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Frequency-dependent spatiotemporal distribution of cerebral oscillatory changes during silent reading: A magnetoencephalograhic group analysis

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ABSTRACT

The frequency profiles and time courses of oscillatory changes when reading words are not fully understood, although there have been many reports that oscillatory dynamics reflect local brain function. In order to clarify oscillatory dynamics, we investigated the frequency and spatiotemporal distributions of neuromagnetic activities during silent reading of words in 23 healthy subjects. Individual data were divided into the following frequency bands: theta (5–8 Hz), alpha (8–13 Hz), beta (13–25 Hz), low gamma (25–50 Hz), and high gamma (50–100 Hz), and were analyzed by synthetic aperture magnetometry (SAM). The time window was consecutively moved in steps of 50 ms. Group analysis was performed to delineate common areas of brain activation. A transient power increase in the theta band occurred first in the bilateral occipital cortices, and then rapidly propagated to the left temporo-occipital areas, left inferior and middle frontal gyri, bilateral medial prefrontal cortices, and finally to the left anterior temporal cortices, which possibly reflects a serial cognitive process. This serial propagation of the transient power increase in the theta band was followed by sustained power decreases in the alpha, beta and low gamma bands. These results suggest that the transient power increase in the theta bands may be associated with priming and propagation of local activities, while sustained power decreases in the alpha, beta and low gamma bands reflect parallel neural processes related to silent reading words. Our results showed a relationship between frequency bands of oscillatory changes and locations. This may have implications in the relationship between frequency bands and functions.

Introduction

The neural process of reading words is complex and multifaceted, involving cognitive, attentional, memory, sensory and motor processes in addition to phonological, lexical and semantic processes. Various neurophysiological models for reading words have been proposed.

Many studies using magnetoencephalography (MEG) examined the neural process of reading words by leveraging its high temporal resolution. A pioneering MEG study advocated the serial processing model (Salmelin and Hari, 1994). In contrast, using spatially filtered MEG, Kober et al. (2001) suggest that language-related brain areas may not necessarily be activated sequentially but might also be activated simultaneously. Although they reported about the possibility of the parallel processing by using spatial filter, they examined spatial localization of the event related fields, not the oscillatory changes.

The signal power of cerebral rhythmic activities changes due to brain activation. Event-related desynchronization (ERD) is an attenuation of, and event-related synchronization (ERS) is an increase of, the oscillation amplitude of a specific frequency band related to a specific neural activity (Pfurtscheller, 1992). These oscillatory changes have been linked to higher cognitive processes such as attention (Klimesch et al., 1998), memory (Krause et al., 2007; Mainy et al., 2007) and reading (Hirata et al., 2004; Ihara et al., 2003b; Singh et al., 2002). It is thought that by understanding the relationships between these cognitive oscillatory processes, their underlying neural networks will be elucidated.

Synthetic aperture magnetometry (SAM) is a spatial filtering technique based on the nonlinear constrained minimum-variance beamformer, and is capable of detecting current density in an arbitrarily chosen voxel within the brain with high spatial resolution (Baillet et al., 2001). Thus, the spatiotemporal distributions of ERD and ERS can be obtained precisely using SAM. We used this technique to investigate language processing based on cerebral oscillatory changes and have previously reported that cerebral oscillatory changes during silent reading are localized in language-related areas (Hirata et al., 2010; Hirata et al., 2004; Hirata et al., 2007; Ihara et al., 2003a). We found that the frontal language areas are consistently desynchronized in the beta and low gamma bands during silent reading (Hirata et al., 2010, 2004). Xiang et al. (2001) found, also with SAM, that a language

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task induces a gamma ERD in Broca and Wernicke areas in healthy subjects. Another MEG study using a spatial filtering technique (Kober et al., 2001) showed the spatiotemporal distribution of current sources during silent reading and silent naming tasks.

Pammer et al. (2004) reported on the activity of the visual word form area (VWFA) during silent reading by applying a group analysis method to SAM results. SAM group analysis was developed by Singh et al. (2003) to eliminate inter-individual differences and to delineate common areas of brain activation. Although the report by Pammer et al. (2004) described the temporal profile of silent reading, the analyzed frequency band was limited to the beta band which had previously been shown to produce changes in cortical desynchronization that are spatially coincident with the hemodynamic response found with functional magnetic resonance imaging (Singh et al., 2002). Hence, the frequency profile and the time courses of language-related oscillatory changes have not been comprehensively studied to date.

The aim of the present study is to clarify the spatiotemporal distribution of the cerebral oscillatory changes during silent reading using synthetic aperture magnetometry. We introduced a sliding time window into SAM group analysis to delineate the temporal distribution of the common cerebral oscillatory changes related to silent reading.

Materials and methods

Subjects

Twenty-three healthy, native Japanese volunteers (mean age 24.6 ± 4.7 years (SD); range 21–39 years old; 6 males and 17 females) participated in this study. To assess the handedness of subjects, Edinburgh Handedness Inventory tests (Oldfield, 1971) were performed and all subjects were judged to be right handed (mean score +95.5 ± 6.2 (SD)). All subjects had no history of neurological or psychiatric diseases, and were with normal or corrected-to-normal vision. In accordance with the Declaration of Helsinki, we explained the purpose and possible consequences of this study to all subjects, and obtained informed consent prior to their study participation. The protocol of this study was approved by the ethics committee of Osaka University Hospital.

Silent reading task

Japanese semantic words, composed of three Japanese hiragana characters, were used as visual stimuli, which were selected from an elementary school dictionary so as to be understood quickly and easily by all participants. A word was presented visually for 3 s after the presentation of a fixation point for 3 s. One hundred words were presented serially. Subjects were instructed to silently read each presented word only one time, immediately after word-presentation, and then to watch the fixation point without repeating the word (Hirata et al., 2010, 2004).

Measurements

Measurements were performed with the subject sitting on a comfortable chair in a magnetically shielded room, using a 64-channel whole-head MEG system equipped with SQUID gradiometers

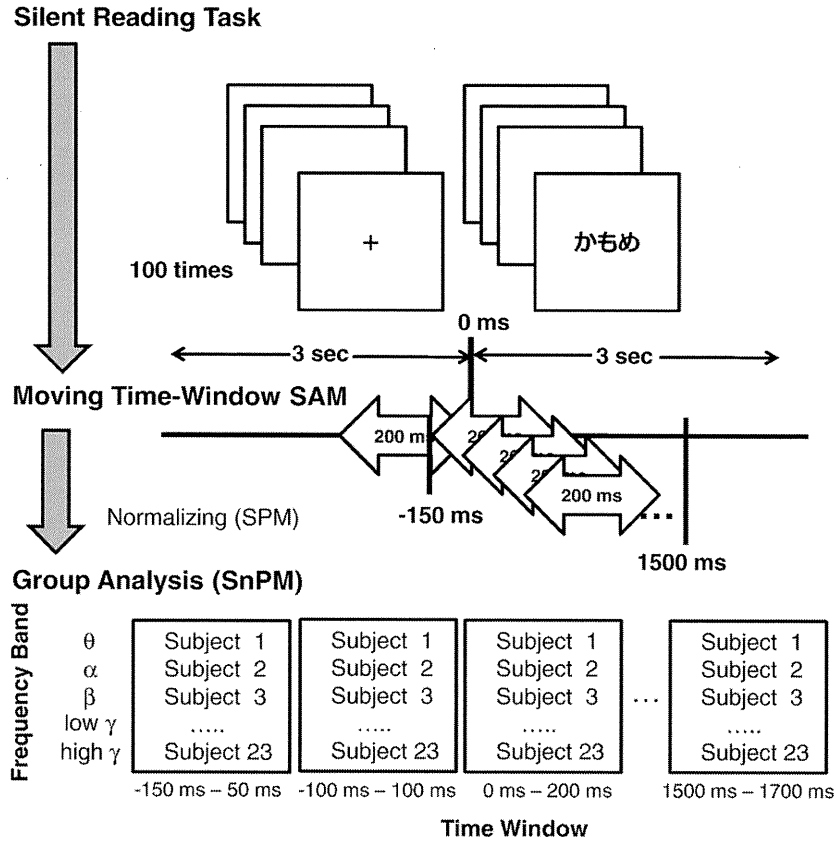
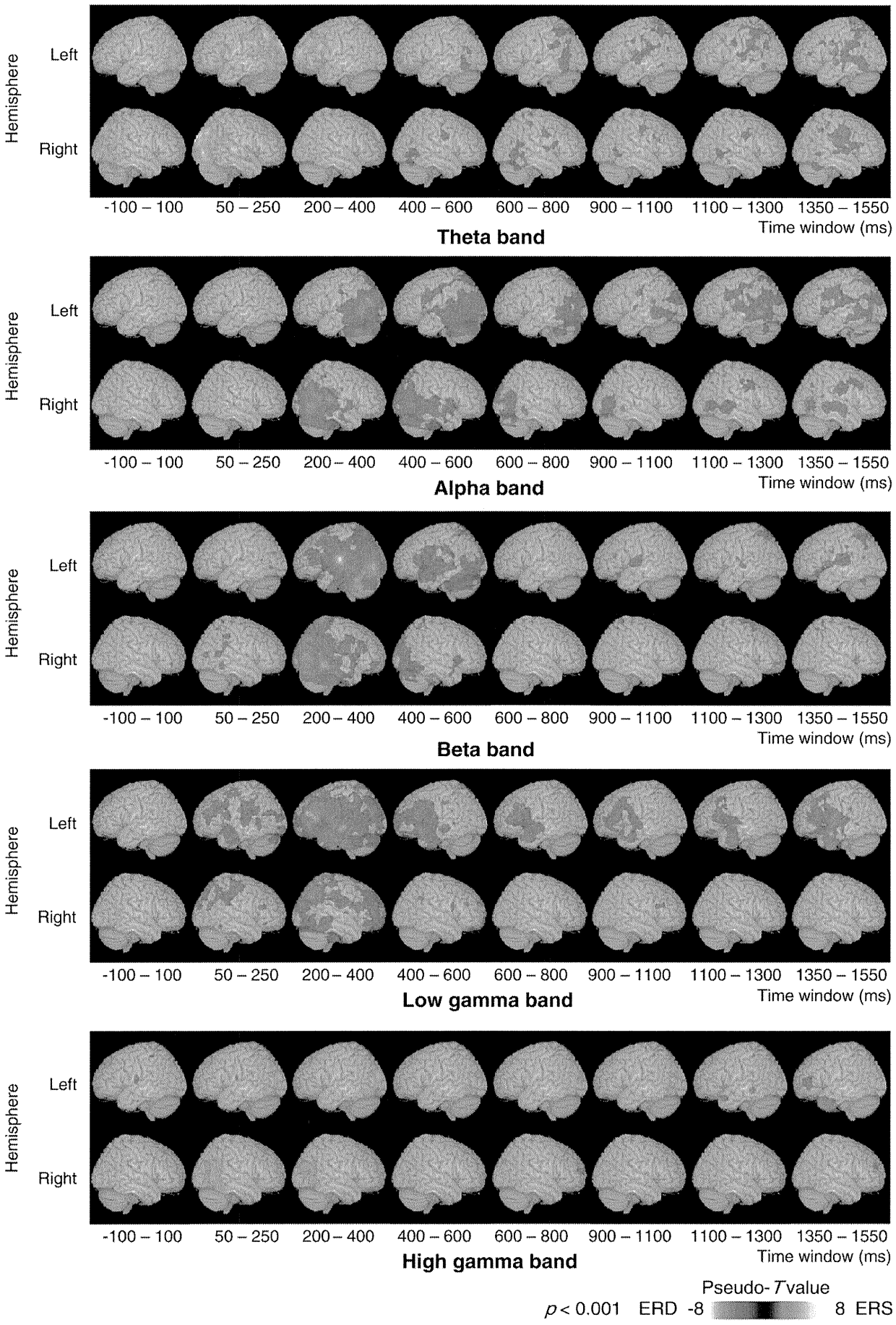


Fig. 1. A schematic diagram of the task and analysis. One hundred Japanese semantic words, composed of three Japanese hiragana characters, were used as visual stimuli. Subjects were instructed to read the presented word only once immediately after word-presentation and to watch a fixation point (+) passively. The MEG data was measured pre- and post-stimulus for 3 s. Each subject's MEG data was evaluated using SAM analysis, which is a spatial filter, for five frequency bands (the theta band, 5–8 Hz; the alpha band, 8–13 Hz; the beta band, 13–25 Hz; the low gamma band, 25–50 Hz, the high gamma band, 50–100 Hz). The control period was defined as the time 200 ms preceding stimulus onset (−200 to 0 ms) and the periods of interest were defined as consecutive 200 ms windows starting 150 ms before stimulus onset (−150 to 50, −100 to 100, −50 to 150, 0 to 200, ... , 1500 to 1700 ms). Each subject's MRI was spatially normalized to the Montreal Neurological Institute (MNI) template using SPM2 and the resulting normalization parameters were applied to the volumetric SAM images. A group statistical analysis was performed using SnPM for the 23 subjects' results of each time-window.


Hemisphere
Left
Right
-100 – 100
50 – 250
200 – 400
400 – 600
600 – 800
900 – 1100
1100 – 1300
1350 – 1550
Time window (ms)
Theta band
Alpha band
Beta band
Low gamma band
High gamma band
Pseudo-T value
p < 0.001 ERD -8 8 ERS

(NeuroSQUID Model 100, CTF Systems Inc., Port Coquitlam, Canada). Stimulus words were displayed using a visual presentation system (ViSaGe, Cambridge Research Systems Ltd., Rochester, UK) and a DLP projector (Depth Q, MacNaughton Inc., Oregon, USA) on a projection screen 2 m away from the subjects' eyes. The word stimuli subtended a horizontal visual angle of 3° and a vertical angle of 1°. MEG signals were digitally recorded with an online low pass filter of 200 Hz at a sampling rate of 625 Hz. Notch filters at 60, 120, and 180 Hz were used to eliminate the AC line noise. One hundred neuromagnetic responses were collected during the time period 1500 ms before and 1500 ms after each word-presentation. Anatomic magnetic resonance image (MRI) data were obtained with a 3.0-T whole-body MR scanner with a standard whole-head coil (Signa VH/i, GE Medical Systems, Milwaukee, WI, USA). Individual MRI data consisted of T1-weighted sequences in 130 sagittal slices (1.4 mm thickness) with fiducial skin markers at the nasion and bilateral preauricular points. The MEG data were superimposed on the individual MRI with an anatomical accuracy of a few millimeters by registration of the head position at these three points.

Group SAM analysis with sliding time window

The MEG data were analyzed using SAM, which is a spatial filtering method to improve the spatial resolution of neuromagnetic sources (Singh et al., 2002; Taniguchi et al., 2000). Differential estimates of source power between the control period and the period of interest (POI) for selected frequency bands and time windows were computed as pseudo-*T* values (Robinson and Vrba, 1999). Distribution of pseudo-*T* values were superimposed on the individual anatomical MRIs co-registered to the MEG data. Positive and negative values indicate ERS and ERD, respectively.

In this study, the SAM analysis created a volume for covering the whole brain in each individual with a voxel size of 5×5×5 mm. The control period was defined as the time period between 200 and 0 ms before stimulus onset, and the POIs were defined as continuously moving 200 ms windows from 150 ms before stimulus onset to 1500 ms after stimulus onset. The windows were moved in steps of 50 ms. Power changes between the POIs and control periods were calculated in the following frequency bands: the theta (5–8 Hz), alpha (8–13 Hz), beta (13–25 Hz), low gamma (25–50 Hz), and high gamma (50–100 Hz) band.

Group statistical maps were generated by normalizing the SAM functional volumes to standard space and then combining these volumes across subjects for each time window and frequency band (Fig. 1). First, each individual's anatomical MRI was resliced to the same orientation and position as the SAM functional volume and statistical parametric mapping was used to find the transformation matrix from this functional space into the Montreal Neurological Institute(MNI) template (SPM; Wellcome Department of Imaging Neuroscience, London, UK). The transformation matrix was then applied to each of the functional SAM volumes, in each time window and frequency band, and for each subject. A permutation test was used to generate group statistical maps over each voxel in the standard brain using statistical non-parametric mapping (SnPM; Wellcome Department of Imaging Neuroscience). Analysis at the voxel level was performed using a pseudo-*T*-statistic incorporating variance smoothing with a Gaussian kernel of width 8 mm. These group statistical maps were then thresholded at $p<0.001$ (corrected), and superimposed on the MNI template brain using mri3dX (CUBRIC, Cardiff, UK) and these time-sequential images of each frequency band were compiled to a movie file (see Supplementary movie file). These procedures are shown in Fig. 1.

SAM virtual sensor and time frequency analysis

After we estimated the spatio-temporal distribution of the cerebral oscillatory changes related to word reading using group SAM analysis, we then estimated more detailed time-frequency profiles using SAM virtual sensors.

The individual's neuromagnetic signals corresponding to the peaks on the group statistical maps were generated by the SAM virtual sensor method and the time-frequency analysis results were applied to these signals. The SAM virtual sensor projects the signals exclusively from the targeted voxel by removing residual noise so as to suppress signals from other parts of the brain or the extracranial environment. The coordinates in the individual's functional space corresponding to the peaks on the group statistical map were calculated by inversely applying the previously obtained transformation matrix from the individual functional space into the standard MNI space. The time frequency analysis was applied to these signals so as to show the oscillatory changes at the locations of the peaks found on the group SAM analysis. The spectrograms of power change with the baseline set at −500 to 0 ms before stimulus onset were averaged across subjects. Using an ANOVA, significant average power changes ($p<0.05$) across subjects were plotted. To compare between induced and evoked responses, we also calculated spectrograms of power changes against averaged wave forms (Supplementary Fig. 1).

Results

Oscillatory changes in the theta band were generally transient power increases. Transient power increases in the theta band first appeared in the bilateral occipital cortices (Brodmann's area (BA) 17, 18, and 19) in the −100 to 100 ms post-stimulus window, and then serially and rapidly propagated to the reading-related cortical areas. Increases then became apparent in bilateral temporo-occipital areas including the fusiform gyrus (BA 37), and the bilateral posterior superior temporal gyri (BA 41 and 42) at 0–200 ms, and then in the left inferior and middle frontal gyri (BA 44, 45, and 46) at 50–250 ms. The left anterior temporal cortices (BA 21 and 38) were then activated at 100–300 ms, which was finally followed by the activation of the bilateral medial prefrontal cortices (Figs. 2 and 3). On the other hand, theta power increases in the anterior temporal gyrus and medial prefrontal cortices were not transient but sustained until 1200 ms. These increases were lateralized to the left hemisphere. A pseudo-*T* value of the left fusiform gyrus (BA37) was higher than that of the right fusiform gyrus, and significant power increases in the inferior and middle frontal gyri (BA 6, 44, 45, and 46) were found only in the left hemisphere.

Oscillatory changes in the alpha, beta and low gamma bands were generally sustained ERDs. The ERDs first appeared in the low gamma band in the 50–250 ms post-stimulus window, and the temporal distribution of ERDs in the alpha, beta, and low gamma bands were parallel; the broadest and the highest occurring at 200–400 ms. Thereafter, the ERDs converged on localized brain areas, that is, the left posterior inferior frontal gyrus, the left anterior superior gyrus, the left supramarginal gyrus, and the precentral gyrus, and were sustained until 1350–1550 ms. These sustained alpha, beta and low gamma ERDs were found following the transient theta power increase. The localization of ERDs was generally concordant with that of the transient theta power increase.

Fig. 2. Representative images of SAM analysis with sliding time window and group analysis (left hemisphere). The SAM group analysis of brain activity during silent reading in five frequency bands (the theta band, 5–8 Hz; the alpha band, 8–13 Hz; the beta band, 13–25 Hz; the low gamma band, 25–50 Hz, the high gamma band, 50–100 Hz) and in eight time windows, were superimposed on the template brain. Event Related Desynchronization (ERD) refers to power decreases in frequency bands and Event Related Synchronization (ERS) refers to power increases in frequency bands. ERDs are represented in a magenta color and ERSs are represented in an orange color.

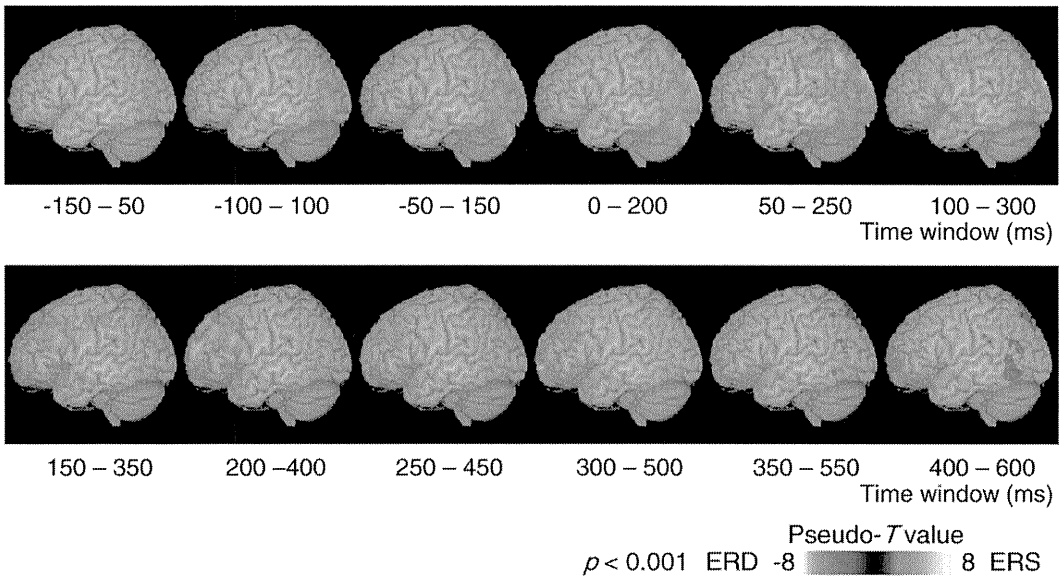


Fig. 3. Consecutive images in the theta band (left hemisphere). The power increase in the theta band was widespread and changed dynamically. Transient power increase in the theta band occurred first in bilateral occipital cortices, then rapidly propagated to left temporo-occipital areas, left inferior and middle frontal gyri, bilateral medial prefrontal cortices, and finally to the left anterior temporal cortices.

The spatial distribution of ERDs depended on their frequency band. We analyzed the relationships between frequency bands and localization at 200–400 ms, when activity was the highest and broadest (Fig. 4, Supplementary Tables 1–3). The peaks of low gamma ERDs in the 200–400 ms post-stimulus window were localized in the frontal lobe and the anterior part of the temporal lobe, that is, the left inferior and middle frontal gyrus (BA 6, 44, 45, and 46), the left posterior temporal gyrus (BA 41 and 42), the bilateral superior marginal gyrus (BA 40), and the left anterior temporal cortices (BA 21 and 38). The peaks of beta ERDs were localized in the perisylvian area and the posterior part of the inferior temporal lobe, including the transverse temporal gyrus (BA 42), the superior temporal gyrus (BA 38), the supramarginal gyrus (BA 40), the middle and inferior frontal gyrus (BA 11 and 46), the inferior temporal gyrus (BA 37), the fusiform gyrus (BA 19), and the occipital lobe (BA 18). The peaks of alpha ERDs were localized in the posterior part of the temporal lobe and the parietal lobe, including the superior and middle temporal gyrus (BA 21, 22, and 39), the cuneus (BA 19), and the paracentral lobule (BA 5). The spatial distributions of ERDs over frequency bands were superimposed on the volume rendered image of the MNI brain and clearly showed low gamma ERDs in the anterior part of the brain, beta ERDs in the middle part, and alpha ERDs in the posterior part (Fig. 4).

The time-frequency spectrograms clearly demonstrated a relationship, especially in time and frequency domain, between the transient ERS and the sustained ERD. Transient increases in the theta band were followed by ERDs in wide frequency bands from about 200 to 500 ms. The frequency bands of the ERDs at the occipital lobe were alpha to beta bands (Fig. 5-**1**, **2**, **3**, and **4**), and those at the frontal lobe and the anterior temporal lobe were alpha to low gamma bands (Fig. 5-5, 6, and 7).

Discussion

In the present study, we investigated the frequency and spatio-temporal distribution of neuromagnetic activities during silent reading by SAM analysis with a sliding time window and group analysis. We demonstrated distinct characteristics of frequency profiles and the time course of language-related oscillatory changes. ERDs in the alpha, beta and low gamma bands and the power increase in the theta band were localized in the word-reading related areas as we previously reported (Hirata et al., 2010; Hirata et al., 2004; Hirata et al., 2007). Spatial distributions of ERDs were different depending on the frequency bands. More specifically, as the frequency band became higher, ERDs distributed more anteriorly. One striking finding is that the transient power increase in the theta band occurred first in the bilateral occipital cortices, and then was rapidly propagated to the left temporo-occipital areas, the left inferior and middle frontal gyri, and the bilateral medial prefrontal cortices, and finally moved to the left anterior temporal cortices. These serial propagations of the transient power increases in the theta band were followed by sustained and parallel alpha, beta and low gamma ERDs in each area. Here we discuss the significance of these findings.

Neurophysiological significance of ERD

In the present study, the different spatial distributions of ERDs between different frequency bands were clearly illustrated, when ERDs were superimposed over frequency bands on an MNI template brain (Fig. 4). In general, we observed low gamma ERDs in the anterior part of the brain, beta ERDs in the middle part, and alpha ERDs in the posterior part. The underlying neural mechanisms that lead to observations of oscillatory changes at the macroscopic level are still a matter of debate (Pineda, 2005; Ward, 2003). ERDs reflect activated cortical areas (Pfurtscheller, 2001), and power decreases are observed within a range of not only motor and sensory paradigms (Neuper et al., 2006) but also cognitive paradigms (Dujardin et al., 1995; Singh et al., 2002). The reported coincidence between regions of ERD and evoked hemodynamic responses observed using fMRI (Singh et al., 2002) supports the notion that ERDs represent increased neural activation in a cortical area. Therefore, our results that the spatial distributions of ERDs changed over time suggest that these responses reflected brain activity involved in the process of reading words and that oscillatory changes were observed in specific frequency bands according to locations.

On the other hand, there have been several reports, which have shown the relationship between frequency bands and brain functions, in addition to locations. Previous reports have showed correspondence between the alpha frequency band and somatosensory function, and between the beta frequency band and somatomotor function (Salmelin et al., 1994; Taniguchi et al., 2000). In our previous reports, correspondence between the low gamma frequency band and

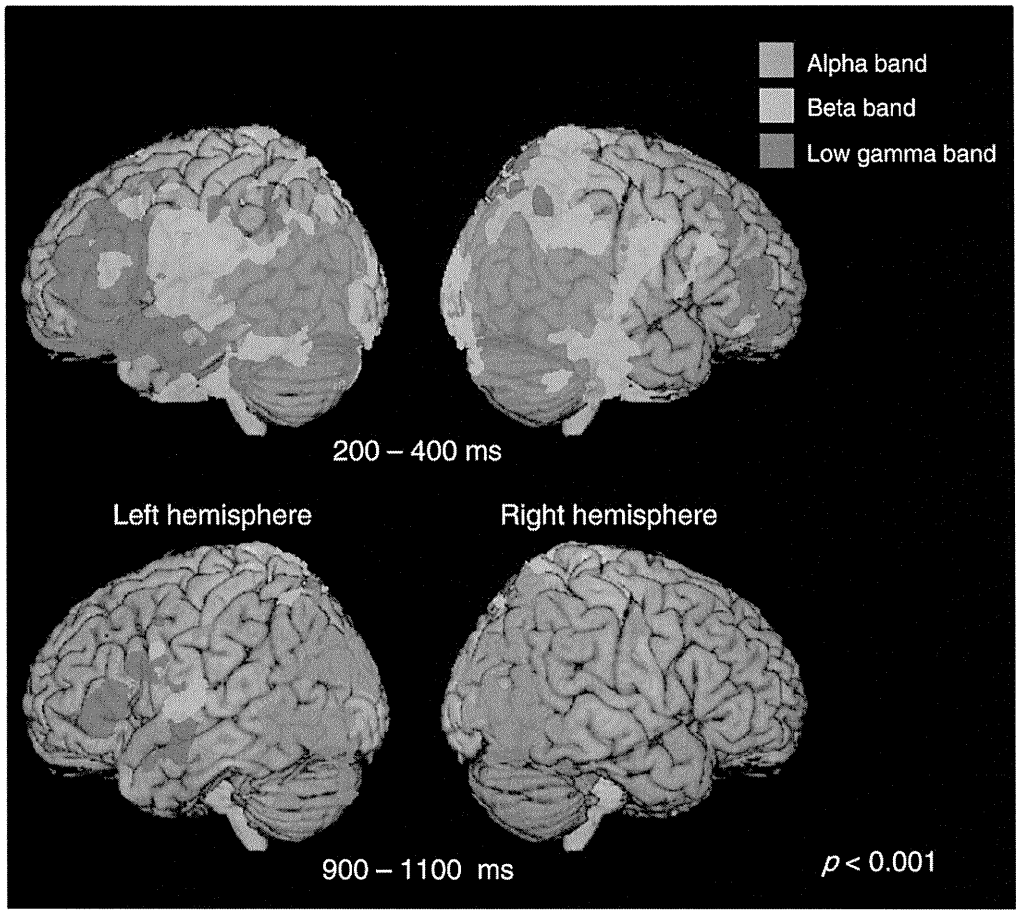


Fig. 4. Event-related desynchronizations (ERDs) in the alpha band (red), the beta band (green), and the low gamma band (blue) in two time-windows (the upper row, 200–400 ms; the lower row, 900–1100 ms) were superimposed on the standard template brain. In the left occipital lobe and the left temporo-occipital cortex including the fusiform gyrus, alpha to beta ERDs were followed by alpha ERDs. In the left inferior and middle frontal gyri and in the left anterior temporal cortex, low gamma ERDs were observed. Beta ERDs were first seen in a broad area in the left occipital and posterior temporal cortices and the left precentral gyrus, but were also seen for longer periods of time in the left perisylvian area (Brodmann's area 40). Note that alpha to beta ERDs were observed in the right posterior temporal cortex.

language function were shown by the fact that lateralization and localization of the low gamma ERDs in the frontal language areas were concordant with the results of Wada test and cortical electrical stimulation mapping, respectively (Hirata et al., 2010; Hirata et al., 2004). In our present study, in addition to this frontal low gamma activity, the following ERD responses were also observed. Alpha and beta ERDs in the bilateral posterior lobe observed in the present study are previously reported to be associated with the primary and the association visual area (Brookes et al., 2005). With respect to beta ERDs in the left fusiform gyrus, this area is notable for visual word form processing, and is referred to as the "visual word form area" (VWFA) (Cohen et al., 2002). We observed alpha ERDs in the superior temporal gyrus and the angular gyrus, and low gamma ERDs in left inferior frontal gyrus in our present study. These areas are associated with semantic functions. The posterior superior temporal gyrus is activated by semantic contrast based on written words (Fiebach et al., 2002). The angular gyrus has been confirmed as processing a semantic role by direct electrical stimulation, which resulted in the transient emergence of transcortical sensory aphasia (Boatman et al., 2000). The inferior frontal areas are proposed to be involved in the retrieval of semantic information (Demb et al., 1995). We observed beta ERDs in the precentral gyrus, the insula, and the superior temporal gyrus. These areas have been reported to be associated with the phonological functions (Heim et al., 2002; Herbster et al., 1997; Jessen et al., 1999). With regard to the right hemisphere, we observed alpha and beta ERDs in the posterior superior/middle temporal gyrus. These areas have been reported to be related to prosodic processes (Fujimaki et al., 2004; Gandour et al., 2004). In short, though these areas of functions were partially overlapping, the spatial distributions of ERDs were, in general, different between frequency bands. In this study, we analyzed the relationship between frequency bands and locations, while other reports have investigated the relationships between functions and locations. Combining the results from our study, and such other reports may allow us to postulate on possible relationships between frequency bands and functions.

Another interesting finding in the present study with respect to ERD is that ERDs were observed simultaneously and parallel. This suggests that ERDs reflect a parallel processing of reading words. Several previous papers already mentioned parallel processing in word reading. An MEG paper based on the cerebral oscillatory changes reported that simultaneous responses in the left inferior frontal gyrus and left superior temporal gyrus indicate parallel processing during the reading process (Kober et al., 2001). It reported parallel processing using event related fields, but not oscillatory changes. Another MEG paper reported that activities in the VWFA are co-active in parallel with the spread of activity in the left anterior middle temporal gyrus, the left posterior middle temporal gyrus, and the inferior frontal gyrus (Pammer et al., 2004). However, analyzed frequency band in the study was limited to 10–20 Hz. In contrast, our results indicated the spatial distribution of oscillatory changes over a

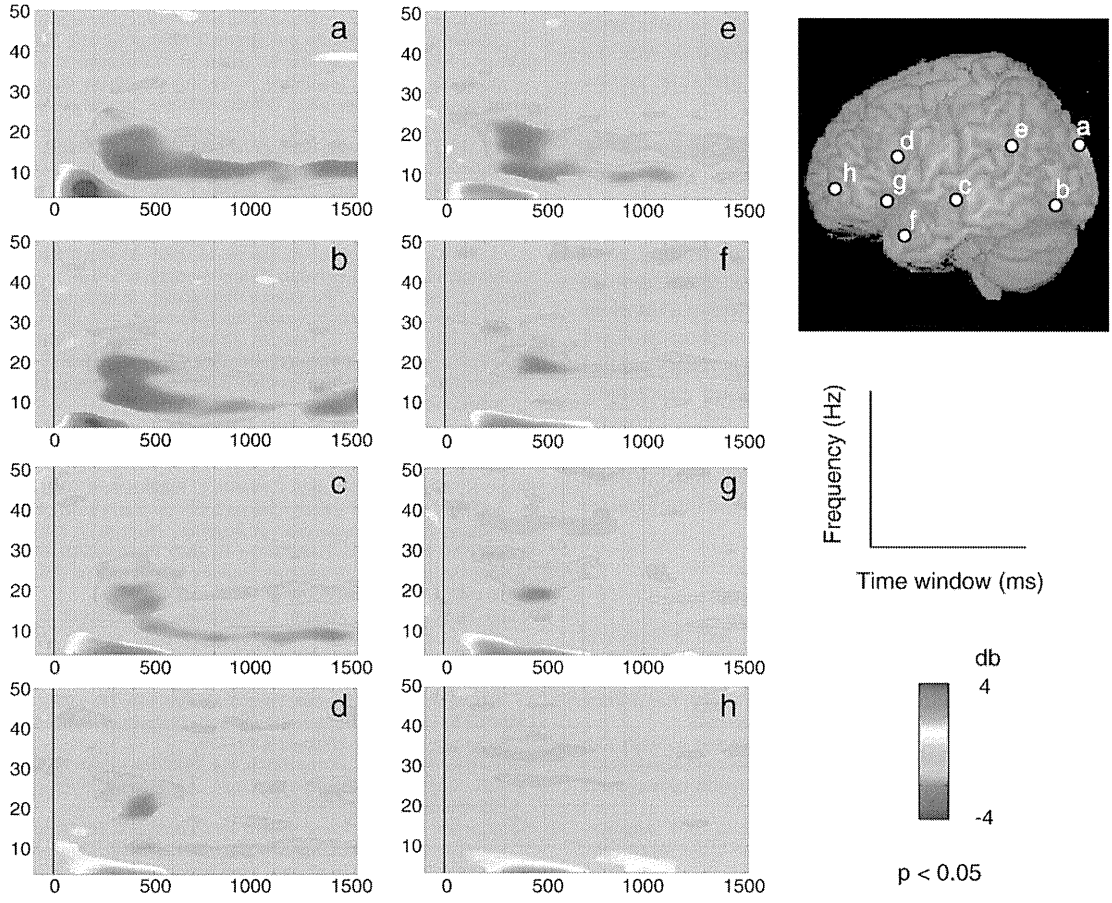


Fig. 5. Time-frequency spectrograms for the data estimated by SAM virtual sensors. Graphs in the left two columns indicate time-frequency spectrograms whose SAM virtual sensors are indicated by the points with corresponding numbers on the right brain image. At these points, the peaks of the power increases in the theta band were found in the 150–350 ms post-stimulus window. The spectrograms of power change with the baseline set at −500 to 0 ms before stimulus onset were averaged across subjects. Using an ANOVA, significant average power changes ($p<0.05$) across subjects were plotted. Power decrease is represented in a magenta color and power increase in an orange color. Transient power increases in the theta band were followed by sustained alpha, beta and low gamma event-related desynchronizations in each area.

wider range of frequency bands and may also represent parallel processing over a wider range of frequency bands.

Neurophysiological significance of transient theta increase

Another important finding of the present study is the serially propagating pattern of the transient power increase in the theta band. The theta power increase first appeared in the occipital lobe as the result of a visual response, then propagated to the posterior inferior temporal gyrus, probably related to the cognition of visual word form. The theta power increase in the posterior inferior frontal gyrus, the supramarginal gyrus, the frontal operculum and the middle temporal gyrus, appeared almost simultaneously. After that, a theta power increase in the frontal operculum related to articulatory planning was observed. This serial processing pattern is consistent with the language process model proposed by Price (2000). In addition, this transient increase in the theta band was observed preceding ERDs in the alpha, beta, and low gamma bands, which were related to local brain function as described above. This result suggests that the transient power increase in the theta band is the priming of the sustained brain activity.

An event-related potential (ERP) study suggested, based on the dual route model of reading, that the peak at 105 ms in the temporal site is related to a phonologic short term memory processes, that the peak at 160–215 ms in the left anterior sites is related to phonologic processes, and that the peak at 185 ms in the lateral occipital/posterior temporal site is related to orthographic/graphemic analysis (Proverbio and Zani, 2003). Because of the limitations of the scalp ERP technique, the intracranial sources of the scalp-recorded signals were not precisely localized in this study. However, the time course and localization of the ERP peaks are roughly concordant with those of the theta power increase in our present study. The serial propagation of the transient power increase and the ERP peaks might be a reflection of the same neurophysiological responses. Therefore, we precisely localized these transient preceding responses as power increased in the theta band by using beamforming analysis with a sliding time window, and comprehensively looked across the neural process of reading with respect to oscillatory changes.

The theta power increase in the mid-frontal area was sustained for as long as 1 s, unlike transient increases typical of other cortical areas. This sustained theta response is most probably related to attention (Ishii et al., 1999) and verbal working memory load (Jensen and Tesche, 2002), which is known as frontal-midline theta.

Limitations

On the other hand, there are some limitations in the present study. First, significant activation in a cortical area on group imaging does not necessarily mean that it is important in the processing of the reading task. It can also mean that the area is weakly activated but highly spatially consistent across subjects (Singh et al., 2003). This means that common activity could be extracted, but that the contribution to the process of silent reading could not be evaluated with certainty. Secondly, in SAM analysis with a sliding time window, time resolution is inferior to ERP analysis, because the intensity of oscillatory changes is

flattened by the time window with 200 ms and is sparsely sampled with a sliding interval of 50 ms. Therefore, by using a variable time window according to the frequency band, short sliding time, and time widow function, temporal resolution could be improved.

Conclusion

In conclusion, using SAM analysis with a sliding time window and group analysis, the neural processes underlying silent reading were found to have a frequency-dependent spatiotemporal distribution of neuromagnetic oscillatory activities. Our results suggest that a transient power increase in the theta band reflects the priming and propagation of local activities, while alpha, beta and low gamma ERDs reflect parallel neural processes related to visual, visual word form processing, phonological, and semantic functions. The relationship between frequency bands of oscillatory changes and locations may have implications in the relationship between frequency bands and functions.

Supplementary materials related to this article can be found online at doi:10.1016/j.neuroimage.2010.08.023.

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LETTER TO THE EDITOR

Importance of distinction between paroxysmal and continuous patterns of pain during evaluation of pain after brachial plexus injury

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We read with great interest the manuscript of Bonilla et al. entitled "Pain and brachial plexus lesions: evaluation of initial outcomes after reconstructive microsurgery and validation of a new pain severity scale" [3]. The authors described a new pain scoring scale to quantify pain after brachial plexus injuries and used it to assess patients' pain before and after reconstructive surgery. Within this scale, [3] the authors integrated pain intensity scale (measured on a scale ranging from 0 to 10), with other parameters like the disability in daily activities and sleep, pain frequency, use of pain medication, and the number of zones affected by pain.

We agree with the authors that the use of such a multi-dimensional pain scale would be useful as a standard outcome measure across studies for BPA pain that would greatly enhance the comparability, validity, and clinical applicability of these studies. Whereas most of the available reports used pain intensity scales, such as the visual analogue scale as the sole outcome measure, the new pain scale integrated factors beyond changes in pain intensity which may be more objective and of more relevance to the patient outcome.

One limitation of the above-mentioned pain scale is that it did not distinguish between the different patterns of BPA pain. It is well known that BPA pain has two patterns which are quite distinct from each other in terms of frequency and pain quality [5, 6]. Continuous background pain is usually described as burning, throbbing, and/or aching sensations and continues for a long duration, whereas paroxysmal pain is usually described as "electrical shock" or "shooting" paroxysms and usually lasts only for a few seconds [5, 6]. Although the authors included pain frequency [3], described as no pain to continuous pain, in their pain scale, this may not be sufficient to allow distinction between the two types of pain. Instead, we suggest that pain character (burning vs shooting) be also included during evaluation [1, 4]. Each type of pain should be quantified separately using visual analogue scale [1, 4]. Separate rating for the two patterns of pain will be particularly useful in evaluating the outcome of neurosurgical procedures for BPA pain [1, 6], thereby allowing clinicians to study the differential effects of the procedures on pain. Sindou et al. reported that DREZotomy was more effective for paroxysmal than continuous pain [6]. They explained the differential effects of DREZotomy based on the distinct pain origin for each type of pain [6]. Paroxysmal pain is said to originate from hyperactive neurons in the dorsal horn, whereas continuous pain extend beyond the dorsal horn up to the thalamus [6]. Also recently, our group reported that electrical motor cortex stimulation was more effective for continuous than paroxysmal pain [1]. Therefore, it can be said that pain classification is important to appropriately select patients

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for treatment and to better understand the underlying mechanisms of pain as well [1, 4]. Finally, such distinction goes in line with several previous reports which have emphathized that classifying neuropathic pain, according to their different components, will help to develop a mechanism-based treatment [2].

Conflicts of interest None.

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Differential Efficacy of Electric Motor Cortex Stimulation and Lesioning of the Dorsal Root Entry Zone for Continuous vs Paroxysmal Pain After Brachial Plexus Avulsion

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BACKGROUND: Pain after traumatic brachial plexus avulsion (BPA) has 2 distinct patterns: continuous burning pain and paroxysmal shooting pain. Lesioning of the dorsal root entry zone (DREZotomy) is more effective for paroxysmal than continuous pain. It is unknown, however, whether electric motor cortex stimulation (EMCS) has a differential effect on continuous vs paroxysmal BPA pain.

OBJECTIVE: To analyze the differential effect of EMCS and DREZotomy on continuous vs paroxysmal BPA pain in a series of 15 patients.

METHODS: Fifteen patients with intractable BPA pain underwent DREZotomy alone (n = 7), EMCS alone (n = 4), or both procedures (n = 4). Pain intensity was evaluated with the Visual Analog Scale, and separate ratings were recorded for paroxysmal and continuous pain. Pain relief was categorized as excellent (> 75% pain relief), good (50%-75%), or poor (< 50%). Favorable outcome was defined as good or better pain relief.

RESULTS: Eight patients had EMCS; 7 were followed up for an average of 47 months. Of those 7 patients, 3 (42%) with continuous pain had favorable outcomes compared with no patients with paroxysmal pain. Eleven patients had DREZotomy; 10 were followed up for an average of 31 months. Of those 10 patients, 7 (70%) with paroxysmal pain had favorable outcomes compared with 2 (20%) with continuous pain.

CONCLUSION: EMCS was ineffective for paroxysmal pain but moderately effective for continuous pain. DREZotomy was highly effective for paroxysmal pain but moderately effective for continuous pain. It may be prudent to use EMCS for residual continuous pain after DREZotomy.

KEY WORDS: Brachial plexus avulsion pain, Continuous pain, Differential efficacy, DREZotomy, Motor cortex stimulation, Paroxysmal pain

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Deafferentation pain is a major disabling symptom after traumatic brachial plexus avulsion (BPA).[1] Of patients with BPA, as many as 90% complain of significant early pain, but only 25% continue to experience severe pain 4 years after injury.[1] Post-BPA pain is known to be almost constantly unbearable and resistant to all classes of analgesic drugs.[2]

ABBREVIATIONS: BPA, brachial plexus avulsion; **CS,** central sulcus; **DREZotomy,** lesioning of the dorsal root entry zone; **EMCS,** electric motor cortex stimulation; **VAS,** Visual Analog Scale

Typically, post-BPA pain has 2 distinct types: continuous background pain described as burning, throbbing, and/or aching sensations and electric shooting paroxysms lasting a few seconds to minutes.[1,2] These 2 distinct types of pain appear to be the clinical expression of 2 different pain generators. Paroxysmal pain is thought to originate from hyperactive neurons in the dorsal horn, whereas continuous pain is thought to originate from supraspinal structures, particularly the thalamus.[2-4]

Since the early work of Sindou et al[5] and Nashold et al[6] in the 1970s, lesioning of the dorsal root entry zone (DREZotomy) has been

the preferred procedure for treatment of intractable BPA pain. DREZotomy is designed to destroy hyperactive neurons in the substantia gelatinosa either by microsurgical incision and bipolar coagulation[5] or by thermocoagulation.[6] The reported pain relief rate immediately after DREZotomy is 75% to 98%, but sustained benefit is observed in only two-thirds of patients after 2 years.[2,7] The major complications of the DREZotomy are weakness in the ipsilateral leg and sensory disturbances, which are seen in 5% to 10% of patients.[7,8]

During the past 2 decades, electric motor cortex stimulation (EMCS) has been used to treat deafferentation pain, particularly central post-stroke pain and trigeminal neuropathic pain.[9-11] Recently, several groups, including ours, used EMCS as a "last resort" treatment for patients with BPA pain who failed or refused DREZotomy.[12-16] In these small studies, EMCS yielded a moderate success rate of 40% to 50%.[12-16] A major limitation for the use of EMCS for BPA pain remains the lack of reliable predictive factors for success, which is particularly important considering the modest success rate of EMCS for BPA and the high cost of treatment.[9-11]

Sindou et al[2] first reported that DREZotomy has a differential effect on the 2 patterns of BPA pain by showing that DREZotomy was more effective for paroxysmal than continuous pain. Conversely, none of the previous EMCS studies analyzed the differential effect of EMCS on continuous vs paroxysmal BPA pain.[12-16] Such a differential effect may be important with regard to selection of treatment for patients. We report our observations in 15 patients with BPA pain who underwent EMCS or DREZotomy and our analysis of the differential effect of EMCS and DREZotomy on continuous vs paroxysmal BPA pain.

PATIENTS AND METHODS

Patient Population

Between January 1997 and January 2010, 15 consecutive patients with intractable pain after BPA were referred to our institute and underwent a total of 19 procedures: DREZotomy alone (n = 7), EMCS alone (n = 4), or both procedures (n = 4). Two patients had EMCS after failed DREZotomy, whereas 2 patients had DREZotomy after failed EMCS. All patients were men. The mean age was 47 years (range, 31-72 years) for DREZotomy patients and 51 years (range, 30-67 years) for EMCS patients. The mean duration of pain was 12.8 years (range, 2-35 years) before DREZotomy and 10 years (range, 0.8-28 years) before EMCS. Injuries were sustained in motorcycle accident (n =13), after a fall from a height (n =1), and by a falling tree (n =1). In the majority of patients (n = 9), pain appeared within 1 month of injury; the longest interval between injury and onset of pain was 2 years. All patients had sensory and motor deficits of varying degrees (Table 1).

Patient Selection

Most patients showed pseudomeningocele on CT myelography. In all patients, pain was severe enough to interfere with normal daily activities. Pain was unresponsive to a wide variety of medications, including tricyclic antidepressants, anticonvulsants, and narcotic analgesics, for at least 12 months.

TABLE 1. Patient Clinical Characteristics[a]

Patient	Procedure	Age y, Sex	Level of Injury	Cause of Injury	Side	Pain Duration, y	Pain Onset	Pain Pattern	Pain Quality	Global VAS	Previous Treatments
1	DREZ	40/M	C6-C8	Motorcycle	R	18	Immediate[b]	Con + Paroxy	B + Elec	8	Medicine
2	DREZ	72/M	C5-C8	Motorcycle	L	12	Immediate	Con + Paroxy	B + Elec	8	Medicine
3	DREZ	35/M	C6-T1	Motorcycle	L	7	3 mo	Con + Paroxy	B + Elec	9	SCS
4	DREZ	43/M	C8-T1	Motorcycle	R	23	Immediate	Con + Paroxy	Squeezing + Elec	8	Medicine
5	DREZ	52/M	C6-T1	Motorcycle	R	35	Immediate	Con + Paroxy	B+ Elec	7	Medicine
6	DREZ	47/M	C5-T1	Motorcycle	L	2	Immediate	Con + Paroxy	B+ Elec	9	Medicine
7	DREZ	35/M	C5-C8	Motorcycle	R	18	1 y	Con + Paroxy	B + Elec	10	Medicine
8	EMCS	64/M	C7-T1	Motorcycle	L	28	NA	Con	Cramping	8	Medicine, SCS
9	EMCS	67/M	C5-T1	Falling tree	R	0.8	Immediate	Con + Paroxy	Cramping + Elec	8	Medicine
10	EMCS	55/M	C5-C7	Motorcycle	L	2.5	Immediate	Con	Paresthesia	8	Medicine, SCS
11	EMCS	30/M	C6-T1	Motorcycle	L	23	1.5 y	Con + Paroxy	B + Elec	7	Medicine
12	DREZ + EMCS	56/M	C5-T1	Fall from a height	L	4.3	Immediate	Con + Paroxy	Throb + Elec	9	Medicine, SCS, DBS
13	EMCS + DREZ	59/M	C6-T1	Motorcycle	L	10.2	2 y	Con + Paroxy	B + Elec	9	Medicine, DBS
14	DREZ + EMCS	31/M	C7-T1	Motorcycle	L	5.9	NA	Con + Paroxy	B + Elec	7	Medicine, rTMS, SCS
15	EMCS + DREZ	49/M	C7-T1	Motorcycle	L	6	Immediate	Con + Paroxy	B + stabbing	3	Medicine, rTMS

[a]B, burning; Con, continuous; DBS, deep brain stimulation; DREZ, dorsal root entry zone lesioning; Elec, electric shooting-like; EMCS, electric motor cortex stimulation; Paroxy, paroxysmal; rTMS, repetitive transcranial magnetic stimulation; SCS, spinal cord stimulation; VAS, Visual Analog Scale.
[b]Within 1 month of injury; throb, throbbing.

We typically recommend DREZotomy as a primary option for intractable BPA and reserve EMCS for intractable residual pain after DREZotomy. However, in the present study, some patients declined DREZotomy and preferred EMCS as a first choice for fear of DREZotomy-related complications such as leg weakness.

Previous Treatment Trials

Six patients (40%) had previous surgical procedures for pain treatment without adequate relief. Four patients had undergone spinal cord stimulation, 1 had deep brain stimulation, and 1 had both procedures. Two patients had undergone repetitive transcranial magnetic stimulation preoperatively to predict the efficacy of permanent EMCS.[14]

Pain Characteristics

Thirteen patients (86%) suffered from both continuous and paroxysmal pain, whereas 2 patients (14%) had isolated continuous pain. Ten patients described the quality of continuous pain as burning, 2 as cramping, 1 as throbbing, 1 as squeezing, and 1 as paresthesia. Twelve patients described the quality of paroxysmal pain as electric, whereas 1 patient described it as stabbing. The frequency of paroxysmal pain was available in 10 patients. Three patients had paroxysms at a rate of 10 to 12 per day, 1 at 2 to 3 per day, 4 at 3 to 5 per hour, 1 at 1 per hour, and 1 at 3 per minute. In most patients, pain predominated in the distal portion of the upper limb, particularly the hand. Median Visual Analog Scale (VAS) for pain was 8 of 10 (range, 3-10; Table 1).

Evaluation of Pain Relief

We distinguished between continuous and paroxysmal pain by their distinct quality and duration (please see above). Using VAS, we recorded separate ratings of pain intensity for each type of pain ranging from 0 (no pain) to 10 (worst possible pain).[17] VAS was evaluated before surgery, immediately after surgery, and at follow-up visits every 6 months.[14] The degree of pain relief was categorized as excellent for VAS reduction $> 75\%$, good for VAS reduction of 50% to 75%, and poor for VAS reduction $< 50\%$. A favorable outcome was defined as good or better pain relief.[2]

Surgical Procedure

EMCS

Eight patients were treated with EMCS alone or in combination with DREZotomy (Table 1). Trial electrodes were implanted in the subdural space over the precentral gyrus in all patients and additionally within central sulcus (CS) in 4 patients. We restricted implantation within CS to patients with severe persistent motor weaknesses, who therefore had low potential for further deterioration.

The location of the CS was identified by its characteristic omega shape on magnetic resonance surface images. Under general anesthesia, a craniotomy of a 5- to 6-cm area was performed over the sensorimotor cortex corresponding to the upper extremity. A 20-grid electrode (4-5 array, 0.3-cm electrode diameter, 0.7-cm separation; Unique Medical Co, Tokyo, Japan) was placed subdurally. The location of the CS was then confirmed by phase reversal of somatosensory evoked potentials. Occasionally, somatosensory evoked potentials could not be obtained because of complete deafferentation. In that case, we relied solely on CS anatomic localization by magnetic resonance imaging.

In case of CS implantation, the arachnoid membrane of the CS was microsurgically dissected, and the vessels within that sulcus were freed to expose the hidden lateral walls of precentral and postcentral gyri. One or two 4-plate electrodes were then additionally implanted within the CS[14] (0.3-cm electrode diameter, 0.7-cm separation; Unique Medical Co, or Resume; Medtronic, Inc, Minneapolis, Minnesota).

After implantation of test electrodes, electrical stimuli were delivered to various parts of the grid electrode and the 4-plate electrode aiming to identify the best location for pain relief. One or 2 weeks later, a second surgery was performed under general anesthesia. The test electrodes were replaced by a Resume electrode, and an implantable pulse generator (ITREL III; Medtronic, Inc.) was then placed subcutaneously in the chest or abdomen.

The stimulation parameters used were an amplitude of 0.9 to 5 V, frequency of 25 to 50 Hz, and pulse width of 210-350 microseconds with bipolar configuration. Chronic stimulation was applied continuously for 15 to 30 minutes on each occasion 3 to 6 times a day.[14]

DREZotomy

DREZotomy was performed in 11 patients (Table 1) according to the Nahold et al[6] radiofrequency thermocoagulation technique. The lesioning electrode was introduced into the intermediolateral sulcus at the site of rootlet avulsion for a depth of 2 mm and angled 25° to 30° in the sagittal plane. A series of radiofrequency coagulation lesions were made along the longitudinal extent of the intermediolateral sulcus, including 1 level above and 1 level below the injured segments. The lesions are made at intervals of 1 mm at 70°C for 30 seconds (Model RFG-3C Graphics RF Lesion Generator, Radionics, Burlington, Massachusetts). Thermocoagulation was performed under monitoring of somatosensory evoked potentials and motor evoked potentials.

Statistical Analysis

We compared the percent VAS reduction of continuous and paroxysmal pain for EMCS using the 2-sample t test and for DREZotomy using the paired t test. A value of $P < .05$ was considered statistically significant.

Ethical Considerations

Written informed consent was given by each patient before the procedure. Approval was obtained from the local Ethics Review Board of Osaka University Hospital for data analysis.

RESULTS

EMCS

Eight patients had trial EMCS: 6 had both paroxysmal and continuous pain, and 2 had isolated continuous pain. Of those 8 patients, 1 patient who had both types of pain declined permanent electrode implantation. The remaining 7 patients underwent permanent EMCS and were followed up long term for an average of 47 months (range, 12-112 months).

The percentage of patients with favorable outcomes ($> 50\%$ VAS reduction) was higher for continuous than paroxysmal pain, both during the trial and with long-term stimulation (Figure 1; Table 2). During the trial, 4 of 8 patients (50%) with continuous pain had favorable outcomes compared with 2 of 6 patients (33%) with paroxysmal pain (Table 2). At the latest follow-up visit, 3 of 7 patients (42%) with continuous pain had favorable outcomes compared with 0 of the 5 patients (0%) with paroxysmal pain

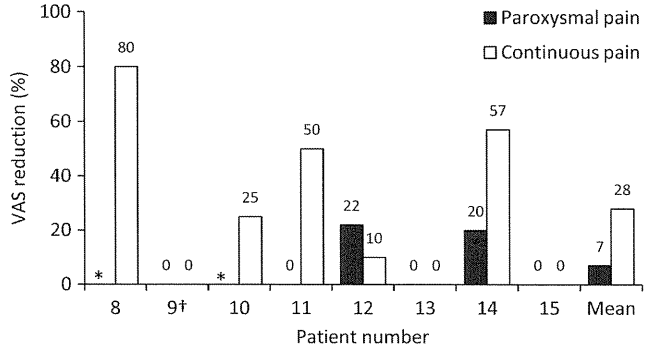

FIGURE 1. *Visual Analog Scale (VAS) reduction percent for paroxysmal and continuous pain in 8 patients who underwent electric motor cortex stimulation (EMCS) and had long-term follow-up. The mean VAS reduction percent tended to be greater for continuous pain than for paroxysmal pain (28% vs 7%; P = .11, 2-sample t test). EMCS was ineffective for paroxysmal pain but moderately effective for continuous pain. *These 2 patients had isolated continuous pain. †Patient 9 failed trial stimulation and had no permanent implantation.*

(Figure 1), and the mean percent VAS reduction was greater for continuous pain than for paroxysmal pain (28% vs 7%; $P = .11$, 2-sample t test). Of the 2 patients who underwent EMCS after DREZotomy, 1 patient had good pain relief for continuous pain, whereas the other had poor pain relief for both types of pain.

DREZotomy

All 11 patients who underwent DREZotomy suffered from both paroxysmal and continuous pain. One patient had < 6 months of follow-up and therefore was excluded from analysis of long-term results. The remaining 10 patients were followed up long-term for an average of 31 months (range, 12-61 months).

The percentage of patients with favorable outcomes was higher for those with paroxysmal than for those with continuous pain in both initial and long-term results (Figure 2 and Table 2). Immediately after surgery, 10 of 11 patients (91%) with paroxysmal pain had favorable outcomes compared with 8 of 11 patients (72%) with continuous pain (Table 2). At the latest follow-up, 7 of 10 patients (70%) with paroxysmal pain had favorable outcomes compared with 2 of 10 patients (20%) with continuous pain (Figure 2), and the mean percent VAS reduction was greater for paroxysmal pain than continuous pain (63% vs 26%; $P = .01$, paired t test).

Complications

There was no perioperative mortality for either procedure.

EMCS

One patient (Patient 13; 12%) had local infection 9 months after implantation. This diabetic patient presented with a deep wound infection and dehiscence but no †meningeal irritation

TABLE 2. Results of 15 Patients With Electrical Motor Cortex Stimulation or Dorsal Root Entry Zone Lesioning for Brachial Plexus Avulsion Pain[a]

Patient	Age, y/Sex	Pain Pattern	Procedure	VAS Reduction, %				Follow-up, mo	Complications or Comments
				Paroxysmal Pain		Continuous Pain			
				Initial	Long-term	Initial	Long-term		
1	40/M	Con + Paroxy	DREZ	100	100	0	33	61	No
2	72/M	Con + Paroxy	DREZ	88	57	66	0	28	No
3	35/M	Con + Paroxy	DREZ	100	66	80	0	15	No
4	43/M	Con + Paroxy	DREZ	100	0	0	0	24	No
5	52/M	Con + Paroxy	DREZ	100	100	100	100	17	No
6	47/M	Con + Paroxy	DREZ	88	100	86	14	12	Sensory disturbances and transient leg weakness
7	35/M	Con + Paroxy	DREZ	100	100	100	100	9	Sensory disturbances
8	64/M	Con	EMCS	NA	NA	90	80	36	Death after 36 mo (ICH)
9	67/M	Con + Paroxy	EMCS	0	0	25	0	0	No permanent implantation
10	55/M	Con	EMCS	NA	NA	25	25	76	Removal after 76 mo
11	30/M	Con +Paroxy	EMCS	88	0	84	50	50	No
12	56/M	Con + Paroxy	DREZ	0	0	0	0	24	No
			EMCS	56	22	76	10	112	No
13	59/M	Con + Paroxy	EMCS	0	0	30	0	9	Removed after 9 mo owing to infection
			DREZ	100	100	75	14	53	No
14	31/M	Con + Paroxy	DREZ	100	11	57	0	60	No
			EMCS	33	20	71	57	19	No
15	49/M	Con + Paroxy	EMCS	0	0	33	0	24	No
			DREZ	100	NA	100	NA	6	Follow-up < 6 mo

[a]Con, continuous; DREZ, dorsal root entry zone lesioning; ICH, intracerebral hematoma; EMCS, electrical motor cortex stimulation; Paroxy, paroxysmal; VAS, Visual Analog Scale.

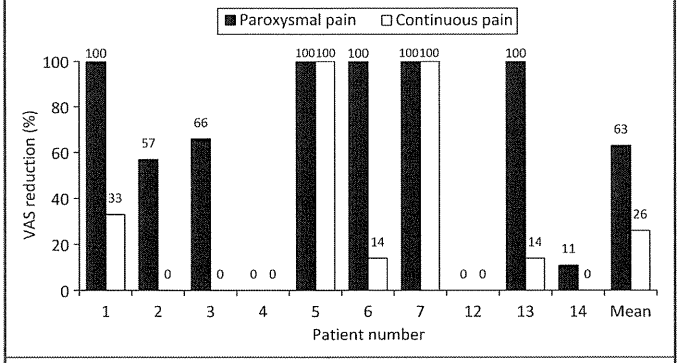

FIGURE 2. *Visual Analog Scale (VAS) reduction percent for paroxysmal and continuous pain in 10 patients who underwent lesioning of the dorsal root entry zone (DREZotomy) and had long-term follow-up. The mean percent VAS reduction was greater for paroxysmal pain than continuous pain (63% vs 26%;* P = *.01; paired t test). DREZotomy was highly effective for paroxysmal pain but moderately effective for continuous pain.*

signs. The infection was cured after removal of the EMCS device and bone flap and antibiotic therapy. At operation, the infection was limited to the subgaleal space and did not extend to epidural or subdural space. No electrode dislocation, cerebrospinal fluid leak, new neurological deficit, or any other complications were recorded in our patients. One patient died 3 years after implantation of a cause unrelated to the surgical procedure (intracerebral hemorrhage).

DREZotomy

Two patients had postoperative neurological complications (18%). Patient 6 had paresthesia and mild weakness of the ipsilateral leg along with diminished pain sensation in the left hemibody. Both sensory disturbances and weakness improved on further follow-up. Patient 7 showed postoperative diminished sensations in the right hemibody, which improved on later follow-up.

DISCUSSION

DREZotomy has been reported to be more effective for paroxysmal than continuous BPA pain.[2] Conversely, there is no report describing a differential effect of EMCS on these 2 types of BPA pain.[12-16] The main finding of this study is that EMCS also had a differential effect. We found that EMCS was ineffective for paroxysmal pain but moderately effective for continuous pain. We also found that DREZotomy was effective for both types of pain but was more effective for paroxysmal pain. With EMCS, 3 of 7 patients with continuous pain (42%) had a long-term favorable outcome, whereas no patients reported improvement of paroxysmal pain. With DREZotomy, 7 of 10 patients with paroxysmal pain (70%) had a long-term favorable outcome compared with 2 of 10 patients (20%) with continuous pain.

Our finding that DREZotomy was more effective for paroxysmal pain than continuous pain is consistent with a previous report.[2] To the best of our knowledge, this is the first study to show that EMCS is effective only for continuous BPA pain.[12-16] Before our investigation, only 10 patients have been reported in the literature to receive EMCS for BPA pain. The overall success rate of EMCS for BPA pain in our study was 42% (3 of 7 patients), which is comparable to the 50% (5 of 10 patients) reported in these previous studies.[12,13,15,16] However, each of these studies evaluated only a single global rating for BPA pain and did not distinguish between continuous and paroxysmal pain.[12-16] Increasingly, the distinction between different patterns of neuropathic pain is thought to be important to better understand the underlying mechanisms for each pattern of pain and to study the differential effects of treatment.[17]

From a practical point of view, the differential effect of DREZotomy and EMCS on the 2 types of BPA pain may be helpful in setting the indication for treatment. The efficacy of DREZotomy for both types of BPA pain makes it the procedure of first choice. On the other hand, EMCS was moderately effective only for continuous pain; therefore, EMCS may be most appropriate for isolated continuous pain or residual continuous pain after DREZotomy. For isolated continuous pain, we had a 50% success rate (1 of 2 patients) after EMCS in our series, which is identical to the 50% success rate (5 of 10 patients) after DREZotomy in the previous report.[2] For residual pain after DREZotomy, EMCS represents one of the few viable therapeutic options.[2,18] Spinal cord stimulation is another option but is associated, in our experience and in that of others, with inconsistent results.[18,19] In our study, some patients preferred EMCS over DREZotomy as a primary option because they wished to avoid the surgical risks associated with DREZotomy such as leg weakness and sensory dysfunction.[7,8] This reflects the most attractive aspects of EMCS, which are its reversible and less invasive nature. Overall, the evidence regarding EMCS for BPA pain is still very limited, long-term follow-up is unavailable, and the cost of treatment is high.

The mechanism by which BPA pain is generated is still not completely understood.[8] Both animal and human studies suggested that neuronal hyperactivity from deafferented dorsal horn neurons is the main generator of BPA pain.[3,20,21] However, neuronal hyperactivity has been also detected in thalamic nuclei, suggesting that supraspinal mechanisms contribute to pain generation.[4] Sindou et al[2] first reported that DREZotomy was more effective for paroxysmal than continuous pain. A possible explanation of this differential effect is that paroxysmal pain originates from hyperactive neurons in the dorsal horn, whereas continuous pain originates from supraspinal structures, particularly the thalamus.[2,3,20,21] Knowing that EMCS is able to modulate the activity of supraspinal structures, particularly the sensory thalamus and cingulate gyrus, may explain its efficacy for continuous pain.[22,23] The failure of EMCS to relieve paroxysmal pain is more difficult to explain. It was reported that EMCS exerts a descending inhibitory effect on the dorsal horn neuronal activity[24]; however, that effect may be interrupted as a result of deafferentiation.[25] It seems that each procedure acted through

a distinct mechanism related to a particular type of pain: DREZotomy eliminated hyperactive neurons responsible for paroxysmal pain, whereas EMCS modulated the activity of supraspinal structures responsible for continuous pain.

Limitations

The main limitations of this study are the small sample size, particularly for subgroup analysis and retrospective design. Although the number of patients is small, it represents the largest population of patients receiving EMCS for BPA in a single center. However, our results are preliminary and should be reproduced in a larger patient population.

In 4 patients who underwent both EMCS and DREZotomy procedures, a residual effect after the first surgery, a "carryover" effect, may be argued. However, such a carryover effect is unlikely to occur after EMCS because its effects are reversible on discontinuation of treatment. Moreover, the negligible pain relief effects of the first procedure (either DREZotomy or EMCS) in those patients (Table 2) argue against such a carryover effect. However, because DREZotomy causes irreversible changes in dorsal horn, a residual effect after DREZotomy cannot be completely ruled out and remains a limitation of the present study.

Despite these limitations, our findings are of interest as the only study to describe a differential effect of EMCS on BPA pain and suggest that treatment and study of BPA pain in the future should carefully distinguish between continuous and paroxysmal pain.

CONCLUSION

We analyzed the differential effect of EMCS and DREZotomy for different types of BPA pain. EMCS was ineffective for paroxysmal pain but moderately effective for continuous pain. DREZotomy was highly effective for paroxysmal pain but moderately effective for continuous pain. It may be prudent to use EMCS for patients who continue to have intractable pain after DREZotomy.

Disclosures

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

Brachial plexus injuries are classically considered a homogeneous traumatic entity, and consecutive pain is thought to be a clinical replica of experimental peripheral deafferentation. In fact, the so-called brachial plexus avulsion (BPA) syndrome has some heterogeneous aspects.

BPA is followed by chronic pain in the deafferented area in 60% of the cases on average (30% to 90% according to the published series). Incidence is quite different in relation to location of the disruptive lesion:

< 33% for postganglionic location, ie, distal to the dorsal root ganglion, as opposed to 90% for predominantly preganglionic locations.[1-4]

Classically, pain after BPA appears in a standard clinical manner: a continuous background of pain described as burning, throbbing, and/or aching sensations or pain with electric shooting–like violent paroxysms. These 2 components may coexist with equal intensity; 1 type may predominate over the other; or, rarely, 1 of the 2 may exist in isolation.

In a previous article devoted to outcome after dorsal root entry zone microsurgical lesioning (DREZotomy) for pain resulting from BPA,[5] we suggested that the 2 distinct types of pain be considered the clinical expression of 2 different mechanisms. There are strong arguments that paroxysmal pain arises from deafferented hyperactive neurons in the dorsal horn.[6–10] Continuous pain might rather be in relation to supraspinal generators, particularly at the thalamus, as the consequence of destruction of the neurons at origin of the ascending spinoreticulothalamic pathways.[11]

So, as pointed out by the Japanese team, to study independently the effects of surgery on the 2 components of pain is wise and of practical importance. We have shown that microsurgical DREZotomy, although effective on both components, had better effectiveness on the paroxysmal component. Pain relief was obtained, in all the patients with paroxysms only, in 75% of the patients suffering from both pain components and in 50 % of the patients who had continuous background only ($P = .04$).[5]

Like us, the authors of the present article found a differential effect by the DREZ procedure: 70% of the patients with paroxysmal pain had favorable outcomes compared with 20% with continuous pain. In addition, they carried out motor cortex stimulation and compared the results; 42% with continuous pain had favorable outcomes compared with no patients with paroxysmal pain. Our experience with motor cortex stimulation for pain after BPA is quite similar.

Because the pain after BPA is almost constantly unbearable and is resistant to all classes of analgesic agents (including opioids), anticonvulsants, and antidepressants, neurosurgery is the only recourse. When patients are referred to the neurosurgeon, the majority have already undergone attempts to nerve repair. According to literature and our experience, spinal cord stimulation is not particularly effective, especially when preganglionic lesions predominate. The reason is that most of the fibers targeted by stimulation underwent degeneration up to the brainstem. Lack of corresponding valid fibers in the dorsal column can be ascertained by somatosensory evoked potentials. It has been shown that impairment in central conduction time, ie, between dorsal root ganglion cells and brain: N13 to N20 for upper limb and N22 to P39 for lower limb, is a valuable predictor of failure of SCS.[12] Thalamic deep brain stimulation, although quite logical from an anatomical/physiological point of view, has not been confirmed as effective on pain after BPA. As proposed by the Japanese authors, DREZotomy has to be considered the first option, at least when paroxysmal pain predominates; motor cortex stimulation[13] may be proposed when the continuous pain component persists after completion of DREZ-lesioning surgery.

The authors have to be acknowledged for adding useful insights to pain surgery. This article shows how surgery for neuropathic pain can be effective if the neurosurgical method precisely targets the appropriate anatomical site(s) and accurately corrects the various pathophysiological mechanisms (and therefore components) of the pain.

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Surgical Approaches to Tumors of the Gyrus Cinguli

To the Editor:

We read the article by Talacchi et al[1] entitled "Surgical Approaches to Tumors of the Anterior Gyrus Cinguli" with great interest. To their credit, the authors have successfully focused attention on a surgical site that rarely receives the attention it deserves, and we applaud them for this. In fact, we believe that it is safe to say that, apart from any functional considerations, tumors involving the cingulate gyrus are significant both because of their deep location and because they are supplied with a specific anatomic pathway like the interhemispheric fissure. In our opinion, however, based on more than 100 interhemispheric approaches performed over the course of 5 years (for a variety of lesions that lie deep in the interhemispheric fissure), there is another approach to reach this region that Talacchi et al might have considered. We are referring to the contralateral transfalcine interhemispheric approach. In 1984, Machado de Almeida et al[2] were the first to take an exclusively contralateral approach to removing a parasagittal arteriovenous malformation. In 1995, Goel[3] systematically elaborated on this specific approach as a means of reaching contralateral tumors involving the cingulate gyrus. He underscored the value of this approach in the treatment of deep-seated brain tumors, emphatically stressing that this approach, if correctly performed, is direct, safe, and helpful in the successful resection of such tumors. He further suggested that this approach also provides an exposure that obviates the need for traversing or retracting the homolateral edematous brain. In 1996, Lawton et al[4] further elaborated on this approach by introducing the concept of a gravity-aided contralateral approach. With the patient lying in a supine position and with the midline orientated horizontally, they were able to make their lesion on the upper aspect (see their Figure 1). They suggested that this position has the following 2 main advantages: Gravity alone will retract the lower hemisphere and, in so doing, open the interhemispheric fissure; and the lesion will naturally come into greater view as removal of the tumor progresses. Recently, Chi and Lawton[5] also stressed the benefits of a gravity retraction that allows a wider operative exposure, which has the additional benefit of reducing morbidity.

We have developed expertise in this approach as a result of time spent with Dr Spetzler in Phoenix in 2003. To date, we have had numerous opportunities to successfully use this approach to treat a variety of neoplastic and/or vascular lesions that were found in or around the cingulate gyrus. It is on the basis of these surgical opportunities that we fully appreciate the advantages that, we believe, are incomparable when it comes to cases of small lesions deep within a motor area that is swollen as a result of the underlying lesion.[6] Because the interhemispheric corridor is tempting but, it should also be noted, rich in dangerous snares, we offer the following strategies that we have found extremely helpful for avoiding these hazards during surgery: (1) use the Lawton-Spetzler position; (2) make a linear incision parallel to the midline; (3) perform magnetic resonance angiography– or image–guided craniotomy perfectly centered between the entry point of bridging veins in the superior sagittal sinus; (4) expose the superior sagittal sinus by ad hoc placed burr holes and craniotome only after full control and detachment of dura mater from the bone; (5) gently retract and release the brain with working instruments rather than with a fixed spatula; and (6) consider the use of indocyanine green videoangiography to evaluate the presence of collateral drainage pathways before sacrifice or putting a bridging vein at risk (Ferroli et al[7]).

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10.1227/NEU.0b013e31821243f1

In Reply:

Ferroli and colleagues note that anterior gyrus cinguli tumors may be approached contralaterally. In our series of anterior gyrus cinguli tumors, we used—among others—the interhemispheric bilateral approach in perigenual tumors extending contralaterally and the unilateral approach in perirolandic tumors, based on the finding that tumors never extend contralaterally at this level. From this observation and evidence for the absence of drawbacks to the ipsilateral interhemispheric approach in small lesions, we believe that the contralateral approach may not necessarily offer

an additional advantage over the ipsilateral approach. Furthermore, maneuvers like falx transection with division of the inferior sagittal sinus and the falcine venous plexus, which can carry unpredictable consequences for venous drainage, are not justified in our opinion.[1] However, we were aware of this approach and mentioned it in the discussion, but, because of its limited indications and the scarce success reported in the literature, we decided not to discuss it further.

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10.1227/NEU.0b013e3182127bee

Spinal Cord Stimulation for Thalamic or Central Pain

To the Editor:

I have read with great interest the paper of Ali et al[1] regarding the usefulness of spinal cord stimulation (SCS) in the treatment of central pain after stroke (CPSP), also well known as thalamic pain.

Patients with focal CPSP instead of generalized pain were considered for treatment by Ali et al.[1] Two cases with complete hemibody pain had circumscribed areas of more severe pain.

Percutaneous tetrapolar epidural electrodes were implanted and held for a 2- to 7-day trial period in 30 patients. Then, the electrode was removed. The analgesic results of the trial period were discussed with the patient. Ten patients received a new tetrapolar electrode. After a second trial period (whose duration is not specified), the internal pulse generator was implanted.

In their discussion the authors claim to be the first to describe good results with the SCS for the treatment of CPSP. The work published by our group[2] shows that this statement is not true. Our series is shorter than the one by Ali et al.[1] Follow-up is longer. They have a 28-month follow-up (range, 6-62), while that ours is longer: 81.6 months (range, 36-149).

I assume with Ali et al[1] that SCS is a much less aggressive surgical method than deep brain stimulation or motor prefrontal cortex. I also agree that better results can be attained in cases of focal pain rather than generalized pain.

I disagree with Ali et al[1] on the appropriateness of a short trial period of 2 to 7 days. I disagree very much with the removal of the electrode test and the return to implant it in the case of the definite implant. It is possible that the second electrode failed to obtain the same paresthesia as did the first. In addition, the rate of local complications could be increased.

Congratulations to Ali et al[1] for his excellent work, which confirms the good results that were previously shown by our work.[2]

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Cadiz, Spain

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2. Lopez JA, Torres LM, Gala F, Iglesias I. Spinal cord stimulation and thalamic pain: long-term results of eight cases. *Neuromodulation.* 2009;12(3):240-243.

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In Reply:

We would like to thank Lopez and colleagues for their interest in our article.[1] Lope et al[2] reported on a small series of spinal cord stimulation (SCS) for thalamic pain; 6 of 8 patients (75%) achieved satisfactory pain relief in the long term. Lopez et al restricted their indication to patients with localized pain distribution that could be entirely covered by stimulation paraesthesia; and this may explain their relatively high success rate.[2] Unfortunately this work had not yet been published when we submitted our report for publication.

Lopez et al reported that our trial period (2–7 days) was short. Actually, within this time frame we were able to unequivocally evaluate the analgesic effect of SCS in all patients. In general, there is no consensus on the length of SCS trial period, and periods of one day to several weeks have been reported.[2,3] There is no doubt that long trial periods give a better opportunity to evaluate the exact response to SCS, but unfortunately this comes with the price of increasing the risk of infection.

In our series, we used to remove the trial electrodes, and discharge patients after the trial period. At the time of counseling the patients in the outpatient clinic, those who decided to proceed were scheduled for the second trial and permanent SCS implantation.[1] Lopez et al disagree with this approach because they think it may increase the rate of local complications and the second electrode may fail to provoke the same paresthesia. The rationale for our approach was that, during trial stimulation, patients tend to respond in an affirmative manner, and therefore overestimate the analgesic efficacy.[4] We believe that repeating trials before permanent implant of SCS electrodes will minimize this phenomenon. However, there is no evidence that our method can improve outcome. We did not have any added complications from the second trial, but it obviously increases the cost of treatment. Finally, it is interesting to find that our results of SCS for central poststroke pain (CPSP) could be reproduced at other institutes. Hopefully these reports will encourage other centers to use SCS for CPSP, particularly in the face of safety of SCS trials and limited therapeutic options for CPSP.

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