Plasticité cérébrale et récupération motrice post-AVC

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Service de MPR CHU Rangueil
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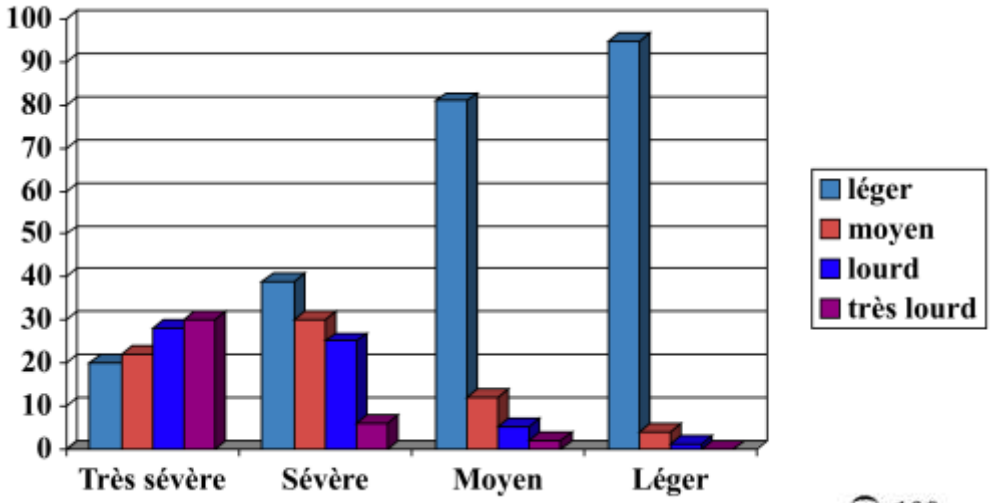
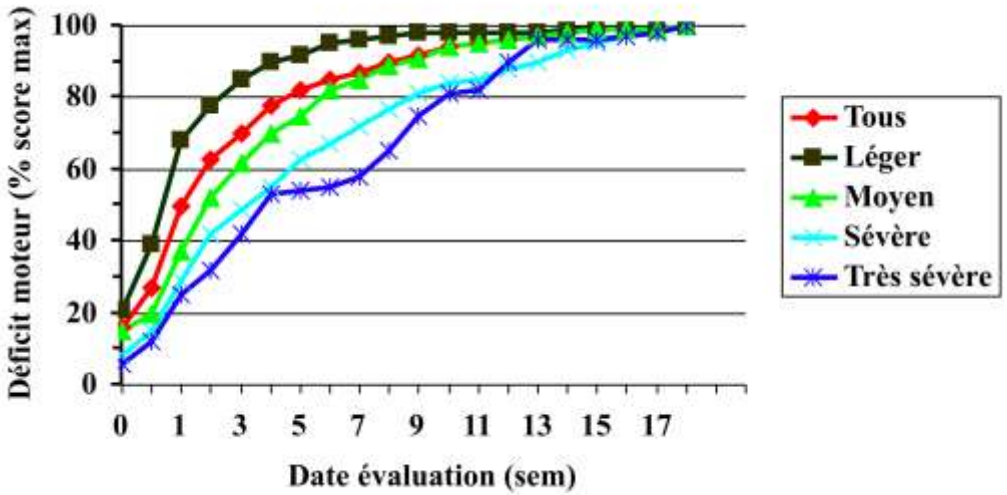
POST-AVC





Jorgensen et al, Arch Phys Med Rehab, 1995

Place de la rééducation après AVC

- **Rééducation efficace: consensus des études épidémiologiques** *(Ottenbacher et al. Stroke 1993, Kwakkel et al, Stroke 2004)*
  - *Performance motrice*
  - *Marche*
  - *Autonomie : ADL*

- **Facteurs d'efficacité :**Précocité et intensité (±) : unité spécialisé

- **Équipe spécialisée multidisciplinaire** :
  - Kinésithérapie
  - Ergothérapie
  - Infirmières, aides soignantes
  - Orthophonistes
  - Assistantes sociales
  - Psychologue

Quelles techniques ?

- **Plusieurs techniques, des concepts très différents:**

  Bobath

  Brunnstrom

  Perfetti…

  ⇨ ***Mais pas de différence entre les techniques*** ***(11 essais comparatifs, Cochrane database review 2004)***

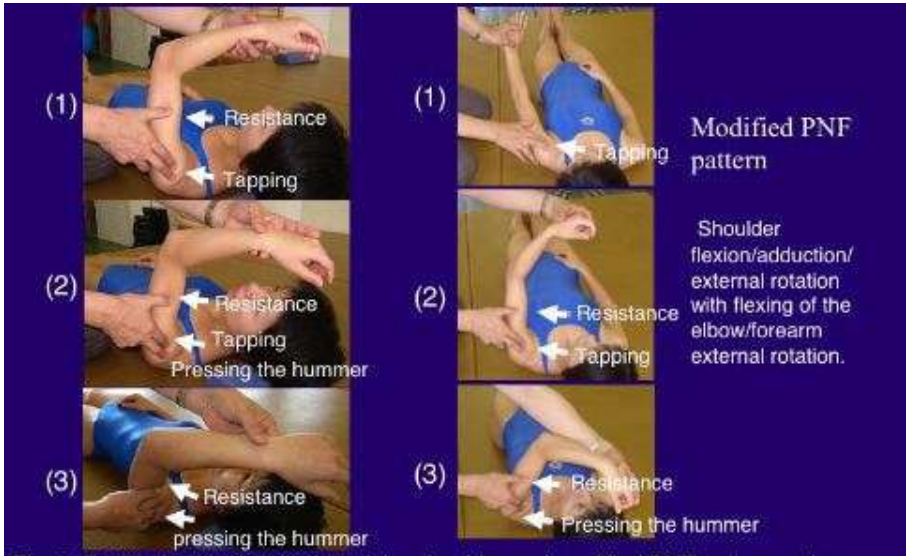
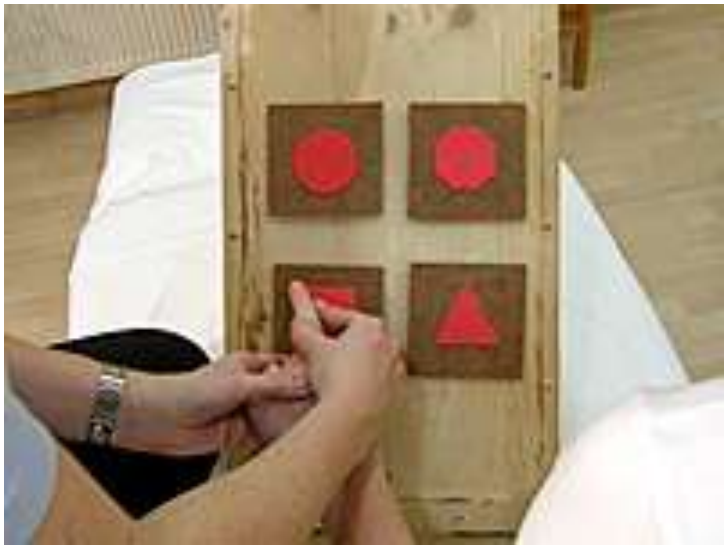


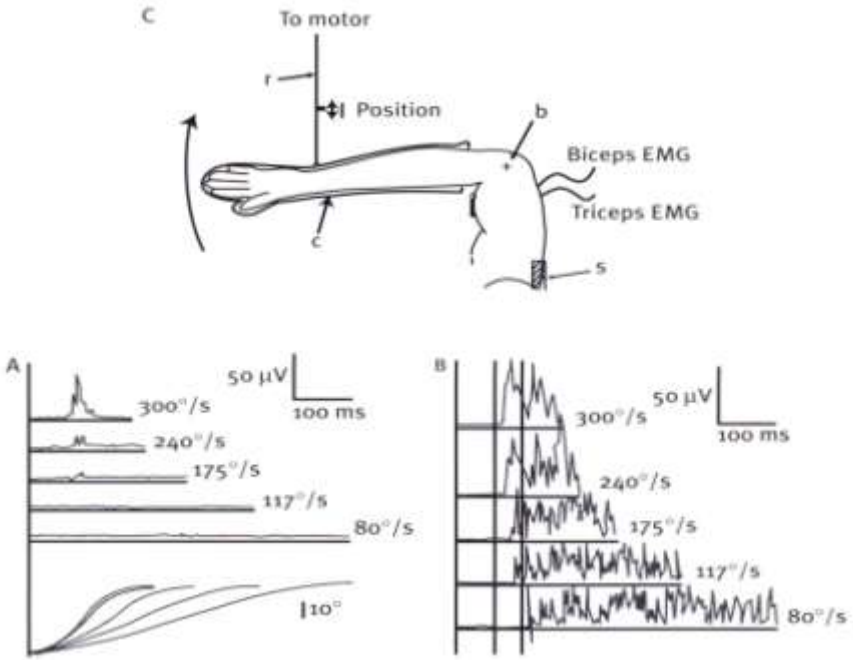
Fig. 7 Facilitation to elicit flexion of the shoulder and modified PNF pattern, using tapping and rubbing on target muscle.



Retentissement fonctionnel de la spasticité

- Retentissement fonctionnel modeste
  - mouvement > 40° /s

Thilman et al, Brain 1991



Le renforcement musculaire

Pour les deux techniques :

- Gain de force
- Bénéfices fonctionnels (marche, AVQ)
- Pas d'aggravation de la spasticité

Groupe Témoin (n=15)

Groupe RDP (n= 20)

La question….

- N’est pas : est-ce que ça marche?
- Mais….
- Comment ça marche?

MÉCANISMES D’ACTION

PLASTICITÉ CÉRÉBRALE

- Définition:
  - ***ensemble des mécanismes cérébraux qui permettent au cerveau d'adapter son fonctionnement afin de répondre à une situation nouvelle.***

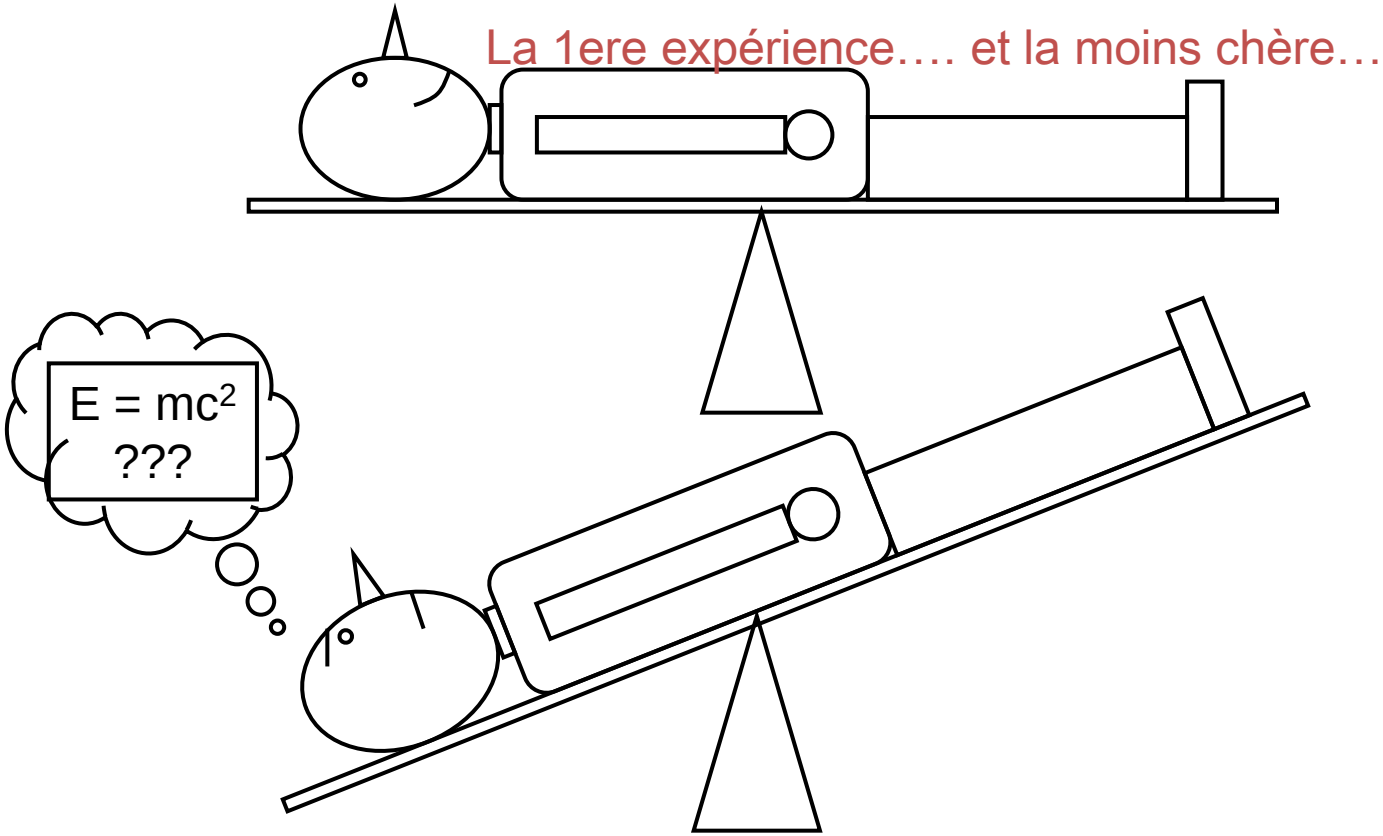
- Mécanismes
  - modification de l'efficacité des synapses déjà existantes : potentialisation à long terme, dépression à long terme,
  - changements globaux de l'excitabilité post-synaptique,
  - changements morphologiques : augmentation du nombre de dendrites, des collatérales axoniques.

Le débit sanguin cérébral : reflet de l'activité cérébrale…

" … an automatic mechanism is well fitted to provide for a local variation of the blood supply in accordance with local variations of the functional activity." Roy and Sherrington (1890)

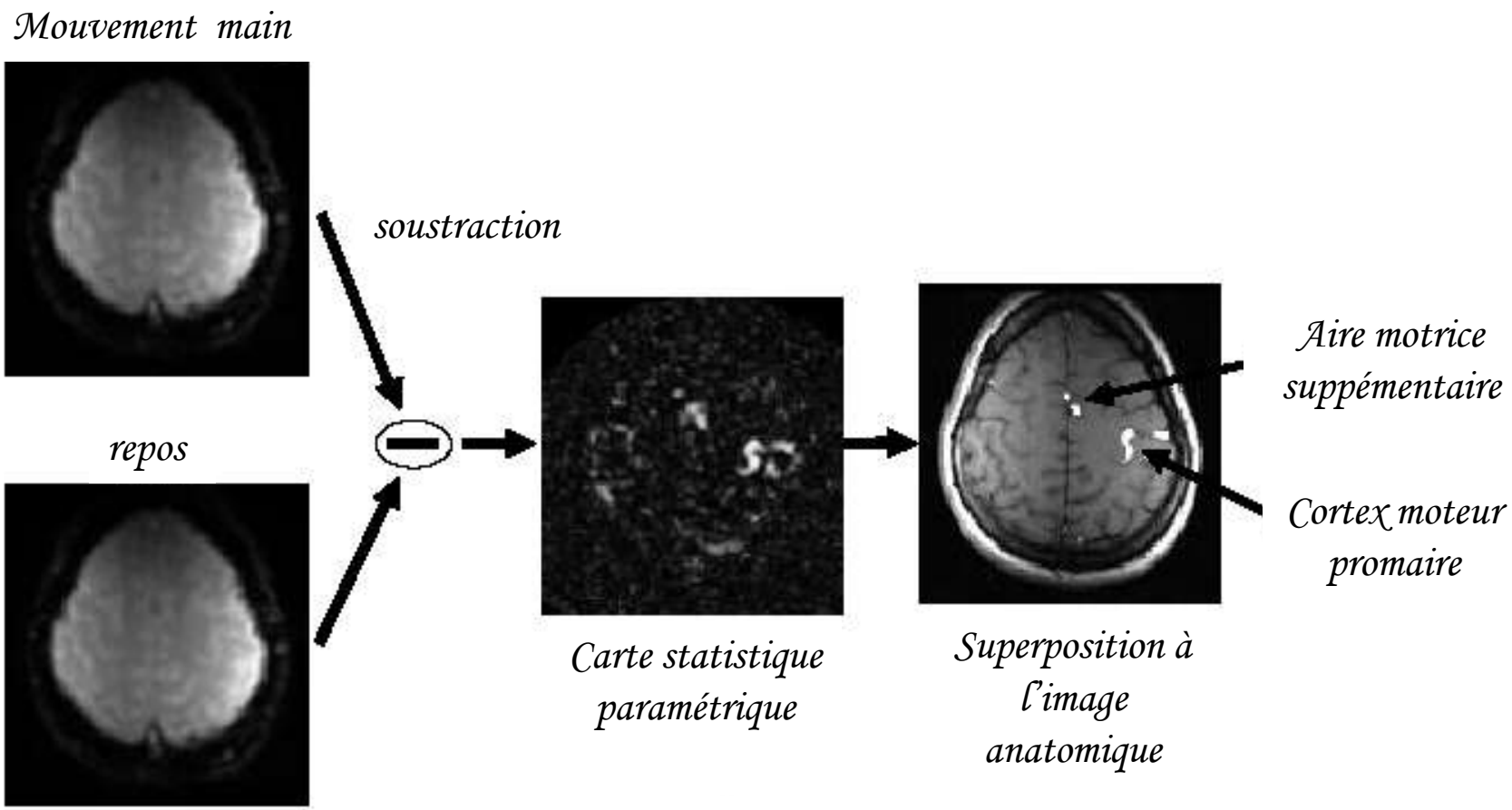
Imagerie fonctionnelle: la pré-histoire

Angelo Mosso
Italian physiologist
(1846-1910)

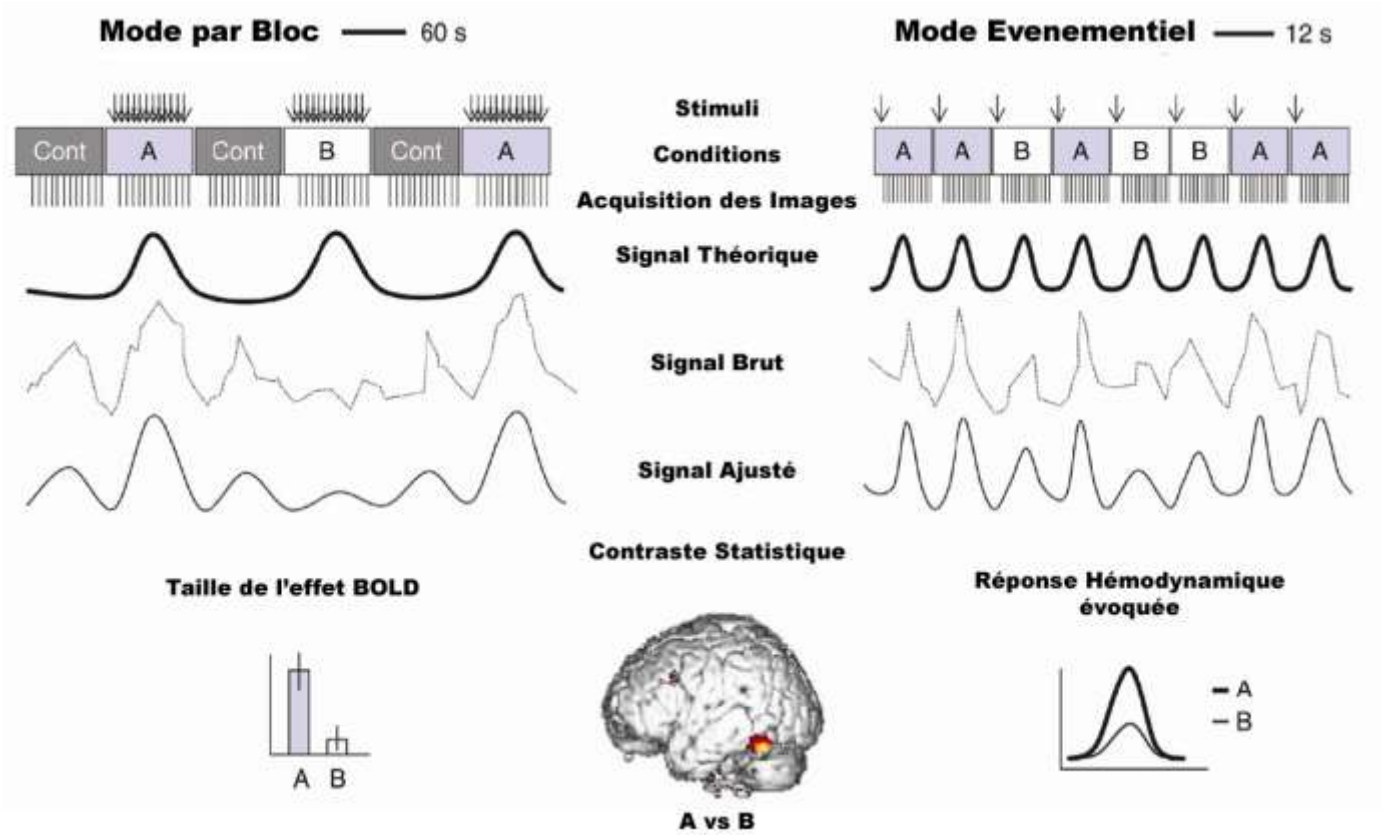


IRMf en pratique…

- L'effet de la déoxy-Hb : 2 à 5 % du signal, non visible directement sur une seule image.



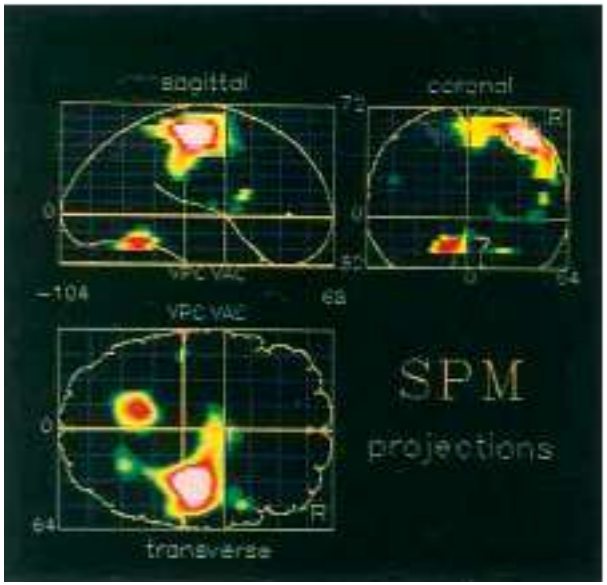
IRMf :
mode par bloc et événementiel



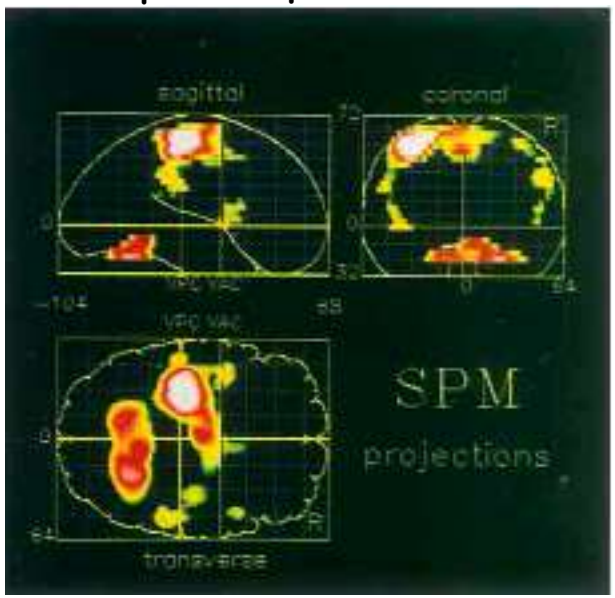
Etude princeps en TEP montrant une réorganisation intracérébrale post-AVC

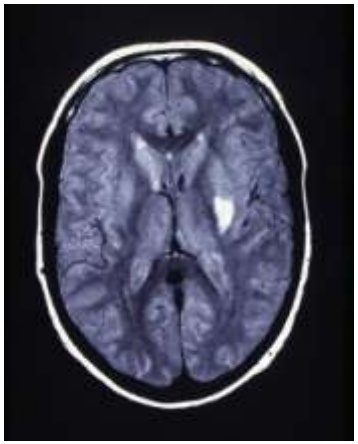
Recrutement de l'hémisphère controlatéral

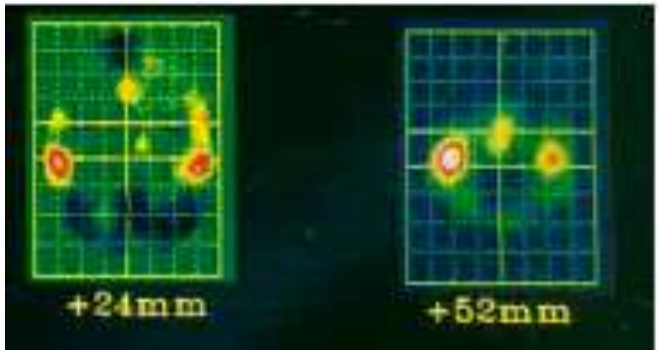
Main saine



Main parétique





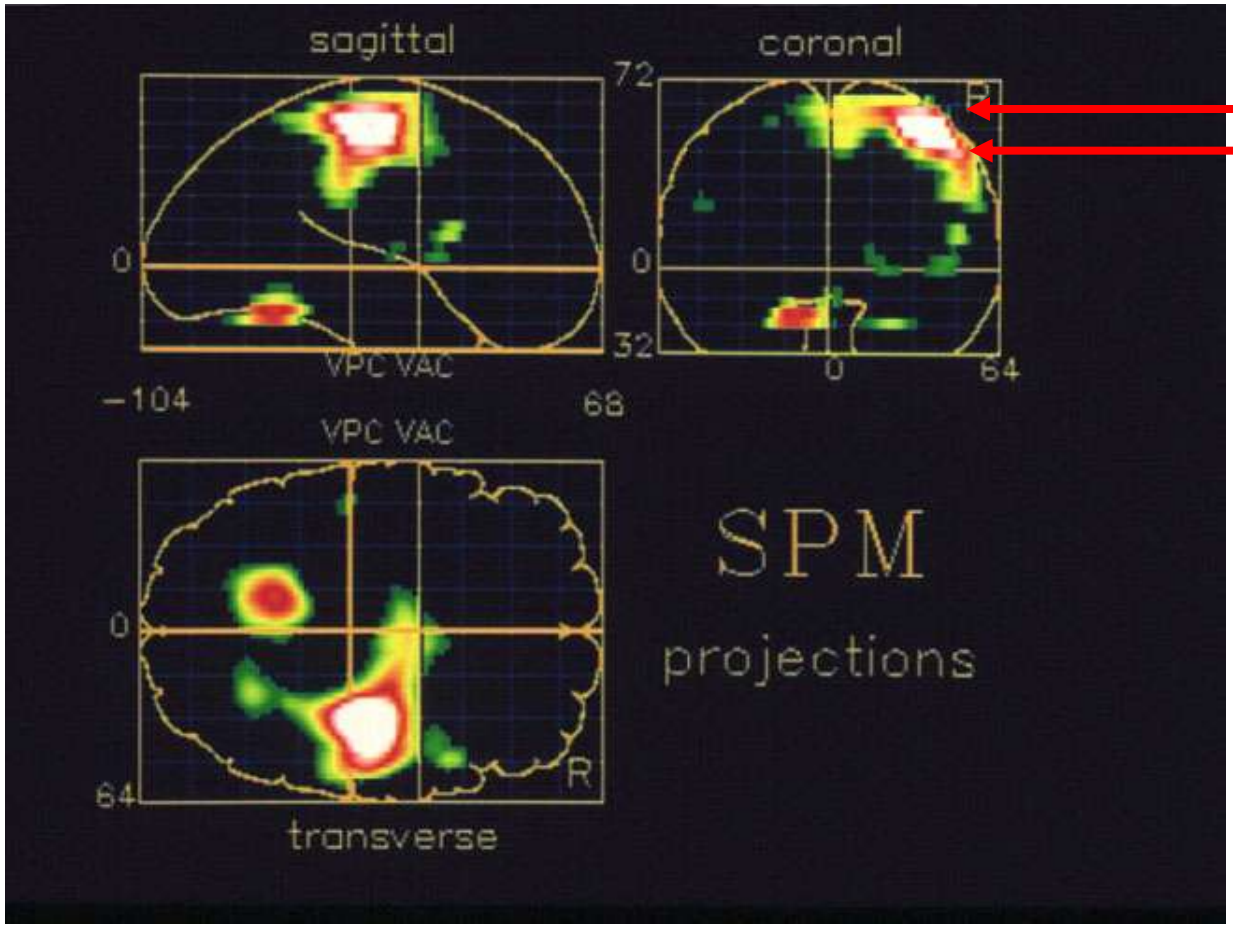


Covariance

Chollet et al., Ann Neurol 91

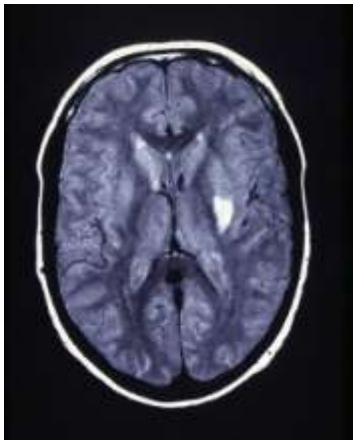
Etude princeps en TEP montrant une réorganisation intracérébrale post-AVC

Hyperactivation / normaux, recrutement d'une aire adjacente (aire de la face)



main

face



Mouvement des doigts

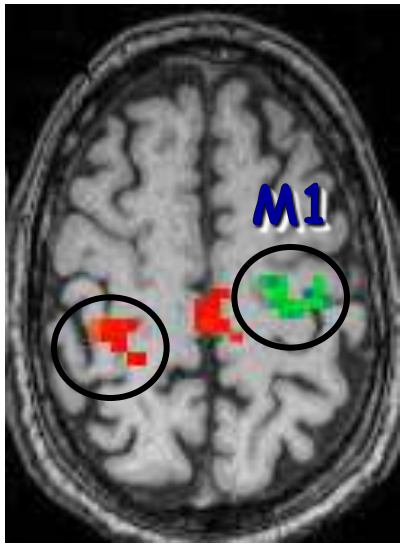
Patients à environ 4 mois post-AVC

Weiller, Chollet et al., Ann Neurol 92

ETUDE LONGITUDINALE

15 jours

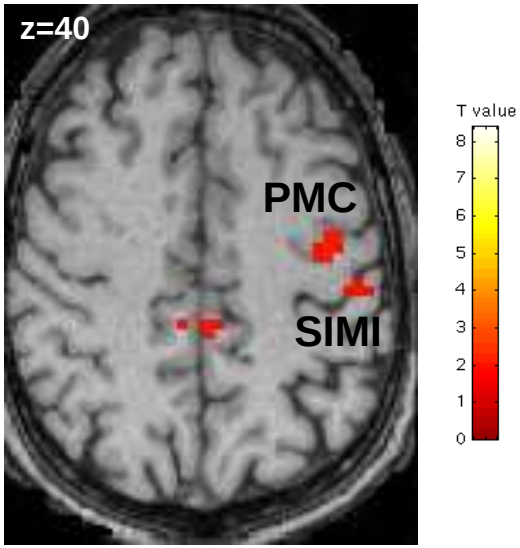
côté lésé



IpsiL: hypoactivation
ControL:hyperactivation

4 mois

côté lésé

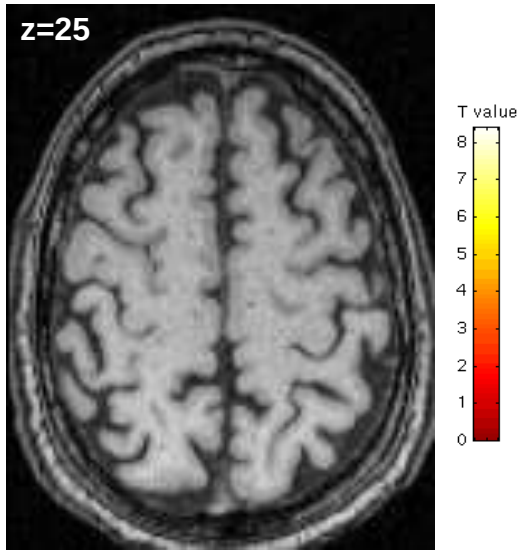


Basculement vers l'hémisphère ipsilésionel

Loubinoux et al., NeuroImage 2003
Tombari et al., Neuroimage 2004

12 mois

côté lésé



Normalisation en localisation et en intensité comparé aux témoins

Hémiparésie et substrats de la récupération

Apport de la NeuroImagerie

Récupération

Léger

Modéré

Sévère

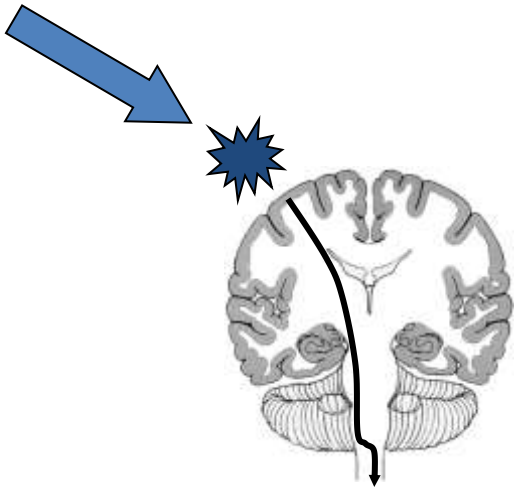
Déficit

1. Réseau « initial » réorganisé
   - <u>S1M1 ipsilésionnel</u>
     Werhahn 2003; Rouiller 2004
   - Cortex prémoteur dorsal ipsilésionnel
     Fridman 2004; Rouiller 1999
   - Cortex prémoteur dorsal controlésionnel
     Johansen-Berg PNAS 2002
   - Cortex pariétal bilatéral, PMC ventral
     Schaechter 2002
     Nelles 2001
   - Cervelet
     Small 2001

2. Recrutement réseau « compensateur »
   - S1M1 ipsilésionnel (**face)**
     Chollet 1991; Zemke 2003
   - S1M1 controlésionnel
     Carey 2002
   - Aires visuelles *(Seitz 1999; Ward 2004)*
   - Cortex préfrontal *(Rossini 2004)*

TOUJOURS UTILE ?

TMS: Transcranial Magnetic Stimulation
Principe



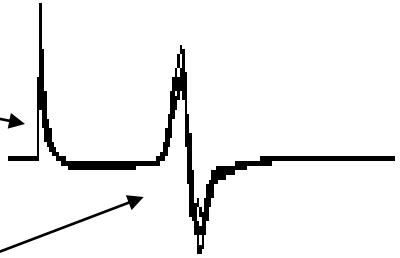
Bobine de stimulation

stimulateur

Recueil du PEM à l'aide d'électrode
(EMG: électromyographie)

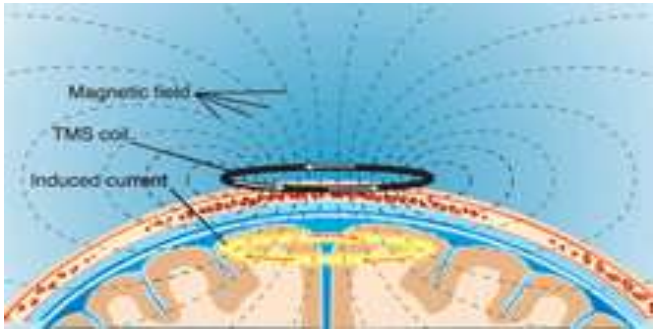
Activation
Voie cortico-spinale

Artefact de stimulation

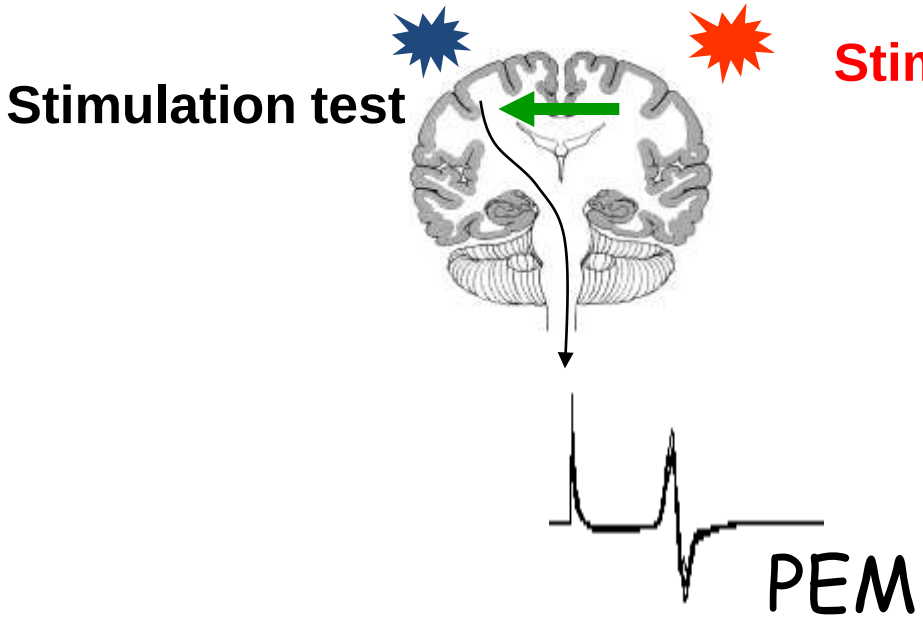


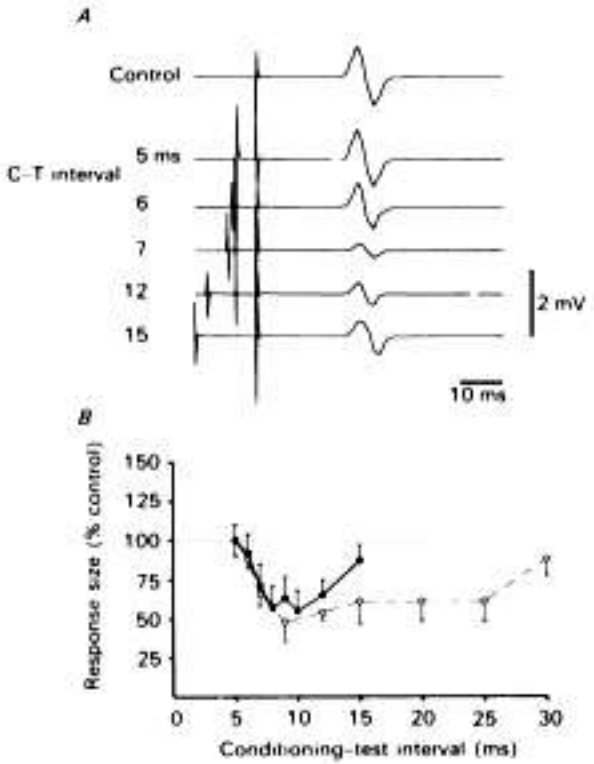
PEM: potentiel évoqué moteur reflète l'activité musculaire induite par la stimulation corticale

TMS active sélectivement les neurones à orientation horizontale



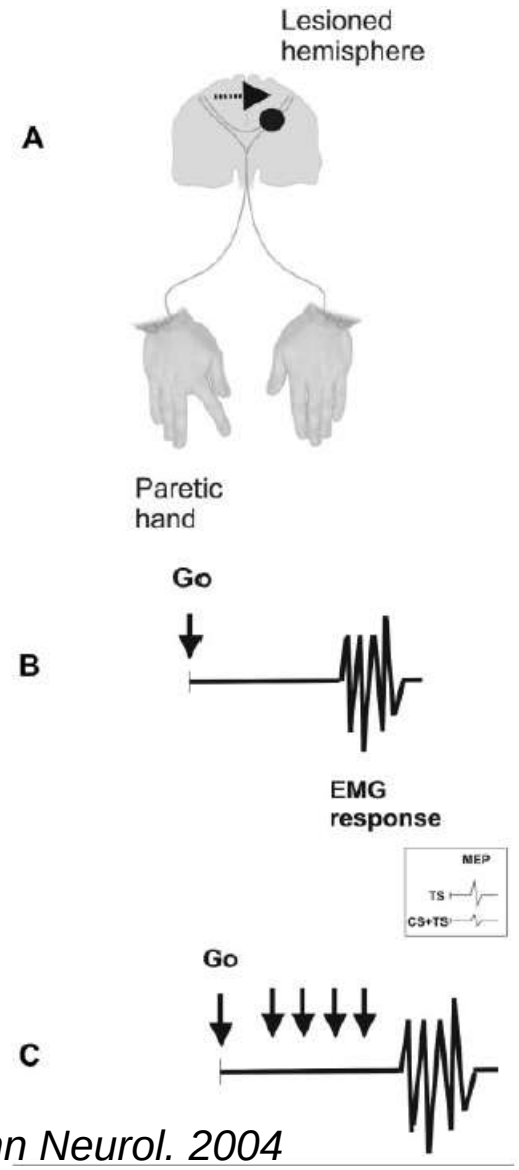
TMS permet de stimuler à travers (« trans ») le crâne
et « mime » les stimulations corticales (ICMS) chez l'animal

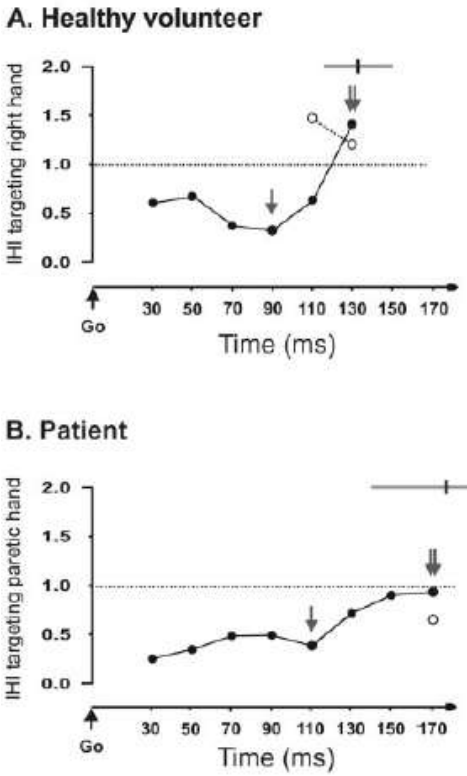


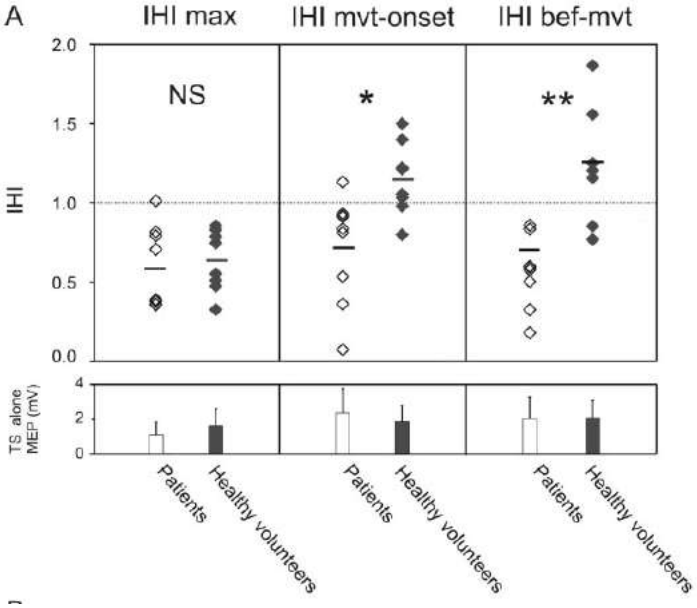


INHIBITION INTERHEMISPHERIQUE

(Ferbert A et al, J Physiol,1992)



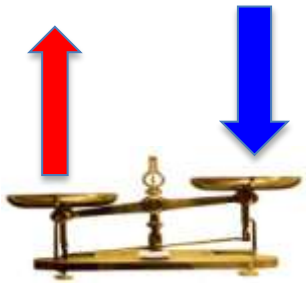




Murase et al, Ann Neurol. 2004

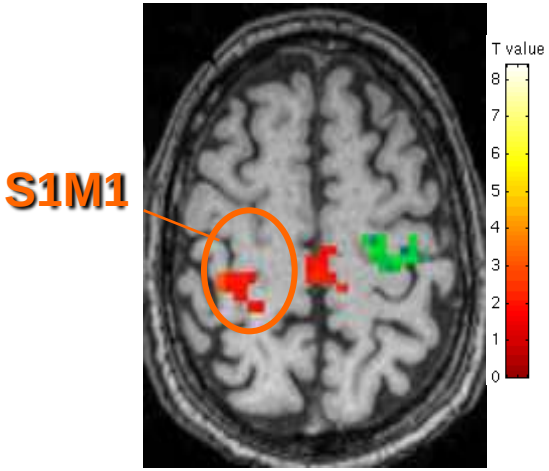
L'Inhibition du cortex sain sur le cortex lésé au moment de la réalisation d'une action motrice est plus importante chez le patient que chez les sujets sains

Patients hémiplégiques



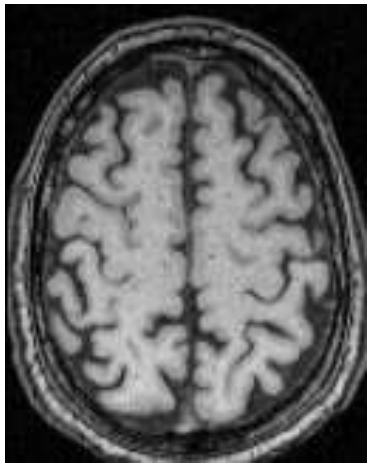
15 jours

côté lésé

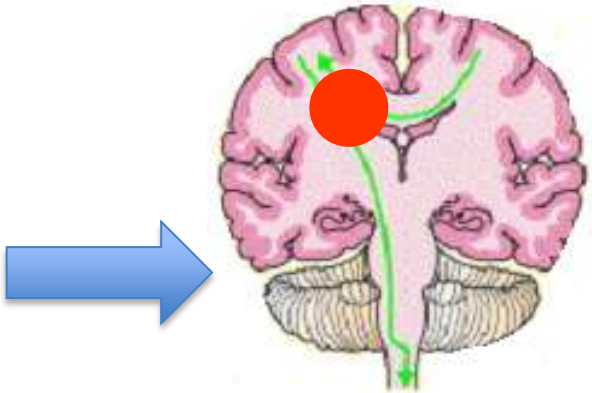


S1M1: cortex sensorimoteur primaire
Ipsilésionel: hypoactivation
Controlésionel: hyperactivation

12 mois



Normalisation en localisation et en intensité comparé aux témoins



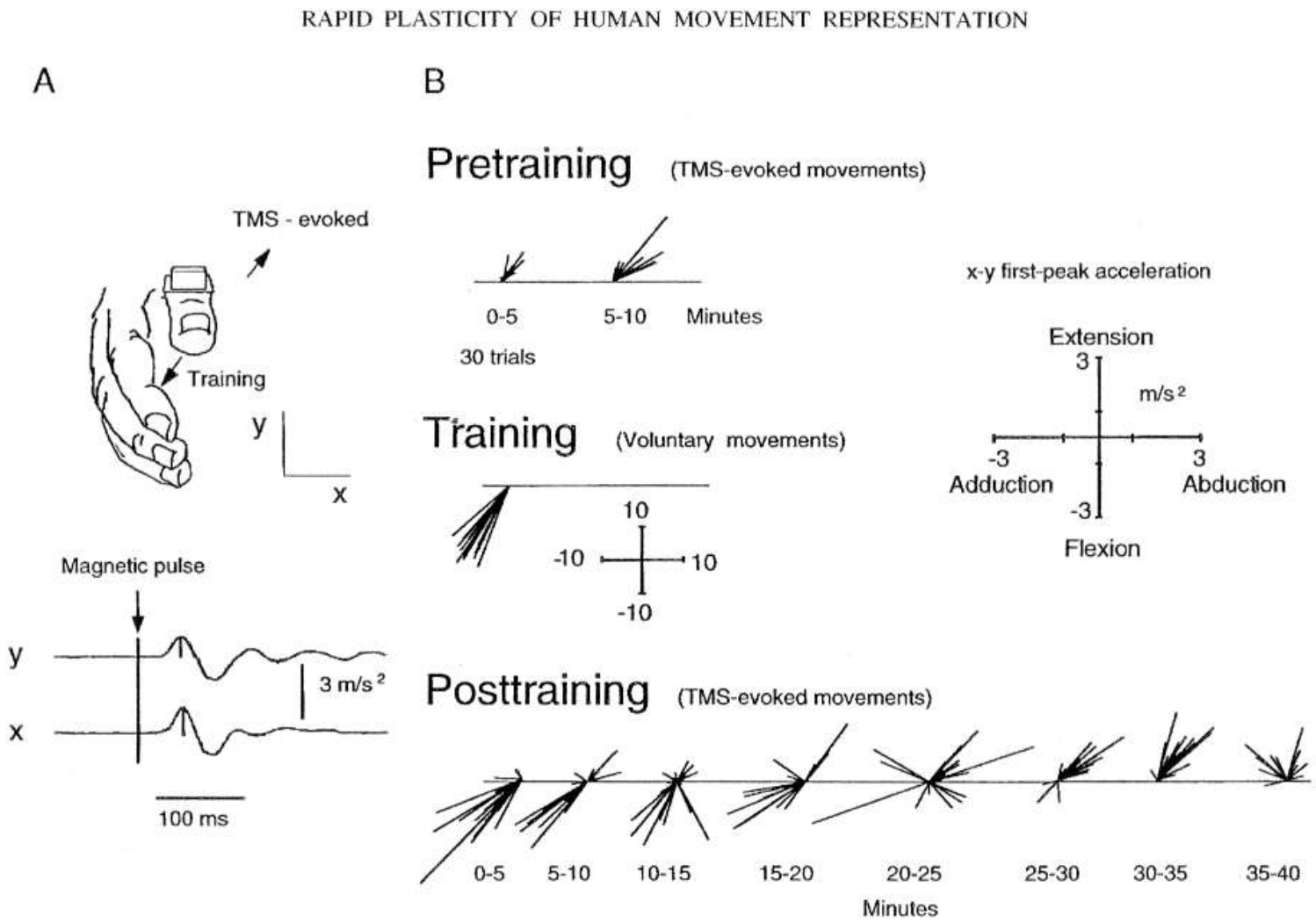
***Objectif :* développer des techniques de neuromodualtion pour rétablir balance interhémisphérique**

8 patients
Comparés à un groupe témoin

Loubinoux et al., NeuroImage 2003
Tombari et al., Neuroimage 2004

PEUT-ON GUIDER LA PLASTICITÉ CÉRÉBRALE?

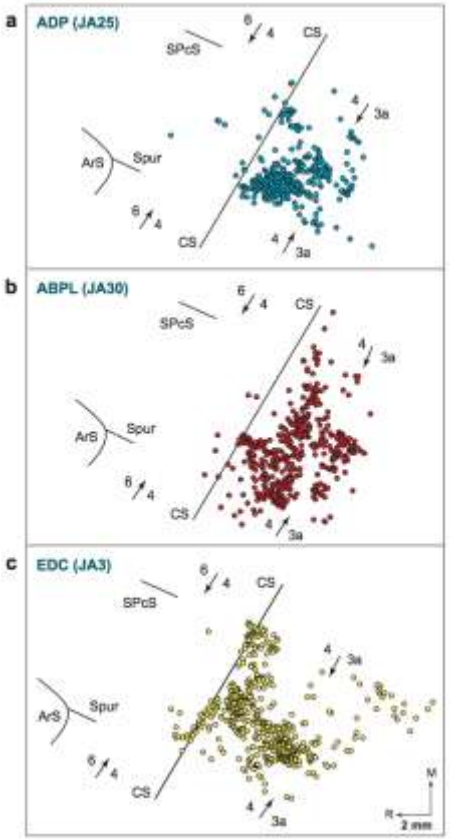
Par la répétitions de tâches

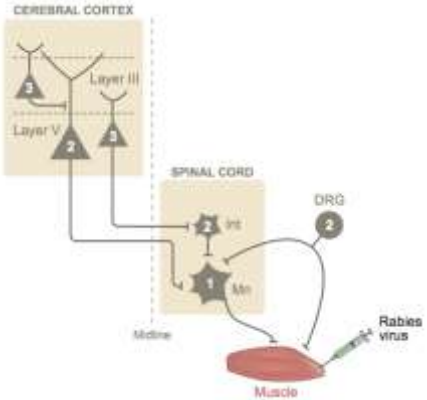


« Rapid plasticity of human cortical movement representation induced by practice. »
Classen et al. (1998) J. Neurophysiol.

Faisceau cortico-spinal

- Un faisceau distribué, largement divergent
- Rôle majeur des collatérales inhibitrices





Muscle representation in the macaque motor cortex: An anatomical perspective

Jean-Alban Rathelot*† and Peter L. Strick*†‡§¶

PNAS | May 23, 2006 | vol. 103 | no. 21 | 8257–8262

Reorganization and plastic changes of the human brain associated with skill learning and expertise

Yongmin Chang*

Table 1 | Imaging evidences for structural and functional plasticity in sports and music.

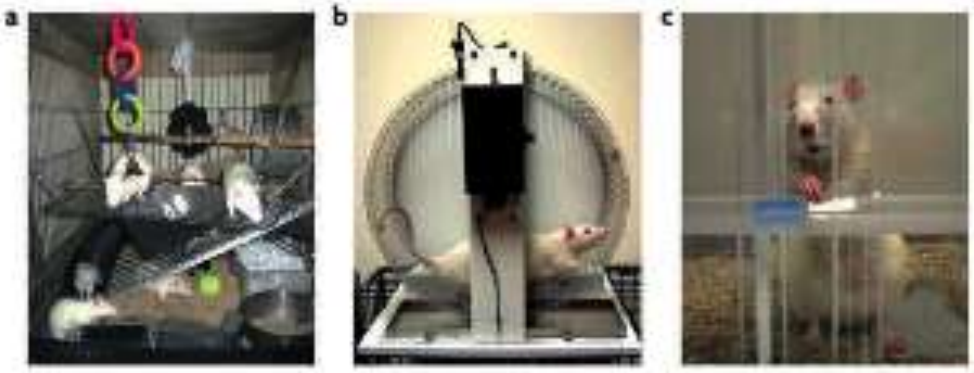
Study	Skill	Design	Method	Main findings
STRUCTURAL PLASTICITY				
Jacini et al., 2009	Sports	Cross-sectional	VBM	Judo players showed larger GM volume in frontal and prefrontal cortex
Jäncke et al., 2009	Sports	Cross-sectional	VBM, DTI	Golfers showed Larger GM volumes in premotor and parietal cortices; smaller FA along the internal and external capsule and the parietal operculum
Di Paola et al., 2013	Sports	Cross-sectional	VBM	Mountain climbers showed significantly larger vermian lobule volumes
Draganski et al., 2004	Sports	Longitudinal	VBM	Three months' practice-induced GM expansion in mid-temporal area and posterior intraparietal sulcus, followed by a decreased to baseline levels after 3 months with no practice
Bezzola et al., 2011	Sports	Longitudinal	VBM	Forty hours of golf training showed an association with gray matter increases in a task-relevant cortical network
Amunts et al., 1997	Music	Cross-sectional	MRI	Hand motor area was larger in professional musicians than in non-musicians
Gaser and Schlaug, 2003	Music	Cross-sectional	VBM	GM volume differences in sensorimotor cortex, premotor cortex, and cerebellum
Han et al., 2009	Music	Cross-sectional	VBM, DTI	Musician showed higher GM density in sensorimotor cortex and cerebellum; higher FA in internal capsule
Hyde et al., 2009	Music	Longitudinal	DBM	Fifteen months of musical training in early childhood showed structural change in brain areas which are known to be involved in control of playing a musical instrument
FUNCTIONAL PLASTICITY				
Pearce et al., 2000	Sports	Cross-sectional	TMS	Cortical representation of the hand used for playing is larger in professional racquet ball players
Milton et al., 2007	Sports	Cross-sectional	fMRI	Elite athletes showed neural efficiency in the cortical processes during the specific challenge in which they are highly practiced
Sekiguchi et al., 2011	Sports	Cross-sectional	fMRI	Elite rugby players differ in visuospatial abilities directly tied to their domain of expertise
Doyon et al., 2002	Sports	Longitudinal	fMRI	Shift of activation from the cerebellar cortex to the dentate nucleus during early learning, and from a cerebellar-cortical to a striatal–cortical network with extended practice
Cross et al., 2009	Sports	Longitudinal	fMRI	Emergence of action resonance processes in the human brain based on 5 day observational learning of dance sequence without physical practice
Lotze et al., 2003	Music	Cross-sectional	EMG	Professional violinists showed focused cerebral activations in the motor network as compared to amateur violinists during the imagination of violin-playing movements
Oechslin et al., 2013	Music	Cross-sectional	fMRI	Levels of musical expertise stepwise modulate higher order brain functioning
Bangert and Altenmüller, 2003	Music	Longitudinal	EEG	Auditory-sensorimotor co-activity occurred within only 20 min and the effect was enhanced after 5-week training, contributing elements of both perception and action to the mental representation of the instrument
Herdener et al., 2010	Music	Longitudinal	fMRI	Following the aural skills training, hippocampal responses to temporal novelty in sounds were increased

MRI, magnetic resonance imaging; VBM, voxel-based morphometry; GM, gray matter; DTI, diffusion tensor imaging; FA, fractional anisotropy; DBM, Deformation based morphometry; TMS, transcranial magnetic stimulation; fMRI, functional MRI; EMG, Electromyography; EEG, electroencephalography

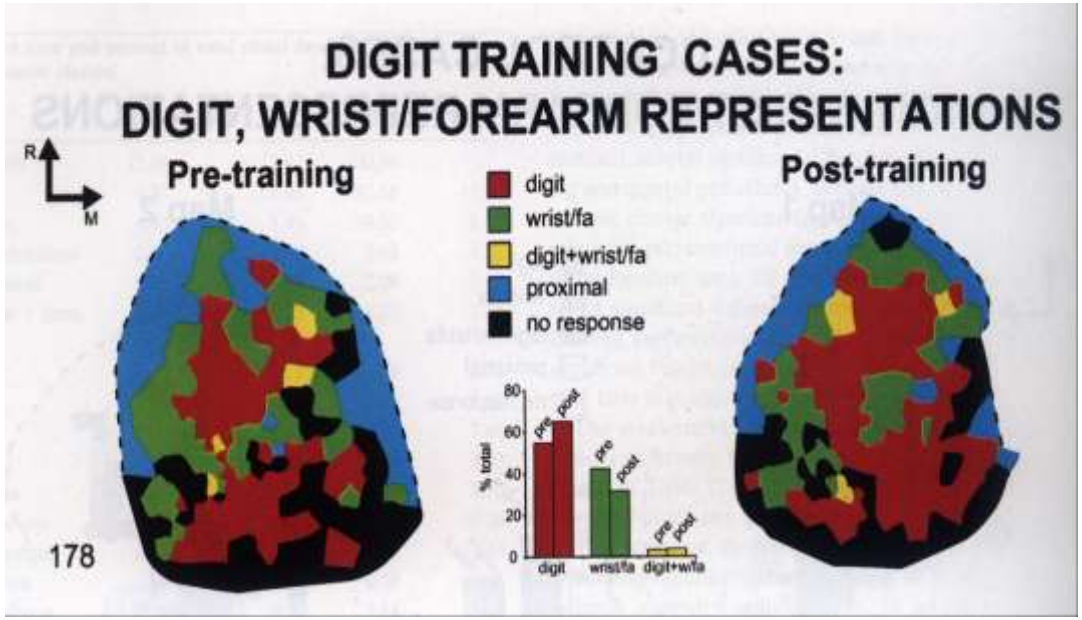
Milieux enrichis

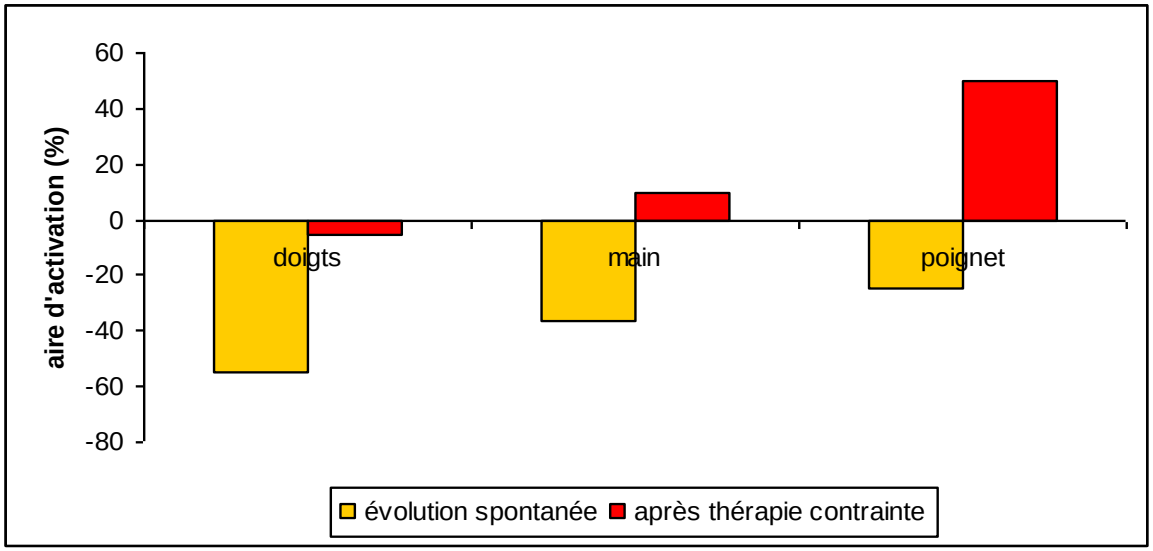
- Meilleure récupération motrice

- Nombre de dendrites et de synapses plus importants



Biernaskie J. & Corbett D. J Neurosci 2001





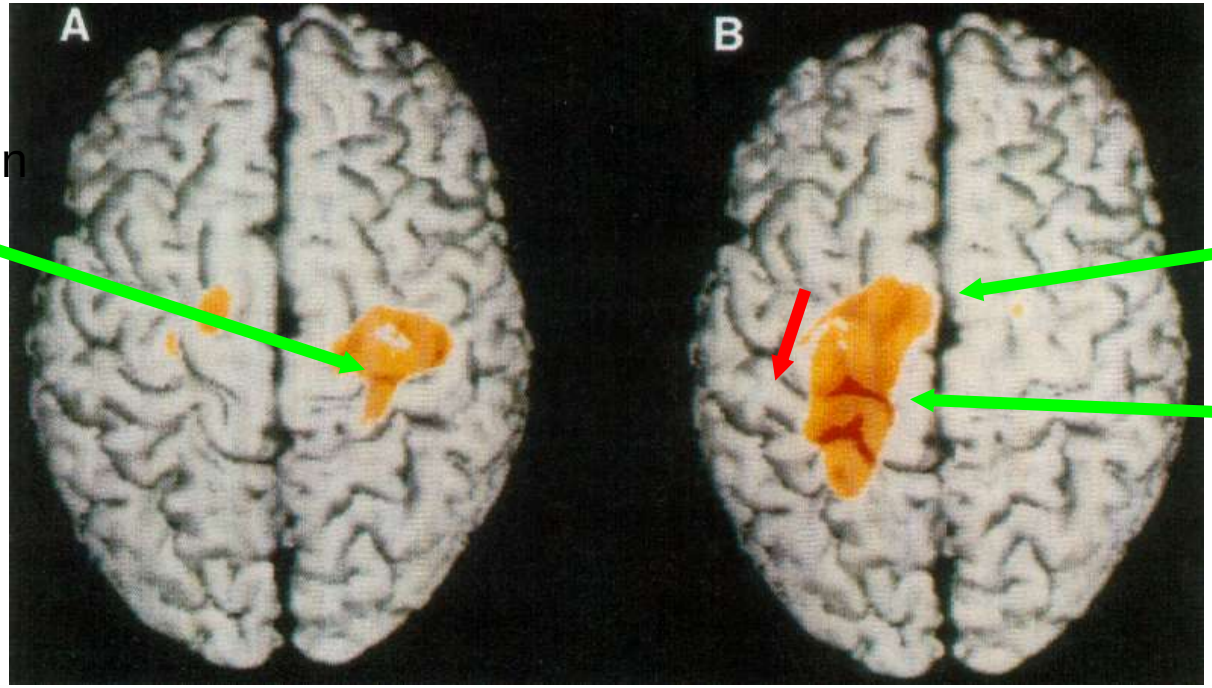
NUDO et al
(J Neurosci 1996 - Science 1996)

Plasticité dépendante de l'utilisation : mécanisme de compétition

Exemple d'envahissement du territoire cortical déafférenté en TEP (dans le cas d'une main amputée)

Mouvements du membre intact Mouvements du membre amputé

Aire de la main intacte



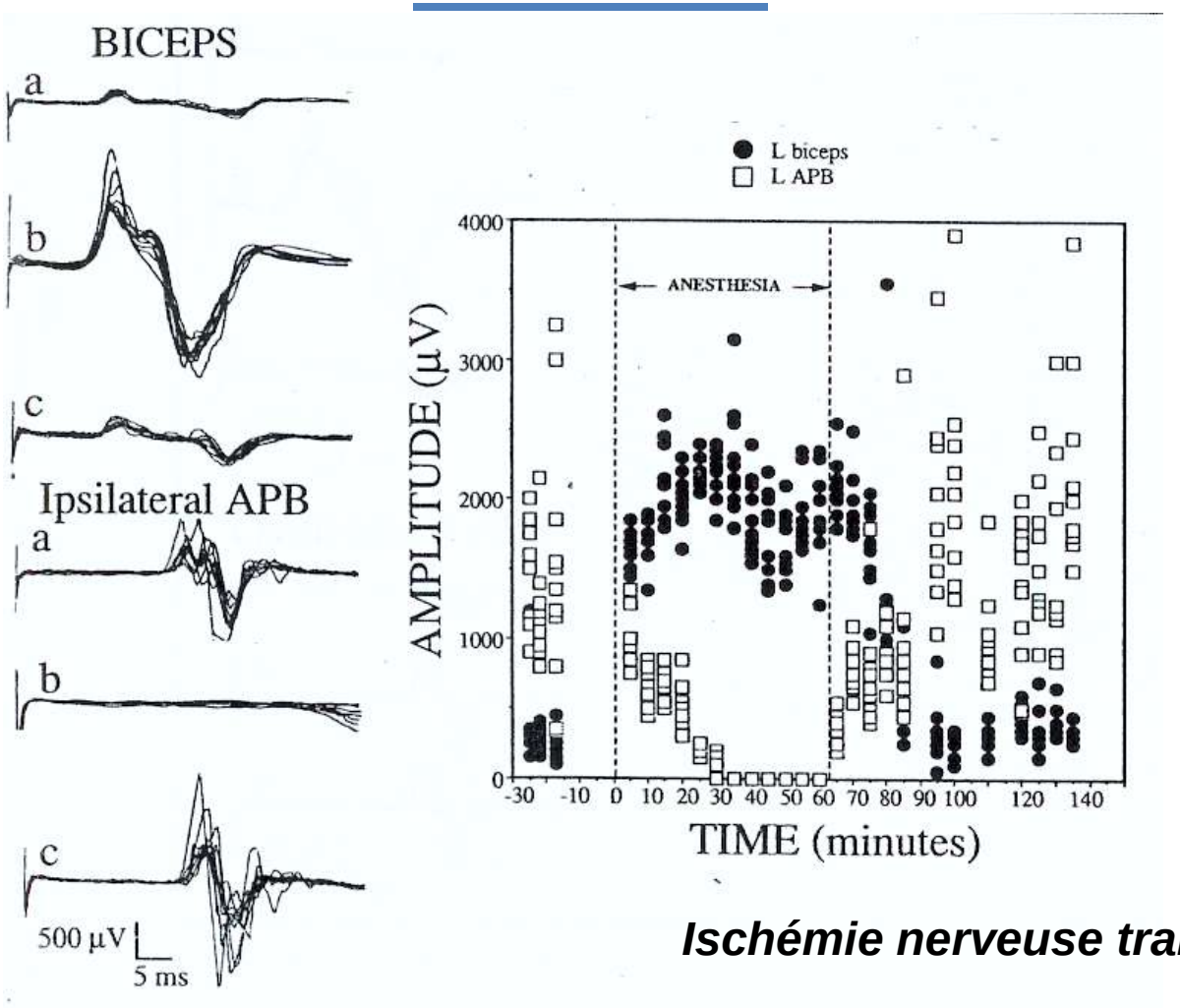
Aire de l'épaule avant amputation

Aire de la main avant amputation, envahie par l'aire de l'épaule après amputation

Mouvement de l'épaule (TEP):
montre que l'aire de l'épaule (côté amputé) envahit l'aire initiale de la main amputée (que l'on localise hypothétiquement symétrique à A)

Kew et al., J Neurophysiol 1994

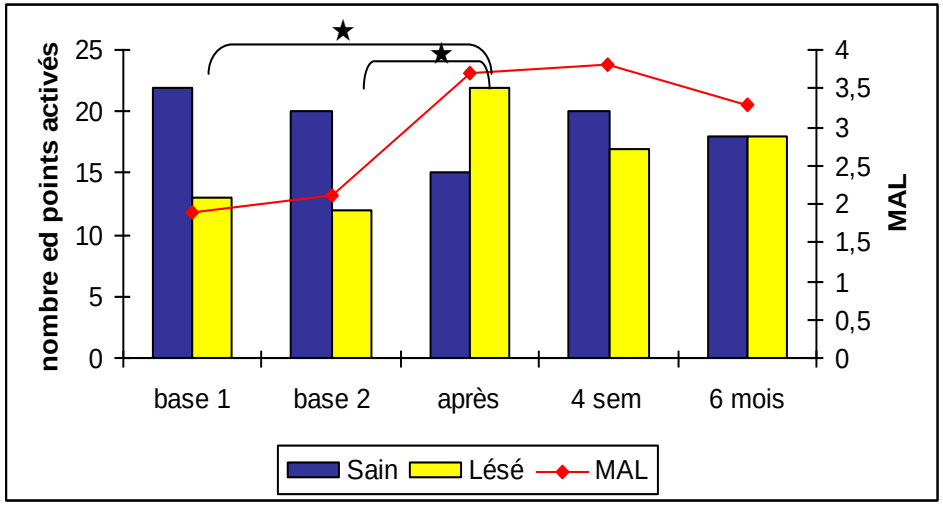
Compétition des représentations corticales



Ischémie nerveuse transitoire

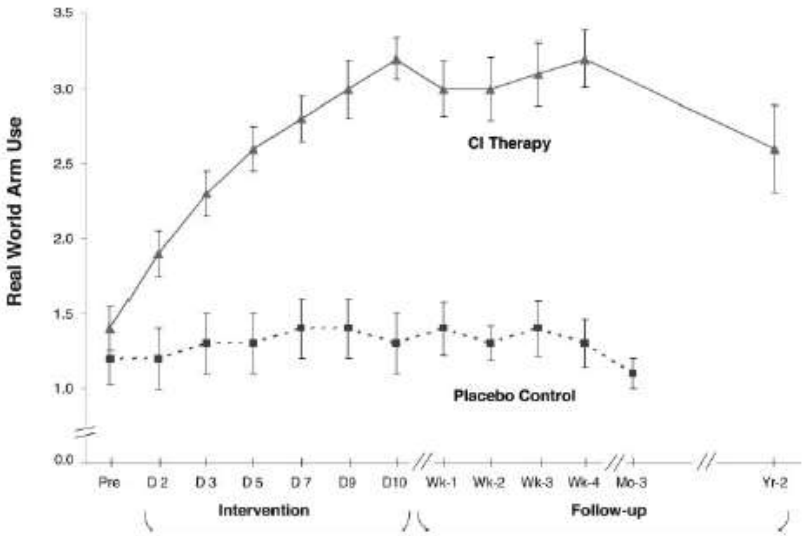
« Rapid reversible modulation of human motor outputs after transient deafferentation of the forearm : a study with transcranial magnetic stimulation », Brasil-Neto et al. (1992) Neurology

Thérapie contrainte



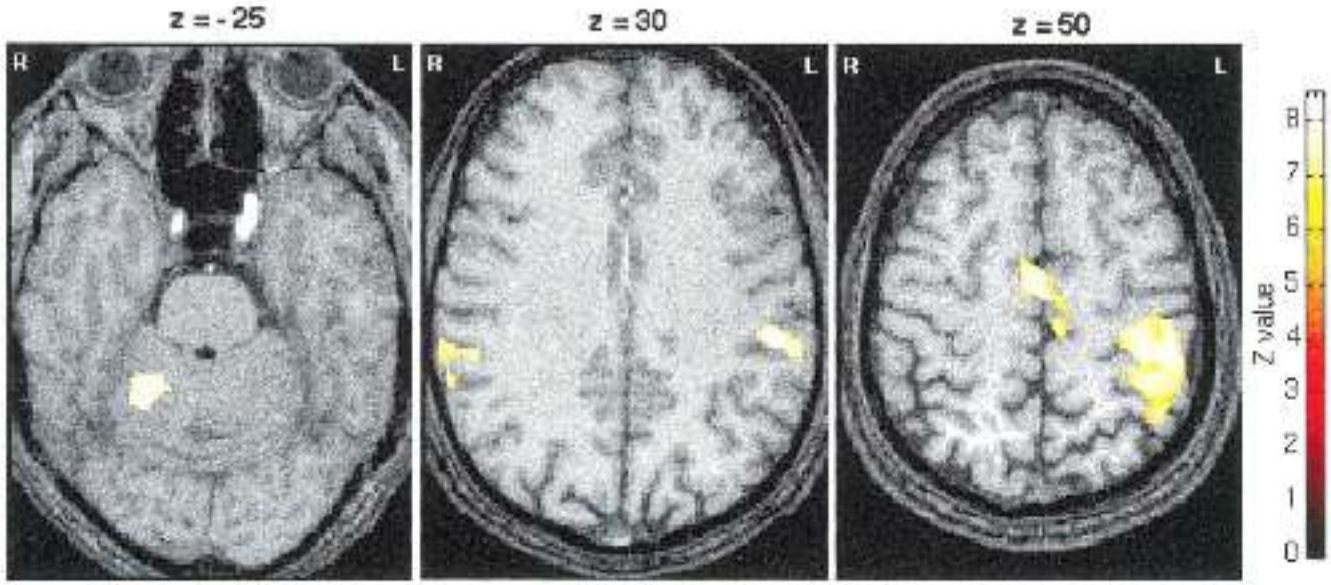
Cartographie TMS muscle de la main

Liepert et al., Stroke 2000



Taub et al, Stroke 2006

Rôle des afférences sensitives



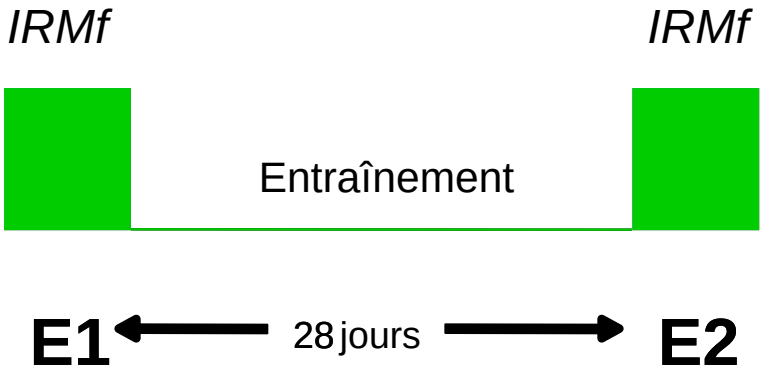
La mobilisation passive active le cortex sensori-moteur

Alary F et al, Neuroimage 1998

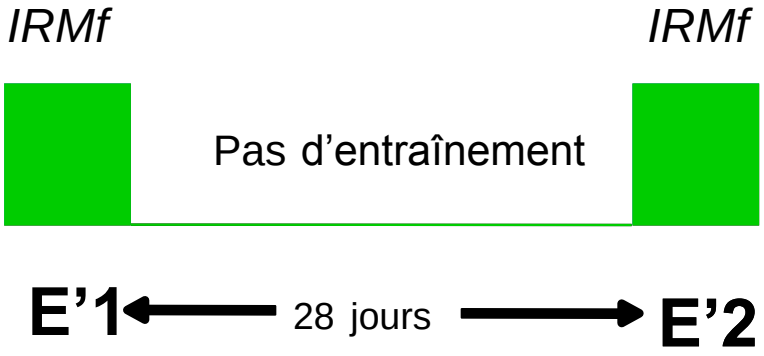
Sujet sain

Stimulation proprioceptive Main Droite

Groupe Entraîné (n = 6)

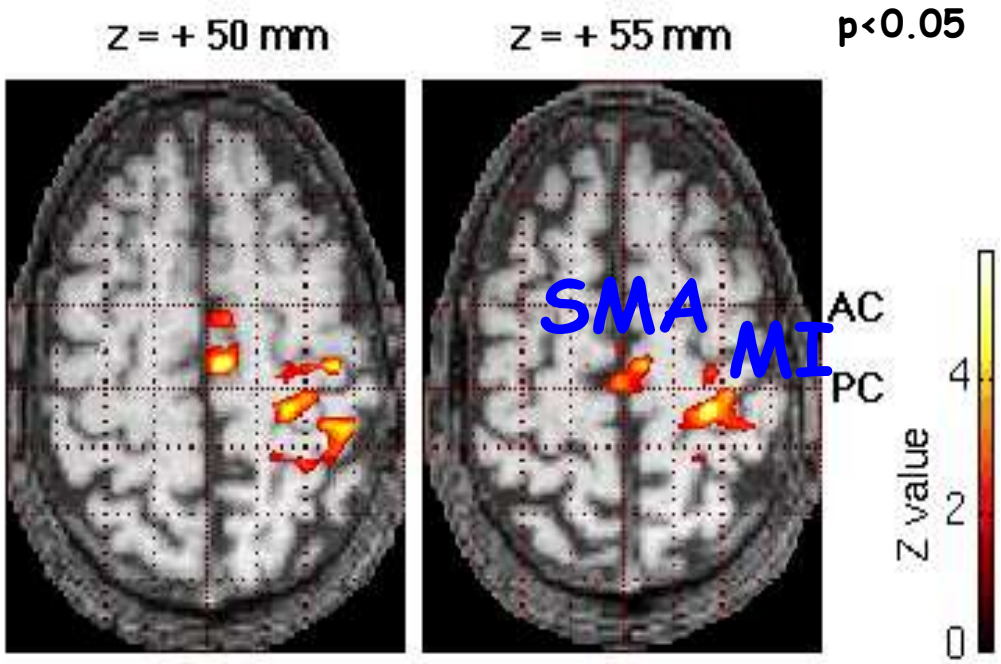


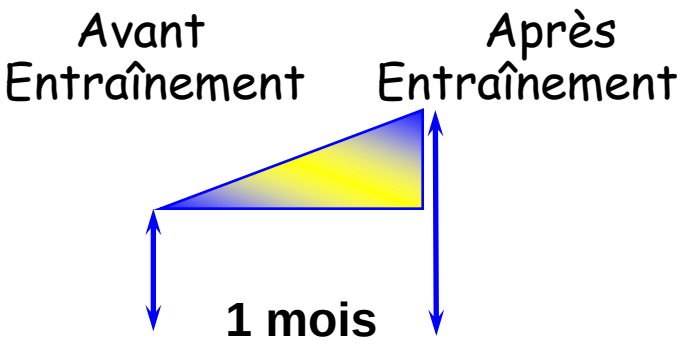
Groupe Contrôle (n = 6)



Sujet sain

Effet entraînement

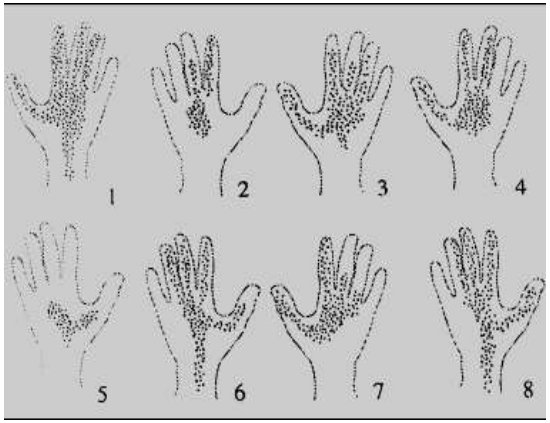


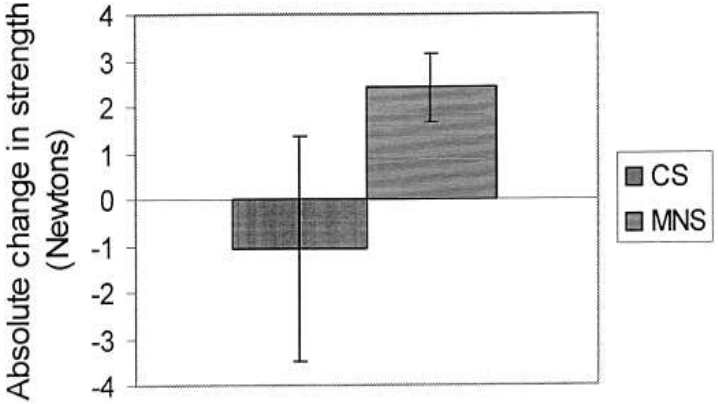


Carel C. et al, JCBF 2000;20:478-484

Chez les patients

- Etudes cliniques :
  - effets des stimulations électriques
  - EMS Powel et al stroke 1999
  - TENS Sonde et al Scand J Rehab Med 1998
  - Electroacupuncture Johanson et al, Neurology 1996
- Conforto et al Ann Neurol 2002
  - 8 hémiplégiques chroniques
  - Stimulation sensitive du médian
  - Augmentation de la force





Déficit moteur pur

Stimulation proprioceptive Main Droite

Groupe Entraîné (n = 6)

IRMf — Entraînement — *IRMf*

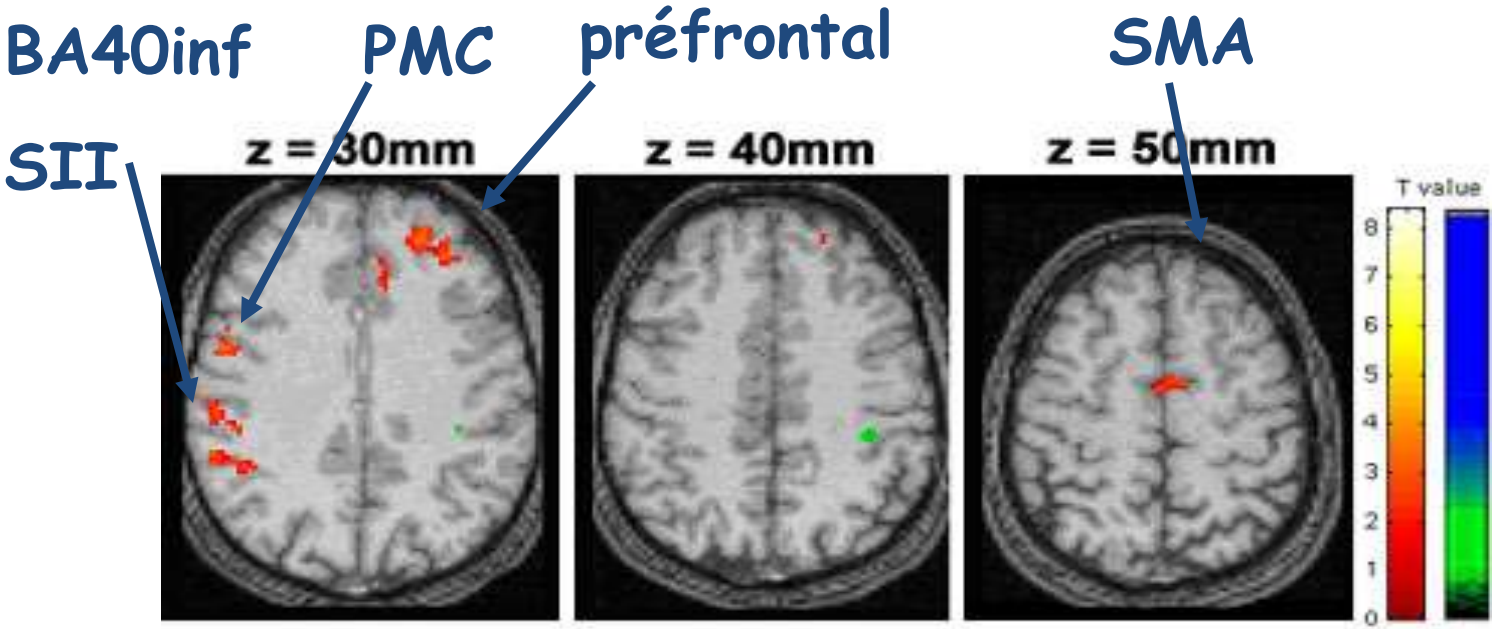
E1 ← 28 jours → **E2**

Groupe Contrôle (n = 6)

IRMf — Pas d'entraînement — *IRMf*

E'1 ← 28 jours → **E'2**

Effet entraînement



p<0.05

Mouvement passif de la main déficitaire

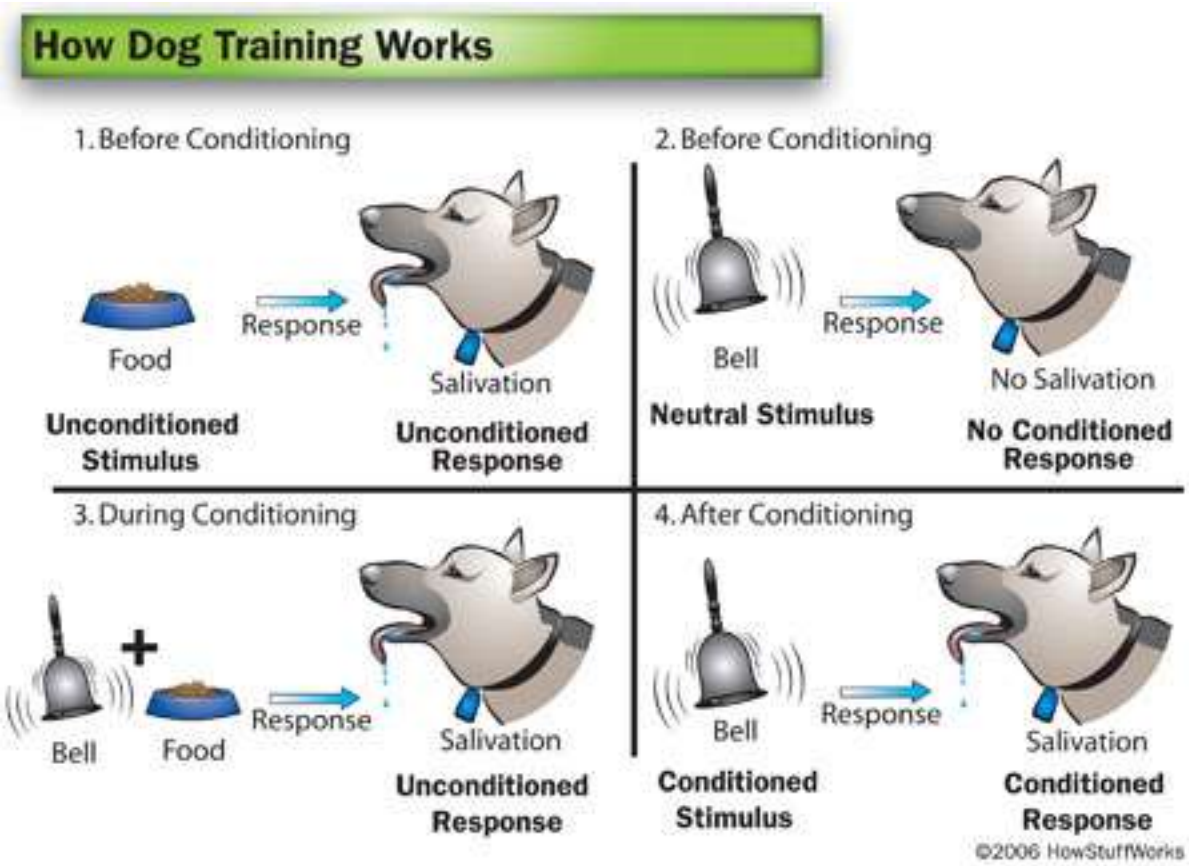
Rééduqués [E2-E1] – contrôles [E'2-E'1]

- Index moteur : E2>E'2 (p<0,05)

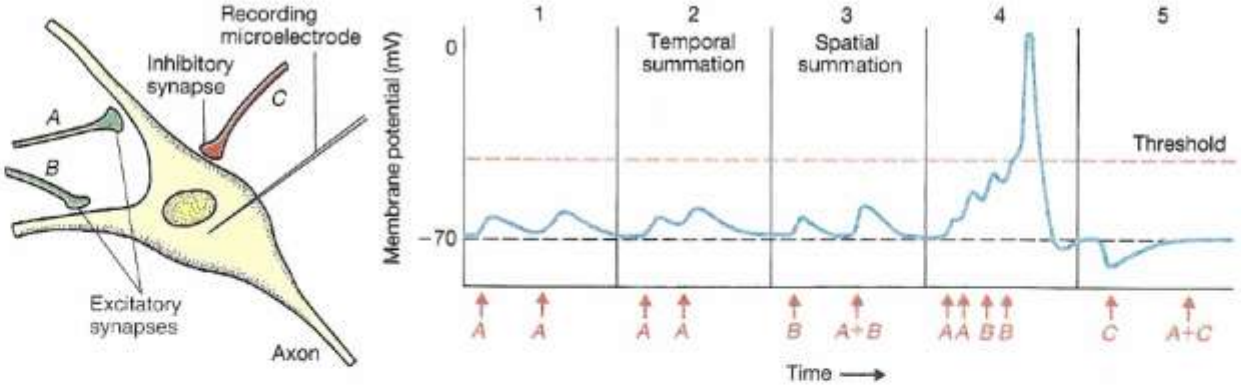
Dechaumont S, J NeuroRehab 2008

Apprentissage moteur

Conditionnement associatif



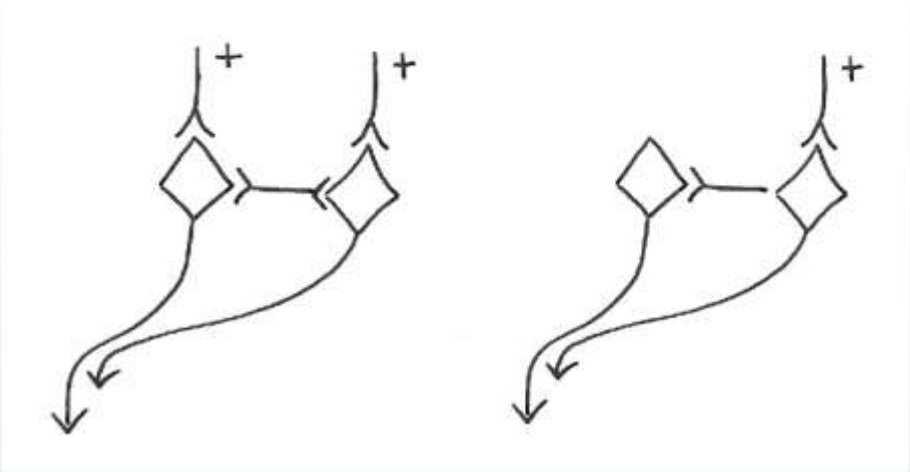
What determines whether a cell fires?



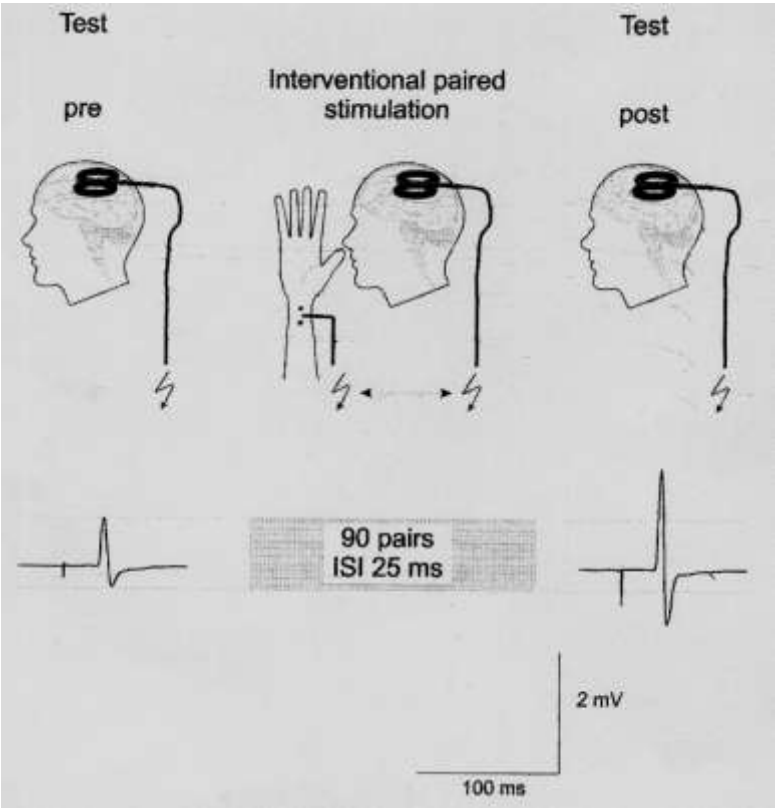
Hebbian learning rule (1949):

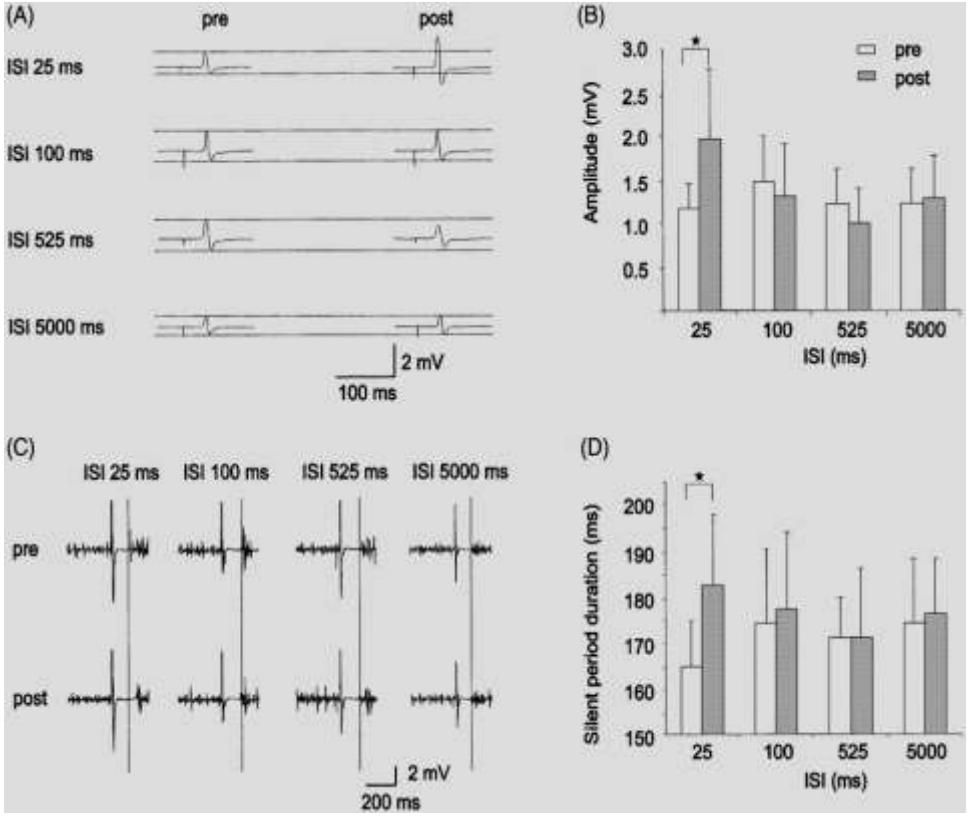
Repetitive activation of a presynaptic neuron together with simultaneous activation of a neighbouring postsynaptic neuron leads to an increase in synaptic strength between them.

Substantiated by experimental evidence and underpins LTP and LTD



Conditionnement associatif : IPAS





Stefan, K. et al. Brain 2000 123:572-584

STIMULATIONS COMBINÉES
chez les sujets sains

Stimulation Électrique
périphérique
muscle Extenseur poignet

5 chocs de 1ms

100 ms

Train 500 ms

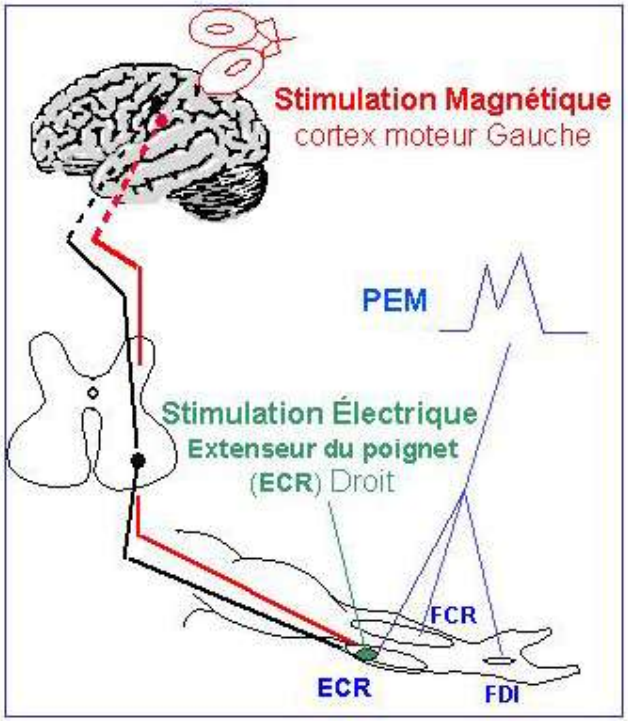
+

Stimulation Magnétique
cortex moteur
Aire du poignet

TMS

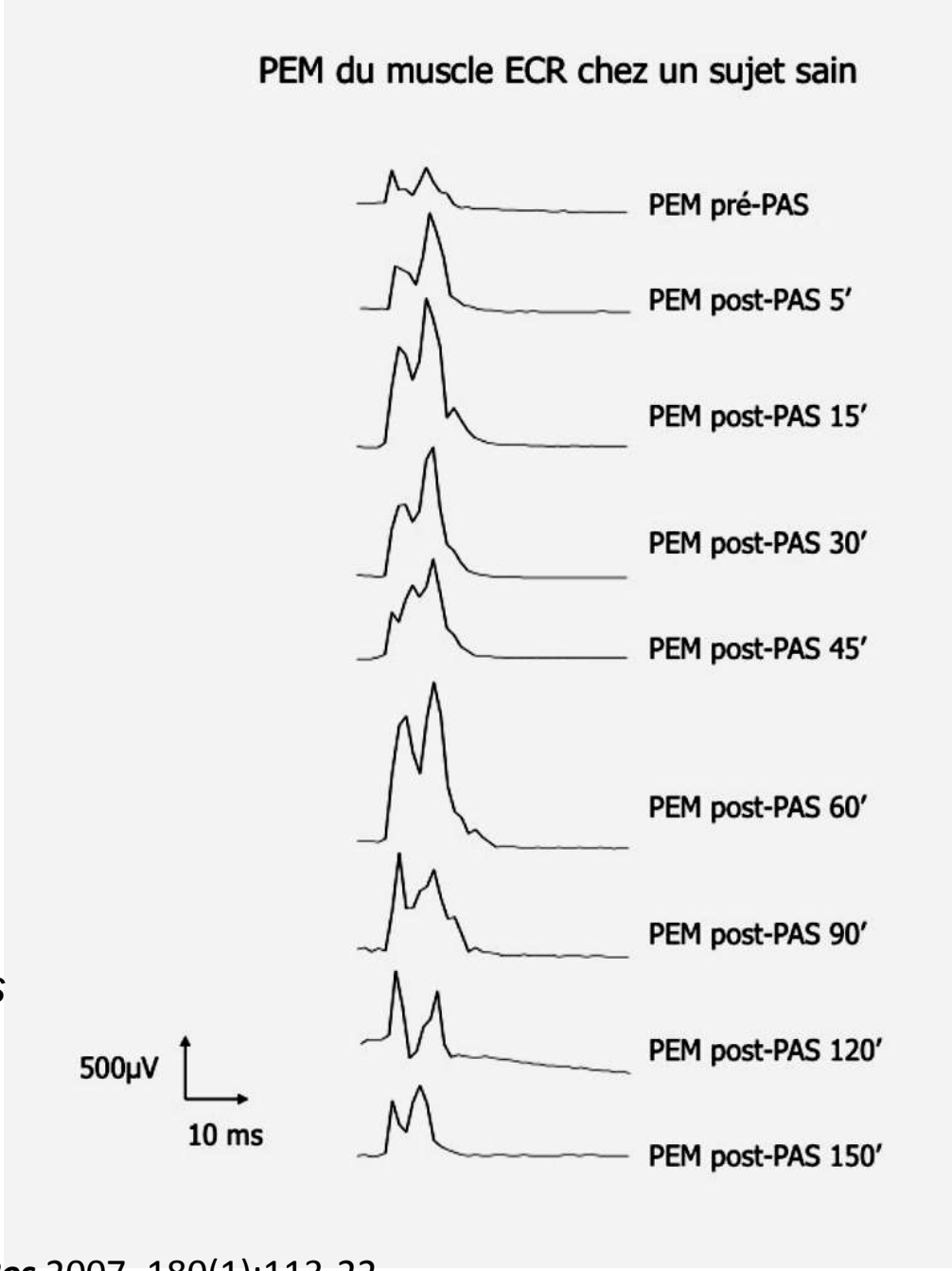
25 ms

1 stimulation combinée toutes les 10s



Pendant 30 minutes = 180 stimuli combinés

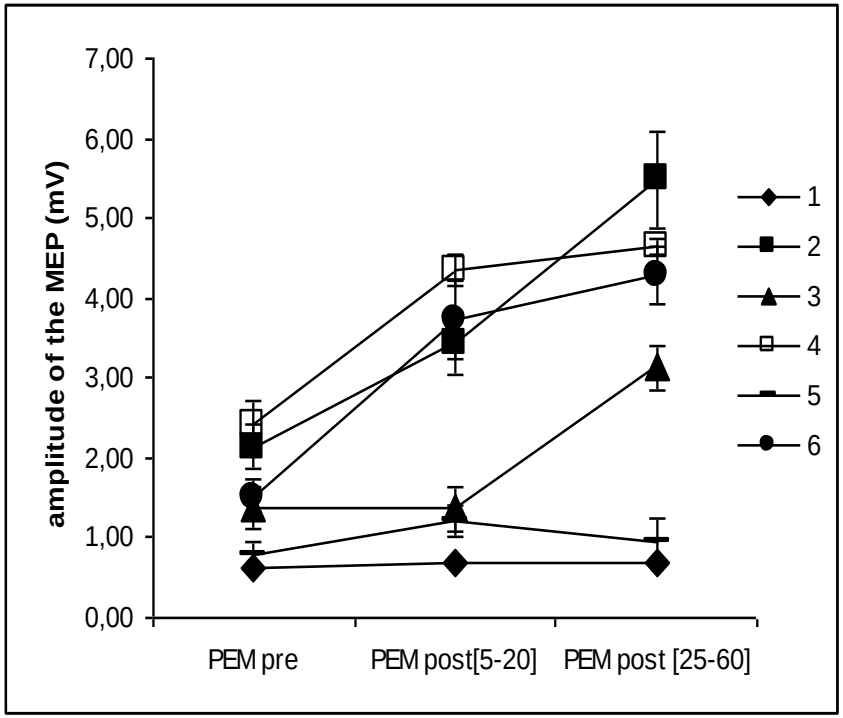
ECR : Extenseur, FCR : Fléchisseur, FDI : muscle des Doigts



PEM redressé
Moyenne de 20 mesures

Castel-Lacanal et al Exp Brain Res 2007, 180(1):113-22

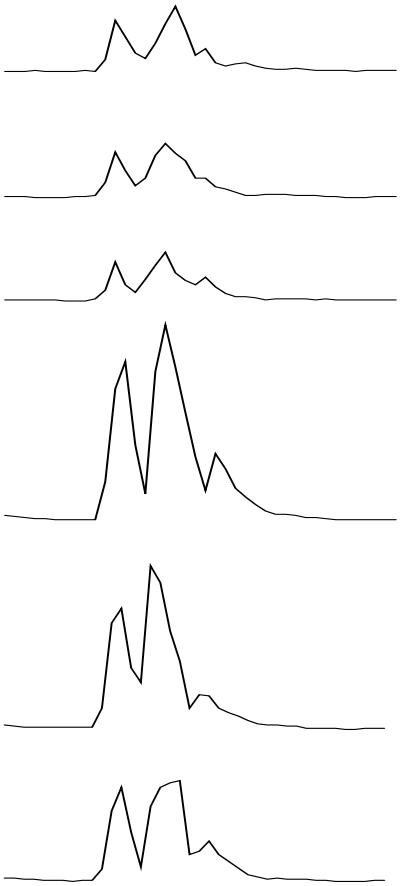
Castel-Lacanal E et al Neurorehabil Neural Repair. 2008;22(2):154-65.



6 patients

ECR gauche (côté hémiplégique)

1 mois après l'AVC



PEM pré-IPAS

PEM post-IPAS 5'

PEM post-IPAS 15'

PEM post-IPAS 25'

PEM post-IPAS 35'

PEM post-IPAS 45'

700µV

10 ms

Neurorehabil Neural Repair. 2008 ; 22(2): 111–121. doi:10.1177/1545968307305457.

Effects of Robot-assisted therapy on upper limb recovery after stroke: A Systematic Review

Gert Kwakkel, PhD[1,2], **Boudewijn J. Kollen, PhD**[3], and **Hermano I. Krebs, PhD**[4,5,6]

DEMAIN?

LES MÉDICAMENTS

Feeney et al, science 1982

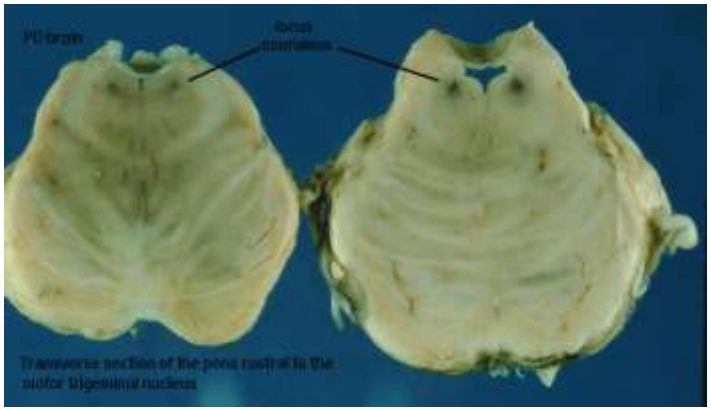
- Ablation chirurgicale du cortex sensori-moteur
- 24 h plus tard, une injection d ’une dose unique de D-amphétamine
- Récupération du déficit moteur en quelques heures
  - marche sur une poutre

Norépinéphrine NE

- **Effet positif sur la récupération**

Administration intra-ventriculaire NE

Boyeson et Feeney, *Pharmacol Biochem Behav*, 1990; 35:497-501.

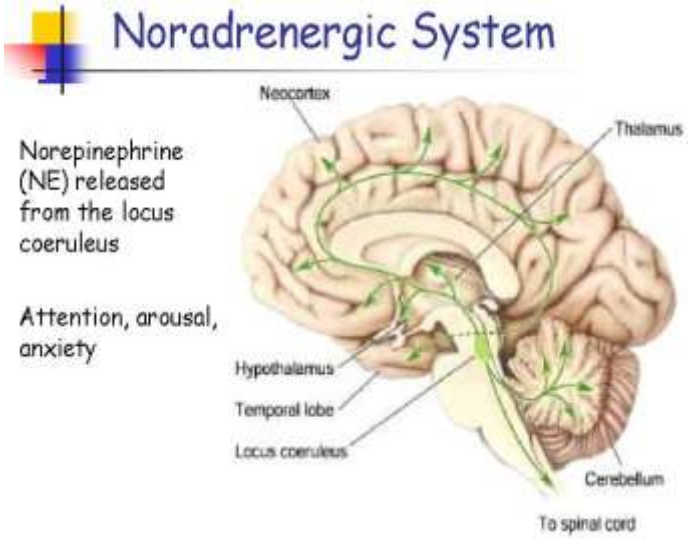


- **Effet délétère sur la récupération**
  - DSP-4 (⇓ NE)

    Boyeson et al, *Behav Neurosci* 1992; 106:964-973.

  - Lésion du locus coereleus

    Boyeson et al, *Pharmacol Biochem Behav*, 1992; 43,771-777.



Concept

- Drogues qui augmentent la sécrétion de NE $\Rightarrow$ effet positif sur la récupération

- Drogues qui diminuent la sécrétion de NE $\Rightarrow$ effet délétère sur la récupération

Les antagonistes

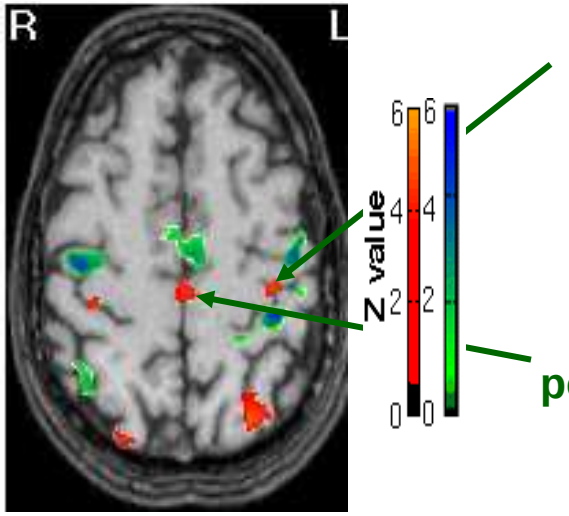
- Etude retrospective :
  - **Goldstein et al, J Neuro Rehab 1990; 4:137-144.**
- Comparaison de 2 groupes
  - patients prenant 1 ou plusieurs drogues délétères :
    - antihypertenseurs : clonidine, prazozine
    - antagoniste dopaminergique : haldopéridol
    - benzodiazépines
    - phénytoïnes
  - patients ne prenant aucune de ces drogues
- Récupération moindre dans le groupe 1

(analyse multifactorielle)

Impact des médicaments mono-aminergiques

6 volontaires sains

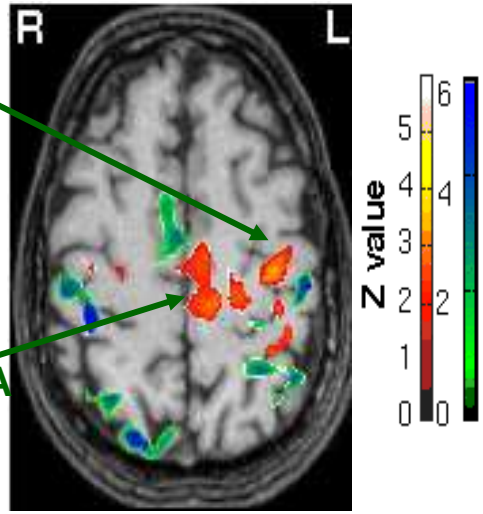
Amphétaminique
fénozolone



p < 0,05

6 volontaires sains

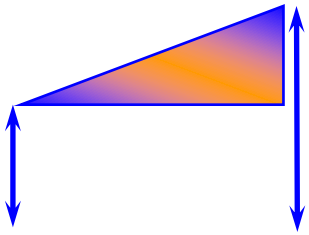
Sérotoninergique
fluoxétine



M1

post-SMA

Sans médicament **Avec médicamen**



Augmentation de l 'activation

sur M1, post-SMA

Amphétaminique, Sérotoninergique:

Même effet

Loubinoux I., *JCBF* 1999;19:1365-75

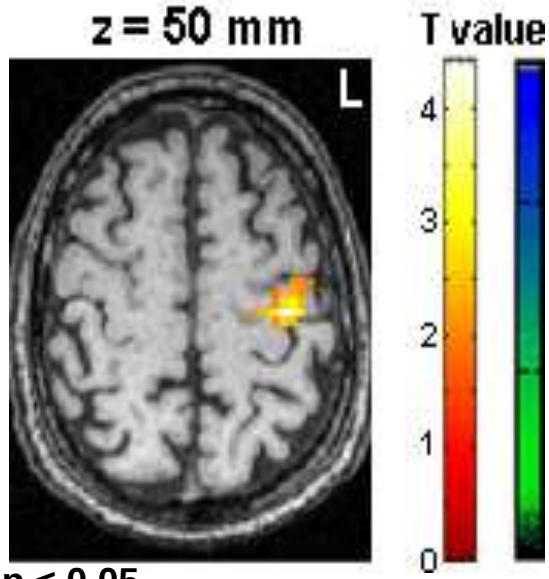
Chez les patients

8 Patients

Sérotoninergique
fluoxétine

Main atteinte

Lesioned side



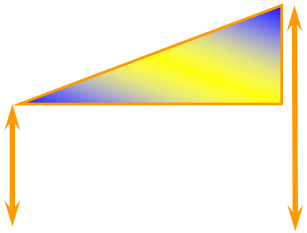
p < 0,05

4 patients M P

4 patients P M

AVC + 14j **AVC + 21j**

Placebo **Médicament**



Pariente J., ***Ann Neurol, 2001;50:718:729***

Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial

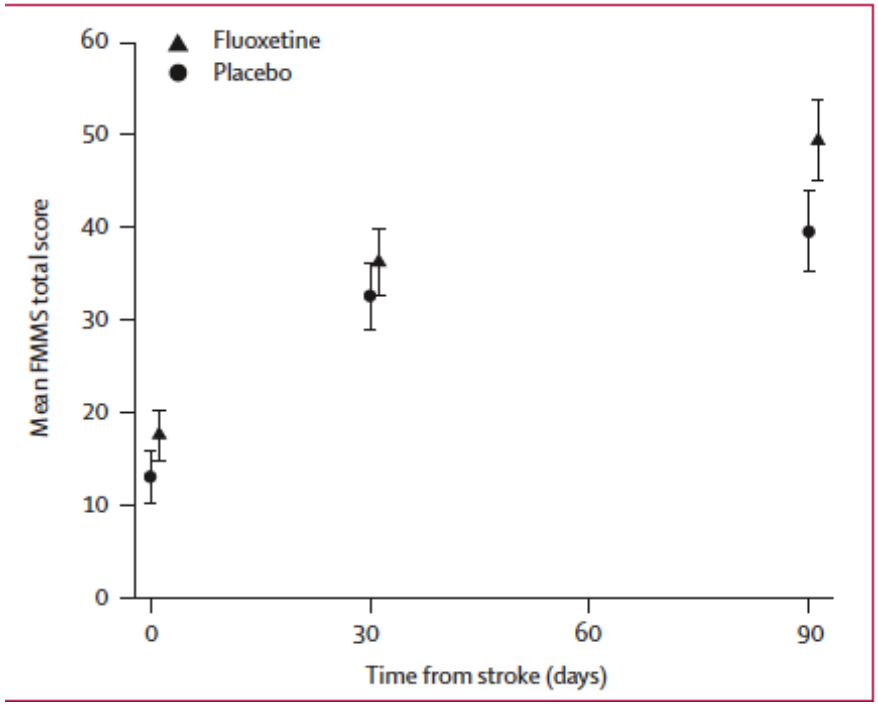
François Chollet, Jean Tardy, Jean-François Albucher, Claire Thalamas, Emilie Berard, Catherine Lamy, Yannick Bejot, Sandrine Deltour, Assia Jaillard, Philippe Niclot, Benoit Guillon, Thierry Moulin, Philippe Marque, Jérémie Pariente, Catherine Arnaud, Isabelle Loubinoux

Lancet Neurol 2011; 10: 123–30

This online publication has been corrected. The corrected version first appeared at

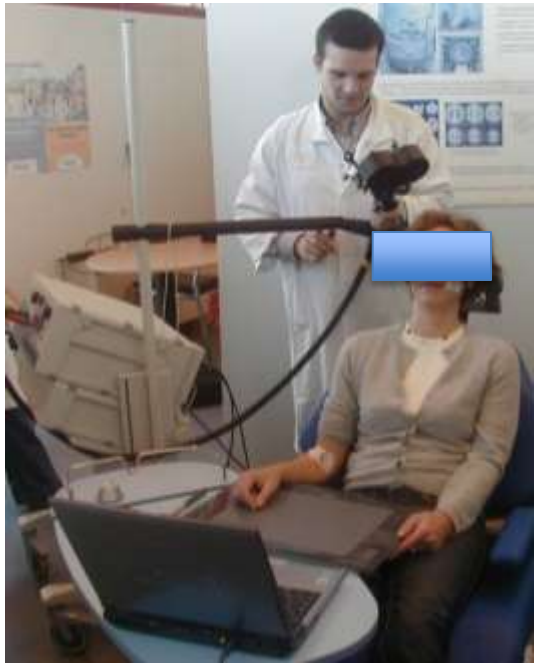
Summary

Background Hemiplegia and hemiparesis are the most common deficits caused by stroke. A few small clinical trials suggest that fluoxetine enhances motor recovery but its clinical efficacy is unknown. We therefore aimed to investigate whether fluoxetine would enhance motor recovery if given soon after an ischaemic stroke to patients who have motor deficits.

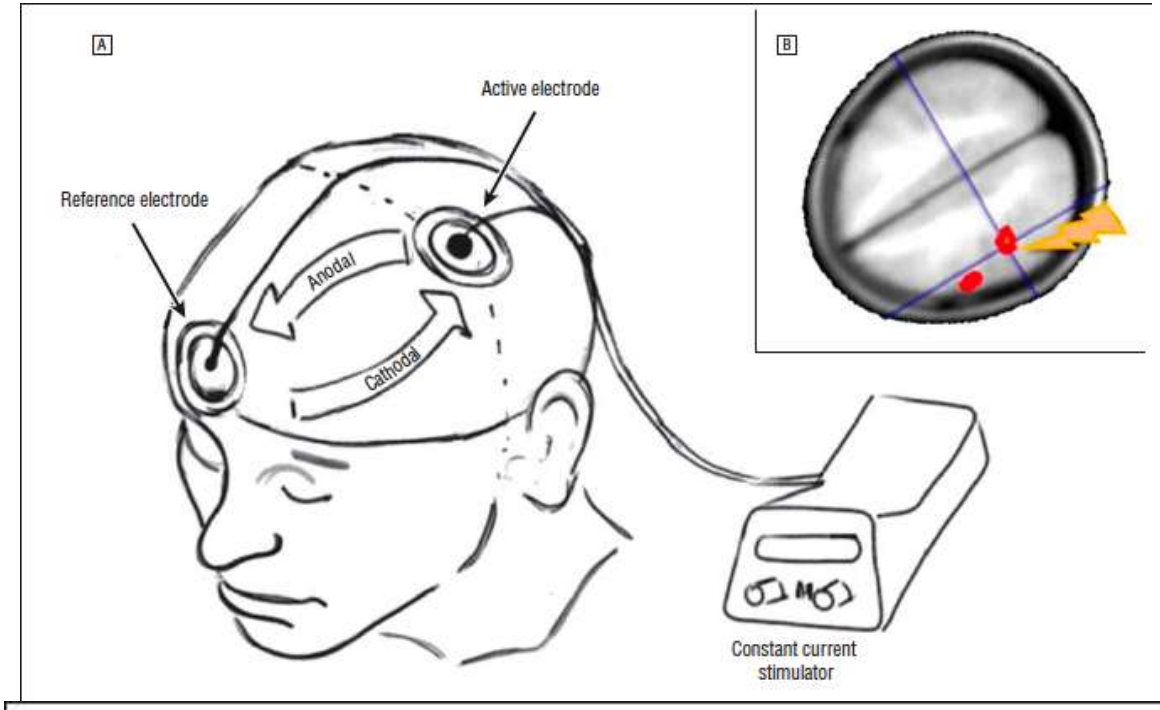


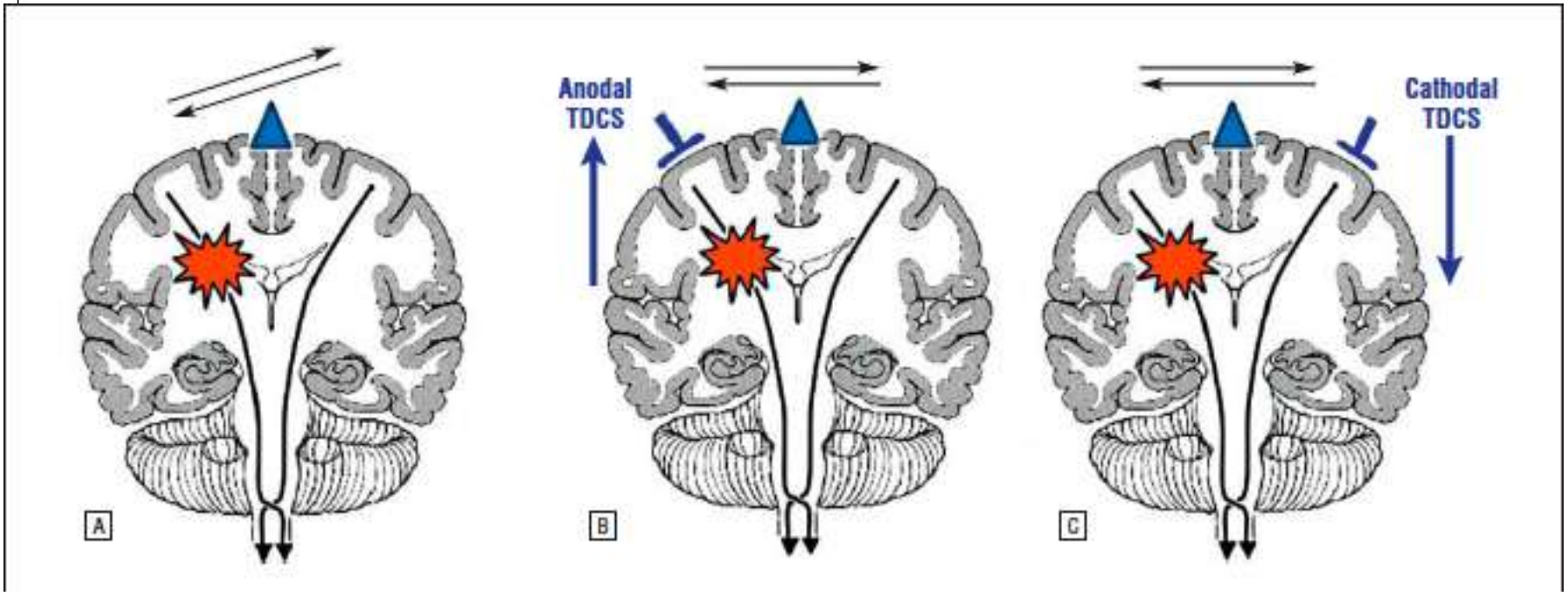
Stimulations cérébrales

tDCS



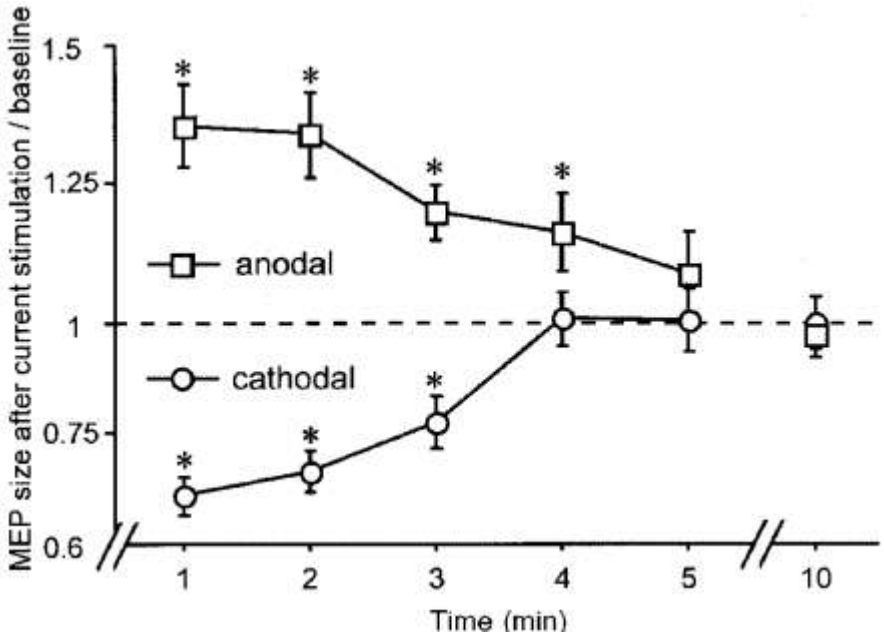
rTMS


A
Active electrode
Reference electrode
Anodal
Cathodal
Constant current
stimulator
B


Anodal
TDCS
Cathodal
TDCS
A
B
C

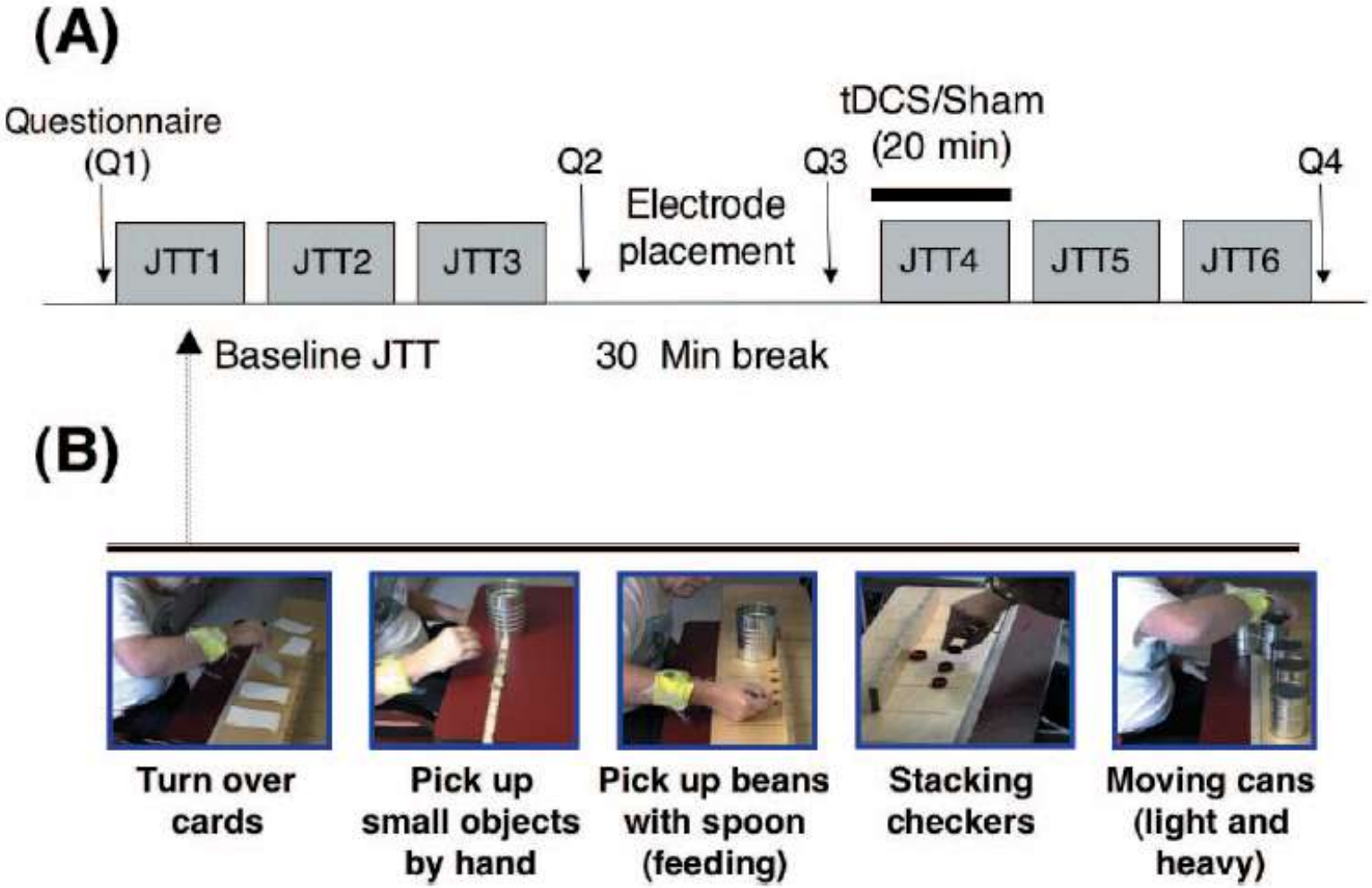
Courants galvaniques :
tDCS (transcranial Direct Current Stimulation)

- Stimulation anodale: excitation
- Stimulation cathodale : Inhibition



✧ Stimulation placebo

Nitsche et al. 2000



A paradigme expérimental :JTT = Jebsen Taylor Test

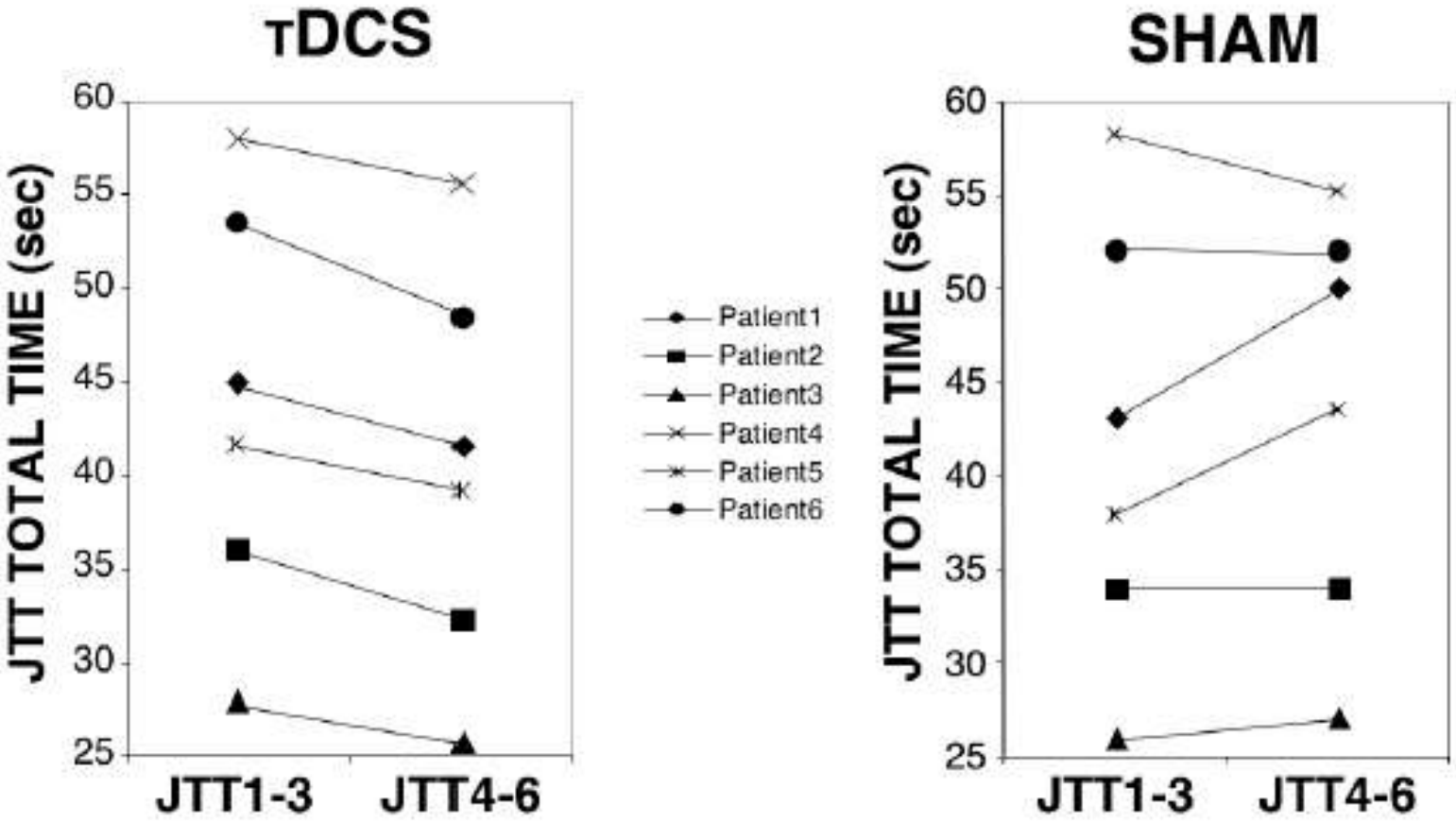
JTT1,JTT2, JTT3 familiarisation avec le test, puis mise en place des électrodes de stimulation: stimulation effective ou placebo,

puis JTT4 = test passé pendant le stimulation, JTT5 et JTT6 tests après la stimulation

Questionnaire : questions concernant la fatigue l'attention, les sensations douloureuses

B épreuves du JTT: tourner les cartes, prendre des petits objets dans la main, prendre des cacahouètes avec une cuillère, empiler des pions déplacer des boites lourdes ou légères

Hummel, et al. Brain 2005



Amélioration significative du temps mis pour réalisé le Jebsen Taylor test lors de la stimulation électrique directe transcranienne (tDCS).

Effets bénéfiques chez tous les patients

Absence de modification lors de la stimulation placébo (sham)

Hummel, et al. Brain 2005

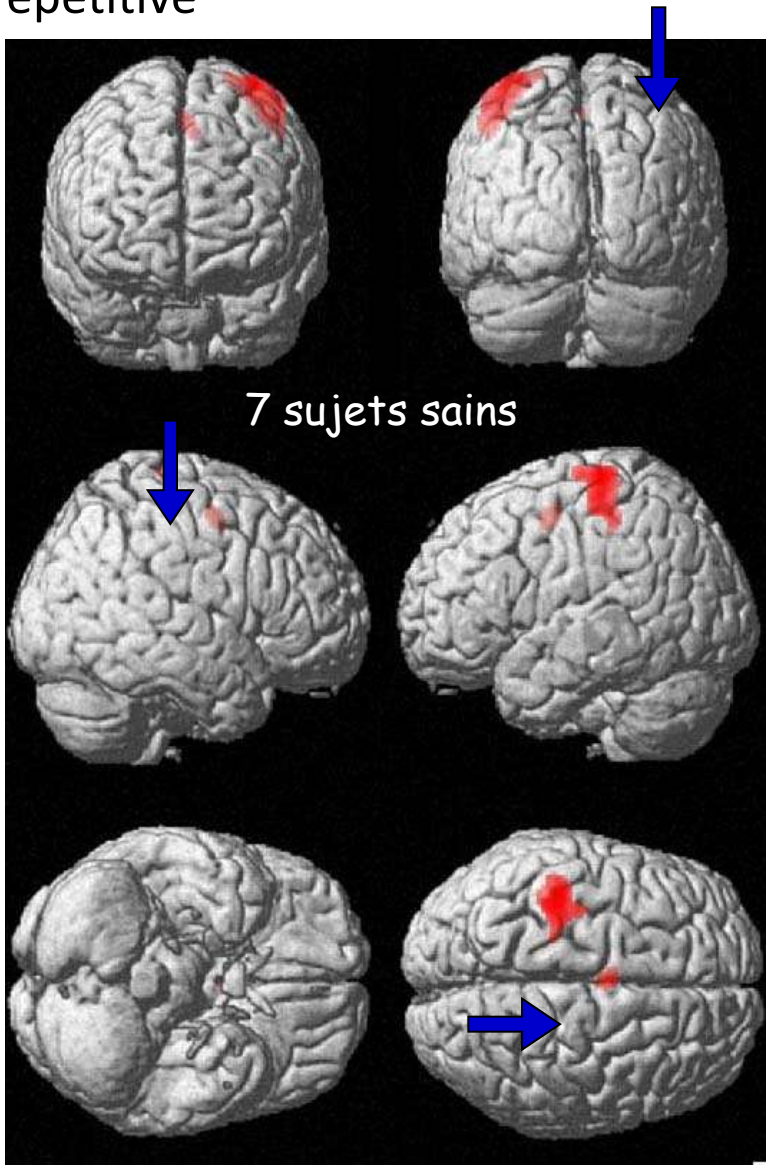
Inhiber le cortex controlésionel

rTMS: Stimulation Magnétique Transcrânienne répétitive

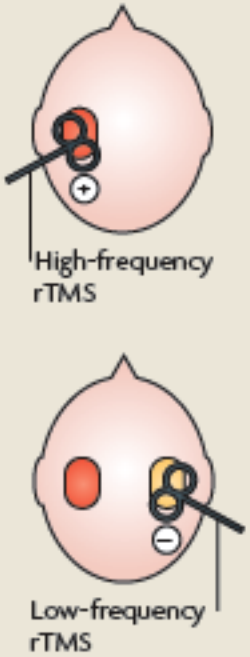
Protocole MOMA: stimuler M1 ipsilésionel en inhibant M1 controlésionel par TMS répétitive **inhibitrice** (1 Hz)

Conchou F et al, HBM 2008

- **Améliorer** les performances motrices de la main atteinte (Mansur et al., 2005; Takeushi et al., 2005)
- TEP: **Augmentation** de l'activation dans le cortex moteur ipsilésionel.



b Stroke



Study	Number of patients	rTMS approach	Functional outcome measures	Results
Mansur *et al.*[83]	8 (< 1 year after stroke)	600 pulses at 1 Hz to contralesional motor cortex	SRT, CRT, PPT, finger tapping speed	M1 stimulation significantly improved performance on RT and PPT
Takeuchi *et al.*[62]	20 (>6 months after stroke) split into two groups, one receiving real rTMS and the other sham	1 Hz for 25 mins to contralesional motor cortex	Pinch task	Real rTMS improved pinch acceleration of affected hand
Fregni *et al.*[55]	15 (>1 year post stroke) randomized into real (n = 10) and sham (n = 5) groups	5 sessions over 5 days of 1 Hz; 1,200 pulses to contralesional M1	JTT, PTT, SRT and CRT	Improvement on all functional measures for affected hand that lasted for 2/52
Khedr *et al.*[54]	52 (5–10 days post stroke) randomized into real (n = 26) and sham (n = 26) groups	10 × 10-sec 3-Hz trains for 10 days	SSS, NIHSS and BI	Real rTMS resulted in significantly greater improvements on all measures
Talelli *et al.*[61]	6 (>1 year post stroke)	Excitatory TBS to lesioned M1 or inhibitory TBS to contralesional M1	SRT, CRT and GS	Inhibitory TBS to contralesional hemisphere improved SRT in affected hand

Quel type de neuromodulation corticale chez les patients hémiplégiques?

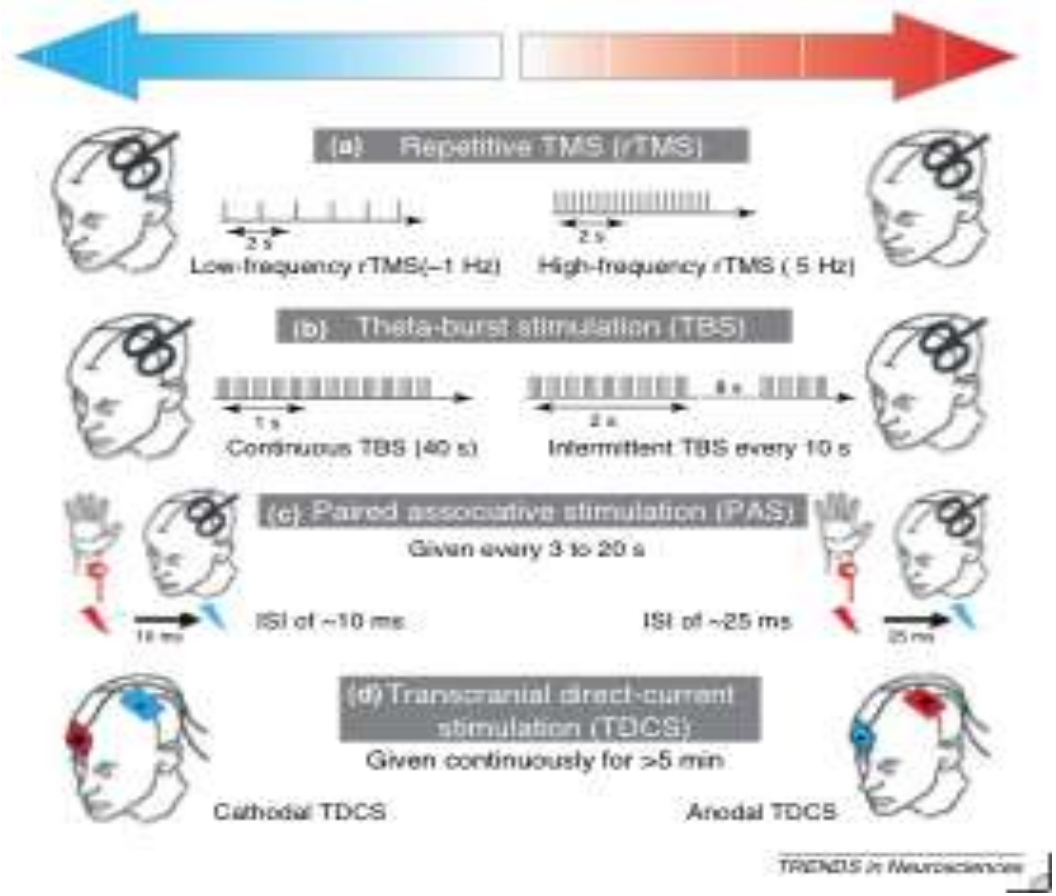
Et quand?

rTMS facilitatrice
rTMS inhibitrice

TBS

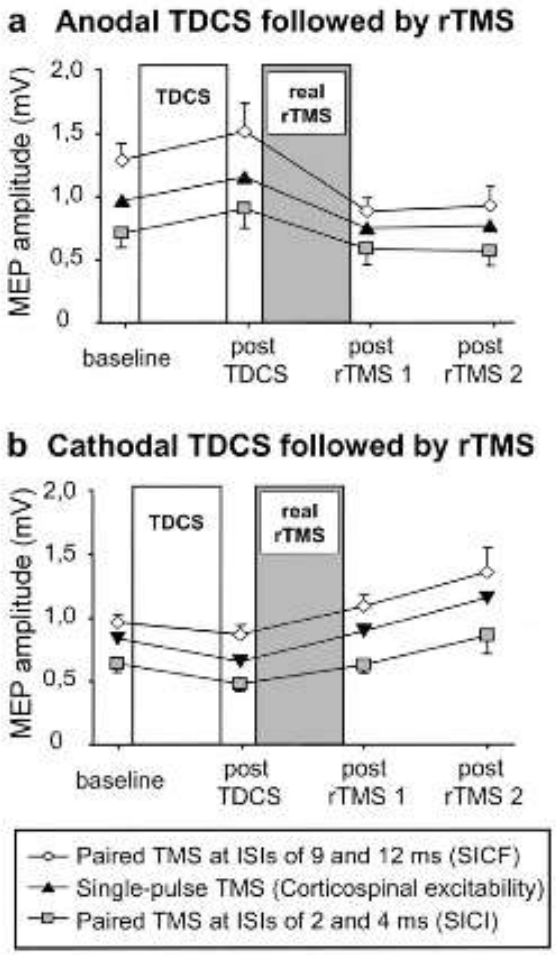
PAS

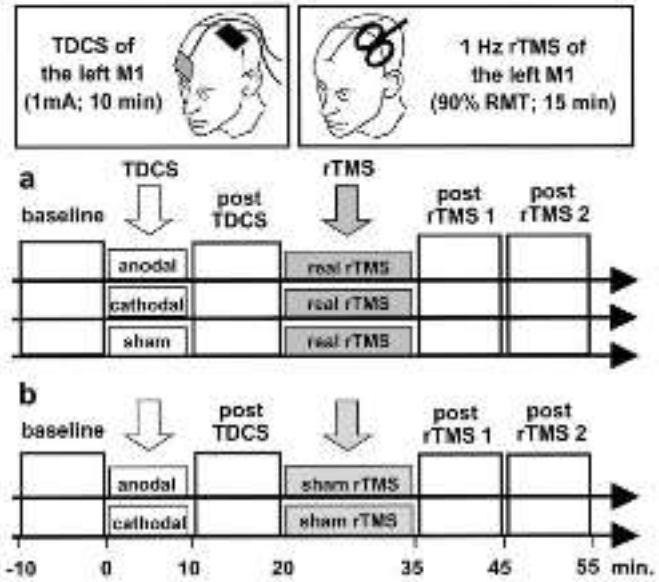
tDCS



MÉCANISMES DE RÉGULATION

Homéostasie de la plasticité

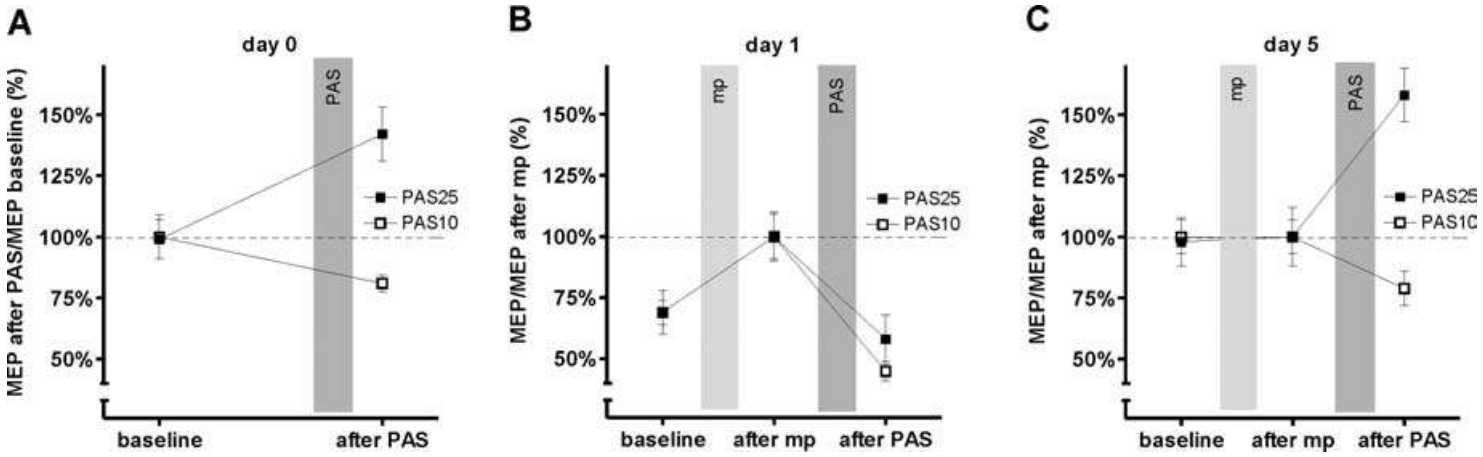




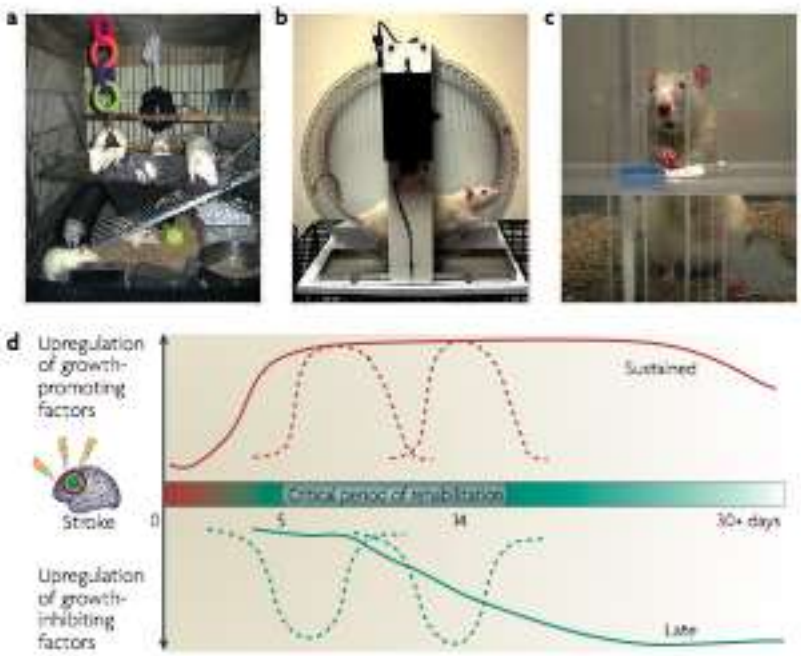
Siebner H et al, J Neurophysiol 2004

Mécanismes de régulation de la plasticité cérébrale : homéostasie

- PAS et apprentissage moteur
  - Sur une session,
    - effet PAS inhibé
  - Répétition sur 5 jours
    - Effet de la PAS restauré

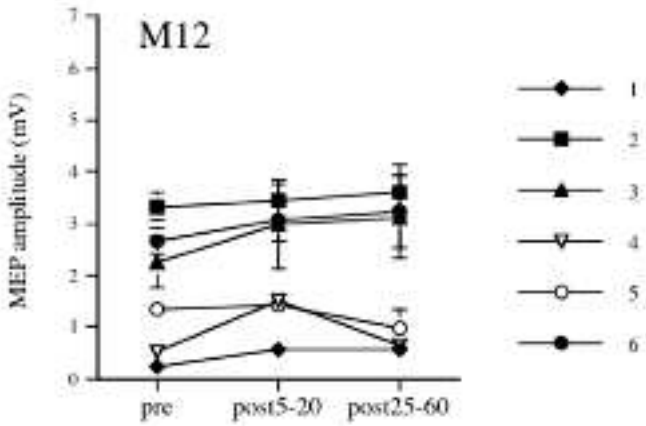


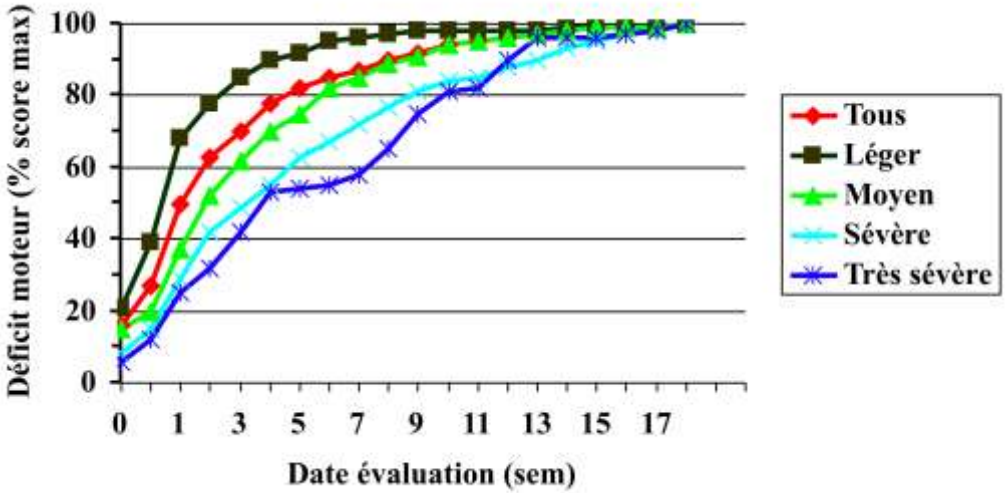
Rosenkranz et al. 2006



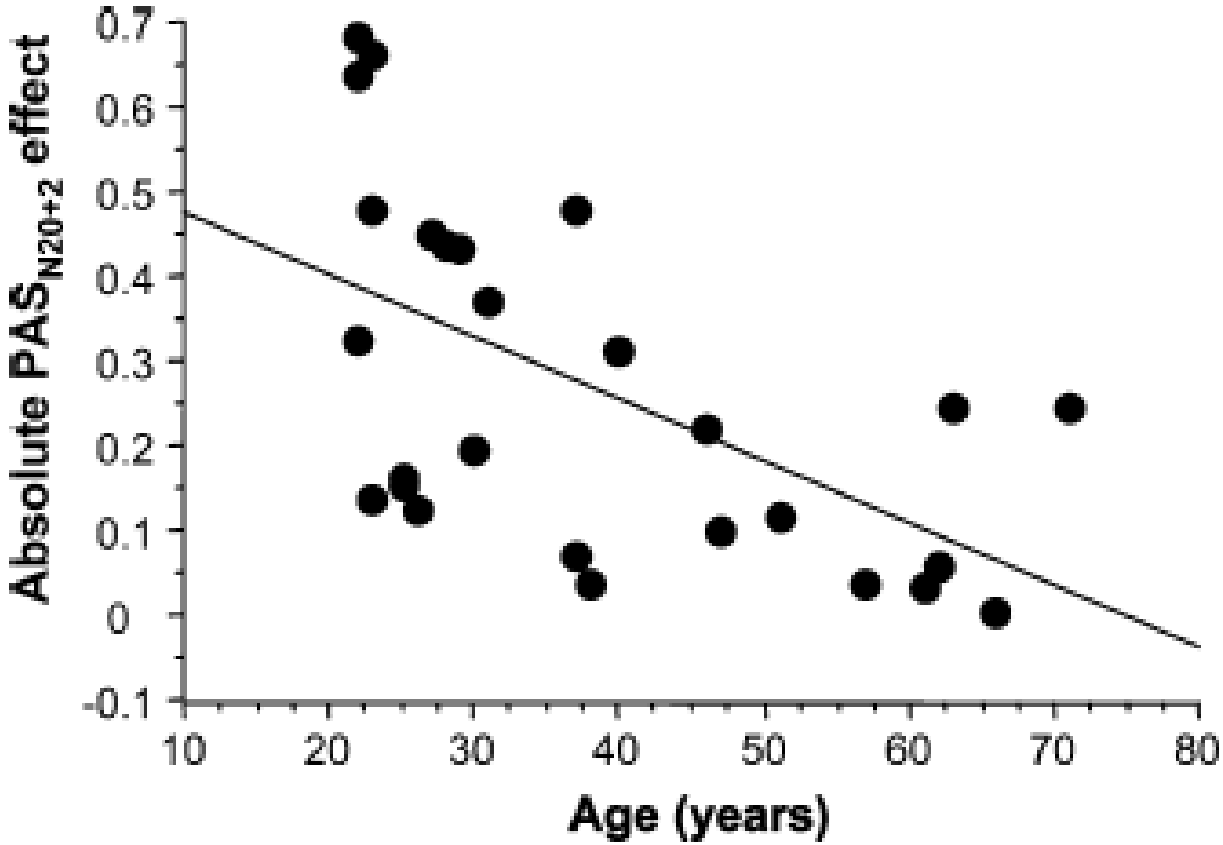
Période critique

Biernaskie et al, J Neurosci 2004





L'âge

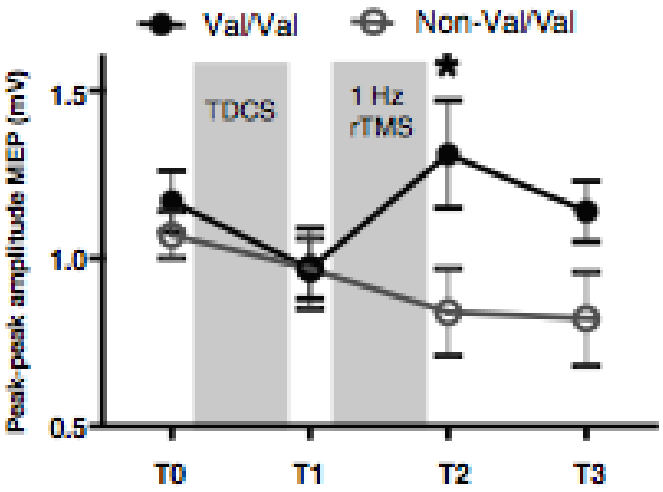


Florian J et al Exp Brain Res 2008

Facteurs génétiques

- Polymorphisme du BDNF gène (Val66Met)

- Modifie la réponse aux stimulations cérébrales



Cheeran B et al, 2008 J Physiol.

Conclusion

- La plasticité cérébrale est un des facteurs essentiels de la récupération motrice après AVC
- L’exercice physique influence positivement ce phénomène
- Nous commençons à peine à comprendre les modalités de cet effet.

The Toulouse team

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