様式3-3

日米科学技術協力事業「脳研究」分野
平成15年度情報交換セミナー実施報告書　[研究分野：　　]

１．セミナー名　(和文) 各種非侵襲的脳機能計測法によるヒト脳生理学研究

(英文) Multimodal non-invasive techniques for the study of human brain physiology

２．開催期間　　平成 15年 1月 16日　～　平成 15年 1月 17日

３．開催地及び開催場所　米国メリーランド州ベセスダ市
NIH

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６．本セミナーの概要及び意義
近年、人間の脳機能イメージング手法および電気生理学的計測手法は急速に進歩し、広範囲の研究者により、容易に利用できるようになってきた。そのため、人間の脳の生理学的研究は、かつては不可能であったような方法で可能となってきた。すなわち異なる方法を用いることにより、多角的に脳機能へアプローチできるようになりつつある。複数の手法がお互いを補うように組み合わせるためには、個々の手法の特徴・長所・短所を把握する必要がある。複数の手法を組み合わせて相乗効果を得ることを重要な論点として、PET, fMRI, EEG, MEG, TMSなどの手法の専門家による、発表と討論を行った（スケジュール、抄録を別添）。

７．本セミナーによって得られた成果及び今後期待できる成果
複数の手法を組み合わせた具体的な研究例を詳細にわたって討議した。これらの議論のなかで、討議者の間で、将来の共同研究の提案も行われた。

８．その他(実施上の問題点等)
米国側参加者費用は、NINDS intramural budgetから支払われた。

US-Japan Workshop
Multimodal non-invasive techniques for the study of human brain physiology
NIH, Building 31, Floor 6C, Room 7

Thursday, January 16		
1:00pm	Welcome	Hallett and Sadato
	Chair: Sadato	
1:10 pm	Introduction: Temporo-spatial analysis of simple voluntary movement production (TMS/EEG/fMRI)	Mark Hallett
1:50 pm	Cortical representation of the pain (MEG+EEG)	Ryusuke Kakigi
2:30 pm	Spatiotemporal Brain Imaging using Combined fMRI, MEG, and EEG	John Belliveau
3:10 pm	Coffee Break	
	Chair: Fujii	
3:40 pm	Station and gait in human (MEG + fMRI + PET)	Hidenao Fukuyama
4:20 pm	Multimodal exploration of cognitive integration in human cortex (fMRI, MEG, EEG, iEEG, CSD/MUA)	Eric Halgren
5:00 to 5:30 pm	Discussion: EEG, MEG, comparisons and integration	Discussion Leader: R. Kakigi
7:00 pm	Meeting Dinner (optional)	
Friday, January 17		
	Chair: Pascual-Leone	
8:30 am	Neuropsychological and neuroimaging studies of human memory (Lesion study + fMRI)	Toshikatsu Fujii
9:10	Visual stimuli of varying duration (intracranial ERPS and fMRI)	Martin McKeown
9:50	Cross-Modal Plasticity in the Blind During Braille Discrimination Tasks (FMRI/PET+ TMS)	Norihiro Sadato
10:30	Coffee Break	
	Chair: Cohen	
11:00	Multimodal studies of the visual system (TMS, EEG, Eps, fMRI, MRS)	Alvaro Pascual-Leone
11:40	The role of the left	Tatsuya Mima

	angular/supramarginal gyrus in Japanese Kanji reading (MEG + fMRI + TMS)	
12:20	Discussion: M/EEG integration with fMRI	Discussion Leader: Eric Halgren
12:50 pm	Lunch	
	Chair: Mima	
1:40 pm	GABA disinhibition, a possible mechanism of deafferentation (TMS, MRS)	Leonardo Cohen
2:20	Near-infrared spectroscopic mapping (NIRS) and other neuroimaging methods (NIR +fMRI + TMS)	Yoshikazu Ugawa
3:00	Interleaving TMS and fMRI (TMS + fMRI)	Mark George
3:40	Coffee Break	
	Chair: George	
4:00	Cortical motor preparation in visuomotor tasks -Insights from gaze tracking and TMS (TMS, gaze tracking)	Yasuo Terao
4:40	Discussion: TMS and fMRI	Discussion Leader: Yoshikazu Ugawa
5:20	Closure	Hallett & Sadato
7:00	Optional informal dinner	

Introduction: Temporo-spatial analysis of simple voluntary movement production

Mark Hallett, M.D.
Human Motor Control Section, NINDS, NIH, Bethesda

A major goal of integrative neuroscience is to determine how the brain works to carry out its functions. A number of useful non-invasive tools are now available, each of which has a distinct view of physiological processes. Putting the different views together is valuable to get a more complete picture.

In determining what the motor cortex does in a no-go task, EEG reveals a potential coming from the central region similar to what is seen with a go task (Leocani et al.2001). On the other hand, fMRI shows no activity in M1 (Waldvogel et al.2000). TMS studies show active inhibition of the motor cortex. Hence, it is likely that EEG shows similar activity with activation and inhibition, and that fMRI does not show inhibition well.

Determining the brain sources of the movement related cortical potential has been difficult. Recently, we have tried to solve this problem by doing a PCA of the EEG activity and related each PCA component to a location identified using fMRI with a similar movement (Toma et al. 2002).

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Cortical representation of the pain

Ryusuke Kakigi
National Institute for Physiological Sciences

Cerebral processing of first pain, associated with Ad-fibers, has been studied intensively, but the cerebral processing associated with unmyelinated C-fibers, relating to second pain, remains to be investigated. This is the first study to clarify the primary cortical processing of second pain by magnetoencephalography (MEG), through the selective activation of C-fibers, by the stimulation of a tiny area of skin with a CO2 laser. In the hemisphere contralateral to the side stimulated, a one-source generator in the upper bank of the Sylvian fissure (secondary somatosensory cortex, SII) or two-source generators in SII and the hand area of the primary somatosensory cortex (SI) were the optimal configurations for the first component. The onset and peak latency of the two sources in SI and SII were not significantly different. In the hemisphere ipsilateral to the stimulation, only one source was estimated in SII, and its peak latency was significantly (approximately 18 msec on average) longer than that of the SII source in the contralateral hemisphere. Our findings suggest that SI and SII are activated and that parallel activation of SI and SII contralateral to the stimulation represents the first step in the cortical processing of C-fiber-related activities, probably related to second pain. We also recorded MEG following stimulation of small myelinated A-delta fiber stimulation relating to first pain and found similar results to those following C fiber stimulation.

Spatiotemporal Brain Imaging using Combined fMRI, MEG, and EEG
John Belliveau

Station and Gait in Human

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The most conspicuous difference between human being and animals is standing and walk by foot. The neuroscientific approach to disclose the neural substrates engaged in the standing and gait is very limited, because observation of the brain activity accompanies with the movement of the position of the head prevented closer examinations on brain functions during walk or standing. We are studying the physiological mechanisms underlying the gait and station in human mainly using neuroimaging technique. Neurophysiological findings in gait revealed the midline activation of neural substrates in evoked potential[Yazawa S. et al]. We have adopted the SPECT study to investigate the station and gait in the physiological as well as pathological conditions. Normal human gait required the activation in the primary sensorimotor cortex as well as the supplementary motor area, cerebellar hemisphere, and vermis. In case of Parkinson disease patients with gait disturbance, they showed a paradoxical gait looking at horizontal bars, and statistical parametric mapping revealed right sided premotor area is activated. Station or standing itself required the strong participation of the cerebellar vermis, but patients with SCA6 suffering from unsteadiness of stance revealed the cerebellar hemisphere and prefrontal cortex are activated in addition to normal controls. To summarize our results, station and gait are performed by the conjunctional activities of the cerebral cortex and cerebellum, and in some cases of pathological conditions, some relevant areas are also incorporated for compensation.

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Human Brain Mapping 2002 in Sendai

Multimodal exploration of cognitive integration in human cortex
Eric Halgren

Meaningful stimuli such as words or faces are understood via a series of processing stages that are embodied in spatiotemporal patterns of brain activation. Earlier stages tend to be more restricted in sensory and then sensory association cortices, culminating with a stage peaking at ~400ms that is sensitive to the difficulty of integrating the event within its cognitive context. This stage was first discovered with EEG, where it was named the N400. More recently, similar phenomena have been found with intracranial EEG (iEEG), fMRI, and MEG. Combining these methods, it appears that the N400 is generated in widespread cortical areas, especially the ventral temporal and prefrontal areas. Further studies using multi-unit activity (MUA) and current-course density (CSD) analysis suggests that this stage represents sustained feedforward associative activation. Later stages, concerned with second-pass re-analysis and higher-level integration of difficult stimuli, may engage top-down associative processes in prefrontal cortex.

Neuropsychological and neuroimaging studies on human memory

Toshikatsu Fujii
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For the research on human memory, both neuropsychological and neuroimaging studies are important, but each of these two methodologies has the merits and demerits. Human lesion data have demonstrated that damage to specific brain regions causes the disruption of human memory. These regions are sites necessary for human memory, but it is usually difficult to determine to what extent the lesion has affected a specific memory process. The recent advent of functional neuroimaging techniques provides an opportunity to examine brain regions related to a specific memory process. However we should be cautious in interpreting the data because activated regions may not be necessary but simply participate in human memory functions.

These two methodologies should be complementary to each other. Thus, if the lesion data and the functional imaging data coincide, it would provide much stronger evidence that the region involved is really crucial.

Data of our recent neuroimaging studies on human memory will be presented together with relevant neuropsychological findings, both of which are relatively consistent with each other.

Visual stimuli of varying duration
Martin McKeown

Cross-Modal Plasticity in the Blind During Braille Discrimination Tasks

Norihiro Sadato
National Institute for Physiological Sciences

The brain is a dynamically changing structure in relation to learning, alterations of the peripheral body parts or brain injury. Braille reading requires the conversion of simple tactile information into meaningful patterns that have lexical and semantic properties. Activation studies using positron emission tomography and functional MRI revealed that Braille reading and other tactile discrimination tasks activated the visual cortices of the blind. Functional MRI revealed age dependency of this plastic change: tactile discrimination activated the primary visual cortex of the early onset blind (< 16 y.o.) whereas suppressed that of the late blind. Irrespective of the onset of blindness, tactile tasks activated the association visual cortices of the blind. Combined with transcranial magnetic stimulation, the early visual deprivation was shown to cause the activation of the primary visual cortex in functionally relevant way by the tactile tasks. Cortical plasticity of human brain can be explored with the combined approach of electrophysiological and hemodynamic imaging methods.

Multimodal studies of the visual system

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Harvard Medical School, and Department of Anatomy, Boston University, Boston, MA

High frequency repetitive transcranial magnetic stimulation (rTMS) of the parietal cortex during the presentation of visual stimuli can result in extinction of the contralateral stimuli mimicking the findings in neglect patients. Applied off-line, prior to the presentation of visual stimuli, low frequency parietal rTMS leads to neglect of contralateral stimuli but increased attention for ipsilateral stimuli. These findings support Marcel Kinsbourne's hypothesis about the neural basis of attention, are consistent with findings in human patients and animal models, and suggest a potential therapeutic effect of rTMS in neglect as demonstrated by Massimiliano Oliveri et al.

Studies combining electroencephalography (EEG) and TMS provide insights into the neurophysiologic basis of these effects. Covert attention shifts have been related to differential EEG changes in occipital alpha activity (increase alpha activity ipsilateral to the location of the attended stimulus). Individual subjects tend to shift attention covertly (and hence detect stimuli) easier on one side than the other. Our results indicate that an EEG lateralization index, derived from occipital alpha activity, determines this perceptual bias and that lateralization of alpha-power can be used for estimation of an attentional vector predicting perceptual bias. Low-frequency repetitive TMS to the occipital cortex can affect alpha activity leading to a suppression of alpha desynchronization without affecting early visual evoked potentials (VEPs). While VEPs are considered to reflect the neural response due to changes in afferent activity, alpha desynchronization reflects changes in local interactions between neurons and interneurons that control the frequency of the ongoing EEG. Low-frequency repetitive TMS appears to affect primarily the latter. This effect is associated with behavioral consequences for covert shifts of attention. Combination of diffusion-weighted magnetic resonance imaging (DWI) or magnetic resonance spectroscopy (MRS) with rTMS provide further insights. Low frequency rTMS appears to induce a transient decrease in the targeted cortical area, a mild decrease in glutamate / creatine-phosphocreatine index, and an increase in cortical GABA that is associated with the behavioral effects on ipsilateral attention.

Studies in cat model of neglect combining C^{14} labeled 2-deoxiglucose (2DG) brain mapping with TMS provide novel insights into the mechanisms of action of TMS and help elucidate the neural basis for the observed effects of TMS on attention. These studies demonstrate that cortical activity during rTMS is suppressed (2DG uptake is decreased) regardless of stimulation frequency. However, following rTMS (offline design), cortical activity is transiently increased by high frequency rTMS (2DG-uptake increased), but decreased by low frequency rTMS. The trans-synaptic, distant effects of rTMS along functional connectivity patterns are clearly demonstrated in this animal model. Behavioral studies on the effects of rTMS on neglect in the brain-lesioned cat allow the investigation of the mechanisms of action of rTMS in humans.

The Role of the Left Angular/Supramarginal Gyrus in Japanese Kanji Reading

Tatsuya Mima
Kyoto Univ

While alphabetic systems are based on the association of phonemes with graphemic symbols, Kanji system is based on the association of meaningful morphemes with graphic units. So Kanji is often regarded as Hieroglyphic rather than as Ideogram, which leads people to the idea that Kanji is
processed in the brain not as a language but as a simplified drawing. To clarify this point, we investigated the dynamic pattern of brain activation associated with the Kanji reading by using multi-modal approach.

Forty normal native Japanese speakers participated in the study (twenty in TMS, ten in fMRI, and ten in MEG study). We prepared the picture and Kanji word corresponding to the same objects. Subjects were asked to read Kanji words or name the picture silently in fMRI and MEG study, and verbally in TMS study. Duration of the stimulus presentation was 400ms. In TMS study, Double-pulse TMS (ISI=50ms) was given over the right or left BA39/40 at 100ms or 250ms following stimulus onset (Magstim200, Magstim co., UK). Stimulus intensity was set at 120% of the phosphene threshold at
V1.

In fMRI study, Brodmann's areas (BA) 39/40 in both right and left hemispheres were activated. In MEG study, magnetic responses were over the temporo-parietal areas in both hemisphere, and peaked around 250 ms following the stimulus onset. For both fMRI and MEG, the Kanji-reading task
showed the left side dominant activation, while the picture naming task showed the symmetric activation. In TMS study, reaction times increased only when TMS was delivered over left BA 39/40 at 250 ms after Kanji presentation.

It is likely that the left BA 39/40 is involved in the processing of Kanji words as an essential part of the cortical network, and that the critical timing of this regional neural activity in Kanji word reading is
around 250ms following the Kanji presentation.

GABA disinhibiton, a possible mechanism of deafferentation)
Leonardo G. Cohen

Hand deafferentation leads to cortical reorganization in the contralateral motor and sensory cortices. In humans, transient hand deafferentation increases the excitability of the upper arm representation in the contralateral motor cortex. This intervention is associated with a decrease in GABA levels in this region as measured by magnetic resonance spectroscopy and deafferentation-induced plasticity is blocked by administration of a GABAergic agent (lorazeparn), suggesting that GABA disinhibition is an operating mechanism. Studies in our lab demonstrated that changes in the upper arm motor representation elicited by hand deafferentation can additionally facilitate use-dependent plasticity.
Hand deafferentation also leads to perceptual changes in the nondeafferented hand, possibly a behavioral compensatory gain that could support the non-deafferented hand's need to tackle enhanced environmental requirements. Overall, multimodality approaches allow the characterization of plastic changes in the central nervous system and the exploration of mechanisms and behavioral relevance of cortical reorganization.

Near-infrared spectroscopic mapping (NIRS) and other neuroimaging methods

Yoshikazu Ugawa
Univ of Tokyo

Several neuroimaging methods have been used to study central neural function in humans, such as fMRI, PET, SPECT, MEG and TMS. Near-infrared spectroscopic mapping (NIRS) of cerebral blood volume is a newly developed method to image human brain activity non-invasively. In the present communication, I show several characteristics of NIRS and studies of neural connection between distant areas using TMS and imaging techniques.

1. Quantitative measurement with NIRS We measured NIRS signal changes at the motor cortex when the subject made 1Hz phasic force-grip at five different force levels. Oxy-Hb concentration at the motor cortex increased with the force levels in a logarithmic fashion. Dexoy-Hb had a tendency to decline with increased force levels, but it was not statistically significant. This result suggests that NIRS can be used for quantitative measurement of brain activation.

2. NIRS and fMRI NIRS and fMRI were simultaneously recorded in 4 normal subjects when they performed a random finger tapping at a rate of 3Hz. We compared time courses of MRI signal changes with those of NIRS signals at the primary motor cortex. We compared activated areas when using a box-car curve as a reference curve with those when using NIRS signals at the motor cortex as a reference. In the primary motor cortex, Oxy-Hb concentration of NIRS changed almost in parallel with fMRI signals during finger tapping. Deoxy-Hb concentration changed in a mirror manner with fMRI signals. In fMRI study, significantly activated areas were smaller when using NIRS signals as a reference than when using a box-car curve. Analysis of fMRI signals using NIRS signals is one of new tools for functional neuroimaging.

3. rTMS and imaging techniques

3.1. CBF/CBV changes during rTMS over the motor cortex

Cerebral blood flow (CBF) or cerebral blood volume (CBV) changes were recorded during 1Hz, subthreshold rTMS over the hand motor cortex by NIRS or SPECT. SPECT demonstrated CBF increases at the contralateral cerebellum, and CBF decreases at the contralateral motor cortex, premoter cortex, supplementary motor cortex and ipsilateral thalamus. NIRS mapping revealed a reduction of CBV at the contralateral motor cortex. This excludes the possibility that regional CBF decrease at the contralateral motor cortex is due to normalization of CBF in the whole brain in SPECT, and confirms a reduction of CBF at the contralateral motor cortex demonstrated by SPECT. Activated and deactivated areas should have a tight connection with the primary motor cortex.

3.2. Lasting effects of rTMS over DLPFC

O15H2O PET were performed before and after 1Hz rTMS over the left/right DLPFC in normal volunteers. rTMS over DLPFC elicited activation of the ipsilateral prefrontal cortex, bilateral anterior cigulate cortex and other areas. rTMS over the left DLPFC reduced CBF of the right DLPFC, whereas rTMS over the right had no significant effects on the left. The therapeutic effects of rTMS over DLPFC may be produced by influence on the distant areas, especially limbic system (ex. anterior cingulate cortex), as well as that on the areas beneath the coil.

Interleaving TMS and fMRI

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In 1997, our group at MUSC demonstrated that it was feasible to perform TMS within an fMRI scanner [1]. Previously, this had been thought not possible due to concerns about magnetic field interactions. In theory, interleaved TMS/fMRI offers several potential advantages compared to other multimodal techniques. BOLD fMRI has relatively high temporal resolution compared to PET, and better spatial resolution compared to either PET or EEG. One can also, within the same setting, use anatomical MRI to position the TMS coil[2], or a modified scan to actually measure the TMS magnetic field [3]. A disadvantage of the technique has to do with the high technical difficulty of actually carrying out truly interleaved studies (for a review of these issues see [4]). This difficulty is perhaps best demonstrated by the fact that in the 6 years since our first feasibility demonstration, only one other lab has successfully performed these types of studies [5], despite several respected groups having tried.

In this talk I review the series of studies we have carried out using this technique. We have tested whether TMS-induced BOLD changes correspond with volitionally activated regions[6-9]. Additionally we have performed single event fMRI studies investigating the BOLD response to singe TMS pulses [10], and whether the response diminishes over time [11]. I will end the talk by addressing some of the potentials, and challenges, of this technique for the near future [12].

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Cortical motor processing in visuomotor tasks

Yasuo Terao, Furubayashi Toshiaki, Shingo Okabe, Noritoshi Arai, Hitoshi Mochizuki, Shunsuke Kobayashi, Nobue K. Iwata, Shouji Tsuji, Yoshikazu Ugawa
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Motor activities in daily life are usually guided by vision and thus involve a process whereby visual information is transformed into plans of motor actions. To investigate the cortical processing required for such visuomotor transformation, we applied focal transcranial magnetic stimulation (TMS) over various cortical regions while the subjects engaged themselves in a visuomotor task. This was to induce a transient derangement in cortical processing ("virtual lesion"), and we observed the resultant behavioral changes.

The task was to press either of the two buttons (either left of right) with the left or right hand quickly in response to two visual cues presented successively at random intervals on a monitor. The first cue (precue) provided the subjects with advance information about the motor action to be performed [full information about the button and the hand, partial information about the button (pb) or the hand (ph), no information], while the second cue fully specified the action and also served as the go-signal for the response. TMS was applied over 15 locations on the scalp [over the dorsolateral prefrontal cortex (dlpfc), premotor cortex, motor cortex, anterior parietal cortex (apc), and posterior parietal cortex (ppc) of both hemispheres; atlocations -5, -2.5, 0, 2.5, 5 cm anterior to Cz on the midline] at various intervals (100, 150, 200, 250, 300, 350 ms) after the second cue and before the reaction time (RT). RT was measured from the time of go-signal, and the delay induced by TMS was calculated by subtracting the control RT from test RTs with TMS delivered over the 15 regions.

RT was 369+/-47 ms (full information), 395+/-52 ms (ph), 457+/-59 ms (pb), 474+/-60 ms (no information) after the go-signal. Regardless of whether the precue provided full or no advance information, the greatest delay was induced bilaterally over posterior cortical sites (apc, ppc) at early intervals of TMS (100-150ms), whereas the delay was largest over the motor cortex at late intervals (300-350ms). At an intermediate interval (200ms), a larger delay was induced over dlpfc when no advance information was given to the subjects as compared to when full advance information was provided.

The results suggest an information flow from posterior to motor cortical regions for visuomotor transformation. Dlpfc was involved when more cortical processing is required when no advance information is provided by the precue.

Contents:

Recent advances in functional neuroimaging and electrophysiological techniques are quite rapid. Imaging devices are becoming more available and software for data analysis has become more user friendly. These advances allow human physiology to be investigated in ways that have previously been impossible. As workers start to use the different methods, it is critical to point out how analysis of each individual method has problems and that some of these problems may be solved by using these methods in a multimodality approach. Ten experts from US and Japan will present the methods at the state of the art including PET, fMRI, EEG, MEG, TMS, pharmacological intervention, and their various combinations. One of the critical themes will be that while single methods are valuable, the combination of methods gives more power.

Organizors
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