Intraoperative Intrinsic Optical Imaging of Neuronal Activity from Subdivisions of the Human Primary Somatosensory Cortex

We performed intrinsic optical imaging of neuronal activity induced by peripheral stimulation from the human primary somatosensory cortex during brain tumor surgery for 11 patients. After craniotomy and dura reflection, the cortical surface was illuminated with a xenon light through an operating microscope. The reflected light passed through a bandpass filter, and we acquired functional images using an intrinsic optical imaging system. Electrical stimulation of the median nerve, or the first and fifth digits, induced biphasic intrinsic optical signals which consisted of a decrease in light reflectance followed by an increase. The decrease in light reflectance was imaged, and we identified a neural response area within the crown of the postcentral gyrus. In experiments on first and fifth digit stimulation, we identified optical responses in separated areas within the crown of the postcentral gyrus, i.e. near the central sulcus and near the postcentral sulcus. In the former response area, separate representations of the two fingers were observed, whereas in the latter response area, the two fingers were represented in the same region. A similar somatotopic representation was observed with electrical stimulation of the first and third branches of the trigeminal nerve. These results seem to support the hypothesis of hierarchical organization in the human primary somatosensory cortex.

Introduction

Since the electrical stimulation study of Penfield and Boldrav (Penfield and Boldrav, 1937) on the human cerebral cortex during neurosurgery, the human somatosensory system has been considered a highly sophisticated system for information processing. The primary somatosensory cortex (SI) is subdivided into four cytoarchitectonic areas, termed Brodmann’s areas 3a, 3b, 1 and 2 (Brodmann, 1909; Vogt and Vogt, 1919). In physiological and anatomical studies of non-human primates, it has been demonstrated that there is a complete topographic representation of the body in each of the four Brodmann’s areas, and that these areas exhibit a hierarchy in sensory information processing (Merzenich et al., 1978; Kaas et al., 1979; Nelson et al., 1980; Sur et al., 1982; Garraghty et al., 1990) [for a review see Kaas (Kaas 1983)]. In the human primary somatosensory cortex, a similar hierarchy has been assumed, but direct evidence has not been obtained.

Recent advances in functional neuroimaging techniques, including positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and near infrared spectroscopy (NIRS), have made it possible to obtain functional images of neuronal activity from the human brain. These techniques have demonstrated several activation sites in the primary somatosensory cortex induced by peripheral stimulation (Lin et al., 1996; Burton et al., 1997; Gelnar et al., 1998; Kurth et al., 1998, 2000; Hluskik et al., 2001; Ruben et al., 2001). However, the spatial and temporal resolutions of these techniques are not sufficient to detect neuronal activity from each Brodmann’s area in the somatosensory cortex.

An optical imaging technique for intrinsic signals has been developed and used to monitor neuronal activity in the cerebral cortex of in vivo preparations (Grinvald et al., 1986; Chapman et al., 1996; Gödecke and Bonhoeffer, 1996). The optical method has proven to be a very useful technique for monitoring neural responses in the central nervous system, and offers advantages for studying functional organization in the cat or monkey visual cortex (Ts’o et al., 1990; Bonhoeffer and Grinvald, 1991; Shumuel and Grinvald, 1996) and the rodent somatosensory (whisker barrel) cortex (Masino et al., 1993; Dowling et al., 1996; Tanaka et al., 2000; Yazawa et al., 2001). In intrinsic optical signals, it is indicated that there are at least three components (Bonhoeffer and Grinvald, 1995; Frostig et al., 1990; Malonek and Grinvald, 1996). The first component originates from activity-dependent changes in the oxygen saturation level of hemoglobin. The second component originates from changes in blood volume that are probably due to dilation of venules in an area containing electrically active neurons. The third component arises from light-scattering changes that accompany cortical activation caused by ion and water movement, expansion and contraction of extracellular spaces, capillary expansion or neurotransmitter release (Cohen, 1973; Salzberg et al., 1985; Sato et al., 1997; Momose-Sato et al., 1998).

The intrinsic optical imaging technique was also applied to the human brain during neurosurgery. Haglund et al. (Haglund et al., 1992) first demonstrated the usefulness of this technique for functional localization in the human brain. They obtained maps during stimulation-evoked epileptiform afterdischarges and cognitively evoked functional activity. Functional images induced by language tasks were also shown by Cennestra et al. (Cennestra et al., 2000) and Pouratian et al. (Pouratian et al., 2000); they detected neuronal responses from the Broca’s and Wernicke’s areas in awake patients.

There are a few reports of intrinsic optical imaging from the human somatosensory cortex in response to median/ulnar nerve stimulation (Toga et al., 1995) or digit stimulation (Shoham and Grinvald, 1994; Cennestra et al., 1998). Although these reports showed neural responses in the primary somatosensory cortex, they did not separate optical responses among the Brodmann’s subdivisions. In the present study, we applied this intrinsic optical imaging technique to brain tumor patients during neurosurgery, and succeeded in clearly detecting neural responses induced by peripheral stimulation in Brodmann’s subdivisions individually. Furthermore, we made functional local maps in the primary somatosensory cortex, and produced supportive data for hierarchical organization in the human brain. The preliminary results have appeared in abstract form (Nariai et al., 2000; Sato and Nariai, 2000).
Materials and Methods

Subjects
We measured intrinsic optical signals from the somatosensory cortex in 11 anesthetized patients undergoing surgical resection of parietal or temporal lobe brain tumors. The patient data are summarized in Table 1. Except for case 4, patients had no past history of neurosurgery. Informed consent was obtained from all patients prior to the surgery and intraoperative intrinsic optical imaging. We also obtained approval from Tokyo Medical and Dental University. The patients were anesthetized with isoflurane, and the head was fixed to the operating table via a Mayfield apparatus. Craniotomy and dura reflection were performed, and the surface of the cerebral cortex around each brain tumor was exposed. Before the intrinsic optical imaging, we recorded cortical somatosensory evoked potentials (SEPs) in response to median nerve, digit I and V, or supraorbital and mental nerve stimulation with a four-channel superficial electrode. It has been reported that a phase reversal of the negative peak of SEPs occurs across the central sulcus (Nuwer et al., 1992). Using the SEPs, we identified the central sulcus as a landmark.

Peripheral Nerve Stimulation
For the optical imaging, the median nerve (for five patients), digit I and V (for five patients) or the supraorbital and mental nerve branch of the ophthalmic nerve (N V1) and the mental branch of the mandibular nerve (N V3) (for two patients) were stimulated transcutaneously with surface electrodes driven by an electrical stimulator. The stimuli, consisting of 10 pulses, were delivered at 5 Hz for 2 s with an interstimulus interval of 20 s. The stimulation intensity was 10 mA, which produced the maximal SEP negative peak of SEPs occurs across the central sulcus (Nuwer et al., 1992). The ratio values were processed with a Gaussian filter (a 4 × 4 Gaussian mask) to remove high-frequency noise, and we defined them as the cortical area surrounded by the curve at half of the normalized difference (Chen-Bee et al., 1996). The ratio values were processed with a Gaussian filter (a 4 × 4 Gaussian mask) to remove high-frequency noise, and we defined them as the cortical area surrounded by the curve at half of the normalized difference (Chen-Bee et al., 1996).

Intraoperative Intrinsic Optical Imaging
After identifying the central sulcus, the recording site of the cerebral cortex was stabilized with a glass plate. This procedure minimized brain movements in the z-axis, as well as in the x- and y-planes. No significant brain damage was induced by this procedure, although the possibility that the plate could affect the local brain environment cannot be excluded. The somatosensory cortex was illuminated using a xenon lamp driven by a stable DC power supply via an operating microscope (Carl Zeiss, Inc., Thornwood, NY). The depth of focus of the operating microscope was set to ~500 µm under the cortical surface. Reflected light from the cortex was passed through interference filters of different wavelengths. The filter used for visualizing the surface of the cortex and its vascular pattern had a transmission maximum at 540 ± 30 nm, and the filter used for intrinsic imaging had a passband at 605 ± 5 nm (Asahi Spectra Co., Tokyo, Japan). We used 605 nm for two reasons. First, this wavelength coincides with the peak of the different spectra between the oxyhemoglobin and deoxyhemoglobin, and maximizes the contribution of oximetry signals relative to other intrinsic signals (Frostig et al., 1990; Bonhoeffer and Grinvald, 1993). Second, in our previous studies on the rat somatosensory cortex (Tanaka et al., 2000; Yazawa et al., 2001), brainstem (Yazawa et al., 1999) and spinal cord (Sasaki et al., 2000), we detected the largest intrinsic signal at a wavelength of 605 nm. In the present study, we could not examine the wavelength dependency of the optical signals because of the limited recording time (30–30 min).

Intrinsic imaging was performed using a different optical acquisition system, IMAGER 2001 (Optical Imaging, Germantown, NY) via a charge-coupled device camera fitted to an operating microscope. Two or three recording sessions were allowed for each patient. One recording session consisted of eight blocks. Each block consisted of six or three stimulation trials and three non-stimulation (control) trials interlaced randomly, with an intertrial interval of 20 s. During each trial, eight optical images were collected over 5.0 s and stored on a computer with IDAQ data acquisition software (Optical Imaging). For stimulation trials, the median nerve, digit I and V, or the supraorbital and mental nerves, were stimulated for 2 s from the onset of data acquisition (also see Fig. 1B). Optical reflectance images were represented by a fractional change (ΔR/R) to correct for uneven illumination using a data-analyzing software program, TVMix (Optical Imaging). It usually took ~15 min to obtain a functional map.

To trace the optical response area, we followed a modified version of the normalized threshold analysis (Chen-Bee et al., 1996), using the data analysis software programs TVMix and Transform (Fortner Research LLC, Sterling, VA). The software first located the local peak within the response area. It then calculated the difference between the local peak and the median, and this was normalized to 100% (normalized difference). The normalization is considered to account for any general changes in activity unrelated to whisker stimulation (e.g. potential changes in overall cortical excitability due to fluctuations in the depth of anesthesia (Chen-Bee et al., 1996)). The ratio values were processed with a Gaussian filter (a 4 × 4 Gaussian mask) to remove high-frequency noise, and we defined them as the cortical area surrounded by the curve at half of the normalized difference (Chen-Bee et al., 1996).

Preoperative Magnetoencephalography (MEG) Recording
We recorded somatosensory evoked fields (SEFs) in seven patients before surgical operations using a whole-head type MEG system with 148 channel magnetometers (Magnes, Biomagnetic Technologies, San Diego, CA). We clearly detected the SEFs in six of seven patients. For four patients (cases 2, 4, 5 and 11 in Table 1), MEG was not performed because of their poor condition. Following the recording, the source current locations in three dimensions of SEFs and the equivalent current dipole (ECD) moments were calculated using a single-dipole model, assuming the brain to be a sphere. The ECDs that best explained the most dominant source were determined using data recorded from a subset of channels, and the ECDs were superimposed on a three-dimensionally reconstructed magnetic resonance (MR) image of the brain.

In Table 1, the summary of patient data is presented. The table includes information on case number, sex, age, diagnosis, tumor location, stimulation site, and the results of intrinsic optical imaging (IOS) and magnetoencephalography (MEG).

Table 1
Summary of patient data

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Tumor Location</th>
<th>Stimulation site</th>
<th>IOS</th>
<th>MEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>52</td>
<td>meningioma</td>
<td>L parietal</td>
<td>R median nerve</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>75</td>
<td>metastatic brain tumor</td>
<td>R parietal</td>
<td>L median nerve</td>
<td>+</td>
<td>NP</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>61</td>
<td>metastatic brain tumor</td>
<td>R parietal</td>
<td>L median nerve</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>68</td>
<td>meningioma</td>
<td>L parasagittal</td>
<td>R median nerve</td>
<td>ND</td>
<td>NP</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>57</td>
<td>anaplastic oligodendroglioma</td>
<td>R postparietal</td>
<td>L 1st/5th digit</td>
<td>+</td>
<td>NP</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>71</td>
<td>metastatic brain tumor</td>
<td>R temporal</td>
<td>L 1st/5th digit</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>47</td>
<td>astrocytoma</td>
<td>L temporal</td>
<td>R V1/V3</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>63</td>
<td>metastatic brain tumor</td>
<td>L temporal</td>
<td>R 1st/5th digit</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>44</td>
<td>glioblastoma</td>
<td>L parietotemporal</td>
<td>L 1st/5th digit</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>51</td>
<td>glioblastoma</td>
<td>L parietotemporal</td>
<td>L V1/V3 nerve</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>50</td>
<td>astrocytoma</td>
<td>L parietal</td>
<td>R 1st/5th digit</td>
<td>+</td>
<td>NP</td>
</tr>
</tbody>
</table>

IOS, intrinsic optical signal; MEG, magnetoencephalography; ND, not detected; NP, not performed.
11 patients, and we detected optical responses in 10 patients, as shown in Table 1.

**Nature of the Optical Signals in Response to Median Nerve Stimulation**

Figure 1A shows a typical example of intrinsic optical images obtained from a 61 year old patient who suffered from anaplastic oligodendroglioma (case 3 in Table 1). The left median nerve was stimulated by surface electrodes, and intrinsic optical signals (optical reflectance changes) were detected from the right parietal lobe. Before making the intrinsic optical recording, we recorded cortical SEPs in response to left median nerve stimulation to identify the central sulcus (indicated by the white line in the right panel of Fig. 1A). The recording site is shown with black squares in a three-dimensionally reconstructed MR image and a photograph of the cortical surface (left panels of Fig.1A). The detected reflectance signals were illustrated by a pseudo-color image, in which a decrease in light reflectance was shown in green to red (right panel of Fig. 1A). In this image, the optical response induced by median nerve stimulation was clearly identified near the central sulcus. To check whether the optical response was definitely detected from a median nerve-related region in the somatosensory cortex, we examined the location of an equivalent current dipole (ECD) measured with MEG, which is illustrated with a green solid circle in the upper left panel in Figure 1A. The optical response area and the ECD were located in nearly the same region of the somatosensory cortex, supporting the idea that the optical responses reflect neuronal activity evoked by median nerve stimulation (also see Discussion).

Figure 1B shows the time course of the intrinsic optical signal obtained in the response area. In this figure, a decrease in light reflectance is plotted against the recording time. The intrinsic optical signal exhibited biphasic features, and showed its maximum amplitude in the third frame (1.4 s from the onset of stimulation); no significant optical change was detected without stimulation. This time course is consistent with that reported previously using a wavelength of 605 nm (Bonhoeffer and Grinvald, 1993; Tanaka et al., 2000). Similar intrinsic signals with a similar time course were obtained from three other patients (cases 1, 2 and 10 in Table 1) whose median nerves were stimulated electrically (data not shown).

**Optical Responses to Digit I and V Stimulation**

Figure 2A shows intrinsic optical images obtained from a 63 year old patient who suffered from a metastatic brain tumor (case 8 in Table 1). Right digits I and V were stimulated individually by surface electrodes, and intrinsic optical signals were detected from the left somatosensory cortex. The detected area is illustrated with a black square in the right panel, which corresponded to the postcentral gyrus (primary somatosensory cortex, SI). The optical responses induced by digit I and V stimulation were clearly detected from different areas of the primary somatosensory cortex. Figure 2B shows the optical response areas identified with three repetitive trials. In this figure, we traced the optical response area of each trial at half the normalized difference of the signal (see Materials and Methods), and three traces from three trials are superimposed for each stimulation. The response area appeared in almost the same region, and trial-to-trial variations were not significant. In Figure 2C, ECDs are superimposed on a three-dimensional MR image. The red closed circle is the ECD to digit I stimulation, and the green closed circle is the ECD to digit V stimulation. As is the case in median nerve stimulation, the relative positions of the optical response areas and ECDs were coincident, suggesting that the optical responses induced by digit I and V stimulation clearly reflected neuronal activity in the primary somatosensory cortex.

Figure 3 shows another example of the intrinsic optical images induced by digit V stimulation in a 57 year old patient who suffered from anaplastic oligodendroglioma (case 5 in Table 1). Left digit V was electrically stimulated with surface electrodes, and the images were detected from the right somatosensory cortex. Eight images were collected in 5 s, and the time course of the images is chronologically represented. In this case, we identified two separated response areas, i.e. area V1 and area V2. Area V1 was located near the central sulcus, whereas area V2 was located near the postcentral sulcus. Figure 4 shows the time course of the intrinsic optical signal in areas V1 and V2. Although the time resolution of the present study was not so high (~0.7 s), a difference in the time course of the optical signal was seen between the two areas; the peak response in area V1 appeared somewhat earlier than that in area V2.

Figure 5A shows intrinsic optical images induced by digit I and V stimulation obtained from the same patient in Figure 3. As can be seen in this figure, digit I stimulation also induced two response areas (areas I1 and I2) (left panel). Area I1 was situated near the central sulcus, whereas area I2 was located in almost the same region as area V2. In Figure 5B, optical response areas are superimposed on the vascular image of the somatosensory cortex. The red curves show the response areas identified with digit I stimulation, and the blue curves show those identified with digit V stimulation.

Figure 6 shows three other examples of optical response areas identified with digit I and V stimulation in three different patients (case 6: metastatic brain tumor; case 9: glioblastoma; case 11: astrocytoma). In each case, optical response areas are superimposed on the vascular image of the somatosensory cortex. Each recording site is shown with a black square on a three-dimensionally reconstructed MR image in the lower panels. In cases 6 and 9, the MEG was performed and ECDs were superimposed on the MR images. The red closed circle is the ECD to digit I stimulation and the blue closed circle is the ECD to digit V stimulation. In case 9, the ECD to median nerve stimulation is also shown by a green closed circle. In all cases, optical response patterns were similar to those observed in case 5 (Fig. 5B). In case 6, two trials were performed and the neural responses appeared in the same location. In case 9, the distribution patterns were a little different from the pattern seen in the other cases. This was probably due to severe transformation of the cerebral cortex caused by the tumor (also see Discussion).

In Figures 5 and 6, we extracted the following characteristics of the neural response patterns: (i) digit I and V stimulation induced neural responses in two different areas on the crown of the postcentral gyrus; (ii) the first response areas were located near the central sulcus (areas I1 and V1), and, in these response areas, digits I and V were separately represented; (iii) the second response area was located near the postcentral sulcus (areas I2 and V2), and digits I and V were represented in the same region.

**Optical Responses to N V1 and N V3 Stimulation**

In other regions of the primary somatosensory cortex, can we find the same functional organization? To answer this question, we applied an optical technique to the face region in the somatosensory cortex. Figure 7A illustrates intrinsic optical images obtained with supraorbital (N V1) and mental (N V3) nerve stimulation in a patient who suffered from an astrocytoma (case 7 in Table 1). Both supraorbital and mental nerve
Figure 1. Intrinsic optical responses induced by median nerve stimulation. (A) An intrinsic optical image recorded from the right somatosensory cortex of a 61 year old patient (case 3 in Table 1). The left median nerve was electrically stimulated. The recording site is shown with black squares on a three-dimensionally reconstructed magnetic resonance (MR) image and a photograph of the cortical surface. The detected signals are illustrated by a pseudo-color image, in which a decrease in reflectance is shown in green to red. The white lines indicate the central sulcus and postcentral sulcus. In the upper left panel, an equivalent current dipole (ECD) to the median nerve stimulation is superimposed (a green closed circle). (B) Time course of the intrinsic optical signal in the response area. The positive direction corresponds to a decrease in light reflectance. The stimulation timing is shown on the bottom. The red line shows the change in the intrinsic signal size with stimulation, and the blue line shows that without stimulation.
stimulation induced optical responses in two separate areas, areas O1 and O2, and areas M1 and M2 respectively. We traced the area of the optical responses induced by the supraorbital and mental nerve stimulation at half the normalized difference. Each trace was superimposed on the vascular image of the somatosensory cortex (Fig. 7B). The recording site is shown with a black square on a three-dimensionally reconstructed MR image in Figure 7C. As in the case with digit I and V stimulation, supraorbital and mental nerve stimulation induced neural responses in different regions near the central sulcus (areas O1 and M1), and in the same region near the postcentral sulcus (areas O2 and M2). This result shows that, in the face region, the functional organization is the same as in the digit region.

We performed similar experiments in another patient (case

Figure 2. Intrinsic optical responses induced by digit I and V stimulation. (A) Intrinsic optical images recorded from the left somatosensory cortex of a 63 year old patient (case 8 in Table 1). Right digits I and V were individually stimulated, and the detected optical responses are illustrated by pseudo-color images. The black square in the right panel represents the detected area, and the yellow line indicates the central sulcus. (B) Traces of the optical response areas induced by three repetitive trials. The traces are superimposed for each trial. (C) Equivalent current dipoles (ECDs) are superimposed on a three-dimensional MR image. The red closed circle is the ECD to digit I stimulation, and the green closed circle is the ECD to digit V stimulation.
Figure 3. The time course of the intrinsic optical responses induced by digit V stimulation. Eight images were collected in 5 s (1 frame/0.7 s) from the right somatosensory cortex of a 57 year old patient (case 5 in Table 1), and the first one was used as a reference image. The yellow lines indicate the central sulcus and postcentral sulcus. In this case, digit V stimulation induced two different response areas (areas V1 and V2). Asterisks indicate noises due to blood flow. The recording site is illustrated with a white square on a three-dimensional MR image in Figure 5C.
to Brodmann’s area 1, while that detected by MEG corresponds to Brodmann’s area 3b. Brodmann’s areas 3b and 1 are closely situated and organized as approximate mirror images of each other (Kaas et al., 1979; Nelson et al., 1980; Sur et al., 1982; Fellemann et al., 1983). Therefore, the fact that the optical signals and MEG signals were detected from nearly the same region of the somatosensory cortex suggests that the intrinsic optical responses in the present study certainly reflect neuronal activity induced by peripheral stimulation.

As shown in Figure 1B, the induced intrinsic optical signal showed a biphasic time course, which is similar to that described in experimental animals using a wavelength of 605 nm (Bonhoeffer and Grinvald, 1993; Tanaka et al., 2000). This result also supports the idea that the optical responses reflect neuronal activity evoked in the somatosensory cortex. In previous reports (Haglund et al., 1992; Toga et al., 1996), optical signals with large amplitudes and a monophasic time course were demonstrated. Similar monophasic optical signals were also recorded in our experiments. As Bonhoeffer and Grinvald (Bonhoeffer and Grinvald, 1995) pointed out, it is possible that such signals are contaminated by noise from the microvascular system. Thus, we did not analyze these signals in the present study.

As a second step, we tried to record neuronal activity separately from Brodmann’s subdivisions. As shown in Figures 5 and 7, we detected optical signals from two separated areas on the crown of the postcentral gyrus with digit I and V or N V1 and N V3 stimulation. Although the human primary somatosensory cortex has been divided microstructurally into four areas, namely Brodmann’s area 3a, 3b, 1 and 2 (Brodmann, 1909; Vogt and Vogt, 1919; White et al., 1997), the borders of these areas vary between researchers. We considered two possible interpretations concerning the origin of the optical signals.

The first interpretation is that the response area near the central sulcus corresponds to Brodmann’s area 1, and that near the postcentral sulcus corresponds to Brodmann’s area 2. This interpretation is based on the traditional context of the division of the somatosensory cortex (Brodmann, 1909; Vogt and Vogt, 1919; White et al., 1997). The second interpretation is that both the optical response areas correspond to Brodmann’s area 1. This interpretation is based on a recent observation by Geyer et al. (Geyer et al., 1999, 2000), who identified cytoarchitectonic borders of Brodmann’s subdivisions with a new observer-independent and statistically testable procedure. In their map, Brodmann’s area 1 occupies the crown of the postcentral gyrus and reaches down into the postcentral sulcus.

In the human brain, Brodmann’s subdivisions are considered to constitute hierarchical stages of cortical processing (Eskensay and Clarke, 2000). In physiological and anatomical studies of non-human primates, it has also been demonstrated that there is a complete topographic representation of the body in each of the four Brodmann’s areas and that these areas exhibit a hierarchy in sensory information processing (Merzenich et al., 1978; Kaas et al., 1979; Nelson et al., 1980; Sur et al., 1982; Garraghty et al., 1990) [for a review see Kaas (Kaas, 1983)]. In electrophysiological studies of the monkey somatosensory cortex, cutaneous thalamic inputs are relayed in parallel to Brodmann’s areas 3b and 1, while kinetic information is relayed to Brodmann’s areas 3a and 2 (reviewed by Gardner and Garrard, 1988) and Jones (Jones, 1986). Somatosensory inputs to the cortex originate from the ventral posterior lateral nucleus of the thalamus. Neurons in this nucleus project to all areas in the primary somatosensory cortex (SI), mainly to Brodmann’s areas 3a and 3b, and also to areas 1 and 2. Neurons in areas 3a and 3b project to areas 1 and 2, while all of them project to the secondary somatosensory cortex (SII) and posterior parietal

**Discussion**

In the present study, we succeeded in detecting intrinsic optical signals related to neuronal activity induced by peripheral stimulation from the primary somatosensory cortex during neurosurgical operations. This is the first report to distinguish responses from subdivisions of the somatosensory cortex using intraoperative optical imaging of the human brain.

**Optical Mapping of the Human Primary Somatosensory Cortex**

Intrinsic optical imaging of neuronal activity is an excellent technique to obtain functional maps of the central nervous system, and it has recently been applied to several sensory systems (Bonhoeffer and Grinvald, 1995). In the present study, we applied this technique to the human primary somatosensory cortex, and clearly detected neural responses induced by median nerve, digit I and V, and N V1 and N V3 stimulation. Although an fMRI study has shown that the primary motor cortex is systematically coactivated by tactile and proprioceptive tasks (Kurth et al., 2000), we did not obtain intrinsic optical signals from the motor cortex. This discrepancy may be due to a difference in the stimulation paradigms. Indeed, an electrophysiological study showed that peripheral electrical stimulation preferentially activates the primary somatosensory cortex (Buchner et al., 1994).

In the present experiment, as a first step, we tried to detect optical signals induced by median nerve stimulation in the primary somatosensory cortex. As shown in Figure 1, median nerve stimulation induced optical changes near the central sulcus, and this response area was located in a median nerve-related region measured with preoperative MEG. Generally, intrinsic optical imaging has the advantage of detecting neuronal activity from the cortical surface, whereas MEG has the advantage of detecting neuronal activity from the cortex perpendicular to the brain surface. Considering the anatomical structure of the somatosensory cortex (Brodmann, 1909; Vogt and Vogt, 1919; White et al., 1997), it is reasonable to assume that the response area detected by optical imaging corresponds to Brodmann’s area 1, while that detected by MEG corresponds...
Figure 5. Intrinsic optical responses induced by digit I and V stimulation. (A) Both digit I and V stimulation induced two separated response areas, areas I₁ and I₂, and areas V₁ and V₂ respectively. The asterisk indicates noises due to blood flow. The yellow line indicates the central sulcus. The images were obtained from the same patient shown in Figure 3. (B) Optical response areas identified with digit I and V stimulation. The red curves show the response areas identified with digit I stimulation, and the blue curves show those identified with digit V stimulation. Each trace is superimposed on a vascular image of the somatosensory cortex. The yellow lines indicate the central sulcus and postcentral sulcus. (C) The recording site of the intrinsic optical signals is illustrated with a white square on a three-dimensional MR image. The green area indicates the brain tumor. The major veins are illustrated in blue.
Figure 6. Examples of optical response areas identified with digit I and V stimulation. The optical signals were detected from three patients (A: case 6, B: case 9, C: case 11 in Table 1). In the upper panels, the red curves show the response areas identified with digit I stimulation, and the blue curves show those identified with digit V stimulation. Each trace is superimposed on a vascular image of the somatosensory cortex. The yellow lines show the central/postcentral sulcus. Black bar: 1 cm. In the lower panels, each recording site is shown with black squares on three-dimensionally reconstructed MR images. In cases 6 and 9, MEG was performed and equivalent current dipoles (ECDs) are superimposed on the MR images. The red closed circle is the ECD to digit I stimulation, the blue closed circle is that to digit V stimulation, and the green closed circle is that to the median nerve stimulation. The blue lines indicate the sagittal sinus.
Figure 7. Intrinsic optical responses induced by trigeminal nerve stimulation. (A) Intrinsic optical responses were induced by stimulation of the supraorbital branch of the ophthalmic nerve (N V1) and the mental branch of the mandibular nerve (N V3) in a 47 year old patient (case 7 in Table 1). Both N V1 and N V3 stimulation induced two separated response areas, area O1 and O2, and areas M1 and M2 respectively. (B) Traces of optical response areas identified with N V1 and N V3 stimulation. The red curves show the response areas identified with N V1 stimulation, and the blue curves show those identified with N V3 stimulation. Each trace is superimposed on a vascular image of the cortex. The yellow lines indicate the central sulcus and postcentral sulcus. (C) The recording site of the intrinsic optical signals. The site is illustrated with a black square on a three-dimensional MR image. The yellow line shows the central sulcus.
cortex. In the present study, digit I and V stimulation, or supraorbital and mental nerve stimulation, induced neural responses in different regions near the central sulcus, and also induced neural responses in the same region near the post-central sulcus. If the first interpretation of the signal origin is the case (see above), our results suggest that neurons in Brodmann’s area 2 are activated by larger peripheral inputs than those in Brodmann’s area 1. Similar observations have been reported in the monkey somatosensory cortex (Gardner, 1988; Iwamura et al., 1985a,b; Pons et al., 1985). On the other hand, if the second possibility is the case, our data show that there are further functional subdivisions within Brodmann’s area 1.

As shown in Figure 4, the optical responses detected near the central sulcus appeared to be evoked earlier than those detected near the postcentral sulcus. This result may reflect the hierarchical organization in the human brain, although we have not obtained direct evidence for neuronal connections from the former to the latter.

In the present study, we could not quantitatively compare the detected areas between subjects for the following reasons: (i) all subjects in the present study had brain tumors and their brains were more or less transformed; (ii) the anesthetic state was not completely the same between the subjects; and (iii) parts of the response area were located outside the detected field (e.g. cases 9 and 11 in Fig. 6). In future studies, more detailed maps of the somatosensory cortex should be obtained.

**Usefulness of Intraoperative Intrinsic Optical Imaging for Neurosurgery**

During neurosurgery on brain tumors, it is very important to make functional local maps of the human cortex to decide the resection area. It is self-evident that the smaller the resection area is, the better the patient’s quality of life will be after the operation. Recent advances in imaging techniques, such as computerized tomography (CT) and MRI, have made it possible to detect the whole shape of the brain tumor. We can also obtain functional images using PET, fMRI and MEG prior to a neurosurgical operation. Although the resection line is usually decided with these neuroimaging examinations, we cannot neglect the possibility that the resection causes neural function deficits in patients, since the spatial resolution of these techniques is limited.

In the present study, we performed intrinsic optical imaging in brain tumor patients and could detect clear functional images in response to peripheral stimulation. The feasibility of this technique for human brain mapping has been pointed out in previous studies (Haglund et al., 1992; Shoham and Grinvald, 1994; Cannestra et al., 1998, 2000; Pouratian et al., 2000). We discussed advantages of the optical technique (Bonhoeffer and Grinvald, 1995), and these were confirmed in the present study.

First, intraoperative intrinsic optical imaging is a highly effective imaging technique to monitor neuronal activity during neurosurgery. In the present study, we obtained clear optical images from 10 of 11 patients. The only unsuccessful case (case 4 in Table 1) was a re-operation case, and the brain was severely conglutinated.

Second, the spatial resolution is higher than with conventional brain-imaging techniques. We obtained topological information on sensory representations in the digit and face regions of Brodmann’s subdivisions. The results demonstrated that the spatial resolution of the intraoperative optical imaging technique is good enough to distinguish neuronal responses in these areas. Brodmann’s subdivisions are located in the same gyrus (postcentral gyrus), and it is difficult to obtain each functional image with other imaging techniques, such as MEG, cortical SEPs, PET or fMRI.

Third, we obtained topological information on sensory representation in a patient whose cortex was severely transformed (Fig. 6B, case 9). Brain tumors often transform the cerebral cortex. In such patients, the pattern of sensory representation is different from that in normal people, and it is much more difficult to decide the brain tumor resection line during the operation.

Finally, the optical imaging apparatus is small enough to set up easily in the operating room. It is difficult to use conventional imaging techniques during surgery, and we believe that, in the near future, intrinsic optical imaging will become a routine examination during neurosurgical operations.

**Notes**

We are grateful to Dr Amiram Grinvald for generous help in constructing the optical recording apparatus. We thank Sharon Beresford and Kayo Nakano (MD Anderson Cancer Center) for critical reading of the manuscript. This research was supported by grants from the Ministry of Education-Science-Culture of Japan [Priority Areas (C) – Advanced Brain Science Project] and research funds from Japan ALS foundation, Brain Science Foundation, Toyota Foundation, Asahi Glass Foundation, Konica Imaging Science Foundation, Iwamura Foundation and Nakatani Electric Measuring Technology Association.

Address correspondence to Katsushige Sato, Department of Physiology, Tokyo Medical and Dental University Graduate School and Faculty of Medicine, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. Email: katsushige.phy2@tmd.ac.jp.

**References**


Eskenasy A-CC, Clarke S (2000) Hierarchy within human SI: supporting...


