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Invited review

Human brain mapping: Hemodynamic response and electrophysiology ☆

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See Editorial, pages 729–730

Abstract

In view of the recent advance in functional neuroimaging, the current status of non-invasive techniques applied for human brain mapping was reviewed by integrating two principles: hemodynamic and electrophysiological, from the viewpoint of clinical neurophysiology. The currently available functional neuroimaging techniques based on hemodynamic principles are functional magnetic resonance imaging (fMRI), positron emission tomography (PET) or single-photon emission computed tomography (SPECT), and near-infrared spectroscopy (NIRS). Electrophysiological techniques include electroencephalography (EEG), magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS). As for the coupling between hemodynamic response and neuronal activity (neurovascular coupling), experimental studies suggest that the hemodynamic response is significantly correlated to neuronal activity, especially local field potential (synaptic activity) rather than spiking activity, within a certain range. The hemodynamic response tends to be more widespread in space and lasts longer in time as compared with the neuronal activity. Since each technique has its own characteristic features especially in terms of spatial and temporal resolution, it is important to adopt the most appropriate technique for solving each specific question, and it is useful to combine two techniques either simultaneously or in separate sessions. As for the multi-modal approach, the combined use of EEG and MEG, EEG and PET, or EEG and fMRI is applied for the simultaneous studies, and for the separate use of two different techniques, the information obtained from fMRI is used for estimating the generator source from EEG or MEG data (fMRI-constrained source estimation). Functional connectivity among different brain areas can be studied by using a single technique such as the EEG coherence or the correlation analysis of fMRI or PET data, or by combining the stimulation technique such as TMS with neuroimaging. Further advance of each technology and improvement in the analysis method will promote the understanding of precise functional specialization and inter-areal coupling, and will contribute to the increased efficacy of rapidly developing physiological treatments of neurological and psychiatric disorders.

Keywords: Human brain mapping; Hemodynamic response; Functional neuroimaging; Electrophysiology; Neurovascular coupling

1. Introduction

Nearly 80 years have passed since Berger successfully recorded the first electroencephalogram (EEG) from the human scalp surface (Berger, 1929; Lucking, 2004), and it is 40 years since the first recording of magnetoencephalogram (MEG) (Cohen, 1968), 30 years since the first report of cerebral blood flow (CBF) activation study using radioactive tracers (Orgogozo and Larsen, 1979; Roland et al., 1980), and 15 years since the development of functional magnetic resonance imaging (fMRI) based on the principle of blood oxygenation level dependent (BOLD) (Ogawa and Lee, 1990; Ogawa et al., 1990). Although functional neuroimaging is now widely used for non-invasively investigating human brain functions in the field of basic and clinical neuroscience, how accurately those images based on the hemodynamic principles reflect neuronal electrical activity is still

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not clearly understood. Furthermore, detailed mechanisms underlying the coupling of neuronal signals to local vasodilation have not been clarified. In view of the rapid advance in functional neuroimaging for the recent 20 years, this review article is aimed at updating the current status of human brain mapping with special emphasis being placed on how human brain mapping based on the hemodynamic principles is correlated with neurophysiological activities.

In this article, human brain mapping is defined as 'to visualize brain areas and their interconnection engaged in a certain function by using non-invasive techniques'. The non-invasive techniques currently available for brain mapping are largely divided into two groups based on their principles: electrophysiological on one hand and hemodynamic on the other. The former group includes EEG, MEG, and transcranial magnetic stimulation (TMS), and the latter group includes positron emission tomography (PET) or single-photon emission computed tomography (SPECT), fMRI, and near-infrared spectroscopy (NIRS). There have been excellent review articles in each special field (Hillebrand et al., 2005; Lauritzen, 2005; Costafreda et al., 2006; Debener et al., 2006; Norris, 2006; Otte and Halsband, 2006; Stern, 2006; van Eimeren and Siebner, 2006), but few attempts have been made to integrate all these techniques from the viewpoint of clinical neurophysiology.

Although TMS is not a technique for directly obtaining brain mapping with exception of 'motor map', it is included here as one of the electrophysiological techniques because it is used in combination with other techniques for functional localization of the underlying cortical areas.

2. Neurovascular coupling

This topic has drawn attention of many neuroscientists over a long period of time. In the famous article published by Roy and Sherrington in 1890, based on a series of their experimental studies in various animals, they suggested that the chemical products of cerebral metabolism contained in the lymph which bathes the walls of the arterioles of the brain can cause variations of the caliber of the cerebral vessels: that in this reaction the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity (Roy and Sherrington, 1890). In this section, the question as to how the hemodynamically-based functional imaging is correlated with and reflects neuronal electrical activity will be discussed.

There have been several experimental studies focusing on this particular subject. Mathiesen et al. (1998) investigated the relationship between regional CBF (rCBF) and neuronal activity in rat cerebellar cortex. They delivered electrical stimuli to the climbing and parallel fibers, and measured CBF with the laser Doppler flow technique and simultaneously recorded single unit activity (spikes) as well as extracellular field potential of Purkinje cells. In response to the climbing fiber stimulation which evoked long-lasting complex spikes in Purkinje cells, they found that the rCBF increased in a frequency-dependent manner and the CBF increase was significantly correlated with the summed field potentials. In contrast, the parallel fiber stimulation inhibited the spiking activity of Purkinje cells, but both the rCBF and the field potentials increased. Thus, they concluded that postsynaptic activity, but not the spiking activity, mainly contributes to the increase in rCBF.

Logothetis et al. (2001) studied the response of monkey visual cortex to checkerboard pattern stimulation by simultaneously measuring the fMRI signals with high spatiotemporal resolution and intracortical recording of single- or multi-unit spiking activity as well as local field potentials. They found that the local field potentials yielded a better estimate of BOLD responses than the multi-unit responses, again suggesting that the BOLD contrast mechanism reflects the synaptic processing of a given area rather than its spiking output.

More recently, Devor et al. (2005) stimulated the whisker of rats and measured the local hemodynamic response by optical imaging and electrical responses from the somatosensory cortex. Both multi-unit activity and local field potentials increased with increasing stimulus intensity, and reached a plateau at a certain level. However, the hemodynamic response kept increasing even beyond the saturation of electrical activity. As regards the spatial distribution of the two measurements, the spatial extent of the hemodynamic response was found to be larger as compared with the neuronal activity. As for the possible mechanisms underlying the spatial spread of hemodynamic response, they pointed out several factors including the contribution from neighboring regions, lateral cortico-cortical connections, diffuse non-lemniscal input, contribution of subthreshold synaptic activity, and diffusion of vasodilator substances, all of which might cause the wider distribution of the hemodynamic response as compared with the neuronal activity. Experimentally, therefore, the hemodynamic response has been shown to be a function of elecrophysiological activity at least within a certain range, but it is seen over a relatively larger area in space than the electrophysiological activity and lasts longer in time beyond the saturation of local neuronal activity.

As for the human brain, Arthurs et al. compared the evoked EEG potential and the functional MRI response to somatosensory stimulation in normal subjects (Arthurs and Boniface, 2002, 2003; Arthurs et al., 2007). They stimulated the median nerve at wrist with electrical shocks of increasing intensity from the sensory threshold to the highest bearable level, with different rate of stimulus presentation between the two sessions: 100 Hz for the fMRI study and 20 Hz for recording the somatosensory evoked potential (SEP). They found a similar increase in the SEP amplitude and the BOLD signal with increasing

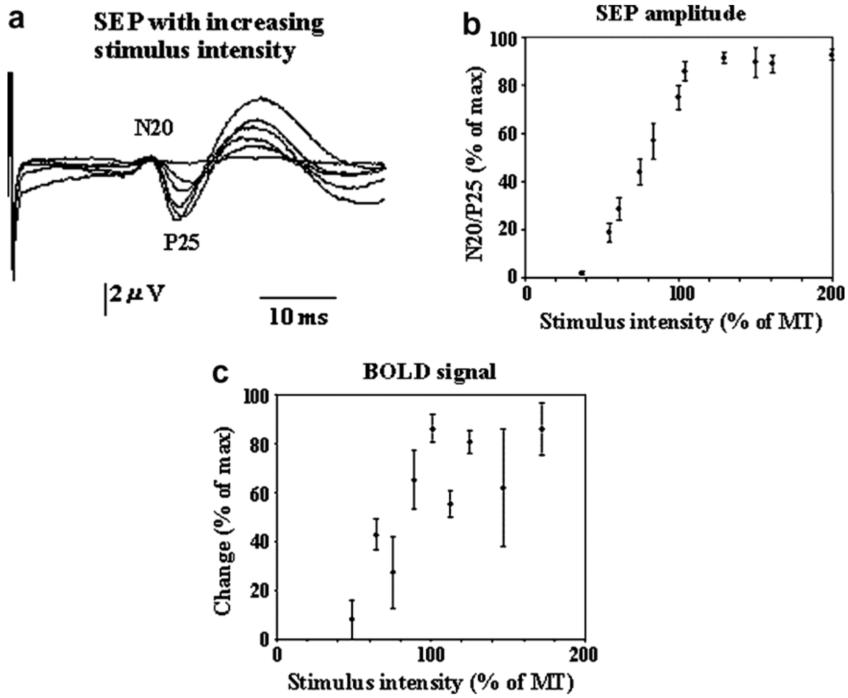

Fig. 1. Amplitude of N20/P25 component of somatosensory evoked potential (SEP) (a,b) and magnitude of fMRI BOLD signal (c) in the primary somatosensory cortex as a function of stimulus intensity in normal subjects. Median nerve was electrically stimulated at wrist with increasing stimulus intensity from the sensory threshold to the highest bearable level with the stimulus presentation rate of 100 Hz for fMRI and 20 Hz for SEP. There is a linear increase of both the SEP amplitude and the BOLD signal as a function of the stimulus intensity within a certain range of stimulus intensity (cited from Arthurs et al., 2007 with permission).

stimulus intensity, at least within a certain range of stimulus intensity (Fig. 1). As the result of a correlation analysis, they found that the BOLD changes in the primary somatosensory cortex significantly correlated with the SEP amplitude, suggesting the linear neurovascular coupling relationship. Furthermore, they also found that the mean changes of BOLD signal across a cluster correlated less well with the SEP amplitude than the peak voxel levels, suggesting that the area of the hemodynamic activity correlating with the SEP amplitude was smaller than the entire cluster observed (Arthurs and Boniface, 2003). Thus, like the above-described experimental data in rats (Devor et al., 2005), the spatial spread of hemodynamic response was also shown in human. It is concluded that, in both animal experiments and human data, the hemodynamic response is correlated to electrical activity at least within a certain range.

As described at the beginning of this section, Roy and Sherrington (1890) postulated some chemical products of cerebral metabolism as responsible for dilating the blood vessels in the activated brain areas. Zonta et al. (2003) showed in rat cortical slices that the dilation of arterioles triggered by neuronal activity is dependent on glutamate-mediated Ca^{2+} oscillations in astrocytes. So far the role of astrocytes in mediating the coupling of synaptic activity to local vasodilation through the glutamatergic receptors has been emphasized (Bonvento et al., 2002; Parri and Crunelli, 2003), but the mediators still remain to be elucidated (Lauritzen, 2005).

3. Characteristics of non-invasive techniques currently available for brain mapping

3.1. Functional neuroimaging based on electrophysiology: EEG vs. MEG

It has been well established that, by both EEG and MEG, we are looking at the electrical activity of apical dendrites of large pyramidal neurons in the cerebral cortex. When an apical dendrite is activated at its certain site in response to an excitatory synaptic input, the extracellular current flows from other sites of that apical dendrite (source) into the activated (depolarized) site (sink). If, for example, the deep layer of the apical dendrite is activated, then the extracellular current flows from the tip of the apical dendrite into the deep layer, thus producing the surface-positive, depth-negative electrical field distribution with respect to the cortical surface. EEG is the summation of these electrical fields generated from a number of neurons and recorded from the head surface, or from the cortical surface in case of electrocorticographic recording. Intracellularly, by contrast, the electrical current flows from the activated (depolarized) site to other sites of that apical dendrite. If we place the right thumb along the direction of this intracellular current flow, magnetic flow is generated in the direction of other fingers of the right hand surrounding the current flow or the apical dendrite. That is why, in order to pick up the magnetic flow, the MEG sensor has to be placed tangentially with respect to the intracellular current or to the apical dendrite. Thus, MEG can record only the current flows tangentially oriented with respect to the head surface whereas EEG can record both the tangentially and radially oriented current flows. Of course, for both EEG and MEG to pick up the neuronal activity from the cortical or head surface, a number of apical dendrites or neurons which are aligned in the same orientation have to be activated simultaneously (Table 1). Furthermore, since the cellular architecture is quite complex being intermixed with different kinds of cells even in the neocortex, what is most important in this kind of discussion is not just whether it is tangentially or radially oriented but is the proportion of large pyramidal neurons oriented either tangentially or radially with respect to the head surface within a given cortical area (Shibasaki et al., 2007).

A good example of discrepant results between EEG and MEG is encountered in functional studies of the structures around the central sulcus, where both the tangentially and radially oriented current sources are activated close together in time and space. For example, cortical activity preceding voluntary or self-paced movement, known as Bereitschaftspotential (BP) or readiness potential, is recorded bilaterally widespread over the central region on EEG whereas it is relatively localized to the central region contralateral to the movement when recorded with an MEG instrument equipped with planar gradiometer (Shibasaki and Hallett, 2006; Shibasaki et al., 2007). Furthermore, BP appears to occur much earlier on EEG than on MEG (see Fig. 3 of Shibasaki and Hallett, 2006). These findings can be explained by postulating earlier bilateral activation of the lateral premotor area (area 6) which is picked up by EEG but not by MEG because of its mainly radial orientation, and later mainly contralateral activation of the primary motor area (area 4) which is mainly located in the anterior bank of the central sulcus generating the tangentially oriented current flow with respect to the head surface. The latter is picked up by both MEG and EEG.

In addition to the major difference in terms of the orientation of current sources between EEG and MEG as described above, electrical fields are strongly influenced by electrical conductivity of the structures overlying the cortical surface. Electrical conductivity of the spinal fluid is estimated to be four times as high as that of brain tissue whereas that of the skull is as low as 1/80 of the latter (Jayakar et al., 1991). More recently, the electrical conductivity of skull was reported to be 1/25 of that of the brain (Lai et al., 2005). Whichever value is correct, electrical activity is markedly attenuated due to this low electrical conductivity of the skull. Furthermore, because of the difference in the electrical conductivity between the spinal fluid and the overlying skull, electrical fields are distributed widely over the head surface, the phenomenon called ‘shunting effect’. Furthermore, since the structural relationship of these tissues is not the same all over the head, this shunting effect causes a significant distortion of the electrical field distribution over the head. By contract, since magnetic fields are not influenced by the difference in electrical conductivity of the tissues overlying the cerebral cortex, at least theoretically MEG is neither attenuated by the skull nor influenced by the shunting effect. Although various source estimation techniques are available also for EEG, this is the biggest advantage of MEG over EEG, which makes MEG superior to EEG for estimating the source of current dipoles (Shibasaki et al., 2007). Therefore, it is reasonable to record EEG and MEG simultaneously if possible, and the information obtained from both techniques will complement each other quite effectively.

Both for EEG and MEG, activated cortical sources are estimated based on two different principles. The conventional method is to estimate the sources based on the distribution of electrical or magnetic fields over the head surface. There are two analysis methods for this purpose. One is to estimate a single source like analysis of an equivalent current dipole (ECD), in which a source is estimated in a brain model so that the field distribution calculated from the estimated source matches best the distribution of the measured field, and the other method is to estimate a distributed source by using the analysis method such as spatial filtering. In the technique called dynamic statistical parametric mapping as an example of the latter analysis method, the cortical surface is partitioned into a large number of small patches, with each patch represented by an ECD in the middle of the patch, thus approximating any arbitrary spatial distribution of synaptic currents within the cortex (Dale et al., 2000). In contrast to these time–domain analyses, methods in the frequency domain for analyzing EEG or MEG rhythmic oscillations have been developed. Analysis of the task- or event-related power change of rhythmic oscillations of a certain frequency band shows either decrease (event-related desynchronization, ERD) or increase (event-related synchronization, ERS) in power (Pfurtscheller and Aranibar, 1977; Pfurtscheller, 2006). The ERD is believed to reflect activation of the underlying

Table 1
Detectability of cortical neuronal activity by EEG, MEG and PET/fMRI

Cortical neurons	Arrangement		Orientation to head surface		Synaptic input	
	Aligned	Random	Radial	Tangential	Excitatory	Inhibitory
EEG	Yes	No	Yes	Yes	Yes	No[a]
MEG	Yes	No	No	Yes	Yes	No[a]
PET/fMRI	Yes	Yes	Yes	Yes	Yes	Yes?

Yes, detectable; No, undetectable; ?, Controversial.

[a] Might be possible by analyzing the power change of rhythmic activity.

cortex while ERS reflects inactivation or return to the resting state. As for ERD or ERS, it is always important to keep in mind that the results are remarkably different depending on which frequency bands are analyzed (Nagamine et al., 1996; see Fig. 6 of Shibasaki and Hallett, 2006).

3.2. Functional neuroimaging based on hemodynamic principles

The currently used non-invasive techniques based on hemodynamic principles are PET, SPECT, fMRI and NIRS. The principle of each technique is only briefly described in this article, because it is not the main purpose of this review.

When PET is used for brain imaging, the tracers labeled with positrons are injected intravenously, and in brain the positrons collide and annihilate local electrons. Then the masses of the positron and electron are entirely converted into two photons emitted in directly opposite directions with exactly the same energy. The photon pairs that exit the subject can be detected with PET scanners (Otte and Halsband, 2006). Thus, the brain areas which are activated either hemodynamically or metabolically are visualized as increased signal. Increase in rCBF is most commonly used as an index of local brain activation. For this purpose, water labeled with oxygen-15 is commonly used as a radioactive tracer. Since the half-life of oxygen-15 is about 2 min, the task is executed during the period of two minutes while scanning is carried out. As the result, the obtained image provides the time information of the order of minutes.

In SPECT, radioisotopes such as technetium 99 and iodine 123 are commonly used as tracers for blood flow study. SPECT is advantageous over PET in terms of no necessity of cyclotron in the neighborhood, lower cost, and use of radioisotopes of longer half-life, although it is disadvantageous over PET by its inferior image quality and inability to bring about absolute quantification (Otte and Halsband, 2006). Since the half-life of those radioisotopes is as long as several hours, the radionuclide remains in the activated region until it decays, thus enabling us to investigate a relatively long-lasting task or event (Marshall et al., 1997). For example, Fukuyama et al. (1996, 1997) developed a method for measuring the CBF activation during daily activities such as voiding and walking. In the study on walking, after injecting the radioactive tracers, the subject walked for 10 min, and then the scanning was done, which allowed us to visualize the image of blood flow change that took place during walking (Fukuyama et al., 1997). This was followed by another injection of double dose of the same radiotracer in the resting condition as a control.

By applying this technique, Hanakawa et al. (1999a) studied the mechanisms of gait disturbance in Parkinson's disease. In age-matched healthy subjects, rCBF activation during walking was seen in the foot and trunk regions of the primary sensorimotor cortex, the supplementary motor area (SMA), lateral premotor cortex, cingulate gyrus, dorsal brainstem and cerebellum. In Parkinson's disease, the activation was significantly less in the right SMA, left precuneus and right cerebellar hemisphere as compared with the control subjects. They further extended the study to clarify the mechanism underlying the phenomenon called 'kinesie paradoxale' which is characterized by an improvement of frozen gait by special visual input or even by showing obstacles such as steps and is commonly seen in patients with Parkinson's disease. They compared walking between two conditions, across transverse lines and along parallel lines drawn on a treadmill which moved at a constant speed. Behaviorally, the cadence (number of steps per min) was significantly less with the transverse lines compared with the parallel lines in the patient group whereas there was no difference between the two in the control subjects. On the SPECT study, the brain region where the difference in activation between the two tasks was greater in the patient group than in the control group was the right lateral premotor area, suggesting a role of this area in kinesie paradoxale (Hanakawa et al., 1999b; Shibasaki et al., 2004).

As regards the principle of fMRI, in the brain area where a neuronal group is activated, deoxyhemoglobin concentration is relatively decreased, and that area can be visualized as high signal intensity when T2-weighted image is obtained under high magnetic field like 1.5 or 3 Tesla and at high speed. This is called BOLD and was first described by Ogawa and co-workers (Ogawa and Lee, 1990; Ogawa et al., 1990). BOLD contrast originates from the paramagnetic nature of deoxyhemoglobin, which perturbs the main magnetic field, leading to a local reduction in main field homogeneity, and the amount of deoxyhemoglobin present depends on three physiological parameters: local rate of metabolic consumption of oxygen, regional cerebral blood volume, and rCBF (Lauritzen, 2005; Norris, 2006).

The experimental paradigms that have been used for fMRI study are categorized into two design classes: blocked design and event-related design. In a blocked design, each of the task conditions comprising an experiment is performed for an extended period of time. Due to the additive nature of the hemodynamic response, the blocking of tightly spaced trials produces roughly homogeneous period of fMRI signals resulting from individual trials. In contrast, an event-related design aims at characterizing the transient changes in fMRI signals that result from individual trials, which enables to randomly intermix trial types. However, since the hemodynamic response starts to develop very shortly after the stimulus presentation or the beginning of the task but it takes about 5 sec to reach its peak, the time resolution of this technique is still limited to the order of seconds (Chein and Schneider, 2005; Otte and Halsband, 2006).

The principle of NIRS was proposed by Jobsis (1977) and its technique has been developed mainly in Japan (Hoshi and Tamura, 1993; Maki et al., 1995). The NIRS signal depends on the different optical properties of oxyhemoglobin and deoxyhemoglobin, and measures the blood volume and blood oxygenation regulation supporting the neural activity (Rovati et al., 2008). In this technique, near-infrared beam is irradiated into the head through optical fibers, and the signals coming out of the head are picked up by optical detectors and transmitted via optical fibers to a photodiode. The advantage of this technique is to be able to measure the oxygenated hemoglobin concentration as an index of CBF continuously and non-invasively. In particular, this technique does not require the strict fixation of the subject's head, so that it can be applied to the study of moving subjects including children. Now the machine with more than 100 channels is available for obtaining the optical topography. By using this technique, Watanabe et al. (1998) demonstrated sequential activation of language areas in association with a word generation task in healthy subjects and in patients with medically intractable partial epilepsy. Although this technique measures only cortical activity and its spatial resolution is limited to a lobar level, at least the hemispheric dominance in terms of language was shown with high concordance rate with the results of Wada test (Watanabe et al., 1998). As another advantage of this technique, the same authors showed the time course of total hemoglobin concentration in the left and right inferior frontal region during the word generation task. By taking advantage of the feasibility of simultaneous recording of EEG during the NIRS data acquisition, Horovitz and Gore (2004) measured event-related potential (ERP) and near-infrared optical topography, and demonstrated correlation of two measurements in the language-related area.

3.3. Electrophysiology and hemodynamic response

As described above, each technique in each group: functional neuroimaging based on hemodynamic principle and electrophysiology, has unique features in terms of temporal and spatial resolution. In addition, there are other essential differences among those techniques as depicted in Table 1, which illustrates the ability of each technique to detect neuronal activation in relation to the anatomical arrangement and orientation of neurons or apical dendrites in the cerebral cortex. First of all, theoretically, hemodynamic responses have little to do with the arrangement of neurons (aligned or random) within a brain area or with the orientation of apical dendrites (radial or tangential) with respect to the head surface. In contrast, EEG and MEG can pick up activity only when the apical dendrites or neurons are aligned in the same direction. Furthermore, as described above, the current sources oriented radially with respect to the head surface can be picked up only by EEG but not by MEG, while the tangentially oriented sources can be recorded by both EEG and MEG.

With regard to the excitatory vs. inhibitory synaptic activity, the inhibitory activity generating inhibitory postsynaptic potentials (IPSPs) is not supposed to be detected either by EEG or MEG. However, the question as to whether the inhibitory synaptic activity is associated with any change in the hemodynamic response or not has still been controversial (Table 1). At least as far as the experimental study in the rat cerebellar cortex is concerned, the parallel fiber stimulation caused increased CBF in the cerebellar cortex while the spiking activity of Purkinje cells was totally abolished (see Section 2) (Mathiesen et al., 1998). Although in this experiment the cells other than Purkinje cells might have been activated to cause an increase in rCBF, a possibility that the inhibitory process might also be associated with change in the hemodynamic response still remains to be confirmed. So far the majority of studies using fMRI focused upon the positive BOLD activity (signal increase by stimulus or task as compared with control condition), but recently the negative BOLD activity (lower level of BOLD response than the control) has drawn attention (Stefanovic et al., 2004; Lauritzen, 2005; Shmuel et al., 2006; Bressler et al., 2007). The significance of the negative BOLD activity and its electrophysiological correlates remain an interesting subject to be investigated.

4. Multi-modal approach

Since each of the non-invasive techniques currently available for human brain mapping has different characteristics as described in the preceding section, the combined use of two or more techniques is expected to complement each other and thus provide more information than the use of a single technique. It is especially true for the combined use of one technique each from each of the two different principles, hemodynamically oriented and electrophysiological techniques. For practical purpose, the multi-modal approach is divided into two categories. Namely, the two different methods can be used simultaneously or in separate sessions. Since the experimental conditions cannot be controlled between the two sessions, separate sessions have the underlying disadvantage of uncontrolled background (Honda et al., 1998).

As regards the acquisition of data by simultaneously using two different techniques in the same experimental set-up or during the same event, the combined use of EEG and fMRI has drawn special attention of many investigators in recent years (Horwitz and Poeppel, 2002; Sammer et al., 2005; Otte and Halsband, 2006; Stern, 2006; Horovitz et al., 2008). In the setting where EEG is recorded in the MR scanning room, the most prominent artifacts arising from the scanner gradients interfere with the EEG, but recently there has been some technical advance in the method of artifact elimination (Ritter et al., 2007). A principle of artifact elimination developed by the author's group for eliminating electrocardiographic artifacts from EEG in real time (Nakamura and Shibasaki, 1987; Nakamura et al., 1990) can be applied for this purpose. Clinically, the simultaneous recording of EEG in the MR scanning room is especially useful for the presurgical evaluation of patients with medically intractable partial epilepsy (Jager et al., 2002; Stern, 2006). Experimentally, the simultaneous recording of EEG and fMRI is especially useful for non-invasively investigating mechanisms of cognitive functions by taking advantage of each technique, providing high resolution in time and space, respectively.

As an example of the simultaneous use of EEG and fMRI, Debener et al. (2005) recorded EEG during functional MR scanning in an experimental paradigm called speeded flanker task for recording the so-called error-related brain activity. In their experiment, the normal subjects were instructed to move either the left or right hand as quickly as possible depending on the direction of an instruction arrow, which was visually presented among four task-irrelevant flanker arrows, and the trials associated with wrong response were compared with those with correct response. On the fMRI, the rostral cingulate zone was found to be activated to a greater extent in the wrong response compared with the correct response. Guided by the information obtained from the fMRI study, the source of the ERP, the error-related negativity, was identified in the rostral cingulate zone (Fig. 2).

Simultaneous recording of EEG during PET scanning is more easily applied than during functional MR scanning because of a much lesser amount of artifact. Oohashi et al. (2000) did a unique study on possible effects of conventionally inaudible high frequency sounds on human brain. By using gamelan music of Bali which contains high-pitched sounds as high as 40 kHz as an auditory stimulus, they subjected normal subjects to the simultaneous acquisition of the EEG data and PET-rCBF activation by using water labeled with oxygen-15 as a radiotracer. As the results of comparison of the whole sound containing both the high frequency (above 20 kHz) and low frequency (below 20 kHz) components with either the high frequency or low frequency component alone, they demonstrated a significant increase in the α-frequency (8.0–13.0 Hz) EEG bands as well as in rCBF in the brainstem and thalamus only when the subject listened to the whole sound. Furthermore, they demonstrated the significant positive correlation between the power of the α-frequency EEG band and the thalamic CBF. These findings were interpreted to have demonstrated a previously unrecognized response of human brain to a complex sound containing the high frequency components above the audible range (‘hypersonic effect’). More recently, some evidence was presented by the same authors to suggest that this effect might involve a biological system, distinct from the conventional air-conducting nervous system, in sensing high-frequency elastic vibration above the human audible range (Oohashi et al., 2006).

Recently Oishi et al. (2007) simultaneously acquired data of EEG and rCBF by PET using oxygen-15-labeled water while healthy subjects performed self-paced movements of hand and foot, and showed negative correlation between the power of 10–20 Hz EEG rhythm and the rCBF increase over the sensorimotor area as well as the occipital region, suggesting the positive correlation between the task-related desynchronization of the EEG rhythm and neuronal activation revealed as the rCBF increase.

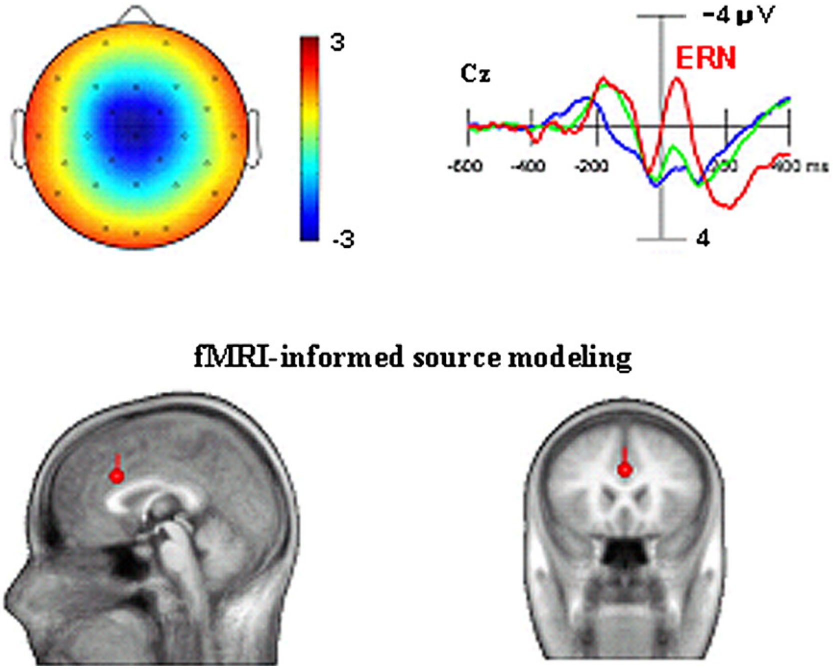

Fig. 2. The source of the error-related EEG negativity (ERN) estimated in the rostral cingulate zone based on the information obtained from fMRI study. Both EEG and fMRI data were simultaneously obtained in the same experimental session employing the speeded flanker task. In the topography of ERN (left top panel), negativity is shown in blue. In the averaged waveforms (right top panel), the data of incompatible error trials are shown in red and those of correct trials for compatible and incompatible are shown in green and blue, respectively (cited from Debener et al., 2005, with permission).

The combined use of two techniques of different principles, among others that of EEG and fMRI, in two separate experimental settings has often been employed. For example, Toma et al. (2002) calculated the source of each component of EEG potentials associated with self-paced hand movements based on the information of fMRI data obtained in the same experimental paradigm. As the results of the fMRI-constrained EEG dipole source analysis, the generator source of BP (early part of Bereitschaftspotential) was estimated in area 6, that of NS′ (late part of Bereitschaftspotential) in both area 6 and area 4, and that of frontal peak of motor potential (fpMP) in the postcentral gyrus (area 3). Bledowski et al. (2004) applied the fMRI-constrained source analysis of an ERP in a visual three-stimulus oddball paradigm while fMRI and ERP were acquired in separate sessions. As the results, the source of P3b was estimated in the parietal and inferior temporal areas whereas that of P3a in the frontal areas and insula. These findings are consistent with another fMRI study focusing on the role of prefrontal and hippocampal regions in automatic detection of unexpected events and orienting response in humans (Yamaguchi et al., 2004).

The combined use of MEG and fMRI is possible only for separate data acquisition for the technical reason. Dale and Halgren (2001) used the fMRI information to analyze the source of magnetic fields evoked by the visual presentation of novel words as compared to repeated words, and demonstrated greater detail in the fMRI-constrained analysis as compared with the conventional, anatomically constrained estimation. Im et al. (2005), by applying the similar analysis technique to a language judgment task, found better localization of the language area on the left hemisphere in the fMRI-constrained data as compared with the distributed sources based on MEG alone (see Fig. 6 of Shibasaki et al., 2007).

As an example of more indirect, correlative methods, the author's group applied fMRI and repetitive TMS (rTMS) to the same tasks of Japanese language processing. Generally, rTMS effects depend on intensity and frequency of stimulation, and there is agreement that low-frequency rTMS, usually 1 Hz or lower, leads to cortical suppression, while high-frequency rTMS (5 Hz and higher) results in enhanced excitation (Siebner and Rothwell, 2003; Tegenthoff et al., 2005). In an fMRI activation study in the right-handed healthy subjects, it was shown that the left posterior inferior temporal cortex played a specific role in transcription of Japanese syllabogram (kana) to morphogram (kanji) or mental recall of kanji but not in oral reading or semantic judgment of kana (Fig. 3-a) (Nakamura et al., 2000). By giving rTMS to the region identified by the functional MRI at a rate of 0.9 Hz for about 10 min, it was shown that the reaction time for the mental recall of kanji and for the kana-to-kanji transcription was delayed only when the left posterior inferior temporal cortex was stimulated but not when the homologous area of the right hemisphere was stimulated for control (Fig. 3-b) (Ueki et al., 2006). These findings support a previously proposed notion that the left posterior inferior temporal cortex plays a significant role in kanji (morphogram) processing (Iwata, 1984).

5. Functional connectivity

Functional relationship or coupling among different brain areas in healthy subjects and its disruption in clinical conditions have attracted recent attention of many investigators in the field of neuroscience (Shibasaki et al., 2002). Theoretically, each of the non-invasive techniques, regardless of electrophysiological or hemodynamic, can be subjected to the analysis of functional connectivity among different brain areas. The most commonly used method for this purpose has been coherence analysis of EEG oscillations recorded from different scalp locations which are estimated to be generated from different cortical areas. Originally, the concept of inter-areal synchronization was proposed by Engel et al. (1991) based on a cross-correlation analysis of unit responses between area 17 and the posteromedial lateral suprasylvian area in cats. Just like ERD or ERS (described in Section 3), the task-related change of coherence between two areas is calculated as a correlation of rhythmic oscillations of a certain frequency band between those areas, time-locked to an event or task (Classen et al., 1998; Gerloff et al., 1998). Increased coherence between two areas in association with or time-locked to an experimental task or an event indicates that those two areas are engaged in the task or event with constant temporal relationship with each other. Recently Wheaton et al. (2005) demonstrated an increasing coherence between the left frontal region (F3 of the International 10–20 System) and the left parietal region in the preparatory period of praxis movements such as gesture and tool use (Fig. 4). The coherence between these two areas started at about 2.4 s before the beginning of the motor task and increased up to the time of the movement onset. This is consistent with the concept of ideational or ideomotor apraxia, which is often caused by a lesion involving the left parietal cortex or its connection to the left frontal lobe. Coherence was also demonstrated on electrocorticogram in human. For example, movement-related increase of coherence among different areas of motor cortices was demonstrated by electrocorticographic recording in patients with medically intractable partial epilepsy as a part of presurgical evaluation (Ohara et al., 2001).

fMRI has often been used to study functional coupling among different brain areas (Biswal et al., 1995; Kondo et al., 2004; Osaka et al., 2004; Habeck et al., 2005; Harrison et al., 2005; Hampson et al., 2006; Abe et al., 2007; Marrelec et al., 2007; Rogers et al., 2007). For example, Osaka et al. (2004) studied correlation of BOLD effects among different brain areas in healthy subjects during a task involving verbal working memory, and demonstrated a higher cross-correlation between the anterior cingulate cortex and the left prefrontal cortex in the high-span performance group as compared with the low-span

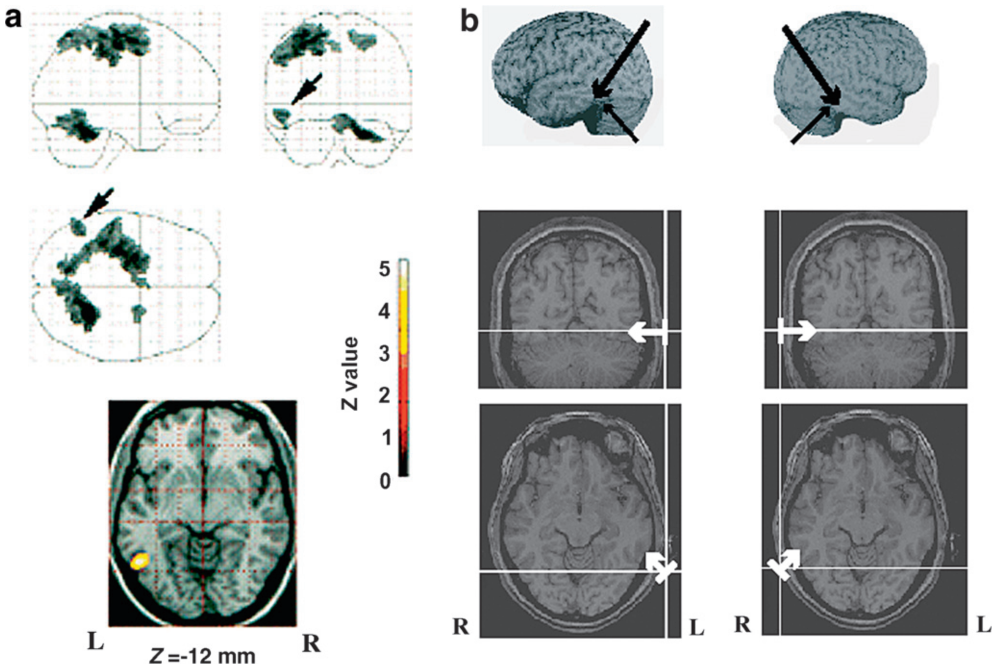

Fig. 3. Specific role of left posterior inferior temporal cortex in kanji (Japanese morphogram) processing shown by fMRI and rTMS study in right-handed healthy subjects. In the fMRI study (a), the left posterior inferior temporal cortex (arrows in the upper panel and yellow spot in the lower panel) was shown to be activated in the tasks of transcription of Japanese syllabogram (kana) to morphogram (kanji) or mental recall of kanji but not in oral reading or semantic judgment of kana. By giving rTMS to the region identified by the functional MRI at a rate of 0.9 Hz for about 10 min (left panel of b), the reaction time for the mental recall of kanji and for the kana-to-kanji transcription was delayed but not when the homologous area of the right hemisphere (right panel of b) was stimulated for control (cited from Nakamura et al., 2000 and Ueki et al., 2006, with permission).

performance group, suggesting an important coupling of these two areas in language-related working memory. By using a structural equation modeling, they further demonstrated a positive effective connectivity from the anterior cingulate to the left prefrontal cortex (Kondo et al., 2004). A similar study related to working memory was done by using fMRI (Hampson et al., 2006). They found a functional coupling between the posterior cingulate cortex and the medial frontal gyrus/ventral anterior cingulate cortex, and it was also found that the performance on the working memory task was positively correlated with the strength of the functional connection between those two areas. Recently Marrelec et al. (2007), by applying a structural equation modeling method to their previous fMRI data obtained in a semantic task, demonstrated its usefulness for investigating effective connectivity with no dependence on any priori information about anatomical or functional connection.

Functional relationship among different brain areas including the deep cerebral structures can also be studied by using PET-rCBF activation paradigm. For example, Ibanez et al. (1999) studied correlation of rCBF increase

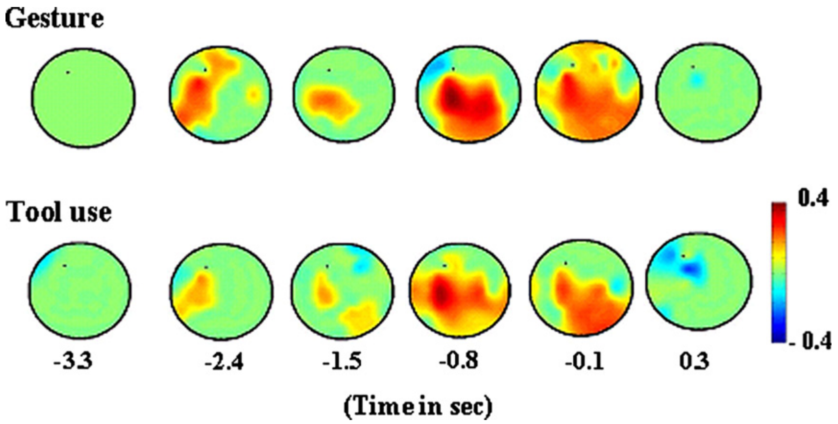

Fig. 4. Coherence of 18–22 Hz EEG activity with respect to the left frontal area corresponding to F3 (shown in a black dot) during the performance of gesture and tool use. Coherence of that area with the left parietal region increases starting at about 2.4 s before and increases up to the movement onset (time 0) (cited from Wheaton et al., 2005, with permission).

among different brain areas by using PET during the task of writing in patients with writer's cramp, and demonstrated deficient coupling between the rostral SMA and the left or right premotor area and between the left premotor area and the putamen in the patient group as compared with healthy control subjects, suggesting possible disruption of coupling between basal ganglia and motor cortices in focal hand dystonia.

Based on the principle that the high frequency rTMS activates the activity of the underlying cortex as described in Section 4, a functional neuroimaging technique can be combined with rTMS to study functional coupling. For example, in terms of cross-modal plasticity, Wittenberg et al. (2004) applied 0.5 s trains of 10-Hz rTMS over the primary somatosensory area (S1) in sighted, early blind and late blind individuals, and measured rCBF activation in the occipital cortex by using PET. As the results, only the early blind group showed significant activation of the primary and neighboring visual areas when rTMS was delivered over S1, suggesting that tactile information may reach the visual areas in early blind humans through cortico-cortical pathways.

One of the most recent topics in relation to functional connectivity is the use of an MRI technique called diffusion tensor tractography (DTT). This technique is based on diffusion characteristics of water molecules and its directional dependence of diffusivity along the myelinated fibers (Basser et al., 2000; Catani et al., 2005; Mesulam, 2005; Le Bihan, 2007). There are various methods for constructing fiber tract trajectories based on diffusion tensor MRI (Basser et al., 2000). This technique is useful to follow the white matter tracks and therefore complements the functional connectivity based on correlations of BOLD or perfusion data. For example, Newton et al. (2006) obtained diffusion-weighted imaging and probabilistic tractography of corticospinal tracts in healthy subjects, and identified the distinct pathways originating from the primary motor area, SMA and dorsal premotor area at the level of internal capsule. This technique can be applied to study the relationship between structural disruption of corticospinal tracts and functional state in patients with stroke as they have already demonstrated in a small number of patients (Newton et al., 2006). Catani et al. (2005) demonstrated by using this technique, in addition to the classical, direct arcuate pathway connecting Broca and Wernicke's areas, a previously undescribed, indirect pathway passing through inferior parietal cortex.

Recently Matsumoto et al. (2004) reported an electrophysiological method called cortico-cortical evoked potential (CCEP). In this method, by using chronically implanted subdural electrodes in patients with medically intractable partial epilepsy who underwent presurgical evaluation, a part of cerebral cortex was electrically stimulated and the response was recorded from different but relevant parts of cerebral cortex. By this new technique, they demonstrated a bi-directional connection between the anterior language area and the posterior language area, although whether the pathway is direct or indirect being mediated by a third brain area such as a deep structure has not been determined. These findings of CCEP are in conformity with the findings of language-related DTT reported by Catani et al. (2005). There have been some attempts to record CCEP non-invasively by combining TMS and the scalp recording of evoked EEG potentials.

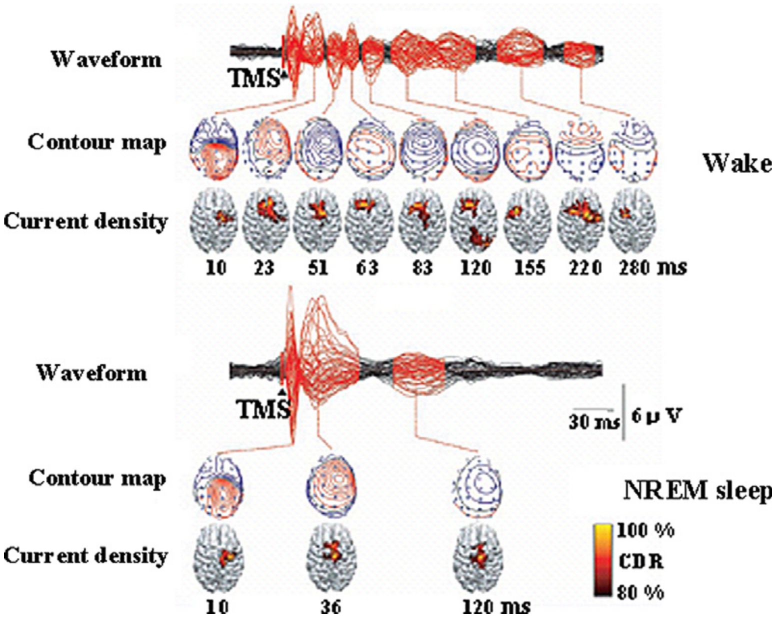

Fig. 5. Spatiotemporal maps of contour voltage (middle of each panel) and current source density (bottom of each panel) of TMS-evoked potentials (top of each panel) in a healthy subject, comparing wakefulness (top) and non-REM (NREM) sleep (bottom). TMS was given to an area corresponding to the right rostral premotor area. In the NREM sleep stage, the location of maximum current density remained confined to the stimulated area in contrast with wakefulness (cited from Massimini et al., 2005, with permission).

Massimini et al. (2005) recorded evoked potentials on high-density EEG following TMS given to the premotor area in healthy subjects during wakefulness and sleep, and found lack of propagation beyond the stimulation site during slow wave sleep, suggesting a breakdown in cortical connectivity during that particular sleep stage (Fig. 5).

6. Future directions of human brain mapping

Obviously this particular field of neuroscience heavily depends on the technical advance and development of new techniques and their analysis methods. Since each technique has its advantages and disadvantages as described in Section 3, for those who apply these techniques for either basic or clinical research, it is particularly important to choose the most appropriate technique available for solving each specific question. Furthermore, as has been emphasized in Section 4, the multi-modal approach is effective when it is technically possible. In terms of the relatively low temporal resolution of fMRI, Le Bihan et al. (2006) recently reported a new technique of fMRI which might have higher temporal resolution than the conventional BOLD analysis of hemodynamic response. By strong contrast with the BOLD signal, this new technique is based on diffusion of water molecules and can be named the diffusion functional MRI. They applied this technique to the response of the occipital cortex to visual stimulation in healthy subjects, and found better localization of the response to discrete areas, and earlier start and faster rising of the response by the diffusion fMRI compared with the BOLD effect (Le Bihan et al., 2006; Le Bihan, 2007). Just recently, however, the validity of this technique was argued in terms of possible contribution of the vascular component to their data (Miller et al., 2007). Significance of this technique remains to be further investigated.

In view of the relatively high correlation of fMRI activation with local neuronal activity at least within a certain range, if the time resolution of MR recording improves as described above, it might be possible to use MR for indirectly recording electrophysiological variables from the cerebral grey matter. This is of particular significance for the grey matters located deep in the cerebral hemispheres.

In addition to demonstration of a physiological coupling between the anterior and posterior language areas by using the technique of CCEP as described above (Matsumoto et al., 2004), the same authors, by using the same technique, more recently reported bidirectional coupling among different subregions of motor cortices with precise somatotopic organization (Matsumoto et al., 2007). With further development of TMS techniques which enable us to more precisely activate a small cortical area, it might be possible to obtain CCEP non-invasively (Massimini et al., 2005).

By taking advantage of rTMS in causing plastic changes or virtual lesions (Rossini and Rossi, 2007), the rTMS is being used for possible treatment of a number of neurological or psychiatric diseases. Further advance in human brain mapping and understanding of precise functional specialization and inter-areal coupling will contribute to the increased efficacy of those physiological treatments of a number of medically intractable conditions.

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