姿勢制御と運動学習における最近の知見

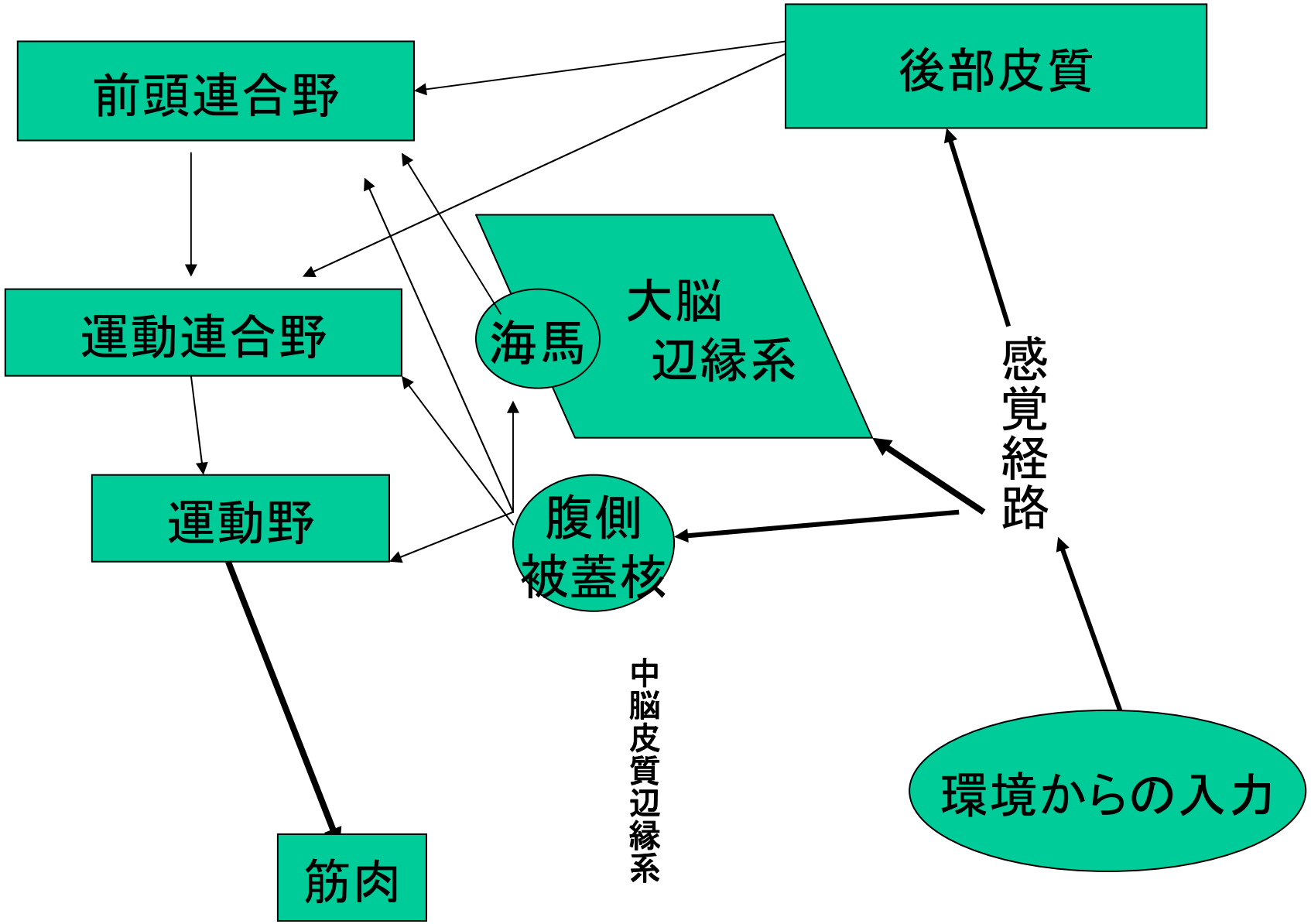
久保田　競

日本ﾎﾞﾊﾞｰｽ研究会
関東甲信越神ブロック合同発表会

会　場：　南大塚ホール

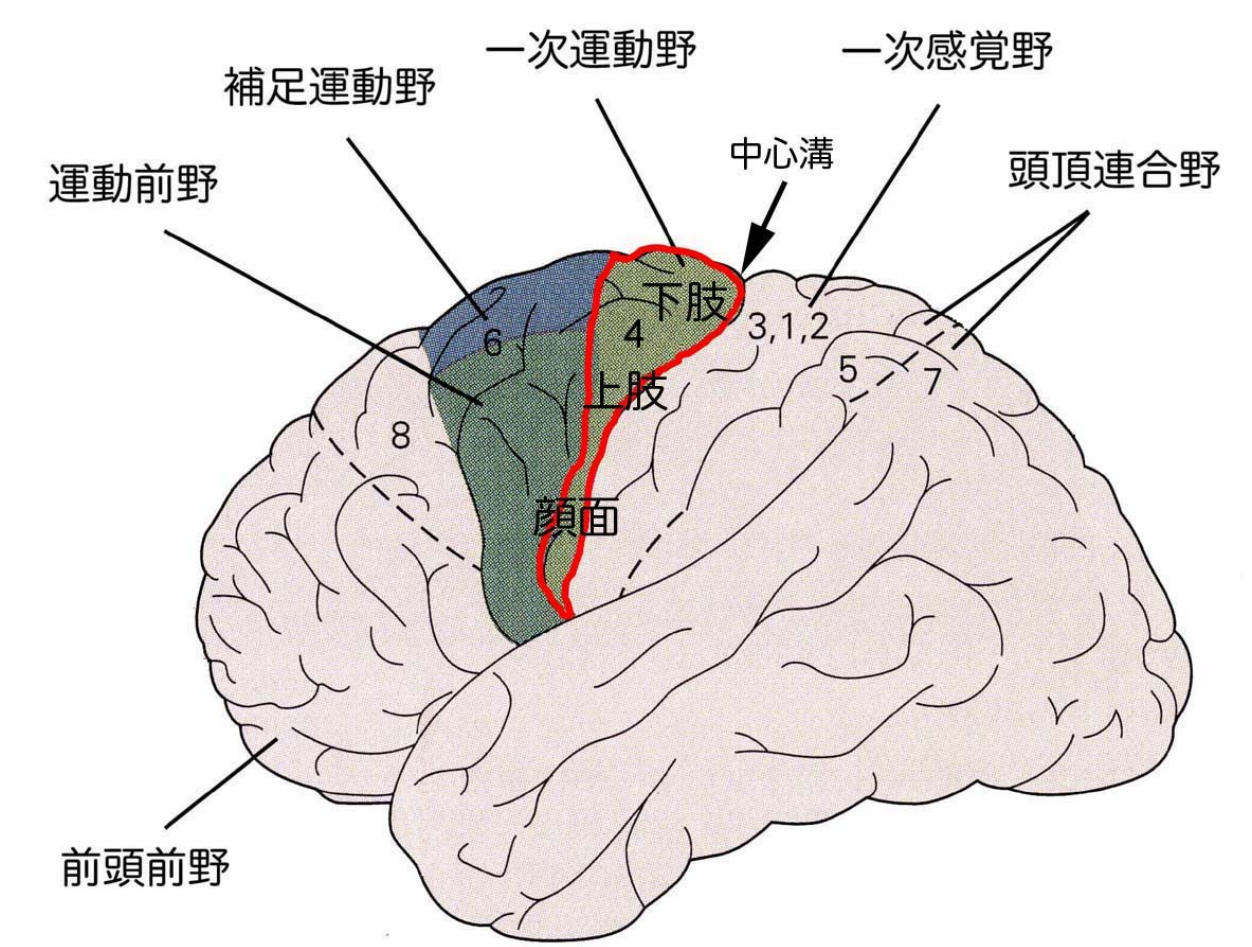
(平成19年2月11日）

行動・運動系



一次運動野と運動前野(運動連合野)

{Motor Area and Premotor Area （Motor Association Area)}



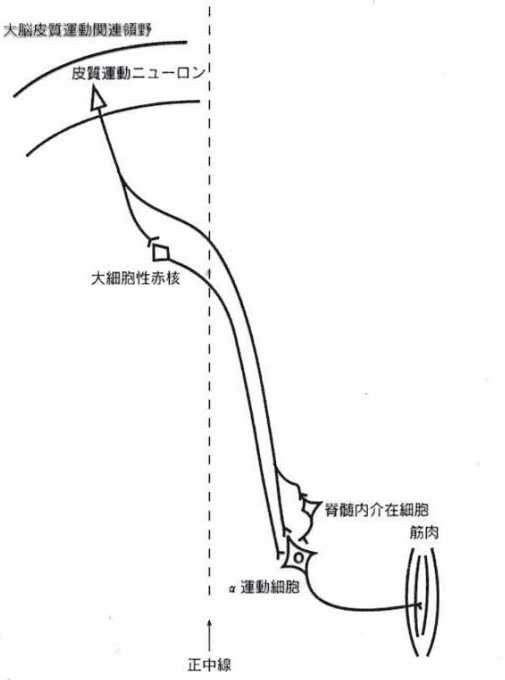


図1 大脳皮質から脊髄のα運動細胞へ投射する経路の模式図
最終運動司令は大脳皮質から直接あるいは赤核や脊髄内介在細胞を経て筋肉を支配するα運動細胞に伝えられる.

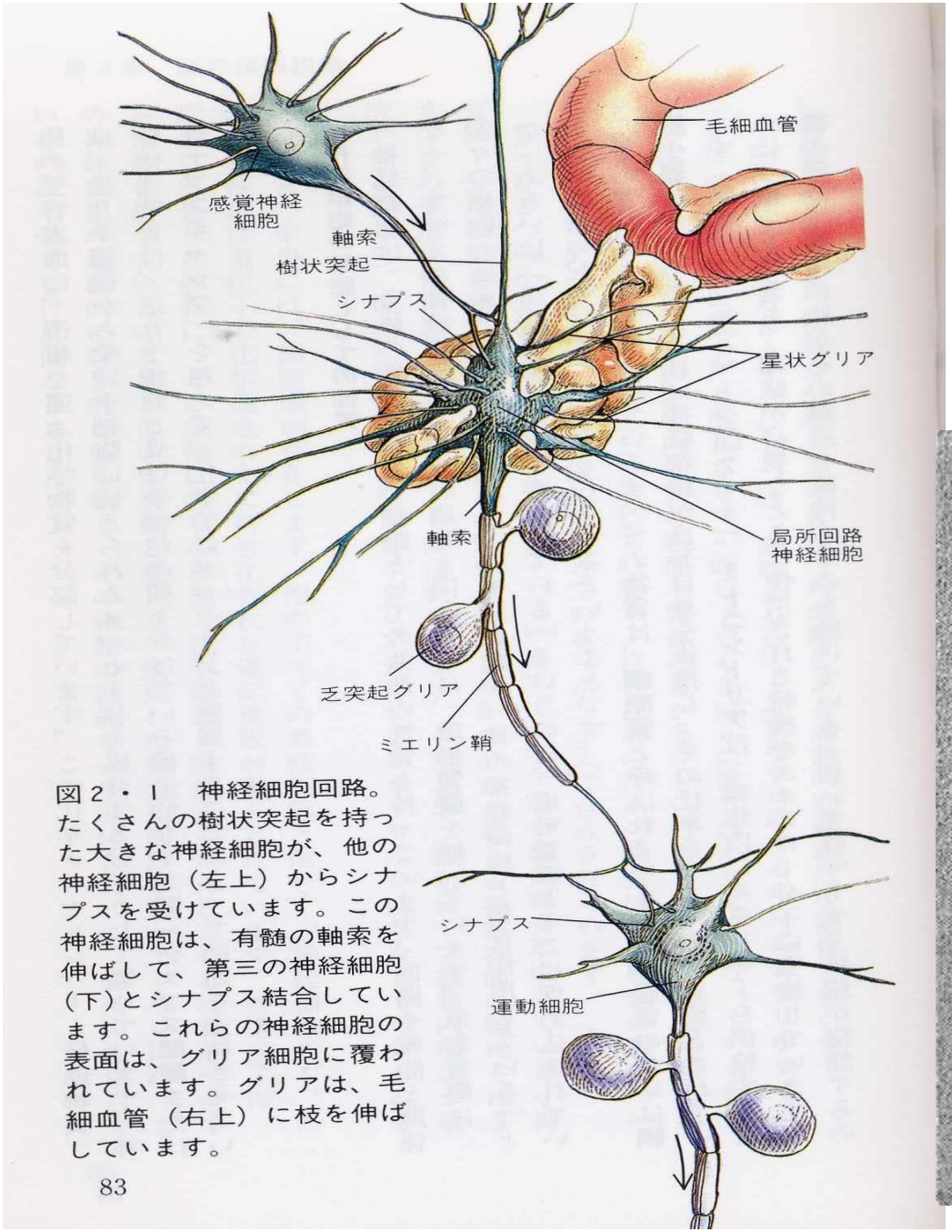
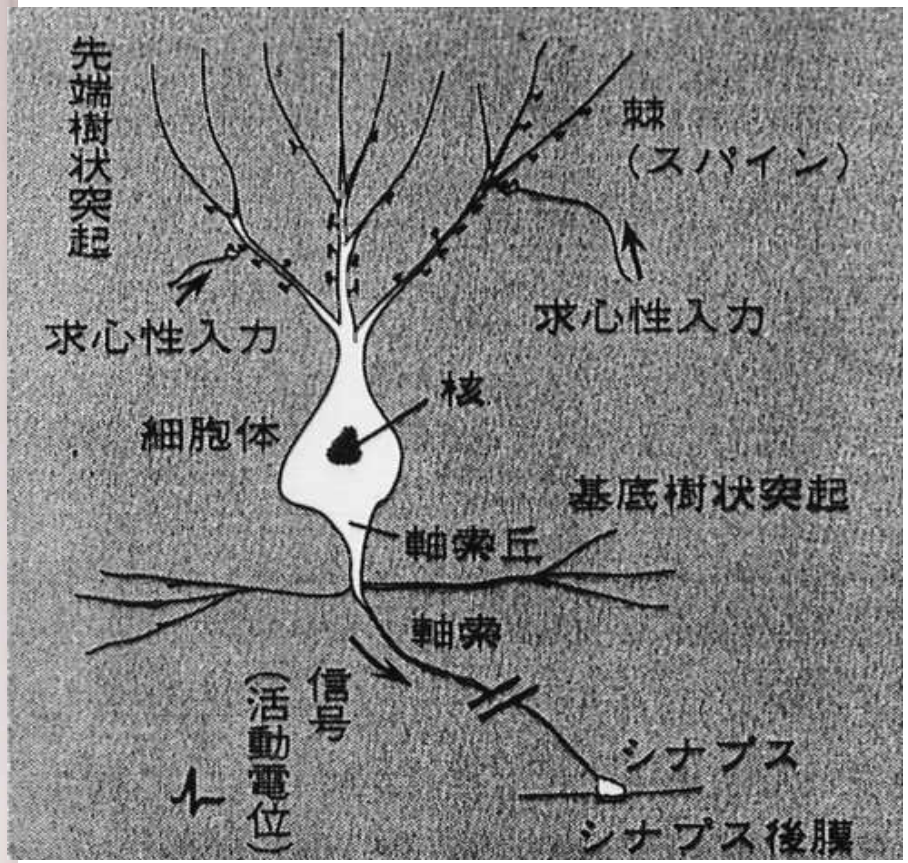
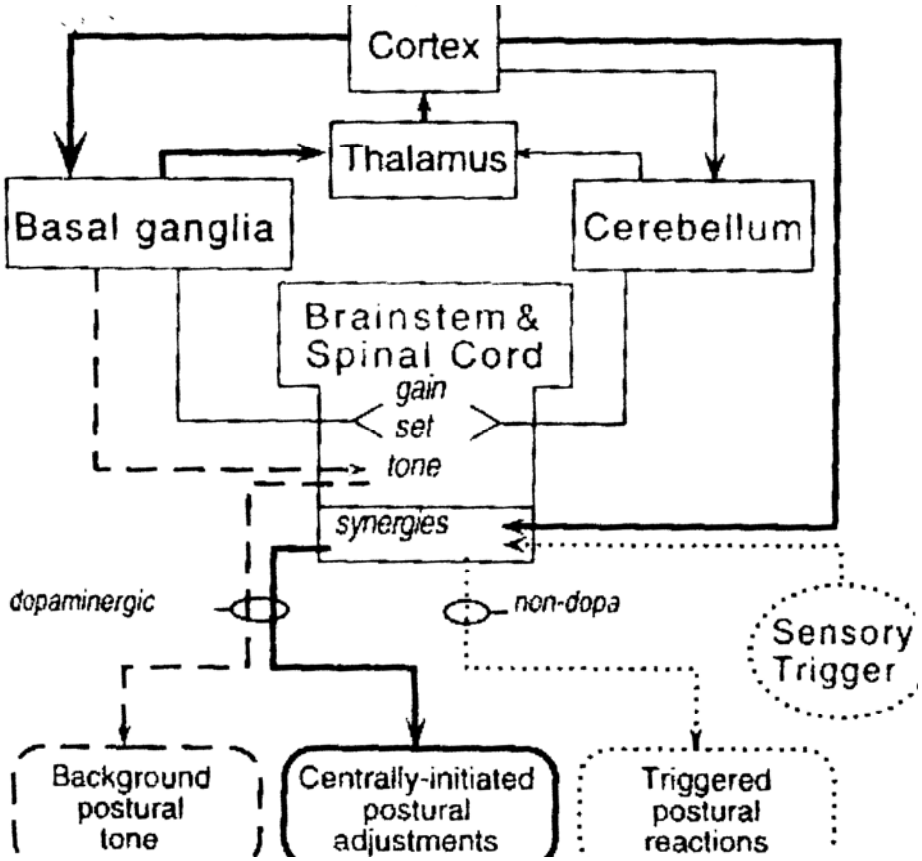


図２・１　神経細胞回路。たくさんの樹状突起を持った大きな神経細胞が、他の神経細胞（左上）からシナプスを受けています。この神経細胞は、有髄の軸索を伸ばして、第三の神経細胞（下）とシナプス結合しています。これらの神経細胞の表面は、グリア細胞に覆われています。グリアは、毛細血管（右上）に枝を伸ばしています。

ニューロン（神経細胞）と　シナプス（継ぎ目）



姿勢調節系と脳


Cortex
Thalamus
Basal ganglia
Cerebellum
Brainstem &
Spinal Cord
gain
set
tone
synergies
dopaminergic
non-dopa
Sensory
Trigger
Background
postural
tone
Centrally-initiated
postural
adjustments
Triggered
postural
reactions

Saccular Projections in the Human Cerebral Cortex

TAMAKI MIYAMOTO,[a] KIKURO FUKUSHIMA,[a] TOSHIHISA TAKADA,[b]
CATHERINE DE WAELE,[c] AND PIERRE-PAUL VIDAL[c]

[a]*Department of Physiology, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan*

[b]*Department of Oral Functional Science, Hokkaido University Graduate School of Dental Medicine, Sapporo, Hokkaido, Japan*

[c]*Laboratoire de Neurobiologie des Réseaux Sensorimoteurs, UMR 7060, CNRS-Paris 5-Paris 7, Paris, France*

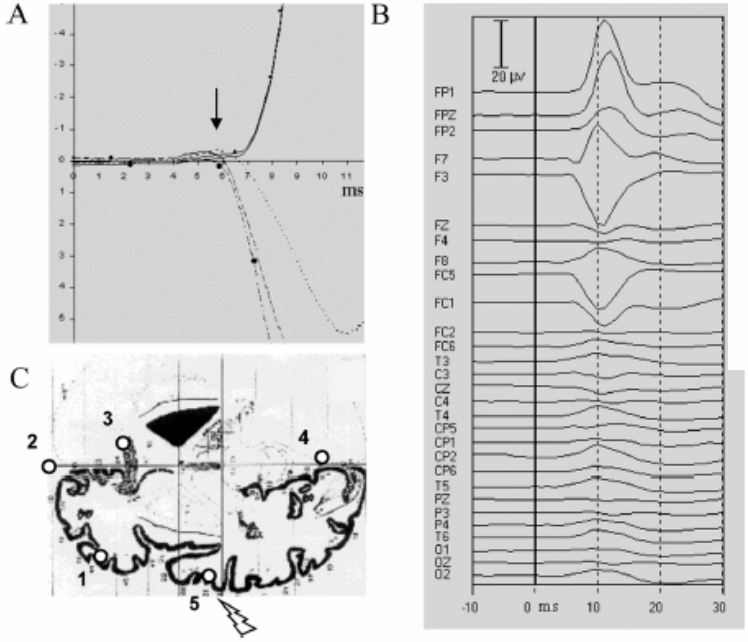


FIGURE 1. Cortical areas activated by electrical stimulation of the vestibular nerve in volunteer patients under anesthesia. (**A**) Latencies of the SLVEPs for the ipsilateral frontal activation (FP1, FC1, FPZ, F3, and FC5). Note that the mean 6- to 7-ms latency to the onset of the response (*arrow* at 2 SD above noise level). (**B**) SLVEPs following stimulation of the left vestibular nerve. The averaged voltages are issued from the pooled data of five curarized Ménière's disease patients (ordinates, amplitude in microvolts). (**C**) Electrical source dipole analysis on the grand average. Dipoles are localized at the limit of the ipsilateral frontal and prefrontal cortex (1); on the transverse frontopolar and/or frontomarginal gyrus of the prefrontal cortex, close to the midline (2); on the contralateral anterior portion of the SMA (3); on the contralateral superior occipital gyrus (4); and on the ipsilateral temporoparietal area (5). (Reproduced with permission and modified from de Waele *et al.*[15])

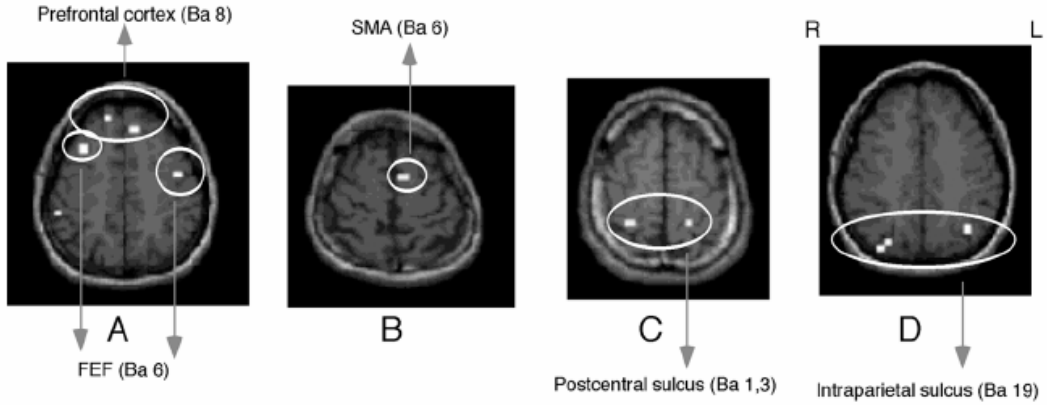
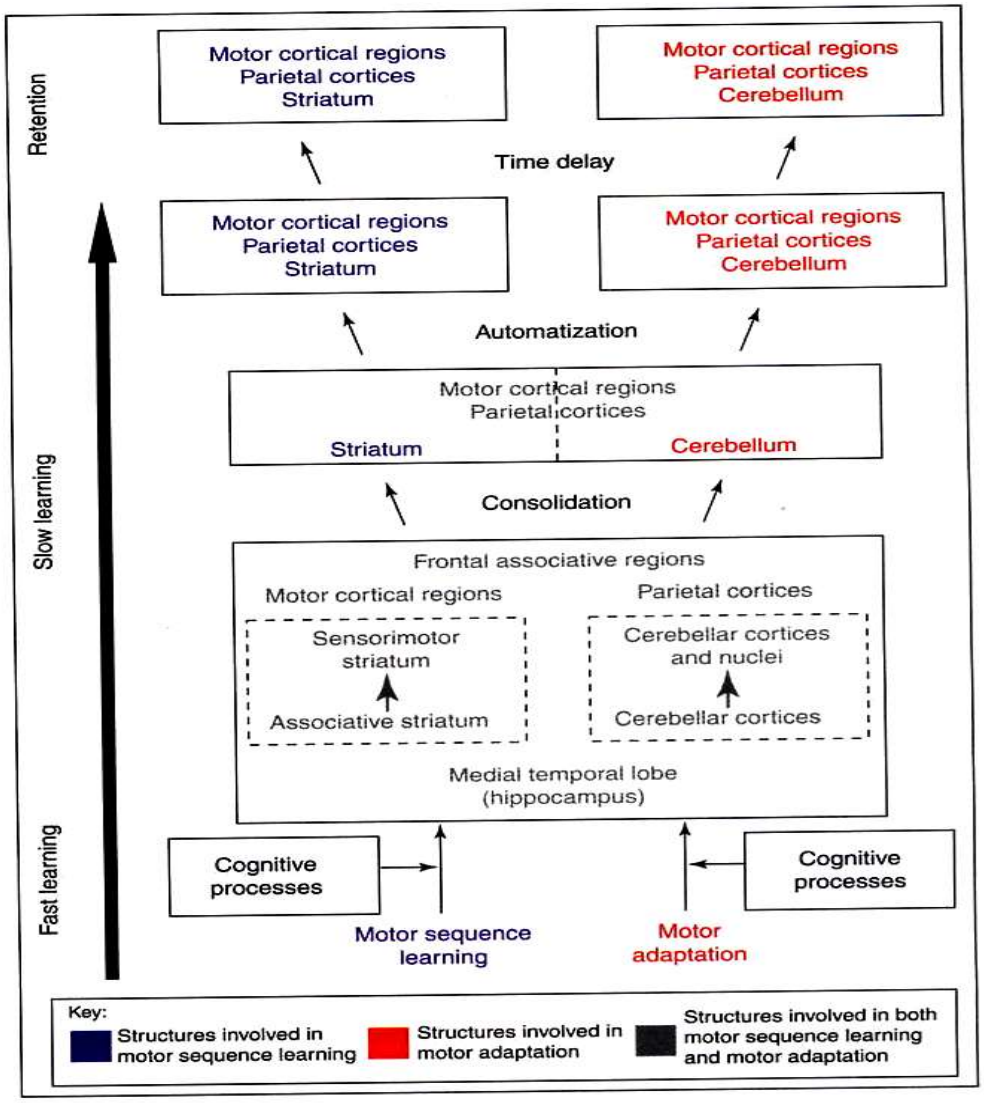


FIGURE 2. Cortical areas activated by 102-dB clicks revealed by fMRI. (**A**) Activation in prefrontal cortex (Brodmann's area, BA 8); anterior part of the superior frontal gyrus and FEF (BA 6) in the middle frontal gyrus (*right*) and the precentral gurus (*left*). (**B**) Activation in SMA (BA 6) in the medial part of superior frontal gyrus. (**C**) Activation in postcentral sulcus (BA 1, 3). (**D**) Activation in posterior part of intraparietal sulcus (BA 19). R and L indicate right and left, respectively.



Reorganization and plasticity in the adult brain during learning of Motor skills

Julien Doyon and Habib Benali

Current opinion in Neurobiology 2005,

15;161-167

Revised model of Doyon and Ungerleider (2002)

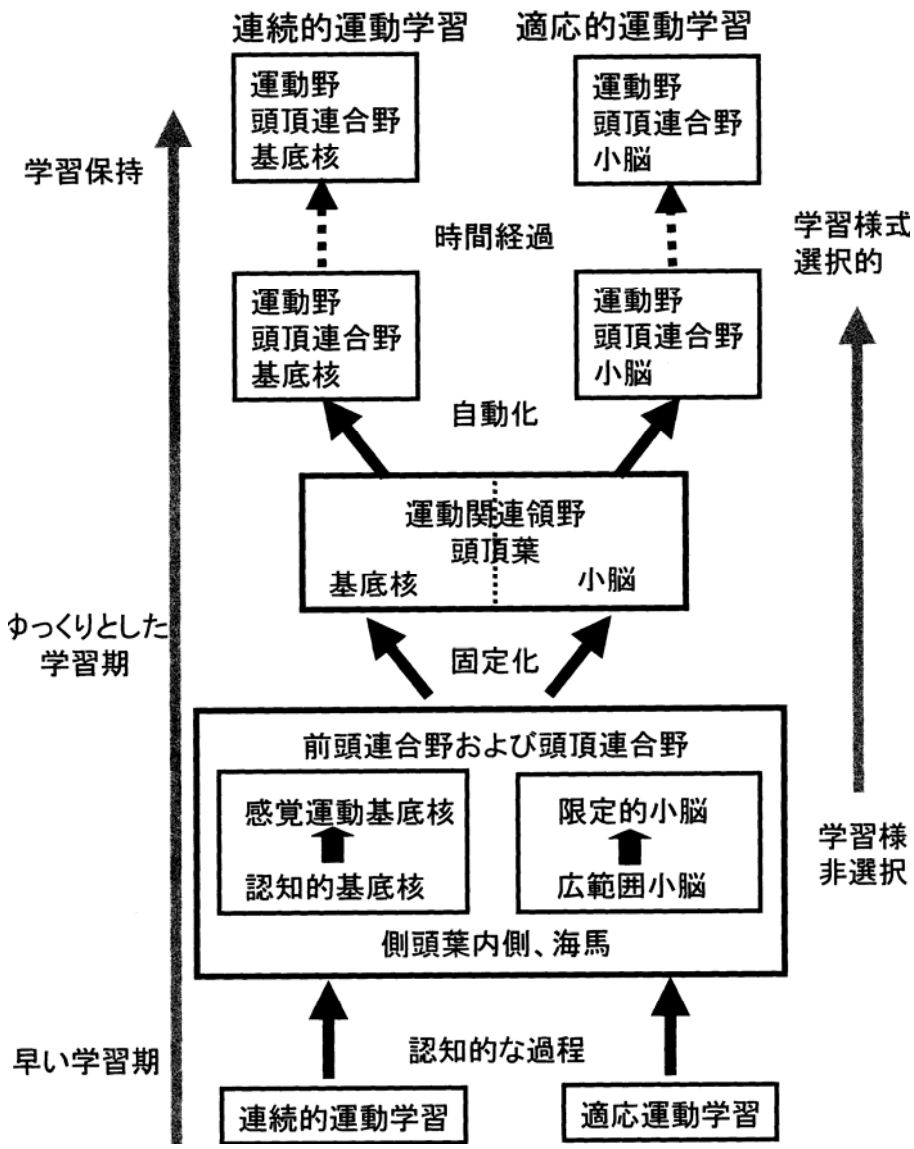
1: fast (early) learning stage(single session)

2: slow (later) stage (several sessions)

3: consolidation stage (6> hrs)

4: automatic stage (less skill, resistent ,time delay)

5: retention stage


連続的運動学習
適応的運動学習
運動野
頭頂連合野
基底核
運動野
頭頂連合野
小脳
学習保持
時間経過
学習様式
選択的
運動野
頭頂連合野
基底核
運動野
頭頂連合野
小脳
自動化
運動関連領野
頭頂葉
基底核
小脳
ゆっくりとした
学習期
固定化
前頭連合野および頭頂連合野
感覚運動基底核
認知的基底核
限定的小脳
広範囲小脳
学習様
非選択
側頭葉内側、海馬
早い学習期
認知的な過程
連続的運動学習
適応運動学習

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NeuroImage 27 (2005) 505 – 519

Brain activation during execution and motor imagery of novel and skilled sequential hand movements

Michael G. Lacourse,[a,c,*] Elizabeth L.R. Orr,[a,c] Steven C. Cramer,[e] and Michael J. Cohen[b,d]

[a]Neuromotor Rehabilitation Research Laboratory, Long Beach Veteran's Affairs Healthcare System, CA 90822, USA
[b]Neuroimaging Research Laboratory, Long Beach Veteran's Affairs Healthcare System, CA 90822, USA
[c]Department of Kinesiology, California State University, Long Beach, CA 90801, USA
[d]Department of Psychiatry and Human Behavior, University of California, Irvine, CA 92697, USA
[e]Department of Neurology, University of California, Irvine, CA 92697, USA

Received 7 July 2004; revised 29 March 2005; accepted 4 April 2005
Available online 19 July 2005

This experiment used functional magnetic resonance imaging (fMRI) to compare functional neuroanatomy associated with executed and imagined hand movements in novel and skilled learning phases. We hypothesized that 1 week of intensive physical practice would strengthen the motor representation of a hand motor sequence and increase the similarity of functional neuroanatomy associated with executed and imagined hand movements. During fMRI scanning, a right-hand self-paced button press sequence was executed and imagined before (NOVEL) and after (SKILLED) 1 week of intensive physical practice (n = 54; right-hand dominant). The mean execution rate was significantly faster in the SKILLED (3.8 Hz) than the NOVEL condition (2.5 Hz) ($P < 0.001$), but there was no difference in execution errors. Activation foci associated with execution and imagery was congruent in both the NOVEL and SKILLED conditions, though activation features were more similar in the SKILLED versus NOVEL phase. In the NOVEL phase, activations were more extensive during execution than imagery in primary and secondary cortical motor volumes and the cerebellum, while during imagery activations were greater in the striatum. In the SKILLED phase, activation features within these same volumes became increasingly similar for execution and imagery, though imagery more heavily activated premotor areas, inferior parietal lobe, and medial temporal lobe, while execution more heavily activated the precentral/postcentral gyri, striatum, and cerebellum. This experiment demonstrated congruent activation of the cortical and subcortical motor system during both novel and skilled learning phases, supporting the effectiveness of motor imagery-based mental practice techniques for both the acquisition of new skills and the rehearsal of skilled movements.

Keywords: Brain activation; Hand movement; Motor imagery

PUSH; 4Hz

4－2－3－1－3－4－2, button press

NOVEL vs SKILLED

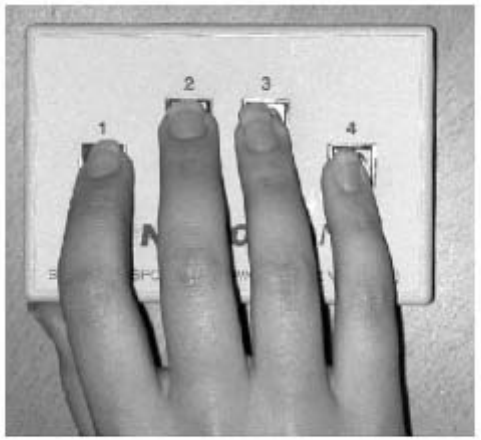


Fig. 1. Neuroscan button box used for hand motor sequence.

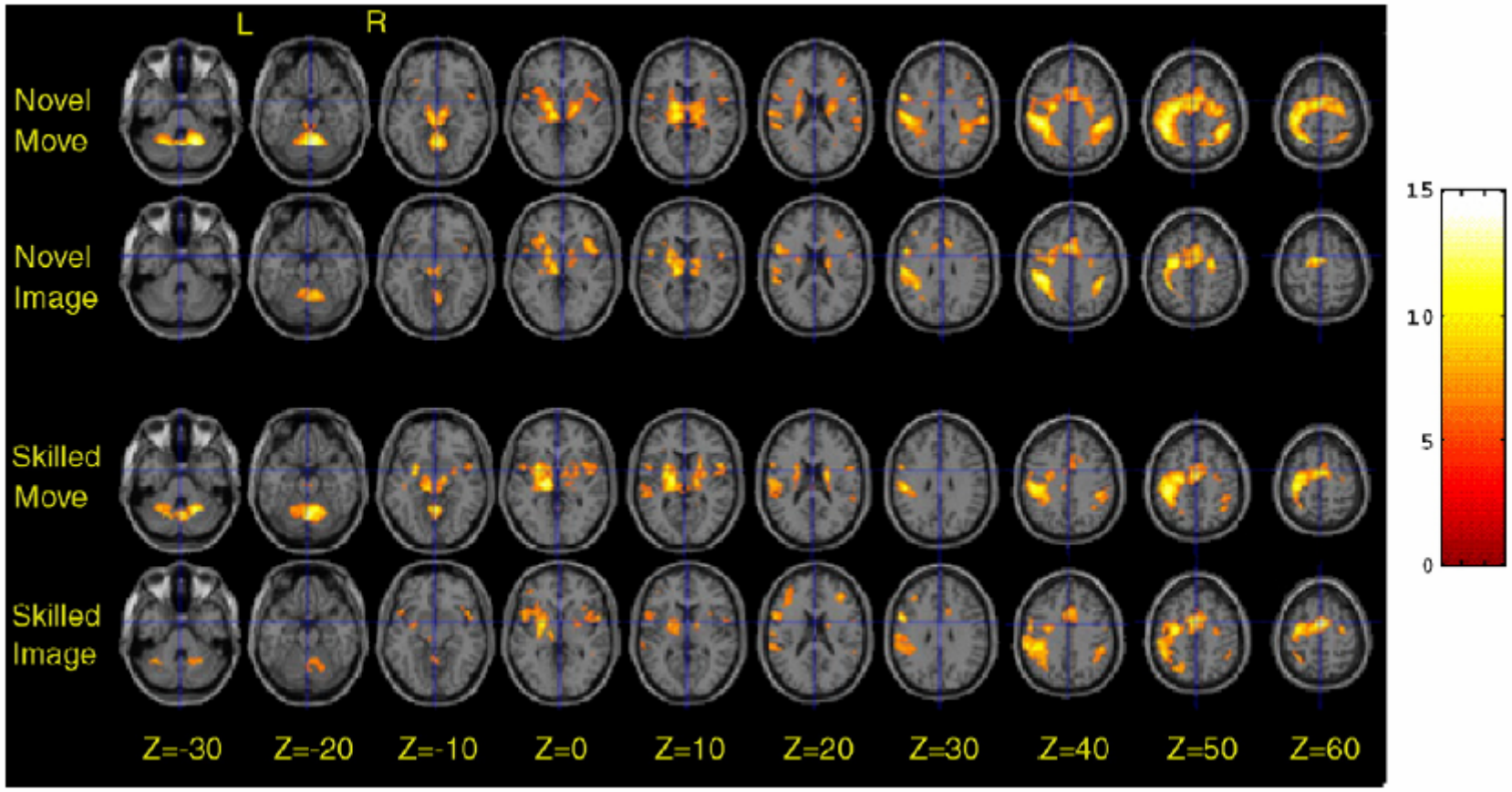
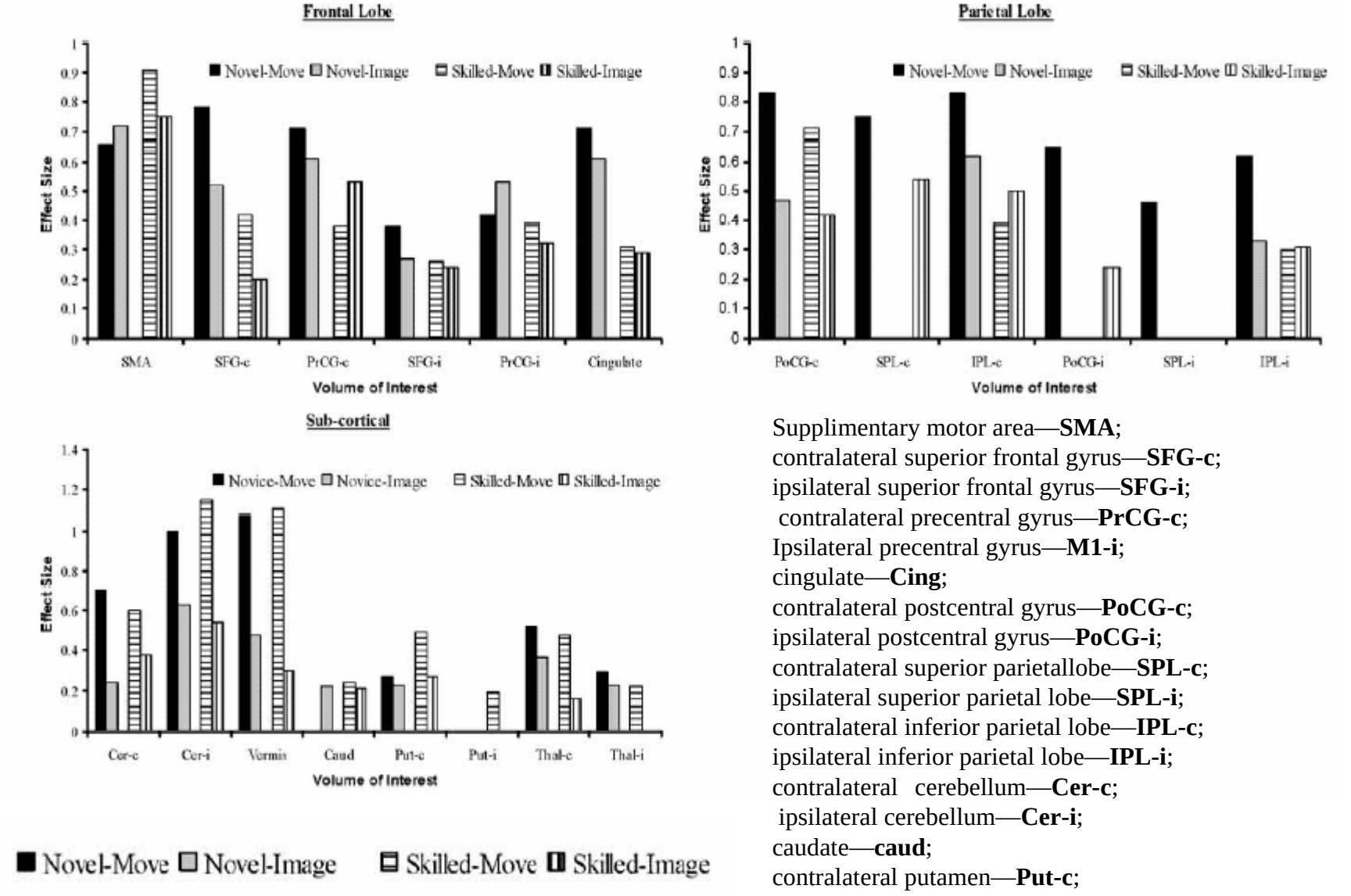


Fig. 4. Statistically significant activation maps using one-sample t test ($n = 54$), shown by condition and incremental z levels. The cluster threshold was set at $P < 0.001$, whole brain corrected with an extent threshold of 5 voxels and a threshold t statistic of 6.5. Crosshairs are centered at (0,0). Image shown per neurological convention: L, left hemisphere; R, right hemisphere.

Effective size: Effect size of the local maxima within volumes of interest during NOVICE and SKILLED execution and motor imagery.

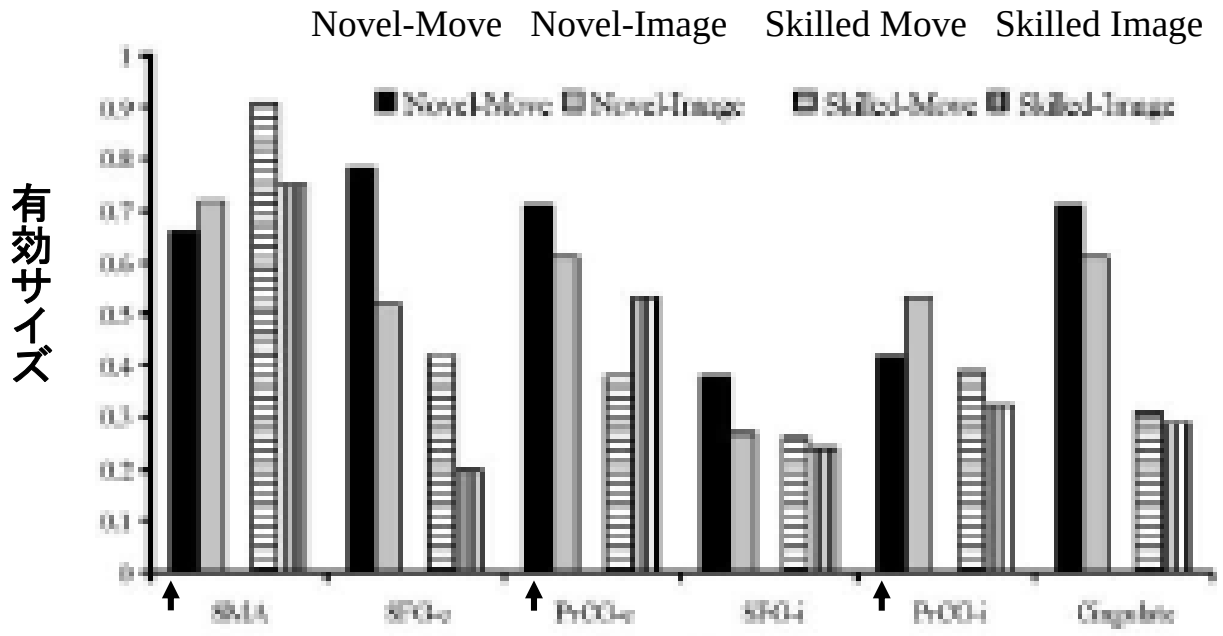


Supplimentary motor area—**SMA**;
contralateral superior frontal gyrus—**SFG-c**;
ipsilateral superior frontal gyrus—**SFG-i**;
contralateral precentral gyrus—**PrCG-c**;
Ipsilateral precentral gyrus—**M1-i**;
cingulate—**Cing**;
contralateral postcentral gyrus—**PoCG-c**;
ipsilateral postcentral gyrus—**PoCG-i**;
contralateral superior parietallobe—**SPL-c**;
ipsilateral superior parietal lobe—**SPL-i**;
contralateral inferior parietal lobe—**IPL-c**;
ipsilateral inferior parietal lobe—**IPL-i**;
contralateral cerebellum—**Cer-c**;
ipsilateral cerebellum—**Cer-i**;
caudate—**caud**;
contralateral putamen—**Put-c**;
ipsilateralputamen—**Put-i**;
contralateral thalamus—**Thal-c**;
ipsilateral thalamus—**Thal-i**.

Novel-M; c-M1,S1 & PMv, c,i-SMA ↑

Novel-Image; same areas, less

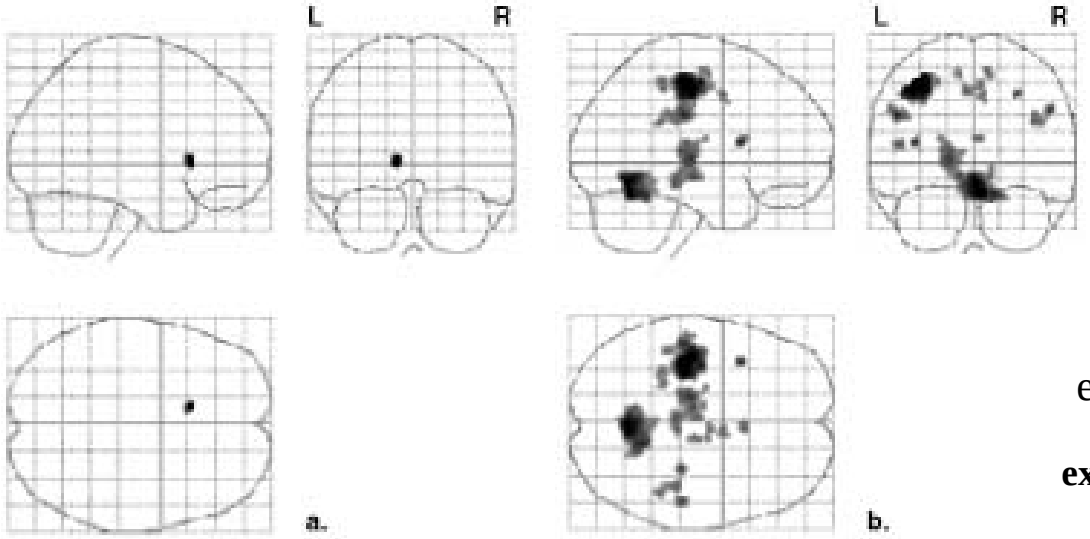
Skilled-M; i- homogous Skilled-M; c>i



Novel condition

i>e

imagery



SMA,Cingulate,c-M1

e>i

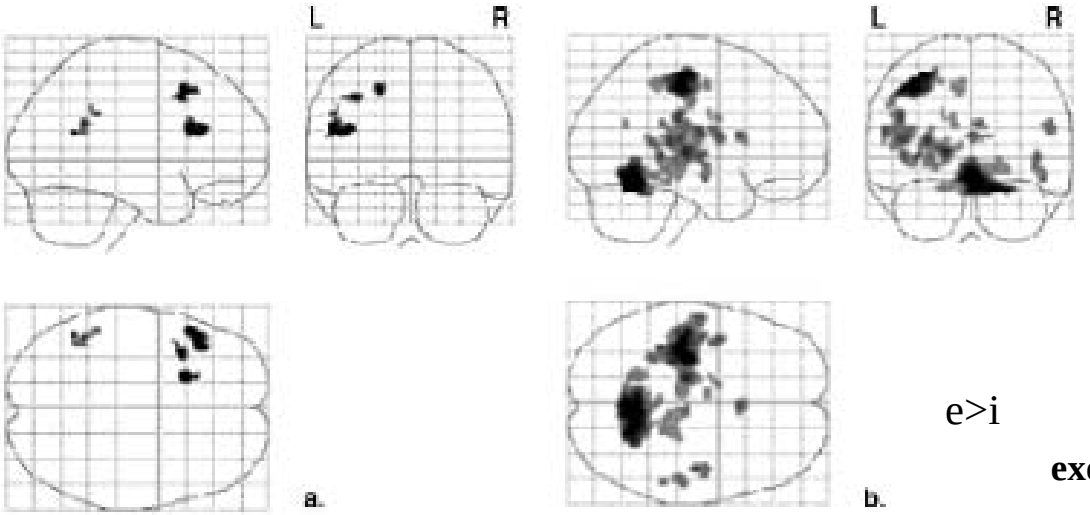
execution

Fig. 6. The glass brain projections represent the statistical parametric map ($P < 0.001$ uncorrected) of regions showing greater activation during imagery versus execution (a) and execution greater than imagery (b) in the novel condition (height threshold = 3.25, extent threshold = 10 voxels, $df = 53$).

Skilled condition

i>e

imagery



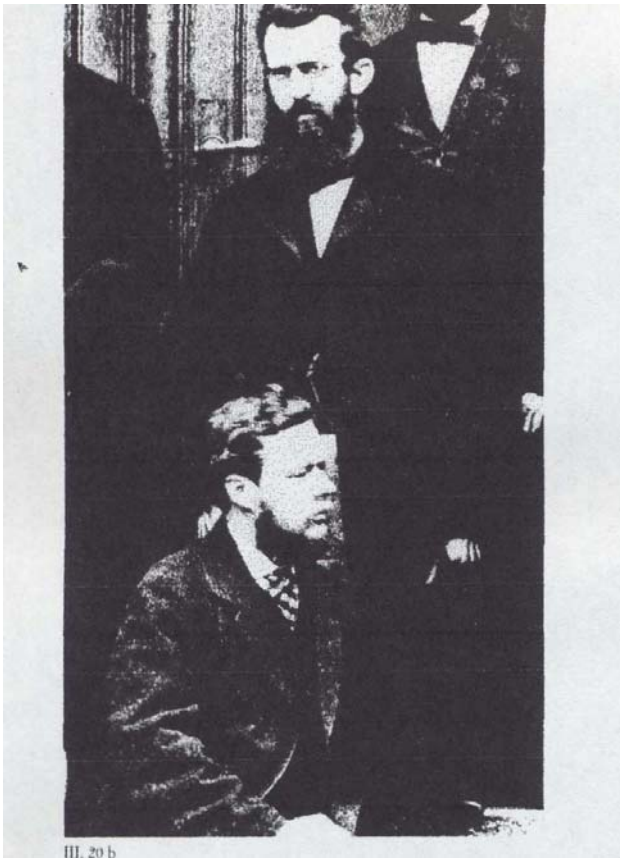
Pc, pre-, post-, SMA, SPL

e>i

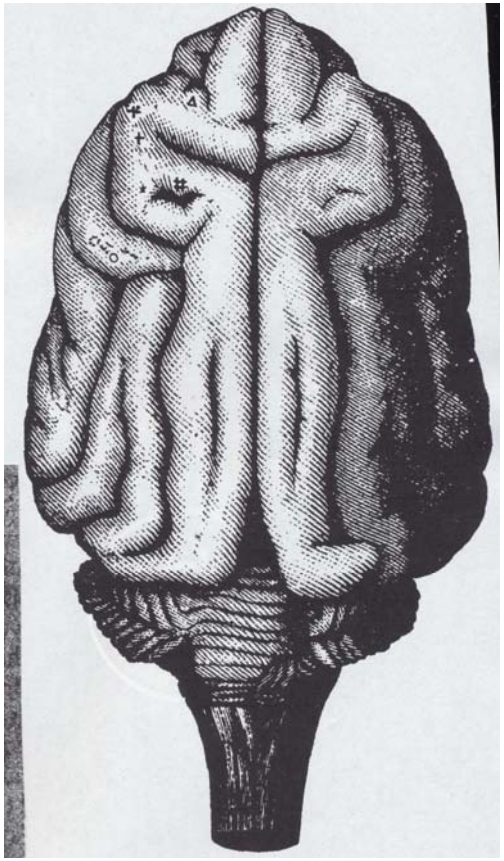
execution

Fig. 7. The glass brain projections represent the statistical parametric map ($P < 0.001$ uncorrected) of regions showing greater activation during imagery versus execution (a) and execution greater than imagery (b) in the skilled condition (height threshold = 3.25, extent threshold = 10 voxels, $df = 53$).

G. Fritsch und J. E. Hitzig, Uber die elektrische Erregbarheit des Grosshirns. (Arch.f. Anat. Physiol. u wiss. Med., 1870, 330–332)



Fritsch und Hitzig



運動野の発見（イヌ）

Gustav Theodor Fritsch

(1838-1927)

isual tracking and neuron activity in the post-arcuate ea in monkeys*

KUBOTA and I. HAMADA

mate Research Institute, Kyoto University, Inuyama City, Aichi, 484, Japan

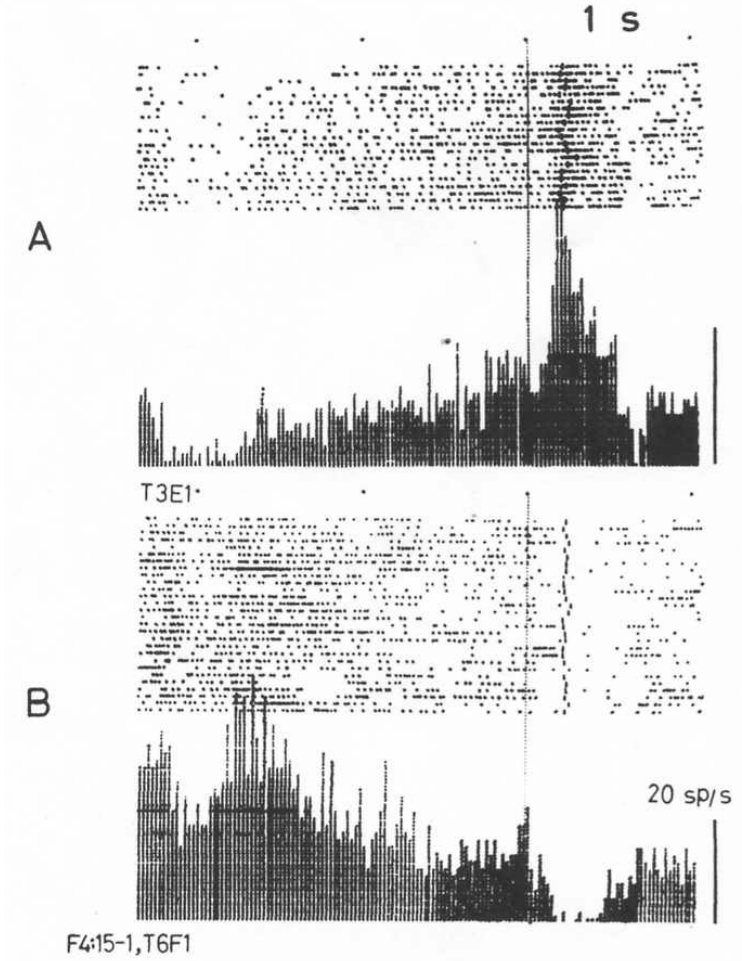


FIG. 10. — *Dot displays and averaged histograms during preparatory periods from an extension type FB neuron.*
A : extension task (22 trials). B : flexion task (28 trials). In dot displays spike activity was sampled every 5 ms and in histograms each bar represented spike numbers every 25 ms. Vertical lines indicate go signal onset. There were 2 s preparatory periods.

運動前野が運動調節に関与するという報告－－－

セレンデイップな発見（1969年夏）

J. Physiol., Paris, 1978, 74, 297-312
Symposium Pyramidal micro-connexions and motor control.
Marseille, July 1977.

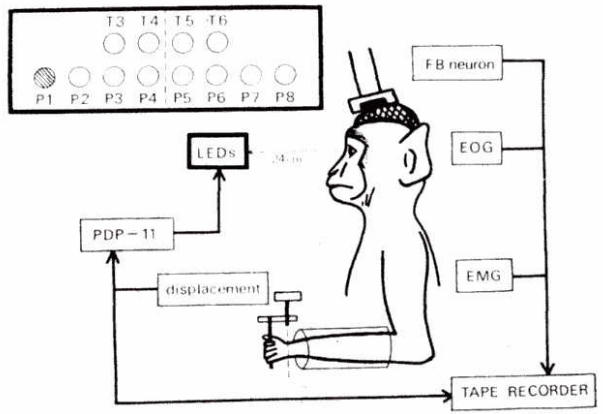


FIG. 1. — *Experimental arrangement and a front panel with LEDs.*

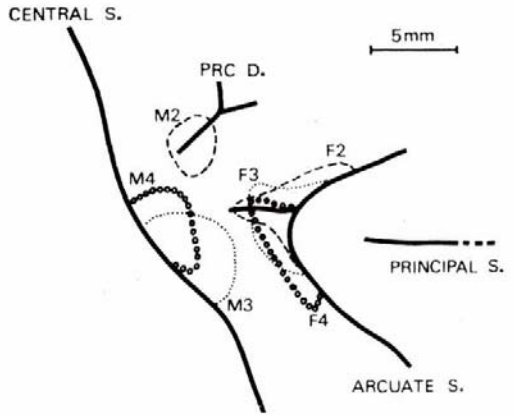


FIG. 2. — *The cortical area where FB neurons were sampled.*

Differential Fronto-Parietal Activation Depending on Force Used in a Precision Grip Task: An fMRI Study

H. HENRIK EHRSSON,[1,2] ANDERS FAGERGREN,[1] AND HANS FORSSBERG[1]
[1]*Motor Control Laboratory, Department of Woman and Child Health and* [2]*Division of Human Brain Research, Department of Neuroscience, Karolinska Institutet, 171 77 Stockholm, Sweden*

Received 13 October 2000; accepted in final form 9 February 2001

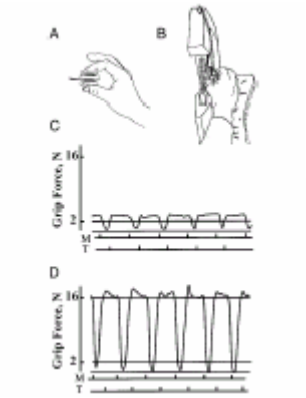


FIG. 1. The precision grip task. The same posture of the hand was adopted in all conditions (*A*); a small handle was grasped between the pulps of the index finger and the thumb with the arm being supported up to the radial side of the hand so that force could be generated practically without movement of the digits, wrist, or arm (*B*). *C* and *D*: a representative force recording from 1 subject while he performed the precision grip task in the small force condition (*C*) and in the large force condition (*D*). Note that the same time course of grip forces was generated in both conditions, only the force was different. In the task (for both force levels), a weak brief vibration was delivered though the handle to signal that the force of 2 N (in small) or 16 N (in large) had been reached (T). The subjects then applied a self-selected static grip force slightly above this force threshold. The pace of the force cycles followed metronome beats (M). For details, see METHODS.

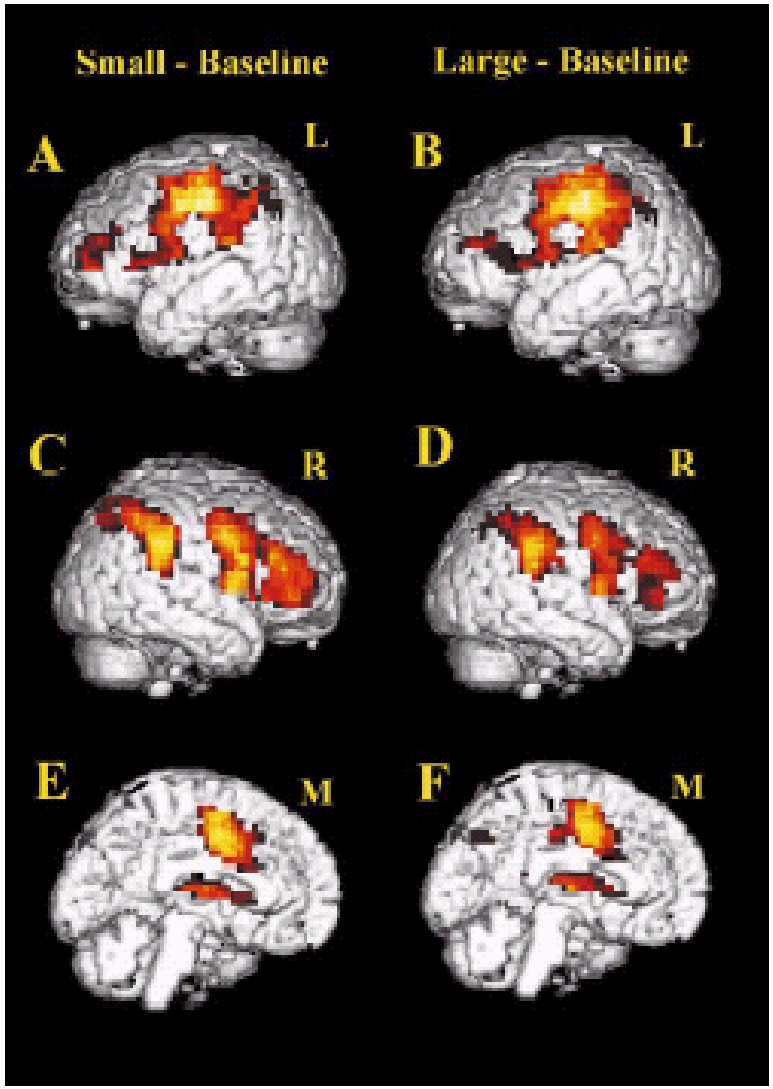
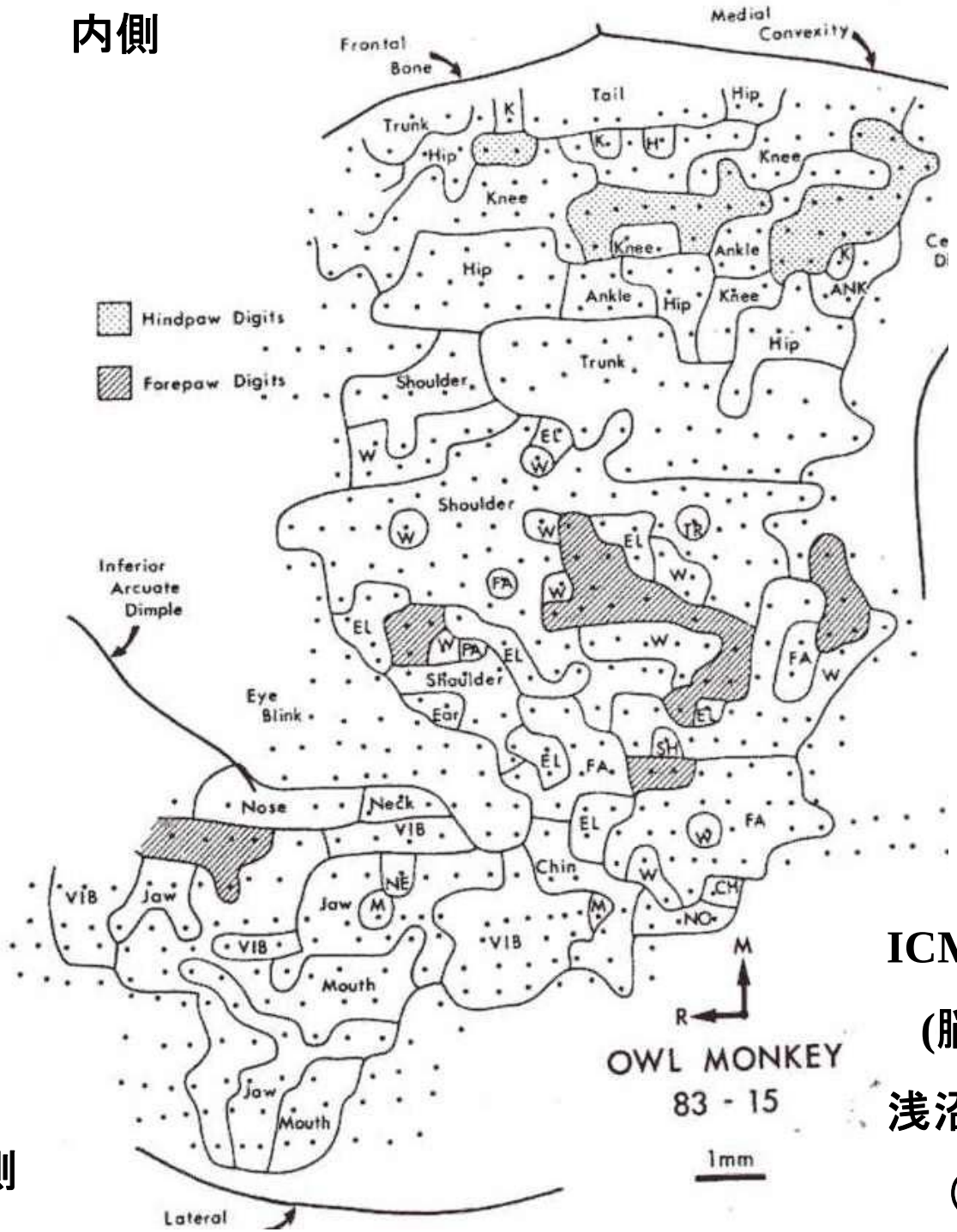


FIG. 3. Brain regions that were significantly activated during the small force condition (*left*, *A*, *C*, and *E*) and the large force condition (*right*, *B*, *D*, and *F*) in comparison with the baseline condition ($P < 0.05$ after correction for multiple comparisons). Both force conditions were associated with very similar activation patterns in the frontal and parietal lobes (the same areas as were detected in the main effect analysis, see Fig. 2 and Table 1). *A* and *B* (the left hemisphere) and *C* and *D* (the right hemisphere): the bilateral activations of the dorsal and ventral premotor cortex (PMD and PMV), parietal operculum (PO), posterior parietal regions (intraparietal cortex and supramarginal cortex), and the ventral prefrontal cortex for both force conditions. The clusters of active voxels overlapped with area 44 and 45 on both hemispheres. *E* and *F* (the medial wall): the activation of supplementary motor area (SMA), rostral cingulate motor area (CMAr), and the thalamus (represented on the medial wall on this 3-dimensional reconstruction) during both conditions. A stronger activation in caudal CMA (CMAc) was seen when the larger forces were generated. The cerebellum was outside the field of view. See Table 1 for details.

内側

後肢の指

前肢の指



ヨザルの運動野「左」

前側

後側

外側

ICMS

(脳内自己刺激)

浅沼広と酒田英夫

(1957)

Contribution of the Monkey Corticomotoneuronal Syste to the Control of Force in Precision Grip

M. A. MAIER, K. M. B. BENNETT, M.-C. HEPP-REYMOND, AND R. N. LEMON
Department of Anatomy, Cambridge University, Cambridge CB2 3DY, United Kingdom; and Brain Research Institute, CH-8069 Zürich, Switzerland

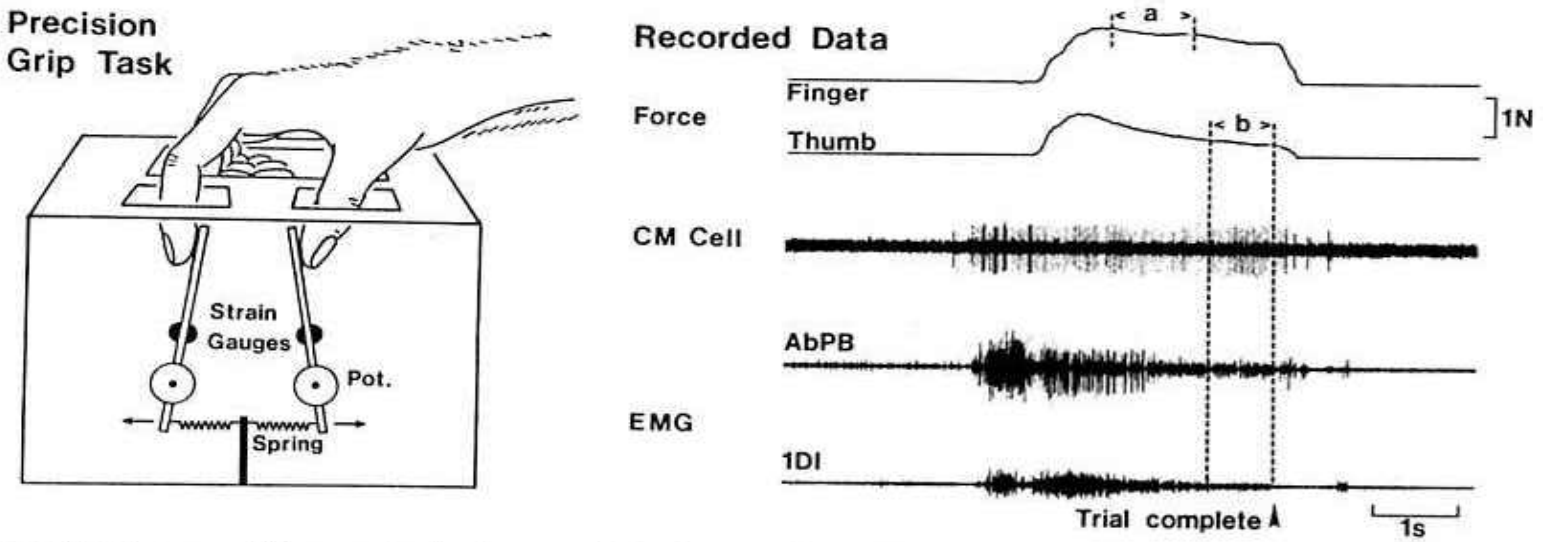


FIG. 1. *Left*: schematic diagram of the manipulandum used for the precision grip task. Actual dimensions of the digit levers are given in the text. For the isometric task, both thumb and index levers were clamped, and the forces exerted registered by the strain gauges shown. For the auxotonic task, the levers moved freely on the shaft of a potentiometer and were spring loaded as shown. *Right*: records of raw data from 1 trial of isometric precision grip. From *top*, records show forces registered by strain gauges in the finger and thumb levers, spike activity of a single identified corticomotoneuronal (CM) cell, and multiunit electromyograms (EMG) recorded from a thumb muscle (abductor pollicis brevis, AbPB) and an index finger muscle (1st dorsal interosseous, 1DI). The selection of typical force segments is indicated (a and b). For segment b the corresponding segment of CM cell and EMG activity is shown by the dotted lines.

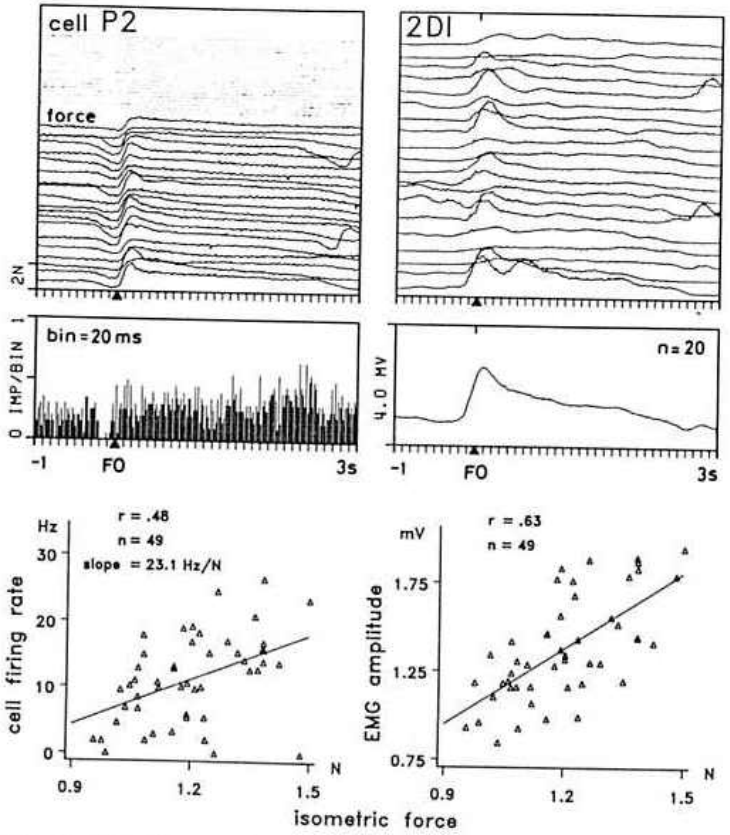


FIG. 3. Data for a corticomotoneuronal cell (*P2*) that increased its firing rate with isometric finger force. *Left, top* to *bottom*: raster of cell discharge with corresponding force traces (index finger) for 20 out of 57 trials, periresponse time histogram (PETH), and scatter diagram of the mean firing rate as a function of mean force from 49 chosen force segments (see Fig. 1). *Right, top* to *bottom*: rectified and smoothed EMG activity of a target muscle (2nd dorsal interosseous, 2DI) for the same 20 trials, periresponse average and scatter diagram of mean EMG activity as a function of the mean force of the same segments shown on *left*. Arrow (FO) indicates the onset of force production. Display time, 4 s. *r*, regression coefficient; *n*, number of data segments; slope, rate-force slope in Hz/N. In the PETH, the ordinate plots spikes/20-ms bin averaged over 20 trials.

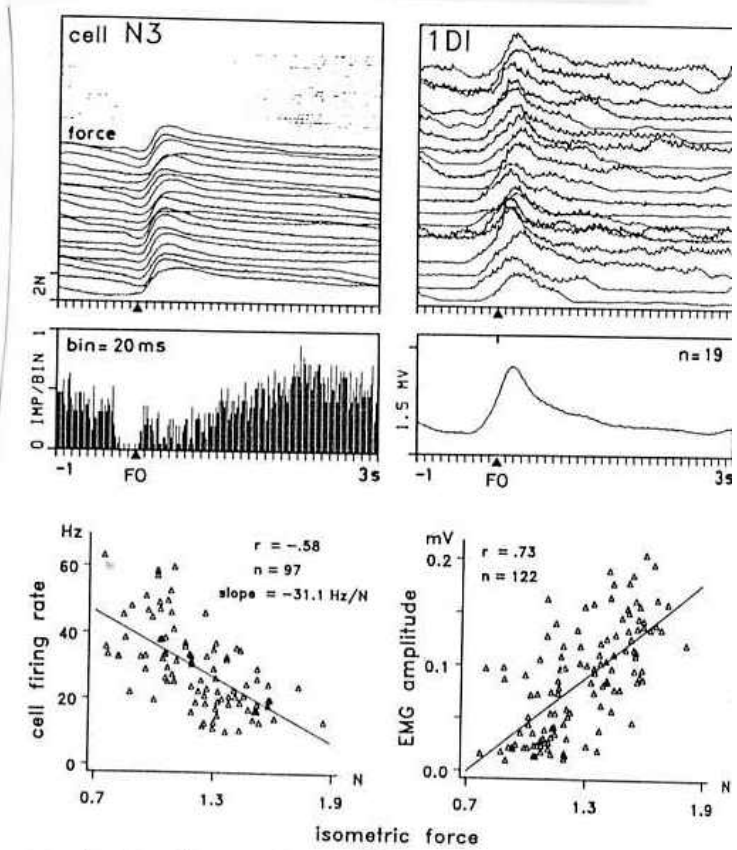
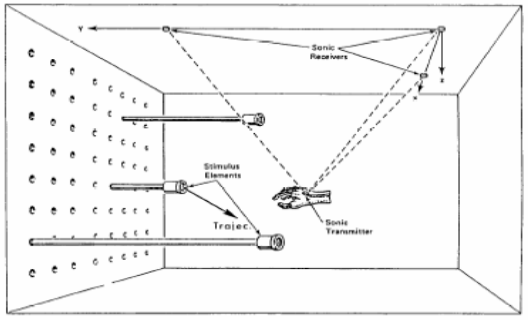


FIG. 4. Data for a corticomotoneuronal cell (*N3*) that decreased i firing rate with isometric finger force. Results are presented in the sam format as Fig. 3. Of 58 trials, 19 are displayed. 1DI, 1st dorsal interosseou

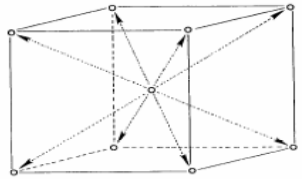
Primate Motor Cortex and Free Arm Movements to Visual Targets in Three-Dimensional Space. I. Relations Between Single Cell Discharge and Direction of Movement

Andrew B. Schwartz,[a] Ronald E. Kettner,[b] and Apostolos P. Georgopoulos

The Philip Bard Laboratories of Neurophysiology, Department of Neuroscience, The Johns Hopkins University, School of Medicine, Baltimore, Maryland 21205



A



gram of the
et lights.

B

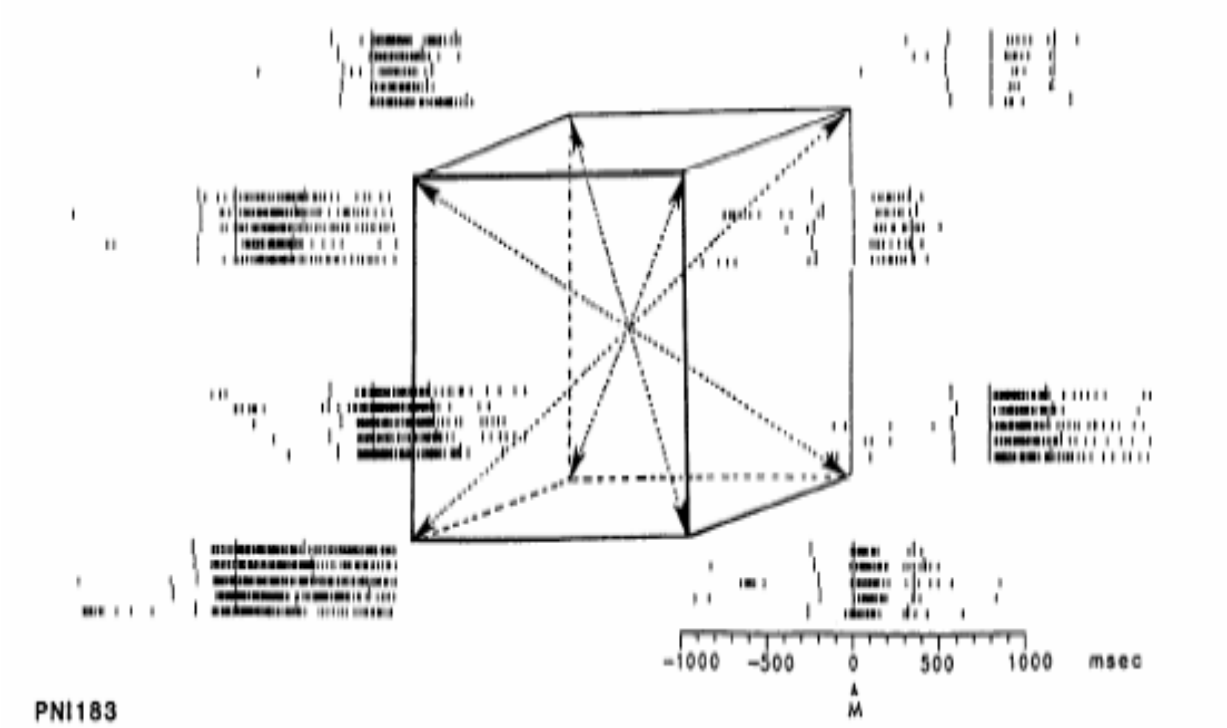


Figure 7. Impulse activity (*short bars*) of a directionally tuned cell with movements in different directions (*arrows*). Rasters of 5 repeated trials for every movement direction are aligned with the onset of movement (*M*). *Longer bars* preceding and following the movement onset indicate the onset of the target and the end of the movement, respectively.

ある所へ手を持って行くと、運動野ニューロンは、方向指示の運動情報を持っている（シュワーツら、1986）

運動学習の初期に運動前野ニューロンが働く

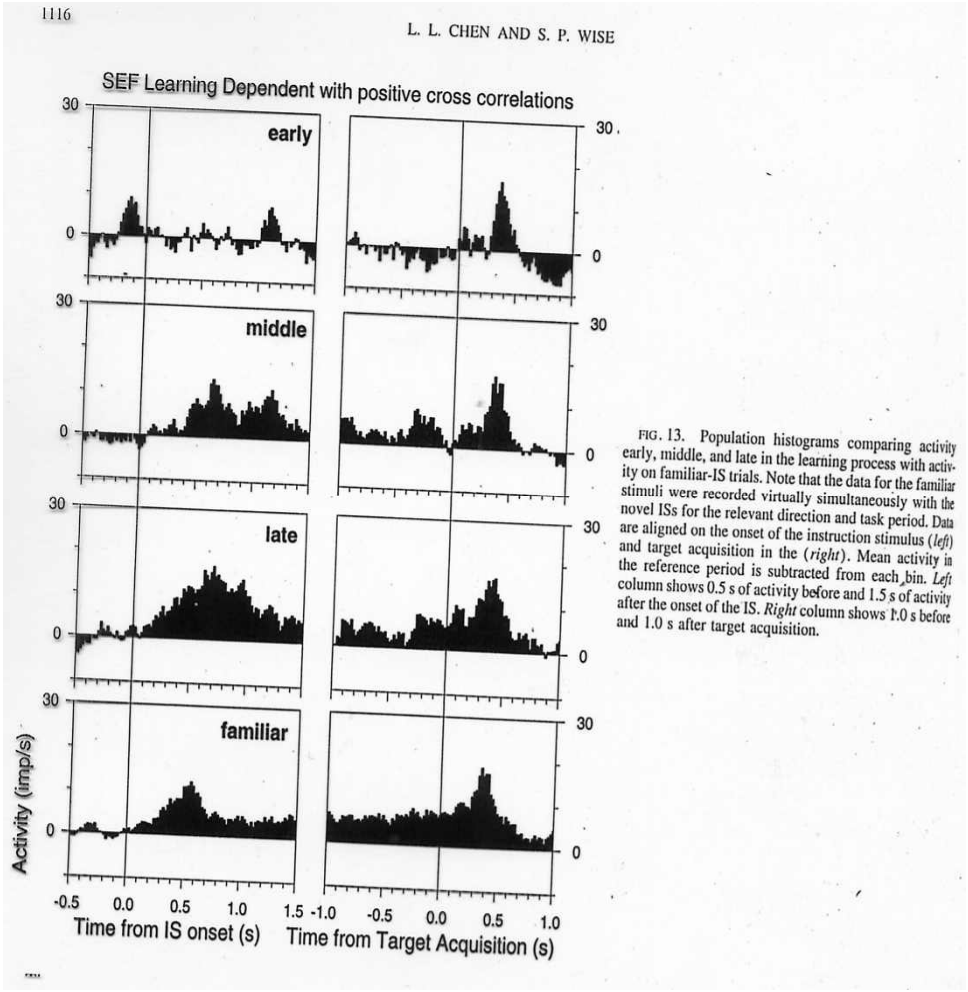


FIG. 13. Population histograms comparing activity early, middle, and late in the learning process with activity on familiar-IS trials. Note that the data for the familiar stimuli were recorded virtually simultaneously with the novel ISs for the relevant direction and task period. Data are aligned on the onset of the instruction stimulus (*left*) and target acquisition in the (*right*). Mean activity in the reference period is subtracted from each bin. *Left* column shows 0.5 s of activity before and 1.5 s of activity after the onset of the IS. *Right* column shows 1.0 s before and 1.0 s after target acquisition.

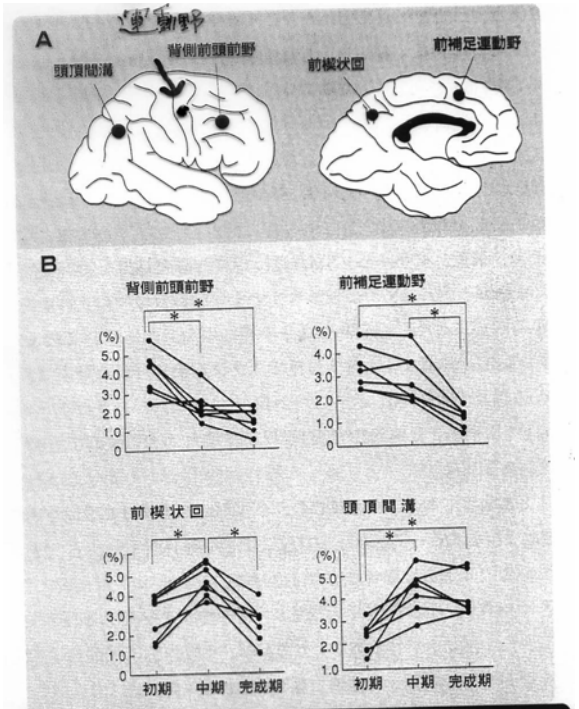


図2-8 運動の手順を学習していくときの，ヒトの脳活動の変化
(Hikosaka et al., 1998)

A：学習に関係して，活動した脳の部位。背側前頭前野，前補足運動野，前模状回，頭頂間溝が示されている。
B：学習の初期，中期，完成期でみられる，それぞれの脳の部位の活動度の推移。

The Journal of Neuroscience, March 1, 1998, 18(5):1827–1840

Transition of Brain Activation from Frontal to Parietal Areas in Visuomotor Sequence Learning

Katsuyuki Sakai,[1,2] Okihide Hikosaka,[1] Satoru Miyauchi,[3] Ryousuke Takino,[4] Yuka Sasaki,[3] and Benno Pütz[5]

[1]Department of Physiology, Juntendo University School of Medicine, Tokyo 113, Japan, [2]Department of Neurology, Division of Neuroscience, Graduate School of Medicine, University of Tokyo, Tokyo 113, Japan, [3]Human Neurosystem Science Section, Intelligent Communications Division, Communications Research Laboratory, Tokyo 184, Japan, [4]Shiraume Gakuen College, Tokyo 187, Japan, and [5]Exploratory Research for Advanced Technology, Japan Science and Technology Corporation, Kyoto 619-02, Japan

視覚運動シーケンスの学習の時、前補足運動野がまず働く（Sakaiら、1998）

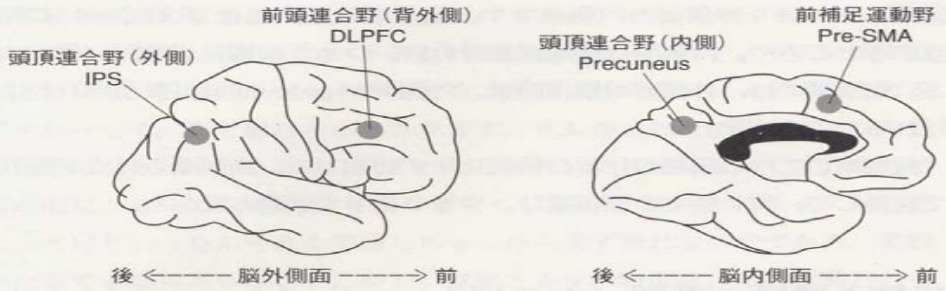


図 23b　手続き学習に伴って活動した 4 つの大脳皮質領域

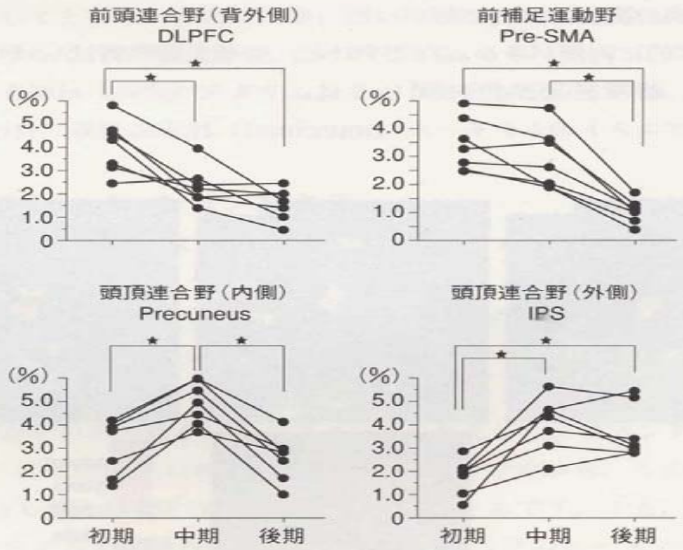


図 23c　手続き学習に伴う 4 つの大脳皮質領域の活動の変化
MRI 信号の変化を，手続き学習の初期，中期，後期の 3 つに分けてプロットしてある。7 人の被験者の結果。

彦坂興秀の課外授業(眼と精神」(2003)医学書院

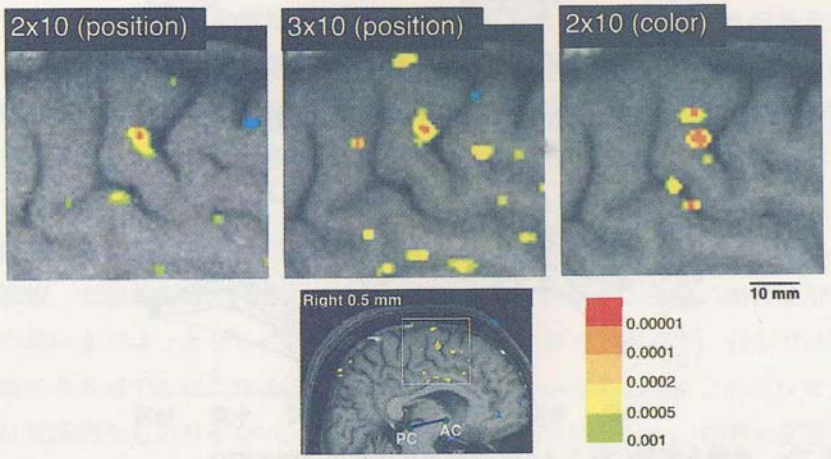


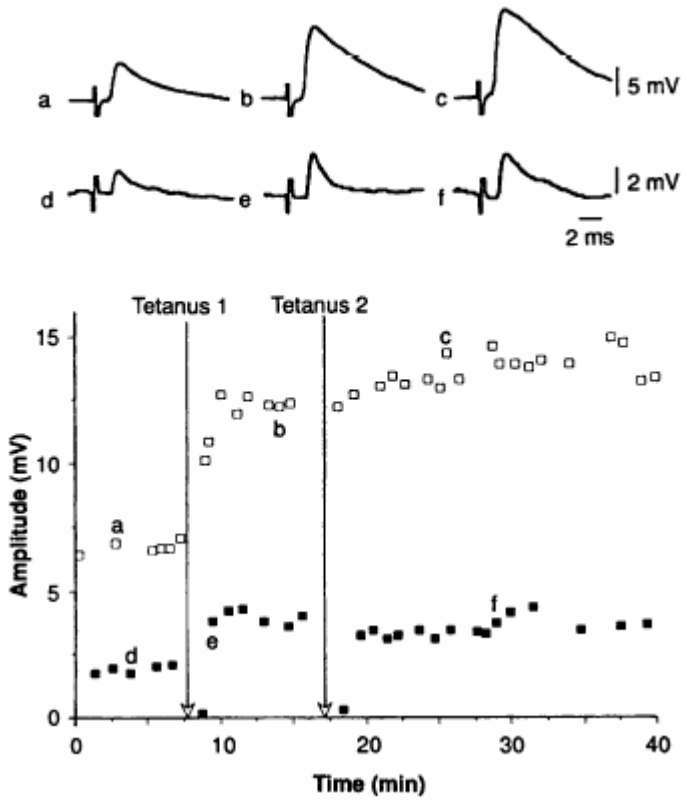
図 23a　手続き学習に伴うヒト前補足運動野の活動：機能的 MRI の実験
1 人の被験者が 3 つの違う順序手続きを学習したときに活動した脳の部位を色で示してある。赤に近いほど高い活動を意味する。下の図は，この被験者の大脳の内側面。右が前。AC，PC は前交連と後交連を示す。四角で囲んだ部分を上に拡大してある。3 つの手続きに共通して活動した部分は前補足運動野である。

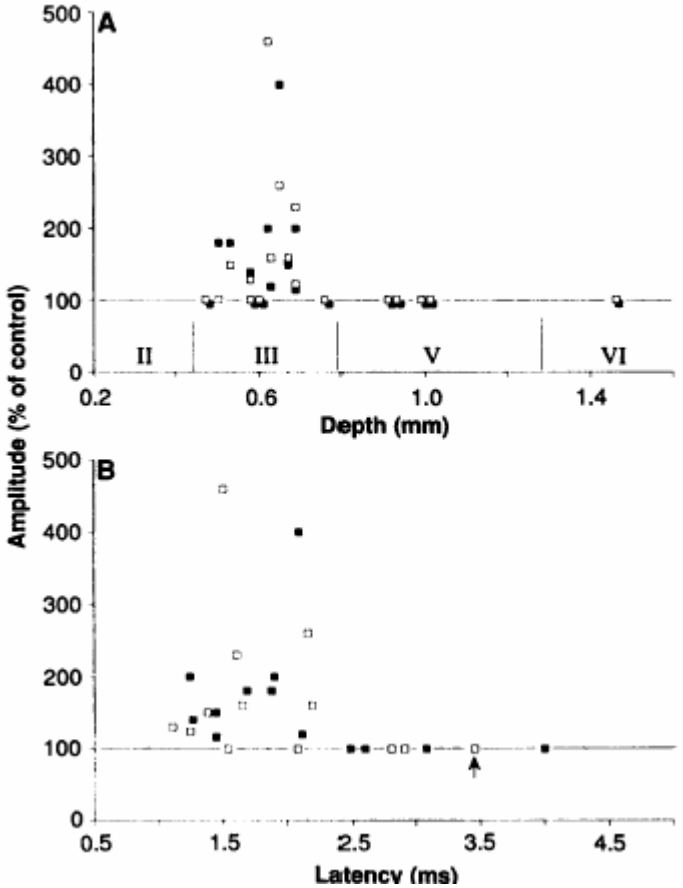
Long-Term Potentiation in the Motor Cortex

ATSUSHI IRIKI, CONSTANTINE PAVLIDES, ASAF KELLER, HIROSHI ASANUMA

Long-term potentiation (LTP) is a model for learning and memory processes. Tetanic stimulation of the sensory cortex produces LTP in motor cortical neurons, whereas tetanization of the ventrolateral nucleus of the thalamus, which also projects to the motor cortex, does not. However, after simultaneous high-frequency stimulation of both the sensory cortex and the ventrolateral nucleus of the thalamus, LTP of thalamic input to motor cortical neurons is induced. This associative LTP occurs only in neurons in the superficial layers of the motor cortex that receive monosynaptic input from both the sensory cortex and the ventrolateral nucleus of the thalamus. Associative LTP in the motor cortex may constitute a basis for the retention of motor skills.

Long-term potentiation in the motor cortex
A Iriki, *et al.*
Science **245**, 1385 (1989);
DOI: 10.1126/science.2551038



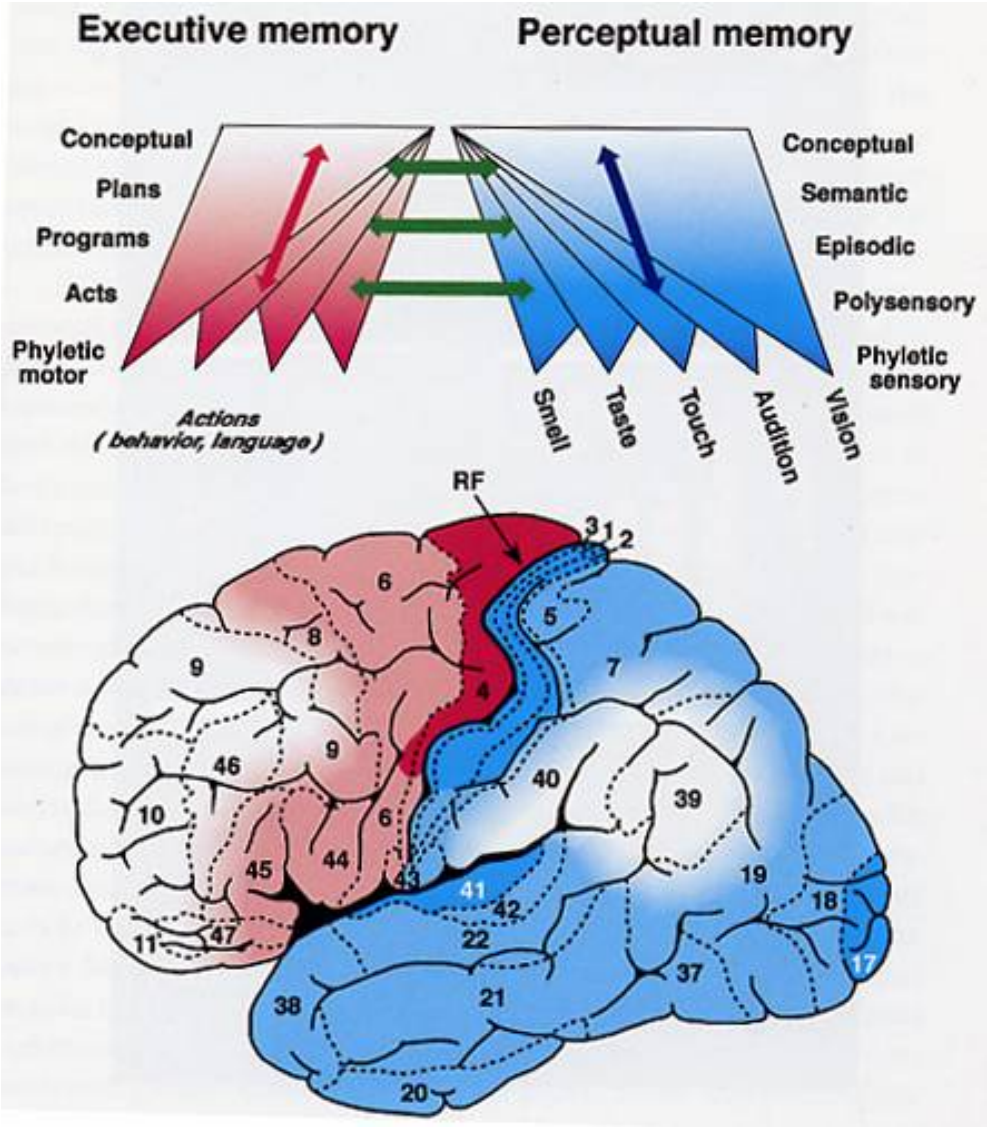


大脳皮質の機能再現の分布

実行系　　知覚系

階層的再現

概念
計画
プログラム
行為
単運動



概念
意味
エピソード
多感覚
単感覚

ブロードマンの細胞構築地図

エピソード的
多感覚的
単感覚的

RF: ﾛﾗﾝﾄ裂

（上下の色の濃さは対応）

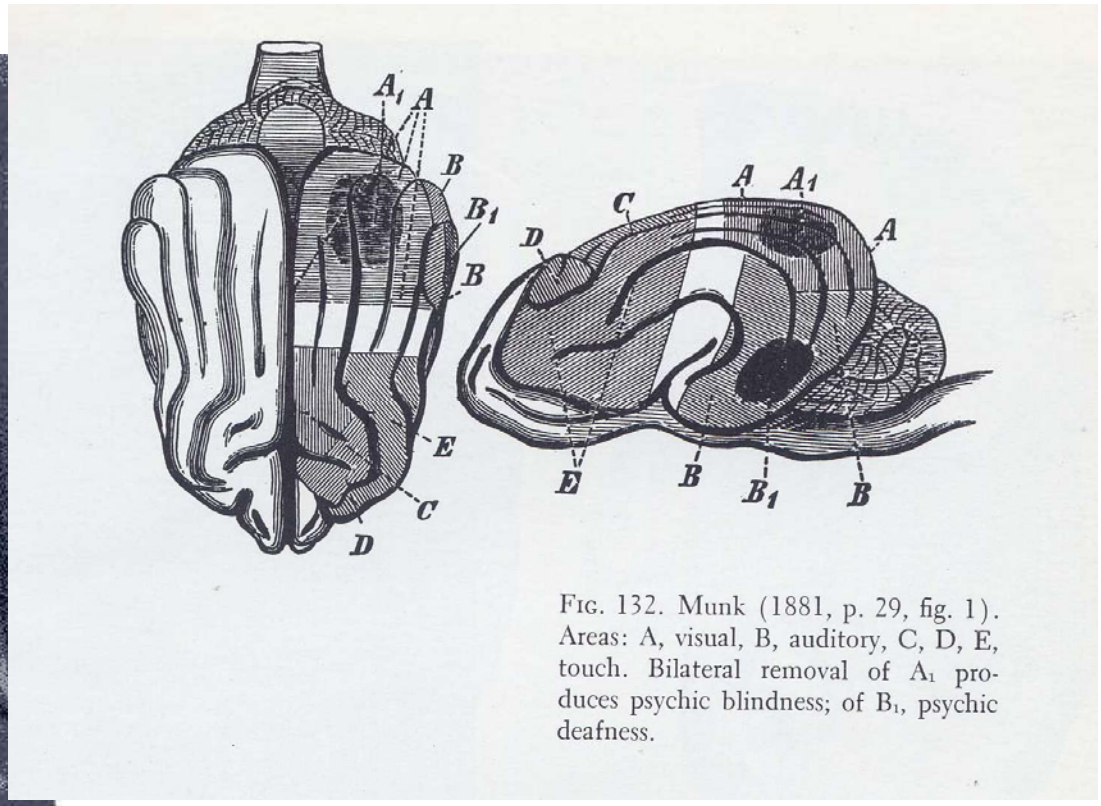
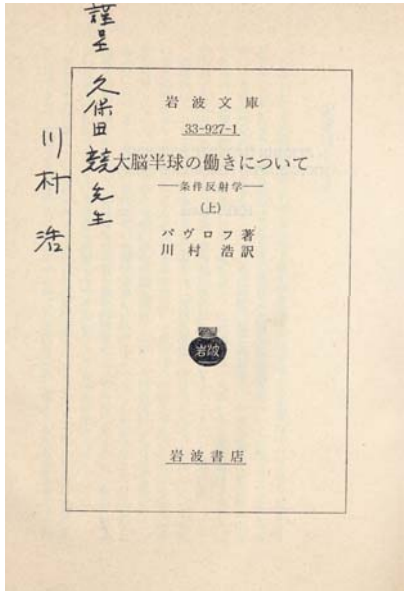


FIG. 132. Munk (1881, p. 29, fig. 1). Areas: A, visual, B, auditory, C, D, E, touch. Bilateral removal of A_1 produces psychic blindness; of B_1, psychic deafness.

Munkは、コイヌで両側視覚野を壊したら、物を認識できない

が見えると考え、別のところがはたらくと考え、Restitutionと呼んだ(1881)。

ig. 5.36. The austere Hermann Munk's role in providing he correct evidence for the localization of the great sensory nodalities is often overlooked (*see* Schiller, 1970a, p. 247). He established "the facts of cortical blindness and mind lindness" and uncovered hemiopia.



ところでこの無限と言って良い大脳半球活動と驚くほどの対照を示しているのは、現在の大脳半球生理学の内容である。前世紀七〇年代までは大脳半球の生理学は存在しなかったと言ってよい。それは生理学者にとって何か近寄り難いものであった。七〇年代になって始めてフリッチュとヒッツィヒ(三)(Fritsch u. Hitzig)が、刺激と破壊という普通の生理学の方法を大脳半球の研究に適用して成功をおさめた。大脳半球皮質のある部分(皮質運動野)を刺激すると、一定の骨格筋群に規則的な収縮がおこる。この部分を切除すると対応する筋群の正常な活動に一定の障害がひきおこされる。

さらにこの直後ムンク(四)、フェリエ(五)(H. Munk, Ferrier)らによって、人工的な刺激では反応しないように見えた大脳皮質の他の部位に、機能的に特殊な部分の存在することが示された。この部分の除去、切除によっていくつかの受容器——眼、耳、皮膚の活動に一定の欠陥が生じた。

(四) ムンク(Munk, Hermann, 1839-1912)。ドイツの生理学者"Ueber die Funktionen der Grosshirnrinde: gesammelte Mitteilungen aus den Jahren 1877-80" Berlin, Hirschwald, 1890.

(一九世紀七〇年代)から何人かの研究者は、大脳半球の前半部も視覚に関係しているという立場に確信をもっていた。しかしこの事実は消極的な性質のものであったため十分な証拠を見出せなかった。すべてを離れた所からの抑制作用に帰することができたわけである。だがわれわれはいま、視覚分析器がそのかなりの程度の機能を実際に大脳半球の前半部、上方ではS状回(g. sigmoideus)のすぐ後から側方を後へシルヴィ回(g. sylviaticus)の前角へ行き、脳底のシルヴィ窩裂(fissura fossae sylvii)へ至る線(第二一講の第一一図)よりも前の部分へ残しているという積極的な成績をあげることができる。われわれの後頭葉のないすべての犬で(カリシャーのように)部屋の全般的照明にたいする条件反射が形成され、かなり細かい照明の差にたいしてもはっきりした分化がみられた。この事実はムンクによって精神盲と名づけられた現象にたいする簡単で純自然科学的な説明である。後頭葉切除後いちじるしく損傷された視覚分析器は、要素的機能つまり

19ページ

下、第20講、145ページ

J Neurophysiol 89: 3205–3214, 2003;
10.1152/jn.01143.2002.

Reorganization of Remote Cortical Regions After Ischemic Brain Injury: A Potential Substrate for Stroke Recovery

S. B. Frost, S. Barbay, K. M. Friel, E. J. Plautz, and R. J. Nudo

Center On Aging, Department of Molecular and Integrative Physiology; and Mental Retardation Research Center, University of Kansas Medical Center, Kansas City, Kansas 66160

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Frost, S. B., S. Barbary, K. M. Friel, E. J. Plautz, and R. J. Nudo. Reorganization of remote cortical regions after ischemic brain injury: a potential substrate for stroke recovery. *J Neurophysiol* 89: 3205–3214, 2003; 10.1152/jn.01143.2002. Although recent neurological research has shed light on the brain's mechanisms of self-repair after stroke, the role that intact tissue plays in recovery is still obscure. To explore these mechanisms further, we used microelectrode stimulation techniques to examine functional remodeling in cerebral cortex after an ischemic infarct in the hand representation of primary motor cortex in five adult squirrel monkeys. Hand preference and the motor skill of both hands were assessed periodically on a pellet retrieval task for 3 mo postinfarct. Initial postinfarct motor impairment of the contralateral hand was evident in each animal, followed by a gradual improvement in performance over 1–3 mo. Intracortical microstimulation mapping at 12 wk after infarct revealed substantial enlargements of the hand representation in a remote cortical area, the ventral premotor cortex. Increases ranged from 7.2 to 53.8% relative to the preinfarct ventral premotor hand area, with a mean increase of 36.0 ± 20.8%. This enlargement was proportional to the amount of hand representation destroyed in primary motor cortex. That is, greater sparing of the M1 hand area resulted in less expansion of the ventral premotor cortex hand area. These results suggest that neurophysiologic reorganization of remote cortical areas occurs in response to cortical injury and that the greater the damage to reciprocal intracortical pathways, the greater the plasticity in intact areas. Reorganization in intact tissue may provide a neural substrate for adaptive motor behavior and play a critical role in postinjury recovery of function.

INTRODUCTION

Cortical injury, as might occur in stroke, is frequently found to affect the initiation and execution of muscular contraction in the extremities opposite the side of the injury. In particular, fine manipulative abilities and skilled use of the upper extremity are often degraded (Bucy 1944; Hoffman and Strick 1995). In the weeks and months after injury, a gradual return of some motor abilities occurs (Lashley 1924; Travis and Woolsey 1956), although complete recovery of function is rare in humans (Gowland 1987).

The theory that structures either adjacent or remote from the injured area can assume the function of the damaged cortex, often referred to as vicariation of function or substitution (Munk 1881), has gained additional support due to recent examples of functional plasticity after injury. One study using microelectrode stimulation techniques showed that areas adjacent to damaged portions of motor cortex reorganize after behaviorally contingent electrical stimulation of the ventral tegmentum in rats (Castro-Alamancos et al. 1992). Another study using microelectrode-recording techniques showed that changes in functional representations in somatosensory cortex parallel sensorimotor skill recovery from stroke in adult monkeys, although it is unclear whether improvements reflect a recovery to normal preoperative strategies or the development of new compensatory behavioral strategies (Xerri et al. 1998).

doi:10.1093/brain/awh456 *Brain* (2005), **128**, 1122–1138

Vicarious function within the human primary motor cortex?
A longitudinal fMRI stroke study

Assia Jaillard,[1,4] Chantal Delon Martin,[4] Katia Garambois,[1] Jean François Lebas[2,4] and Marc Hommel[1,3,4]

[1]*Department of Neurology, Stroke Unit,* [2]*Unité de RMN Service of Neuroradiology,* [3]*Inserm, CIC 003, University Hospital and* [4]*Inserm, U594-University Joseph Fourier, Grenoble, France*

Correspondence to: Dr Assia Jaillard, Département de Neurologie—Unité Neuro-vasculaire, Centre Hospitalier Universitaire de Grenoble, BP 217-38043 Grenoble Cedex 9, France
E-mail: AJaillard@chu-grenoble.fr

Summary

While experimental studies in the monkey have shown that motor recovery after partial destruction of the hand motor cortex was based on adjacent motor reorganization, functional MRI (fMRI) studies with isolated primary motor cortical stroke have not yet been reported in humans. Based on experimental data, we designed a study to test if recovery after stroke within primary motor cortex (M1) was associated with reorganization within the surrounding motor cortex, i.e. the motor cortex was able to vicariate. Since motor recovery is time-dependent and might be inflected according to the tested task, the delay after stroke and two motor tasks were included in our design. We examined four patients with one ischaemic stroke limited to M1, and four sex- and age-matched healthy controls in a temporally balanced prospective longitudinal fMRI study over three sessions: <20 days, 4 months and 2 years after stroke. The paradigm included two motor tasks, finger tapping (FT) and finger extension (FE). Distinct patterns of motor activation were observed with time for FT and FE. At the first session, FT-related activation was lateralized in the ipsilateral hemisphere while FE-related activation was contralateral, involving bilateral cerebellar regions for both tasks. From 4 months, skilled motor recovery was associated with contralateral dorsal premotor and sensorimotor cortex and ipsilateral cerebellum motor-related activations, leading to lateralized motor patterns for both tasks. For the left recovered hand, FT and FE-related activations within M1 were more dorsal in patients than in controls. This dorsal shift progressively increased over 2 years, reflecting functional reorganization in the motor cortex adjacent to the lesion. In addition, patients showed a reverse representation of FT and FE within M1, corresponding to a greater dorsal shift for FT than for FE. This functional dissociation might reflect the structural subdivision of M1 with two distinct finger motor representations within M1. Recovery of FT, located within the lesioned depth of the rolandic sulcus in controls, might be related to the re-emergence of a new representation in the intact dorsal M1, while FE, located more dorsally, underwent minor reorganization. This is the first fMRI study of humans presenting with isolated M1 stroke comparable with experimental lesions in animals. Despite the small number of patients, our findings showing the re-emergence of a fingers motor task in the intact dorsal M1 instead of in ventral M1 are consistent with 'vicariation' models of stroke recovery.

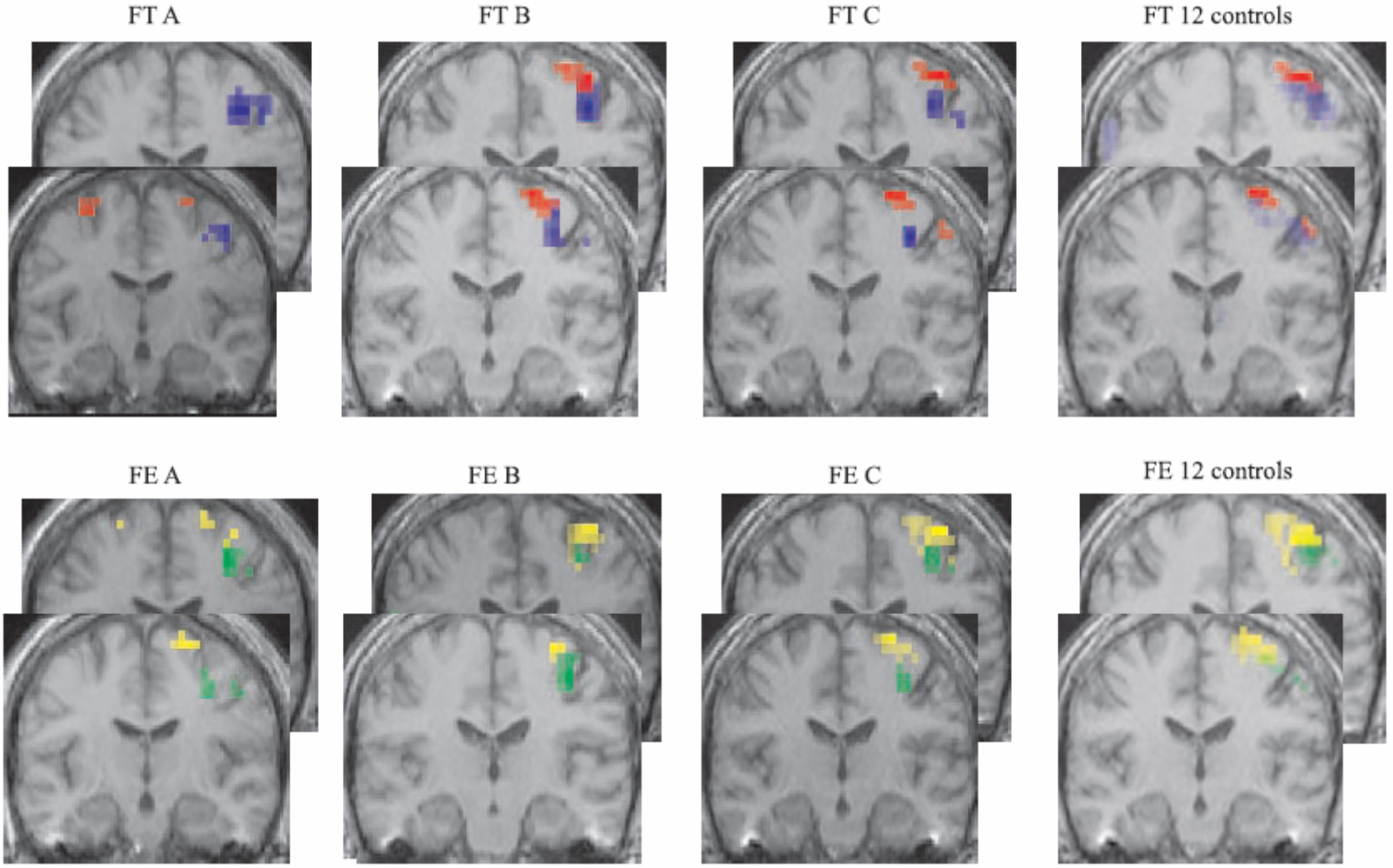
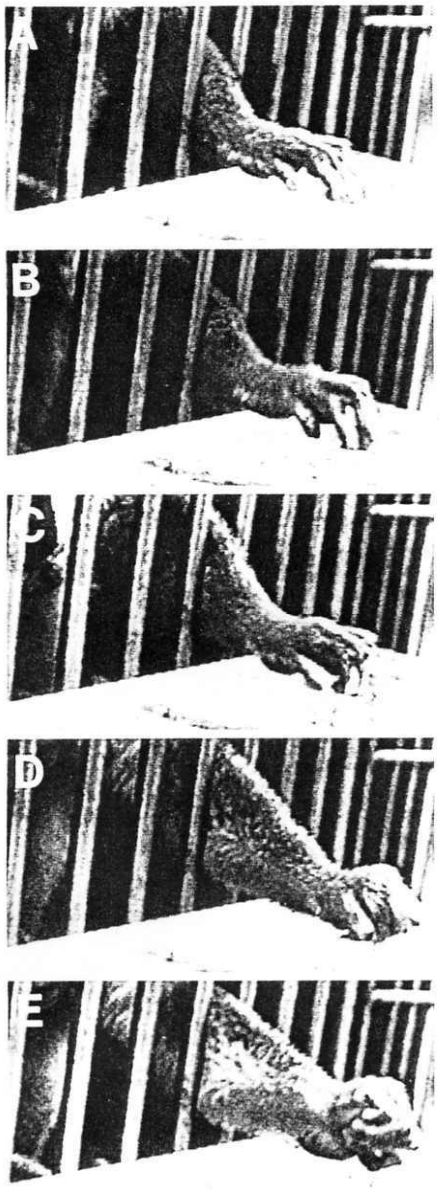


Fig. 2 Representative coronal sections from patient and control maps showing FT and FE-related activations for the left hand over time. (A) First session at 10 days after stroke. (B) Second session at 4 months after stroke. (C) Third session at 2 years after stroke. 12 controls = patients' third session and single session for 12 normal controls). MNI coordinates (mm) $y = -16$ in the lower row and $y = -20$ in the upper row for FT and FE. Red areas represent FT-related activation in patients; blue areas represent FT-related activation in controls; yellow areas represent FE-related activation in patients; green areas represent FE-related activation in controls. All voxels are significant at $P < 0.05$ corrected for multiple comparisons. Sections are arranged in neurological orientation (i.e. right side of brain to viewer's right). See Tables 2 and 3 for exact coordinates of voxels.

リスザルが餌台の穴からペレットを取る

（ヌードら、1996）

図1　ケージ内にいるリスザルが一番大きい穴に右手を伸ばしてペレットをつかんでいるところ
穴は9.5～25 mmの径がある.



Finger Extension
指の伸展

Finger Flexion
指の屈曲

Finger Flexion +
Wrist Extension
指の屈曲と手首の伸展

Wrist Extension
指の伸展

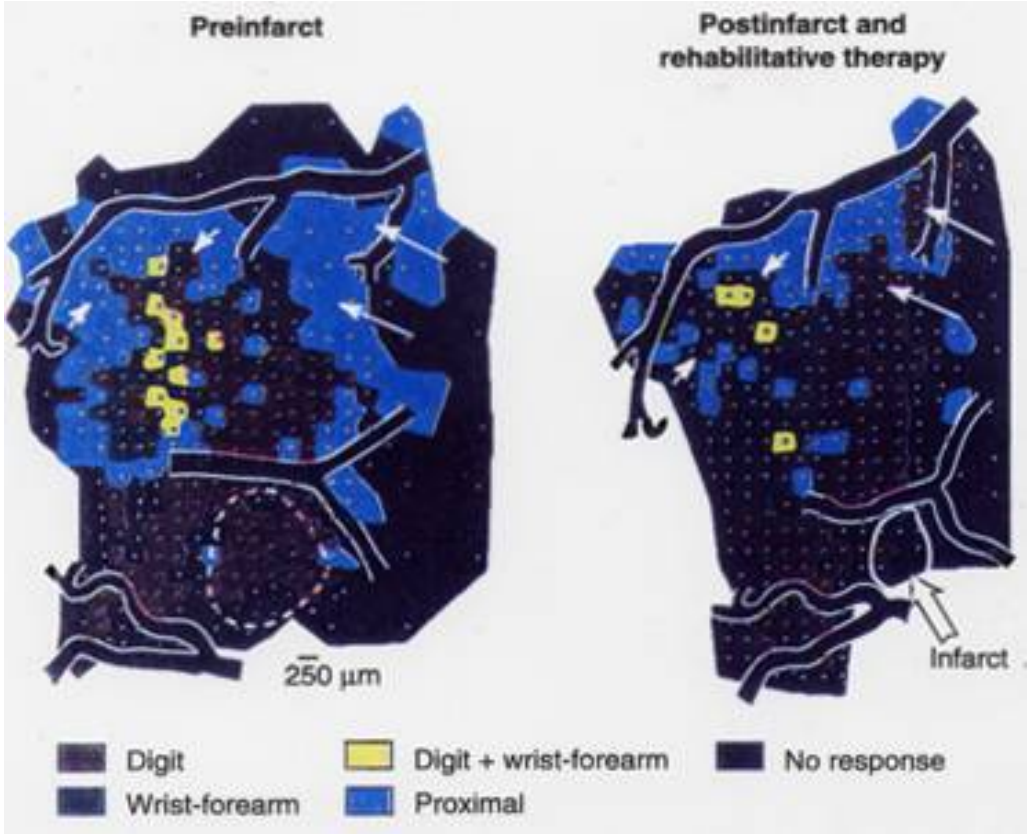
Forearm Supination
前腕の回外

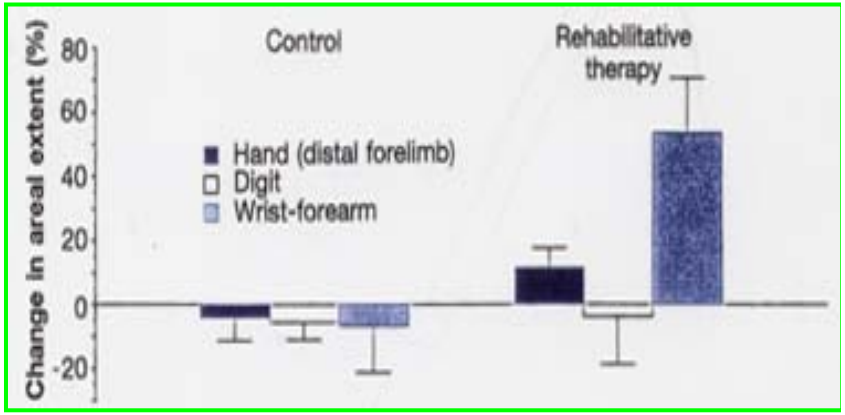
Figure 2. Sequence of photographs showing movements used to retrieve a pellet from a 9.5 mm well (well 4) of a Klüver board. *A*, The fingers extended as the arm moved toward the well. *B*, The fingers flexed within the well and then stopped. *C*, A second finger flexion occurred, but before the finger flexion movement was completed the wrist extended. *D*, The wrist continued to extend as a discrete movement and then stopped when the wrist was fully extended. *E*, As the pellet was retrieved from the well, the forearm gradually supinated.

Neural Substrates for the Effects of Rehabilitative Training on Motor Recovery After Ischemic Infarct

リスザルの運動野の手指領域に乏血性梗塞のあと、リハで手指の麻痺が回復するが手首の領域がはたらくようになった。

代行作用 （Vicariation)





Nudo（ヌード）et al.、 Science 1996; 272;1791

梗塞後の指訓練の経過

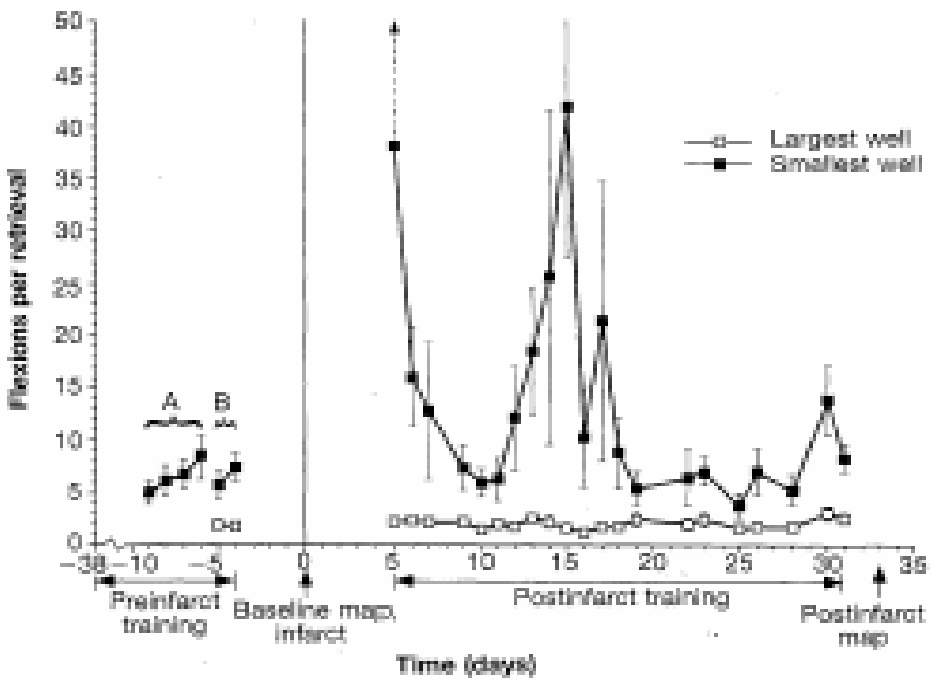
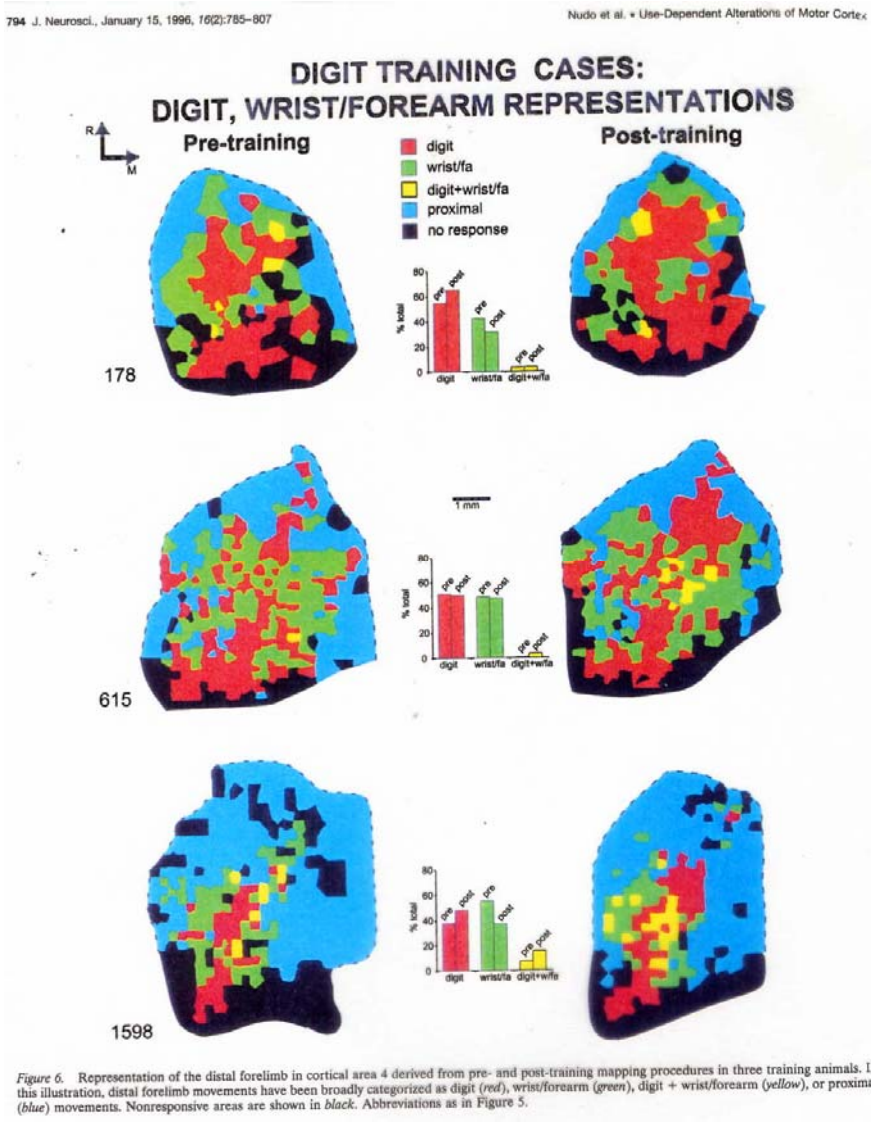


Fig. 1. Effects of ischemic infarct on manual skill. Four squirrel monkeys underwent daily training on a task requiring skilled use of the hand, especially the fingers. Normal retrieval of food pellets from the smallest well required the insertion of one or two fingers, as well as specific movement sequences and combinations (8). Normal retrieval from the largest well was accomplished by insertion and simultaneous flexion of all fingers. Data points represent the mean (±SEM) number of flexions per retrieval for each day, with optimal performance being one flexion per retrieval. The shaded regions indicate the 95% confidence intervals for preinfarct performance (dark shading, smallest well; light shading, largest well). Bracket A represents the final phase of the titration procedure, during which trials were conducted only on the smallest well, and bracket B represents the preinfarct probe phase (2 days), during which random probe trials were conducted on each of five wells. During postinfarct training, random probe trials were conducted on each day. The dashed arrow above the data point on postinfarct day 5 indicates that no retrievals were made from the smallest well on that day. Although the number of flexions per retrieval is plotted here as a daily measure of manual skill, final criterion performance (both pre- and postinfarct) was based on the total number of pellets retrieved per day from the smallest well (*11*).



手を使う使わないで、
運動野再現が変わる

（リスザル）

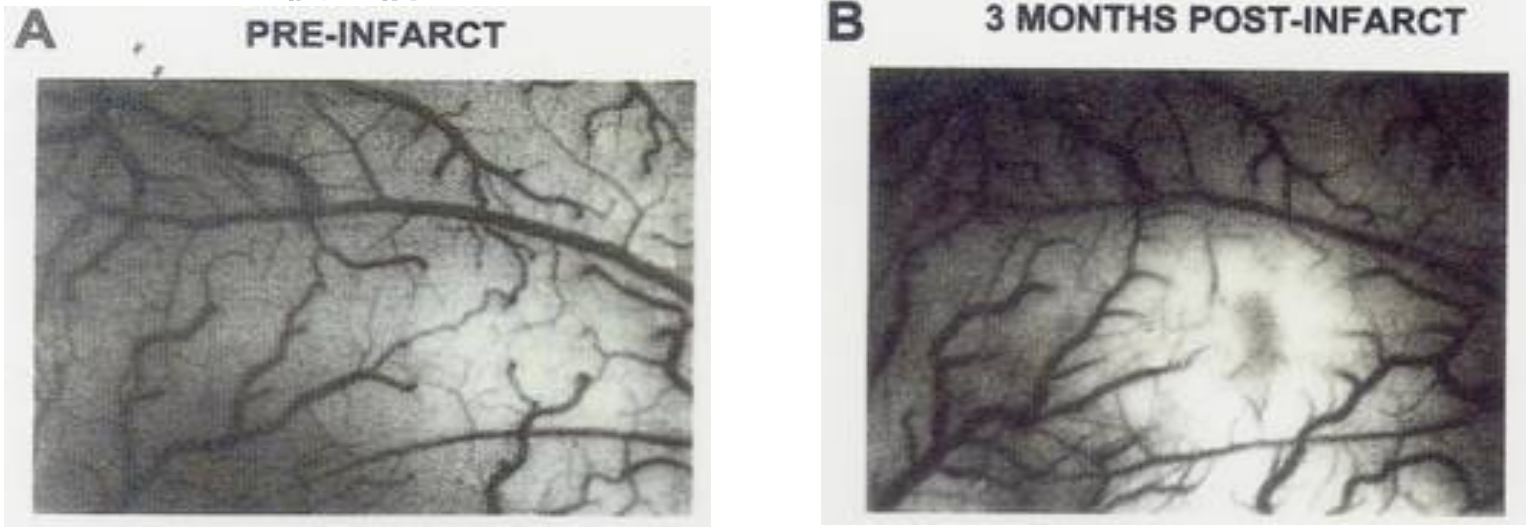
Reorganization of Movement Representation in Area 4 after focal ischemic infarcts

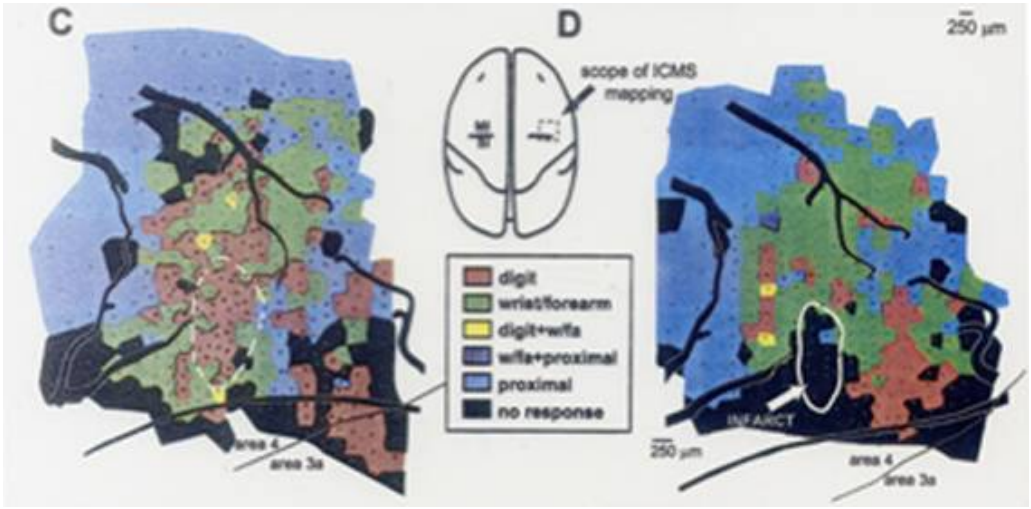
R.J . Nudo and G.W. Millikn J Neurophysiol 75: 2144-2149,1996.

リスザル手の運動野に乏血梗塞を起こして、手を動かさないと、指が動かせなくなる

梗塞前

梗塞後3ヶ月





Constraint-Induced movement therapy

強制使用法

制限運動療法

Treatment-Induced Cortical Reorganization After Stroke in Humans

Joachim Liepert, MD; Heike Bauder, PhD; Wolfgang H.R. Miltner, PhD;
Edward Taub, PhD; Cornelius Weiller, MD

Background and Purpose—Injury-induced cortical reorganization is a widely recognized phenomenon. In contrast, there is almost no information on treatment-induced plastic changes in the human brain. The aim of the present study was to evaluate reorganization in the motor cortex of stroke patients that was induced with an efficacious rehabilitation treatment.

Methods—We used focal transcranial magnetic stimulation to map the cortical motor output area of a hand muscle on both sides in 13 stroke patients in the chronic stage of their illness before and after a 12-day-period of constraint-induced movement therapy.

Results—Before treatment, the cortical representation area of the affected hand muscle was significantly smaller than the contralateral side. After treatment, the muscle output area size in the affected hemisphere was significantly enlarged, corresponding to a greatly improved motor performance of the paretic limb. Shifts of the center of the output map in the affected hemisphere suggested the recruitment of adjacent brain areas. In follow-up examinations up to 6 months after treatment, motor performance remained at a high level, whereas the cortical area sizes in the 2 hemispheres became almost identical, representing a return of the balance of excitability between the 2 hemispheres toward a normal condition.

Conclusions—This is the first demonstration in humans of a long-term alteration in brain function associated with a therapy-induced improvement in the rehabilitation of movement after neurological injury. (***Stroke.*** **2000;31:1210-1216.)**

Key Words: plasticity, neuronal ■ transcranial magnetic stimulation ■ reorganization ■ physical therapy ■ stroke

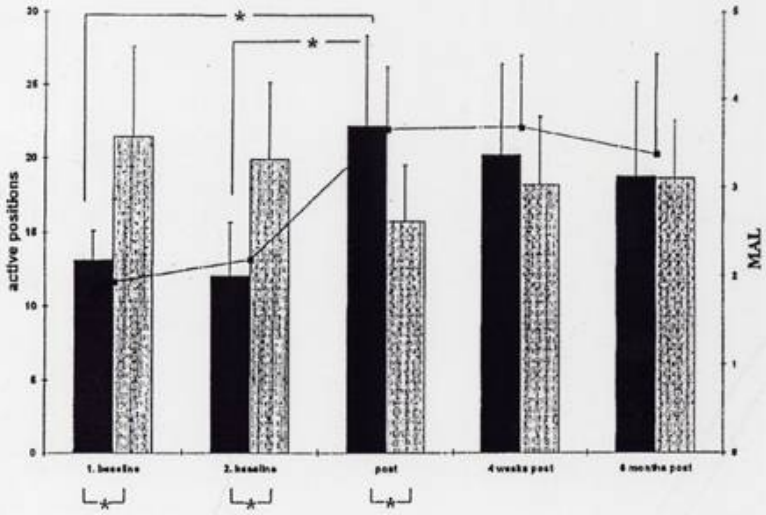
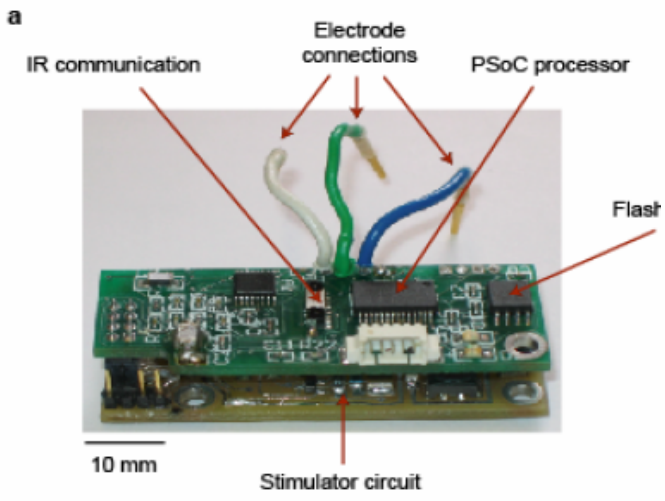


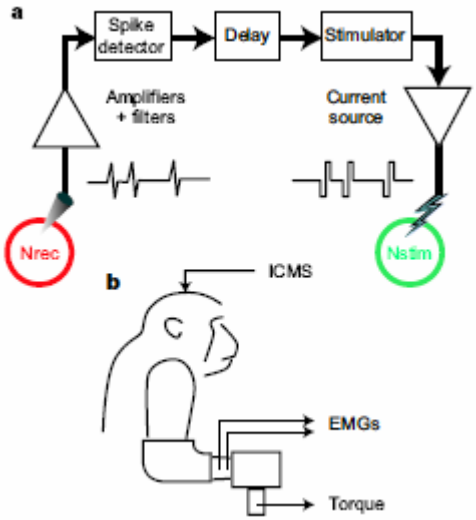
Figure 2. Number of active TMS positions in the infarcted (black bars) and noninfarcted (gray bars) hemisphere 2 weeks and 1 day pretreatment and 1 day, 4 weeks, and 6 months after treatment. ■, Corresponding MAL data for the paretic limb. *$P<0.05$

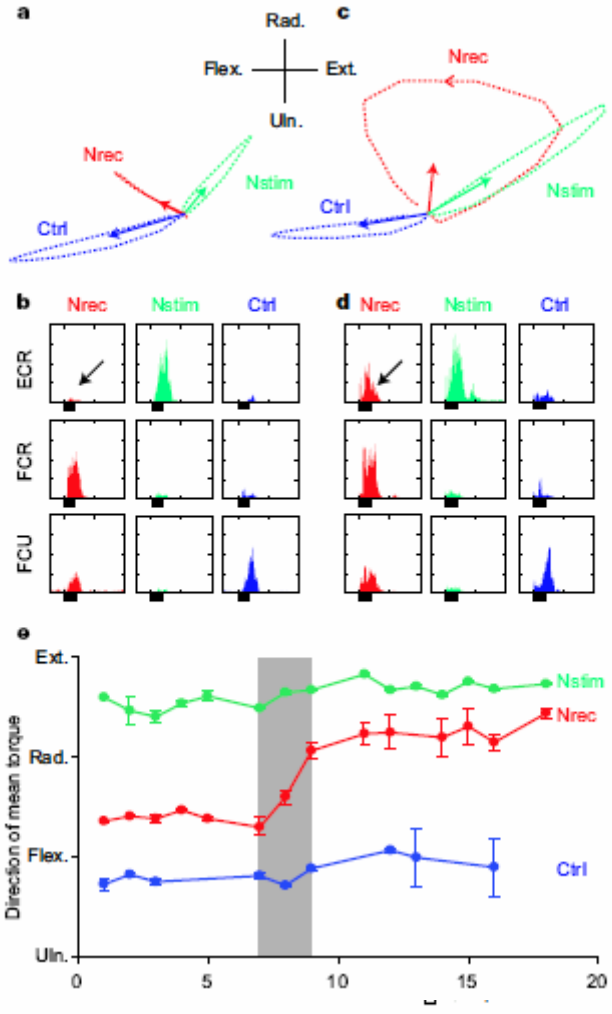
Long-term motor cortex plasticity induced by an electronic neural implant

Andrew Jackson[1], Jaideep Mavoori[2] & Eberhard E. Fetz[1]

It has been proposed that the efficacy of neuronal connections is strengthened when there is a persistent causal relationship





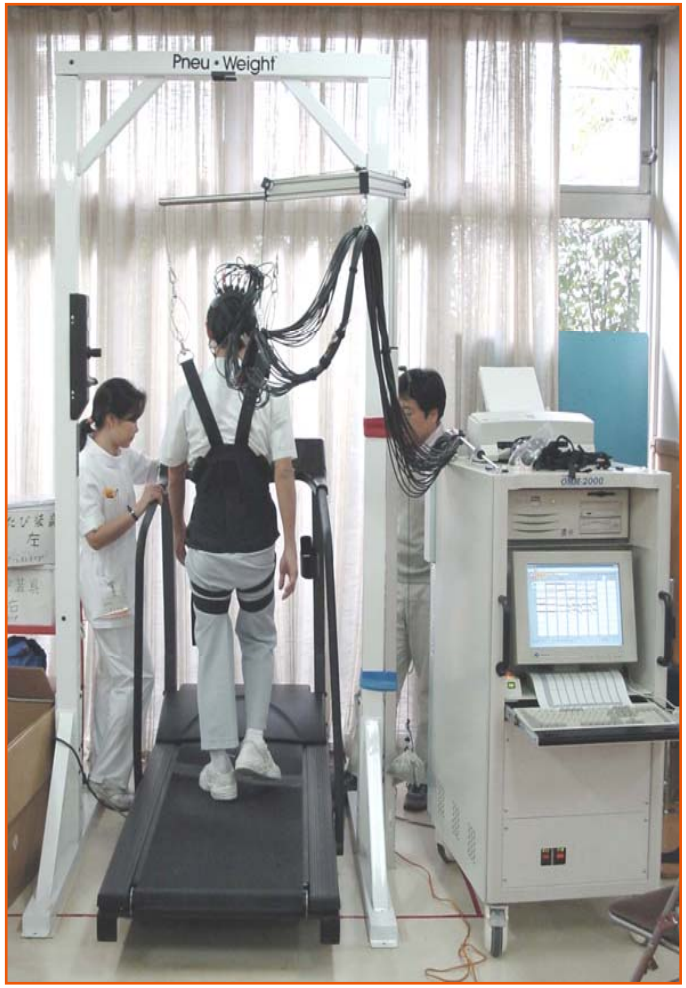


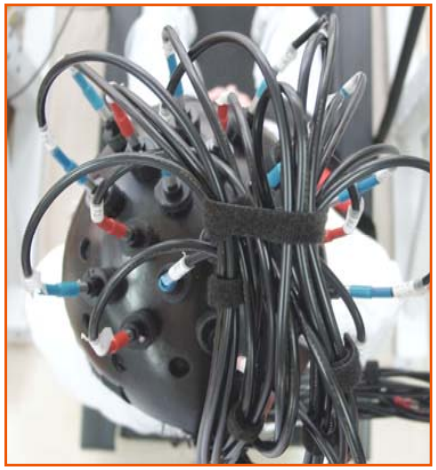
[1]Department of Physiology and Biophysics and Washington National Primate Research Center, [2]Department of Electrical Engineering, University of Washington, Seattle, Washington 98195, USA.

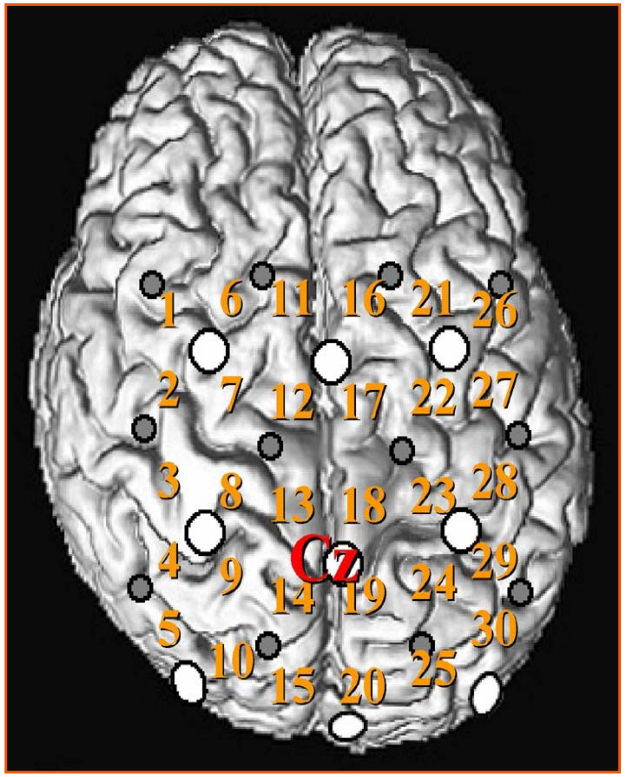
NeuroImage **14,** 1186–1192 (2001)
doi:10.1006/nimg.2001.0905, available online at http://www.idealibrary.com on IDEAL®

Cortical Mapping of Gait in Humans: A Near-Infrared Spectroscopic Topography Study

Ichiro Miyai,* Hiroki C. Tanabe,† Ichiro Sase,† Hideo Eda,† Ichiro Oda,‡ Ikuo Konishi,‡ Yoshio Tsunazawa,‡ Tsunehiko Suzuki,* Toshio Yanagida,†,§ and Kisou Kubota*,¶







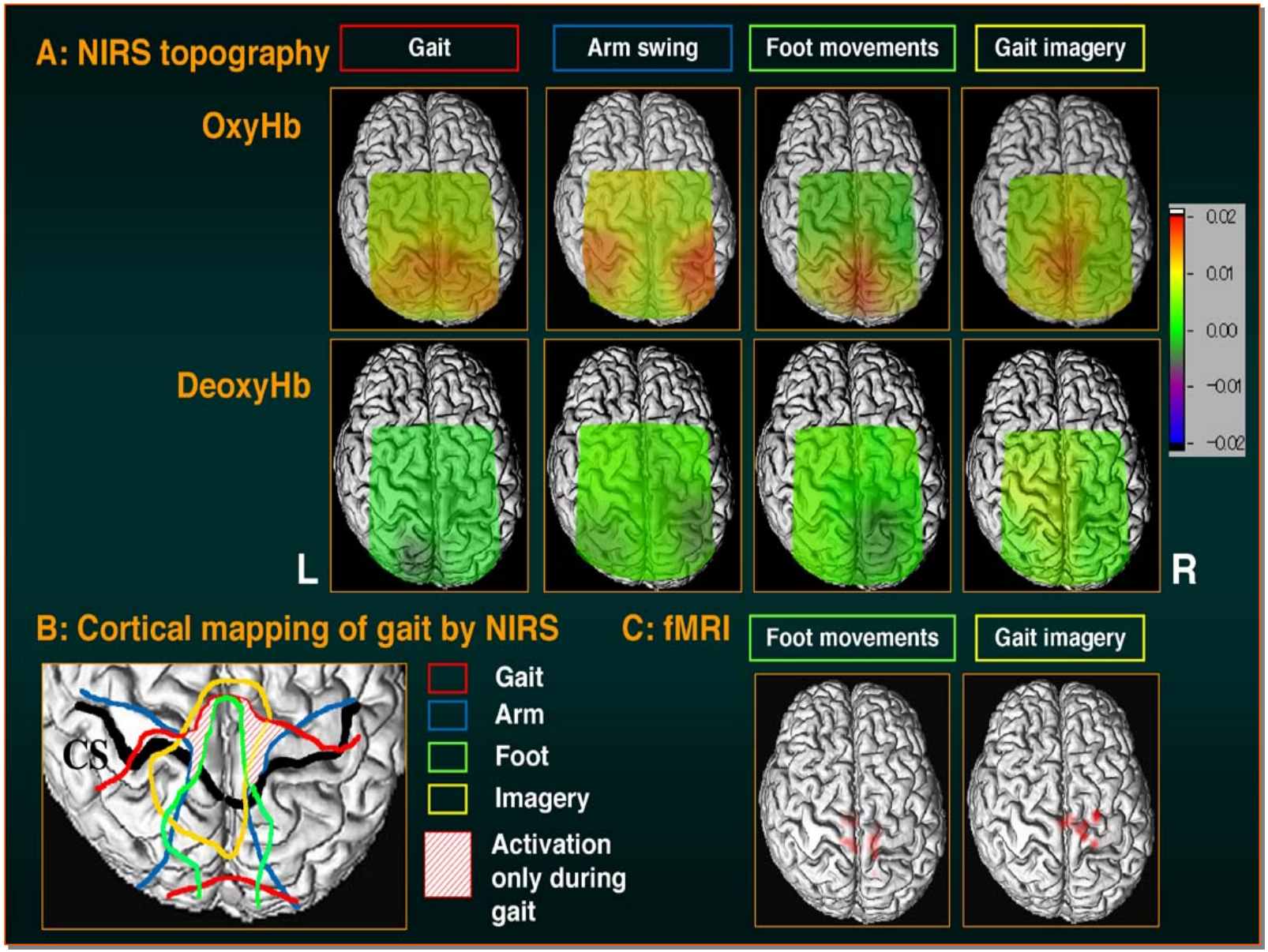
近赤外線投射で脳の血流変化を測定する

Light source fibers (N=9)

Detectors (N=12)

Miyai I, et al. NeuroImage 2001;14:1186-92.

歩行時の脳賦活 ~ 健常人



Miyai I, et al. NeuroImage 2001;14:1186-92.

Premotor Cortex Is Involved in Restoration of Gait in Stroke

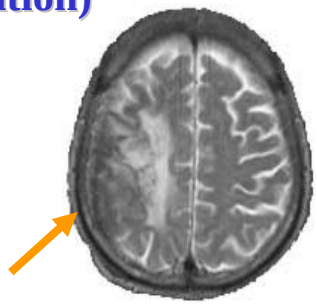
Ichiro Miyai, M.D., Ph.D. [1], Hajime Yagura, M.D. [1], Ichiro Oda, Ph.D. [2], Ikuo Konishi, Ph.D. [2], Hideo Eda, Ph.D. [3], Tsunehiko Suzuki, M.D., Ph.D. [1], and Kisou Kubota, M.D., Ph.D. [1].

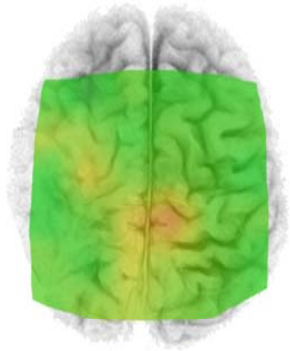
運動前野の働くことが歩行回復に重要
ヒトでの遠隔代行作用の最初の報告
(Remote Vicariation)

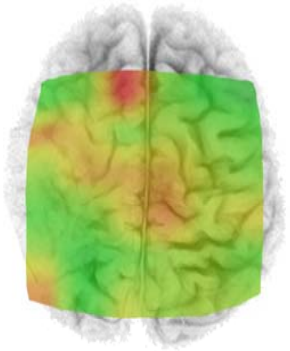
(Ann Neurol 2002:52;188-94.)

Control　　Facilitation

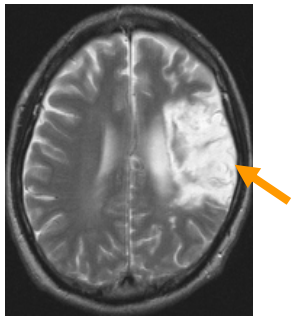
70歳　男性
脳梗塞発作
106 日目

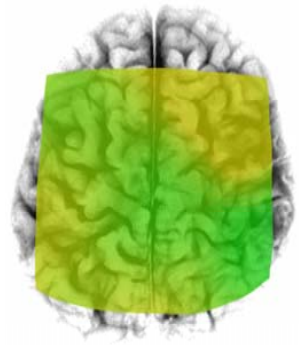


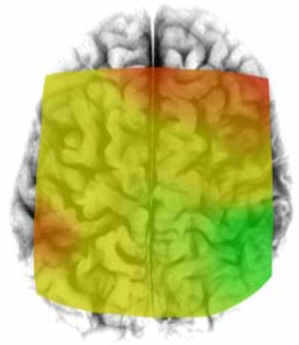


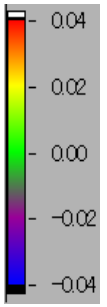


58歳　男性
脳梗塞発作
102 日目

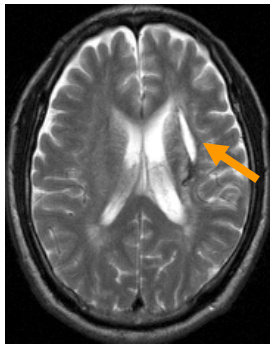


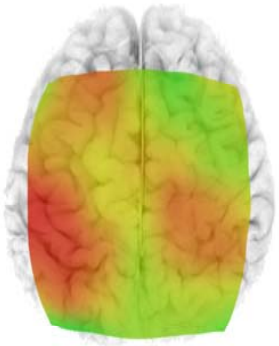






71歳　男性
脳梗塞発作
112日目





L

Control

Facilitation

Stroke.34:2866(2003)

Longitudinal Optical Imaging Study for Locomotor Recovery After Stroke

Ichiro Miyai, MD, PhD; Hajime Yagura, MD; Megumi Hatakenaka, MD; Ichiro Oda, PhD; Ichiro Konishi, PhD; Kisou Kubota, MD, PhD

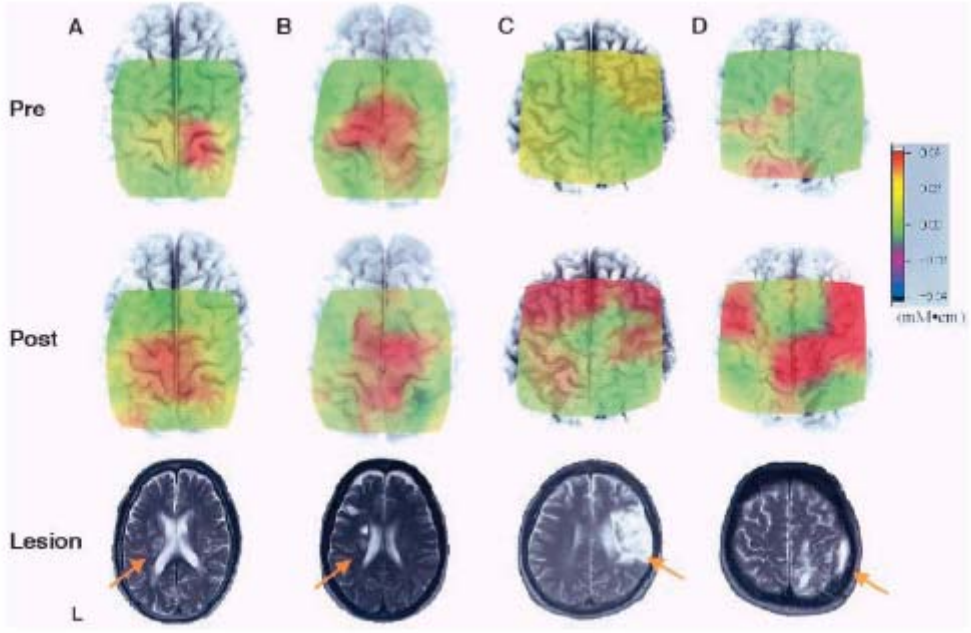


Figure 2. Cortical mapping of hemiparetic gait in patients with stroke. Cortical activation maps are based on changes in oxyHb levels during gait before (pre) and after (post) inpatient rehabilitation. Images in bottom row show site of lesions on T2-weighted MRI. L indicates left. A, Cortical mapping of gait in case 2, with infarction in the left corona radiata (arrow). On day 53 after stroke, the patient needed moderate assistance to take a step. SMC activation was much less in affected hemisphere than in unaffected hemisphere. After inpatient rehabilitation (118 days after stroke), the patient needed minimal assistance to perform the task. SMC activation was symmetrical, and new activation was seen in SMA and PMC, especially in affected hemisphere. B, Cortical mapping of gait in case 3, with infarction in left corona radiata (arrow). On day 107 after stroke, the patient needed mild assistance with gait. There was less SMC activation in affected hemisphere than in unaffected hemisphere, but PMC and SMA were bilaterally activated. On the second imaging (176 days after stroke), the patient needed little assistance with gait. SMC were symmetrically activated, and there was persistent activation in PMC and SMA. C, Cortical mapping of gait in case 6, with diffuse infarction in right frontoparietal lobe. On day 102 after stroke, the patient needed maximal assistance with gait; this was the patient's first opportunity to walk after the ictus. Mild activation was observed in PMC and prefrontal regions in affected hemisphere, parietal regions in unaffected hemisphere, and bilateral pre-SMA. There was little activation in the medial SMC. On the second evaluation (173 days after stroke), the patient needed mild assistance. NIRS imaging revealed enhanced activation in bilateral PMC, pre-SMA, and prefrontal areas and mild SMC activation in unaffected hemisphere. D, Cortical mapping of gait in case 8, with a large hemorrhagic lesion centered in right parietal lobe (arrow). On day 32 after stroke, the patient needed moderate assistance with gait. NIRS imaging showed prominent activation in unaffected hemisphere. After inpatient rehabilitation (98 days after stroke), the patient needed minimal assistance with gait, and enhanced activation was observed in the bilateral SMC, PMC, SMA, and prefrontal cortices.

J Neurophysiol 89: 3205–3214, 2003;
10.1152/jn.01143.2002.

Reorganization of Remote Cortical Regions After Ischemic Brain Injury: A Potential Substrate for Stroke Recovery

S. B. Frost, S. Barbay, K. M. Friel, E. J. Plautz, and R. J. Nudo

Center On Aging, Department of Molecular and Integrative Physiology; and Mental Retardation Research Center, University of Kansas Medical Center, Kansas City, Kansas 66160

Submitted 18 December 2002; accepted in final form 19 February 2003

Frost, S. B., S. Barbary, K. M. Friel, E. J. Plautz, and R. J. Nudo. Reorganization of remote cortical regions after ischemic brain injury: a potential substrate for stroke recovery. *J Neurophysiol* 89: 3205–3214, 2003; 10.1152/jn.01143.2002. Although recent neurological research has shed light on the brain's mechanisms of self-repair after stroke, the role that intact tissue plays in recovery is still obscure. To explore these mechanisms further, we used microelectrode stimulation techniques to examine functional remodeling in cerebral cortex after an ischemic infarct in the hand representation of primary motor cortex in five adult squirrel monkeys. Hand preference and the motor skill of both hands were assessed periodically on a pellet retrieval task for 3 mo postinfarct. Initial postinfarct motor impairment of the contralateral hand was evident in each animal, followed by a gradual improvement in performance over 1–3 mo. Intracortical microstimulation mapping at 12 wk after infarct revealed substantial enlargements of the hand representation in a remote cortical area, the ventral premotor cortex. Increases ranged from 7.2 to 53.8% relative to the preinfarct ventral premotor hand area, with a mean increase of 36.0 ± 20.8%. This enlargement was proportional to the amount of hand representation destroyed in primary motor cortex. That is, greater sparing of the M1 hand area resulted in less expansion of the ventral premotor cortex hand area. These results suggest that neurophysiologic reorganization of remote cortical areas occurs in response to cortical injury and that the greater the damage to reciprocal intracortical pathways, the greater the plasticity in intact areas. Reorganization in intact tissue may provide a neural substrate for adaptive motor behavior and play a critical role in postinjury recovery of function.

INTRODUCTION

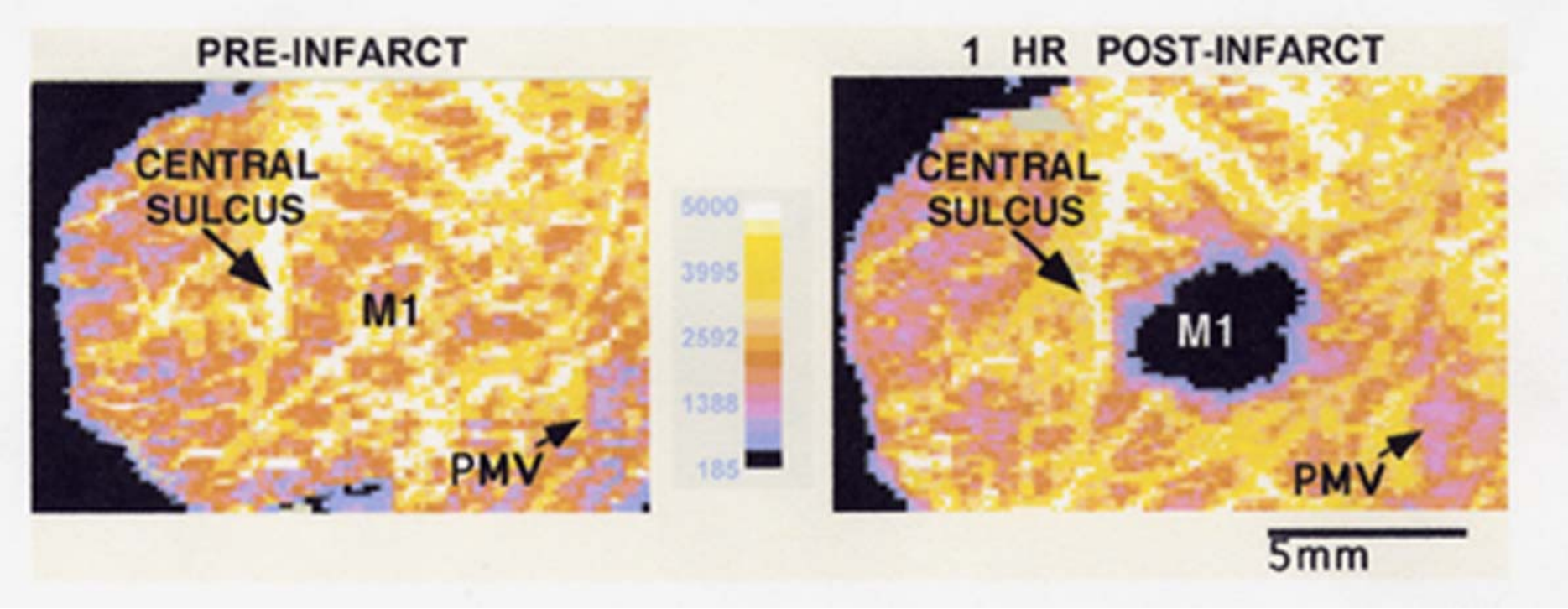
Cortical injury, as might occur in stroke, is frequently found to affect the initiation and execution of muscular contraction in the extremities opposite the side of the injury. In particular, fine manipulative abilities and skilled use of the upper extremity are often degraded (Bucy 1944; Hoffman and Strick 1995). In the weeks and months after injury, a gradual return of some motor abilities occurs (Lashley 1924; Travis and Woolsey 1956), although complete recovery of function is rare in humans (Gowland 1987).

The theory that structures either adjacent or remote from the injured area can assume the function of the damaged cortex, often referred to as vicariation of function or substitution (Munk 1881), has gained additional support due to recent examples of functional plasticity after injury. One study using microelectrode stimulation techniques showed that areas adjacent to damaged portions of motor cortex reorganize after behaviorally contingent electrical stimulation of the ventral tegmentum in rats (Castro-Alamancos et al. 1992). Another study using microelectrode-recording techniques showed that changes in functional representations in somatosensory cortex parallel sensorimotor skill recovery from stroke in adult monkeys, although it is unclear whether improvements reflect a recovery to normal preoperative strategies or the development of new compensatory behavioral strategies (Xerri et al. 1998).

リスザルの運動野（M1)に人工梗塞をつくると、反対側の手指が動かせなくなる（対側麻痺）
リハビリテーション訓練をすると指が動かせるようになる。 腹側運動前野（PMV）が大きくなる
ーーーー遠隔代行作用の報告

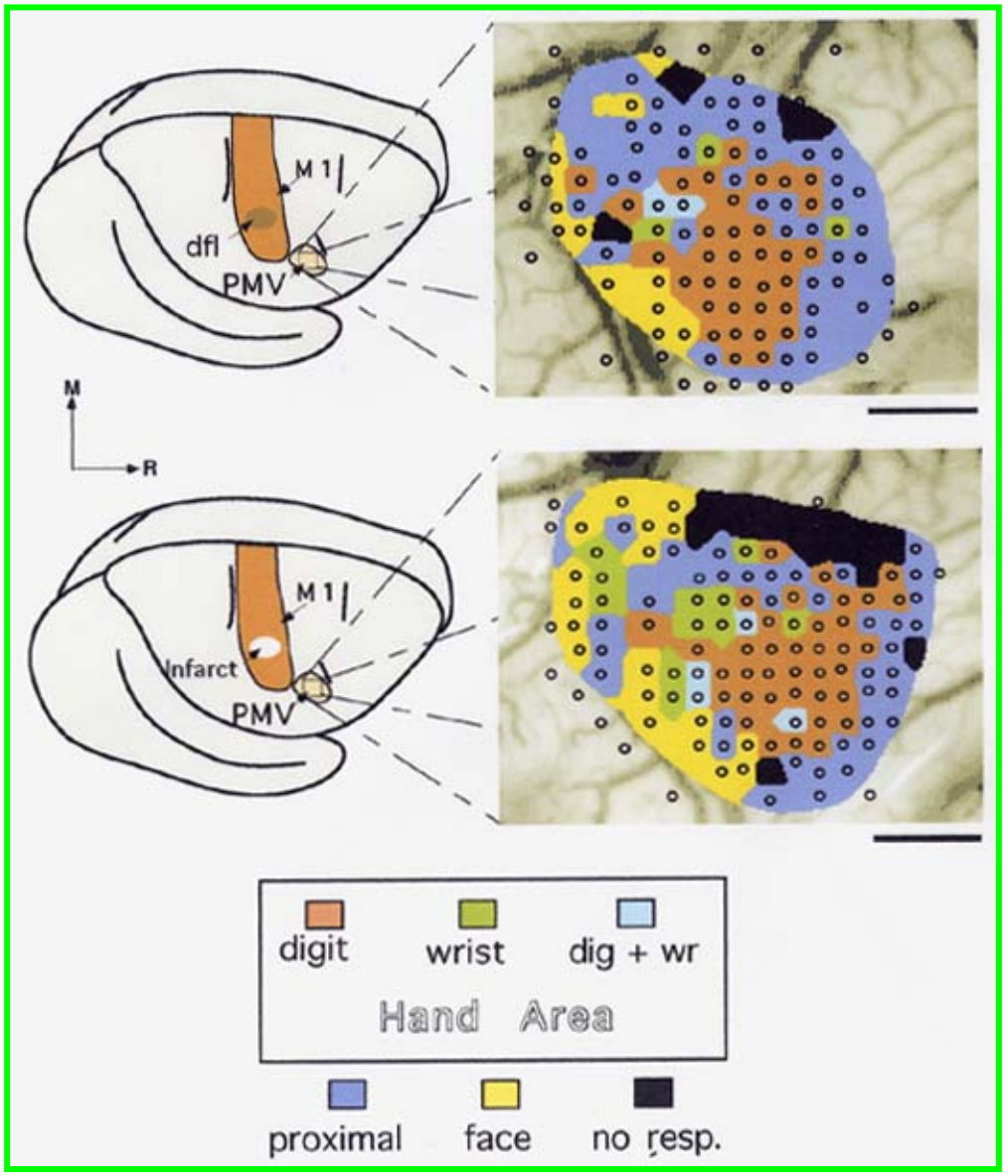
Reorganization of Remote Cortical Regions After Ischemic Brain Injury： Potential Substrate for Stroke Recovery

S.B. Frost, S. Barbay, K.M. Friel, E.J. Plautz and R.J. Nudo



J Neurophysiol 89: 3205-3214 (2003)

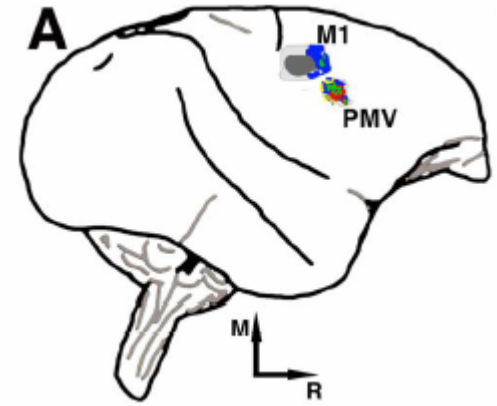
運動野（M1)の手の再現部位に梗塞を起したあと、リハビリテーション訓練（2ヶ月）で、腹側運動前野（VPM)の手の再現部位が大きくなった。

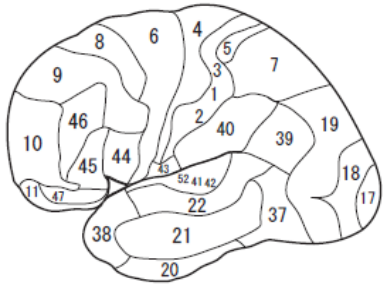


Extensive Cortical Rewiring after Brain Injury

Numa Dancause,[1-3] Scott Barbay,[1-3] Shawn B. Frost,[1-3] Erik J. Plautz,[1-3] Daofen Chen,[4] Elena V. Zoubina,[1-3] Ann M. Stowe,[1-3] and Randolph J. Nudo[1-3]

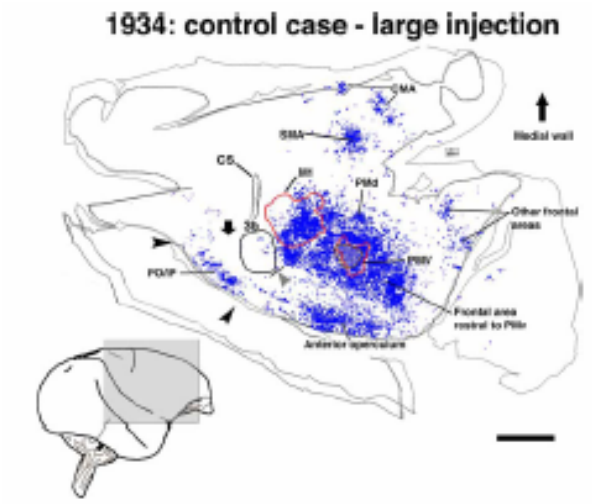
J. Neurosci. ,2005,25:10167-10179

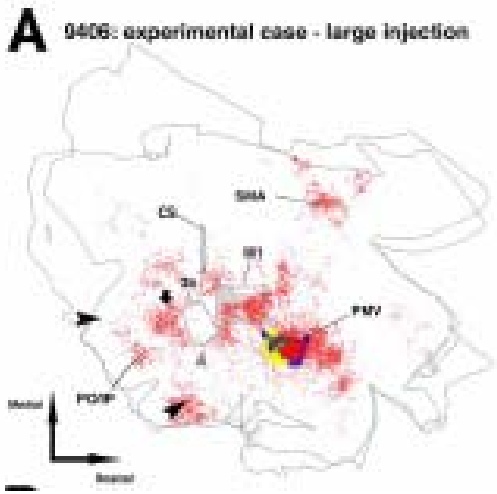


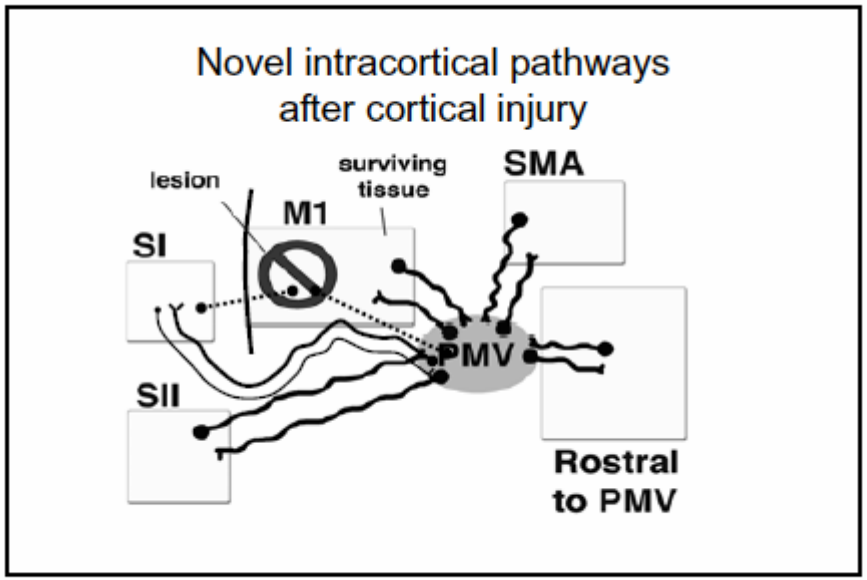


BDA–
Biotinylated

Dextan
Amine






Novel intracortical pathways
after cortical injury
lesion
surviving
tissue
SMA
M1
SI
PMV
SII
Rostral
to PMV

Vicarious Function of Remote Cortex following Stroke: Recent Evidence from Human and Animal Studies

NUMA DANCAUSE
Department of Neurology
University of Rochester

Following a lesion, the adult central nervous system undergoes dramatic structural and physiological reorganization in diverse subcortical and cortical areas. Our knowledge of the events that parallel recovery within the tissue surrounding the lesion and other distant cortical areas has evolved greatly in the past few years. Particularly, recent efforts have increased our understanding of the potential implication of premotor areas in recovery from lesions disturbing the primary motor cortex (M1) and its corticospinal outputs. Because these areas share extensive connections with M1 and have direct access to the spinal cord through corticospinal projections, they are particularly well positioned to take over the role of M1 in a vicarious manner and thus compensate for the neuronal loss resulting from M1 lesions. The impressive postlesional reorganization known to occur in many areas of the CNS including the premotor cortex traditionally has been assumed to play a beneficial role in recovery. However, recent experiments suggest that in some cases, reorganization of distant cortical areas correlates with poor recovery, raising the concept of maladaptive vicarious process. This concept might be particularly critical in the development of new treatment approaches favoring postlesion plasticity and even more so for interventions targeting specific area(s). Here, the author reviews human and animal studies that show the plastic potential of the adult CNS after stroke, highlighting the vicarious role of the premotor cortex in the recovery of motor control. NEUROSCIENTIST 12(6):489–499, 2006. DOI: 10.1177/1073858406292782

KEY WORDS *Motor control, Plasticity, Premotor cortex, Recovery, Stroke*

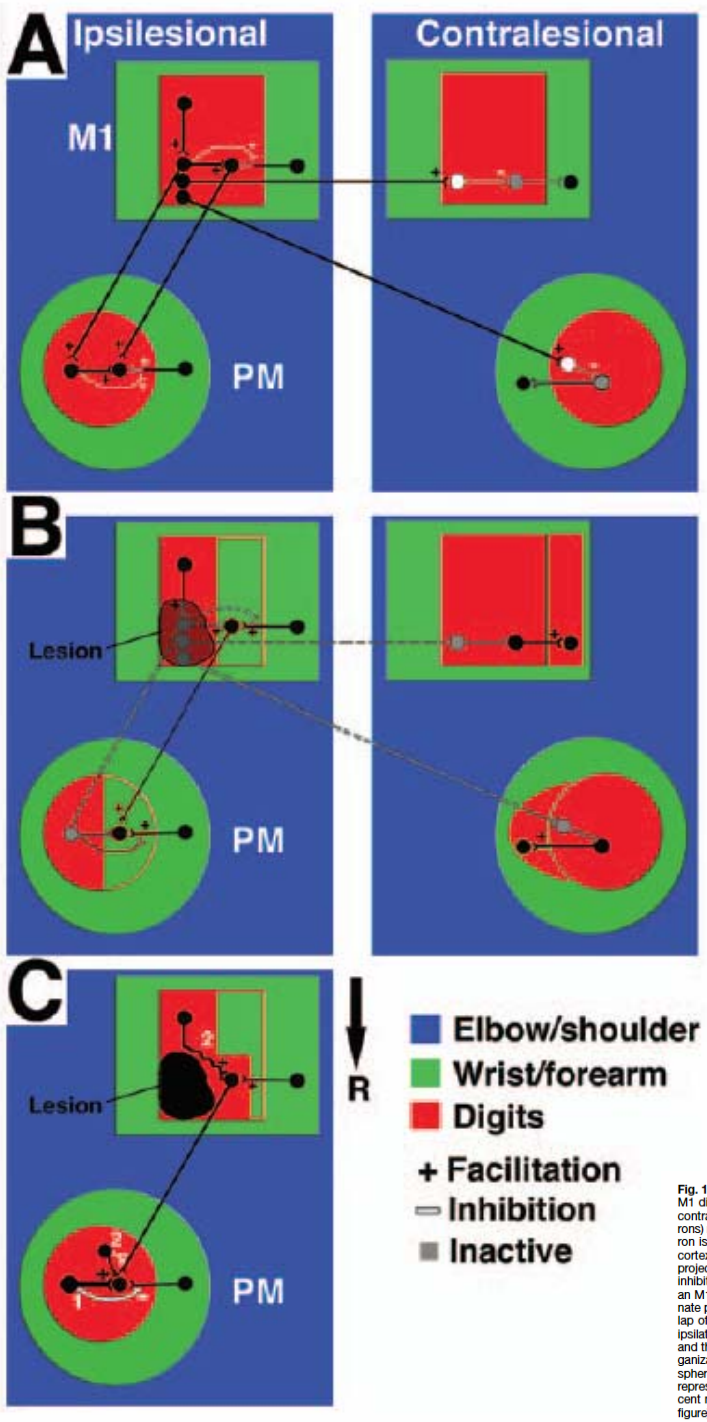


Fig. 1. Cortical reorganization following lesion in M1.

A, Cartoon showing a simplified hypothetical network including the M1 digit representation (red), the M1 wrist/forearm representation (green), and other cortical areas of the ipsilateral and contralateral hemispheres. Within M1, at the border of the digit representation, a neuron (in reality a population of neurons) receives inputs from both the digit representation and the wrist/forearm representation. Prior to the lesion, this neuron is included within the digit representation. Facilitatory projections from the M1 digit representation to the premotor cortex (PM) in the same hemisphere also contribute to the definition of PM digit representation borders. Finally, callosal projections from M1 also contribute to the definition of M1 and PM digit representation borders through facilitation of inhibitory interneurons. Rectangles are M1 representations; circles are premotor representations.

B, Immediate effect of an M1 digit representation lesion resulting from the unmasking of latent connections or recruitment of preexisting alternate parallel pathways. Within M1, there is a further loss of digit representation at the border due to the preexisting overlap of digit and wrist/forearm networks. A comparable reduction of digit representation can be observed in the distant ipsilateral PM area. However, the loss of the callosal projections results in a decrease of inhibition by the interneurons and thus an increase of the digit representation in both M1 and PM.

C, Potential mechanisms underlying the slower reorganization that occurs in association with recovery, learning, and practice. Similar phenomena could occur in both hemispheres, but they are depicted only in the ipsilesional hemisphere here. First (no. 1 in the figure), the later increase of digit representation in M1 and PMv could be due to the increase of facilitation of prelesional network or of inhibition on adjacent networks. For example, this could be due to changes in receptor density or synaptogenesis. Second (no. 2 in the figure), reorganization of the network through formation of novel connections and axonal sprouting could play a role.

Fig. 1. Cortical reorganization following lesion in M1. *A*, Cartoon showing a simplified hypothetical network including the M1 digit representation (red), the M1 wrist/forearm representation (green), and other cortical areas of the ipsilateral and contralateral hemispheres. Within M1, at the border of the digit representation, a neuron (in reality a population of neurons) receives inputs from both the digit representation and the wrist/forearm representation. Prior to the lesion, this neuron is included within the digit representation. Facilitatory projections from the M1 digit representation to the premotor cortex (PM) in the same hemisphere also contribute to the definition of PM digit representation borders. Finally, callosal projections from M1 also contribute to the definition of M1 and PM digit representation borders through facilitation of inhibitory interneurons. Rectangles are M1 representations; circles are premotor representations. *B*, Immediate effect of an M1 digit representation lesion resulting from the unmasking of latent connections or recruitment of preexisting alternate parallel pathways. Within M1, there is a further loss of digit representation at the border due to the preexisting overlap of digit and wrist/forearm networks. A comparable reduction of digit representation can be observed in the distant ipsilateral PM area. However, the loss of the callosal projections results in a decrease of inhibition by the interneurons and thus an increase of the digit representation in both M1 and PM. *C*, Potential mechanisms underlying the slower reorganization that occurs in association with recovery, learning, and practice. Similar phenomena could occur in both hemispheres, but they are depicted only in the ipsilesional hemisphere here. First (no. 1 in the figure), the later increase of digit representation in M1 and PMv could be due to the increase of facilitation of prelesional network or of inhibition on adjacent networks. For example, this could be due to changes in receptor density or synaptogenesis. Second (no. 2 in the figure), reorganization of the network through formation of novel connections and axonal sprouting could play a role.

めざして開発した**強制使用法**は、有効な療法かもしれません。

脳損傷後の回復理論

そもそも、なぜ脳は回復するのでしょうか？　脳機能回復に関しては三つの説が提唱されています。

一つ目は、一九一四年にフォン・モナコウが紹介した、**ディアシーシス**（diaschisis）という概念です。これは、脳のどこかの部位が損傷を受けたとき、位置的には隣接していなくとも神経線維によって結ばれている別の部位が、損傷のあおりを受けて急激に機能障害を起こし、働きが一時的に低下してしまうことをいいます。損傷部位と神経結合をもつ部位は、なにもダメージを受けていないにもかかわらず、結合先からの影響を受けて脳血流が減少し、代謝も減少してしまいます。この場合、数日～数週後には血流量が増し、代謝もさかんになり、機能が回復しはじめます（ディアシーシスの逆転）。

第二の説に**行動学的補償**があります。麻痺などの障害によってできなくなってしまった動作を、いままでとは違ったやり方を発達させることで補うものです。実際、多くの医療関係者はこの説に頼っており、この考え方による治療の最終目標は、いままでとは違った別のやり方を訓練することになります。

たとえば、右手に障害があれば単純に左手を使うことや、遠位筋（指先のほうにある筋肉）に障害があれば近位筋（体幹に近いところにある筋肉）を使うことなどで、多くの手法がこの行動学的補償に分類できます。これはとても重要です。なぜなら、新しいやり方を発達させる場合には、脳が可塑的に変化しているからです。

最後の三番目は**適応的可塑性説**です。長年、機能の**代行作用**（ビカリエーション vicariation）という用語が使われてきた考え方です。損傷を受けていない脳部位が、損傷している脳部位の機能にとって代わるというもので、神経的代償とよばれることもあります。脳の正常な部位が、おそらく脳内に新しい経路をつくり、残されている正常な組織が働いて機能を回復させるというわけです。この章で解説するのは、おもにこの考え方によるものです。

つぎにこれらが脳卒中後にどのように起こるかについて、いくつかの例をあげます。

局所虚血による間接的影響

図3・10は脳梗塞が起きた部位を表す模式図です。これを一次運動野の局所的損傷部位とします。局所虚血の中心部に損傷の中心部があって、そこの神経細胞はすべて死んでいます。そのまわりの領域は梗塞周辺部（ペナンブラ）です。さらにそれを取り囲んでいる、損傷を受けなかっ

教育論文

運動前野の乏血性梗塞のあとの運動前野による代行性機能回復について

日本福祉大学

医師　久保田　　競

ポバースジャーナル　2003年12月　第26巻　第2号（通巻70号）

運動前野の乏血性梗塞のあとの運動前野による代行性機能回復について

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1．Vicarviation（機能代行），Diaschisis（機能中断）について

脳血管が起こると、神経細胞再生しないから、出血で破壊が起これば、すべて結合組織に変わることになる。それでも、失われた機能が回復する場合があるので、そのメカニズムについて考察されて来た。

リハビリテーション訓練する事なしに、機能が回復すれば、自然回復（spontaneous recovery）と考えられてきた。この場合、恒久的な出血が起こってなくて、機能回復があれば、そのように考えなければならないが、機能に関わった神経細胞が死んでも、機能回復することは理解できないことであった。自然回復は、関係した神経細胞が死んでないために起こるのであると考えられてきた。

急性の症状に対してvon Monakow（1914）はdiaschisisディアシージスと呼んだ。適当な日本語訳はない。普通ディアシージスと呼ばれている。

diaschisisに機能中断のことであり、局所の病変によって起こり、遠隔部への興奮性出力がなくなるためと考えるのである。ランダムハウスの辞書ではvon Monakowの考えを正しく伝えている。a disturbance or loss of function in one part of the brain due to a localized injury in another part.とある。ギリシャ語でdiaschisisは分裂（division）を意味する。このように考えられる機能回復もあり、そう考えた神経科学者もいるが今や何もメカニズムを説明しないので捨てられるべき概念である。

機能代行も考えられる。最初に考えたMunk（1881）でvicariation（Vikarierung）とかsubstitutionとかいわれる。失われた機能が、それまでは直接関係なしてなかった神経構造によって引き受けられると考えられるのである（vicarious=performed, exercised, received or suffered in place of another; taking the place of another person or, thinging）。

再現の損傷後の機能回復はこの説を支持する物である。Nudoらがリスザルの運動野に人工梗塞を起こして、強力に手指のリハビリテーションをして機能回復させたのは、機能代行の例である（Nudo ら 1996）。

「手の運動野の梗塞のあと、隣接する手の運動野の、運動再現が変わって、新しく手指の運動の指令を出すようになったと考えられる（隣接代行と呼ばれてよい）。

最近の神経イメージングの研究は、梗塞のあとの可塑的な変化が、離れた場所でも起こる事が報告されている。第一次運動野の除害では血流量の変化が運動前野、補足運動野、対側の運動野で起こる事が報告されている。いくつも論文があり、総説もでている（ramerら、2000）。

これらの変化の起こるメカニズムはまだ発表されていない。機能的な結合のある領域なので、変化の起こる事は予想される。最近、Frostら（2003）が、リスザルで運動前野の人工梗塞のあと、ここと機能結合の強い領域である運動前野が働くようになることを報告した。これが連絡領域でのvicariationの最初の報告例である。

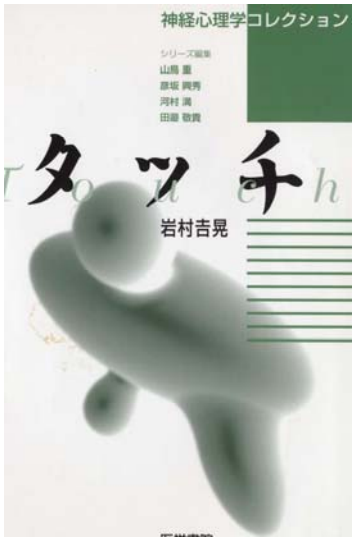
2．簡単なCI療法による治療効果について

CI療法（CIT, Constraint - Induced Movement Therapy）という用語は、欧米の神経学の論文や発表に普通に使われるようになっている。日本ではまだまだ理解されていないので使われていない。神経生理学の基礎的な研究から生まれてきた、証拠に基づいた慢性運動麻痺の治療法といわれるようになって来た。

Liepertsら（2000）が、脳卒中患者でCI療法を試みた時には、健側の1日の運動と覚醒時にはほとんど完全に拘束できるような保定具を使っている。厳重な拘束のためだろう、臨床上の普及が遅れているように思える。

CI療法の簡単なやり方で治療効果があがったという論文が出て来たので紹介する（Sterrら、2003）。

Vicarvation by Premotor Area after Ischemic Infarction in Motor Area
Nihon Fukushi University
Kisou Kubota, M.D.
<キーワード>　CI療法・Vicarvation（機能代行）・運動前野
〒475-0012　愛知県半田市東生久町26-2



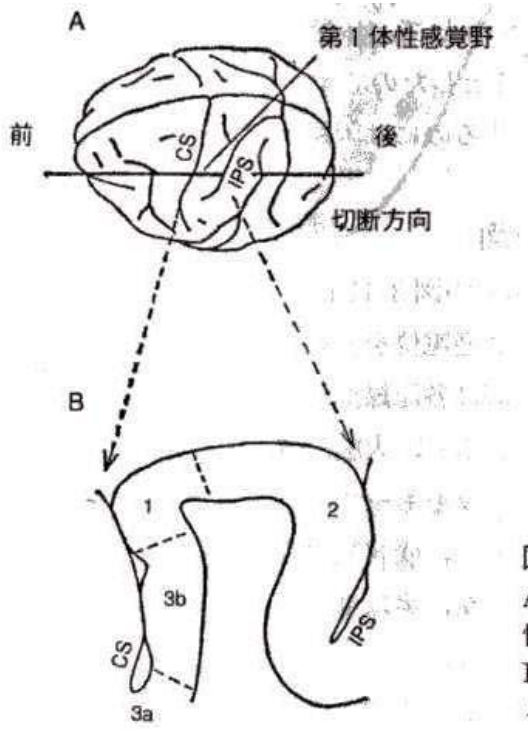


図 3-13　サルの中心後回
A はサルの大脳皮質背側面と第一体性感覚野，CS は中心溝，IPS は頭頂間溝，B は体性感覚野の矢状断面と細胞構築学的区分。

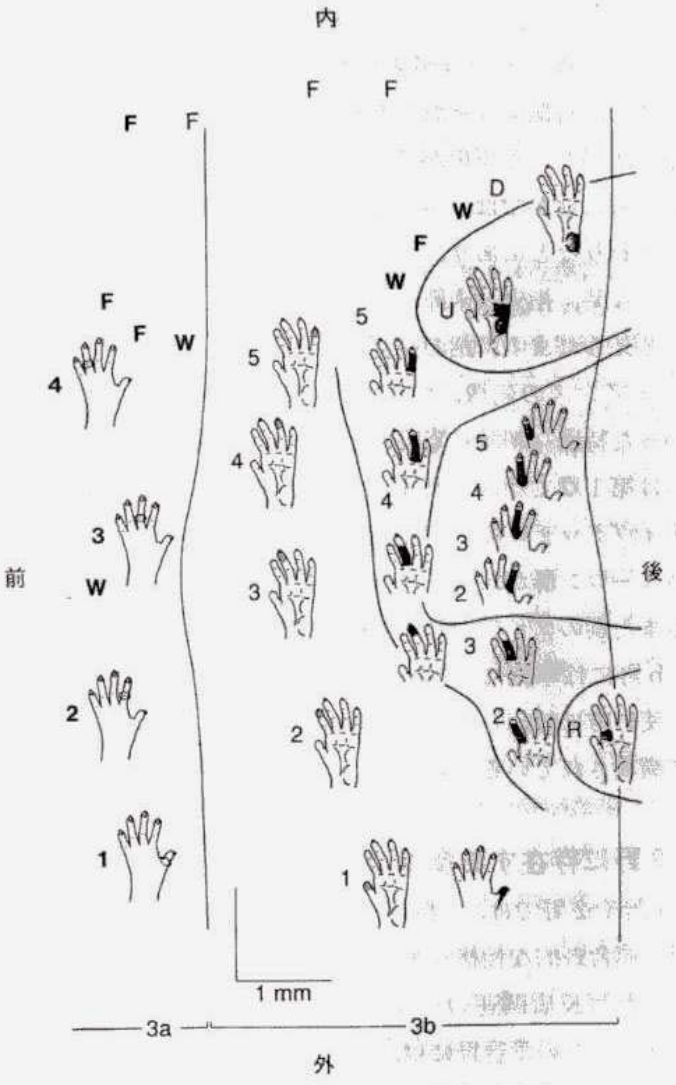


図 3-14　サル第一体性感覚野，3 野における手指再現[29]
数字は指を表す。R：橈側，U：尺側の手掌，D：手背，F：前腕，W：手首関節，細字は皮膚，太字は深部刺激に応じたことを示す。細い線は 3 a，3 b 野の境界（解剖学的）または 3 b 野内のニューロンの受容野からみた機能的区分を示す。

Plasticity of Primary Somatosensory Cortex Paralleling Sensorimotor Skill Recovery From Stroke in Adult Monkeys

CHRISTIAN XERRI, MICHAEL M. MERZENICH, BRET E. PETERSON, AND WILLIAM JENKINS
Keck Center and Coleman Laboratory, University of California at San Francisco, San Francisco, California 94143-0435

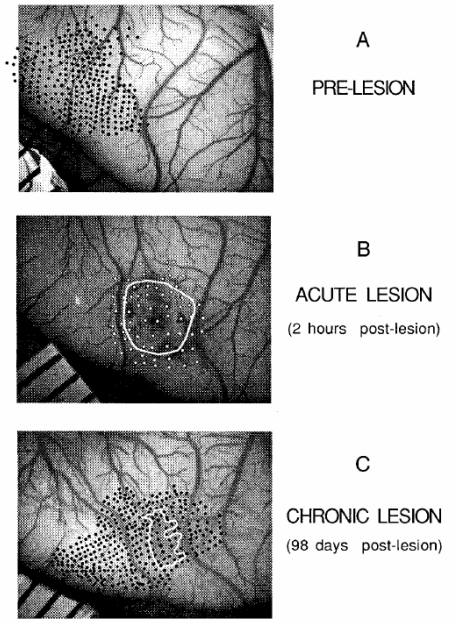
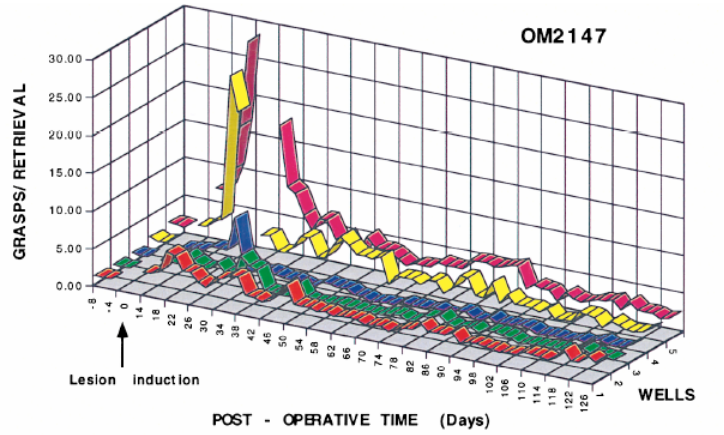


FIG. 1. Typical samples of cortical sites recorded before and after a cortical infarct. ●, microelectrode penetration sites shown over enlarged video images of the right-hemisphere parietal cortex surfaces. These images were captured before *(A)*, immediately after (*B;* acute lesion), and 98 days after the cortical lesion induction *(C)*. Hand zone maps of the primary somatosensory cortex derived from multiunit recordings were reconstructed on the basis of receptive field location (see METHODS). Maps corresponding to the samples shown here are illustrated in Fig. 7. Acute and chronic lesion areas determined electrophysiologically during the 1st 2 h and on the 98th day postlesion are outlined. Note that the area of the cortical zone of injury became smaller after 98 days, as was demonstrated by directly by mapping the ''dead'' cortical zone, and as indicated by a decrease in the distances between cortical surface vascular landmarks, e.g., the large vessels flanking the lesion zone rostrally and caudally. Chronic lesion extent was estimated by determining this reduction in cortical surface area added to the area of the chronically remaining profoundly inactive tissue.



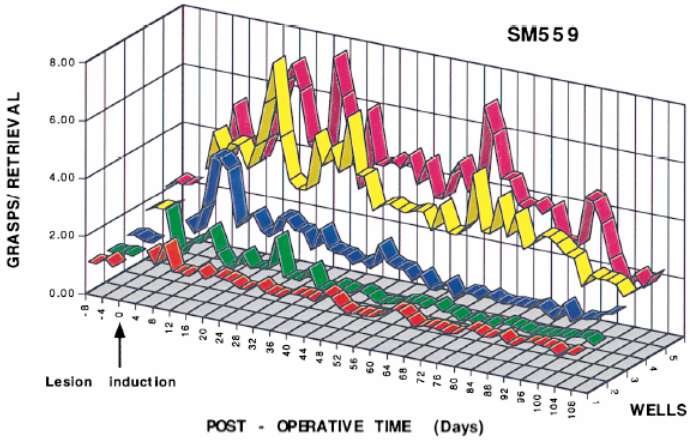


FIG. 2. Postlesion deficits and recovery of mean retrieval performance on a Klüver board. Average number of finger flexions/extensions (grasps per pellet retrieval) as a function of postoperative time, for 5 different-sized food wells for a typical owl monkey *(A)* and squirrel monkey *(B)*. Control data recorded in the final testing sessions preceding the cortical lesion are plotted. Discontinuities in the owl monkey's curves (*wells 4* and *5*) correspond to testing sessions in which the monkey failed to retrieve food pellets in most trials. Note the difference in scale on the ordinate axis for the 2 monkeys cases.

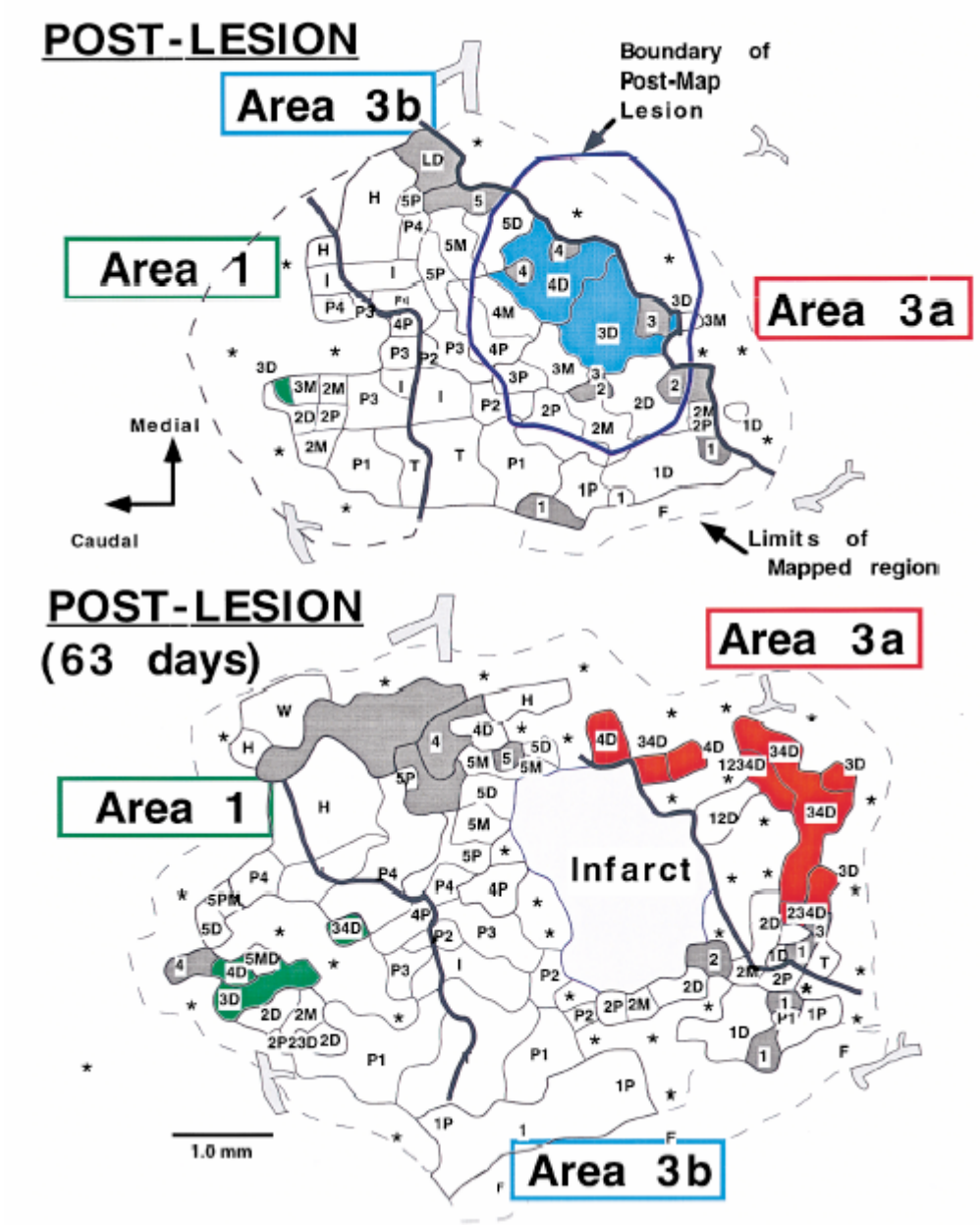


FIG. 6. Postlesion reorganization of the hand representation in owl monkey *OM 2149*. Topographic maps of representation of different skin surfaces on the hand before (in the right hemisphere) and 63 days after induction of a cortical lesion in the digit representation of area 3b. A contralateral-hemisphere control map for this case is illustrated in Fig. 9. Infarcted zone determined on the basis of electrophysiological recordings during the 1st 2 h after the lesion induction is outlined on the prelesion map. Cortical zones of representation of hand surfaces that were employed most heavily in the final phases of recovered behavior (the tips of digits 3 and 4) are highlighted in these map reconstructions: blue for area 3b representations; green for area 1; red for area 3a. Other glabrous (volar) finger representational zones are indicated in light gray. Note that the lesion extended into area 3a. Large numbers 1–5 denote the digits (e.g., 1 = thumb); D, M, and P, distal, middle, and proximal phalanges, respectively; multiple digit representations are shown (e.g., 34D indicates cortical zones in which neurons displayed receptive fields located on the tips of digits 3 and 4); P1–P4, palmar pads at the bases of the digits; H, hypothenar eminence; I, insular zone in the center of the palm; T, thenar eminence; W, wrist; F, face; LD, large dorsum surfaces; * zones over which no cutaneous responses could be evoked. Dorsal skin representational zones are indicated in dark gray. – – –, approximate line of reversal in receptive field sequences that functionally defines the area 3b/area 1 border (Merzenich et al. 1978). ——, estimated area 3a-area 3b border. Black infarct area delimits the zone over which neither cortical spontaneous or driven neuronal discharges could be recorded in the postlesion mapping experiment. Constant vascular landmarks are shown in each map in the experimental hemisphere, to facilitate comparisons. Note the emergence of cutaneous representational zones in both area 3a and area 1.

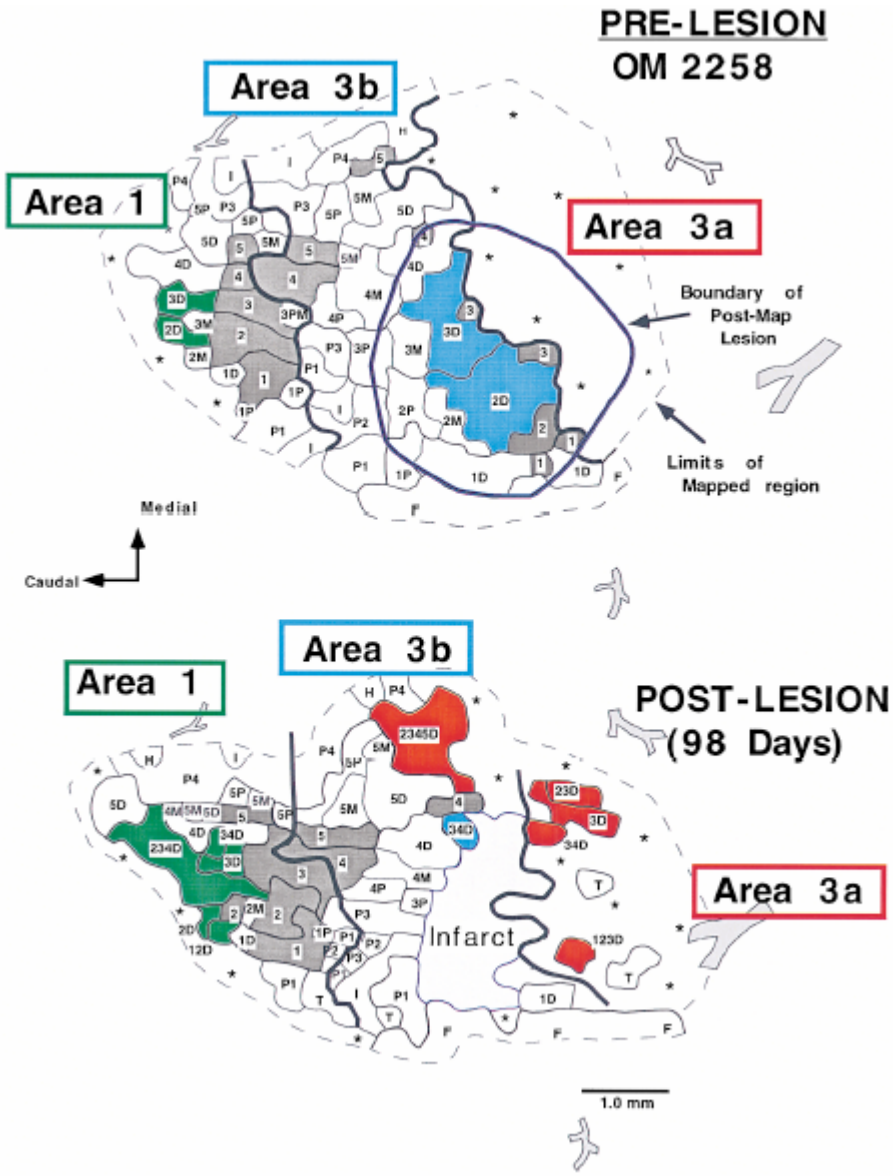


FIG. 7. Postlesion reorganization of the hand representation in owl monkey *OM 2258*. Topographic representations of the hand skin surfaces before and 98 days after induction of a cortical lesion in the digit representation of area 3b. Same conventions as for Fig. 6. Representations of most heavily behaviorally engaged digit tips under the most difficult task conditions in the recovered behavior are again highlighted in color. Contralateral "control" map from this case is illustrated in Fig. 9.

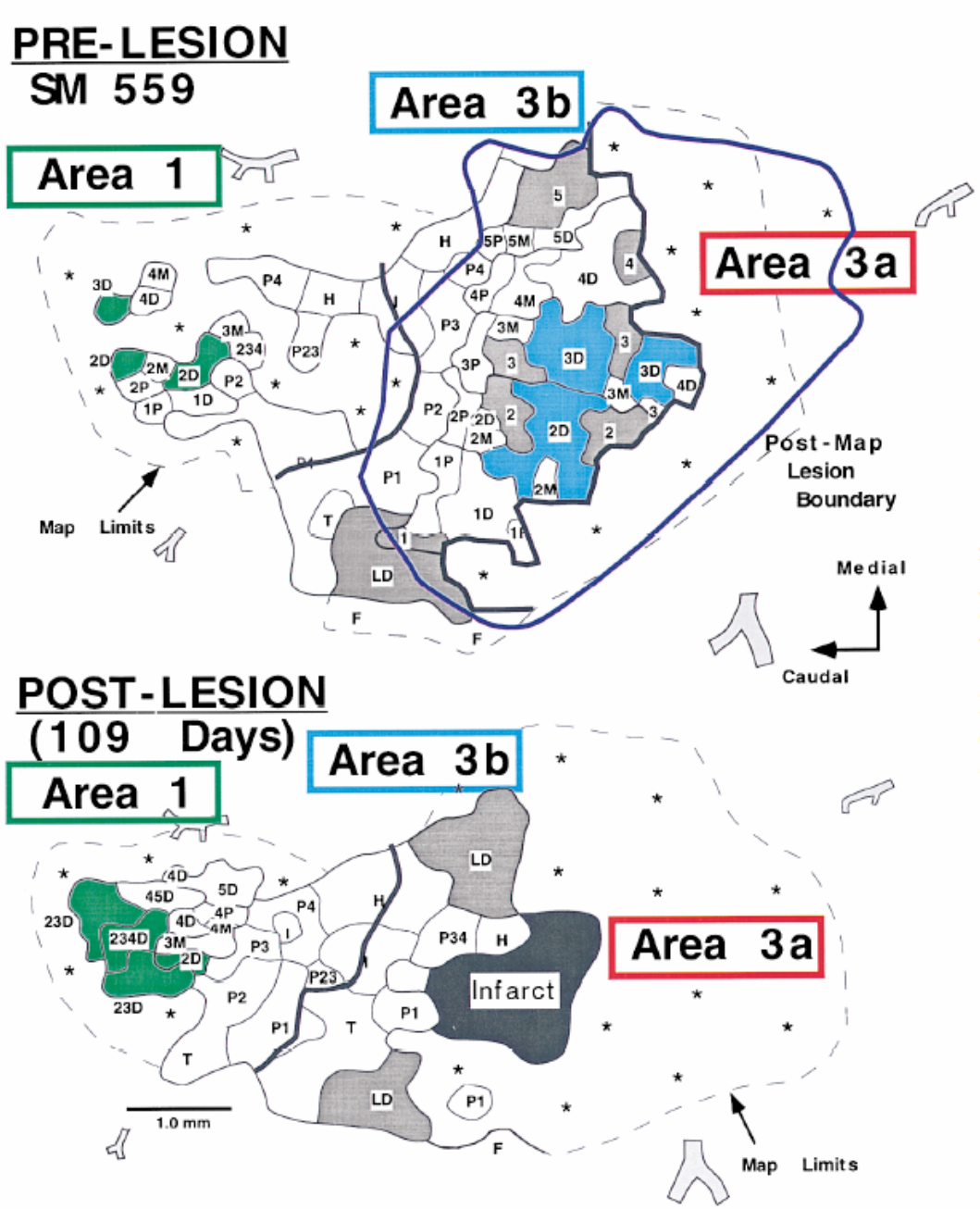


FIG. 8. Postlesion reorganization of the hand representation in squirrel monkey *SM 559*. Topographic representations of the hand before and 109 days after induction of a cortical lesion damaging the entire digit representation in area 3b and a substantial part of area 3a. Same conventions as for Fig. 6. Representations of most heavily behaviorally engaged digit tips in the recovered behavior are again highlighted in color.

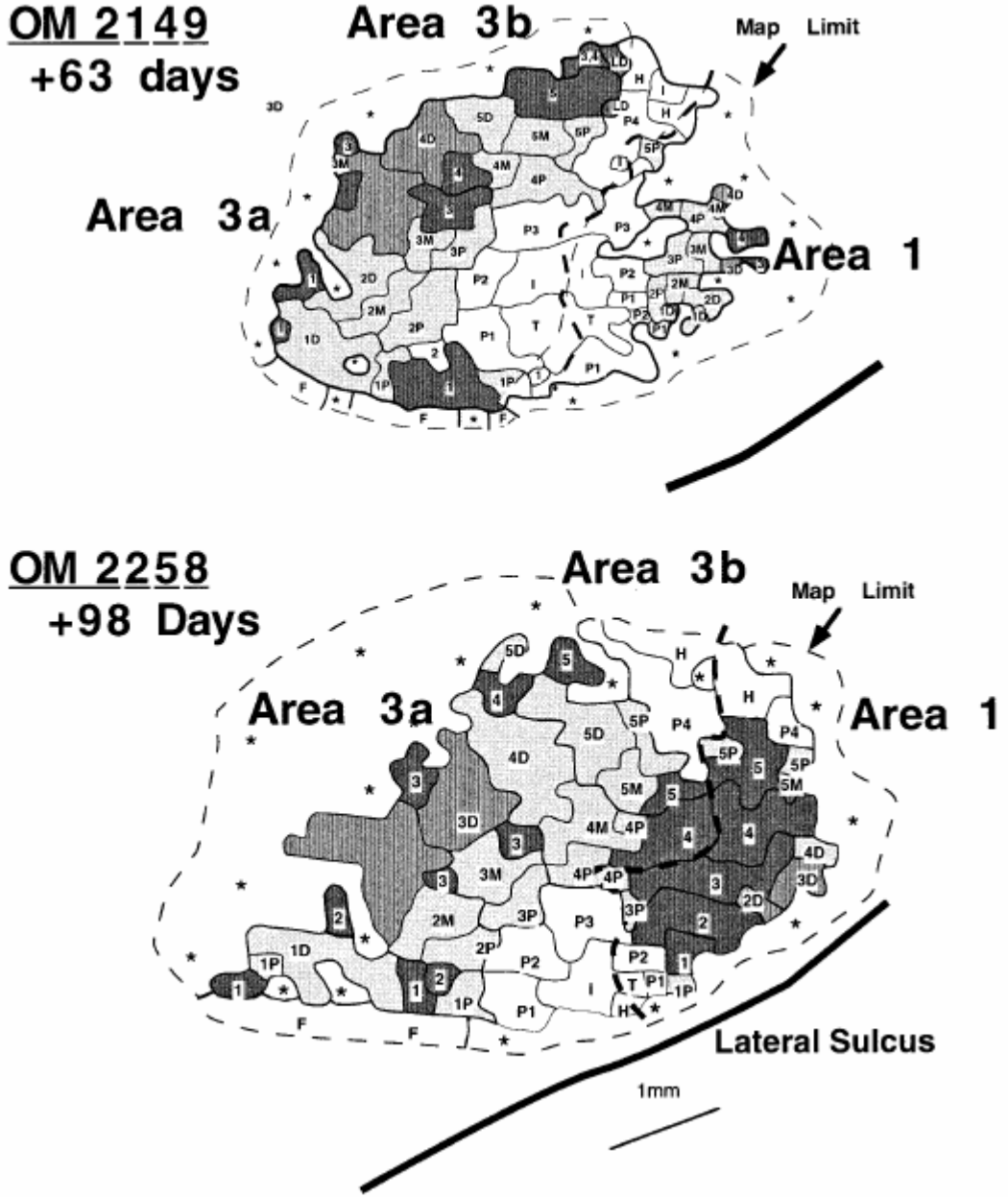


FIG. 9. Contralateral hemisphere "control" maps for *OM 2149* and *OM 2258*. Somatosensory cortex (SI) maps from the lesioned hemispheres in the representative cases illustrated in Figs. 6 and 7. Cross-hatched and dotted cortical zones highlight the territories of representation of digit tips in cortical areas 3b and 1, respectively, that correspond to hand surfaces that were employed most predominantly in pellet retrieval in behaviorally recovered monkeys (see Figs. 6 and 7). Lightly shaded zones mark the territories of representation of the rest of the glabrous (volar) finger surfaces. Dorsal (hairy) skin representational zones are darkly shaded. * Zones in which no cutaneous responses were recorded.

Repetitive Bilateral Arm Training and Motor Cortex Activation in Chronic Stroke

A Randomized Controlled Trial

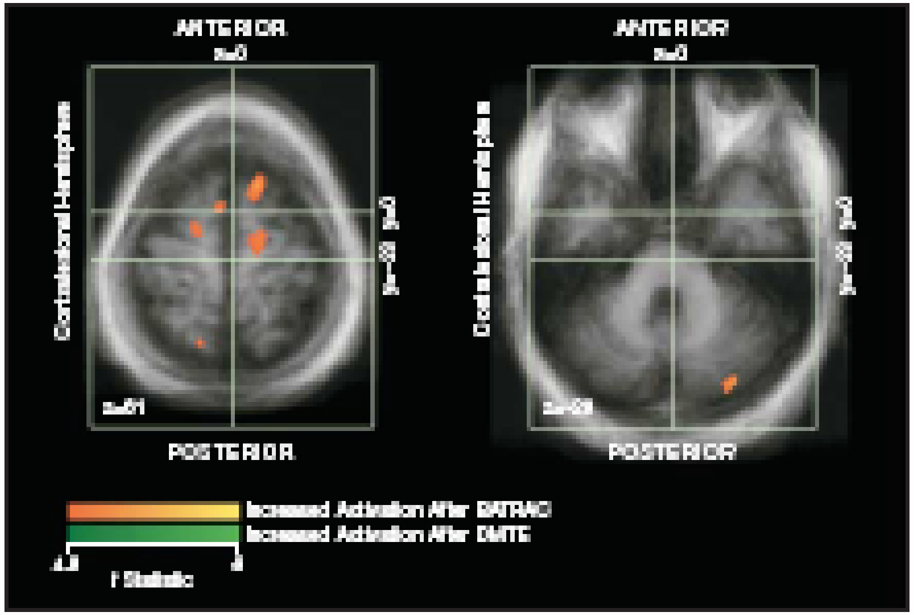
Andreas R. Luft, MD
Sandy McCombe-Waller, PT, PhD
Jill Whitall, PhD
Larry W. Forrester, PhD
Richard Macko, MD
John D. Sorkin, MD, PhD
Jörg B. Schulz, MD
Andrew P. Goldberg, MD
Daniel F. Hanley, MD

Training and Physical Therapy

BATRAC training consisted of hour-long therapy sessions (four 5-minute movement periods interspersed with 10-minute rest periods) 3 times per week for 6 weeks. Upon auditory cues at individually determined rates of 0.67 to 0.97 Hz, participants pushed and pulled bilaterally, in synchrony or alternation, 2 T-bar handles sliding in the transverse plane.[26] DMTE was based on neurodevelopmental principles[27] and included thoracic spine mobilization, scapular mobilization, weight bearing with the paretic arm, and opening a closed fist. DMTEs were administered

in standardized format equal to the time used for BATRAC.

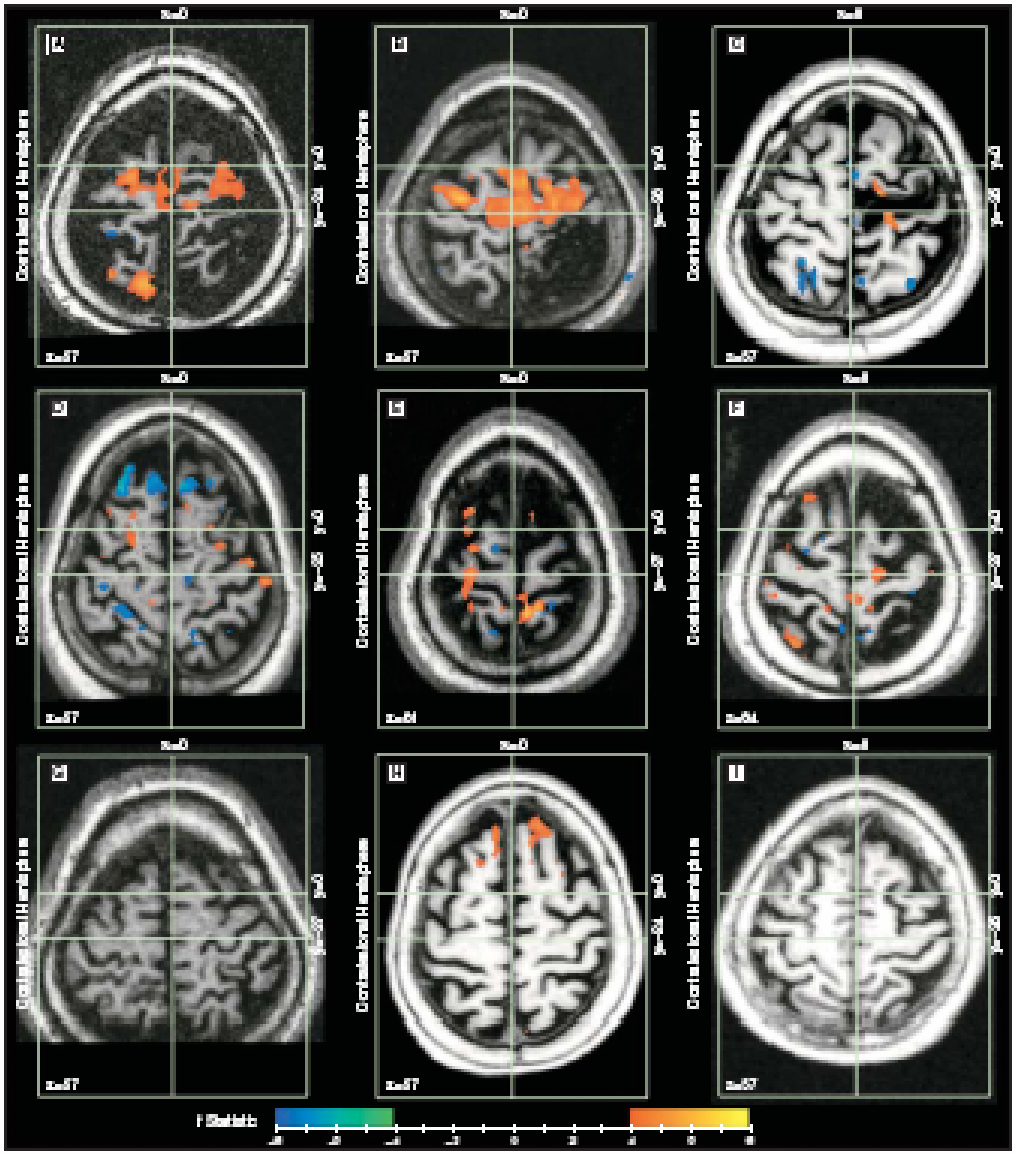
Figure 2. fMRI Images Before and After Intervention (All Patients) During Motion of the Paretic Arm



Two axial sections at different z coordinates representing changes of activation are shown. Areas of yellow-orange indicate increased activation after bilateral arm training with rhythmic auditory cueing (BATRAC); areas of green would indicate increased activation in control patients but none were detected (probability threshold P<.005, corrected for multiple comparisons). In neither group were any areas of decreased activation identified after the intervention. Left panel, Talairach coordinates x, y, z (from anterior to posterior): contralesional: −5/−8/61 (Brodmann area [BA] 6), −17/−7/61 (BA 6), −15/−60/61 (BA 7); ipsilesional: 12/14/61 (BA 6), 12/−13/61 (BA 6). Right panel, ipsilesional: 29/−77/−29 (posterior lobe of cerebellum). DMTE indicates dose-matched therapeutic exercises (control).

JAMA, October 20, 2004—vol. 292, 1853-1861

Figure 3. Functional Magnetic Resonance Images Representing the Difference in Activation in Each Patient Undergoing BATRAC



Lesions are on the right side of the brain; probability threshold P<.001, uncorrected; green-blue indicates decreased activation; yellow-orange, increased. A-F, In 6 of 9 patients, increased activation was seen in the postcentral and posterior inferior gyri (orange-yellow). In a few cases (blue) there was decreased activation. G-I, In 3 patients there was no change in activation of precentral, postcentral, or premotor areas. BATRAC indicates bilateral arm training with rhythmic auditory cueing.

The treatment of chronic behavioural loss following stroke is a major problem in clinical neuroscience. One way to develop new treatments is to use animal models, which have been developed principally in

European Journal of Neuroscience, Vol. 18, pp. 1950–1962, 2003

A comparison of different models of stroke on behaviour and brain morphology

C.L.R. Gonzalez and **B. Kolb**
Department of Psychology and Neuroscience, Canadian Centre for Behavioural Neuroscience, University of Lethbridge, 4401 University Drive, Lethbridge, Alberta T1K 3M4, Canada

Keywords: brain plasticity, Golgi–Cox, ischemia, Long-Evans rat, sensorimotor cortex

Abstract

We compared the effects of three models of permanent ischemia, as well as cortical aspiration, on behaviour and brain morphology. Rats received a stroke either by devascularization or by two different procedures of medial cerebral artery occlusion (MCAO; small vs. large). Animals were trained in a reaching task, forepaw asymmetry, forepaw inhibition, sunflower seed task and tongue extension. Behaviour was assessed 1 week after the lesion and at 2-week intervals for a total of 9 weeks. One week after the surgery all animals were severely impaired on all tasks and although they improved over time they only reached preoperative base lines on tongue extension. Animals with small MCAOs performed better in reaching and sunflower tasks; no other behavioural differences were detected among the groups. Pyramidal cells in forelimb and cingulate areas as well as spiny neurons of the striatum were examined for dendritic branching and spine density using a Golgi–Cox procedure. Each lesion type had a different impact on cell morphology. Overall, different changes (atrophy or hypertrophy) were observed with each kind of lesion and these changes were specific for the region (forelimb, cingulate, striatum) and the condition (intact vs. damaged hemisphere). These results suggest that: (i) different lesions to the motor cortex produce subtle differences in behaviour, and (ii) the method used to induce the lesion produces striking differences in cortical and subcortical plasticity.

Introduction

The treatment of chronic behavioural loss following stroke is a major problem in clinical neuroscience. One way to develop new treatments is to use animal models, which have been developed principally in rodents, to mimic the pathology of stroke and to try to understand the basic mechanisms which might underlie functional improvement. There are a wide variety of models of stroke (for a review see Hossmann, 1998), however, including models of global and focal ischemia (e.g. transient vessel occlusion) and focal infarction (e.g. permanent vessel occlusion). Behavioural studies of transient ischemia have tended to focus on hippocampal-dependent behaviour (and hippocampal cell loss) whereas studies of focal infarction have neuronal plasticity such as growth-associated protein-43 (GAP-43) and basic fibroblast growth factor (bFGF; Szele *et al.*, 1995; Uryu *et al.*, 2001). In another experiment, Voorhies & Jones (2002) compared the effects of electrolytic vs. aspiration lesions of the motor cortex and found hypertrophy in layer V pyramidal cells of the forelimb area opposite to the lesion after electrolytic but not aspiration lesions. Furthermore, interventions after stroke can have different effects depending on the method used to induce the lesion. Zeng *et al.* (2000), for example, have suggested that the host-to-graft connections are better when fetal neocortical tissue is transplanted into an infarct cavity than into an aspiration cavity.

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Evidence for bilateral control of skilled movements: ipsilateral skilled forelimb reaching deficits and functional recovery in rats follow motor cortex and lateral frontal cortex lesions

Claudia L. R. Gonzalez, Omar A. Gharbawie, Preston T. Williams, Jeffrey A. Kleim, Bryan Kolb and Ian Q. Whishaw
Canadian Centre for Behavioural Neuroscience, University of Lethbridge, 4401 University Dr., Lethbridge, AB T1K 3M4, Canada

Keywords: ipsilateral motor impairments, ipsilateral motor recovery, Long-Evans rat, middle cerebral artery stroke, motor cortex stroke, skilled forelimb use, stroke and recovery of function

Abstract

Unilateral damage to cortical areas in the frontal cortex produces sensorimotor deficits on the side contralateral to the lesion. Although there are anecdotal reports of bilateral deficits after stroke in humans and in experimental animals, little is known of the effects of unilateral lesions on the same side of the body. The objective of the present study was to make a systematic examination of the motor skills of the ipsilateral forelimb after frontal cortex lesions to either the motor cortex by devascularization of the surface blood vessels (pial stroke), or to the lateral cortex by electrocoagulation of the distal branches of the middle cerebral artery (MCA stroke). Plastic processes in the intact hemisphere were documented using Golgi–Cox dendritic analysis and by intracortical microstimulation analysis. Although tests of reflexive responses in forelimb placing identified a contralateral motor impairment following both cortical lesions, quantitative and qualitative measures of skilled reaching identified a severe ipsilateral impairment from which recovery was substantial but incomplete. Golgi-impregnated pyramidal cells in the forelimb area showed an increase in dendritic length and branching. Electrophysiological mapping showed normal size forelimb representations in the lesioned rats relative to control animals. The finding of an enduring ipsilateral impairment in skilled movement is consistent with a large but more anecdotal literature in rats, nonhuman primates and humans, and suggests that plastic changes in the intact hemisphere are related to that hemisphere's contribution to skilled movement.

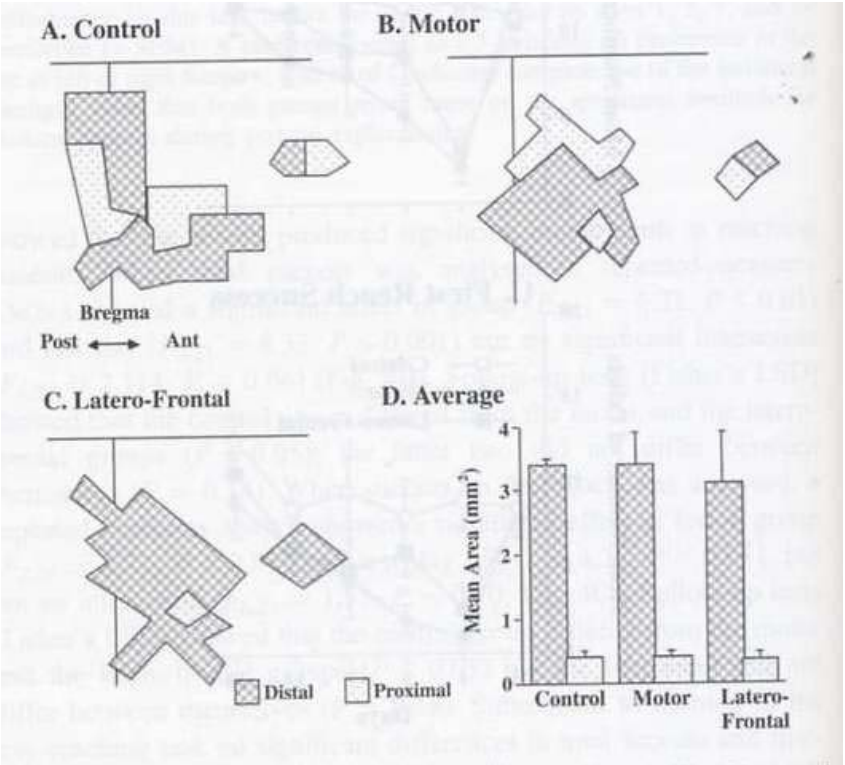


FIG. 8. Representative maps of (A) control, (B) motor cortex lesion, and (C) latero-frontal cortex lesion showing distal (digit and wrist) and proximal (elbow and shoulder) areas. (D) Mean area (mm^2) of movement representations.

ELSEVIER

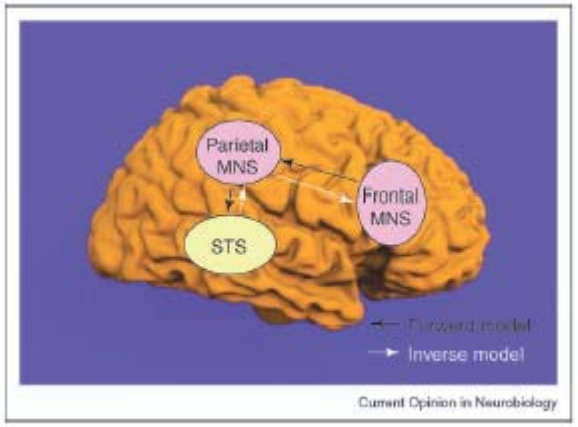
Neural mechanisms of imitation

Marco Iacoboni

Neural mechanisms of imitative learning and social mirroring. In this model, imitative learning is implemented by interactions among the core imitation circuit, the dorsolateral prefrontal cortex (BA46) and a set of areas relevant to motor preparation (PMd, pre-SMA, SPL), whereas social mirroring is implemented by the interactions among the core imitation circuit, the insula and the limbic system. Abbreviations: BA46, Brodmann area 46; MNS, mirror neuron system; PMd, dorsal premotor cortex; pre-SMA, pre-supplementary motor area; SPL, superior parietal lobule STS, superior temporal sulcus.

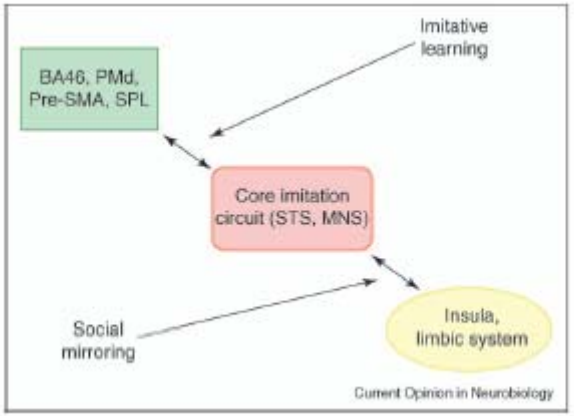
真似学習と社会的ミラー関係

真似に関係する中心回路



MNS:鏡ニューロン系

STS:上側頭溝



Neural mechanisms of imitation. Shown is a representation of the core circuitry for imitation on the lateral wall of the right cerebral hemisphere, together with the internal models the circuitry implements during imitation. Abbreviations: MNS, mirror neuron system; STS, superior temporal sulcus.

Current Opinion in Neurobiology 2005, 15:632–637 www.sciencedirect.com

BA46（ブロードマン46野）と運動準備領域（背側運動野、前補足運動野と上側頭回が働いて真似学習が起こる。

社会的ミラーニューロン系は、島部（BA44），辺縁系が働く。

サルの運動前野の腹外側部でミラーニューロンが見付かった（Mirror neuron in PMv （Rizzolatti ら, Cog Brain Res 1996）。

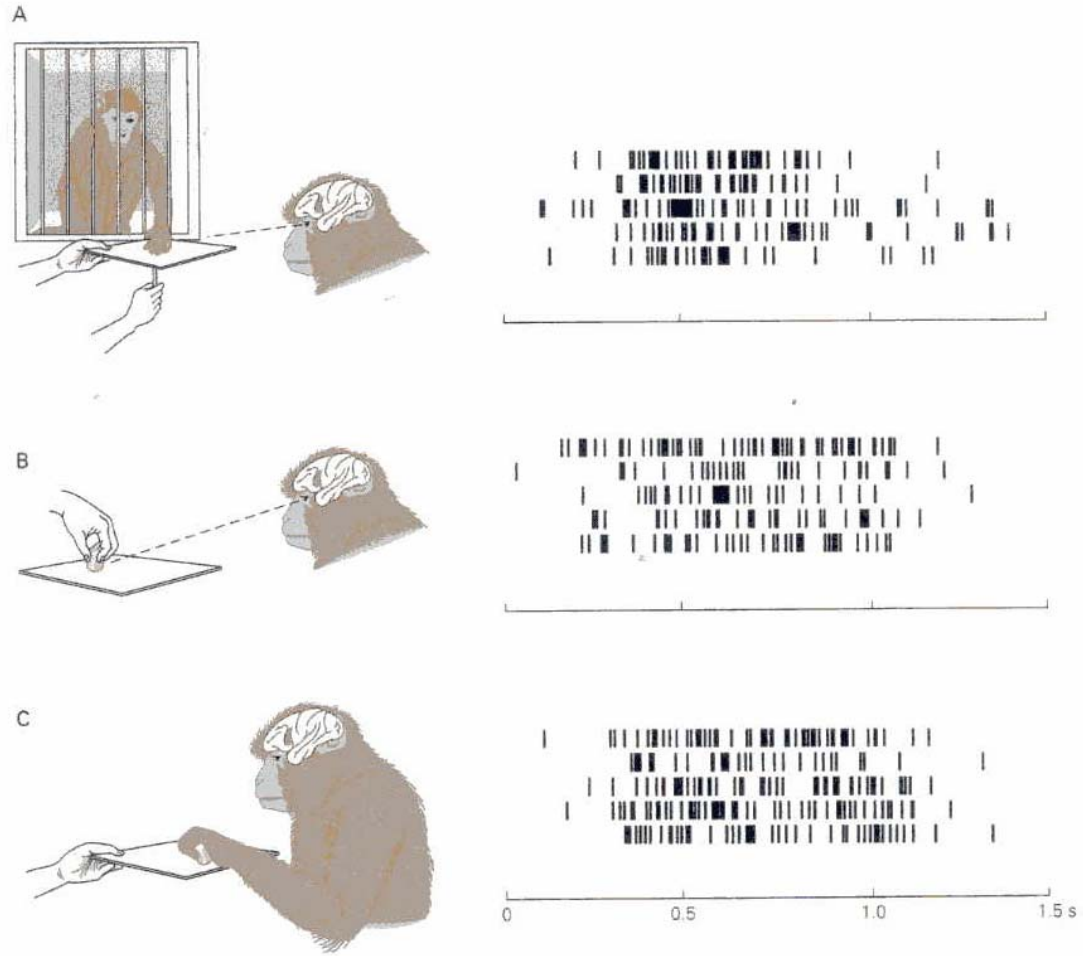


Figure 38-22 An individual cell in the ventral premotor area is active whether the monkey performs a task or observes someone else perform the task. The fact that the same cell is active during action or observation suggests that it is involved in the abstract representation of the motor task.

A. Activity in the neuron as the monkey observes another monkey make a precision group.

B. Activity in the same neuron as the monkey observes the human experimenter make the precision grip.

C. Activity in the same neuron as the monkey itself performs a precision grip. (From Rizzolotti et al 1996.)

SHORT COMMUNICATION

Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study

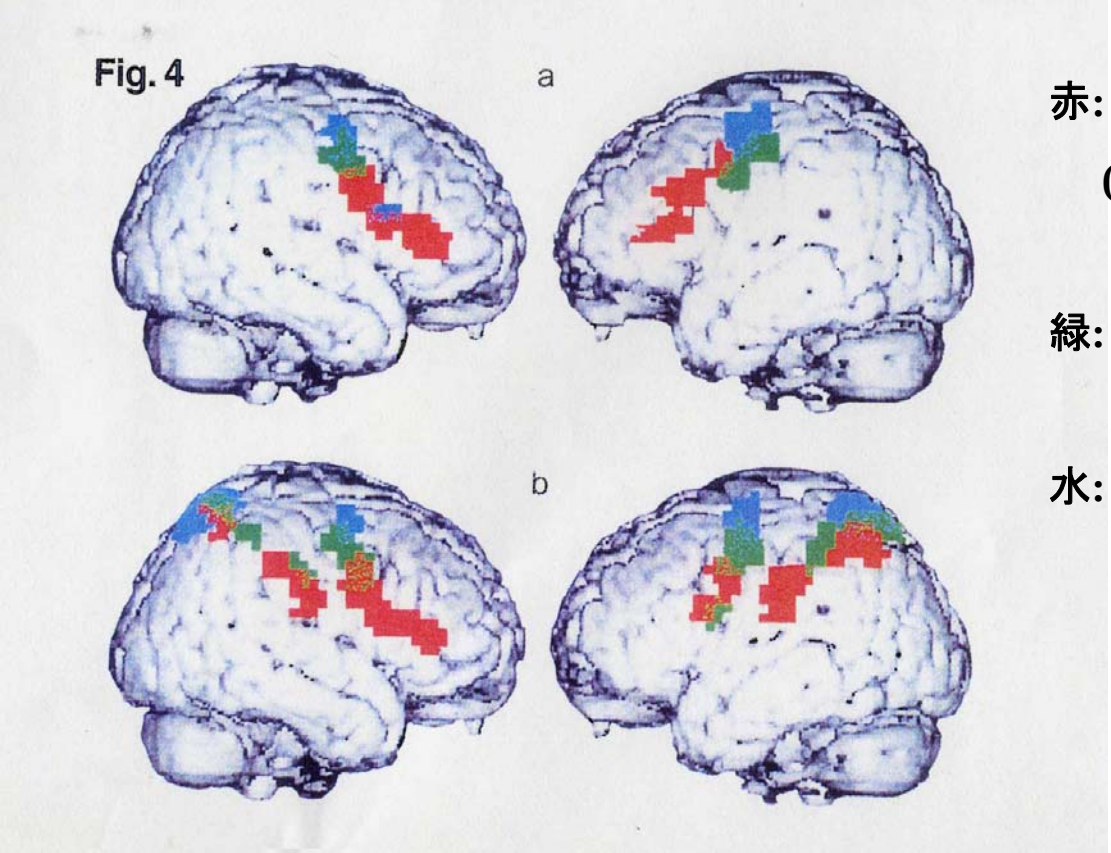
G. Buccino, F. Binkofski,[1] G. R. Fink,[1,2] L. Fadiga, L. Fogassi, V. Gallese, R. J. Seitz,[1] K. Zilles,[2] G. Rizzolatti and H.-J. Freund[1]

Istituto di Fisiologia Umana, Università di Parma, Via Volturno 39, I-43100 Parma, Italy
[1]Department of Neurology, Heinrich Heine University of Duesseldorf, 5 Moorenstrasse, D-40225, Duesseldorf, Germany
[2]Institute of Medicine, Research Center Juelich GmbH, Germany

Keywords: action observation, humans, mirror system, parietal lobe, premotor cortex

ブッチ―ノらによる（2001）、

動作を見ると運動前野と頭頂連合野が、体部位局在的に、働く。



赤: (a) 噛むのを見る

(b)リンゴを噛むのを見る

緑: (a)ボールを掴む真似を見る

(b)ボールを掴むのを見る

水: (a) ボールを蹴る真似を見る

(b)ボールを蹴るのを見る

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Motor Facilitation During Action Observation: A Magnetic Stimulation Study

L. FADIGA, L. FOGASSI, G. PAVESI, AND G. RIZZOLATTI
Istituto di Fisiologia Umana and Clinica Neurologica, Università di Parma, I-43100 Parma, Italy

SUMMARY AND CONCLUSIONS

1. We stimulated the motor cortex of normal subjects (transcranial magnetic stimulation) while they *1*) observed an experimenter grasping 3D-objects, 2) looked at the same 3D-objects, *3*) observed an experimenter tracing geometrical figures in the air with his arm, and *4*) detected the dimming of a light. Motor evoked potentials (MEPs) were recorded from hand muscles.

2. We found that MEPs significantly increased during the conditions in which subjects observed movements. The MEP pattern reflected the pattern of muscle activity recorded when the subjects executed the observed actions.

3. We conclude that in humans there is a system matching action observation and execution. This system resembles the one recently described in the monkey.

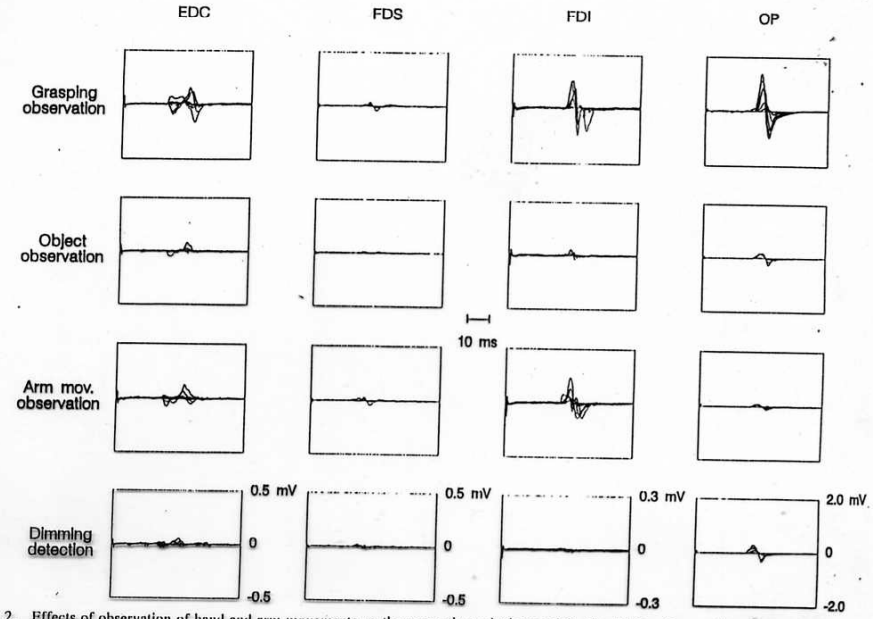


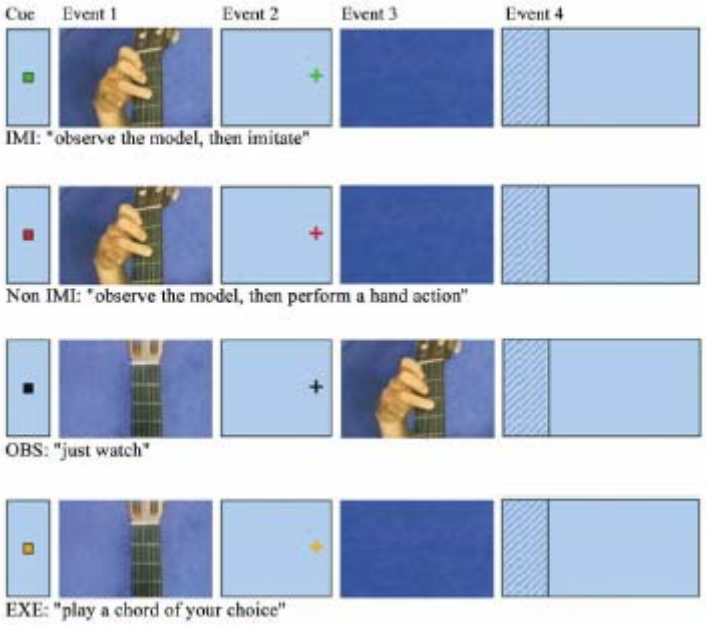
FIG. 2. Effects of observation of hand and arm movements on the magnetic evoked potentials. The MEPs of one subject are presented. Each panel shows all superimposed responses ($n = 8$) evoked from the indicated muscle in one condition. Traces are aligned with and shown from the stimulus onset.

手の運動を見たときに運動前野を磁気刺激すると、手が動く

Neuron, Vol. 42, 323–334, April 22, 2004, Copyright ©2004 by Cell Press

Neural Circuits Underlying Imitation Learning of Hand Actions: An Event-Related fMRI Study

Giovanni Buccino,[1] Stefan Vogt,[2] Afra Ritzl,[3]
Gereon R. Fink,[3,4] Karl Zilles,[3,5]
Hans-Joachim Freund,[3] and Giacomo Rizzolatti[1,*]
[1]Dipartimento di Neuroscienze
Università di Parma
Parma 43100



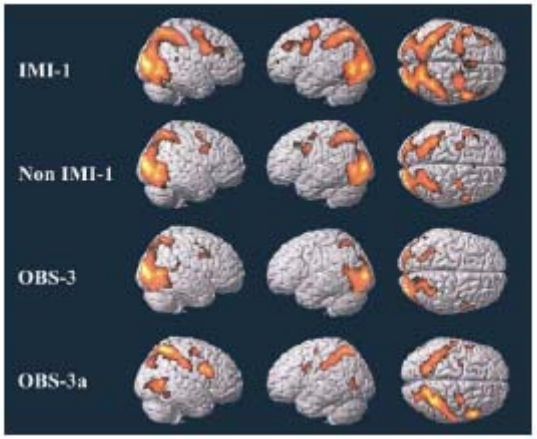


Figure 2. Cortical Areas Activated during the Event in Which Participants Observed the Guitarist Executing the Guitar Chords

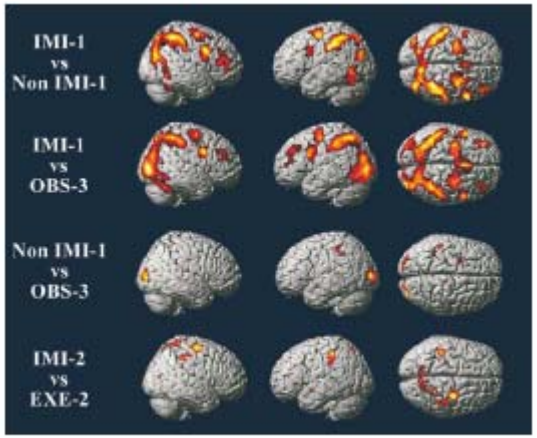


Figure 3. Direct Comparison between Identical Events in Different Conditions

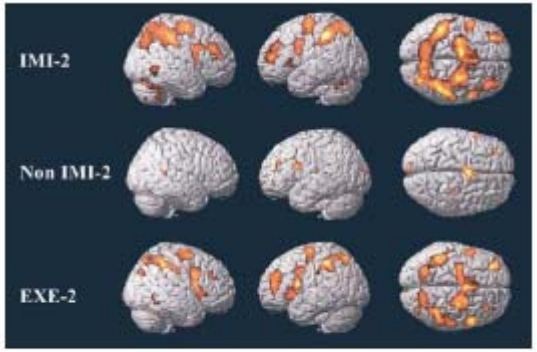


Figure 4. Cortical Areas Activated during the Pause Event in the Different Experimental Conditions

TMS

EPB
FPB

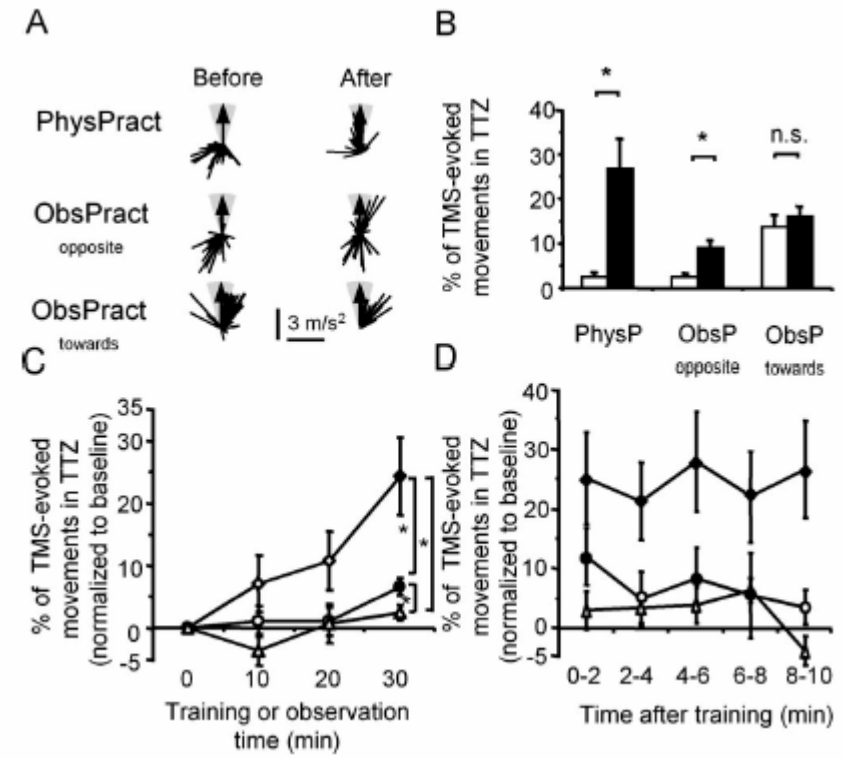
Behavioral/Systems/Cognitive

Formation of a Motor Memory by Action Observation

Katja Stefan,[1,3] Leonardo G. Cohen,[1] Julie Duque,[1] Riccardo Mazzocchio,[1] Pablo Celnik,[1] Lumy Sawaki,[1] Leslie Ungerleider,[2] and Joseph Classen[3]
[1]Human Cortical Physiology Section, National Institute of Neurological Disorders and Stroke–National Institutes of Health (NIH), Bethesda, Maryland 20892, [2]Laboratory of Brain and Cognition, National Institute of Mental Health–NIH, Bethesda, Maryland 20892, and [3]Human Cortical Physiology and Motor Control Laboratory, Department of Neurology, University of Würzburg, 97080 Würzburg, Germany

Mirror neurons discharge with both action observation and action execution. It has been proposed that the mirror neuron system is instrumental in motor learning. The human primary motor cortex (M1) displays mirror activity in response to movement observation, is capable of forming motor memories, and is involved in motor learning. However, it is not known whether movement observation can lead directly to the formation of motor memories in the M1, which is considered a likely physiological step in motor learning. Here, we used transcranial magnetic stimulation (TMS) to show that observation of another individual performing simple repetitive thumb movements gives rise to a kinematically specific memory trace of the observed motions in M1. An extended period of observation of thumb movements that were oriented oppositely to the previously determined habitual directional bias increased the probability of TMS-evoked thumb movements to fall within the observed direction. Furthermore, the acceleration of TMS-evoked thumb movements along the principal movement axis and the balance of excitability of muscle representations active in the observed movements were altered in favor of the observed movement direction. These findings support a role for the mirror neuron system in memory formation and possibly human motor learning.

Key words: action observation; motor cortex; human; plasticity; mirror neuron system; memory



観察した運動の記憶は運動野に残る

10秒1回

親指の運動

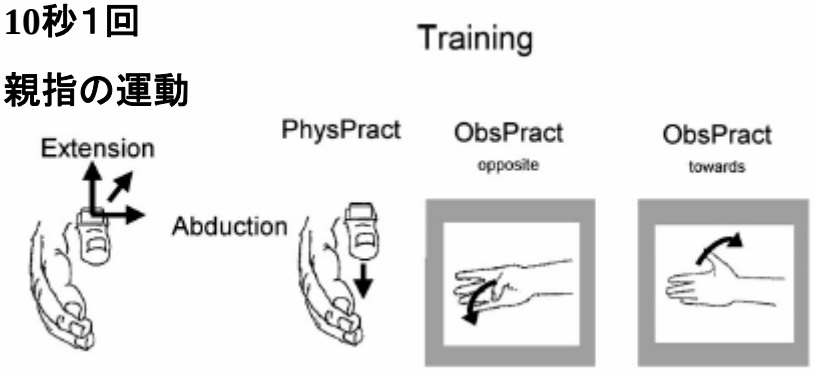


Figure 1. Experimental design. At the beginning of each session, the direction of TMS-evoked movements ("baseline before training") was determined in each individual by assessing the first-peak accelerations along the extension/flexion and abduction/adduction axes (Classen et al., 1998). Subsequently, subjects participated in three different training sessions: physical training, which consisted of performance of voluntary thumb movements in a direction opposite the baseline direction and observation of thumb movements directed opposite the baseline direction and toward the baseline direction.

Figure 2. Effect of different training interventions on TMS-evoked movement direction. ***A***, Example of one subject. First-peak acceleration vectors of TMS-evoked thumb movements before (left) and after (right) each of the three interventions (PhysPract, $ObsPract_{opposite}$, and $ObsPract_{toward}$). For better comparability, all examples are aligned to the training direction indicated by the arrow. The TTZ is shown in gray. PhysPract and $ObsPract_{opposite}$, but not $ObsPract_{toward}$, led to substantial changes in the direction of TMS-evoked movements. ***B***, Group data ($n = 10$) showing the P_{TTZ} before and after PhysPract, $ObsPract_{opposite}$, and $ObsPract_{toward}$. Before the training interventions, the percentage of TMS-evoked movements in TTZ was similar in PhysPract and $ObsPract_{opposite}$. PhysPract and $ObsPract_{opposite}$, but not $ObsPract_{toward}$, led to a significant increase in the percentage of TMS-evoked movements falling into TTZ. Data show means ± SEM. *$p < 0.005$. n.s., Not significant. ***C***, Time course of changes of P_{TTZ} as a function of training intervention. To compare between conditions, ΔP_{TTZ} was computed as the baseline-normalized, intervention-dependent change in percentage of TMS-evoked thumb movements falling into the TTZ (see Materials and Methods). At the end of 30 min, the percentage change of TMS-evoked movements in TTZ was larger in PhysPract than in $ObsPract_{opposite}$ or $ObsPract_{toward}$ and with $ObsPract_{opposite}$ than with $ObsPract_{toward}$. Rhombi, PhysPract; circles, $ObsPract_{opposite}$; triangles, $ObsPract_{toward}$. Filled symbols, Time points significantly different from baseline; two-tailed *t* tests; false discovery rate correction. *$p < 0.05$. ***D***, Duration of changes of P_{TTZ} as a function of training intervention. Symbols as in ***C***. Error bars represent SEM.

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SHORT COMMUNICATION
The essential role of Broca's area in imitation

Marc Heiser,[1,7] Marco Iacoboni,[1,2,6] Fumiko Maeda,[1,3] Jake Marcus[1] and John C. Mazziotta[1,3,4,5,6]

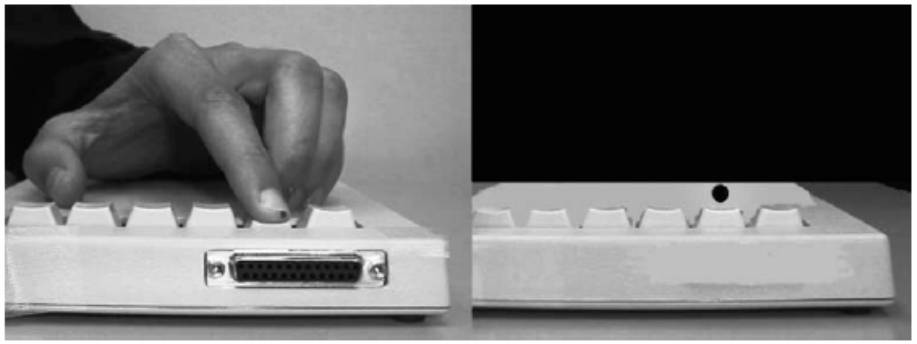

FIG. 1. Left (imitation task): subjects were shown a sequence of finger movements pressing keys on a keypad and were instructed to imitate the finger movements with their right hand. Right (control task): subjects were shown a moving dot and were instructed to use the right finger corresponding to the starting position of the dot to press the keys on the keypad cued by the moving dot. In the case depicted here, subjects would be using the little finger.

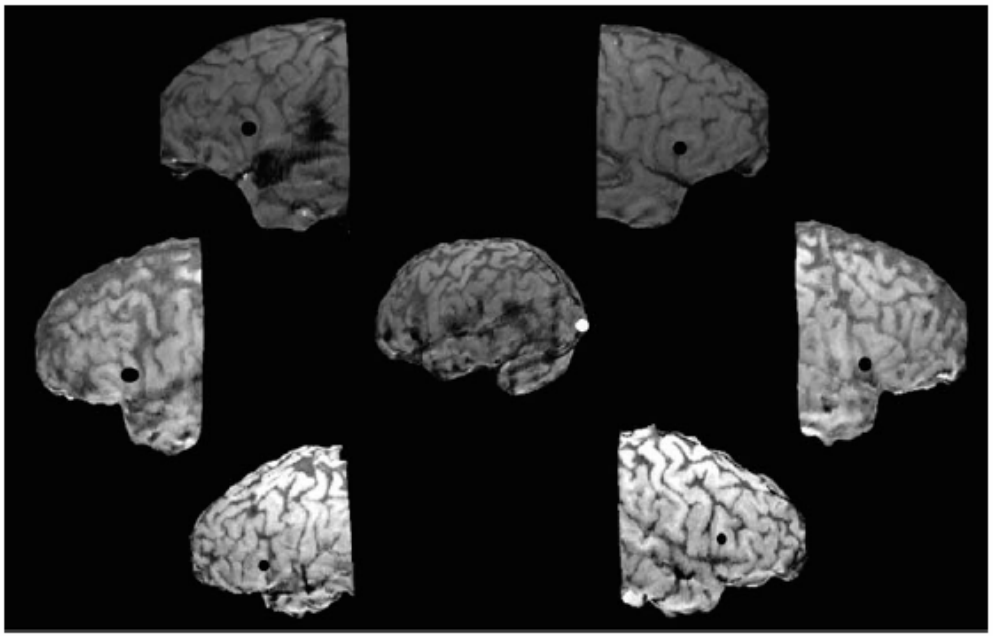

図2．3人の被験者の左右の弁蓋部（黒）を示す。

中央の白点は視覚野。

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Grasping the Intentions of Others with One's Own Mirror Neuron System

Marco Iacoboni[1,2,3,4*], Istvan Molnar-Szakacs[1,3,4], Vittorio Gallese[5], Giovanni Buccino[5], John C. Mazziotta[1,3,6,7,8], Giacomo Rizzolatti[5]

1 Ahmanson-Lovelace Brain Mapping Center, Neuropsychiatric Institute, David Geffen School of Medicine, University of California, Los Angeles, California, United States of America, **2** Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles, California, United States of America, **3** Brain Research Institute, David Geffen School of Medicine, University of California, Los Angeles, California, United States of America, **4** Center for Culture, Brain, and Development, University of California, Los Angeles, California, United States of America, **5** Department of Neurosciences, University of Parma, Italy, **6** Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, California, United States of America, **7** Department of Pharmacology, David Geffen School of Medicine, University of California, Los Angeles, California, United States of America, **8** Department of Radiological Sciences, David Geffen School of Medicine, University of California, Los Angeles, California, United States of America

Understanding the intentions of others while watching their actions is a fundamental building block of social behavior. The neural and functional mechanisms underlying this ability are still poorly understood. To investigate these mechanisms we used functional magnetic resonance imaging. Twenty-three subjects watched three kinds of stimuli: grasping hand actions without a context, context only (scenes containing objects), and grasping hand actions performed in two different contexts. In the latter condition the context suggested the intention associated with the grasping action (either drinking or cleaning). Actions embedded in contexts, compared with the other two conditions, yielded a significant signal increase in the posterior part of the inferior frontal gyrus and the adjacent sector of the ventral premotor cortex where hand actions are represented. Thus, premotor mirror neuron areas—areas active during the execution and the observation of an action—previously thought to be involved only in action recognition are actually also involved in understanding the intentions of others. To ascribe an intention is to infer a forthcoming new goal, and this is an operation that the motor system does automatically.

Figure 1. Six Images Taken from the Context, Action, and Intention Clips

The images are organized in three columns and two rows. Each column corresponds to one of the experimental conditions. From left to right: Context, Action, and Intention. In the Context condition there were two types of clips, a "before tea" context (upper row) and an "after tea" context (lower row). In the Action condition two types of grips were displayed an equal number of times, a whole-hand prehension (upper row) and a precision grip (lower row). In the Intention condition there were two types of contexts surrounding a grasping action. The "before tea" context suggested the intention of drinking (upper row), and the "after tea" context suggested the intention of cleaning (lower row). Whole-hand prehension (displayed in the upper row of the Intention column) and precision grip (displayed in the lower row of the Intention column) were presented an equal number of times in the "drinking" Intention clip and the "cleaning" Intention clip.

DOI: 10.1371/journal.pbio.0030079.g001

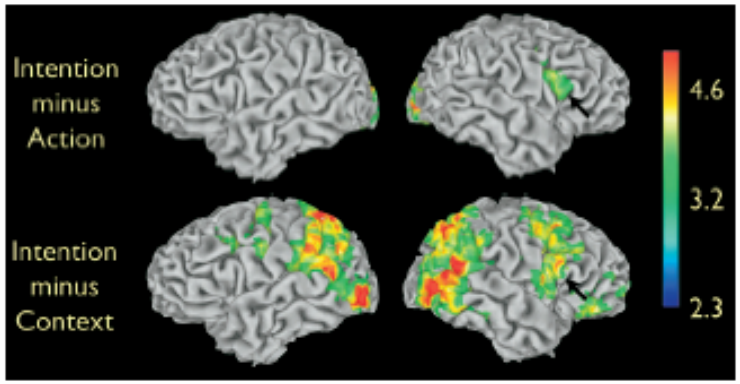

Figure 3. Signal Increases for Intention minus Action and Intention minus Context

Threshold of $Z = 2.3$ at voxel level and a cluster level corrected for the whole brain at $p < 0.05$. The black arrow indicates the only area showing signal increase in both comparisons. The area is located in the dorsal sector of pars opercularis, where mirror activity has been repeatedly observed [10,11,12,13,14,15,16,17,18,19,20,27]. See Tables S1 and S2 for coordinates of local maxima.

DOI: 10.1371/journal.pbio.0030079.g003

The mirror neuron system and the consequences of its dysfunction

Marco Iacoboni and Mirella Dapretto

Abstract | The discovery of premotor and parietal cells known as mirror neurons in th macaque brain that fire not only when the animal is in action, but also when it observes others carrying out the same actions provides a plausible neurophysiological mechanism for a variety of important social behaviours, from imitation to empathy. Recent data also show that dysfunction of the mirror neuron system in humans might be a core deficit in autism, a socially isolating condition. Here, we review the neurophysiology of the mirror neuron system and its role in social cognition and discuss the clinical implications of mirror neuron dysfunction.

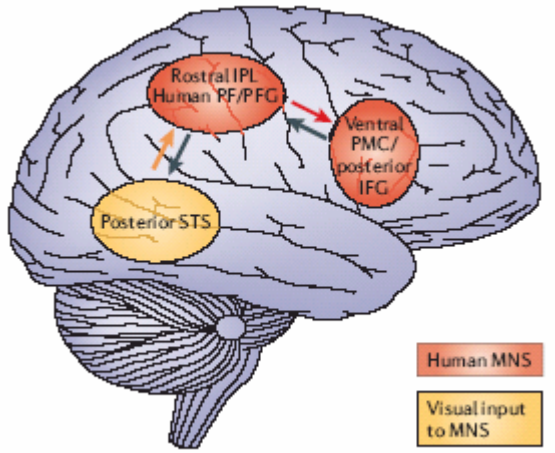

Figure 1 | **Neural circuitry for imitation.** Schematic

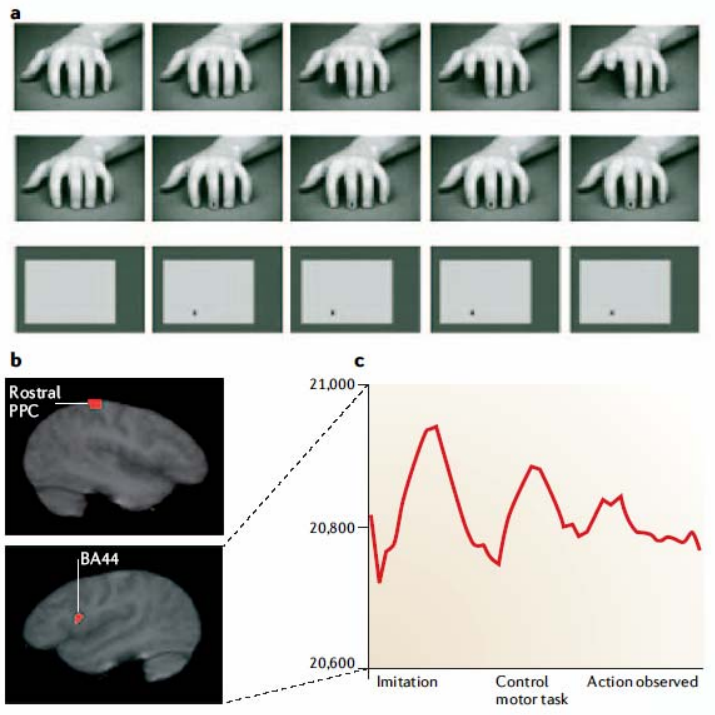

Figure 3 | **The human mirror neuron system and imitation.** Functional MRI (fMRI) study of imitation of finger movements showing two human cortical areas with the predicted pattern of activity for mirror neuron areas[33]. **a** | Participants observed or imitated the lifting of the index or the middle finger (top). In visual control conditions they observed a cross appearing on the index or middle finger of a static hand (middle), or appearing on the left or right side of a grey rectangle (bottom). In motor control conditions, partipants lifted the index or middle finger in response to the appearance of the cross. **b** | The two areas showing the predicted pattern of higher activity for the control motor task compared with action observation, and highest activity during imitation, were located in the inferior frontal cortex (Brodmann's area 44; BA44) and in the rostral part of the posterior parietal cortex (PPC)[33]. **c** | Blood-oxygen-level-dependent (BOLD) fMRI activity in signal intensity rescaled by smoothing measured in BA44 shows the predicted pattern of activity for mirror neuron areas. Panels **a** and **b** reproduced, with permission, from REF. 33 © (1999) American Association for the Advancement of Science.

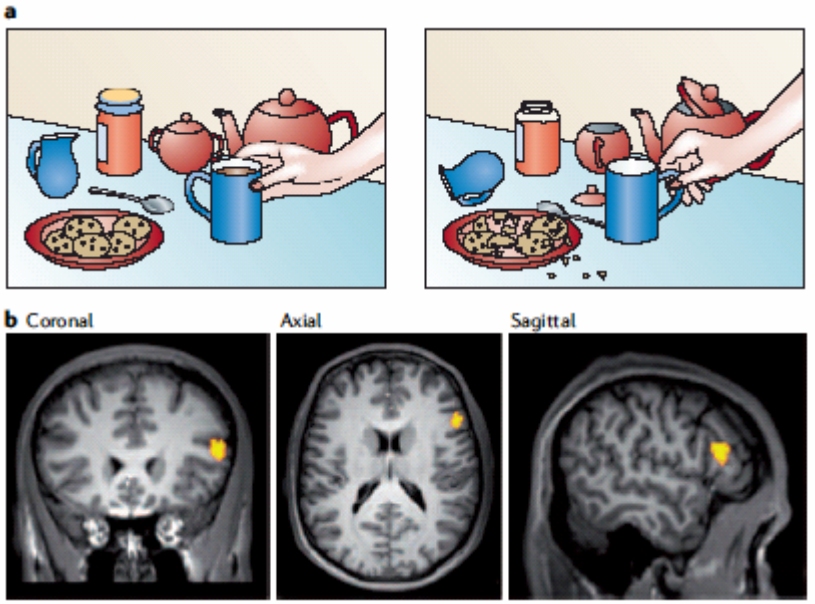

Figure 4 | **Grasping intentions with mirror neurons.** The observation of a grasping action embedded in two different contexts (**a**) that suggest two different intentions—drinking on the left and cleaning up on the right — elicits differential activity (greater for drinking) in the mirror neuron area located in the right posterior inferior frontal gyrus[55] (**b**). This shows that the mirror neuron system does not simply code the observed action ('that's a grasp') but rather the intention associated with the action ('that's a grasp to drink'). Panel **a** modified from REF. 55.

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NeuroImage xx (2006) xxx–xxx

Observing complex action sequences: The role of the fronto-parietal mirror neuron system

Istvan Molnar-Szakacs,[a,b,e,g,*] Jonas Kaplan,[a,d,f]
Patricia M. Greenfield,[b,c] and Marco Iacoboni[a,b,d,e,f]

A fronto-parietal mirror neuron network in the human brain supports the ability to represent and understand observed actions allowing us to successfully interact with others and our environment. Using functional magnetic resonance imaging (fMRI), we wanted to investigate the response of this network in adults during observation of hierarchically organized action sequences of varying complexity that emerge at different developmental stages. We hypothesized that fronto-parietal systems may play a role in coding the hierarchical structure of object-directed actions. The observation of all action sequences recruited a common bilateral network including the fronto-parietal mirror neuron system and occipito-temporal visual motion areas. Activity in mirror neuron areas varied according to the motoric complexity of the observed actions, but not according to the developmental sequence of action structures, possibly due to the fact that our subjects were all adults. These results suggest that the mirror neuron system provides a fairly accurate simulation process of observed actions, mimicking internally the level of motoric complexity. We also discuss the results in terms of the links between mirror neurons, language development and evolution.

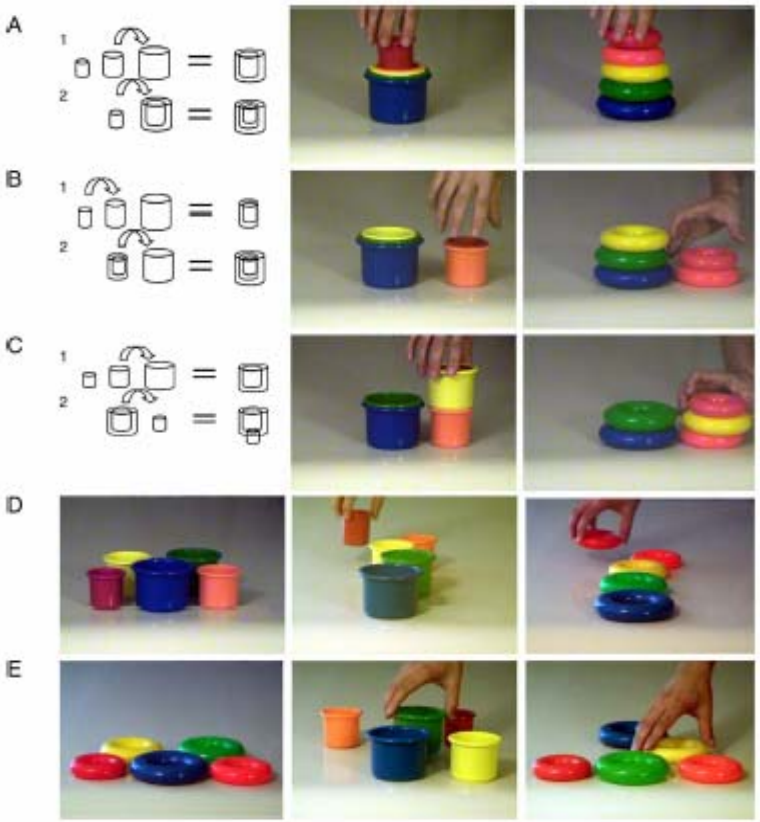

Fig. 1. Experimental conditions showing strategies for combining seriated cups in diagrammatical form [adapted from Greenfield et al. (1972)] and still images taken from the corresponding stimulus video clips showing both seriated cups and stacking rings: (A) seriated pot, (B) seriated subassembly and (C) stacked subassembly conditions. Still images illustrating the starting position and the final position of the objects: (D) size-ordered control, (E) random movement control. The arrangement of objects at the start of a clip was the same for experimental (A–C) and control (D–E) conditions. For more information, please see Methods.

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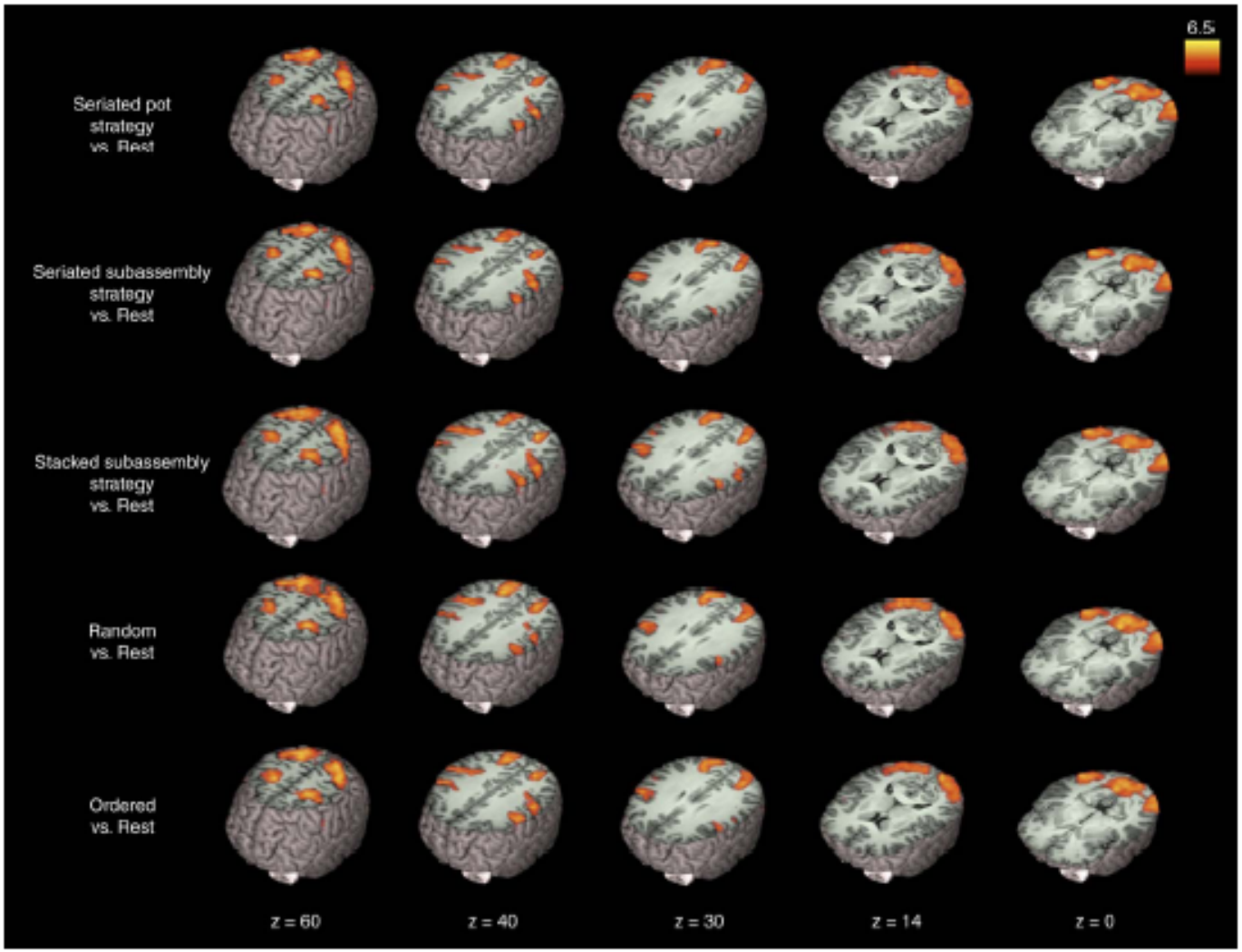

Fig. 2. Signal increases during observation of the five object manipulation conditions (Seriated pot, Seriated subassembly, Stacked subassembly, Random control and Ordered control) versus rest showed activity in a largely overlapping network including: the cuneus (BA 17, 19), lingual gyrus (BA 18), middle occipital gyrus (BA 19), the superior parietal lobule and precuneus (BA 7), the inferior parietal lobule (BA 40), the middle frontal gyrus (BA 6), the ventral premotor cortex (BA 6) and the posterior IFG (BA 44).

Behavioral/Systems/Cognitive

Lateralization of the Human Mirror Neuron System

Lisa Aziz-Zadeh,[1,2] Lisa Koski,[1,3] Eran Zaidel,[2,4] John Mazziotta,[1,4,5,6,7] and Marco Iacoboni[1,3,4]
[1]Ahmanson Lovelace Brain Mapping Center, Neuropsychiatric Institute, [2]Department of Psychology, [3]Department of Psychiatry and Biobehavioral Sciences, [4]Brain Research Institute, David Geffen School of Medicine, and Departments of [5]Neurology, [6]Pharmacology, and [7]Radiological Sciences, University of California, Los Angeles, Los Angeles, California 90095

A cortical network consisting of the inferior frontal, rostral inferior parietal, and posterior superior temporal cortices has been implicated in representing actions in the primate brain and is critical to imitation in humans. This neural circuitry may be an evolutionary precursor of neural systems associated with language. However, language is predominantly lateralized to the left hemisphere, whereas the degree of lateralization of the imitation circuitry in humans is unclear. We conducted a functional magnetic resonance imaging study of imitation of finger movements with lateralized stimuli and responses. During imitation, activity in the inferior frontal and rostral inferior parietal cortex, although fairly bilateral, was stronger in the hemisphere ipsilateral to the visual stimulus and response hand. This ipsilateral pattern is at variance with the typical contralateral activity of primary visual and motor areas. Reliably increased signal in the right superior temporal sulcus (STS) was observed for both left-sided and right-sided imitation tasks, although subthreshold activity was also observed in the left STS. Overall, the data indicate that visual and motor components of the human mirror system are not left-lateralized. The left hemisphere superiority for language, then, must be have been favored by other types of language precursors, perhaps auditory or multimodal action representations.

Key words: motor; sensorimotor; premotor; language; hemisphere; lateralization

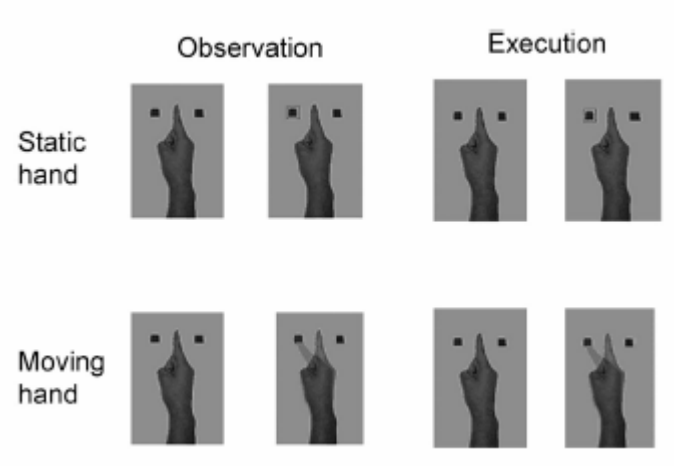

Figure 1. Stimuli used in fMRI study of action observation, execution, and imitation. Stimuli consisted of two frames of right or left hands, consecutively flashed for a total of 150 ms to the right or left visual field. Participants participated in four task conditions: observation of a static hand, observation of a moving hand, execution to a static hand, or imitation. The right-hand stimuli shown here all appeared to the right of a fixation cross. Left-hand stimuli appeared to the left of a fixation cross. Both left- and right-hand stimuli were presented in color.

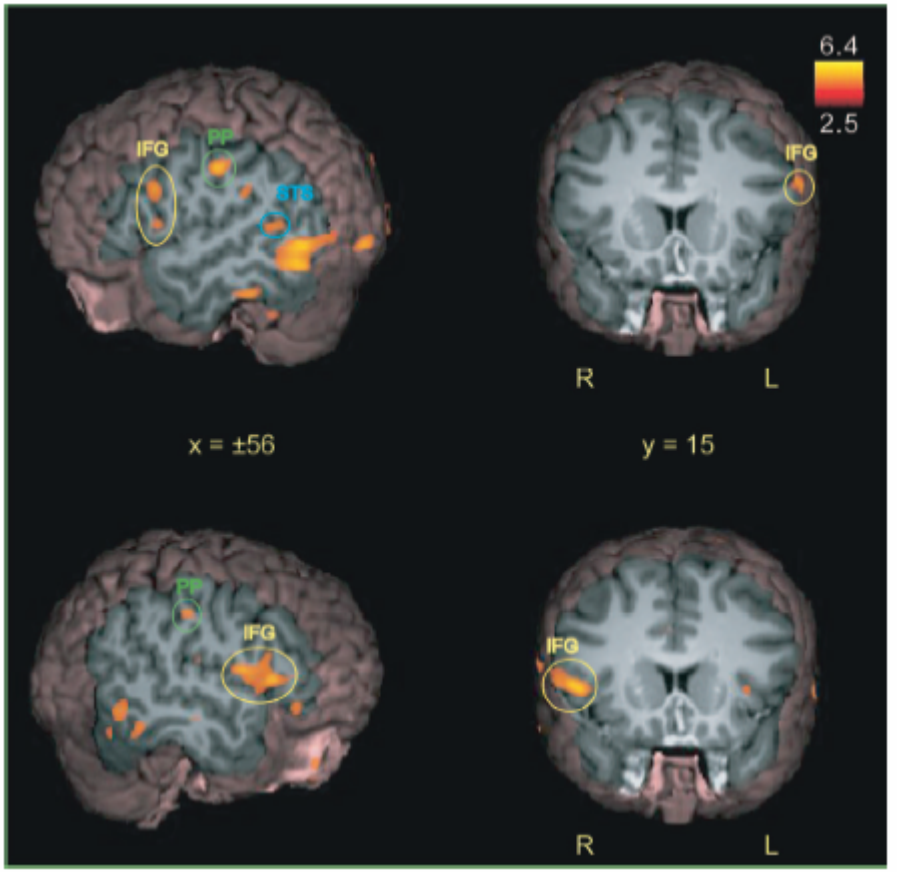

Figure 3. Views of the activation for areas that are activated in a mirror-like pattern (imitation>execution>observation> observation of static hands) for LVF-RVF trials (top) and RVF-LVF trials (bottom). The pars opercularis of the inferior frontal gyrus (IFG) is activated ipsilaterally. Furthermore, we show activation in areas associated with the human mirror system: the right STS ($x = -58; y = -58; z = 6$) and bilaterally the posterior parietal (PP) areas ($x = -56; y = -26; z = 36; x = 52; y = -30; z = 38$).

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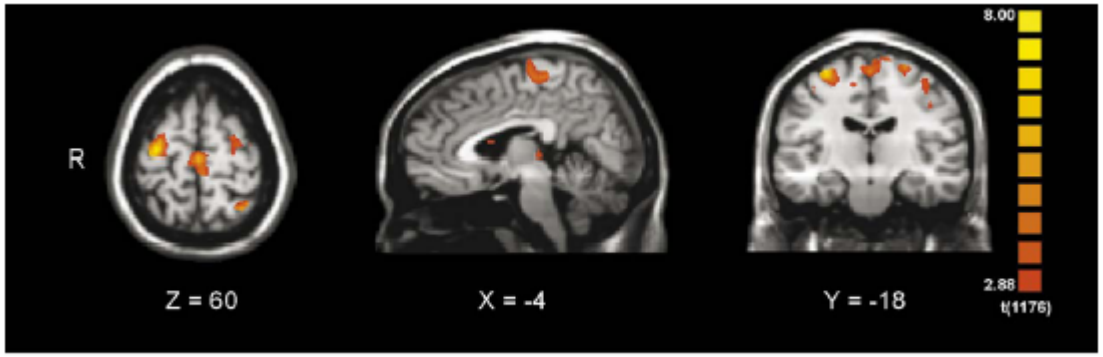
Motor imagery of walking following training in locomotor attention The effect of 'the tango lesson'

K. Sacco,[a,b,*] F. Cauda,[a] L. Cerliani,[a] D. Mate,[a] S. Duca,[b] and G.C. Geminiani[a]



The hypothesis " focusing attention on walking motor schemes could modify sensorimotor activation of the brain."

In locomotor imagery tasks before and after one week of training consisting of physical and mental practice the functional changes in the activity of the cerebral areas involved. Subjects were asked to perform basic tango steps, which require specific ways of walking; each tango lesson ended with motor imagery training of the performed steps.

Training determines an expansion of active bilateral motor areas during locomotor imagery, with a reduction of visuospatial activation in the posterior right brain, suggesting a decreased role of visual imagery processes in the post-training period.

Fig. 1. Results for the post-test condition minus pretest condition during locomotor imagery. The table indicates the Talairach coordinates of local maxima of cortical and cerebellar structures showing significant ($P < 0.05$, corrected for multiple comparisons) activity. Increased activations (+) and decreased activations (−) are specified in the first column. Note that in this comparison positive t values indicate an increased activation in the post-test condition compared to the pretest condition, and negative t-values indicate a decreased activation in the post-test condition compared to the pretest condition.

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Anatomical Differences in the Mirror Neuron System and Social Cognition Network in Autism

Nouchine Hadjikhani[1,2], Robert M. Joseph[3], Josh Snyder[1] and Helen Tager-Flusberg[3]

[1]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA, [2]Division of Health Sciences and Technology, Harvard–Massachusetts Institute of Technology, Cambridge, MA 02139, USA and [3]Boston University School of Medicine, Boston, MA 02118, USA

Autism spectrum disorder (ASD) is a neurodevelopmental disorder associated with impaired social and emotional skills, the anatomical substrate of which is still unknown. In this study, we compared a group of 14 high-functioning ASD adults with a group of controls matched for sex, age, intelligence quotient, and handedness. We used an automated technique of analysis that accurately measures the thickness of the cerebral cortex and generates cross-subject statistics in a coordinate system based on cortical anatomy. We found local decreases of gray matter in the ASD group in areas belonging to the mirror neuron system (MNS), argued to be the basis of empathic behavior. Cortical thinning of the MNS was correlated with ASD symptom severity. Cortical thinning was also observed in areas involved in emotion recognition and social cognition. These findings suggest that the social and emotional deficits characteristic of autism may reflect abnormal thinning of the MNS and the broader network of cortical areas subserving social cognition.

Keywords: autism, cortical thickness, empathy, mirror neuron system

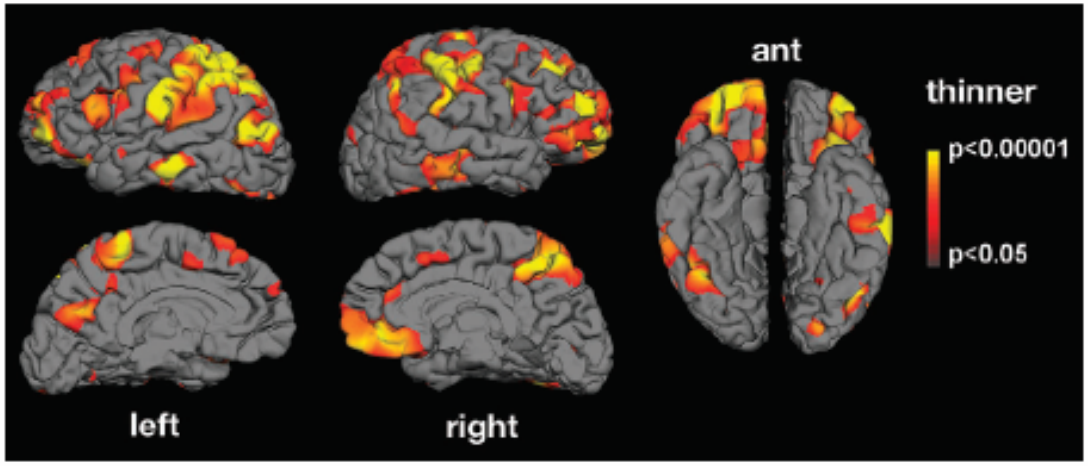

Figure 1. Mean thickness difference significance maps. Lateral, medial, and ventral views of the brain showing areas presenting cortical thinning in the autism group compared with normal controls. No area showed cortical thickening. Significant thinning was found in areas belonging to the MNS as well as in areas involved in facial expression production and recognition, imitation, and social cognition.

Decision-making and the frontal lobes

Volz KG, Schuboltz RI, von Cramon DY

Current Opinion in Neurology 2006 19:401-406

Orbital and median PFC—evaluative judgement processes

Lateral PFC—evaluative judgement processes

amalgam problems

transfer problems or

insight problems

Four levels of decisions, depending on predictability of reward probability and reward variability

1. **The first level----recognized as being similar to a previous situation.**

   (recognition-primed decision)

2. **The second level--- a decision with a reference to his or her values. (O/VMPFC)**

   (stereotyped, 'Shall I take the fruit salad or go for the crème brulee?' holistic, intuitive)

3. **The third level----to relate his or her value system to the attributes by incorporating long-term information**

   (anterior-medial and dorsomedial prefrontal areas)

   (Reflective desion often affective or motivational)

4. **The fourth level--- novel or unprecedented**

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NeuroImage 23 (2004) 1020–1026

Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study

Mitsuo Suzuki,[a,b,*] Ichiro Miyai,[a] Takeshi Ono,[a,b] Ichiro Oda,[c] Ikuo Konishi,[c] Takanori Kochiyama,[d] and Kisou Kubota[a,b]

[a]Rehabilitation Department, Neurorehabilitation Research Institute, Bobath Memorial Hospital, Osaka 536-0023, Japan
[b]Department of Social and Information Sciences, Graduate School of Management Information Systems, Nihon Fukushi University, Aichi 475-0012, Japan
[c]Technology Research Laboratory, Shimadzu Corporation, Kyoto 619-0237, Japan
[d]Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan

Received 29 January 2004; revised 7 June 2004; accepted 6 July 2004
Available online 30 September 2004

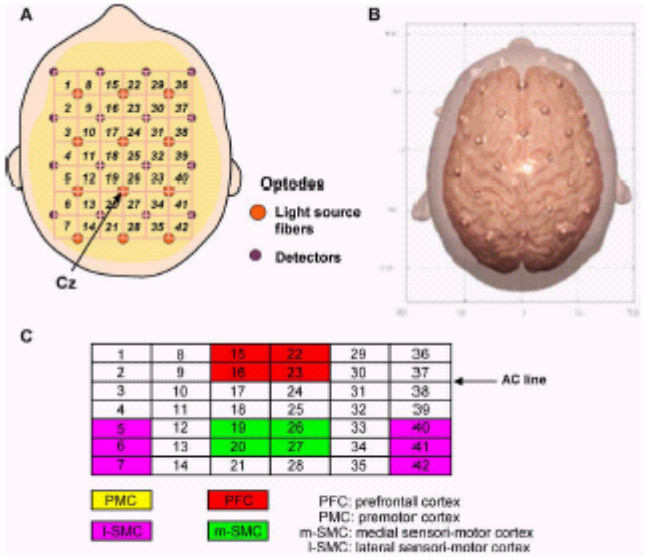


Fig. 2. Schematic for location of the optodes. (A) Twenty-eight optodes, constituting 12 light-source fibers and 16 detectors, were arranged on the scalp that enabled 42-channel measurement. (B) The anatomical location of the optodes exposed onto the normalized brain surface. (C) The channels covering the PFC are shaded in red, those covering the PMC in yellow, those covering the m-SMC in green, and those covering the l-SMC in purple. See text for details. AC indicates anterior commissure.

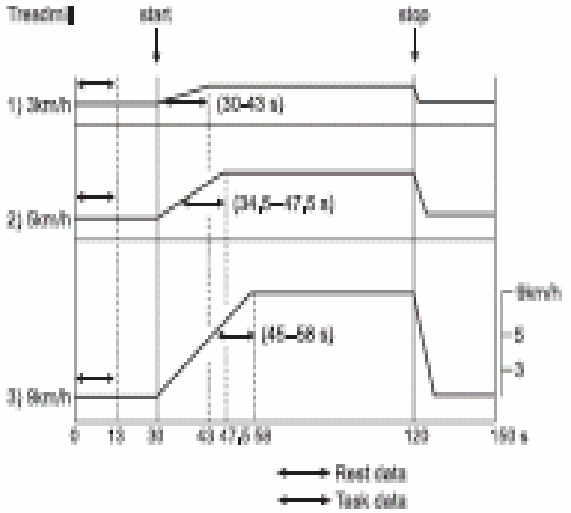


Fig. 1. Design for the sequence of three tasks with (1) 3 km/h walking, (2) 5 km/h walking, and (3) 9 km/h running. Subjects performed 150-s of locomotor tasks consisting of 30-s rest period before the locomotion, 90-s locomotion period, and 30-s rest period after task for three repetitions at each speed. Data were sampled for the 13-s period from 0 to 13 s as Rest data and for 13-s period just before reaching each constant speed as Task data. See text for details.

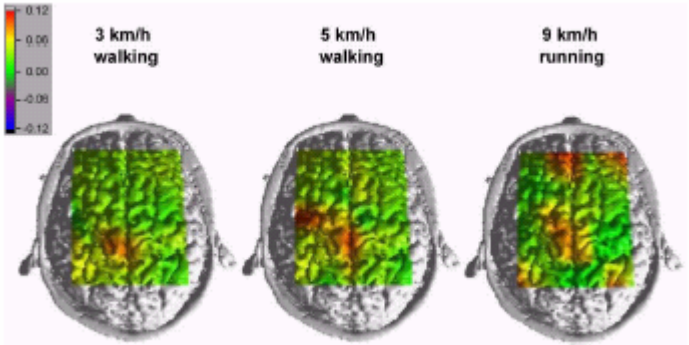


Fig. 4. Cortical mapping of locomotion tasks based on changes in oxyHb levels. The scale indicates the color coordinates of concentration changes (mMol·cm). See text for details.

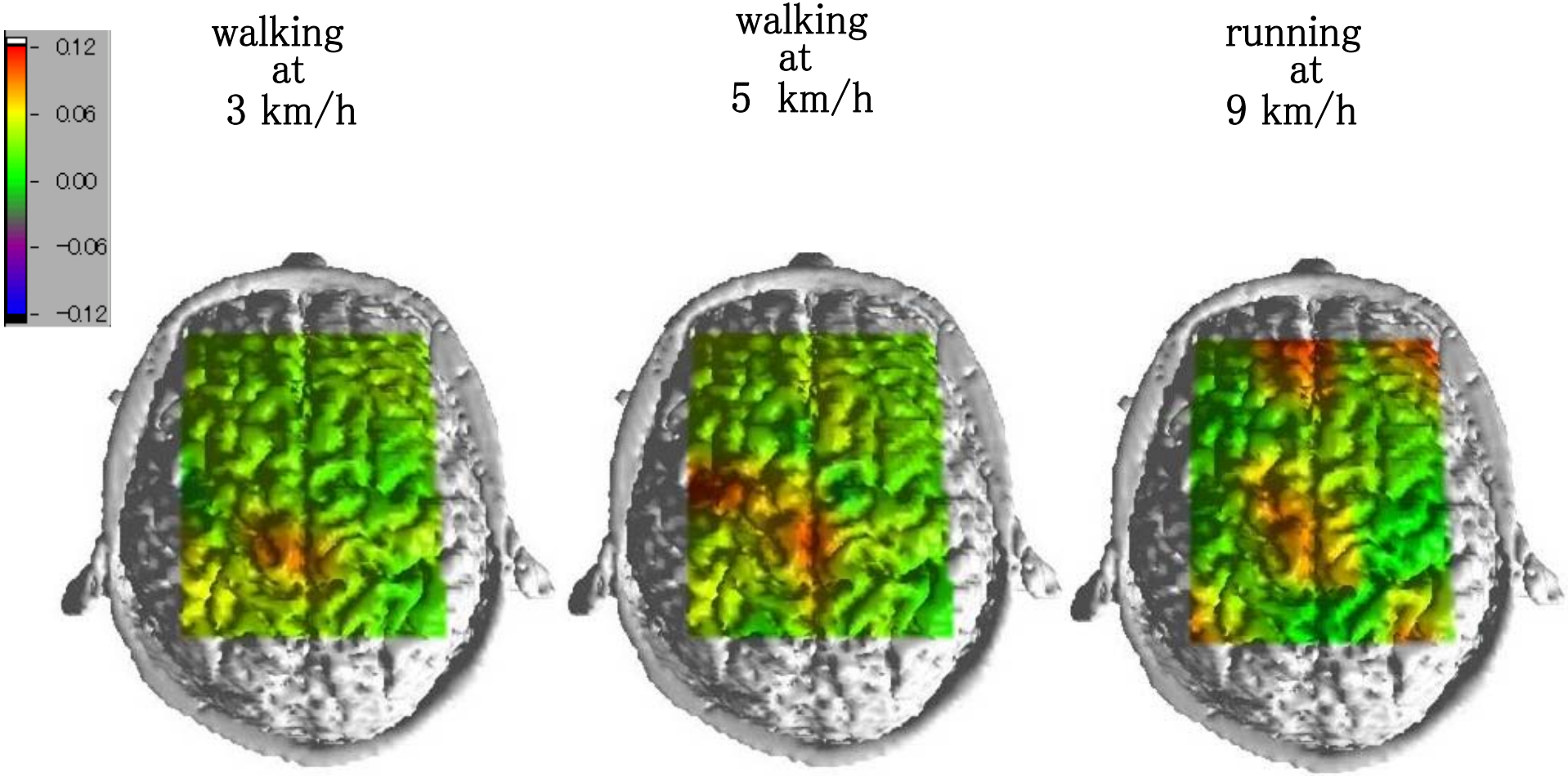

0.12
0.06
0.00
−0.06
−0.12
walking
at
3 km/h
walking
at
5 km/h
running
at
9 km/h

Fig.4

Walking and Dementia in Physically Capable Elderly Men

2257人、71-93歳、

Honolulu-Asia Aging study

JAMA, 2004;292;1447−1453

痴呆

アルツハイマー

脈管系の痴呆

その他の痴呆

Table 3. Estimated Relative Hazard of Dementia Comparing Ranges of Distance Walked per Day

Dementia	Estimated Relative Hazard (95% CI) 0.25 vs 2. mile/d	P Value*	0.25 to 1 vs 2. mile/d	P Value*	1 to 2 vs 2. mile/d	P Value*
Total dementia						
Unadjusted	2.12 (1.25-3.60)	.006	2.06 (1.23-3.44)	.006	1.50 (0.83-2.69)	.18
Adjusted†	1.93 (1.11-3.34)	.02	1.75 (1.03-2.99)	.04	1.33 (0.73-2.45)	.35
Alzheimer disease						
Unadjusted	2.24 (1.12-4.48)	.02	2.21 (1.13-4.31)	.02	2.01 (0.97-4.17)	.06
Adjusted†	2.21 (1.06-4.57)	.03	1.86 (0.91-3.79)	.09	1.88 (0.87-4.04)	.11
Vascular dementia						
Unadjusted	1.34 (0.49-3.70)	.57	1.34 (0.51-3.51)	.56	0.18 (0.02-1.46)	.11
Adjusted†	1.17 (0.42-3.27)	.77	1.21 (0.45-3.22)	.70	0.16 (0.02-1.36)	.09
Mixed and other dementia						
Unadjusted	3.75 (0.81-17.35)	.09	3.43 (0.76-15.45)	.11	2.63 (0.51-13.56)	.25
Adjusted†	2.83 (0.59-13.55)	.19	2.84 (0.62-12.92)	.18	2.00 (0.36-11.01)	.43

Conclusions Findings suggest that walking is associated with a reduced risk of dementia. Promoting active lifestyles in physically capable men could help late-life cognitive function.

Physical Activity, Including Walking, and Cognitive Function in Older Women

Jennifer Weuve, ScD
Jae Hee Kang, ScD
JoAnn E. Manson, MD
Monique M. B. Breteler, MD
James H. Ware, PhD
Francine Grodstein, ScD

Context Physical activity may help maintain cognitive function in older adults.

Objective To examine the relation of long-term regular physical activity, including walking, to cognitive function.

Design Women reported participation in leisure-time physical activities on biennial mailed questionnaires beginning in 1986. We assessed long-term activity by averaging energy expenditures from questionnaires in 1986 through participants' baseline cognitive assessments (1995 to 2001). We used linear regression to estimate adjusted mean differences in baseline cognitive performance and cognitive decline over 2 years,

アメリカの看護師121,700人

2年間追跡

Table 5. Mean Differences in Change in Cognitive Function Scores by Quintile of Physical Activity*

Test	Quintile of Physical Activity					*P* Value for Trend
	1 (Lowest)	2	3	4	5 (Highest)	
TICS (n = 16 466)						
Adjusted mean difference (95% CI)	Reference	0.17 (0.05 to 0.30)	0.17 (0.04 to 0.29)	0.28 (0.15 to 0.41)	0.34 (0.21 to 0.47)	<.001
Category fluency (n = 15 835)						
Adjusted mean difference (95% CI)	Reference	0.04 (−0.16 to 0.25)	0.07 (−0.13 to 0.29)	0.18 (−0.03 to 0.39)	0.19 (−0.02 to 0.40)	.05
Working memory and attention (n = 14 376)						
Adjusted mean difference (95% CI)	Reference	0.12 (0.01 to 0.23)	0.13 (0.02 to 0.24)	0.20 (0.08 to 0.31)	0.25 (0.13 to 0.36)	<.001
Verbal memory score (n = 14 363)†						
Adjusted mean difference (95% CI)	Reference	0.04 (0 to 0.07)	0.01 (−0.02 to 0.04)	0.04 (0.01 to 0.08)	0.07 (0.04 to 0.11)	<.001
Global score (n = 14 344)†						
Adjusted mean difference (95% CI)	Reference	0.03 (0 to 0.05)	0.01 (−0.01 to 0.04)	0.04 (0.01 to 0.07)	0.06 (0.03 to 0.08)	<.001

Abbreviations: CI, confidence interval; TICS, Telephone Interview for Cognitive Status.

*Mean differences are adjusted for age, education, husband's education, alcohol use, smoking status, aspirin use, ibuprofen use, vitamin E use, balance problems, health limitations in the ability to walk a block, osteoarthritis, emphysema or chronic bronchitis, fatigue, poor mental health (see Table 1), antidepressant use, moderate to severe bodily pain, and baseline score.

†Verbal memory score averages performance in immediate and delayed 10-word recalls and immediate and delayed East Boston Memory Tests. Global score averages performance on all cognitive tests. Composite scores were computed only for women who completed all component tests.

＜1．9MET-hrs；特に運動しない，マイル21-30分/で38分/週以下

2.マイル/ 38分 -1、4時間　　3. 1.5-2.8時間　4. 2.4時間/週

Table 4. Mean Differences in Baseline Cognitive Function Scores by Quartile of Walking*

Test	Quartile of Walking (MET-hours/wk) 1 (<1.9)	2 (1.9-4.2)	3 (4.3-8.5)	4 (>8.5)	*P* Value for Trend
TICS (n = 7982) Adjusted mean difference (95% CI)	Reference	0.19 (0.02 to 0.36)	0.30 (0.13 to 0.47)	0.31 (0.13 to 0.48)	.003
Category fluency (n = 7674) Adjusted mean difference (95% CI)	Reference	0.28 (–0.01 to 0.57)	0.33 (0.03 to 0.63)	0.40 (0.10 to 0.70)	.03
Working memory and attention (n = 6968) Adjusted mean difference (95% CI)	Reference	0.14 (–0.02 to 0.30)	0.21 (0.04 to 0.37)	0.35 (0.18 to 0.51)	<.001
Verbal memory score (n = 6969)† Adjusted mean difference (95% CI)	Reference	0.03 (–0.02 to 0.08)	0.06 (0.01 to 0.10)	0.05 (0 to 0.10)	.07
Global score (n = 6957)† Adjusted mean difference (95% CI)	Reference	0.04 (0 to 0.08)	0.06 (0.02 to 0.10)	0.07 (0.02 to 0.11)	.007

Abbreviations: CI, confidence interval; MET, metabolic equivalent.
*Includes only the 7982 women who did not report any vigorous activity. Adjusted for the variables listed in the footnote to Table 2 as well as for MET-hours expended on stair-climbing and low-intensity exercise (eg, yoga, stretching, toning).
†Verbal memory score averages performance in immediate and delayed 10-word recalls and immediate and delayed East Boston Memory Tests. Global score averages performance on all cognitive tests. Composite scores were computed only for women who completed all component tests.

サルが空間的ワーキングメモリ課題をおこなっているときの、記憶を保持している前頭連合野のニューロン活動の例：

久保田ら： J. Neurophysiol. 1974

Visuokinetic Activities of Primate Prefrontal Neurons During Delayed-Response Performance

KISOU KUBOTA, TAKASHIGE IWAMOTO, AND HISAO SUZUKI

Department of Neurophysiology, Primate Research Institute, Kyoto University, Inuyama, Aichi 484, Japan

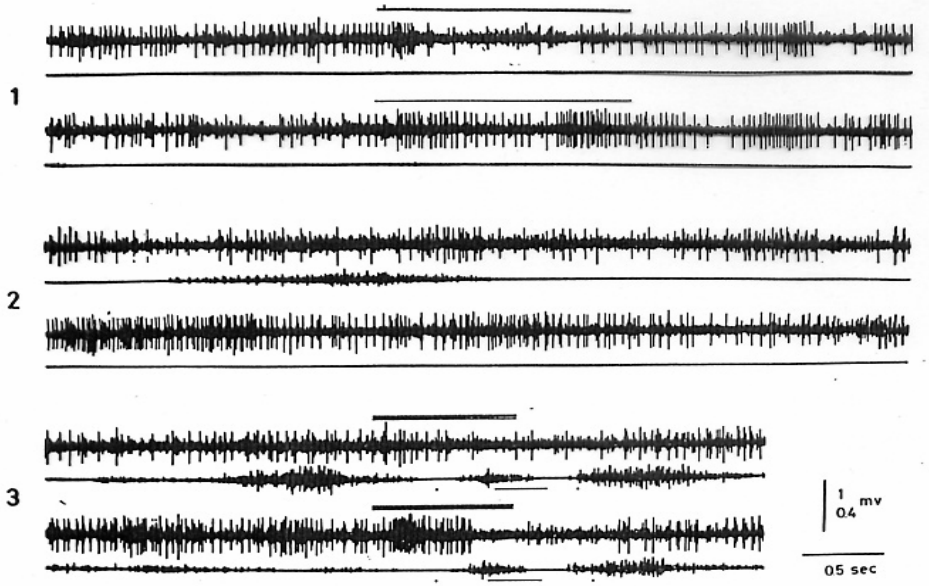


FIG. 6. Differential visuokinetic-unit activity in delayed-response performance. 1, 2, and 3 are continuous records spanning a 9-s delay period. Left (upper two traces) and right (lower two traces) sequences are illustrated with the unit activity in the upper and EMG in the lower trace. Dots to either side of the lever-press line at the bottom of the paired traces in 3 indicate release and repress of the holding key. Calibrations are at lower right.

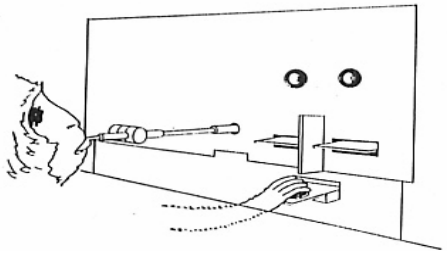


FIG. 1. Schematic drawing showing a monkey, facing the panel in front and depressing the holding key with his right hand. On the panel are two levers at the level of the mouth and two lamps at or slightly above the level of eyes. The holding key at the level of the monkey's shoulder extends 12 cm from the panel toward the monkey. Levers were 6.5 cm below lamps. Reward juice was guided to the mouth with a solenoid valve between the mouth and panel. A small Plexiglas plate was placed between levers to avoid simultaneous depressing of two levers by a single hand. Distance between holding key and the lever was about 14 cm.

nature neuroscience

Increased prefrontal and parietal activity after training of working memory

Pernille J Olesen, Helena Westerberg & Torkel Klingberg

Working memory capacity has traditionally been thought to be constant. Recent studies, however, suggest that working memory can be improved by training. In this study, we have investigated the changes in brain activity that are induced by working memory training. Two experiments were carried out in which healthy, adult human subjects practiced working memory tasks for 5 weeks. Brain activity was measured with functional magnetic resonance imaging (fMRI) before, during and after training. After training, brain activity that was related to working memory increased in the middle frontal gyrus and superior and inferior parietal cortices. The changes in cortical activity could be evidence of training-induced plasticity in the neural systems that underlie working memory.

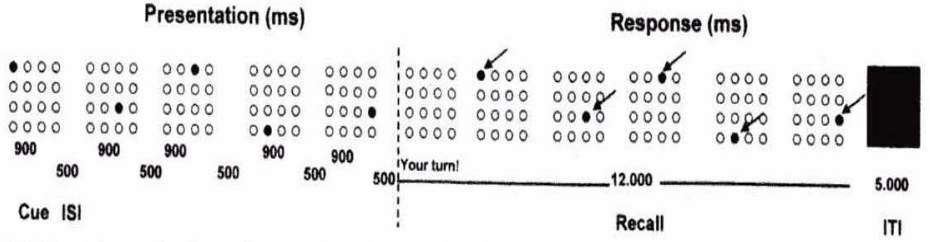


Figure 1 Working memory task carried out during scanning in Experiment 2. Five or seven red circles (cues) were presented sequentially in a 4 × 4 grid. Each cue was presented for 900 ms, with a 500-ms interstimulus interval (ISI). The cue presentation was followed by a blank grid and a text line indicating the start of the response phase, which lasted 12,000 ms. The subject indicated the location and order of the presented cues by clicking on a computer screen with an optic track-ball. The intertrial interval (ITI) was 5,000 ms after low-load trials and 2,200 ms after high-load and control trials. In the control task, seven green circles were presented sequentially in the two uppermost rows. The circles stayed on the grid when the text line appeared, and the task was to click them away in random order.

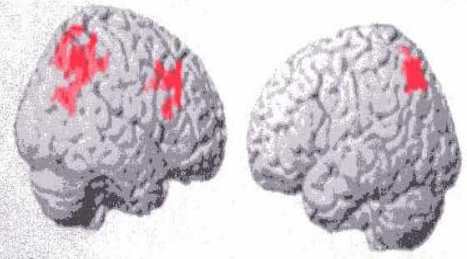


Figure 2 Increase in brain activity after working memory training (Experiment 1). Subtraction images of mean responses from the fMRI analysis were overlaid on a single-subject T1-weighted image. Regions with an increase in brain activity after training were found in the right middle frontal gyrus (*x y z*, 36 21 18; $t = 3.9$), in the right inferior parietal cortex (42 –57 45; $t = 4.1$) and bilaterally in the intraparietal cortex (18 –69 48, $t = 6.6$; –15 –69 60, $t = 5.6$).

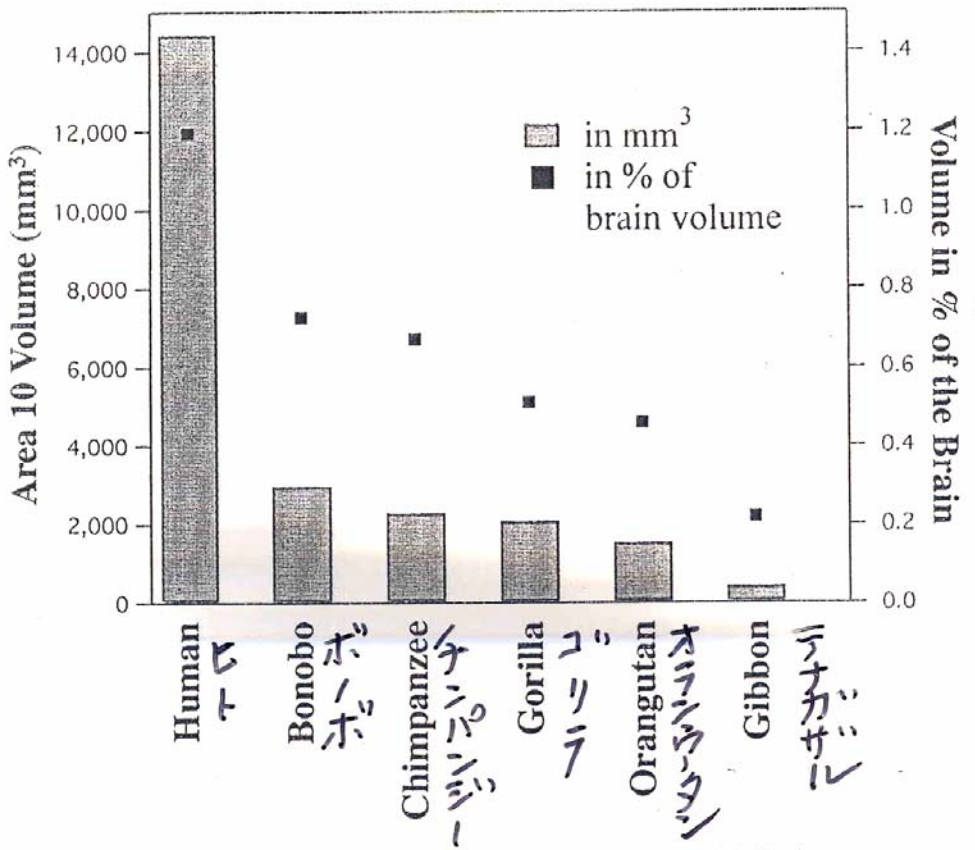


Fig. 3. The relative and absolute size of area 10 in humans and apes, modified after Semendeferi and others (2001).

Frontal polar region was activated by Branching Task

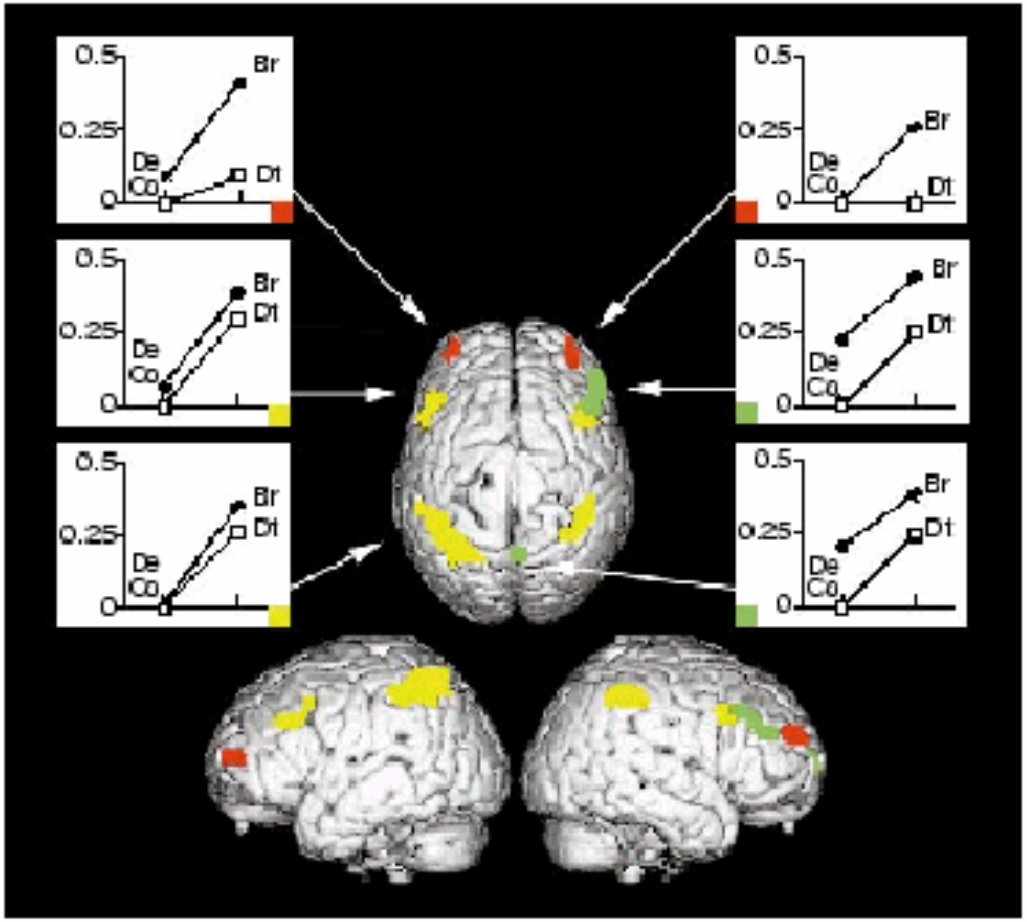


Figure 3 Topography of brain regions with distinct activation profiles. Yellow, main effects of dual-task performance. Green, additivity of the dual-task and delayed-response performance effects. Red, Interaction of dual-task and delayed-performance effects or branching-specific activations. See Methods for details and Table 2 for coordinates of activation foci. Inserts, data points are the mean signal changes (vertical axis, percentage) in the delay (De), dual-task (Dt) and branching (Br) conditions (measured in the stationary state, that is, in the second half-block) relative to the adjusted signal mean in the control condition (Co).

Branching task

(BR; combined, main DR Test, and subroutine GNG Test)

During the delay period of the DR Test (2), the GO/No-GO Test (3) was performed.

Press the mouse

Press the panel,
Releasing the mouse

Visual cue
stim

delay

response

0.2s

10s

10s

Ⅰ Ⅱ Ⅴ

Go
A
No-Go
B

Go
A
No-Go
B

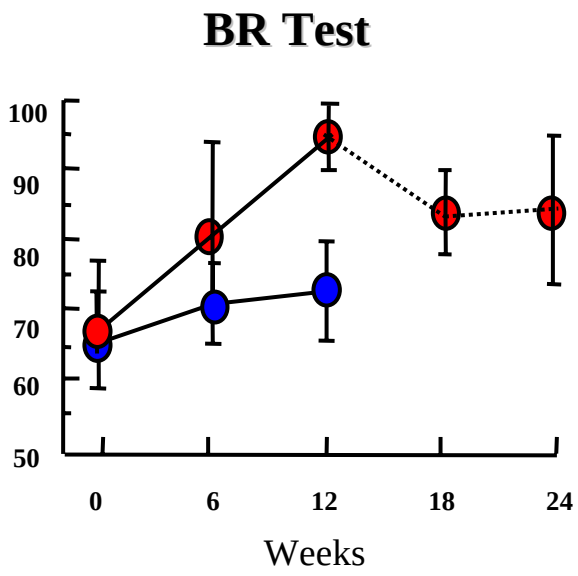
Ⅲ

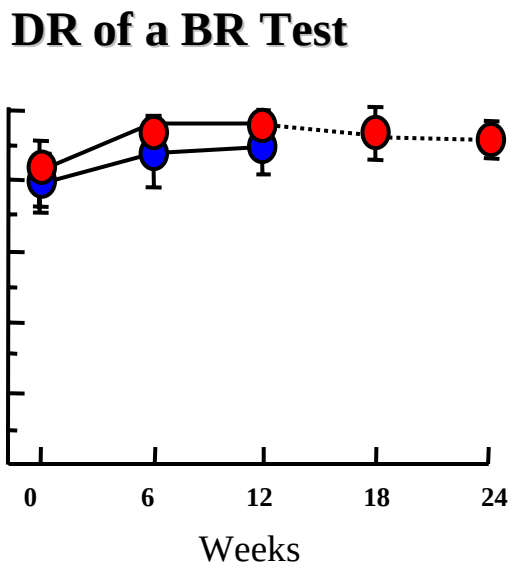
Press the
mouse

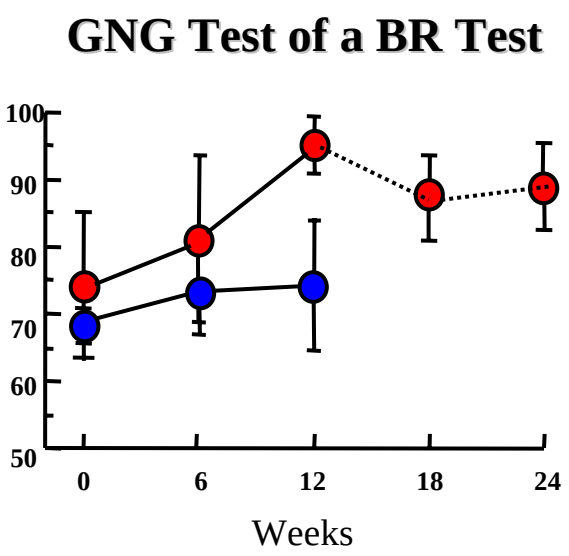
Ⅳ

Press the
mouse

Correct Performance Rate in the frontal Test

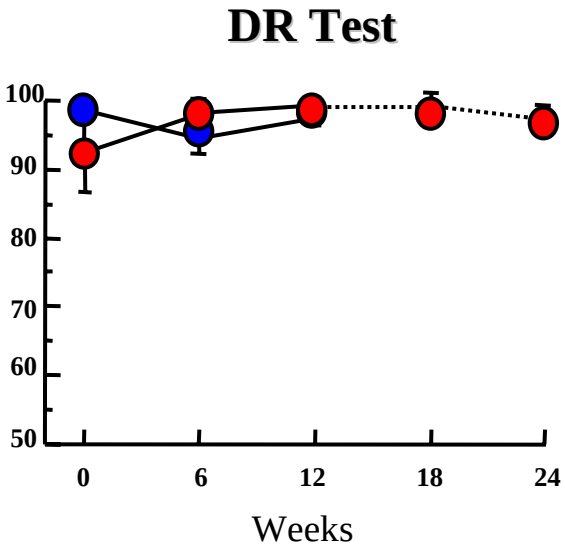


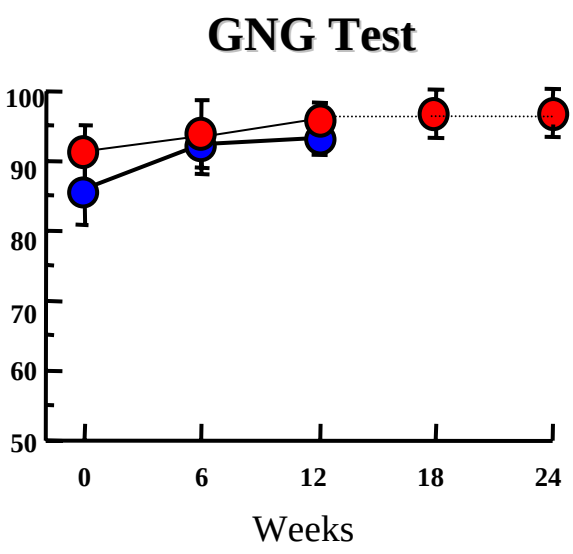


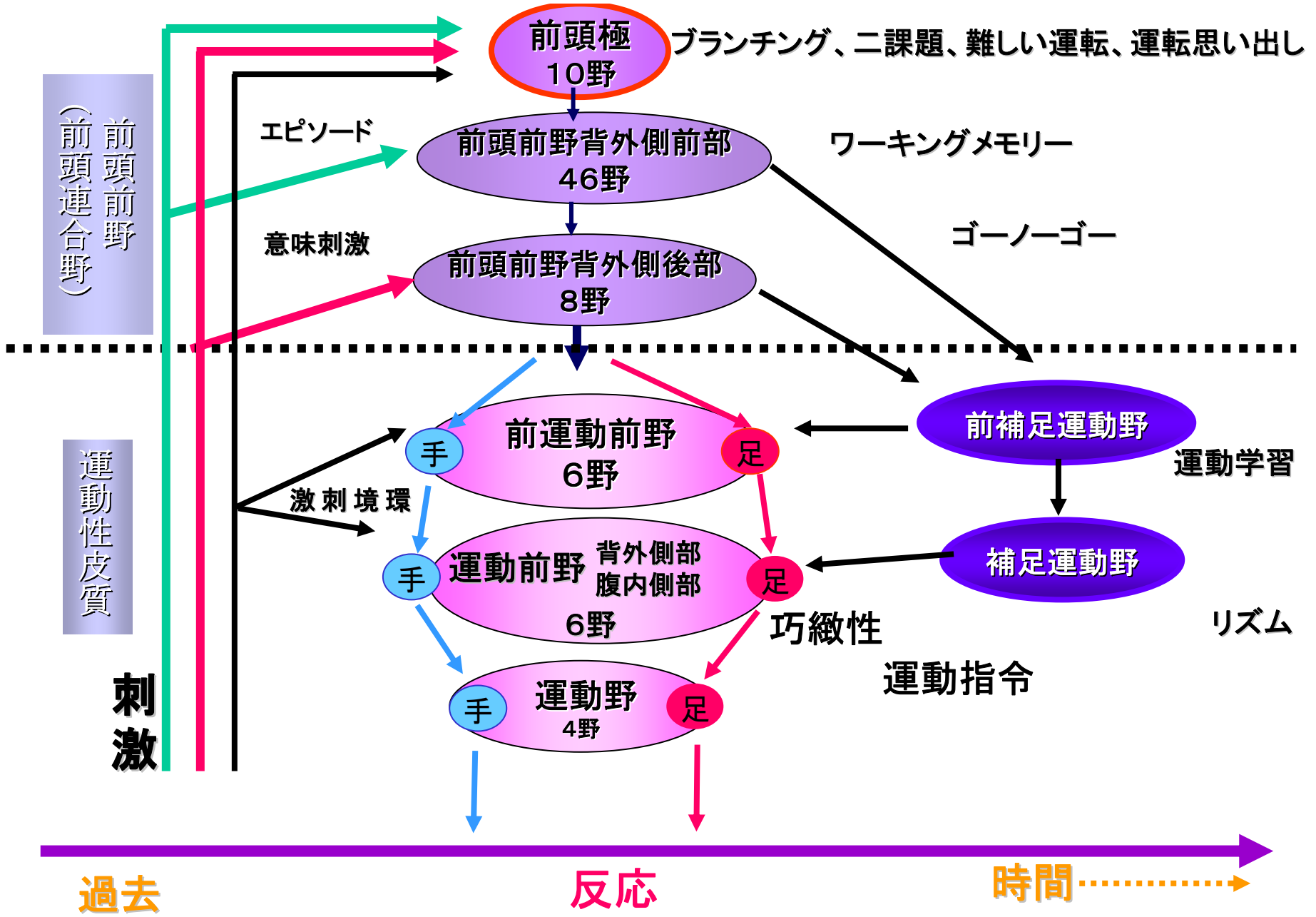


● Jogging trained group

● Jogging untrained group







行動・運動制御の階層性

(Kubota, 2004)