cortex when writing meaningful sentences

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Abstract

Involvement of frontal and parietal cortices when writing single characters or words has been shown extensively in clinical and neuroimaging studies. However, brain activity when writing long sentences with a natural posture seen in the daily life has not been studied . Using near-infrared spectroscopy, we measured brain activities during sentence writing. Oxy-hemoglobin signals were compared between two test conditions: writing natural sentences with meaning, as compared to writing randomized letter combinations made from the same sentences. The right frontopolar area showed significantly higher activity while writing meaningful sentences than when writing random character combinations. These results differ from those of previous neuroimaging studies of writing single characters or words with a comparatively unnatural posture. The right frontopolar cortex is suggested by these results to be involved in processing sentence meanings, in combination with motor control of the hands in a natural posture.

INTRODUCTION

Writing by hand encompasses very complex cognitive processes (Lubrano, 2004). Since the classical and influential research of Paul Broca and Carl Wernicke reported in the mid 19th century, a very large amount of clinical and neuroimaging work has been applied to find the neural substrates for writing, suggesting the involvement of widely distributed cortical areas in the process of writing, such as the frontal (Bockova, 2007; Sugihara, 2006), temporal (Bockova, 2007; Sakurai, 2008a) and parietal (Bockova, 2007; Tokunaga, 1999) cortices. However, these studies have been limited to the process of writing single characters or words. Writing sentences, which are composed of a complex arrangement of characters and words within a context, is expected to involve far more complicated processes than just writing a simple character or word, and may involve additional cortical areas as the writing center.

The frontopolar cortex is a candidate component of the sentence-writing network, an area well developed in humans compared with in other primates (Fuster, 1989; Stuss, 1986). It has been suggested to have become specialized and enlarged during hominid evolution (Semendeferi, 2001). Writing is possibly linked to phylogenetically recent cortical zones (Critchley, 1970), and frontopolar cortical involvement has been shown in language processing, not only in understanding written and auditory words or sentences, but also in speaking (Bottini, 1994; Takizawa, 2008; Tan, 2001). The frontopolar cortical region is therefore suggested to be involved in the process of writing meaningful sentences.

In the present study, we examine rostral prefrontal cortical activity in Japanese subjects writing sentences with *kana* characters. Near-infrared spectroscopy (NIRS) was used to measure change of regional cerebral blood volume in a natural and comfortable posture during the task (Otsuka, 2007; Sato, 2007).

MATERIALS AND METHODS

Subjects

This study includes 16 healthy volunteers (9 males and 7 females), between the ages of 22 and 65 years (mean+SD = 40.0 + 14.5 years). All were right-handed according to the Edinburgh Handedness Inventory and had normal or corrected-to-normal vision. Experimental procedures were approved by the Institutional Ethics Review Committee of the University of Tsukuba and the National Institute of Advanced Industrial Science and Technology. They were performed in accordance with the 1964 Declaration of Helsinki. All subjects gave their informed consent prior to participating the study.

Task procedures

Visual stimuli: During the transcription task (see below), the subjects viewed original ‘meaningful’ sentences extracted from novels written by three famous Japanese writers (“Be not defeated by the rain” by Kenji Miyazawa; “Botchan” by Soseki Natsume; and: “Run, Melos!” by Osamu Dazai) in *kana* characters (Japanese phonograms). Learning these sentences is obligatory in Japanese elementary schools, so they were thought to be reasonably familiar to all subjects (who were all Japanese). For controls, a task comprising the same amount of visual information and motor movements was required. For this purpose, we used ‘meaningless’ sentences, which were artificially-made by randomizing the order of *kana* characters of the original sentences.

The sentences were vertically written in *kana* characters with 22 pt. HG font (*Sei-Kaisho-tai*) on a sheet of white A4 paper with height and width of approximately 1.00° × 0.72° and shown 40 cm apart from the subjects’ eyes (Figure 1A). Each column of sentences was separated by a vertical black line and the size of each column was 2.2° (width) × 23.7° (height). On average, 15 *kana* characters were printed in each column. The same sentence was printed in two neighboring columns: odd-numbered columns printed with light gray ink and even-numbered columns with black ink. The subjects transcribed (traced) the *kana* characters printed with light gray ink.

Transcription Task: The task was to trace each *kana* character of either meaningful or meaningless sentences that were printed in light gray ink on even columns for 120 s (task period) using an HB pencil (Uni; Mitsubishi Pencil Co. Ltd., Tokyo, Japan). Task periods were preceded by a 30-second resting period and each period was separated by the sound of a beep. During the resting period, subjects were asked to stare at a red fixation point (0.79° diameter) on a blank sheet of paper in order to avoid eye and head movement (Figure 1B). Immediately after the beep, the sheet of paper was quickly exchanged for an appropriate one (a paper with sentences or red fixation point). Subjects were told to start transcribing as soon as the sheet of paper was prepared, or to stop transcribing. Prior to the start of the task, subjects were told to maintain their posture so that their eyes would be 40 cm from the sentences on the paper.

One experiment consisted of four sessions: two sessions for transcribing only meaningful sentences and two sessions for transcribing only meaningless ones. Each session was composed of three task periods and four resting periods. In each task period, subjects had to transcribe sentences of one of three authors. The order of the four sessions was randomized and counterbalanced across subjects. Throughout the experiment, subjects were instructed to take the most comfortable posture for writing while reducing body movement as much as possible.

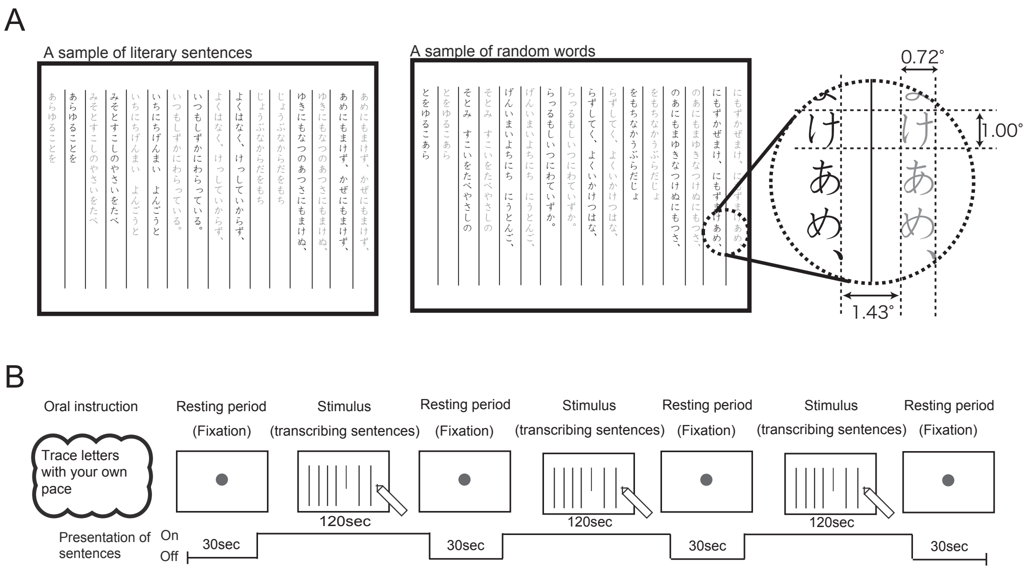

Figure 1. (A) Examples of meaningful (by Kenji Miyazawa) and meaningless sentences with their arrangement and sizes of *kana* characters presented on a sheet of paper (B) Sequence of a session
A session consisted of a 30-s resting period and a 120-s task presented alternatively 3 times and ended with a 30-s resting period. Subjects were instructed to focus upon a fixation point during the resting period with no limb or head movement. They were also instructed to trace gray-printed *kana* characters at their own pace during the task. They were not instructed which sentence (meaningful or meaningless) would be presented in the session.

NIRS data acquisition

Concentration changes in oxygenated hemoglobin (oxyHb), deoxygenated hemoglobin (deoxyHb), and their sum (totalHb) were recorded every 100 ms using a NIRS system (ETG-4000, Hitachi Medical Corporation, Tokyo, Japan). We analyzed only oxyHb because its concentration changes are thought to be the most sensitive indicators of changes in regional cerebral blood volume by providing the strongest correlation with the blood-oxygen-level-dependent signal (Hoshi, 2001; Strangman, 2002).

Identification of probe location

We measured oxyHb changes from 6 cm × 6 cm areas in each side of the frontal cortex by placing probes of 3 × 3 arrangement which comprised of channels (Ch) 1–12 on the left hemisphere and Ch 13–24 on the right hemisphere (Figure 2). The most rostro-medial probes were located at Fp1 (left hemisphere) and Fp2 (right hemisphere) of the 10/20 international electroencephalography system. Following the method used in earlier studies, Fp1 and Fp2 probes covered bilateral frontopolar and dorsolateral prefrontal areas (Okamoto, 2004a; Okamoto, 2004b; Takizawa, 2008). The positions of the probes were identified in two subjects by T2-weighted MRI images scanned by Signa Horizon (3T) and reconstructed on an MNI image (Figure 2), by using Vitamin E tablets placed on the probe positions.

Statistical analysis

We used the total number of *kana* characters transcribed within 120 s as a behavioral index. In transcribing meaningful sentences, we first examined whether the rank of preference of sentences (first – third; factor of RANK) or authors (Kenji Miyazawa, Soseki Natsume and Osamu Dazai; factor of AUTHOR) had an effect on behavior by one-way ANOVA. These factors showed no difference in total number of letters traced (see results), so we then tested the difference in the total number of *kana* characters transcribed between meaningful and control (randomized meaningless) sentences (factor of SENTENCE) by paired *t*-test after performing the Shapiro-Wilk test to test the data normality.

The following statistical analysis of the NIRS signals was the same as described in our previous work (Horaguchi, 2008). The oxyHb values obtained were smoothed with a 5-second moving average filter to reduce high-frequency artifacts (Sato, 2007). We defined the preceding 18 s period prior to the task period as the 'pre-task period' and the last 18 s of the following resting period as the 'post-task period' (Figure 3). Linear baseline correction with the use of the mean value during each pre- and post-task period was applied to remove any longitudinal signal drift. Data from the channels positioned over a hair-covered area often show a low signal-to-noise ratio due to the paucity of near-infrared light detected (Kameyama, 2004; Kameyama, 2006; Sato, 2007), so we excluded the oxyHb values with SDs > 0.03 during the pre-task period from further analysis.

Raw NIRS data from each channel were converted into *z*-scores (Matsuda, 2006; Otsuka, 2007) for comparison of channel to channel and among subjects. The *z*-score was calculated for time point t1 of each trial using the mean and SD of oxyHb values during the pre-task period:

z-score of t1= (oxyHb at t1 - mean oxyHb in pre-task period) / SD of oxyHb in pre-task period

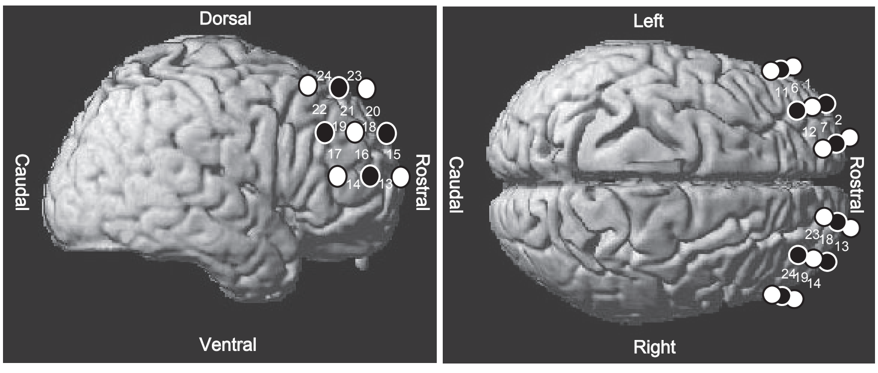

Figure 2. Arrangement of two 3 x 3 probes on the bilateral prefrontal cortex (white dot, emitter; black dot, detector)
Left and right images show the arrangement of probes in horizontal and sagittal direction, respectively. The emitters located at the rostro-medial most of each 3 x 3 probe was set at Fp1 and Fp2 of the 10/20 international electroencephalography system. Numbers between the emitter and detector indicate the channel number.

The integrated *z*-score of oxyHb values from the stimulus onset (0 s) up to 120 s afterward (until the end of task period) were averaged for each channel for a single subject (Figure 3). Data from some channels showed non-normal distributions by Shapiro-Wilk test ($p<0.05$), so we performed the non-parametric test on all the following NIRS data.

First, we analyzed the signal increase in oxyHb values from the baseline in each channel during transcribing sentences by testing changes of oxyHb value from the baseline by one-sample Wilcoxon signed rank test with the correction of the false discovery rate (Nakato, 2009; Singh, 2006) to eliminate the risk of Type I errors.

Each statistical analysis for the factors of RANK and AUTHOR by Friedman test was performed only in the meaningful sentences, because these factors could not be judged in the meaningless sentences.

Then, we contrasted the changes of oxyHb values between meaningful and randomized sentences in order to see whether NIRS activities significantly vary between two conditions by Wilcoxon test. All statistical analyses were performed using SPSS 27.0J and for Windows (SPSS Inc., Illinois, USA).

RESULTS

Behavioral Results: Number of letters transcribed

The average number of *kana* characters transcribed within 120 s (Figure 4) was 90.5 [mean] ± 25.5 [SD] for meaningful sentences, and 88.0 ± 26.2 for meaningless sentences, and was thus not significantly different ($p > 0.05$, paired *t*-test).

In the meaningful sentences, the numbers of letters transcribed for the factors of RANK were as follows: the most preferred sentence, 94.4 ± 26.6; second most-preferred sentence, 93.9 ± 26.3; third most preferred sentence, 94.3 ± 25.8. For the factor of AUTHOR, the number of letters transcribed were Kenji Miyazawa: 88.3 ± 26.7 letters, Soseki Natsume: 89.2 ± 26.2, and Osamu Dazai: 90.3 ± 26.1. One-way ANOVA revealed that there was no main effect ($p > 0.05$) of the factor of RANK (preference; first vs. second vs. third) ($p>0.05$) or of the factor of AUTHOR (Kenji Miyazawa vs. Soseki Natsume vs. Osamu Dazai). Interactions were not significant either. Preference of author therefore had no effect on the number of transcribed letters.

Brain Activity: Change in oxyHb value

When subjects transcribed sentences, a significant increase from the baseline was observed in multiple channels (channels 5, 6, 9, 10, 12, 13, 23, Figure 5) ($p < 0.05$; false discovery rate-corrected one-sample Wilcoxon signed rank test, t [9–14] = 3.002–3.895). However, no significant difference was observed in any channels in the factors of RANK or AUTHOR by Friedman test ($p > 0.05$); we used combined data of all RANK and AUTHOR of meaningful (original) sentence for further analysis.

The changes from the baseline in oxyHb value could include contributions from various components in the light path between brain parenchyma and NIRS probes such as blood flow changes of the skin, muscles or bones (Horaguchi, 2008; Kameyama, 2006; Sato, 2007). To eliminate the effects of other components that lie along the light paths, we used a control task with randomized sentences. The control task requires the same level of visual and motor function as writing original sentences, so contrasting these two

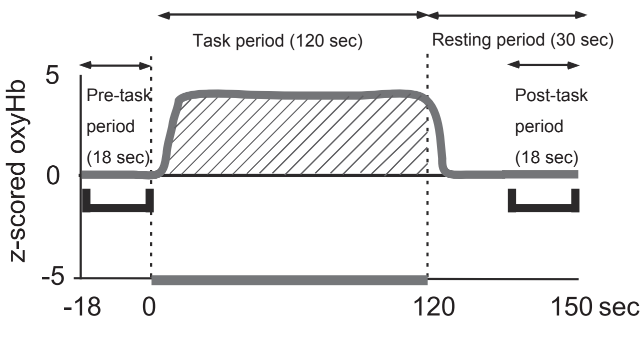

Figure 3. Example of a grand-averaged waveform obtained by near-infrared spectroscopy (NIRS)
Y and X axes represent z-scored oxyHb value and time (s). The zero and light gray bar on the X axis show initiation of the task and its duration (120 s). In this study, the integrated values of shaded area obtained at the same channel were compared between different conditions.

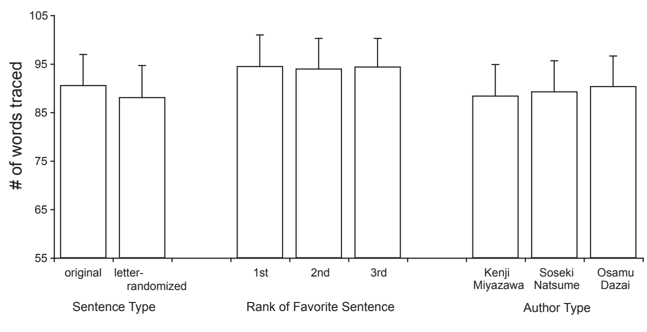

Figure 4. Number of *kana* characters transcribed under different conditions
Bars indicate SD. Statistical analysis revealed no significant difference between conditions.

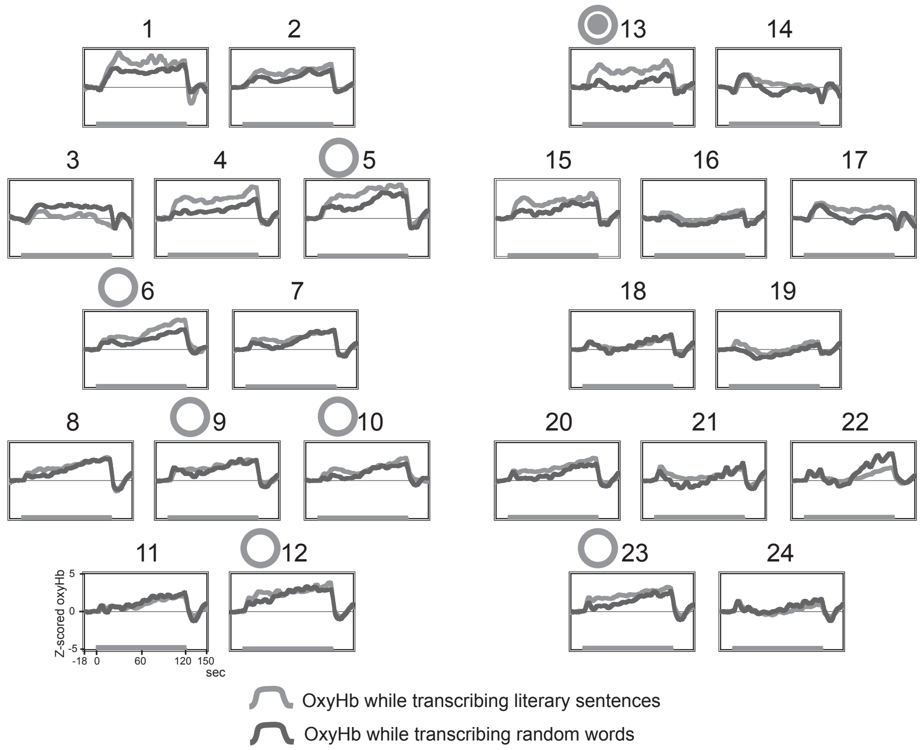

Figure 5. Changes in oxyHb value during transcribing meaningful (light gray lines) and meaningless (dark gray lines) sentences
Y and X axes represent z-scored oxyHb values and time (s), respectively. Numbers on each graph indicate channel number. Zero and light gray bar on the X axis show the initiation of task and its duration (120 s). The light gray open circle and dot represent a channel with significant increase from the baseline and that with significant difference between writing meaningful and meaningless sentences, respectively.

conditions supposedly eliminates the effect of components of the light path.

The change in grand-averaged waveforms of oxyHb values among 16 subjects at 1 to 24 channels in the original-sentence vs. control-sentence conditions are shown in Figure 5. A Wilcoxon test between two conditions revealed a significant difference of oxyHb value only at Ch 13 (t [9] = 2.545, p = 0.031), while in other channels, the oxyHb value showed no significant difference between the two conditions.

The probe of Ch 13 was located at Fp2 which corresponds to the right frontopolar area (Okamoto, 2004a; Okamoto, 2004b; Takizawa, 2008), so we considered that Ch 13 monitored the activity of the right frontopolar area (Figure 2).

DISCUSSION

Features of NIRS measurement

Recently, a number of papers have been published in which human brain activities were measured by the use of near-infrared spectroscopy (NIRS). The major obstacle of the NIRS method from becoming a general tool for measuring brain activity has been the issue of 'Light Path', as described in the Results section. In order to cancel out signal change in tissues other than brain parenchyma, a task should be carefully designed in terms of body posture and movements. In this study, in order to evaluate brain activity for a writing task that required a series of movements, a control task was designed such that it had exactly the same movements and posture as the experimental task, i.e., to transcribe randomized *kana* characters from the original sentences. Under such conditions, the number of *kana* characters that were written within a task period was not significantly different between meaningful and meaningless sentences. The hand movements and posture therefore seemed to be similar and blood flows in skin and muscles underneath the probes could also be similar in the two writing conditions. Consequently, the observed differences in blood flow between the conditions may be attributed to variations in the brain parenchyma. The higher Oxy-Hb level in the meaningful-sentence task than the control-task may therefore represent brain activity when subjects understand the meaning of the sentence in writing, instead of automatically writing without understanding the meaning.

Brain areas related to writing

The neural substrates of writing have long been studied. Since an influential report regarding localization of language function in the brain (Broca, 1861), many scientists (Trousseau, 1864; Jackson, 1866), seemed to consider that the function of written language shared the same neural substrate as that of spoken language. The impairments of writing were considered to be a reflection of the same linguistic deficiency as speech and reading because writing was always to some extent impaired in cases of aphasia or alexia.

However, there was one earlier report based on a number of cases (Marcé, 1856) stating that spoken and written language disorders were not parallel. A later paper (Ogle, 1867) reported a case of aphasia without agraphia and argued that 'the faculty of speech and the faculty of writing are not subserved by one and the same portion of cerebral substance'. Direct and detailed evidence that neural substrates for writing could be distinguished from those for speech and reading was first reported by Pitres (Pitres, 1884; Pitres, 1894). He described a patient who could not 'write words' with his right hand, even though his ability to read, speak and move his right hand were totally intact. The condition was named 'pure agraphia' (Barriere, 2003; Lorch, 2003).

Recent clinical studies have reported that lesions of a wide variety of cortical areas such as the frontal (Sakurai, 1997; Tohgi, 1995), temporal (Rapcsak, 2004; Sakurai, 2008b) and parietal (Alexander, 1992; Otsuki, 1999; Rapcsak, 1997; Roeltgen, 1993; Sakurai, 2007) cortices, especially on the left hemisphere, induce various writing disorders (agraphia) which can be classified into various subclasses. 'Pure agraphia' is a writing disorder, in which other disorders that may prevent motor activity for writing are not associated with (Lorch, 2003; Pitres, 1884). 'Alexia with agraphia' (Iwata, 1984; Sakurai, 1994) and 'aphasic agraphia' (Paolino, 1983) are writing disorders with reading and speaking disabilities. Agraphia due to sensorimotor disorders is classified as 'apraxic agraphia' (Alexander, 1992; Popescu, 2007), and is due to a defect in spatial recognition called 'spatial dysgraphia' (Cubelli, 2000; Rode, 2006). The brain areas that induce each of these subclasses of agraphia have not yet been fully determined, but in many cases it emerged when frontal or parietal cortices were injured.

Neuroimaging studies have shown that writing activates several cortical areas including the prefrontal and parietal areas (Bockova, 2007; Siebner, 2001; Sugihara, 2006; Tokunaga, 1999), which clinical studies have also inferred as the writing center. However, in these neuroimaging studies, subjects were required to write just a single letter or a word in an alphabet or *kana* characters, sometimes without writing devices such as pens or pencils (e.g., they wrote the letter or word in the air using a finger). In some experiments these were sometimes performed even without writing actions (self-imagination of writing actions) lying on a bed with the head immobile, which is an unnatural condition for normal writing (Lubrano, 2004). Whether these cortical areas are activated during the writing of long meaningful sentences while seated in a normal position is unknown.

Frontopolar cortex and language

The frontopolar cortex is well developed in humans compared with in other primates (Fuster, 1989; Stuss, 1986). This region, where in the present study we found significant difference between writing meaningful and meaningless sentences, has already been reported to be involved in processing language. In one study, for example, fMRI showed activation of the frontopolar region while subjects were judging semantic similarity of a pair of Chinese characters (Tan, 2001). The frontopolar cortex is suggested by this result to be involved in semantically understanding 'a single character', as each Chinese character is not just phonetic, it has meaning. In other PET and fMRI studies, the frontopolar cortex was shown to be activated when 'metaphor sentences' were presented visually (Bottini, 1994; Ferstl, 2001; Shibata, 2007) or verbally (Ferstl, 2002), suggesting that it is involved in processing visually read and auditory heard 'sentences'. Using NIRS, frontopolar activation has been shown in normal subjects while generating (speaking) as many words as possible (Takizawa, 2008; Pu, 2008). Activation during face-to-face conversations has also been shown by measurement with NIRS in this area, particularly when speaking rather than listening (mute segments) (Suda, 2009).

Functions of the frontopolar region have been suggested, such as integrating (Ramnani, 2004) and coordinating ventro- and dorsolateral prefrontal cortices for maximizing task performance (Braver, 2002; Fletcher, 2001; Koechlin, 1999). The frontopolar cortex reportedly selectively mediated the human ability to hold in mind the final goal while exploring intermediary goals, a process generally required in planning and reasoning (Koechlin, 1999). Our task is thought to match this description because it required subjects to hold sentences (words) in a working memory system to process the meaning of the sentences while writing *kana* characters, which could be the final goal. This area is also known to be activated in processing sentences with increasing difficulty (Bottini, 1994; Cohen, 1993; Grasby, 1993; Jonides, 1997; Owen, 1999). Understanding sentences written by literary masters is expected to be of greater difficulty to interpret than understanding simple sentences of daily use. In other reports, complex problem-solving and planning are considered to be involved in the most anterior part of the frontal lobes including the frontopolar cortex (Baker, 1996; Grafman, 1995; Owen, 1996; Sirigu, 1995; Spector, 1994; Wharton, 1998). Measurement of frontopolar activity with NIRS is considered to have advantages over fMRI in some aspects, such as efficiency of measuring oxyHb and anatomical features of frontopolar region, which might induce severe distortions and regional signal losses in long-TE gradient-echo images at a high magnetic field (Takizawa, 2009). These reasons may explain the comparatively small amount of evidence that exists for frontopolar activity during writing in the previous studies that used fMRI and our successful measurement from frontopolar region using NIRS. To the best of our knowledge, this is therefore the first study to show stronger frontopolar activity while writing, especially when writing meaningful long sentences.

Hemisphere specialization

Broca's and Wernicke's areas are located within the left hemisphere, while many clinical and neuroimaging studies have shown that the writing center is located in the left hemisphere. Previous studies on the writing center have reported the involvement of the left frontal region, for example, Exner's area (Exner, 1881) is located at the left inferior frontal area just dorsal to Broca's area. Others have also reported the importance of the left parietal region for writing characters or words (Alexander, 1992; Auerbach, 1981; Basso, 1978; Otsuki, 1999; Rapcsak, 1997; Roeltgen, 1993; Sakurai, 2007). Overall function of language processing is therefore generally localized to the left hemisphere. However, one paper reported that cued retrieval of paired associates of words from episodic memory in comparison with semantic word generation produced right frontopolar activation (Grasby, 1993). Extensive damage to the entire right medial area, including the frontopolar area, reportedly produces a dramatic behavioral syndrome that includes emotional flattening, inappropriateness, apathy, and confabulation (Alexander, 1989; Alexander, 1992; Stuss, 1978). Some kind of emotion from reading and writing semantic sentences might therefore exert right frontopolar activation. Further, damage to the right frontopolar area is also reported to cause disability in understanding social context (Alexander, 1989; Alexander, 1992; Ross, 1981; Stuss, 1978). The right frontopolar area might therefore be involved in understanding the context of meaningful sentences.

Connections between the frontopolar cortex with other language areas

Information flow for spontaneous writing is thought to be initiated from Wernicke's area, which gives rise to two different pathways to access motor areas. One of them is the phonologic (dorsal) pathway leading directly from Wernicke's area to the angular gyrus, where visual images of the individual *kana* characters are thought to be stored. In the angular gyrus and the adjoining lateral occipital gyri, phonemes are considered to be converted into graphemes so that the visual images of *kana* characters are linked to their phonetic value in these areas (Sakurai, 1997). The other route is the morphologic (ventral) pathway, in which visual images of a whole-word (*kana* characters, letters of the alphabet, or Chinese characters) are sent from Wernicke's area to the angular gyrus and the superior parietal lobule via the posterior part of the middle and inferior temporal gyri, where visual images of Chinese characters are stored and correct characters/letters are selected according to the meaning of the word. Inputs to angular gyrus, both from dorsal and ventral pathways, are then sent through the arcuate fasciculus, to frontal areas such as Broca's and Exner's areas. Exner's areas might then send the information to areas corresponding to writing areas in the primary motor cortex, to produce the action of hand-writing.

The frontopolar cortex has strong connections with the multimodal cortical region in the upper bank of the superior temporal sulcus (Petrides, 2004), where Wernicke's area is located (Bockova, 2007; Embick, 2000), and with the ventrolateral prefrontal cortex (Petrides, 2004), where Broca's area lies (Embick, 2000), and dorsolateral prefrontal cortex, the working memory center. The frontopolar cortex may therefore exert influences upon major language centers to allow higher order linguistic information processing. The activation of frontopolar cortex was higher when subjects transcribed meaningful sentences than when they transcribed those that were randomized, so this may indicate that the frontopolar cortex has some role in processing the semantic information of words. Further, the connections are reported to be bilateral (Moayedi, 2015), so it is not surprising that the right frontopolar area processes the semantic sentences and shows emotion and context related activity by reading and writing meaningful words or sentences.

As a limitation of this study, we did not assess whether the subjects considered the 'meaningful sentences' to be meaningful, but we believe the meaningful sentences used are widely known and famous Japanese sentences, so we believe that all subjects might know and recognize them as soon as they start transcribing.

CONCLUSIONS

Using NIRS, we recorded frontopolar activations while transcribing both meaningful and meaningless sentences. This is perhaps the first study to record frontopolar activity while subjects were writing long sentences, achievable owing to the unique properties of NIRS. The right frontopolar area showed stronger activity while transcribing meaningful sentences compared with meaningless sentences.

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AUTHOR CONTRIBUTIONS

In this study, TH performed all experiments and analyses, designed this study. SM contributed to the discussion and revision of the manuscript. All authors have approved the submitted version of the manuscript and agreed to be accountable for any part of the work.

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