

ACCIDENT VASCULAIRE CÉRÉBRAL ET NEUROPLASTICITÉ

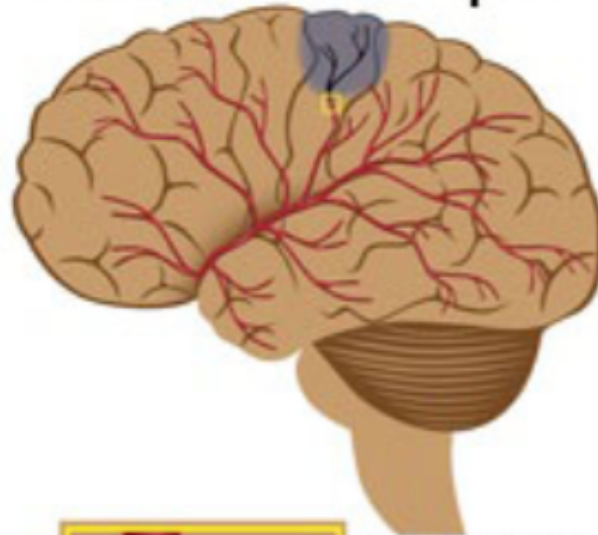
Hiba SOUISSI

hiba.souissi@umontpellier.fr

Accident Vasculaire Cérébral

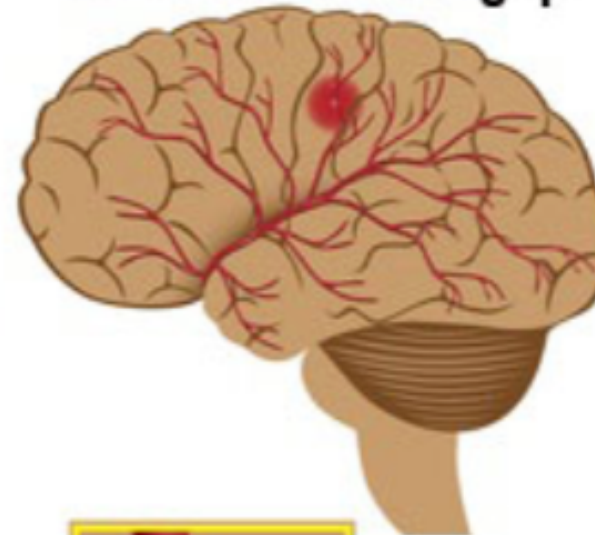
AVC: accident vasculaire cérébral

Accident ischémique



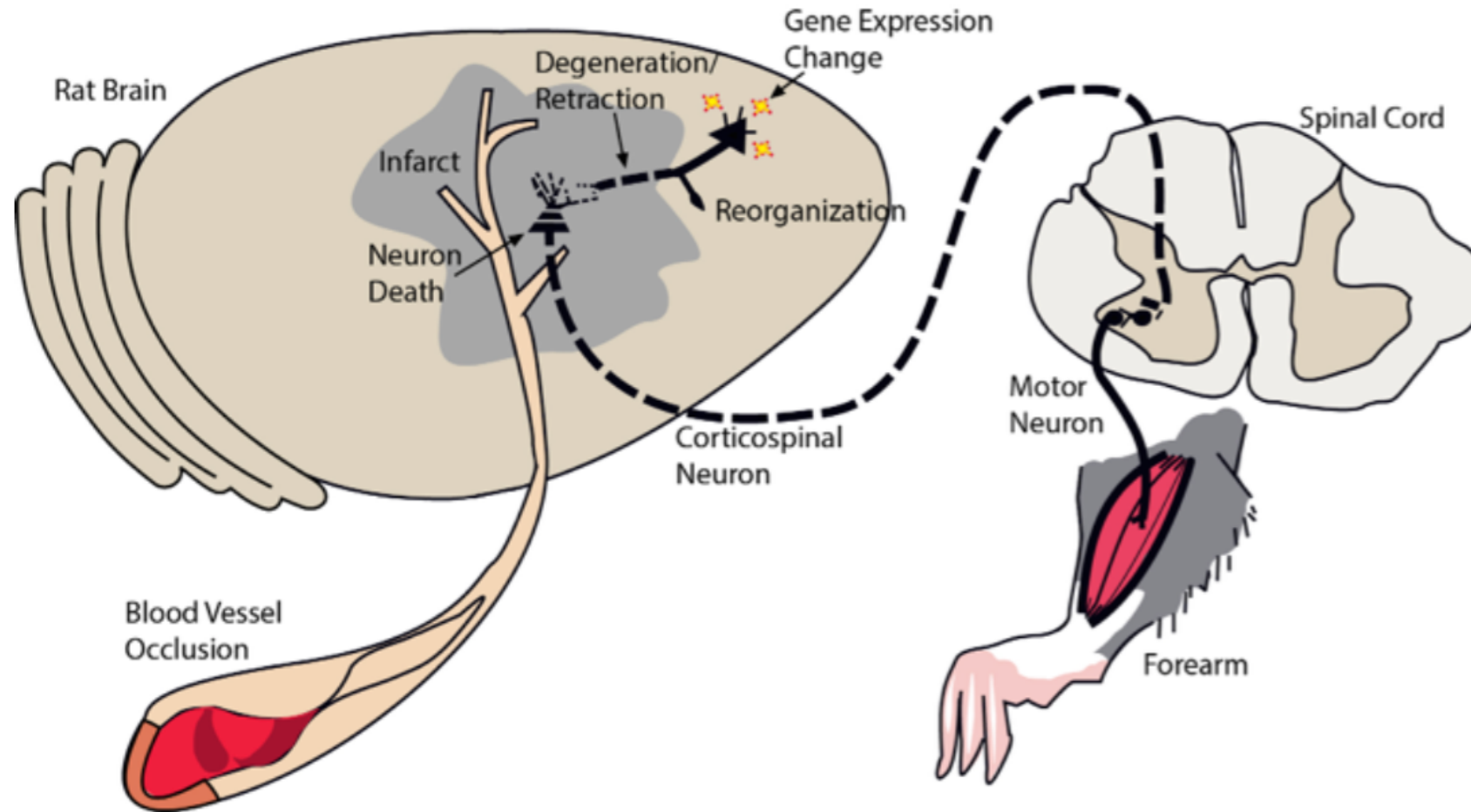
Vaisseaux
bouchés,
interruption
du flux sanguin
dans la zone
affectée

Accident hémorragique



Rupture des
vaisseaux,
fuites de
sang

Accident Vasculaire Cérébral



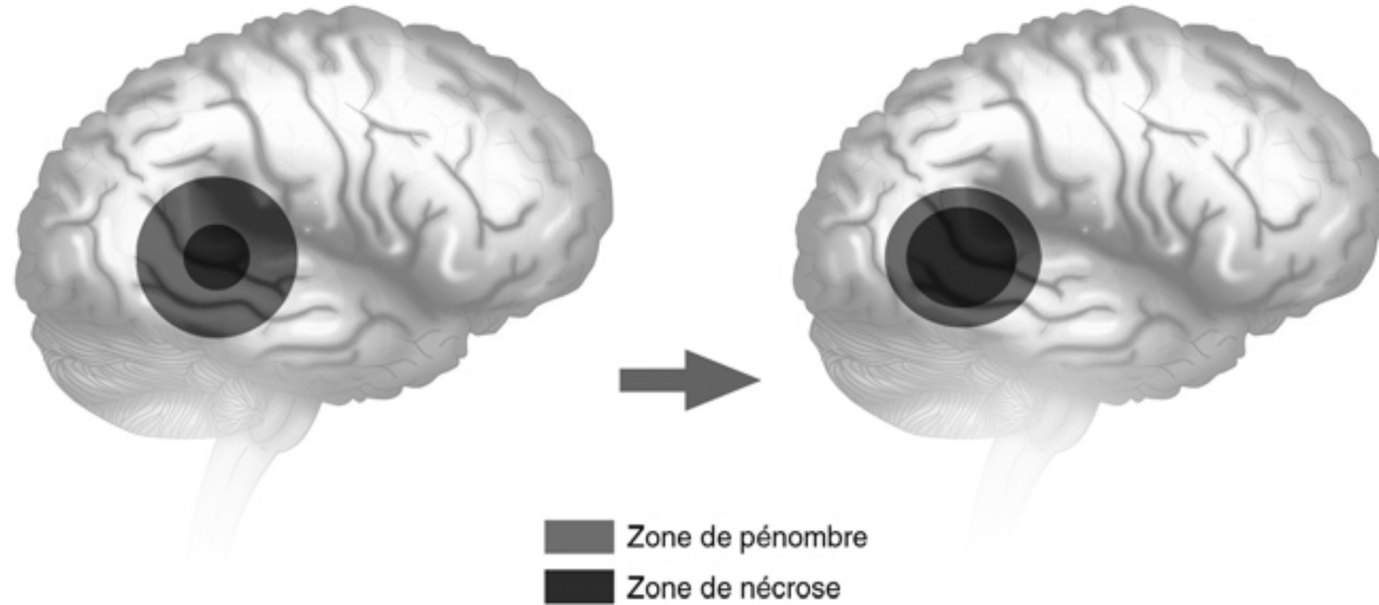
Gene expression changes of interconnected spared cortical neurons 7 days after ischemic infarct of the primary motor cortex in the rat. **Mol Cell Biochem.** 2012;369(1-2):267-86

Accident Vasculaire Cérébral

“ Jusqu’à cette dernière décennie, le dogme, selon lequel toute lésion cérébrale chez l’homme adulte était irréversible et ne pouvait pas être réparée, a prévalu aussi bien dans les facultés de médecine que dans la chambre du patient. Pourtant, cette vue statique de l’organisation cérébrale est en contradiction avec de nombreuses observations : après un accident vasculaire cérébral (AVC), les patients peuvent s’améliorer spontanément dans les trois premiers mois puis de manière plus lente dans l’année qui suit.”

Deroide et al. (2010). Plasticité cérébrale : de la théorie à la pratique dans le traitement de l’accident vasculaire cérébral. ***La revue de médecine interne***

Accident Vasculaire Cérébral



Zone de pénombre : Partie du cerveau directement affectée au cours d'un AVC

→ EN l'absence d'intervention thérapeutique, une bonne part de cette zone finit par **se nécroser**

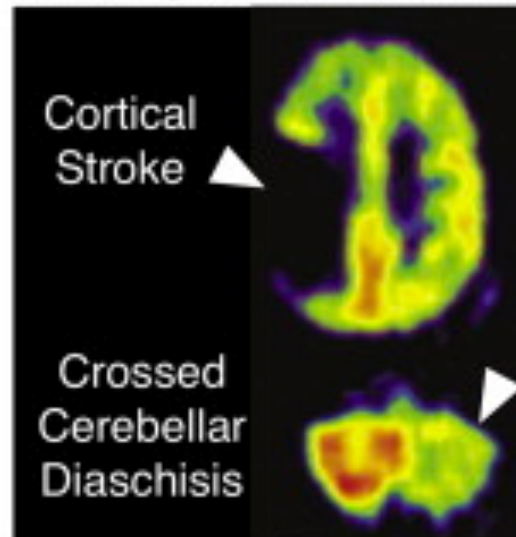
Accident Vasculaire Cérébral

Effet à distance - Diaschisis

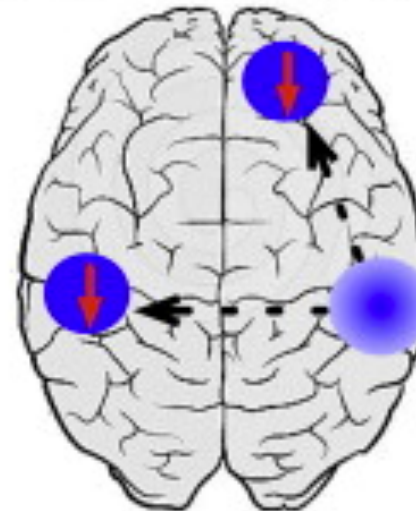
Phénomène d'inhibition fonctionnelle d'une partie du cerveau située à distance de la lésion

Par exemple, baisse de l'excitabilité dans les zones normalement activées par la zone lésée.
– cortex cérébral controlatéral (via le corps calleux) ou le cervelet controlatéral (via les pédoncules cérébelleux).

A Diaschisis in distal brain regions (cerebellum)



B Diaschisis in functionally connected cortical areas



Accident Vasculaire Cérébral

“In patients who survive stroke, there is invariably some degree of functional recovery, ranging from minimal to complete (Twitchell, 1951).”

LA RÉCUPÉRATION APRÈS UN AVC

What Do Motor “Recovery” and “Compensation” Mean in Patients Following Stroke?

[Mindy F. Levin, PhD, PT mindy.levin@mcgill.ca](mailto:mindy.levin@mcgill.ca)

[Jeffrey A. Kleim, PhD](#)

[Steven L. Wolf, PhD, PT, FAPTA, FAHA](#)

Abstract

There is a lack of consistency among researchers and clinicians in the use of terminology that describes changes in motor ability following neurological injury. Specifically, the terms and definitions of *motor compensation* and *motor recovery* have been used in different ways, which is a potential barrier to interdisciplinary communication. This Point of View describes the problem and offers a solution in the form of definitions of compensation and recovery at the neuronal, motor performance, and functional levels within the framework of the International Classification of Functioning model.

What Do Motor “Recovery” and “Compensation” Mean in Patients Following Stroke?

Après la destruction de neurones par un AVC, il y a deux manières principales de récupérer une fonction perdue :

- 1) Faire exécuter la même fonction par d'autres neurones : De nouvelles zones corticales controlatérales au début puis ultérieurement ipsilatérales et périlésionnelles à la lésion, contribuent à la **récupération neurologique**
- 2) Obtenir le même résultat fonctionnel, mais par des voies physiologiques différentes : c'est **la compensation**, complément indispensable à la récupération lorsque celle-ci est insuffisante.

La récupération spontanée

“there is a process of spontaneous recovery that is maximally expressed in the first 4 weeks post-stroke and then tapers off over 6 months. Several mechanisms are likely for this spontaneous recovery, including **restitution of the ischemic penumbra, resolution of diaschisis, and brain reorganization.**”

La récupération spontanée

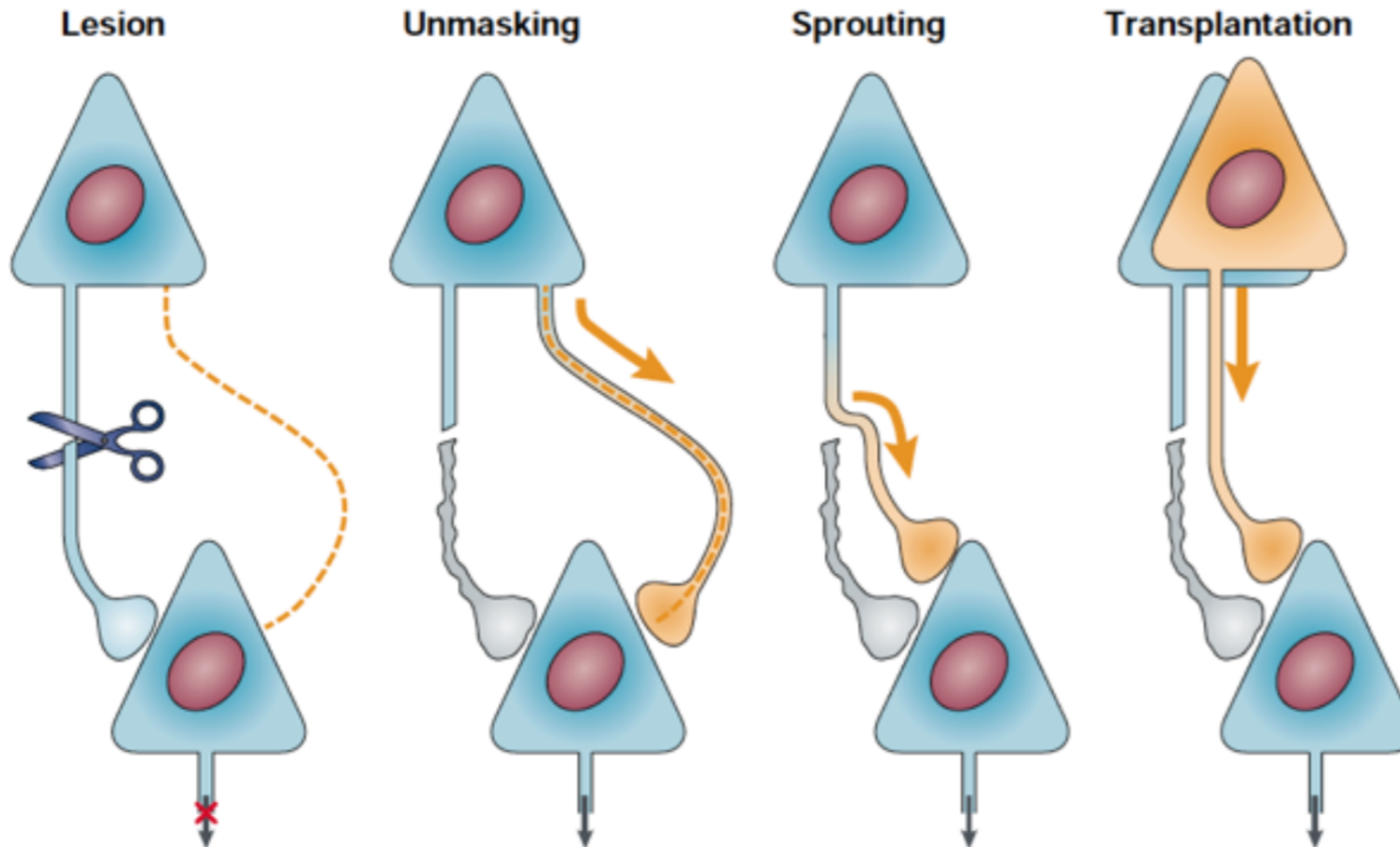
La levée du diaschisis

- Une partie de la récupération, au moins initiale, correspond à une reprise fonctionnelle des connexions inhibées mais restées anatomiquement intactes (“levée du diaschisis”)
 - Le diaschisis peut être considéré comme une déafférentation ; la levée du diaschisis correspond à une réafférentation des neurones cibles
- Les modalités de la réafférentation sont multiples et se mettent en jeu très rapidement après la lésion
 - au niveau synaptique, lorsque un neurone est privé d’une partie de ses afférences on observe un changement fonctionnel qui conduit à augmenter sa sensibilité à d’autres afférences conservées

La récupération spontanée

- Recherche animale
 - Nombreux processus biochimiques et cellulaires déclenchés par l'avc... prennent place rapidement (minutes / heures) – pas seulement dans le voisinage de la lésion mais aussi dans des régions à distance et dans l'hémisphère controlatéral
 - Ces processus conduisent à la formation de nouvelles synapses et au bourgeonnement d'axones pour se reconnecter au tissu préservé

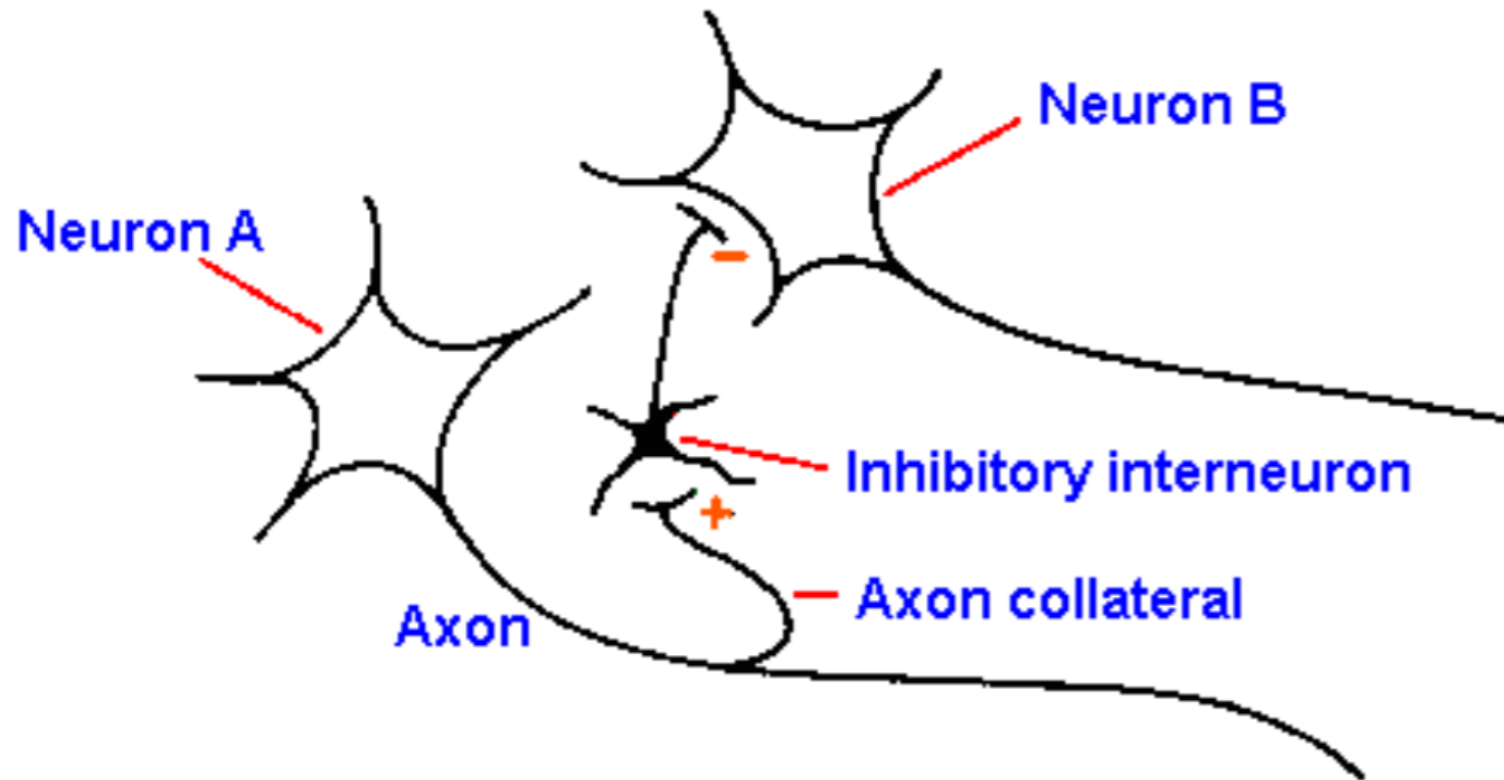
Les différentes formes de plasticité neurale



Taub et al. *Nature Neuroscience reviews*, 2002, 3, 228-236.

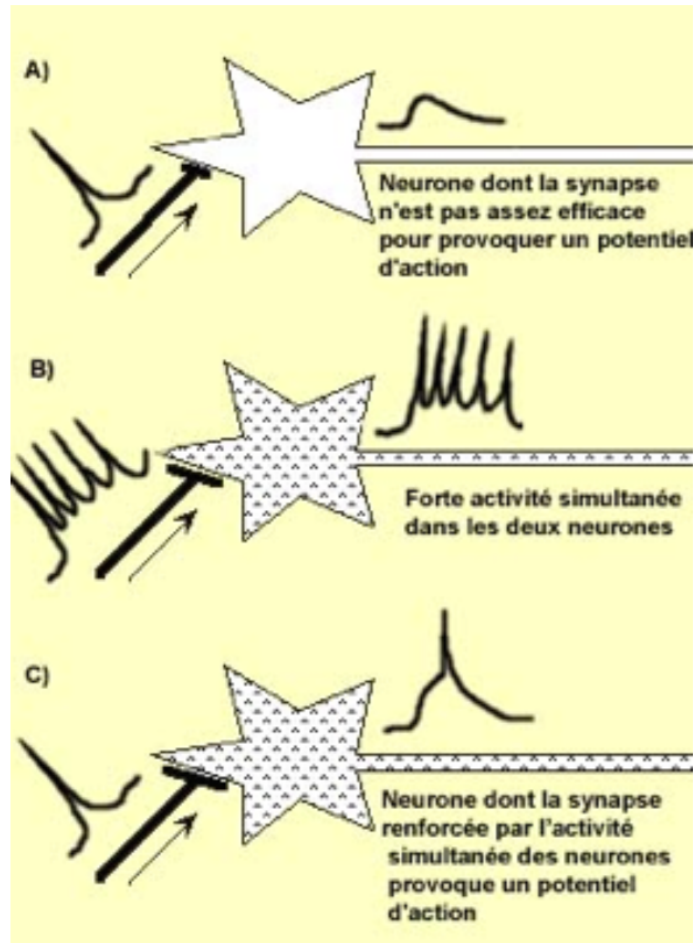
Les différentes formes de plasticité neurale

Démasquage de synapses inactives
Changements des effets modulateurs de connexions latérales



Les différentes formes de plasticité neurale

Renforcement / Affaiblissement synaptique



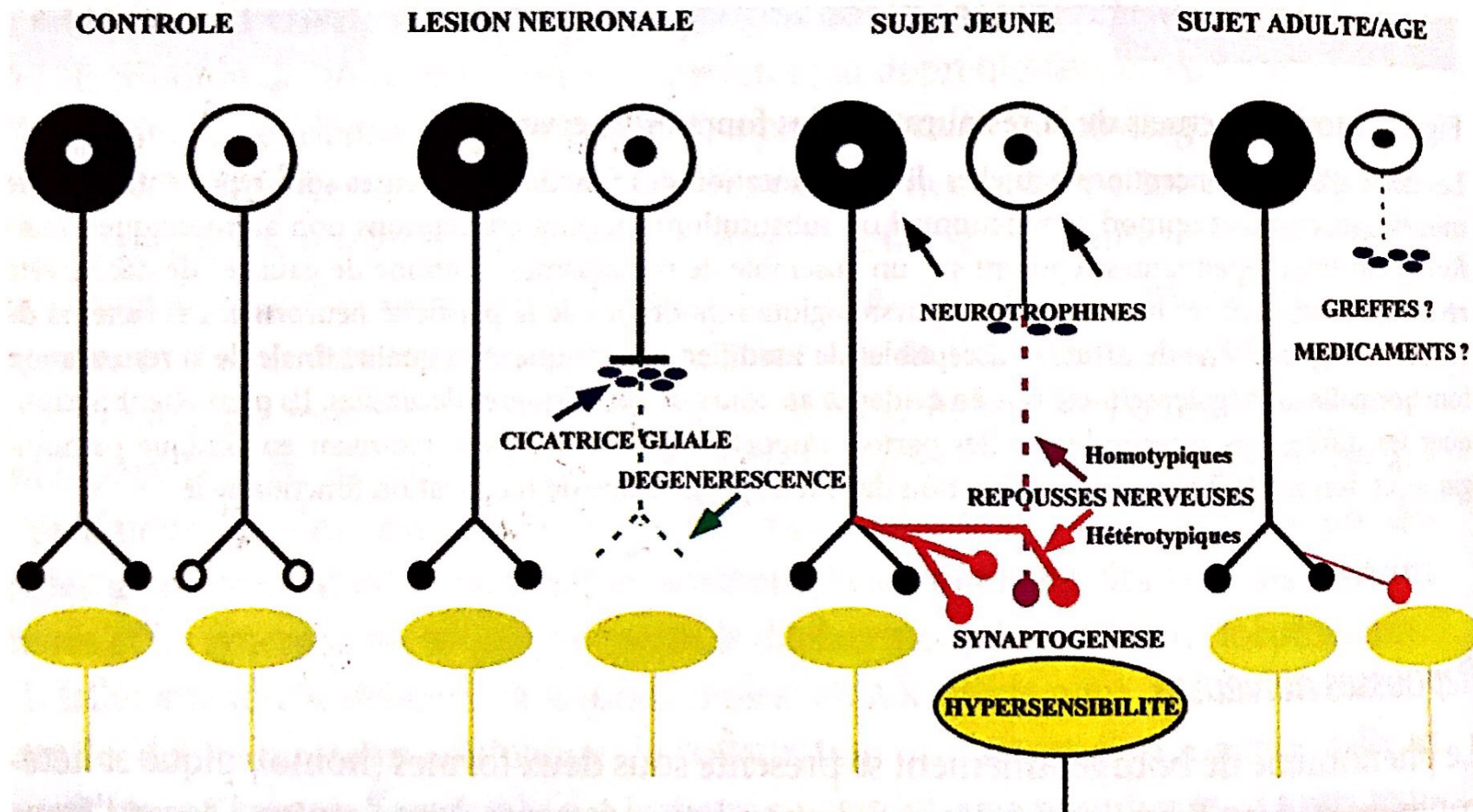
la loi de Hebb (1949)

1. **Renforcement synaptique** : si deux neurones de chaque côté d'une connexion sont activés simultanément (de manière synchrone), alors la force de cette connexion est sélectivement renforcée

2. **Affaiblissement synaptique** : si deux neurones de chaque côté d'une connexion sont activés de manière asynchrone, alors cette connexion est sélectivement affaiblie ou éliminée

Les différentes formes de plasticité neuronale

La synaptogenèse



Evidence for stroke-induced neurogenesis in the human brain

Kunlin Jin^{*†}, Xiaomei Wang^{†‡}, Lin Xie^{*}, Xiao Ou Mao^{*}, Wei Zhu[‡], Yin Wang[§], Jianfeng Shen[¶], Ying Mao[‡], Surita Banwait^{*}, and David A. Greenberg^{*¶}

^{*}Buck Institute for Age Research, Novato, CA 94945; Departments of [†]Neurosurgery and [§]Neuropathology, Huashan Hospital, Fudan University, Shanghai 200040, China; and [‡]Department of Neurosurgery, First Affiliated Hospital, Zhejiang Medical University, Zhejiang 310031, China

Edited by Solomon H. Snyder, Johns Hopkins University School of Medicine, Baltimore, MD, and approved July 10, 2006 (received for review May 9, 2006)

Experimental stroke in rodents stimulates neurogenesis and migration of newborn neurons from their sites of origin into ischemic brain regions. We report that in patients with stroke, cells that express markers associated with newborn neurons are present in the ischemic penumbra surrounding cerebral cortical infarcts, where these cells are preferentially localized in the vicinity of blood vessels. These findings suggest that stroke-induced compensatory neurogenesis may occur in the human brain, where it could contribute to postischemic recovery and represent a target for stroke therapy.

penumbra. Moreover, DCX (Fig. 2*c*), β III tubulin (Fig. 2*d*), and TUC-4 (Fig. 2*e*) were detected in cells that also expressed Ki-67, and multiple immature neuronal markers were expressed in a given cell (Fig. 2*f*), confirming that these were newborn neurons. Consistent with this interpretation, some Ki-67/DCX-positive cells exhibited a migratory phenotype consisting of an elongated cellular profile with a leading edge and trailing nucleus (Fig. 2*g*).

In the hippocampal dentate gyrus (which, together with the subventricular zone, accounts for most neurogenesis in the adult brain), new neurons arise in proximity to blood vessels, which are thought to provide a “vascular niche” that supports their pro-

Evidence for stroke-induced neurogenesis in the human brain

Kunlin Jin^{*†}, Xiaomei Wang^{†‡}, Lin Xie^{*}, Xiao Ou Mao^{*}, Wei Zhu[‡], Yin Wang[§], Jianfeng Shen[¶], Ying Mao[‡],

L'AVC expérimental chez les rats stimule la neurogenèse et la migration des neurones nouveaux-nés de leurs sites d'origine dans les régions cérébrales ischémiques.

- ➔ **Chez les patients post-AVC, les cellules qui expriment des marqueurs associés aux neurones nouveau-nés sont présents dans la pénombre ischémique entourant les infarctus corticaux cérébraux, où ces cellules sont localisées préférentiellement dans le voisinage des vaisseaux sanguins.**
- ➔ **Ces résultats suggèrent que la neurogenèse compensatoire induite par un AVC peut se produire dans le cerveau humain, où elle pourrait contribuer à la récupération post-ischémique et représenter une cible pour la thérapie de l'AVC.**

The age and genomic integrity of neurons after cortical stroke in humans

Hagen B Huttner^{1,2,13}, Olaf Bergmann^{1,13}, Mehran Salehpour³, Attila Rácz², Jemal Tatarishvili⁴, Emma Lindgren¹, Tamás Csonka⁵, László Csiba⁶, Tibor Hortobágyi⁵, Gábor Méhes⁵, Elisabet Englund⁷, Beata Werne Solnestam⁸, Sofia Zdunek¹, Christian Scharenberg^{9,10}, Lena Ström¹, Patrik Ståhl¹, Benjamin Sigurgeirsson⁸, Andreas Dahl¹¹, Stefan Schwab², Göran Possnert³, Samuel Bernard¹², Zaal Kokaia⁴, Olle Lindvall⁴, Joakim Lundeberg⁸ & Jonas Frisén¹

It has been unclear whether ischemic stroke induces neurogenesis or neuronal DNA rearrangements in the human neocortex. Using immunohistochemistry; transcriptome, genome and ploidy analyses; and determination of nuclear bomb test–derived ¹⁴C concentration in neuronal DNA, we found neither to be the case. A large proportion of cortical neurons displayed DNA fragmentation and DNA repair a short time after stroke, whereas neurons at chronic stages after stroke showed DNA integrity, demonstrating the relevance of an intact genome for survival.

“The present data uncover that, contrary to some experimental studies in animal models, **the adult human neocortex is incapable of regenerating neurons, even in response to stroke.**”

The age and genomic integrity of neurons after cortical stroke in humans

Hagen B Huttner^{1,2,13}, Olaf Bergmann^{1,13}, Mehran Salehpour³,

l'AVC ischémique induit une neurogenèse ou des réarrangements de l'ADN?

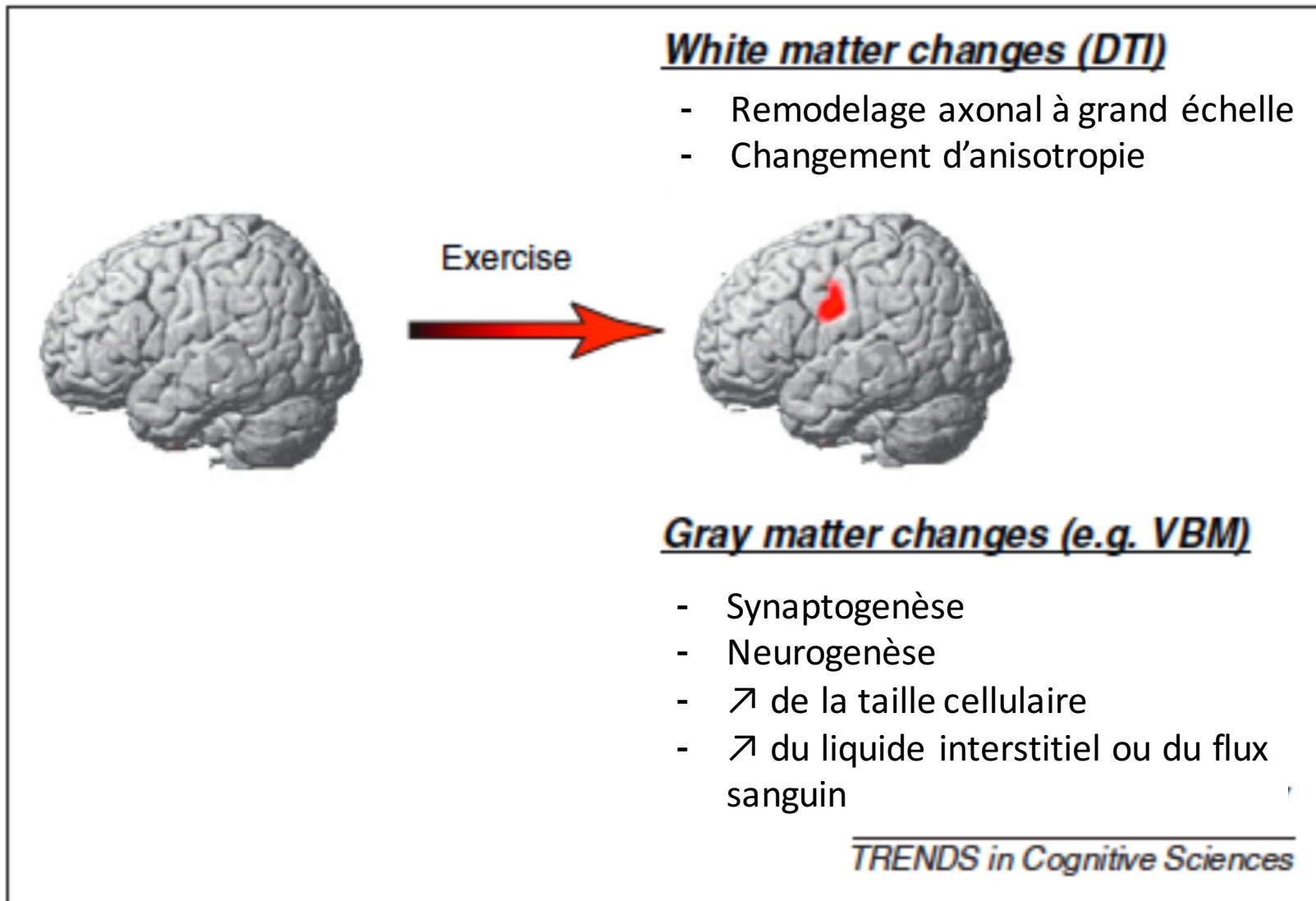
Neither was the case

Exploration de l'ADN neural:

- Peu de plasticité en terme de neurogenèse
- Une grande partie des neurones présentaient une fragmentation et une réparation de l'ADN, peu de temps après l'AVC
- Les neurones aux stades chroniques présentaient intégrité de l'ADN

“The present data uncover that, contrary to some experimental studies in animal models, the adult human neocortex is incapable of regenerating neurons, even in response to stroke.”

Les principes de la plasticité



“ Les futures études devraient se concentrer sur la compréhension des mécanismes qui définissent la fenêtre temporelle critique de récupération fonctionnelle après un AVC.

Une meilleure compréhension de la cinétique des mécanismes qui contribuent à la récupération fonctionnelle, comme la plasticité, la levée de la diaschisis, et des mécanismes comportementaux qui permettent des stratégies de compensation, peut avoir un impact significatif sur la gestion de la réadaptation des patients.”

Les différentes formes de plasticité neurale

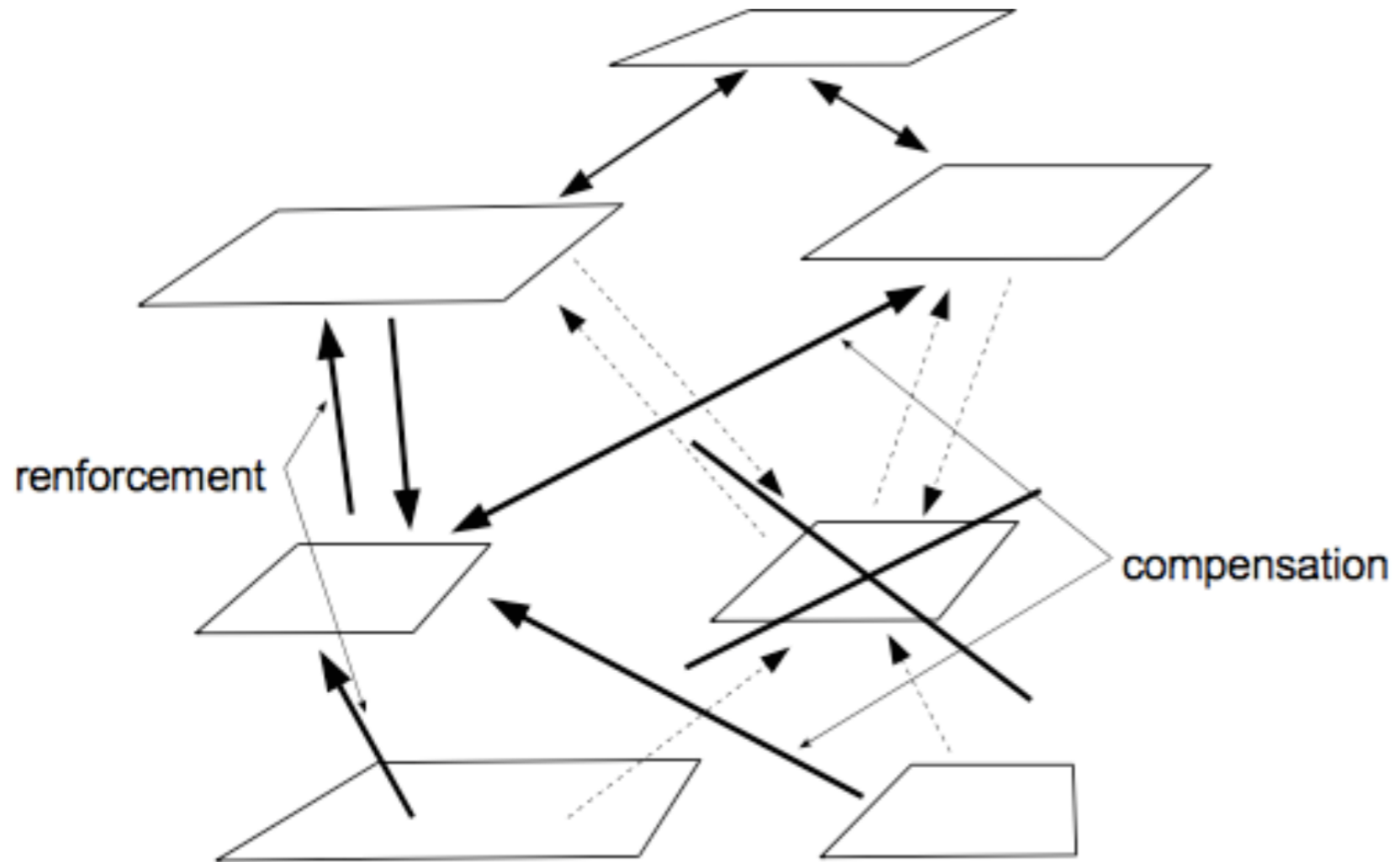
Le réentraînement

« Quelques soient les mécanismes en jeu dans la réorganisation neuronale il paraît évident que la sollicitation constante et systématique par le réentraînement systématique est essentielle pour ouvrir une voie inhibée, reconstruire un circuit interrompu, stabilisé un circuit nouveau, définir et mobiliser un nouvel ensemble neuronal »

Jeannerod et Hecaen

Les différentes formes de plasticité neuronale

Le réentraînement



Les différentes formes de plasticité neurale

La vicariance fonctionnelle

La commande volontaire de déglutition dépend d'une zone restreinte du cortex moteur qui est normalement bilatérale avec dominance du cortex droit.

Après un AVC dans cette région, la récupération est liée à la prise en charge de la fonction par l'aire correspondante de l'HD. Par TMS, on peut observer une extension considérable de la carte motrice à cet endroit

Les différentes formes de plasticité neurale

Augmentation du volume des faisceaux de substance blanche

Published in final edited form as:

Ann N Y Acad Sci. 2009 July ; 1169: 385–394. doi:10.1111/j.1749-6632.2009.04587.x.

Evidence for Plasticity in White Matter Tracts of Chronic Aphasic Patients Undergoing Intense Intonation-based Speech Therapy

Gottfried Schlaug, Sarah Marchina, and Andrea Norton

Dept. of Neurology, Music, Stroke Recovery, and Neuroimaging Laboratories, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA 02215

Abstract

Recovery from aphasia can be achieved through recruitment of either peri-lesional brain regions in the affected hemisphere or homologous language regions in the non-lesional hemisphere. For patients with large left-hemisphere lesions, recovery through the right hemisphere may be the only possible path. The right hemisphere regions most likely to play a role in this recovery process are the superior temporal lobe (important for auditory feedback control), premotor regions/posterior inferior frontal gyrus (important for planning and sequencing of motor actions and for auditory-motor mapping) and the primary motor cortex (important for execution of vocal motor actions). These regions are connected reciprocally via a major fiber tract called the arcuate fasciculus (AF), but this tract is usually not as well developed in the non-dominant right hemisphere. We tested whether an intonation-based speech therapy (i.e., Melodic Intonation Therapy) which is typically administered in an intense fashion with 75–80 daily therapy sessions, would lead to changes in white matter tracts, particularly the AF. Using diffusion tensor imaging (DTI), we found a significant increase in the number of AF fibers and AF volume comparing post with pre-treatment assessments in 6 patients that could not be attributed to scan-to-scan variability. This suggests that intense, long-term Melodic Intonation Therapy leads to remodeling of the right AF and may provide an explanation for the sustained therapy effects that were seen in these 6 patients.

Les différentes formes de plasticité neurale

Augmentation du volume des faisceaux de substance blanche

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Evidence for Plasticity in White Matter Tracts of Chronic Aphasic Patients Undergoing Intense Intonation-based Speech Therapy

La récupération de l'aphasie

Pour les patients avec de grandes lésions de l'hémisphère gauche, la récupération à travers l'hémisphère droit peut être la seule voie possible.

Les régions de l'hémisphère droit → rôle dans ce processus de récupération sont:

- Lobe temporal supérieur
- Lobe parétal
- Cortex moteur

Ces régions sont connectées réciproquement via un faisceau de fibres principales appelé le faisceau arqué (AF)



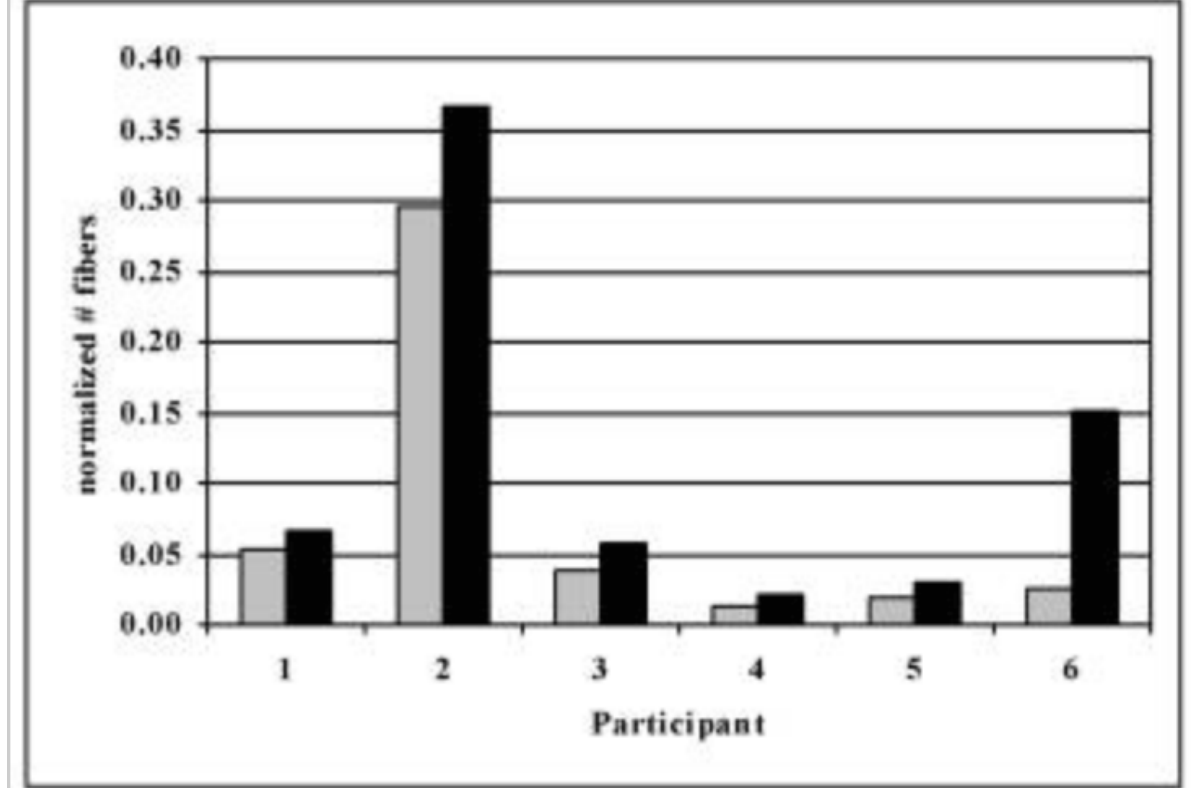
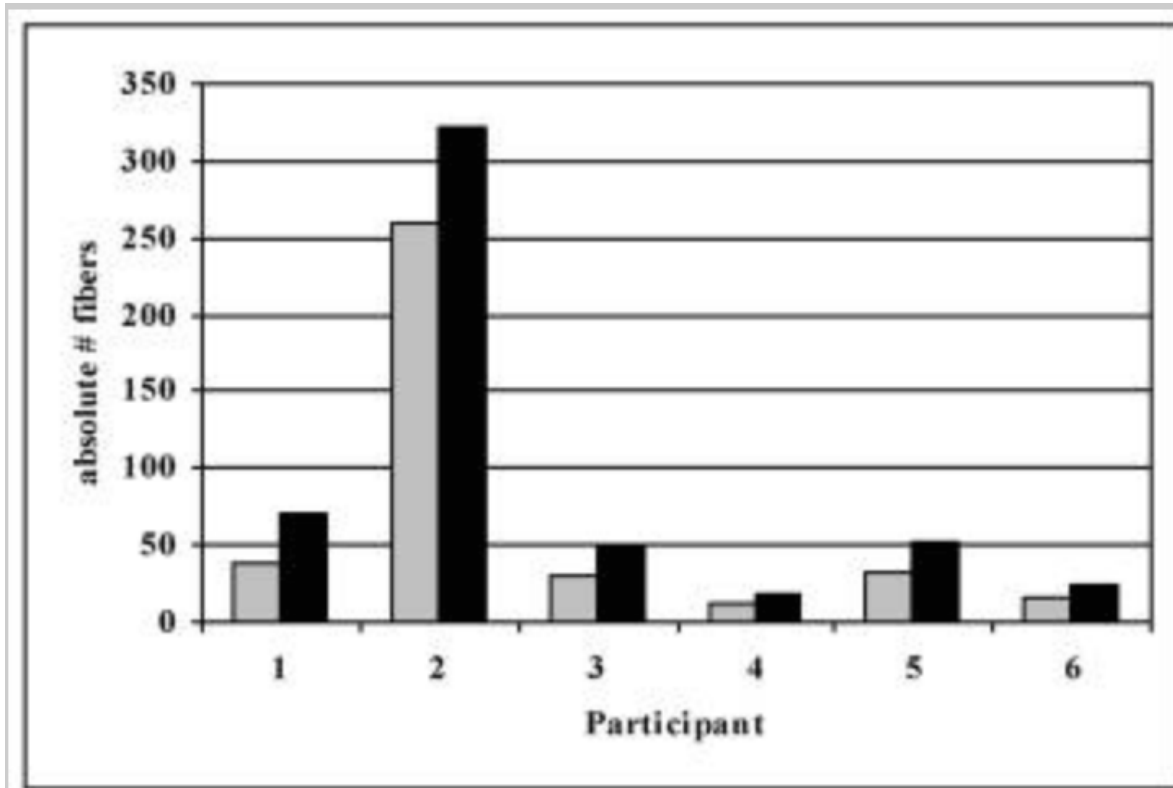
pas assez développé dans l'hémisphère droit non dominant

Objectif: Etudier l'effet d'une thérapie de la parole basée sur l'intonation avec 75-80 séances/ jour sur les faisceaux de la matière blanche, particulièrement (AF)

Les différentes formes de plasticité neurale

Augmentation du volume des faisceaux de substance blanche

↗ du nbr de fibres (AF)

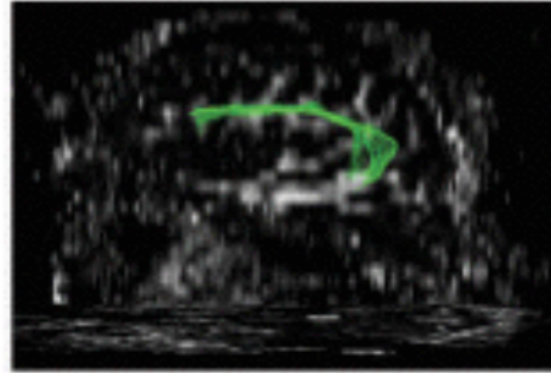


Absolute and relative fiber number of the right arcuate fasciculus (AF) before (gray bars) and after therapy (black bars) in all 6 participants.

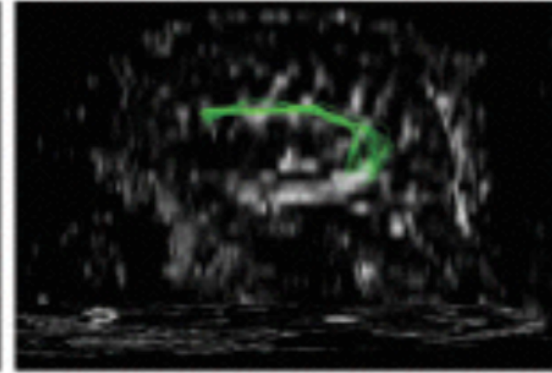
Les différentes formes de plasticité neurale

Augmentation du volume des faisceaux de substance blanche

AF; Pre-Treatment 1

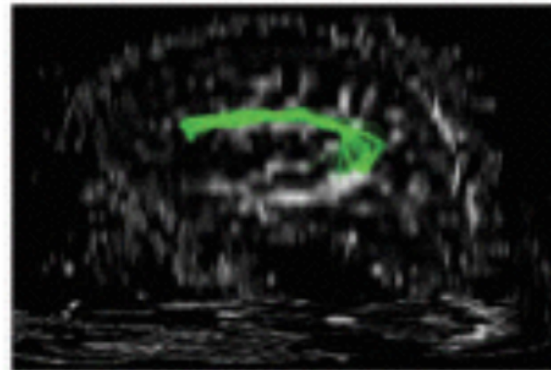


AF; Pre-Treatment 2

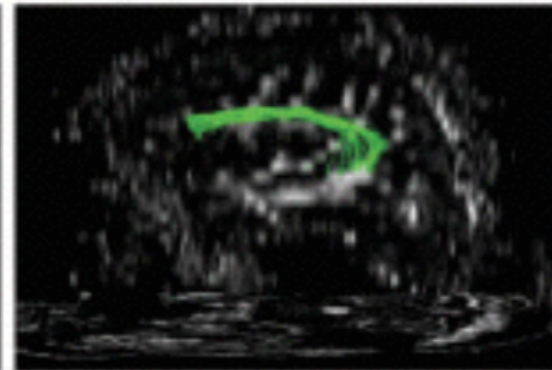


↗ du volume (AF)

AF; Post-Treatment 1



AF; Post-Treatment 2



Right AF in one patient with two scans before therapy and two scans after 75 sessions of Melodic Intonation Therapy. The scan-to-scan variability is minimal before therapy and a clear difference in the number of fibers and fiber volume can be seen comparing the AF before and after therapy.

Les différentes formes de plasticité neurale

Réorganisation des cartes motrices corticales

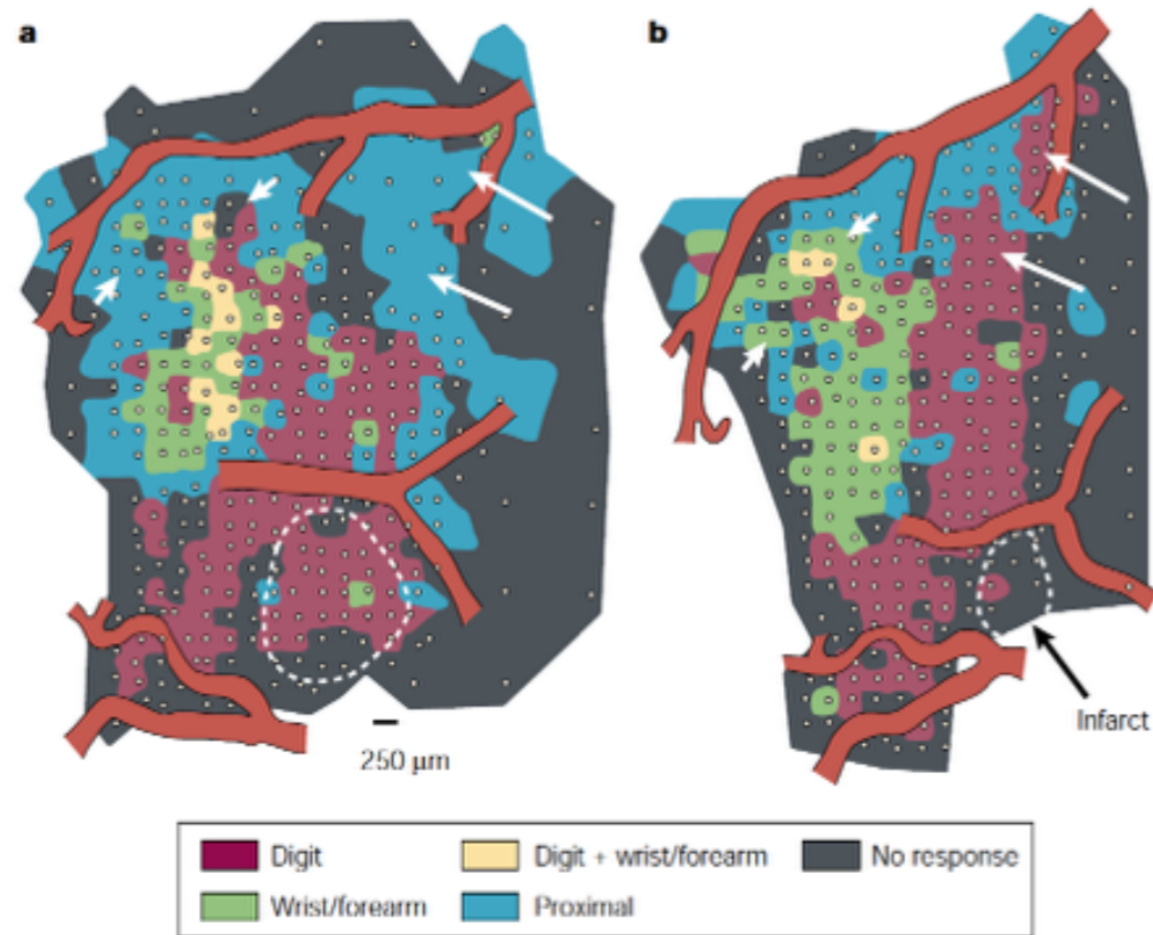
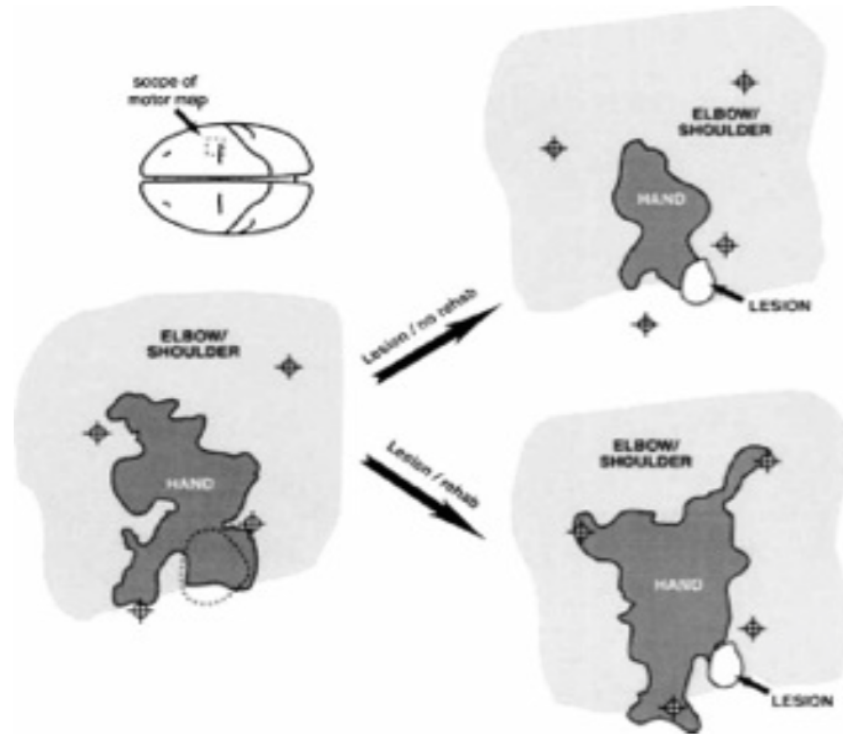


Figure 4 | **Reorganization in the motor cortex of a monkey after rehabilitative therapy.**
a | Before infarct. **b** | After infarct and rehabilitative therapy. Note the large increase in the cortical representation of the wrist/forearm after therapy. Adapted with permission from REF. 51 © 1996 American Association for the Advancement of Science.

Les différentes formes de plasticité neurale

Réorganisation des cartes motrices corticales



Plasticité **adaptive** de la carte motrice de l'épaule et du coude après lésion corticale – Effet de la réhabilitation

- Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science* 1996;**272**: 1791-1794.
- Adapté: Nudo et al. Role of adaptive plasticity in recovery of function after damage to motor cortex. *Muscle Nerve*. 2001 Aug;24(8):1000-19.

Increased Cortical Representation of the Fingers of the Left Hand in String Players

Thomas Elbert, Christo Pantev, Christian Wienbruch,
Brigitte Rockstroh, Edward Taub

Magnetic source imaging revealed that the cortical representation of the digits of the left hand of string players was larger than that in controls. The effect was smallest for the left thumb, and no such differences were observed for the representations of the right hand digits. The amount of cortical reorganization in the representation of the fingering digits was correlated with the age at which the person had begun to play. These results suggest that the representation of different parts of the body in the primary somatosensory cortex of humans depends on use and changes to conform to the current needs and experiences of the individual.

OPINION

The musician's brain as a model of neuroplasticity

Thomas F. Münte, Eckart Altenmüller and Lutz Jäncke

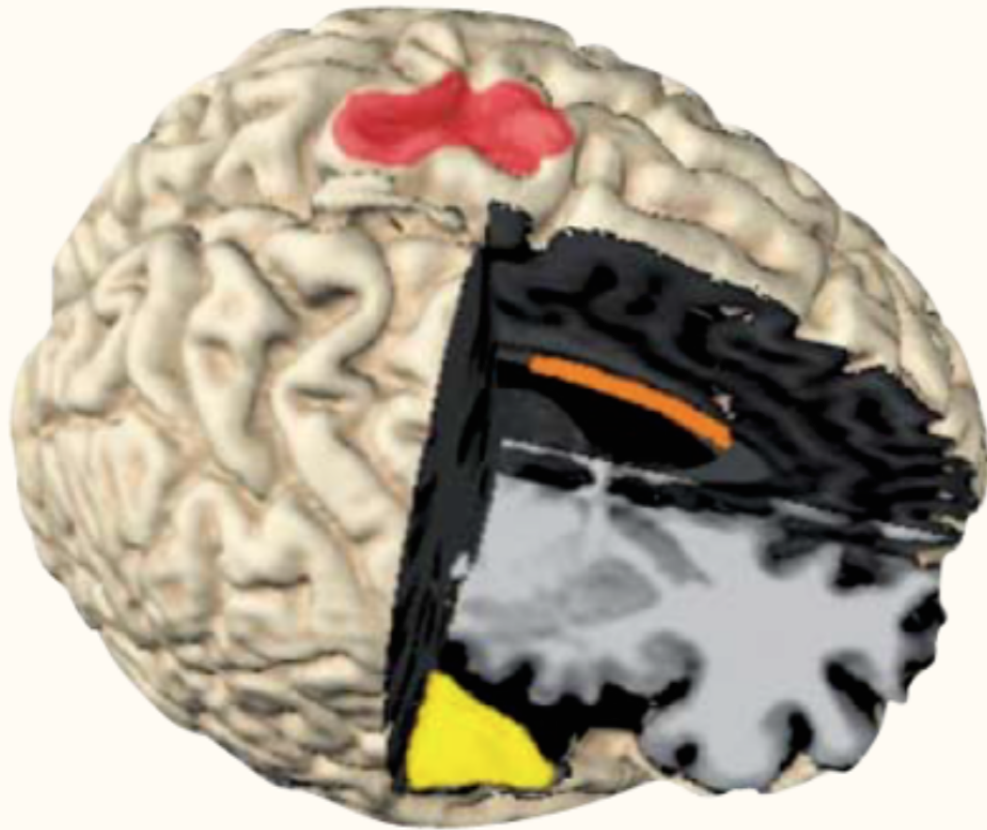
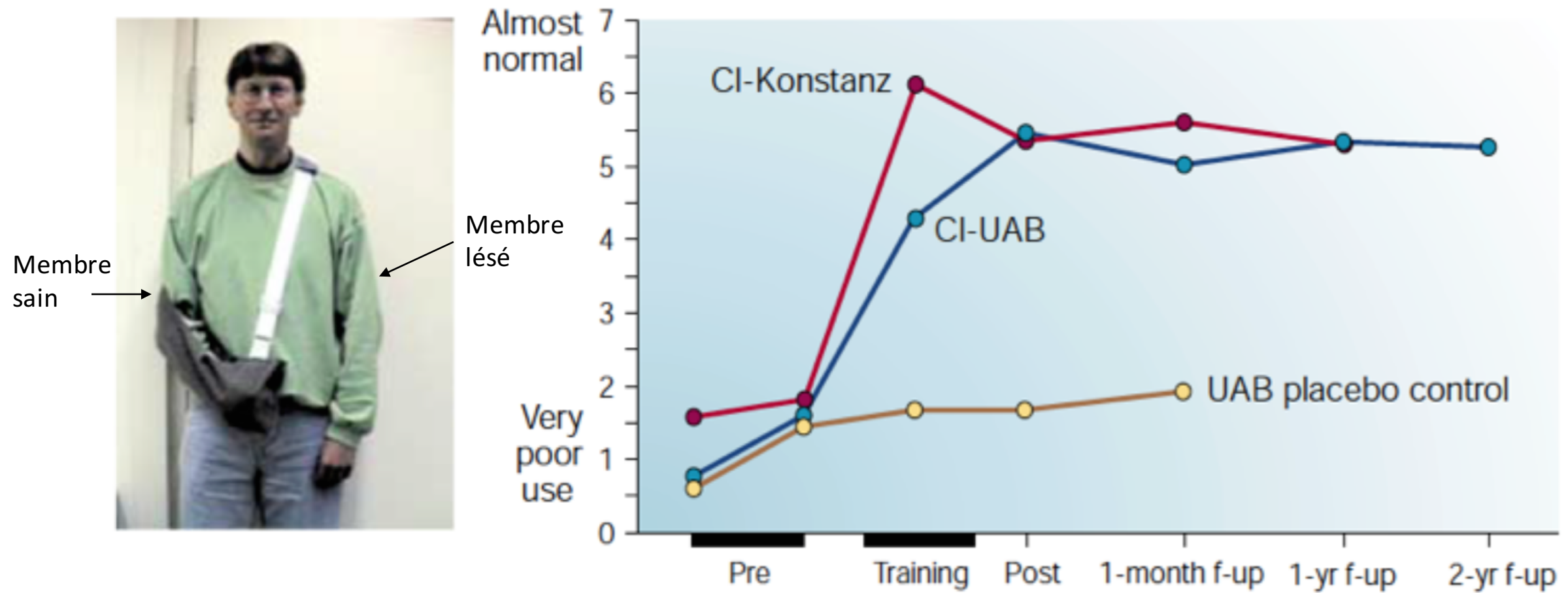


Figure 2 | **Structural changes in the brains of musicians.** Some of the brain areas that have been found to be enlarged in musicians in morphometric studies based on structural magnetic resonance imaging. Red, primary motor cortex; yellow, planum temporale; orange, anterior part of the corpus callosum.

LA RESTAURATION PAR CHANGEMENT DE STRATÉGIE



| **Constraint-Induced Movement therapy.**

Taub et al., 2002

| Development and overcoming of 'learned nonuse' of an upper extremity.

a Development of learned nonuse

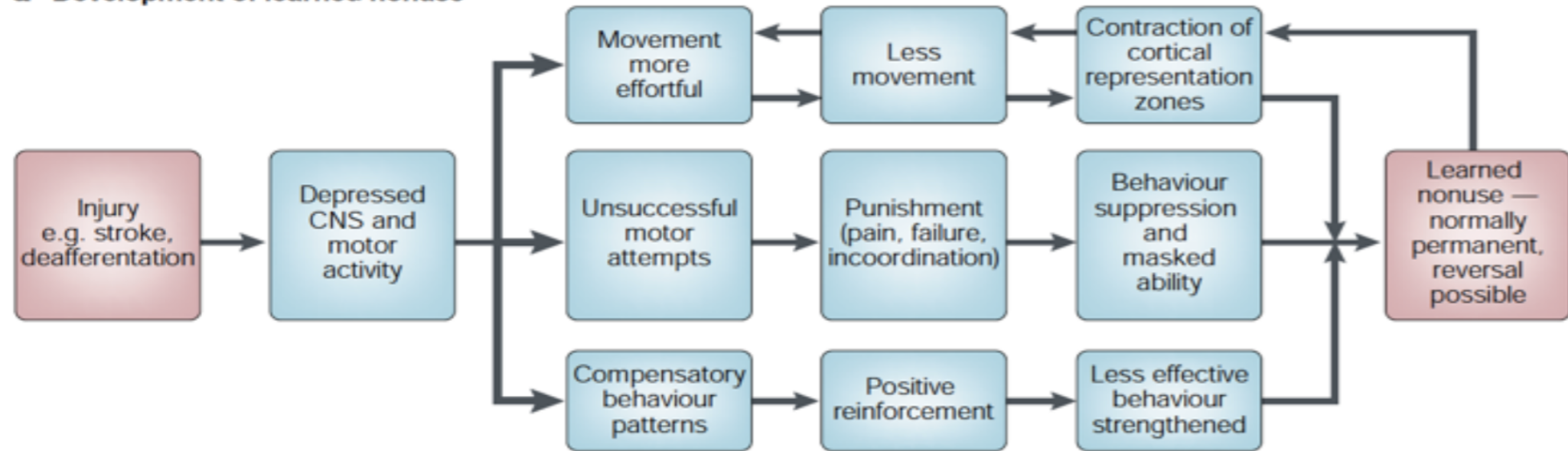
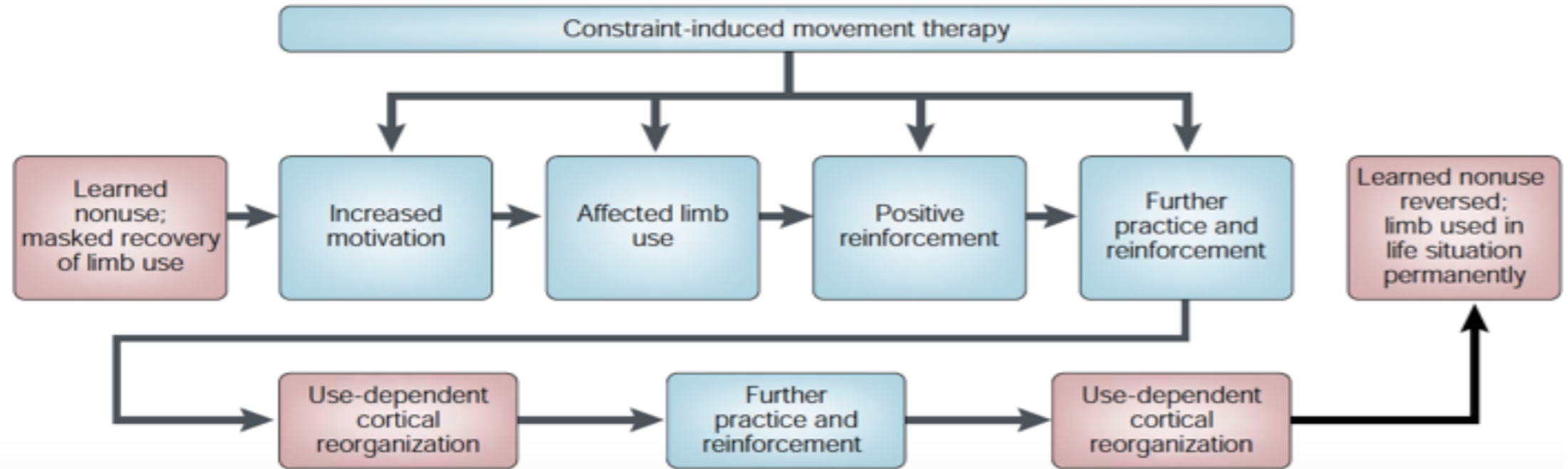


Figure 1 | **Development and overcoming of 'learned nonuse' of an upper extremity. a** | Substantial neurological injury usually leads to a substantial depression in motor and/or perceptual function. During this period, the subject cannot use the affected extremity effectively. Attempts to use the affected limb generally lead to failure. These punishing consequences result in suppression of the use of the limb (middle row). Moreover, the subject might manage reasonably well using only the uninvolved upper extremity, and is therefore rewarded for this pattern of behaviour, which as a result is strengthened (bottom row). In addition, after stroke^{36,37}, and presumably after extremity deafferentation, there is a marked contraction in the size of the cortical representation of the limb. This probably correlates with the report of patients with stroke that movement of that extremity is effortful (top row). These three processes interact to produce a vicious downward spiral that results in 'learned nonuse' of the affected extremity, which is normally permanent.

| Development and overcoming of 'learned nonuse' of an upper extremity.

b Overcoming learned nonuse



b | When appropriate techniques are applied, learned nonuse can be overcome. Training procedures can be used to reward patients systematically for using the affected arm for a period of consecutive weeks. In addition, use of the uninvolved limb can be restricted, such that the subject is rendered virtually helpless unless he/she tries to use the affected limb. Increased use of the limb leads to a use-dependent enlargement of the cortical representation of the affected extremity^{36,37}, which reduces the effort in using it and provides a neural basis for the long-term retention of gains made in the laboratory or clinic. (CNS, central nervous system.)

ORIGINAL ARTICLE

Social interaction plays a critical role in neurogenesis and recovery after stroke

VR Venna¹, Y Xu¹, SJ Doran¹, A Patrizzi¹ and LD McCullough^{1,2,3}

Stroke survivors often experience social isolation. Social interaction improves quality of life and decreases mortality after stroke. Male mice (20–25 g; C57BL/6N), all initially pair housed, were subjected to middle cerebral artery occlusion (MCAO). Mice were subsequently assigned into one of three housing conditions: (1) Isolated (SI); (2) Paired with their original cage mate who was also subjected to stroke (stroke partner (PH-SP)); or (3) Paired with their original cage mate who underwent sham surgery (healthy partner (PH-HP)). Infarct analysis was performed 72 h after stroke and chronic survival was assessed at day 30. Immediate post-stroke isolation led to a significant increase in infarct size and mortality. Interestingly, mice paired with a healthy partner had significantly lower mortality than mice paired with a stroke partner, despite equivalent infarct damage. To control for changes in infarct size induced by immediate post-stroke isolation, additional cohorts were assessed that remained pair housed for three days after stroke prior to randomization. Levels of brain-derived neurotrophic factor (BDNF) were assessed at 90 days and cell proliferation (in cohorts injected with 5-bromo-2'-deoxyuridine, BrdU) was evaluated at 8 and 90 days after stroke. All mice in the delayed housing protocol had equivalent infarct volumes (SI, PH-HP and PH-SP). Mice paired with a healthy partner showed enhanced behavioral recovery compared with either isolated mice or mice paired with a stroke partner. Behavioral improvements paralleled changes in BDNF levels and neurogenesis. These findings suggest that the social environment has an important role in recovery after ischemic brain injury.

Translational Psychiatry (2014) **4**, e351; doi:10.1038/tp.2013.128; published online 28 January 2014

Keywords: brain-derived neurotrophic factor; infarct; middle cerebral artery occlusion; neurogenesis; post-stroke recovery; social isolation

MÉCANISMES DE LA RÉCUPÉRATION DE L'APHASIE APRÈS UN AVC

Rôle de la stimulation cérébrale non-invasive

Brain Lang. 2011 July ; 118(1-2): 40–50. doi:10.1016/j.bandl.2011.02.005.

Mechanisms of Aphasia Recovery After Stroke and the Role of Noninvasive Brain Stimulation

Roy H. Hamilton^{1,2}, Evangelia G. Chrysikou³, and Branch Coslett^{1,2}

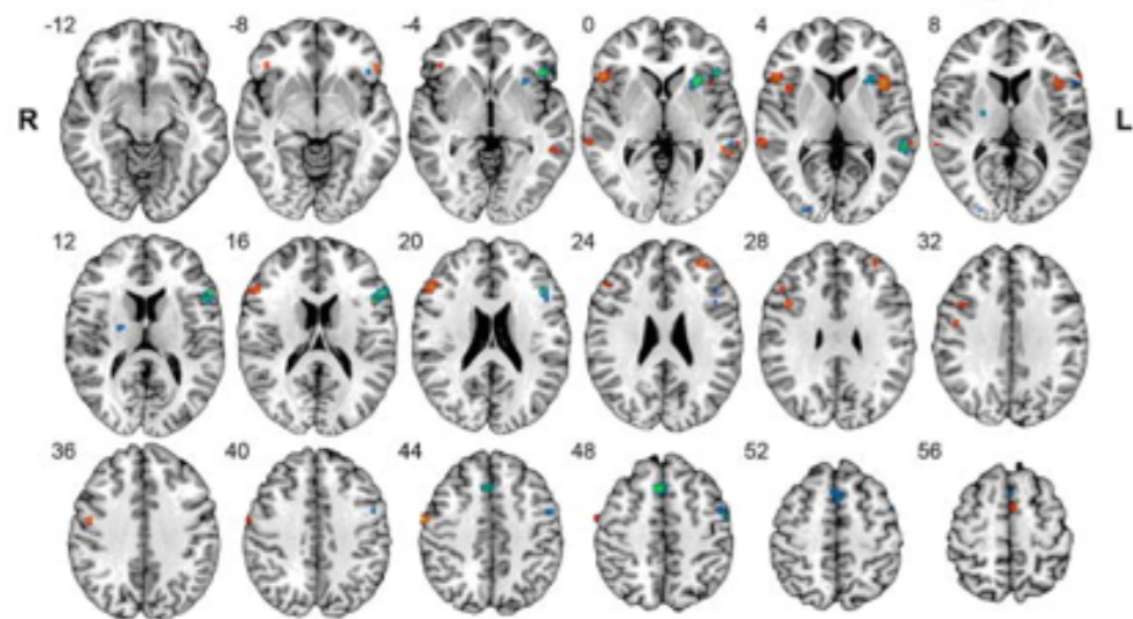
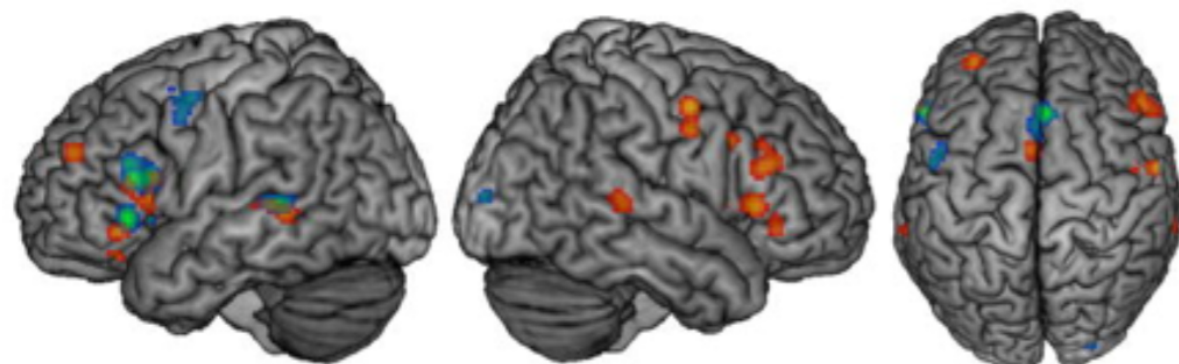
¹ University of Pennsylvania, Department of Neurology, Center for Cognitive Neuroscience, Philadelphia, PA

² Laboratory for Cognition and Neural Stimulation, University of Pennsylvania, Philadelphia, PA

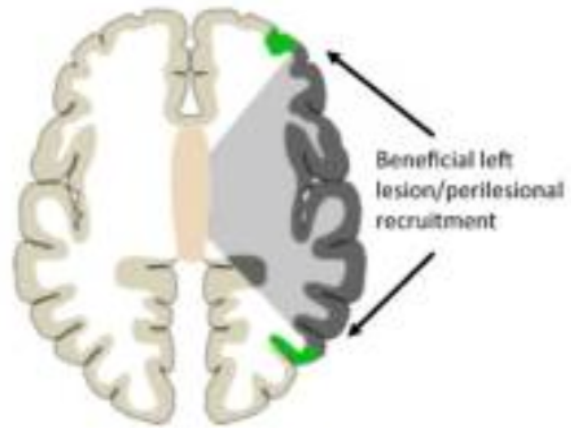
³ University of Pennsylvania, Department of Psychology, Center for Cognitive Neuroscience, Philadelphia, PA

Abstract

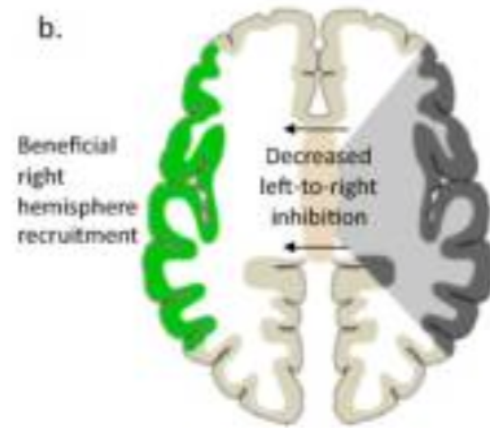
One of the most frequent symptoms of unilateral stroke is aphasia, the impairment or loss of language functions. Over the past few years, behavioral and neuroimaging studies have shown that rehabilitation interventions can promote neuroplastic changes in aphasic patients that may be associated with the improvement of language functions. Following left-hemisphere strokes, the functional reorganization of language in aphasic patients has been proposed to involve both intrahemispheric interactions between damaged left-hemisphere and perilesional sites and transcallosal interhemispheric interactions between the lesioned left-hemisphere language areas and homotopic regions in the right hemisphere. A growing body of evidence for such reorganization comes from studies using transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), two safe and noninvasive procedures that can be applied clinically to modulate cortical excitability during poststroke language recovery. We discuss a hierarchical model for the plastic changes in language representation that occur in the setting of dominant hemisphere stroke and aphasia. We further argue that TMS and tDCS are potentially promising tools for enhancing functional recovery of language and for further elucidating mechanisms of plasticity in patients with aphasia.



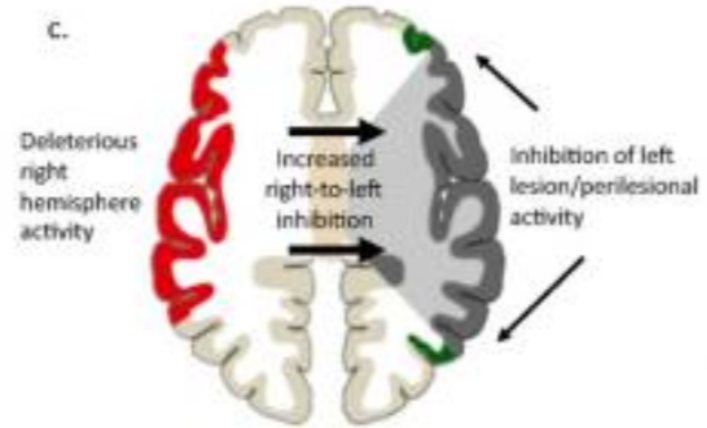
a.



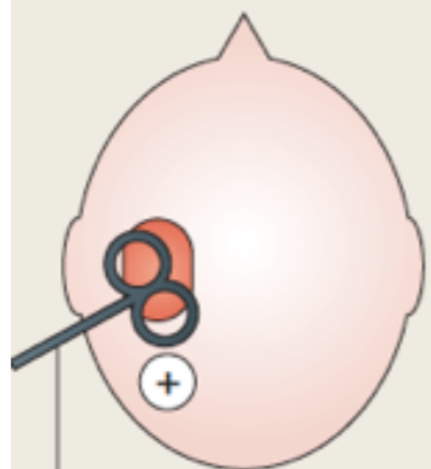
b.



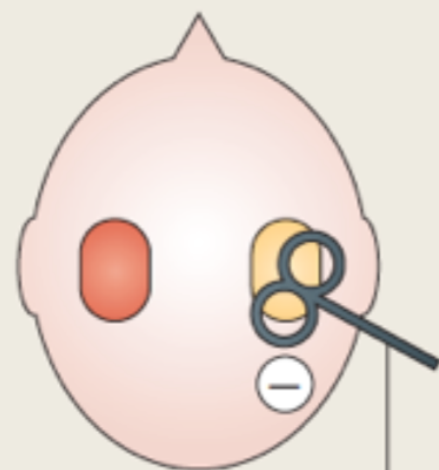
c.



Stroke



High-frequency
rTMS



Low-frequency
rTMS

From: **Mechanisms Underlying Recovery of Motor Function After Stroke**

Arch Neurol. 2004;61(12):1844-1848. doi:10.1001/archneur.61.12.1844

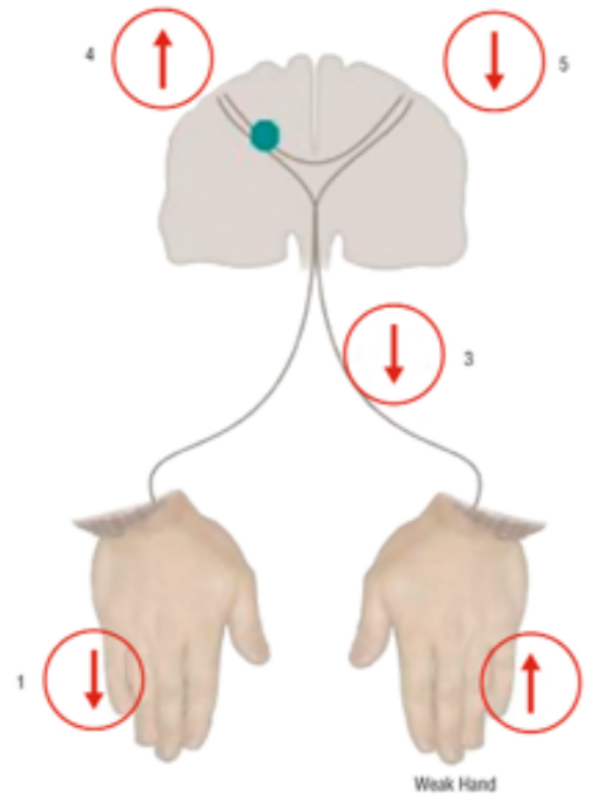
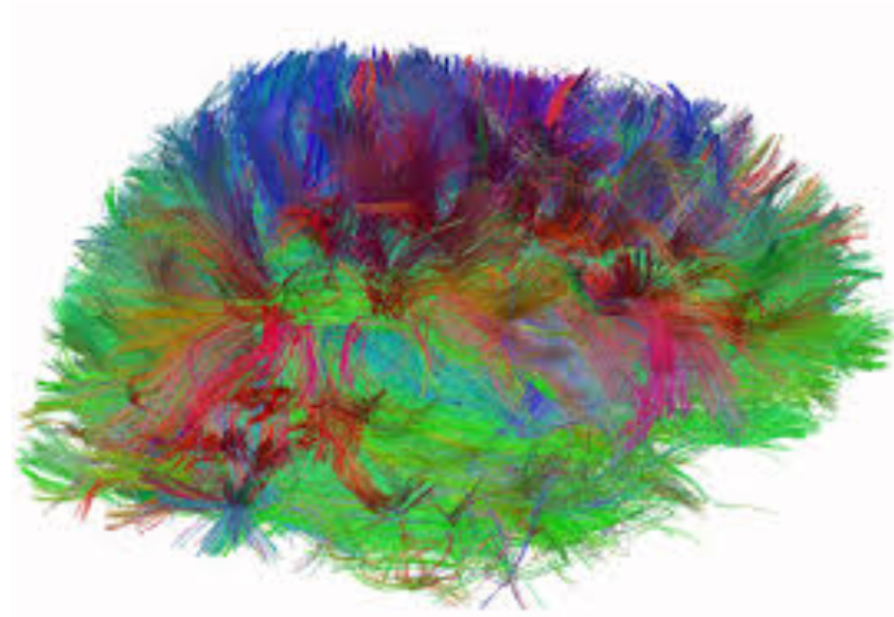


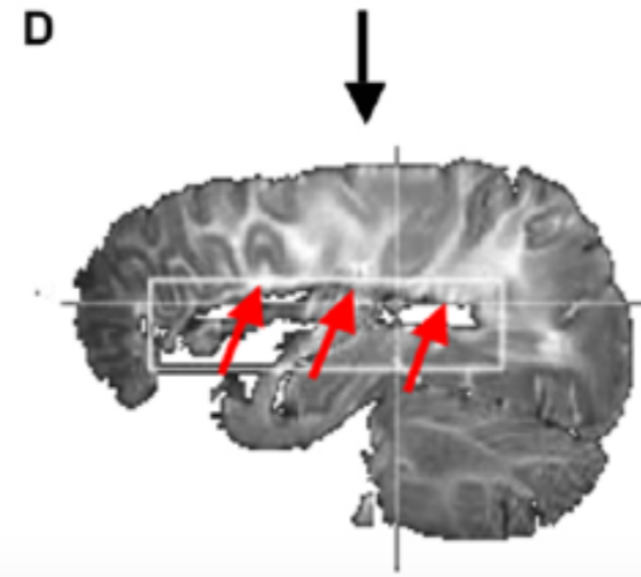
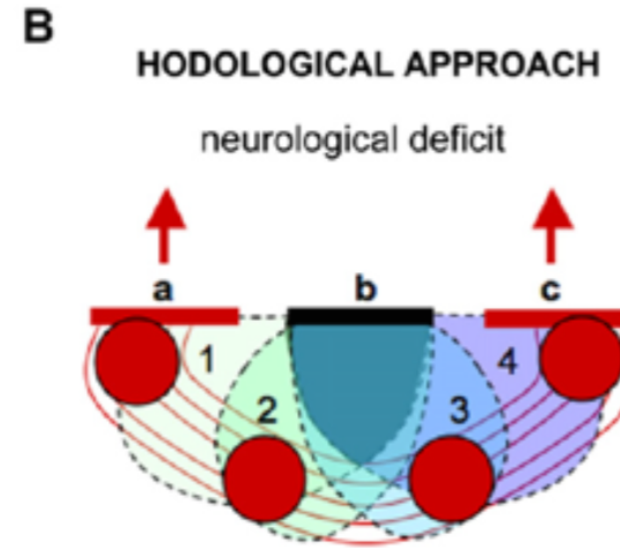
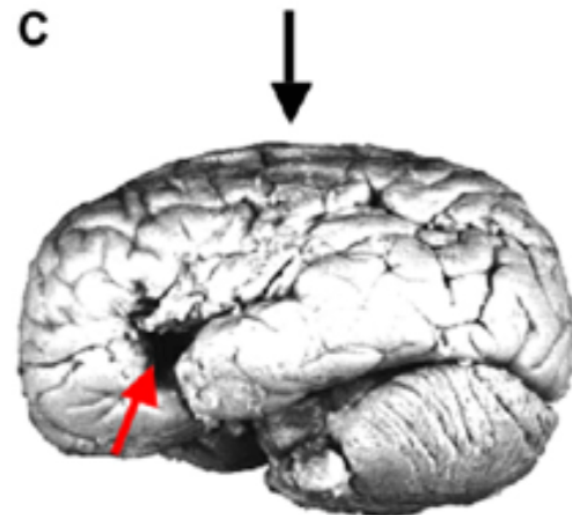
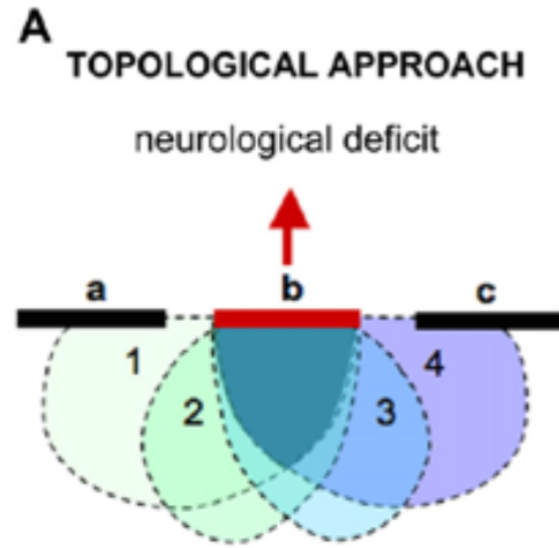
Figure Legend:

Diagram showing possible operational strategies to influence hand function (see “Possible Strategies to Enhance the Human Brain’s Response to Injury” section for details).

APPROCHE « EN RÉSEAU » DE LA RÉCUPÉRATION APRÈS UN AVC



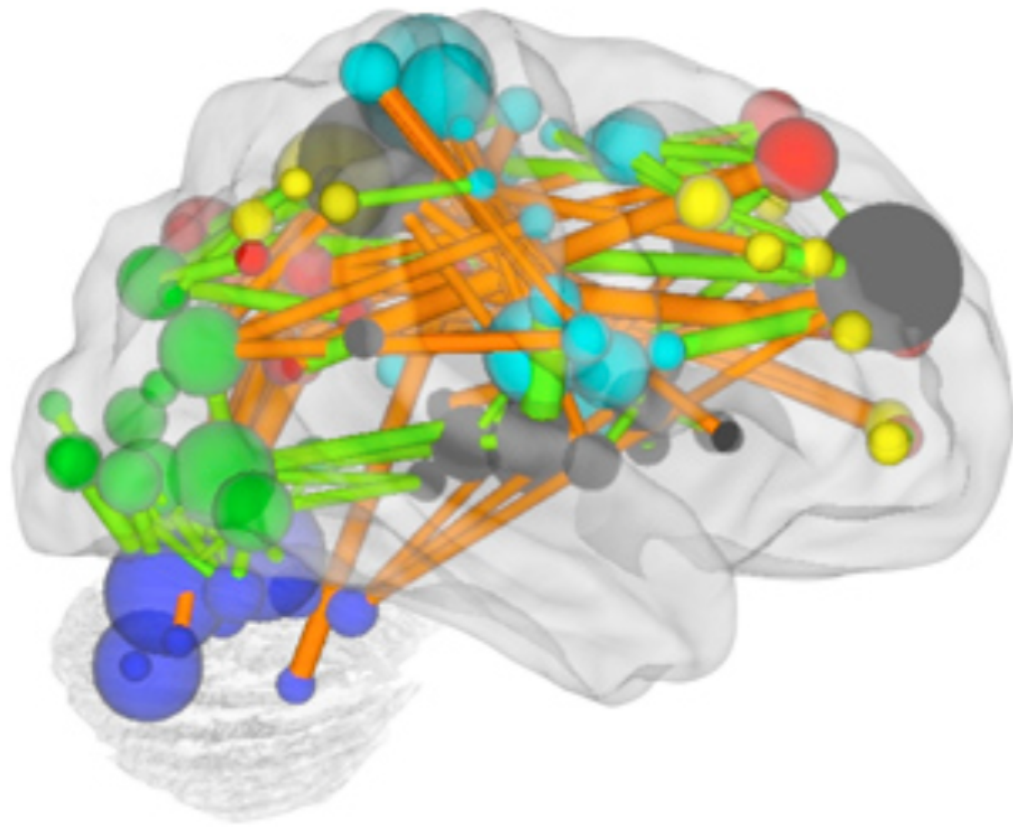
Approche « en réseau » de la récupération après un AVC



Approche « en réseau » de la récupération après un AVC

En neuroimagerie, **la connectivité fonctionnelle** entre les régions cérébrales peut être mesurée au cours d'une tâche particulière ou pendant le repos (en l'absence d'une tâche structurée). Pendant le repos, les participants doivent rester allongés et immobiles dans le scanner sans penser à quelque chose de particulier (tout en restant éveillés).

Approche « en réseau » de la récupération après un AVC



Approche « en réseau » de la récupération après un AVC



Connectivity-based approaches in stroke and recovery of function

Christian Grefkes, Gereon R Fink

Lancet Neurol 2014; 13: 206–16

Department of Neurology,
University Hospital Cologne,
Köln, Germany (Prof C Grefkes
PhD, Prof G R Fink PhD);
Neuromodulation and
Neurorehabilitation,
Max Planck Institute for
Neurological Research, Köln,
Germany (C Grefkes); and
Cognitive Neuroscience,

After focal damage, cerebral networks reorganise their structural and functional anatomy to compensate for both the lesion itself and remote effects. Novel developments in the analysis of functional neuroimaging data enable us to assess in vivo the specific contributions of individual brain areas to recovery of function and the effect of treatment on cortical reorganisation. Connectivity analyses can be used to investigate the effect of stroke on cerebral networks, and help us to understand why some patients make a better recovery than others. This systems-level view also provides insights into how neuromodulatory interventions might target pathological network configurations associated with incomplete recovery. In the future, such analyses of connectivity could help to optimise treatment regimens based on the individual network pathology underlying a particular neurological deficit, thereby opening the way for stratification of patients based on the possible response to an intervention.

Approche « en réseau » de la récupération après un AVC

“..recent developments in computational neuroscience enable us to **move beyond the mere localisation of brain activity**. In particular, they allow us **to consider the dynamics within an ensemble or an entire network of areas sustaining a particular cognitive process or behaviour.**”

Approche « en réseau » de la récupération après un AVC

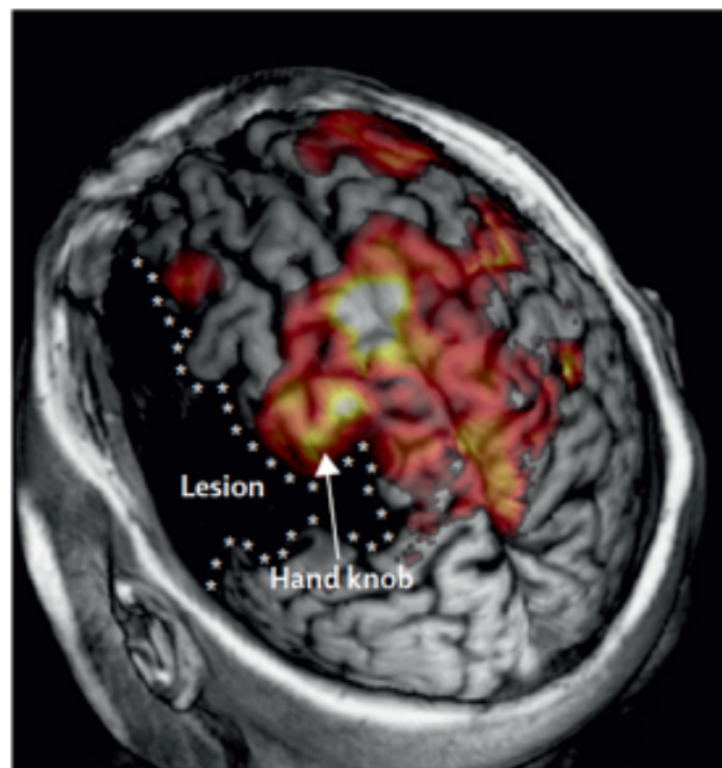
“..the exact functional role that brain regions such as the contralesional M1 have during recovery seems to be complex. Most likely, time since stroke, severity of deficit at baseline, lesion size, location, and other biological factors (eg, age of the patient) all contribute to interindividual differences.”

Functional connectivity analyses based on resting-state fMRI have identified stroke-induced disturbances of the functional network architecture in both animals and patients (figure 2B). For example, **resting-state measurements in rats recovering from induced stroke showed that impaired sensorimotor performance was associated with a loss of interhemispheric connectivity between sensorimotor regions, whereas recovery of function weeks after stroke was paralleled by normalisation of interhemispheric connectivity.**

Similar effects have been reported in fMRI studies of stroke in human beings.

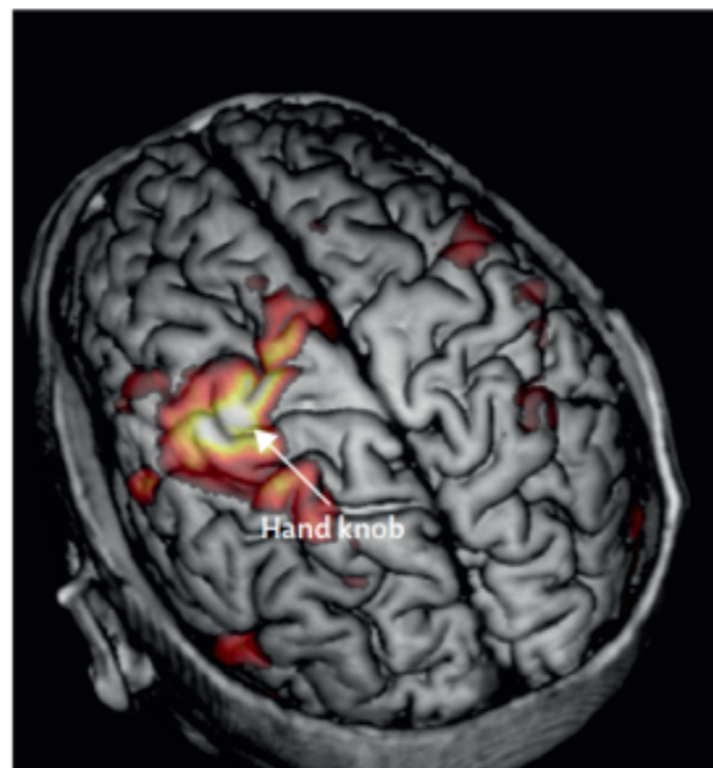
A

Patient who had a stroke



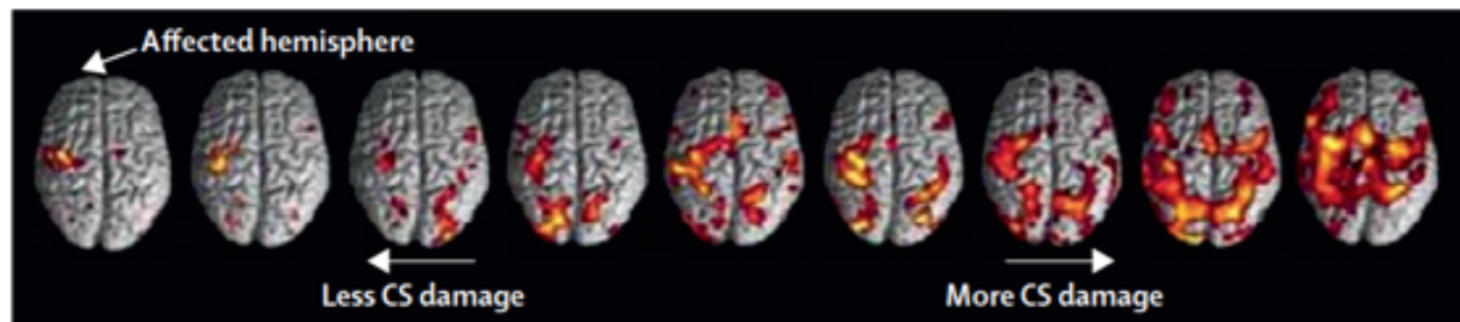
Fist closures with paretic hand

Healthy control

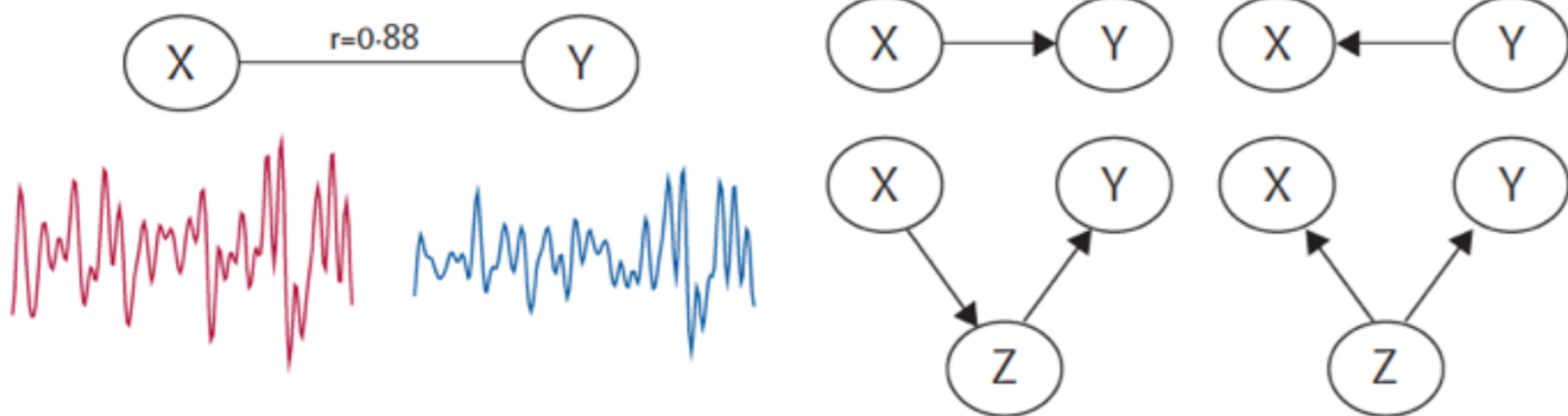


Fist closures with right hand

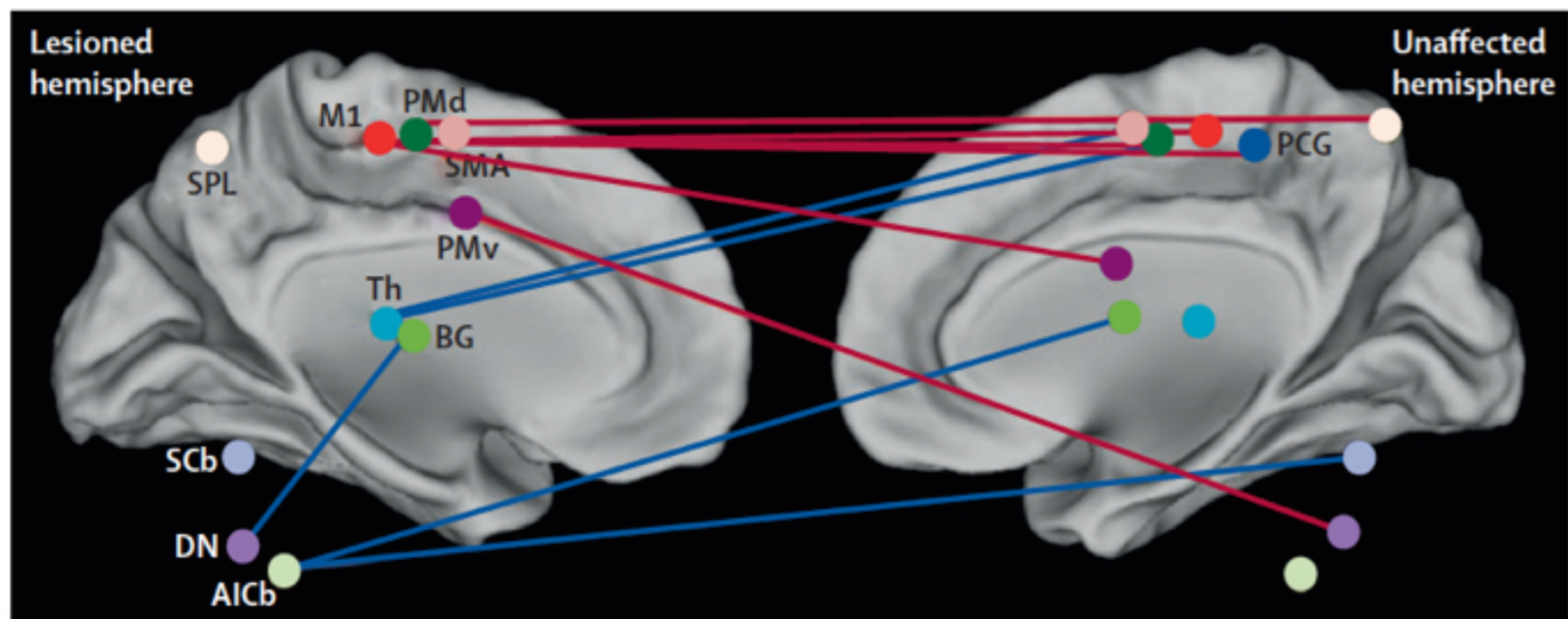
B



A



B



“Consistently, transient downregulation of contralesional M1 excitability has been used to improve motor function of the paretic hand, suggesting an inhibitory role of this area for functional recovery.”

BRAIN

A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches

Christian Grefkes^{1,2} and Gereon R. Fink^{2,3}

The motor system comprises a network of cortical and subcortical areas interacting via excitatory and inhibitory circuits, thereby governing motor behaviour. The balance within the motor network may be critically disturbed after stroke when the lesion either directly affects any of these areas or damages-related white matter tracts. A growing body of evidence suggests that abnormal interactions among cortical regions remote from the ischaemic lesion might also contribute to the motor impairment after stroke. Here, we review recent studies employing models of functional and effective connectivity on neuroimaging data to investigate how stroke influences the interaction between motor areas and how changes in connectivity relate to impaired motor behaviour and functional recovery. Based on such data, we suggest that pathological intra- and inter-hemispheric interactions among key motor regions constitute an important pathophysiological aspect of motor impairment after subcortical stroke. We also demonstrate that therapeutic interventions, such as repetitive transcranial magnetic stimulation, which aims to interfere with abnormal cortical activity, may correct pathological connectivity not only at the stimulation site but also among distant brain regions. In summary, analyses of connectivity further our understanding of the pathophysiology underlying motor symptoms after stroke, and may thus help to design hypothesis-driven treatment strategies to promote recovery of motor function in patients.

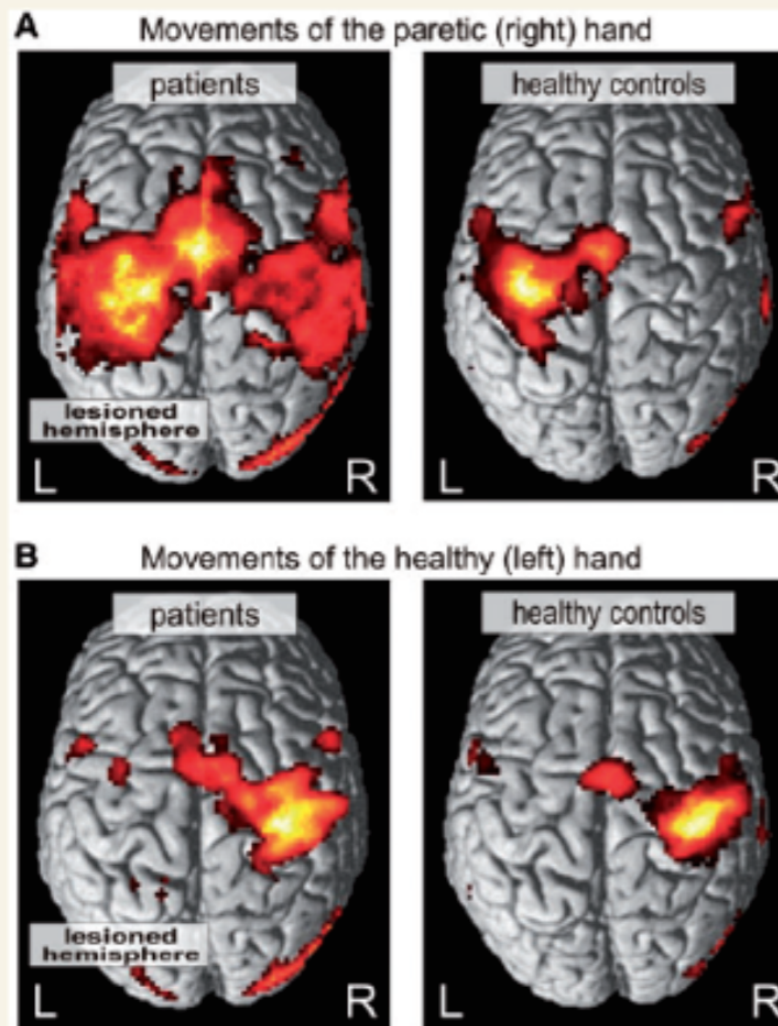
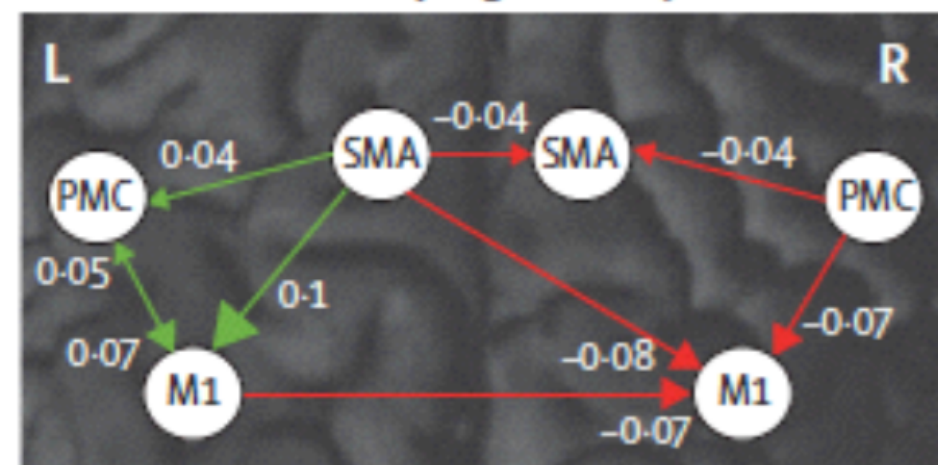
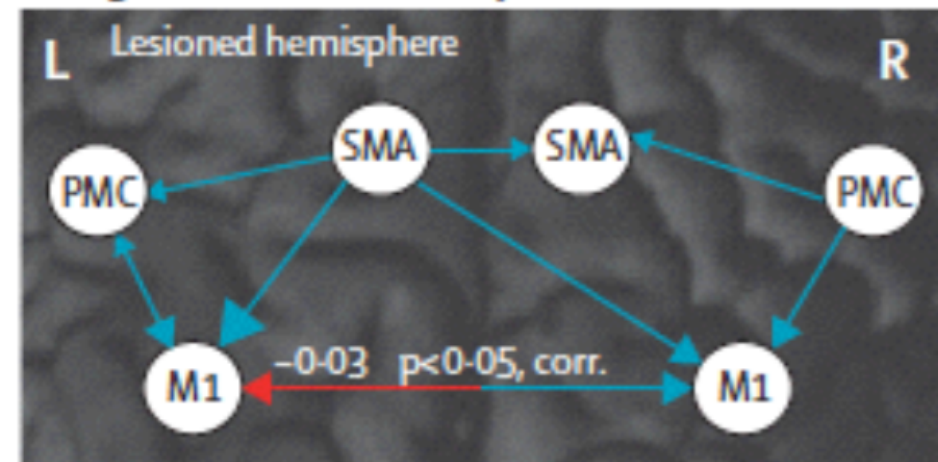


Figure 1 Neural activity during movement of the left or right hand in healthy subjects and in stroke patients with left-sided subcortical lesions ($P < 0.05$, corrected on the cluster level). Activation clusters were surface rendered onto a canonical brain. In stroke patients, movements of the impaired hand were associated with significant activations in ipsilateral (= contralateral) motor areas, which were absent in the healthy controls (A) or when moving the unaffected hand (B) (adapted from Grefkes *et al.*, 2008b, with permission).

A Modulations of coupling in healthy controls

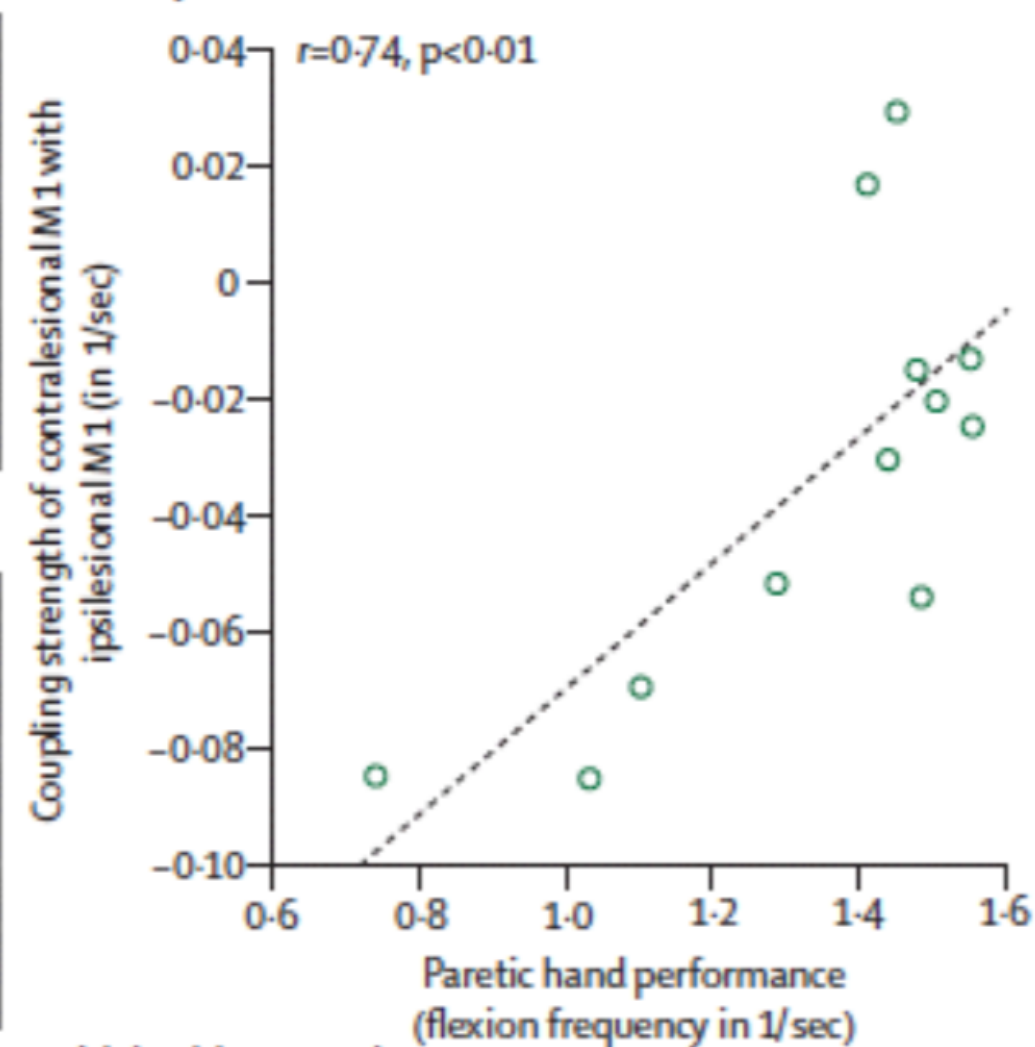


B Significant difference in patients



→ Negative coupling
→ Positive coupling

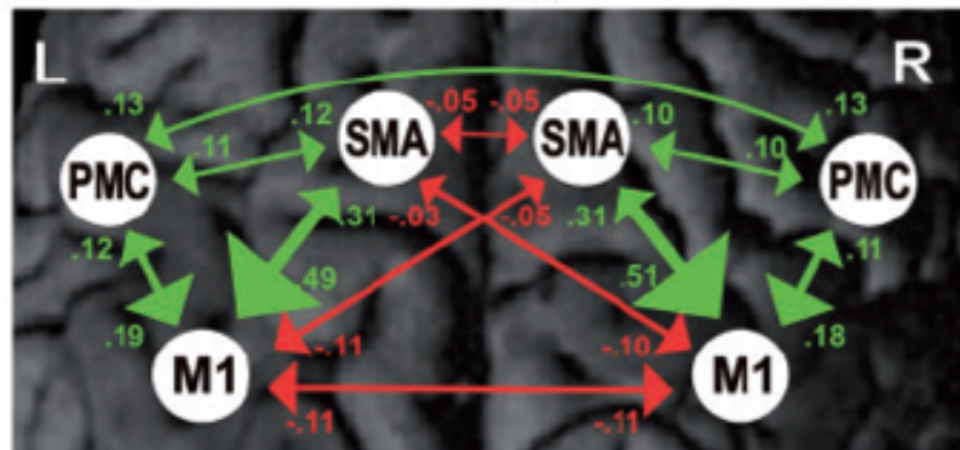
C Hand performance and effect of contralesional M1



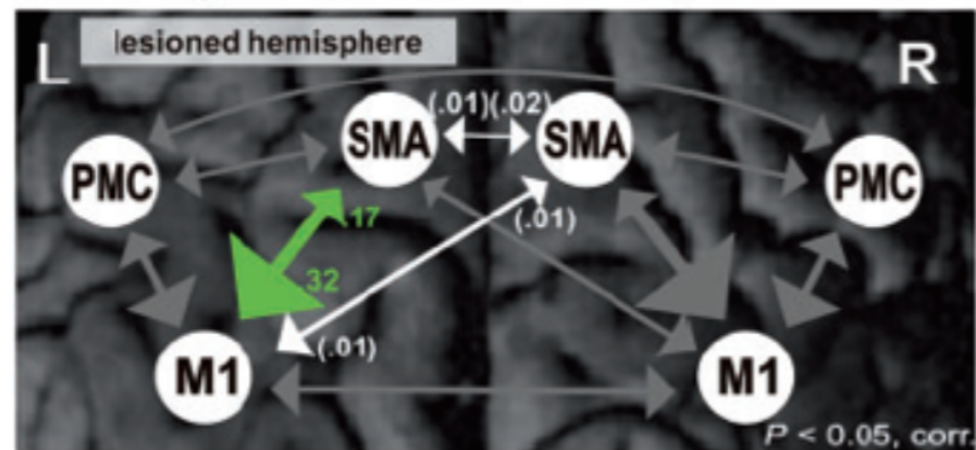
“The brain can be regarded as a system of elements (e.g. neuronal populations in distinct cortical areas) that interact with each other in a temporally and spatially specific fashion. Functional neuroimaging can be used to investigate two fundamental dimensions of how the system ‘brain’ is organized (Friston, 2002).”

“the results of the functional connectivity studies in stroke thus far discussed imply that recovery of motor function depends on reorganization processes within both hemispheres leading to enhanced inter-hemispheric connectivity which might occur, however, at the cost of network efficiency underlying recovered function.”

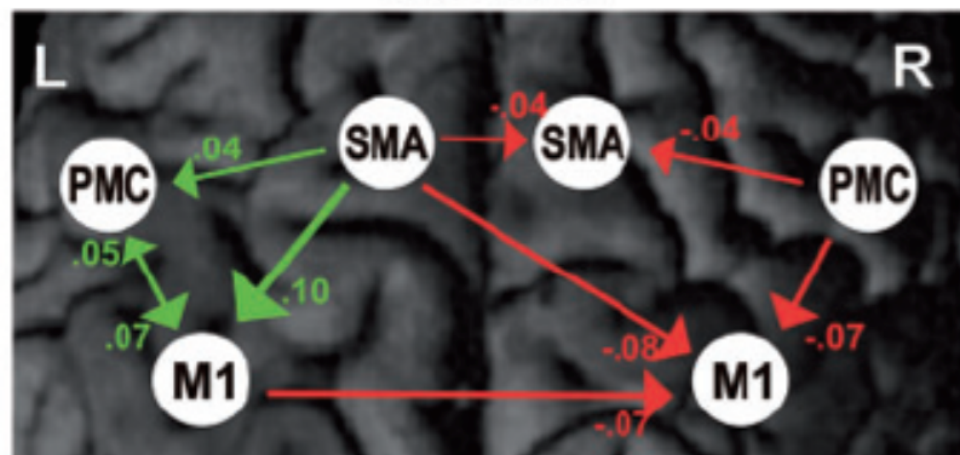
A Intrinsic coupling in controls



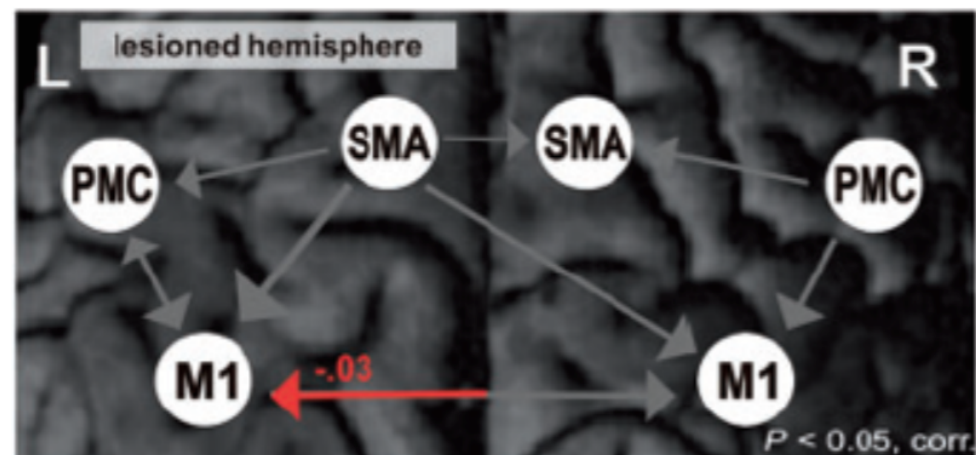
Significant differences in patients



B Hand-specific modulation of coupling in controls



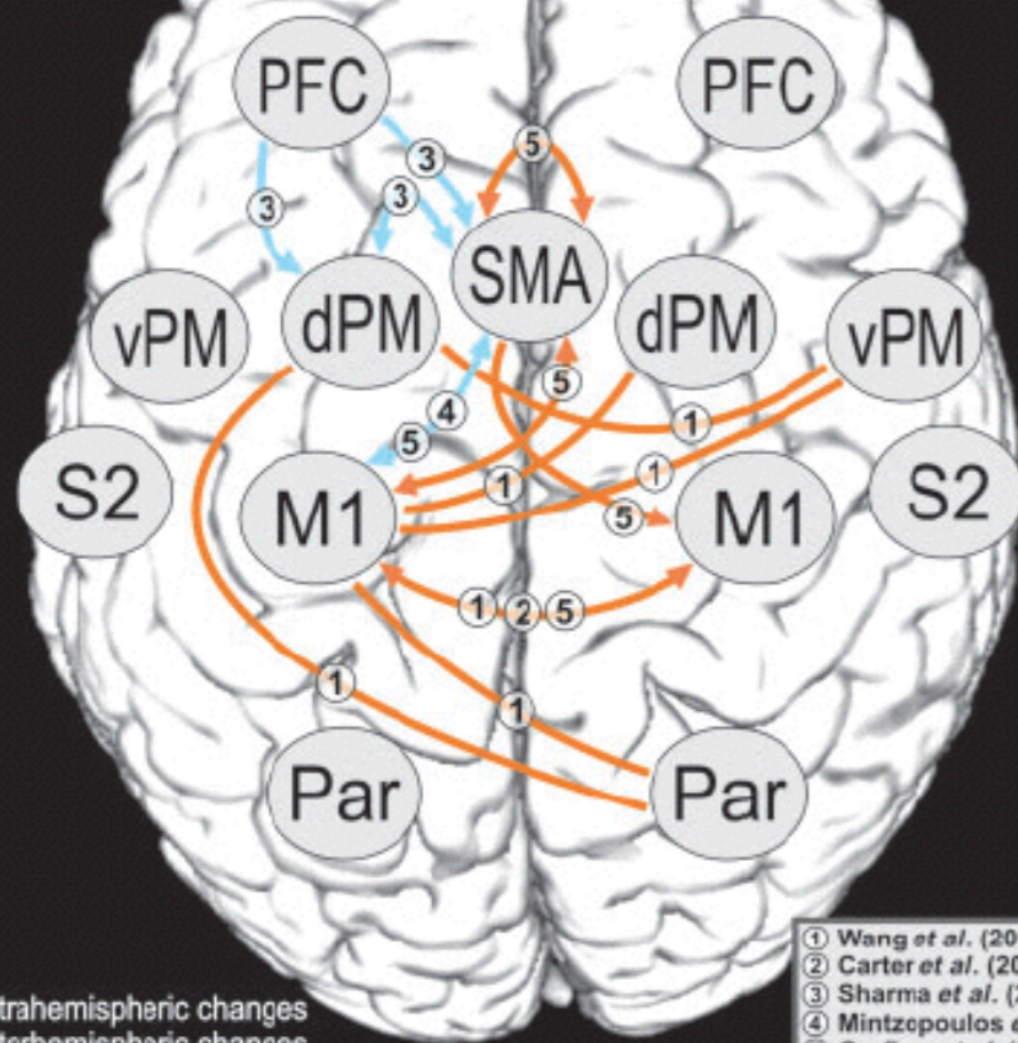
Significant differences in patients



$n = 12$

Movements of the right/paretic hand

lesioned
hemisphere



— intrahemispheric changes
— interhemispheric changes

- ① Wang *et al.* (2010)
- ② Carter *et al.* (2010)
- ③ Sharma *et al.* (2009)
- ④ Mintzopoulos *et al.* (2009)
- ⑤ Grefkes *et al.* (2008b)