

2nd Korea-US Joint Workshop on Brain Science

Cognitive and Behavioral Neuroscience



January 12~13, 2000
LG Semicon Hall, KAIST, Taejeon, Korea

Organized by
Brain Science Research Center, KAIST

Supported by
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**Second Korea-US
Joint Workshop on Brain Science
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Scientific Researches**

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Invited Speakers

Hyung-Cheul Shin (Hallym Univ.)

Joseph Malpeli (Univ. of Illinois)

Kyoung-Min Lee (SNU)

Peter Fox (Univ. of Texas, San Antonio)

Stephen Karlik (Univ. of Western Ontario)

Eunjoo Kang (SNU)

Kichun Nam (Korea Univ.)

Edgar Zurif (Brandeis Univ.)

Geraint Rees (Cal Tech)

Min-Shik Kim (Yonsei Univ.)

Organizing Committee

Hemin Chin (NIH)

ChanSub Chung (Yonsei Univ.)

Choongkil Lee (SNU)

Jung-Mo Lee (Sungkyunkwan Univ.)

Yong Shin (NIH)

Preface

It is my great pleasure to welcome you all to the Brain Science Research Center at KAIST in Taejeon. We join together to hold the second Korea-US Joint Workshop on Brain Science – Cognitive and Behavioral Neuroscience. We expect this workshop provide the opportunities to understand different areas in brain science, and to promote the bilateral cooperation between Korea and US researchers. It must be exciting to explore the mysteries of brain, and it is a critical issue how brain enables mind. These issues and mysteries are broadly discussed in this workshop. The theme of the second workshop covers high cognitive brain functions such as single cell recording and brain imaging studies, selective attention, and language.

I would like to thank the organizing committee, Drs. Hemin Chin, Yong Shin, ChanSub Chung, Jung-Mo Lee, and Choongkil Lee. Our thanks also go to the invited speakers for their sharing their exciting results with us. I also would like to thank the BSRC researchers and staffs for their hard work in organizing this workshop.

Thanks are also due to our sponsors, i.e., Korean Ministry of Science and Technology and Asian Office of Aerospace Research & Development, US Air Force Office of Scientific Researches. Thank you all for your participation.

January 2000

Soo-Young Lee

Director, Brain Science Research Center (BSRC)

Korea Advanced Institute of Science and Technology (KAIST)

Program

January 12 (Wed)

9:00 - 9:30 am

Registration

9:30 - 10:00 am

Opening Remark

Soo-Young Lee (BSRC, KAIST)

Congratulatory Remark

Chair: Choonkil Lee (Department of Psychology, SNU)

10:00-11:00 am

**Temporary Deafferentation -Induced Changes of Neural Networks
in the SI Cortex of rats**

Hyung-Cheul Shin (Department of Physiology, Hallym Univ.)

1

11:00-12:00 am

**Integration of Eye Movements and Visual Inputs at the Level
of the Lateral Geneculate Nucleus**

Joseph Malpeli (Department of Psychology, Univ. of Illinois)

5

12:00-1:30 pm

Lunch

Chair: Dongsoo Lee (Department of Nuclear Medicine, SNU)

1:30-2:30 pm

Functional MRI on Cortical Control of Motor Behaviors

Kyoung-Min Lee (Department of Neurology and Interdisciplinary Program of
Cognitive Science, SNU)

9

2:30-3:30 pm

Mapping and Modelling Human Neural Systems

Peter Fox (Department of Psychology, Univ. of Texas at San Antonio)

12

3:30-4:00 pm

Coffee Break

Chair: SungIl Kim (Department of Industrial Psychology, Kwangwoon Univ.)

4:00-5:00 pm

Imaging Brain Function and Dysfunction

Stephen J. Karlik (Diagnostic Radiology and Nuclear Medicine,
Univ. of Western Ontario)

16

5:00-6:00 pm

Prefrontal Activations during Different Memory Processing: fMRI Studies

Eunjoo Kang (Department of Neurology, SNU)

20

6:30-

Reception

January 13 (Thu)

Chair: Jung-Mo Lee (Department of Psychology , Sungkyunkwan Univ.)

10:00-11:00 am	Agrammatism in Broca's aphasia: Dissociation of Sentence Production and Comprehension	
	Kichun Nam (Department of Psychology, Korea Univ.)	27
11:00-12:00 am	The Neuroanatomy of Sentence Comprehension	
	Edgar Zurif (Volen Center for Complex System, Brandeis Univ.)	31
12:00-1:30 pm	Lunch	

Chair: ChanSub Chung (Department of Psychology, Yonsei Univ.)

1:30-2:30 pm	Linking Visual Attention and Awareness with Functional MRI	
	Geraint Rees (Division of Biology, Cal Tech)	34
2:30-3:30 pm	Implicit and Explicit Representations of Visual Space: Effects of Bilateral Parietal Damage	
	Min-Shik Kim (Department of Psychology, Yonsei Univ.)	38
3:30 pm	Closing Remark	
	Soo-Young Lee (BSRC, KAIST)	
4:00-6:00 pm	Closed Discussion	

Hyung-Cheul Shin, Ph.D.

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College of Pharmacy, Seoul National Univ. Researcher
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Korea Science Foundation
1992 Dept. of Physiology, Coll. Med. Hallym Univ., Professor

Current Research Interests

- Beta-amyloid actions on the neural information processing
- Brain Mechanisms of Acupuncture-induced Immune Activation & Thermoregulation
- Sensory Substitution: Visual to Tactile Conversion
- Plastic changes of neural networks and neural circuits in the somatosensory system
- Hypothermia-induced changes of afferent sensory transmission & receptive field changes in the CNS
- The effects of Interleukins on the somatosensory transmission
- Membrane excitability changes of single nerve fibers dissected from rats exhibiting neuropathic pain
- Interhemispheric transfer of plasticity in VPL thalamus
- Activity dependent changes of synaptic transmission in the somatosensory cortex

Temporary Deafferentation – Induced Changes of Neural Networks in the SI Cortex of Rats

Hyung-Cheul Shin

Department of Physiology, College of Medicine, Hallym University

We have carried out simultaneous many (up to 15) single unit recordings from the primary somatosensory (SI) cortex of anesthetized rats before and after temporary deafferentation (TD) to the receptive field (RF, forepaw digits) by the injection of lidocaine (1-2%). The blocking of afferent transmission and the emergence of new RF were quantitatively determined by the analysis of the post-stimulus time histograms. Responsiveness to the RF stimulation was diminished by $86.44 \pm 3.5\%$ at 10 min after lidocaine injection to the RF center, while it was augmented by $21.58 \pm 9.5\%$ at 10 min after TD to the outside of the RF. Changes of functional connectivity patterns among simultaneously recorded neurons were determined by analyzing spike-triggered cross-correlograms. Co-firing patterns were frequently observed either from spontaneously active neurons or from peripherally activated neurons and they were usually diminished and then recovered during TD. Cells showing less strong responsiveness to the RF activation received both strong excitatory inputs from RF center cells and weak excitations from RF boundary cells. During TD, inputs from RF center cells were reduced and then recovered, while weak excitations from RF boundary cells became stronger and then weakened. These results provide evidences that the emergence of new RF after TD may actually involve the activation of originally weak, latent connections. (supported by a '98 grant to HCShin from the Korean Ministry of Science & Engineering and the Brain Science Research Program).

Introduction

It is well known that peripheral sensory deprivation (deafferentation) induces receptive field (RF) changes and consequent reorganization of the body representation (somatotopy) within the central somatosensory system of adult animals after pathological/experimental lesions at various levels of this system (Nicoletti et al., 1993; Faggin et al., 1997). Reversible changes RF (such as changes of RF size or appearance of new RF (NRF)) of somatosensory neurons can occur rapidly, within minutes, in response to temporary RF lesions (Merzenich et al., 1983; Calford and Tweedale, 1988; Donoghue et al., 1990). This somatosensory plasticity involves: 1) increase of the excitability of neurons, 2) disinhibition of lateral inhibition and 3) changes of synaptic strength among neurons. Thus, there is a strong possibility of the dynamic changes neuronal networks among somatosensory neurons during temporary deafferentation (TD) of peripheral RF. However, there has been no systematic study to verify this possibility.

Purpose

Simultaneous many-single unit recordings from the primary somatosensory (SI) cortex and the ventral posterior lateral (VPL) thalamus of anesthetized rats were done to characterize the changes of neural networks among somatosensory neurons following temporary deafferentation (TD) of local anesthesia to the RF (forepaw).

Methods

Adult Sprague-Dawley rats (200-300g n=10) were anesthetized with urethane (i.p. 20%, 7ml/kg). For

single unit recording, craniotomy was done over the forepaw area of the SI cortex (0-1mm rostral from bregma, 3-5mm lateral from midline). Tungsten wire (diameter 50 μ m, teflon-coated, 4X2 array) electrodes were driven to the layer IV of the SI cortex. Bipolar concentric stimulating electrode (1Hz, 1ms duration, 1.5-3V) was subcutaneously inserted under the RF (forepaw digit) to activate peripheral sensors. Isolation of individual units was done by using spike sorting function of the NEX program. After 30 min of neural recording, 2% lidocaine (30 μ l) was injected under the peripheral RF, s.c., to induce temporary deafferentation (TD). Post-stimulus time histogram (PSTH) was analyzed to quantitate neuronal responsiveness to the peripheral stimulation and spike-triggered crosscorrelation analysis was carried out to examine any changes of neural connectivities among neurons.

Results and Discussion

Evoked unit responses of SI cortex and VPL thalamic neurons were facilitated by the local anesthetic deafferentation (TD) in the RF boundary, but they were suppressed by TD in the RF center. This suggests that the presence of lateral suppressions among neurons (Smith and Gilbert, 1994). We have also shown TD-induced disappearance of the lateral suppressions from RF center cells to the RF boundary cells. It has been reported that the blockade of GABAergic transmission caused the expansion of neuronal RF (Land et al., 1995).

TD-induced abolition or weakening of the cofiring activities among RF center cells were frequently observed in this study. These RF center cells were excited by unknown common inputs(s), which may be thalamocortical afferents (Jensen and Killackey, 1987). However, TD enhanced the cofiring activities among RF boundary cells. Present study also showed the appearance of newly firing neurons and new crosscorrelation among neurons following TD to the RF center. TD strengthened the originally weak excitatory inputs from the RF boundary cells to the RF center cells. This may explain the previously reported RF expansion to the RF neighbour after TD to the RF center (Calford & Teedale, 1988). We have also noticed that a newly firing cell was activated by a RF boundary cell after TD. This emergence of new excitatory connections from RF boundary to RF outside cell may be responsible for the emergence of the NRF. During TD, occurrence of new firing and new excitatory connections were more frequently observed in the SI cortex than in the VPL thalamus. This indicates that SI cortex is more plastic than VPL thalamus. In this study, corticothalamic components were facilitated, while thalamocortical ascending transmissions were suppressed by TD in the RF center cells, suggesting thalamic reorganization may also involve corticofugal projections. Krupa et al have shown that cortical inactivation also significantly reduced but did not completely eliminate the occurrence of VPM receptive field reorganization resulting from the reversible peripheral deafferentation (PNAS, 1999).

Conclusion

These results of this study provide evidences that the reversible RF changes of the central somatosensory system after TD may actually involve dynamic alterations of the global as well as local neural networks present in SI cortex and VPL thalamus.

References

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Integration of Eye Movements and Visual Inputs at the Level of the Lateral Geniculate Nucleus

Joseph Malpeli

Department of Psychology, University of Illinois

Background

For higher mammals, the density of cells in the retina decreases dramatically with distance from the center of the retina. This is why visual acuity is highest for foveal vision. Consequently, we continually make rapid eye movements (called saccades) to sample different regions of visual space with this narrow, high-resolution window on the world. Saccadic eye are particularly interesting because they reflect the decision to attend a novel object. They are distinct from other types of eye movements, both in their characteristics and in the brain structures that have evolved to generate them. For example, saccadic eye movements are very fast, typically reaching several hundred degrees per second, whereas the brain systems for following moving objects with smooth, tracking eye movements fail at speeds greater than 30-50 degrees per second. Saccades are too fast to be controlled in real time by visual feedback - once initiated, they are terminated on target by internal motor circuits that estimate the distance the eye traveled.

The Problem

It has long been appreciated that the strategy of viewing the world through fast, frequent, sequential samples of small regions of visual space presents several challenges. Because of their high speed, saccades smear the image on the retina. However, such smearing does not disturb our perception, which suggests that there are active mechanisms in the brain that inhibit visual perception during saccades. It turns out that much of this "saccadic suppression" results because retinal ganglion cells don't respond well when images are rapidly swept across them at saccade speeds (i.e., "visual masking"), but there is good evidence that active central suppression has a role as well. A more interesting problem is that images acquired over successive saccades must be integrated into a unified view of the world. We often make several saccades a second, so clearly, each image needs to be evaluated rapidly. This suggests the need for close coordination of perceptual and oculomotor systems at early levels of visual processing.

The first opportunity for interactions between visual and oculomotor signals is in the lateral geniculate nucleus (LGN), the thalamic structure that relays information from the eye to the cerebral cortex. Axons of retinal ganglion cells terminate on the relay cells making up the LGN, which in turn relay activity to visual cortex. However, of the several million axons terminating in the LGN, only about 10% originate in the eye. The rest come from several areas of cerebral cortex and a variety of subcortical structures, some of which are known to be involved in the generation of eye movements. In this talk, I will describe our efforts to reveal effects of eye movement signals on the responses of cells in the LGN, and to understand their purpose. I will argue that these signals likely facilitate the processing of new images acquired by saccades,

and are not responsible for suppressing perception during saccades. For additional information, see Lee, D. and J.G. Malpeli. *J. Neurophysiol.* 79: 922-926, 1998.

Methods

These experiments were performed on awake cats, trained to perform an oculomotor task for food reward. Eye position was monitored by the magnetic search coil technique. All aspects of the behavioral paradigm and data collection were under computer control.

The cats were trained to fixate a small laser spot presented on a rear projection screen. At the start of each trial, a laser spot came on, which the animal had to quickly fixate. After a variable delay, the first fixation point went off, and simultaneously, a second laser spot came on at another location, to which the animal made a saccade. If a successful saccade was made from the initial fixation point to the second target, the animal was rewarded with a bolus of food. Failure to acquire targets with sufficient speed or accuracy terminated the trial without reward. In recording sessions, the activity of single LGN cells was monitored via conventional microelectrodes.

During various phases of saccades, a large (20 X 20 deg) area of the screen, centered on the receptive field of the LGN cell, was uniformly dimmed or brightened (depending on whether the LGN cell was excited by light decrement or light increment) for 500 msec. These flashed squares were dynamically centered on the receptive field of the recorded cell during the saccade, using instantaneous eye position to determine the location of the stimulus. They were never related to the reward paradigm, and the animal quickly stopped reacting to them during preliminary behavioral sessions. Because the retinal stimulus did not change during or immediately after the saccade, any variation in response that was temporally linked to a particular phase of the saccade must be due to non-retinal signals synchronized with the saccade.

Activity of the same LGN cells was also recorded for spontaneous saccades made in total darkness to determine if any saccade-related modulations of activity require that the saccade be made to a visual target.

Results

LGN activity was modulated in synchrony with the saccade, both for saccades to visual targets and for saccades in the dark. To quantify these effects, we compared activity in brief temporal epochs spanning the saccade with activity levels during a baseline period well after completion of the saccade. Activity levels in the dark were relatively low, typically averaging about 30 spikes/sec. In contrast, the response to the flash was complex and robust, reaching, on average, more than 200 spikes/sec. Nevertheless, when expressed as a fraction of the post-saccadic baseline, activity in the LGN underwent identical changes for saccades to visual targets and saccades in the dark. This means that over a very wide range of activity, these changes in response may be considered multiplicative variations in gain - that is, variations in the ratio of output (LGN) spikes to input (retinal) spikes. Beginning 200-300 msec prior to the onset of the saccade, the gain of transmission began to decrease, reaching a modest 10% drop at about the time the saccade began. During the eye movement, gain rapidly increased, reaching and surpassing baseline near the end of the

saccade, peaking at about a 20% increase in gain roughly 100 msec after the eye came to a stop, and gradually declining to baseline over the next several hundred msec.

These gain changes were qualitatively similar across LGN layer, cell class, retinal eccentricity, and saccade size. However, they differed greatly for the two major classes of LGN cells - X and Y cells. X cells are the most common class of LGN (and retinal ganglion) cells. They form a high-resolution system, and they give a relatively sustained response to a maintained stimulus. Y cells are less common. They form a high-sensitivity, low-resolution system, and they give transient responses to maintained stimuli. The saccade-linked changes in transmission were much larger for X cells than for Y cells.

Conclusions

Non-retinal, saccade-related signals orchestrate a biphasic change in the gain of transmission through the LGN that is time-locked to the saccade. This change does not seem to be related to the motivation for making the saccade, because it is identical for rewarded saccades to visual stimuli and spontaneous saccades made in darkness. It is stable over activity levels varying from minimal firing rates during darkness to vigorous firing rates evoked by visual stimuli. The initial decrease begins so early that it probably reflects the decision to break fixation with the previous target, rather than the subsequent motor signal initiating the saccade. This stereotyped swing from a modest presaccadic decrease in gain to a larger postsaccadic increase maximizes both the absolute change and the rate of change of visually-induced activity associated with a shift of gaze. We think it likely that this speeds up the activation of cortical cells by the new image. Thus we propose that these saccade-related effects on the LGN function to enhance the rapid analysis of new images following each saccade. The observation that the gain swings are much larger for X cells than for Y cells adds additional support to this notion. Y cells respond transiently to maintained images, so in effect, their responsiveness to the current image will be automatically reduced by the time the next saccade is launched, and there is less need for an active gain resetting mechanism.

These saccade-related signals are unlikely to have much to do with perceptual saccadic suppression, because the timing is all wrong. The suppression begins 200-300 msec before the eye begins to move, and it begins to dissipate while the saccade is at peak velocity. Furthermore, LGN cells respond robustly to visual stimuli during all phases of the saccade. If their response produced perceptual confusion because of retinal smearing during saccades, it is difficult to see how this modest and ill-timed reduction would alleviate such confusion.

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Research interests

- Behavioral Neurology
- Functional Brain Mapping

Functional MRI on cortical control of motor behaviors

Kyoung-Min Lee

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Understanding neural mechanisms by which voluntary movements are produced has been one of the key issues in neuroscience. Previous studies on motor-related cortical areas have suggested a hierarchy among them in terms of stages of motor control. The primary motor area (M1) appears to be involved in actual execution of a motor program, while higher motor areas, such as the pre-motor area (PreMA) and supplementary motor area (SMA), seem involved in its preparation. Regarding the functional role of SMA, however, ideas have been widely varying. Evidence has been put forth that suggests SMA involvement in movement selection, preparation, initiation, execution, and feedback-monitoring of a motor program as well as in motor learning and in planning of complex sequences of movement. We have conducted a series of experiments using the high temporo-spatial resolution of functional magnetic resonance imaging (fMRI) to study the relationship between activation of these motor-related cortical areas and various stages in generation and comprehension of motor programs including gestures.

Experiment 1.

The first study aimed at examining the timing of activation of SMA and other motor-related areas with respect to stages of movement generation using a delayed motor task and event-related functional MRI. Seven normal volunteers performed a delayed-motor task in which the preparation of finger movements was dissociated in time from movement execution, while event-related fMRI was obtained.

The M1 and PreMA showed expected activation associated with execution and preparation stages, respectively. Within SMA, sub-regions with different temporal profiles of activation were identified: The anterior part became activated early in the preparation period whereas the posterior part only with movement execution. This confirmed in human brain the notion that the classic SMA consists of the pre-SMA and SMA proper each with different functions.

Experiment 2.

Recently, Rizzolatti and his colleagues suggested that primate premotor cortex harbors a neural system for communication using gesture, which in human might have evolved into a system for linguistic communication. In order to investigate how the gestures or movements of other conspecifics are processed in human brain, event-related functional MRI experiments were conducted comparing brain activation associated with gesture mimicking and gesture comprehension only with no actual movement made. Novel gestures with no apparent meaning are designed to keep the linguistic component of the task

to a minimum.

The SMA and premotor area of both hemispheres as well as visual areas in the occipital lobe and inferior parietal lobules were activated in association with presentation of the novel gestures in both gesture mimicking and comprehension-only tasks. During a delay period when the mental image of the gestures were supposedly maintained for future execution in mimicking condition, activation of premotor areas extended into the primary motor areas, but not in comprehension-only task. In contrast, left inferior frontal areas or Broca's area was highly activated only in comprehension only condition, where the subjects tried to find out the meaning of gestures, despite the fact that the gestures were novel and deliberately made meaningless.

These findings suggest, first, that the human premotor area are involved in a system by which behaviors of conspecifics are perceived and mimicked and in which the "mirror neuron" found in F5 of non-human primate brain may participate. Second, human linguistic system, including left inferior frontal cortex, appears to be separately involved in the processing of gesture comprehension only when semantic aspects of the same gestures are of importance.

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Mapping and Modeling Human Neural Systems

Peter T. Fox

Department of Psychology, University of Texas at San Antonio

The purpose of this lecture is to demonstrate that non-invasive brain-imaging techniques can now be used to create comprehensive maps and sophisticated models of the neural systems supporting perceptions, actions, cognitions, and emotions. The operational definition of a neural system is the functional brain regions and inter-regional connections employed in the performance of a specific task. The majority of the examples are drawn from studies of language. In particular, speaking a written word was used as a model task for which a neural system map/model was desired.

Neural systems mapping and modeling, it is argued, requires data of three types: 1) operations (task locations), 2) connections, 3) order. An operation is defined as the information-processing step performed at each brain region activated in the execution of the task. A function:location association must be defined as precisely as possible in terms both of the mental operation and of the brain location. A connection is the pathway by which information flows from one activated region to the next. Order is the sequence and timing with which information moves from one location to the next in the performance of a task. The need for these three components in defining a model of a neural system can be found as early as the work of Rene Descartes (1662) and has been a consistent feature in models offered by researchers in this field since the late 1800's and to the present day.

Functional brain imaging includes a range of techniques: positron-emission tomography (PET), functional magnetic resonance imaging (fMRI), event-related electrical potentials (ERPs), and magnetoencephalography (MEG) are the most widely used. A feature common to all functional imaging techniques is the ability to detect task-induced changes in brain activity either directly through emitted electrical and magnetic fields (ERP, MEG) or through changes in hemodynamics or metabolism triggered by the changes in neural activity. More specifically, these techniques are used to detect differences between a task state and a control state: here termed a "conditional contrast" (CC).

Conditional contrasts form the great majority of functional imaging studies to date. CC studies, for example, have been used extensively to map the functional organization of language comprehension and production. The operational maps thus derived differ in many important ways from operational maps derived from lesion-deficit associations (see below). The most initially controversial and now universally accepted example is the discovery of a semantic processing zone lying in front of Broca's area (Brodmann area 46/47). This region is active in virtually any task requiring word selection, word completion and, to a lesser degree, word comprehension. Another notable example is the very recent acceptance of the role of the cerebellum in sensory processing and attention; that is, the cerebellum is not solely -- likely not even primarily -- a motor organ. CC studies have also been used to map functions for

which lesion-deficit studies provided little or no information, such as brain organization for musical comprehension, specific emotions, and vegetative appetites.

Performance correlation is a newly developed strategy for functional imaging that records a measure of a covert (e.g., hallucinations) or overt (e.g., spoken syllables) task performance. Image data are then queried for regional correlations with the behavioral measure. This strategy is invaluable in instances when the behavior cannot be controlled sufficiently well for a conditional contrast. It is also valuable when graded performance is possible or specifically desired.

Connectivity mapping, unheard of even a few years ago, is now in rapid evolution. Effective connectivity is the measurement of inter-regional covariation in functional data during the performance of a task. The source of variance from which the inter-regional connectivity matrix is derived is of two types: inter-trial variations; intra-trial variations. Surprisingly, it appears that repetitive performance of a brief (e.g., 1-2 second) task over the course of one minute is associated with a change in strategy that can be used to segregate sub-systems from one another. The chief disadvantage of this method is that it confounds anatomical connectivity with physiological activations in a manner not readily deconvolved.

TMS/PET (transcranial magnetic stimulation during PET) and TMS/fMRI are very recently developed techniques for mapping inter-regional connectivity. Focal neuronal depolarizations are induced immediately under the center of an B-shaped TMS coil. This activation is then transmitted trans-synaptically to remote regions connected with the stimulated site. Both the local and remote activations can be imaged with PET and fMRI. Thus, TMS can provide a non-invasive means of imaging and quantifying inter-regional connectivity.

TMS is also being combined with imaging as a means of making a bridge between traditional, lesion-deficit correlations and current research in functional brain imaging. It has long been known that brain imaging identifies areas participating in a task but does not distinguish between critical areas (those whose absence will impair task performance) and non-critical areas, in which a lesion produces no detectable impairment of task performance. Lesion-deficit analysis identifies only "critical areas"; functional brain imaging identifies both critical and non-critical. TMS, when used in combination with functional brain imaging, can help distinguish critical regions from non-critical.

Order (timing) is the third type of data needed for mapping and modeling human neural systems. For mapping/modeling task performance at a systems level (i.e., differences in timing between regions, not between processing levels within a region) temporal resolution on the order of tens to hundreds of milliseconds is required. The most well-known methods for achieving high temporal resolution in brain imaging are electrical (event-related electrical potentials or ERPs) and magnetic (magnetoencephalography or MEG). Both of these methods, however, are hampered by the "inverse problem", which states that there exists no unique solution for identifying the brain sources of externally detected electrical potentials or magnetic fields. In short, these methods have poor spatial resolution and are fraught with spatial ambiguities. For this reason, much effort has been placed on the development of

event-related fMRI methods. Despite the slow time course of the hemodynamic response to neural activity (used by both fMRI and PET as an index of brain activity), fMRI can be used to distinguish differences in response onset as fine as 250 msec, with the promise of even higher time resolution in the near future. TMS chronometry -- in which the TMS pulse is presented at a range of latencies relative to stimulus delivery, to identify the precise latency of processing in the area being stimulated -- is a non-imaging technique which appears capable of providing processing latency information precise to the order of tens of milliseconds.

Collectively, then, functional brain imaging and adjunct techniques (such as TMS) can now provide the three types of data needed for mapping and modeling human neural systems: operations/locations, connections, and sequence.

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Imaging Brain Function and Dysfunction

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Imaging the complex functioning of the brain is a challenging task. Those techniques that have high temporal resolution may have inadequate spatial resolution. Unfortunately, the opposite is also true. From the point of view of the neuroscientist, the ultimate technique for imaging function would identify sites of local electrical activity throughout the brain with very high spatial resolution in real time. This goal has yet to be achieved.

Functional imaging is the heart of the newest attempts of neuroscience to investigate the operation of the brain, whether applied to functional MRI, multi-channel EEG, magneto-encephalography or other techniques, such as infrared imaging. These complimentary techniques can be used to establish patterns of activity in the brain which can lead to an understanding of a given system or behavior. The purpose of this presentation is to highlight a number of techniques that are being pursuing in the quest for imaging brain function. These examples are taken from my own work and that of other members of the Imaging Research Laboratory (www.irus.rii.on.ca).

Localizing functional activity: Current techniques for deep brain microsurgery require identification of targets by preoperative imaging localization. Many critical structures targeted in this way (the thalamic nuclei) are functionally distinct but not discernable on MR images. Critical brain areas that must not be damaged by the surgical procedure also surround these structures; these factors make accurate localization of lesion targets crucial. Digitized anatomical atlases derived from histological stained brain specimens registered to patient MRI data sets aid in delineating targets, but the accuracy of registration within homogeneous anatomy remains questionable. To illustrate this problem, a searchable and expandable database of functional organization for the sensorimotor thalamus, internal capsule, and internal pallidum has been designed from a population of patients (n=52). Data were obtained through microcellular recording, microstimulation, and macrostimulation mapping performed during stereotactic thalamotomies and pallidotomies. After registration of the database into standard stereotactic space, clustering of like-physiological responses was noted in the internal capsule and sensorimotor thalamus and an articulated joint-based organization were observed in the internal pallidum. Furthermore, a clear delineation of the kinesthetic-paresthetic functional border was observed within the thalamus. When registered to a patient MRI within an image-guided visualization platform, this type of database provides a visual representation of deep brain functional organization facilitating physiological exploration of normal functional anatomy and permitting preoperative planning. This portion of the presentation is thus focused on the techniques needed to coregister electrophysiological and conventional 3D MRI data in a large patient population.

fMRI at high resolution spatial and temporal resolution: Advances in single-event functional magnetic resonance imaging (MRI) have allowed the extraction of relative timing information between the onset of activity in different neural substrates as well as the duration of brain processing during a task, offering new opportunities in the study of human brain function. Single-event fMRI studies have also facilitated

increased spatial resolution in fMRI, allowing studies of columnar organization in the human cortex. Since important processes such as object recognition, binocular vision and other processes are thought to be organized at the columnar level, these advances in the spatial and temporal capabilities of fMRI allow a new generation of basic neuroscience studies to be performed, investigating the temporal and spatial relationships between these cortical sub-units. Such experiments bear a closer resemblance to single-unit or evoked-potential studies than to classical static brain activation maps and might serve as a bridge between primate electrophysiology and human subjects. This section of the talk will describe specific examples of the latest advances from our 4T fMRI unit. Some of the research topics are: object versus facial identification in the fusiform gyrus, motor learning tasks, understanding saccades and anti-saccades, analysis of ocular dominance in amblyopia, and examining the motor-sensitive MT/V5 cortex.

fMRI of the visual system in multiple sclerosis: We are performing experiments to examine the functional MRI (fMRI) response in MS patients with optic neuritis - an impairment of the optic nerve. We compared neuronal activation measured with fMRI to the delay in visual evoked potentials (VEPs - a common clinical measure of optic nerve damage) and found significant correlation. Thus, MRI may be capable of providing not only an anatomical indication of disease

presence and evolution, but also a functional indication as it correlated with an independent measure of brain function measured by electrical activity. This section of the presentation will examine the novel approach of understanding altered cortical evoked potentials in reference to underlying physiological deficits measurable with fMRI techniques.

Brain circulatory parameters measured with CT: Although fMRI typically represents the new modality of choice for the examination of functional activity of the brain, contrast-enhanced CT can provide a valuable look at hemodynamic properties, especially as a response to an insult. A technique has been developed to acquire and model CT data to yield images of blood volume and blood flow in the brain. The important responses of the vasculature to a tumor or stroke can be visualized and quantified. Such measurements are currently unavailable for MRI and serve to illustrate that advanced image processing techniques can extract new and important information from an established technology.

Multispectral analysis: MRI can provide multiple images of the same anatomy, each with different contrast characteristics. Contrast is controlled by selection of imaging pulse sequence parameters. Images can be produced with contrast weighted by a variety of factors including proton density (PDw), T1 relaxation time (T1w), T2 relaxation time (T2w), diffusion (Dw) and magnetization transfer (MTw). Multi-contrast MR images are also referred to as "multi-spectral" images - each contrast is treated as a component, or "band" making up an "MR spectrum". Typically, multi-spectral MR images are acquired such that tissues-of-interest have different contrast characteristics in one or more of the spectral bands. Analysis of multi-spectral MR data is one of the most exciting and promising areas of medical image processing. This technology is based on remote sensing software developed for the analysis of satellite data. Consequently, multi-spectral images can provide much more information than analysis of a single contrast image and in so doing provide an opportunity to extract additional new information. The use of multispectral analysis on medical images is a unique idea. This portion of the talk will examine the

computer programs used and the results that can be obtained from multiple data sets.

There are a number of very interesting other imaging modalities that should be also considered. Included among these are: magnetoencephalography, infrared imaging, multi channel (256 channel) EEG, positron emission tomography and single photon emission tomography. Key to employing any of these techniques is not only a detailed knowledge of the technique itself, but an essential appreciation of their strengths and weaknesses to enable the investigator to design the appropriate study. This even holds for established techniques, such as fMRI, where today the experimental paradigm is far more important than the imaging technique itself. However difficult the inherent challenges of an imaging modality, each type of imaging can provide additional new information on brain function when the best experimental paradigms are selected.

One critical area for future research will be in the general area of molecular imaging. Many imaging modalities have had a substantial increase in image resolution due to technological improvements over the past 10 years. We have microCT and MRI facilities that have microscopic imaging abilities. This equipment allows the non-destructive examination of tissues or animals with the eventual goal being histopathological analysis. Molecular imaging takes this idea another step forward in the assessment of function and can do so in a three-dimensional way, to replace time-consuming and labor-intensive methods used at present. The techniques are based on the ability of the imaging system to identify molecules rather than structures. Some examples are identifying labeled macrophages invading a tissue using MRI, tracking gene therapy using scintigraphy, or optical imaging of enzyme activity. It is essential to consider this line of investigation when imaging of function and dysfunction of the brain.

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Current Research Interests

- Learning and Memory
- Encoding and Retrieval Specificity

Prefrontal activations during different memory processings : fMRI studies

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Functional Neuroanatomy has been studied using fMRI method during repetition priming (implicit memory) and recognition (explicit memory) tasks. Material-specific effects were examined by comparing brain activations associated with encoding and retrieval of picture and word stimuli. To investigate material specific effects on priming (Study I), picture or word stimuli were presented while participants performed a semantic classification task (man-made/natural). Initial performance and following repeated performance of the same classification task were compared for picture and word each. Reduction of brain activation was found during the repeated performance in brain regions that were involved in initial encoding processing. Depending on perceptual format of stimuli, the brain activation reduction was found mainly in left inferior prefrontal region for word while it was in bilateral occipital cortex for picture. Change of perceptual format between encoding and retrieval episodes also studied by comparing word-studied-picture-tested condition (WP condition) and picture-studied-picture-tested condition (PP condition). In WP priming condition, right prefrontal activation was observed, relative to PP priming condition, in addition to bilateral occipital activation. Explicit retrieval (recognition) was also examined (Study II) both during PP recognition condition and WP recognition condition. In PP recognition condition, increases of brain activations were found in bilateral prefrontal cortexes, parietal cortex, and occipital cortex, relative to fixation baseline. In WP recognition condition, however, increased activation was found in left prefrontal region only. These findings suggested that not only the type of memory but also perceptual format of stimulus between encoding and retrieval episode should be considered to understand functional role of prefrontal cortex in memory.

INTRODUCTION

The idea that memory involves multiple processings and systems, has been supported by a number of researches, both with human and animal models. Functional neuroimaging studies have shown brain activation in various brain regions associated with different memory processing. Previous experience of episodes or events affects behavior, either with or without intentional or conscious recollection of the previous episodes. Retrieval of previous episodes with conscious recollection is called explicit retrieval whereas retrieval without conscious recollection is called implicit retrieval. Repeated processing of previous events often resulted in fast and accurate behavioral responses in later processing. This phenomenon is referred as repetition priming, considered as retrieval of implicit memory. It has been often observed with reduction of brain activations, during repeated processing, in areas involved in initial processing. In contrast to repetition priming, increases of brain activations were also observed during conscious recollection of previous episode, considered as retrieval of explicit memory. A number of studies indicated that prefrontal cortex (mainly right side) was involved in explicit retrieval, whereas the left prefrontal cortex is involved in encoding. However, the precise role of right prefrontal and left prefrontal regions during episodic retrieval have not yet been settled among researchers^{3,4}. Considering prefrontal cortex is not the only candidates of neural substrates of memory⁵, further investigations are needed to understand the nature of memory processing and its functional neuroanatomy.

While debating asymmetry among left and right brain regions in retrieval processing, researchers have often ignored the way in which material type of encoded items during study episodes interacts with retrieval processing, which also depends on the perceptual format, i.e., material type, of retrieval cues.

This might be the case whether it is explicit retrieval or implicit retrieval processing. In literatures, it has been well documented that encoding involves both perceptual processing and conceptual processing, especially during a semantic task. Therefore, different perceptual formats might elicit different perceptual processing, which in turn, result in different brain activations both during encoding and retrieval. If that is the case, it is very likely that perceptual format of encoding interacts with that of retrieval and the brain activation patterns as well. If material types (i.e., word, picture, or face) or stimulus modalities (visual, auditory) of retrieval cue are consistent with the format in which the target items have been encoded, it will affect the perceptual processing of retrieval. In explicit retrieval, this consistency might be a basis of the perceptual familiarity which needs to be evaluated, or utilized during the recollection process. In implicit retrieval, this consistency might be a basis of facilitation in perceptual processing during repeated processing. In other words, the former requires further processing of evaluation whereas the latter requires less processing requirement. These differences in retrieval processing might be associated with increase of brain activation (explicit memory) or decrease of brain activation (implicit memory). Still, it has not been well defined which retrieval process might occur when physical format of encoded stimulus was changed at the time of retrieval. Furthermore, it has seldom been studied which brain areas are involved in this cross format retrieval processing, either in implicit memory task, such as repetition priming, or explicit memory task, such as recognition.

In the following two studies, it was investigated the brain regions that activated, or deactivated in retrieval/encoding processing, depending on the perceptual format of stimulus at the time of encoding and retrieval. This type of studies will provide further insights in various information processing components of retrieval.

Study I.

Priming and Reduction of Brain Activation

It has well been known that speed and accuracy increases when same events or episodes are processed repeatedly, relative to initial processing. Evidences suggested that repeated processing of identical events is associated with reduction of brain activation of the brain areas involved in initial processing of the episodes^{1,2}. Modality change between study and test seemed to affect both implicit and explicit memory, but more in implicit memory, probably due to reduction of perceptual priming. For example, words studied as visual modality, were better recognized or primed with visual words than auditory word, vice versa. Even though this implies influence of past experience on perceptual processing, priming effect was reported to still exist in cross-modality condition, reflecting contribution of semantic priming or semantic retrieval. The studies, reported here, were performed in the interest of two questions. The first was to investigate material type effects on semantic repetition priming and its brain activation patterns, while the second was to dissociate brain regions involved in perceptual processing and conceptual processing of semantic task. Material specific effect was studied with two different kinds of visually presented stimulus type, i.e., word (WW scan) and picture (PP scan). Brain activations during initial presentation and repeated presentation were compared to observe the priming effects for each stimulus types (Study I). To identify the brain areas involved in semantic processing, priming condition was designed to contain different perceptual processing, but repeated semantic processing. This particular priming condition, called a cross priming condition, was compared with a regular priming condition in a scans. In other words, the perceptual feature of previous episode was changed during retrieval in cross priming condition (word-studied-picture-tested: WP condition). This was compared with a within priming condition (picture-studied-picture-tested: PP condition) in the third scan (CROSS scan). The WP priming condition and PP priming condition shared same amount of semantic priming

but only the PP priming condition had both conceptual priming and perceptual priming. Therefore, the difference, if there was any, between cross priming condition and within priming condition must reflect difference in perceptual priming, not conceptual priming. The difference observed between WP priming and PP priming could be related with difference in perceptual priming. Any observed difference in brain activations between two conditions in CROSS scan, therefore, must be associated with perceptual processing specific to the stimulus format.

Methods and Procedures: Scan was performed in a 1.5 T GE MR machine with T2*-sensitive gradient echo spiral pulse sequence (TE = 40 ms, TR = 1440 ms, flip angle = 80°, FOV = 24 cm and inplane resolution = 1.875 mm, 6mm thick 16 slices, two spiral interleaves). Healthy participants (n=9) were scanned during three scans while semantic classification tasks were performed for pictures (PP scan: initial picture vs. repeated picture; CROSS scan: WP priming vs. PP priming), word (WW scan: initial word vs. repeated word), WP scan (WP scan: word-to-picture vs. picture-to-picture). Participants viewed the visually presented line drawing image or word (100ms duration/2sec) from a mirror mounted above the subject's head, which reflected the image from the screen. Reaction time was recorded by a computer outside of the scanner. Encoding was achieved while semantic classification judgment task (man-made/natural) was performed both for picture stimulus list and for word stimulus list. In WW scan and PP scan, a scan were composed of eight cycles of alternating initial presentation condition (15 trial/half-cycle) and repeated representation condition. WP scan was consisted of eight cycles of WP priming condition (word-studied-picture -tested) and PP priming condition (picture-studied-picture-tested).

Behavioral Results: The performance of semantic classification task was measured in accuracy and reaction time. There was significant reduction in reaction time (PP: $p < .001$, WW: $p < .005$) and accuracy (picture: $p < .001$) during repeated cycles, in comparison to the initial cycles during the first two scans. WP priming condition was associated with longer latency ($p < .05$) and lower accuracy ($p < .01$) in comparison to PP priming condition of CROSS scan.

Brain Activation: Reduction of brain activation was found during semantic classification processing of the repeated picture, relative to initial presentation. Significant reduction with repeated picture (PP scan) was found in occipital cortex bilaterally, such as left fusiform gyrus, right middle occipital gyrus, and bilateral cuneus. With repeated word presentation (WW scan), reduction of brain activation was also found in left inferior prefrontal cortex (BA 44), medial superior prefrontal (BA 3/32), and bilateral cuneus. In CROSS scan, WP priming (word-studied-picture-tested condition), relative to PP priming (picture-studied-picture-tested condition), resulted in greater activation in various brain regions, such as left fusiform gyrus, left tempo-parietal-occipital region, and right middle occipital region. A greater activation was also observed in posterior region of the right middle prefrontal cortex (BA 6) during the WP priming condition, in comparison to PP priming condition.

Study II.

Explicit Retrieval and Brain Activation

Explicit retrieval processing was investigated both in PP condition and WP condition respectively. Recognition task was given following incidental encoding of picture items and word items. In PP recognition condition, the previously studied picture items were given as target items along with distracters. In WP recognition condition, the studied word items were presented as picture form as target items, along with picture distracters. Therefore, the target items of PP condition provided both perceptual and conceptual familiarity, whereas the target times of WP condition did conceptual familiarity, but not perceptual familiarity. Recognition occurred based on these familiarities coming from old stimuli, in comparison to new items. Therefore, it was expected that PP recognition condition might

have been easier for recognition task than the WP condition. Greater activation of brain of PP condition, relative to WP condition, could have reflected the retrieval processing based on perceptual familiarity.

Methods and Procedures: Scan was performed in a 1.5 T GE MR machine with EPI capability. Healthy participants ($n=16$) were scanned during picture/word semantic classification tasks (two study scans), and followed by two memory tasks (two test scans). Encoding was achieved while semantic classification judgment task (man-made/natural) was performed both for picture stimulus list and for word stimulus list. Each test scan (PP scan, WP scan) was composed of five alternating cycles of recognition condition and repeated encoding condition, even though only the results of explicit memory condition were reported here. During the recognition task cycles, memory was tested with all picture form. Therefore, in recognition condition cycle of PP scan, the target items came from the picture study list and tested with picture stimuli, while, in WP scan, they did from the word study list and tested with picture stimuli. A rest period with a cross hair fixation point was given beginning and end of all the scans, serving as common baseline for both scans.

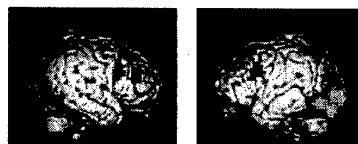
Behavioral Results: The performance of recognition task was measured from eleven participants during scanning and the behavioral data were subject to further analysis. Level of recognition performance differed between PP condition and WP condition. The recognition performance of PP condition was better in term of reaction time ($p < .0001$) and correct response rate ($p < .0005$) but not in error rate ($p > .73$).

Brain Activation: Brain activation was found in occipital cortex and posterior parietal cortex bilaterally during both recognition conditions, relative to baseline condition. In PP condition that was a typical recognition condition, brain activations were also found in left inferior prefrontal cortex, medial superior prefrontal cortex, and right prefrontal cortex. Unlike PP condition, no right prefrontal activation was found during WP recognition conditions in which no perceptual familiarity was given by target items (See Figure 1). This suggested that the right prefrontal activation may not be necessarily associated with retrieval process itself, but may be associated with evaluation of perceptual familiarity during retrieval. These findings also suggest that left prefrontal area might involve in explicit retrieval of semantic aspects of previous episodes. No additional brain areas were recruited in order to compensate changes in physical format of stimulus between encoding and retrieval.

Recognition Test with Picture Stimulus Form

PP condition

(picture-studied-picture-tested)



WP condition

(word-studied-picture-tested)

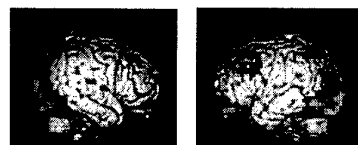


Figure 1: Brain activation during PP and WP recognition tasks, relative to fixation. Prefrontal activation was observed bilaterally, relative to simple fixation condition, during the PP recognition task but only in the left side during the WP recognition condition.

DISCUSSION

Implicit memory and explicit memory were studied in within- and cross- stimulus form conditions, using repetition priming (Study I) and recognition task (Study II). In both studies, pictures and word stimuli were incidentally encoded during a semantic classification tasks. In repetition priming study, during the later performance, relative to initial performance, different stimulus types resulted in reduction of brain activation in different brain regions. Recognition task, however, resulted in increase of brain activation in various brain regions, relative to encoding task, or simple baseline fixation (Study II). These findings indicated that brain activation/deactivation patterns differed depending on memory task types and stimulus types.

The reduction of activation due to priming (implicit memory) during semantic classification task was consistent with previous findings in other studies of repetition priming^{1,6}. First, material specific effect of implicit memory was observed during repetition priming. The brain regions showing brain deactivation were mainly in left prefrontal activation for word stimulus but bilateral occipital cortex for picture stimulus. This material-specific difference might suggest difference in degree to which conceptual processing and perceptual processing were involved in semantic classification task, even though the task requirement was identical. Second, WP priming, in comparison to PP priming, resulted in activations in occipital cortex but not in left prefrontal cortex, indicating need of initial stimulus-specific perceptual processing but not conceptual processing.

Increase of brain activation (Explicit memory) was found during recognition task. First, right prefrontal activation was found in relation with explicit retrieval of PP recognition condition, as well as left prefrontal activation. However, the right prefrontal activation, which has been suggested as brain activation associated with explicit retrieval, was found in PP recognition condition but not in WP recognition condition. Right prefrontal cortex in this explicit retrieval task may have been associated with perceptual familiarity monitoring, not necessarily retrieval processing per se. Second, inferior left prefrontal activation was found in PP recognition condition while middle prefrontal activation was found in WP recognition condition. The difficulty of performance in WP recognition condition, relative to PP recognition condition, might explain the left middle prefrontal cortical activation. Lower recognition performance of WP recognition condition (lower accuracy, greater latency) indicates a possibility that participants might have been involved in strategic evaluation during retrieval process.

The WP (word-studied-picture-tested) conditions, both in repetition priming and recognition tasks resulted in different activation patterns. The function of right prefrontal activation observed during WP priming condition is difficult to understand, but still very intriguing. Usually, right prefrontal cortical activation could be attributed to explicit retrieval during a nominal implicit memory task, even though it was not intended in Study I. However, it is unlikely the case since the explicit retrieval of WP condition in the following recognition study (Study II) was associated exactly with left prefrontal cortex, not with the right prefrontal cortex. According to a follow-up priming study⁷, the right prefrontal activation was observed again in WP condition, but not in PW condition (picture-studied-word-tested condition). The left prefrontal activation observed in explicit retrieval task was often attributed to additional encoding of distracters or re-encoding of weekly-encoded target materials, instead of retrieval requirements. According to the results of this study, it was less likely since new materials were pictures whose encoding was more likely bilateral, instead of left only. Also the precise location of left prefrontal activations in the WP recognition between the brain activation during new picture encoding differed. Several possibilities can be considered. The left prefrontal activation in WP condition might be understood as

strategic processing of WP recognition condition, or related with the fact that the target item was originally encoded as word form, whose activation was usually associated with left prefrontal activation. These possibilities remained to be further explored in future studies. These interesting contrasts between implicit memory task and explicit memory task need further investigation in near future.

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- Memory

Agrammatism in Broca's Aphasia: Dissociation of Sentence Production and Comprehension

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In the current study, the syntactic processing related with the comprehension and production processes was examined. In order to see whether the agrammatic Broca aphasic has difficulty in comprehending and producing the subjective and objective cases and these processes are modular, the sentence-picture matching task and two sentence completion tasks were employed.

The sentence-picture matching task was to evaluate the comprehension performance of the semantically reversible sentences. The semantically reversible sentences can't be understood correctly without understanding the subjective and objective case markers. For example, in the sentence-picture matching task, "악어가 상어를 문다" (in English, the sentence means that "a crocodile bites a shark") was presented to the Broca aphasic, and then the Broca aphasic was asked to choose a correct picture to describe the sentence. As shown in table 1, the result of the sentence-picture matching task showed that the agrammatic Broca patient comprehended the semantically reversible sentences almost 100% correctly. The incorrect responses(4 out of 32) can't be interpreted as real errors, because 4 pairs of pictures describing the sentences were ambiguous. Thus, the patient comprehends the subject and object case markers almost perfectly. Because the semantically reversible sentences can't be comprehended without understanding the case markers correctly, this result suggests that he can use the case markers in comprehension successfully.

Table 1. Performance in the sentence-picture matching task

Correct Response	Incorrect Responses	Total
87.5% (28/32)	12.5% (4/32)	100% (32 cases)

Two sentence completion tasks were used to evaluate the production processing of the case markers and morphological inflections: one was to select the correct case markers among several alternative case markers to fill in the empty blanks involved in the test sentence(hereafter, it is named "the case selection task"), and the other was to generate an appropriate case markers without any alternative presentations(hereafter, it is named "the case generation task"). One example sentence presented in the case selection task is as follows.

어머니□₁ 밀가루□₂ 끓는 물□₃ 반죽하였다(in English, which means that "my mother

mixed flour with boiling water").

The correct answers for the 1st, 2nd, and 3rd blanks are "가" (subject case marker), "를" (object case marker) and "에" (place case marker?) respectively. In this task, the Broca patient selected around 50% correct case makers as presented in Table2.

Table 2. Performance in the case selection task

Correct Responses	Incorrect Responses	Total
50% (20/40)	50% (20/40)	100% (40 cases)

After selecting the case markers, the patient was asked to judge whether the sentences filled by wrong and correct case markers are grammatical or ungrammatical. Interestingly, the patient judged the sentences as the grammatical sentences, even though those sentences are ungrammatical. According to the results of the case selection task, the Broca patient made many errors in selecting case markers and filling in the empty blanks(50%). The dissociation in comprehending and producing the subjective and objective case markers found in the sentence-picture matching and the case selection task implicates that the syntactic processes involved in comprehending and producing the case postpositions are separated and modular in the respects of language processing or structure.

In order to reevaluate the validity of the case selection task and in order to see whether producing the subject case is different from generating the object case, the case generation task was employed. One example sentence presented to the patient in the case generation task is shown at the below. The patient task was to generate an appropriate case marker without any alternatives.

대통령□₁ 어제 전화□₂ 받□₃ 다(in English, which means that "the president received a phone call yesterday").

The correct answers at the above blanks are the subjective case marker(for the 1st blank), the objective case marker(for the 2nd blank), and the suffix to represent the past tense(for the 3rd blank). The 1st and 2nd blanks are to generate the case markers and the 3rd blank is to produce the suffix(which is called "선어말어미")(which suffixes are used to express the tense and to enrich the meaning of the word stem) and is placed before the terminal suffix(which is called "어말어미" and is used to terminate the sentence). In the current study, two kinds of "선어말어미" were evaluated. One is to evaluate the tense and the other was to see the honorific "선어말어미". The performance of the Broca patient in the case generation task was shown in the table 3. As found in the case selection task, the Broca patient generated the wrong case markers around 50%, which suggests that the agrammatic Broca patient has difficulty in generating case marker. Also, it was found that the performance in producing correctly the subject case

markers was much lower than that in the objective case. And the patient produced the wrong case postpositions about 50%. He made errors about 50% for the tense generation, whereas he did not make many errors in the honorific "선어말어미" generation.

Table 3. Performance in the case generation task

	Correct Response	Incorrect Response	Context-Inappropriate Response	Total
Subjective Case	(6/23)	(14/23)	(3/23)	23
Objective Case	(17/22)	(4/22)	(1/22)	22
Tense Suffix	4	4	4	12
Aspect Suffix	5	1	1	7

This fact provides the double dissociation in considering the previous studies (Kim, 1997; Lee, 1998). That is, Kim (1997) and Lee (1998) reported that two Broca patients showed superior performance in producing the objective cases to the performance in the subjective cases. Thus, the current and the previous studies suggest that the different case postpositions are processed differently and producing the different case markers are performed in the modular fashion. One hypothesis to explain this double dissociation, which is named VP-internal subject hypothesis, is to assume that the subject case is governed and role-assigned by the tense of the main verb and the object case is determined by the verb.

Also, the single dissociation in inflection for tense and honorific "선어말어미" was found. Based on this single dissociation, it is possible that the inflections for the tense and aspect might be modular in the respects of the functional localization or information processing.

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The Neuroanatomy of Sentence Comprehension

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My research partners and I study the relation between brain and language. We focus primarily on the neuroanatomical organization of the system for natural language comprehension. To establish this perspective, we rely on data from aphasia research and, more recently, on functional neuroimaging data.

APHASIA RESEARCH

Our aphasia research is guided by a functional analysis of the normal system - a description of some of its components (broadly, those having to do with syntactic and semantic processing) and of the way in which these components, or modules, interact. This much is standard. Also standard: We take the specific deficits following focal brain damage to be explicable in terms of disruptions to one or more these components.

What sets us somewhat apart from many other researchers, however, are the kinds of details that enter into our componential analysis and that support our inferences concerning "functional lesions." The difference turns on the way in which we isolate modules. Unlike other approaches, we do not license processing modules solely on the basis of formal linguistic theory. We do not distinguish, say, between a syntactic processing constituent and a semantic processing constituent simply because the representational formats they operate on are different. Rather, we also seek evidence for the uniqueness of processing constituents in terms of their real-time fixed and mandatory operating characteristics.

The point here is that modules and their representations constitute evanescent, intermediate stages in the chain of comprehension; they are, therefore, most directly revealed by measurements taken during the brief course of their operation. And in line with this notion, we chart "functional lesions" in terms of alterations to their operating characteristics. In effect, we seek a functional layout of the comprehension system that is elaborated in real-time terms. That's one feature of our research program.

Another feature turns on neurological matters. In the first instance, we try to provide evidence that the effects of brain damage distinguish between modules, sparing one, disrupting another. In this way we check whether our theory is neurologically defensible. But we seek more: We also seek data on the neuroanatomical layout of the system - on how the modules are geographically distributed.

Our connection to neuroanatomy is based on the fact that the aphasic syndromes we study - Broca's and Wernicke's for the most part - are distinguishable both clinically and with respect to lesion site. So, clinically, we can contrast, among many other things, the nonfluent telegraphic speech of Broca's aphasic patients and the fluent, rather empty speech of Wernicke's aphasic patients (Goodglass & Kaplan, 1972).

And neuroanatomically, we can contrast the two syndromes along an anterior posterior axis. Although variable, the generally large anterior lesions associated with Broca's aphasia cluster about a modal site that is quite different from that for Wernicke's aphasia. For the latter, the greatest involvement appears to be confined to more posterior regions, implicating especially the posterior superior portion of the first temporal gyrus. (For details see, e.g., Alexander et al., 1990; Benson, 1985; Naeser et al., 1989; Vignolo, 1988)

We capitalize on this difference. Our work shows that the brain area implicated in Broca's aphasia, but not Wernicke's, is necessary for the real-time formation of syntactically-licensed dependency relations. These are linking operations that allow the listener to identify the referents of pronouns and reflexives, and more abstractly, to interpret constituents in non-canonical positions - to determine for example, that "the boy" in "It was the boy that the girl chased" is to receive its argument as the direct object of "chased", even though it is near the beginning of the sentence instead of after the verb. Further, our work connects such operations to timing parameters, thereby suggesting that the brain region marked by Broca's aphasia is involved in syntactic processing, not because it is the locus of syntactic representations per se, but because it provides necessary elementary processing resources - resources that intuitively appear to be biologically fixed or "wired in."

That is the first half of a double dissociation. The second half is based on our demonstration that the region associated with Wernicke's aphasia, but not Broca's, is crucially involved in semantic combinatorial operations. Such operations are required when semantic composition is not syntactically transparent, as in the sentence, "The girl jumped until dawn" where somehow (either by type-shifting or interpolation) the sense of repetition - of repeated jumping - must be generated or pasted into the interpolation as comprehension unfolds in real-time.

FUNCTIONAL NEUROIMAGING

Imaging studies of comprehension in neurologically intact subjects both support and refine the cortical localization patterns observed in aphasia research. So in a recent study carried out with colleagues at The University of Pennsylvania, we observed recruitment of left inferior frontal cortex (Broca's area) specifically for the comprehension of non-canonical sentences in which the syntactically-licensed dependency relations had to be established over relatively long "distances." By contrast, no such syntactic specialization was shown by a core region of left posterior superior temporal cortex (Wernicke's area). What we are now trying to determine is whether Wernicke's area is recruited for compositional processing that is entirely semantic. Evidence - emerging from a study that we are carrying out in collaboration with researchers at McLean Hospital - is beginning to suggest this possibility. But this work is just starting and the evidence is preliminary.

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Linking visual attention and awareness with functional MRI

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What we see is not dictated solely by where we point our eyes, but also by how we direct our visual attention. The effects of directed attention on visual perception can be profound. While attending to a stimulus can substantially enhance a subject's capacity to perform fine discriminations, an ignored stimulus sometimes appears not even to reach awareness. However, the nature and extent of processing for attended versus ignored stimuli has been a subject of controversy for many decades, and the brain mechanisms leading to such effects have until recently been unclear. This presentation will consider our recent investigations of the nature and extent of processing for unattended stimuli using functional magnetic resonance imaging (fMRI) in humans.

Cortical processing of ignored stimuli depends on perceptual load

Observations in monkeys suggest that attention can modulate neural responses to stimuli in functionally specialised areas of the visual system. To investigate this in humans, subjects were scanned with fMRI during repeated presentations of identical visual motion stimuli while only the attentional component of the task was varied (1). Enhanced haemodynamic responses during attentive conditions defined an occipito-parieto-frontal network, including sensory and association areas. Attentional modulation was not restricted to extrastriate areas (including V3a and the V5 complex) but was also evident, to a lesser degree, in early visual areas close to the calcarine fissure.

These findings show that attending to a stimulus enhances processing of relevant stimuli in extrastriate cortex compared to a passive viewing baseline. However, as the unattended stimulus is not manipulated independently of attention, it is not possible to conclude whether the effects observed on cortical activity represent the effects of attention, those of unattended stimulus processing, or an interaction of the two. This issue, the extent to which unattended stimuli are processed, is one of the longest standing controversies in the psychology of attention. While some have suggested that unattended stimuli receive only a cursory processing of elementary physical attributes, others have concluded that unattended stimuli are fully processed.

Lavie's theory of attention proposes a resolution to this longstanding controversy by suggesting that the processing load in a relevant task determines the extent to which irrelevant distractors are processed. This theory was tested by asking participants in a study to perform linguistic tasks of low or high load while ignoring irrelevant visual motion in the periphery of the display (2). Although task and distractor were unrelated, both functional imaging of motion-related activity in cortical area V5 and psychophysical measures of the motion after-effect showed reduced motion processing during high load in the linguistic task. These findings fulfil the prediction that perception of irrelevant distractors depends on the relevant processing load. Moreover, an interesting implication of these findings is that ignoring an irrelevant stimulus is not under voluntary control, but instead depends critically on perceptual load in the relevant task.

Neural systems for attention and visual awareness are linked

The effects of attention on brain responses described above included not just modulation of sensory processing, but also delineated a parietofrontal network that has been repeatedly implicated in both spatial and non-spatial attention. Is this network specific to the control of attention, or does it subserve some more general function?

We investigated this by studying the neural basis of perceptual transitions during binocular rivalry (3). Rivalry occurs when dissimilar images are presented to the two eyes. Perception alternates spontaneously between each monocular view and is not under voluntary control. Functional brain imaging in humans was used to study the neural basis of these subjective perceptual changes. Cortical regions whose activity reflected perceptual transitions included extrastriate areas of the ventral visual pathway, and parietal and frontal regions, all of which have been implicated in spatial attention. However, whereas the extrastriate areas were also engaged by nonrivalrous perceptual changes, activity in the frontoparietal cortex was specifically associated with perceptual alternation only during rivalry. The location of the frontoparietal areas was strongly overlapping with areas previously implicated in the control of visual attention. This suggests that frontoparietal areas play a central role in conscious perception, biasing the content of visual awareness toward abstract internal representations of visual scenes, rather than simply toward space. One possibility is that right frontoparietal structures perform a general selective function, choosing between alternative interpretations of the visual scene competing for awareness in the ventral stream.

Inattentional blindness occurs under conditions of high perceptual load

As has already been alluded to, whether the identity of meaningful stimuli is still extracted when ignored is a classic issue in attention research. Recent studies, including the data presented here, show that visual attention can modulate stimulus-evoked activity in early visual brain areas. However, the stimuli used were typically meaningless (patches or moving dots), so cannot resolve the issue for meaningful stimuli such as ignored words. Furthermore, if the response to an unattended stimulus is merely attenuated rather than eliminated at early levels of processing, it might continue through to the level of meaning. A hybrid theory of attention such as Lavie's predicts that processing of higher order cognitive properties will be suppressed under conditions of high perceptual load. We therefore constructed a situation where subjects could look directly at a word without attending to it, under conditions of high perceptual load (4). We measured brain activity with fMRI, in humans viewing rapid successive displays of overlapping pictures plus letter-strings, which could be meaningful words or non-words. Directing attention to letter-strings versus pictures strongly modulated activity in extrastriate cortex, despite the spatial overlap of the stimuli. Cortical regions whose activity reflected word identity of letter-strings when attended included areas of left temporal, parietal and frontal cortex classically associated with language. Critically, when the letter-strings were ignored, the activity related to word identity was abolished. These findings demonstrate 'inattentional blindness' even for highly familiar and foveated stimuli. We suggest that subjects fail to remember these unattended stimuli due to the absence of brain activity reflecting their identity at the time of presentation.

Unconscious activation of V1 in parietal extinction by an unseen stimulus.

The findings presented above imply a close link between the availability of visual attention, cortical processing of unattended stimuli and visual awareness. Furthermore, damage to frontoparietal structures

results in disorders of attention and awareness. Visual extinction is a sign classically associated with right parietal damage. The patient can see a single stimulus presented in the ipsilesional or contralesional visual field, but is characteristically unaware of the same contralesional stimulus during simultaneous stimulation of both fields. The ipsilesional stimulus is said to "extinguish" the contralesional stimulus from awareness during bilateral stimulation, perhaps due to a pathological bias in attention towards the ipsilesional side. Recent psychophysical evidence suggests that, although extinguished stimuli are not consciously seen, they may undergo residual processing and exert implicit effects on performance. However, the neural structures mediating such residual processing for extinguished stimuli remain unknown. We therefore studied the neural activity evoked by an extinguished visual stimulus using event-related fMRI, in a patient with circumscribed right inferior parietal damage and profound left-sided extinction (5). Monochrome objects (faces or houses) were presented in the left or right field, either unilaterally or bilaterally on each trial, with the patient indicating by button press whether he saw an object on the left, the right, or on both sides. He usually saw only the right object on bilateral trials, yet the fMRI data showed activation of visual cortex contralateral to the extinguished left stimulus on these trials (as compared with right-only stimulation), in both striate and early extrastriate areas of the right hemisphere. This activity had a similar location and timecourse to that resulting from a single stimulus in the left versus right visual field. Cortical pathways involved in the normal processing of a single seen stimulus can thus still be activated by an unseen, extinguished stimulus after right parietal damage. This in turn suggests that activation of primary visual cortex may not be sufficient to evoke awareness.

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Research Interests

- Attentional control of the visual system.
- Representations of visual information, and their use in "everyday" visual tasks.
- Computational modeling of visual processing and the allocation of visual attention, guided by findings from visual neuroscience and Psychophysics.
- Neuropsychology: Visual Agnosia, Neglect, etc.

Implicit and Explicit Representations of Visual Space:

Effects of Bilateral Parietal Damage

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There is substantial evidence that the parietal lobes are involved in locating items in space. In humans bilateral parietal lobe damage can result in a neuropsychological disorder known as Balint's syndrome in which single shapes that define objects are perceived but their location is not explicitly known. Recent evidence also demonstrates that surface features such as color and size are abnormally bound with shape after parietal damage. This finding supports the role of parietal function in co-locating two features for the purpose of feature integration. Features such as color, size and shape are represented in ventral areas of the temporal lobe (the ventral what pathway), while location is associated with the parietal and frontal lobes (the dorsal where pathway). The data reported in the present paper demonstrate that although distinctive features may not be located accurately when bilateral parietal lobe damage occurs, their spatial location is represented, albeit below the level of awareness. The results indicate that spatial location of features is coded even when both parietal lobes are damaged. They also support recent evidence for multiple spatial maps in other primates.

It has long been known that parietal lobe damage in humans can result in severe spatial disorientation (De Renzi, 1986), with more recent accounts suggesting a deficit in spatial attention (Posner, Walker, Friedrich, & Rafal, 1984) or spatial representation (Bisiach, Capitani, Luzzatti, & Perani, 1981). However, there appear to be multiple spatial maps in the primate brain that are widely distributed across cortical and subcortical areas (Graziano & Gross, 1996; Stein, 1992). What spatial information is necessary for attentional control and spatial awareness associated with parietal function and what spatial information can be encoded in spatial maps when conscious access is denied, as in the case of parietal damage (Robertson, Treisman, Friedman-Hill, & Grabowecky, 1997).

Evidence for multiple spatial maps has taken on added importance in light of recent findings demonstrating that the disruption of spatial abilities due to damage to both parietal lobes also disrupts the ability to correctly bind features such as color and shape and size and shape (Friedman-Hill, Robertson, & Treisman, 1995). This binding problem in turn makes it very difficult to accurately search a cluttered array for the conjunction of two features. For instance, searching for a red X among red Os and green Xs may be impossible even in the presence of only a few distractors. Without conscious access to an adequate spatial representation of the external world to guide spatial attention, features of objects such as shape and color seem to migrate to produce illusory conjunctions in perception.

Other spatial maps associated with the temporal lobes has been suggested on the basis of animal research, but if they exist in humans, neuropsychological observation suggests that they are not sufficient to support the normal perception of correctly bound features or their location.. The present paper reports data collected with a patient with bilateral parietal lobe lesions and Balint's syndrome (R.M.) in whom feature binding and location deficits were reported previously (Friedman-Hill, et. al., 1995). The present study first shows that feature binding deficits were still present in this patient and could be observed under the conditions of this experiment. This study then demonstrates that location information exists in R.M.'s visual system below the level of awareness and verifies that a feature can be perceived without explicit awareness of its location.

Balint's syndrome is fortunately quite rare, as it renders a person functionally blind in its classical form. The patients typically see only one shape and can report what it is, but they do not know where it is. They cannot accurately reach for it or track it despite intact primary motor abilities. This problem disrupts activities of every day living such as navigation, dressing, watching TV, reading, eating, etc., and leaves the patient with very few options. Language and other cognitive abilities remain intact. R.M.

presented with the classic Balint's syndrome just described in 1992 but has improved somewhat over time.

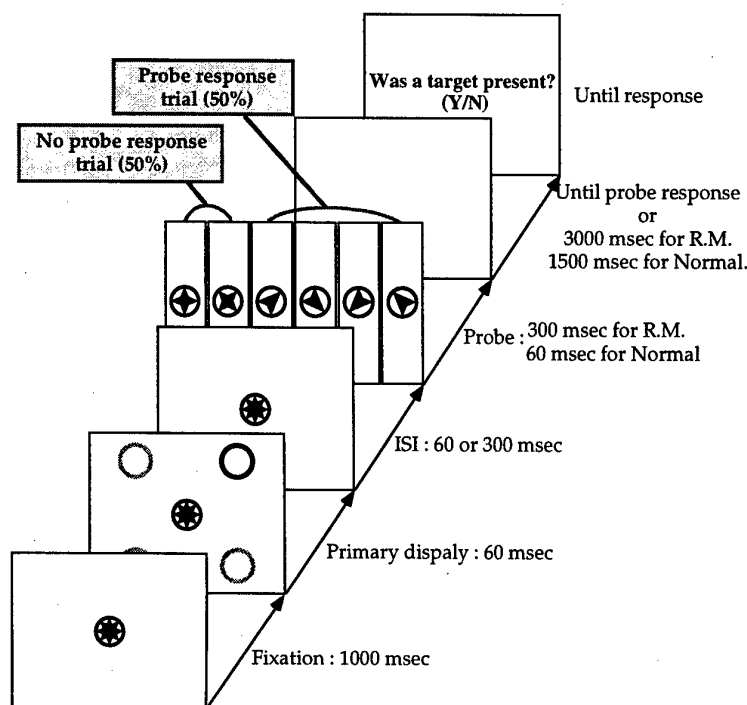


Figure 1. The sequence of displays in feature search with a central arrow probe.

An indirect measure was used to test whether or not spatial information was coded implicitly. Using a probe technique and a dual task, we presented a 4 item feature display containing 1 green circle target and 3 red circle distractors along with a central fixation pattern that changed into an arrow at variable times after the feature display appeared (see Figure 1). Instructions were to press a response key as rapidly as possible when an arrow and to withhold a response if the fixation pattern changed to anything other than an arrow. After their response participants were to report whether the target had been present or not in the feature display by saying yes or no.

Experiments with young normal subjects showed that response times to the arrow were faster when the arrow pointed to the target location than when it pointed to one of the distractor locations even though neither the direction of the arrow nor the location of the search item was necessary to perform either task (Fig. 2a). These results demonstrate that the direction of the arrow probe and its spatial relationship to the location of the target is encoded (probably automatically).

Despite his spatial deficits, R.M. showed a similar pattern of results as normal subjects: when the arrow pointed to the target, he detected the arrow faster than when it pointed to one of the distractors. Surprisingly, R.M. showed this probe RT pattern even when his ability to detect the feature target was very poor (R.M. produced 28% hits and 15% false positives, while normal subjects produced 98% hits and less than 3% false positives) (Fig. 2b). Although R.M. showed great difficulty in correctly reporting the presence of the feature target in this experiment, it may have been because the target faded rapidly from memory or that the dual task directly interfered with the perceptual registration of the target. Whatever the reason for the difficulty in feature detection accuracy, it is clear that the target's **location** and its spatial relationship to the **orientation** of the arrow continued to exert control.

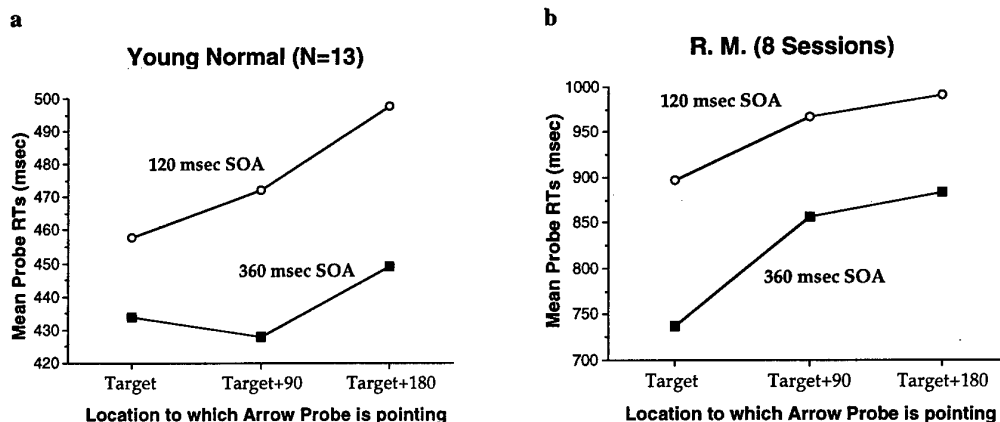


Figure 2. RT results with young normal subjects (a) and R.M. (b). The probe RTs were organized by the direction of the arrow, relative to the target location.

To address the question of whether the spatial relationship between the arrow and the feature was explicitly known, we presented the arrow and the target display simultaneously and they remained on the screen until R.M. responded. In this study, he was simply asked to report whether the arrow pointed at a target or one of the circle distractors. Only target present displays were used. He was unable to do this task above chance (51% accurate). He also reported that this was a difficult task for him and shook his head side to side while performing the task. It should be noted that this was not due to spatial confusions per se. R.M. had full spatial awareness of the location of his own body parts and the spatial relationship between them even when his Balint's symptoms were more severe than at the time of this study.

These results support the existence of separate spatial maps within the human brain that remain intact even when both parietal lobes are damaged. Furthermore, they demonstrate that intact parietal lobes are necessary to explicitly access and utilize this information for the purpose of guiding attention or action to a location. In turn, attention to a location is necessary to properly bind features such as shape and color in cluttered arrays. The present findings are also consistent with electrophysiological data in monkeys for the existence of multiple spatial representations. The evidence presented here supports these observations but also demonstrates that some spatial information can be coded without awareness and is not accessible without intact parietal lobes.

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