DEPARTAMENT DE MEDICINA
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TREBALL DE RECERCA
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Autor:

- **Dª Isabel Asunción Serrano Tendero**, Llicenciada en Medicina i Cirurgia, MIR de Neurofisiologia Clínica en l'Hospital Universitari de la Vall d'Hebrón, Barcelona.

Títol:

- ***"Cortical mapping of the neuronal circuits modulating the muscle tone. Introduction to the electrophysiological treatment of the spastic hand".***

- (Mapeig Cortical dels circuits neuronals moduladors del tò muscular. Introducció al tractament electrofisiològic de la mà espàstica).

Director i Co-Director del Treball:

- **Dr. Josep Maria Espadaler Gamissans**, Professor Associat del Departament de Medicina de la Universitat Autònoma de Barcelona i Cap de Secció de Neurofisiologia Clínica del Hospital del Mar, Barcelona.
- **Dra. Núria Raguer Sanz**, Cap Clínic del Departament de Neurofisiologia Clínica del Hospital Universitari de la Vall d'Hebrón, Barcelona.

Annex 1
CERTIFICAT DEL DIRECTOR I CO-DIRECTOR DEL TREBALL DE RECERCA

El Dr. Josep Maria Espadaler Gamissans, Professor Associat del Departament de Medicina de la Universitat Autònoma de Barcelona i Cap de Secció de Neurofisiologia Clínica del Hospital del Mar, i la **Dra. Núria Raguer Sanz**, Cap Clínic del Departament de Neurofisiologia Clínica del Hospital Universitari de la Vall d'Hebrón,

FAN CONSTAR,

que el treball titulat **"Mapeig Cortical dels circuits neuronals moduladors del tò muscular. Introducció al tractament electrofisiològic de la mà espàstica",** ha estat realitzat sota la nostra direcció per la llicenciada **Na Isabel Asunción Serrano Tendero**, trobant-se en condicions de poder ser presentat com a treball d'investigació de 12 crèdits, dins el programa de doctorat en Medicina Interna / Diagnòstic per la Imatge (curs 2009-2010), a la convocatòria de juny.

Barcelona, a 14 de Maig de dos mil deu.

Annex 2: DADES DEL TREBALL DE RECERCA – RECERCAT (UAB i CBUC)

a. **Autor: Dª Isabel Asunción Serrano Tendero.**
b. **Títol:**

- **Cortical mapping of the neuronal circuits modulating the muscle tone. Introduction to the electrophysiological treatment of the spastic hand.**
- **Mapeig Cortical dels circuits neuronals moduladors del tò muscular. Introducció al tractament electrofisiològic de la mà espàstica.**

c. **Any de elaboració: 2009-2010.**
d. **Director i Co-Director del Treball:**
    - **Dr. Josep Maria Espadaler Gamissans**
    - **Dra. Núria Raguer Sanz**
e. **Tipus de treball: Pilot recerca.**
f. **Titulació: Llicenciada en Medicina i Cirurgia.**
g. **Departament / Centre: Departament de Neurofisiologia Clínica; Hospital Universitari de la Vall d'Hebrón.**
h. **Paraules clau i resum:**

Keywords: neuroplasticity, neuromodulation, connectivity, tractography, navigated TMS.

Paraules clau: neuroplasticitat, neuromodulació, connectivitat, tractografia, TMS navegada.

Abstract (100 words):

The purpose of this study is to investigate the motor cortex organisation together with the cortico-subcortical connectivity in healthy subjects, as a preliminary study. Cortical maps have been performed by navigated TMS and the motor points have been exported to DTI to study their subcortical connectivity.

The precise knowledge of localization of the primary motor cortex area and its connectivity is the base to be used in later studies of cortical and subcortical re-organisation in stroke patients.

This re-organisation is due to the neuroplascity and can be influenced by the neuromodulation effects of the non-invasive cerebral stimulation therapy by TMS.

Resum (100 paraules):

L'objectiu d'aquest estudi es investigar l'organització cortical junt amb la connectivitat còrtico-subcortical en subjectes sans, com a estudi preliminar. Els mapes corticals s'han fet per TMS navegada, i els punts motors obtinguts s'han exportant per estudi tractogràfic i anàlisi de las seves connexions.

El coneixement precís de la localització de l'àrea cortical motora primària i les seves connexions es la base per ser utilitzada en estudis posteriors de la reorganització cortical i sub-cortical en pacients amb infart cerebral.

Aquesta reorganització es deguda a la neuroplasticitat i pot ser influenciada per els efectes neuromoduladors de la estimulació cerebral no invasiva.

CORTICAL MAPPING OF THE NEURONAL CIRCUITS MODULATING THE MUSCLE TONE. INTRODUCTION TO THE ELECTROPHYSIOLOGICAL TREATMENT OF THE SPASTIC HAND.

Autor: Isabel Asunción Serrano Tendero

Directors: Dr. Josep María Espadaler Gamissans. Dra. Núria Raguer Sanz

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3.1. To **assess normal primary motor areas (M1)** in five **normal** subjects and their **connectivity** by means of three techniques: MR, nTMS and DTI.

3.2. To find the **excitability threshold** and the **stimulation's coordinates** for the APB point.

3.3. **"Functional assessment prior to neuromodulatory treatment" protocol** oriented to the neuro-rehabilitation of patients with **spastic hand after stroke**.

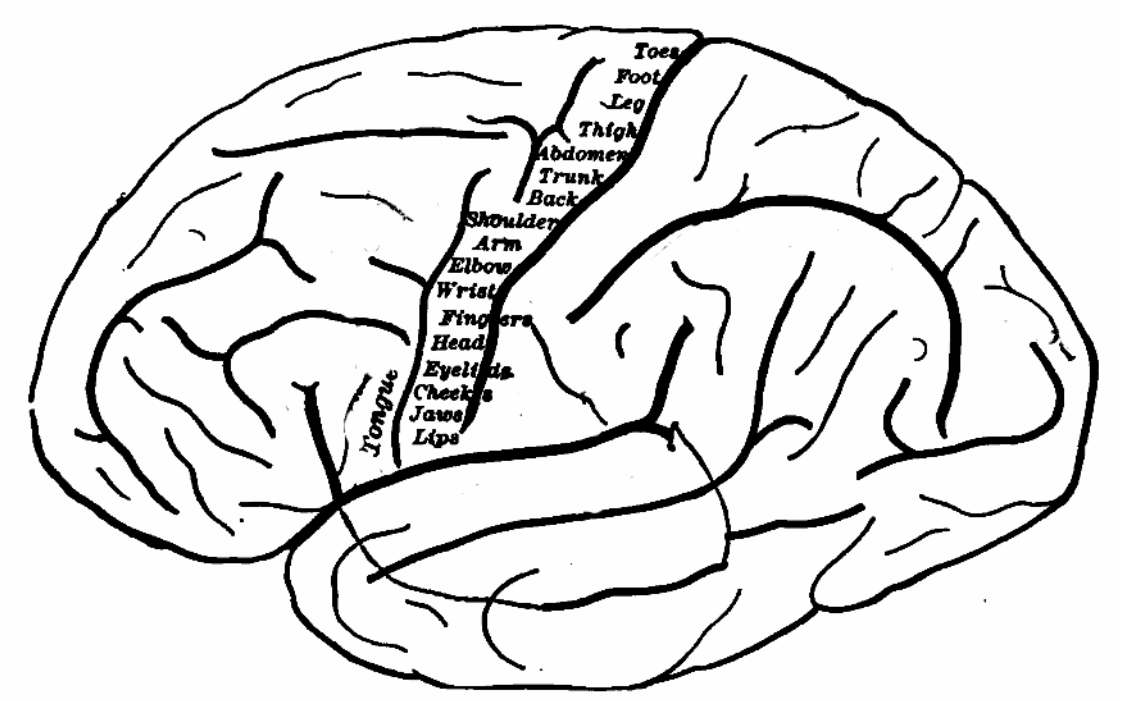
CORTICAL MAPPING OF THE NEURONAL CIRCUITS MODULATING THE MUSCLE TONE. INTRODUCTION TO THE ELECTROPHYSIOLOGICAL TREATMENT OF THE SPASTIC HAND.

2. INTRODUCTION

2.1. **ANATOMICAL AND PHYSIOLOGICAL BASIS OF THE DESCENDING MOTOR PATHWAYS** 1-3, 18

2.1.1. MOTOR CORTEX

Primary motor cortex labeled as somatomotor cortex.
Brodmann area 4 of human brain.



Topography of the primary motor cortex, on an outline drawing of the human brain. Different body parts are represented by distinct areas, lined up along a fold called the central sulcus.
Date original published 1920, modification date 2008. Source: This file is modified from a scan of p 315 of the book "Anatomy of the Nervous System", by Stephen Walter Ranson, WB Saunders, 1920.

The primary motor cortex (or M1) is a brain region that in humans is located in the posterior portion of the frontal lobe. It works in association with pre-motor areas to plan and execute movements. M1 contains large neurons known as Betz cells which send long axons down the spinal cord to synapse onto alpha motor neurons which connect to the muscles. Pre-motor areas are involved in planning actions (in concert with the basal ganglia) and refining movements based upon sensory input (this requires the cerebellum).

Location

The human primary motor cortex is located in the dorsal part of the precentral gyrus and the anterior bank of the central sulcus. The precentral gyrus is in front of the postcentral gyrus from which it is separated by the central sulcus. Its anterior border is the precentral sulcus, while inferiorly it borders to the lateral fissure (Sylvian fissure). Medially, it is contiguous with the paracentral lobule.

Layers

The internal pyramidal layer (layer V) of the precentral cortex contains giant (70-100 micrometers) pyramidal neurons (a.k.a. Betz cells), which send long axons to the contralateral motor nuclei of the cranial nerves and to the lower motor neurons in the ventral horn of the spinal cord. These axons form the corticospinal tract. The Betz cells' along with their long axons are referred to as the upper motor neuron (UMN).

"Homunculus" or "Little Man"

There is a broadly somatotopic representation of the different body parts in the primary motor cortex in an arrangement called a motor homunculus (Latin: little man). The leg area is located close to the midline, and the head and face area located laterally on the convex side of the cerebral hemisphere (motor homunculus). The arm and hand motor area is the largest, and occupies the part of precentral gyrus, between the leg and face area. In humans, the lateral area of the primary motor cortex is arranged from top to bottom in areas that correspond to the buttocks, torso, shoulder, elbow, wrist, fingers, thumb, eyelids, lips and jaw. Interior sections of the motor area folding into the medial longitudinal fissure correspond with the legs.

These areas are not proportional to their size in the body with the lips, face parts and hands enjoying particularly large areas. Following amputation or paralysis, motor areas can shift to adopt new parts of the body.

Two representational areas

In primates, the primary motor cortex is unusual in having in its anterior and posterior areas two representations of the digits and wrist. The posterior areas can be activated by attention without any sensory feedback and has been suggested to be important for initiation of movements, while the anterior areas is dependent on sensory feedback. It can also be activated by

imaginary finger movements and listening to speech done without actual movements. This anterior representation area has been suggested to be important executing movements involving complex sensorimotor interactions.

Pathway

As the motor axons travel down through the cerebral white matter, they move closer together and form part of the posterior limb of the internal capsule.

They continue down into the brainstem, where some of them, after crossing over to the contralateral side, distribute to the cranial nerve motor nuclei. (Note: a few motor fibers synapse with lower motor neurons on the same side of the brainstem).

After crossing over to the contralateral side in the medulla oblongata (pyramidal decussation), the axons travel down the spinal cord as the lateral corticospinal tract.

Fibers that do not cross over in the brainstem travel down the separate ventral corticospinal tract and most of them cross over to the contralateral side in the spinal cord, shortly before reaching the lower motor neurons.

Blood supply

Branches of the middle cerebral artery provide most of the arterial blood supply for the primary motor cortex.
The medial aspect (leg areas) is supplied by branches of the anterior cerebral artery.

Pathology

Lesions of the precentral gyrus result in paralysis of the contralateral side of the body (facial palsy, arm-/leg monoparesis, hemiparesis) - see upper motor neuron.

Penfield's concept

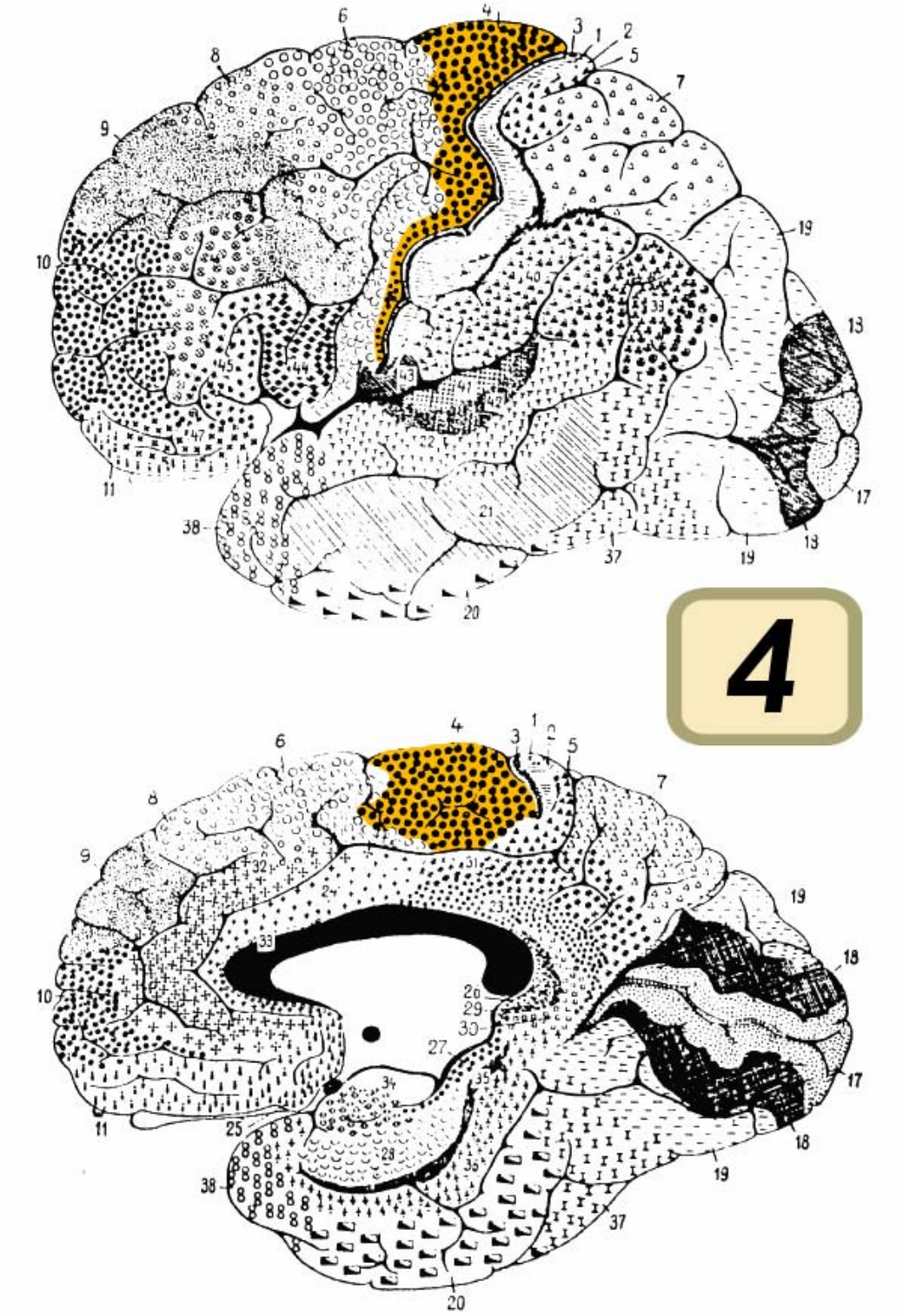
As described, Brodmann area 4 comprises the primary motor cortex of the human brain. It is located in the posterior portion of the frontal lobe.

Brodmann area 4 is about the same as the precentral gyrus. The borders of this area are: the precentral sulcus in front (anteriorly), the medial longitudinal fissure at the top (medially), the central sulcus in back (posteriorly), and the lateral sulcus along the bottom (laterally).

This area of cortex, as shown by Wilder Penfield and others, has the pattern of a homunculus. That is, the legs and trunk fold over the midline; the arms and hands are along the middle of the area shown here; and the face is near the bottom of the figure. Because Brodmann area 4 is in the same general location as primary motor cortex, the homunculus here is called the motor homunculus.

The term area 4 of Brodmann-1909 refers to a cytoarchitecturally defined portion of the frontal lobe of the guenon. It is located predominantly in the precentral gyrus. Brodmann-1909 regarded it as topographically and cytoarchitecturally homologous to the human gigantopyramidal area 4 and noted that it occupies a much greater fraction of the frontal lobe in the monkey than in the human. Distinctive features (Brodmann-1905): the cortex is unusually thick; the layers are not distinct; the cells are relatively sparsely distributed; giant pyramidal (Betz) cells are present in the internal pyramidal layer (V); lack of an internal granular layer (IV) such that the boundary between the external pyramidal layer (III) and the internal pyramidal layer (V) is indistinct; lack of a distinct external granular layer (II); a gradual transition from the multiform layer (VI) to the subcortical white matter.

Genon (n.): Any of various chiefly arboreal African monkeys, primarily of the genus Cercopithecus, having long hind legs and a long tail.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2.1.2. MOTOR PATHWAYS

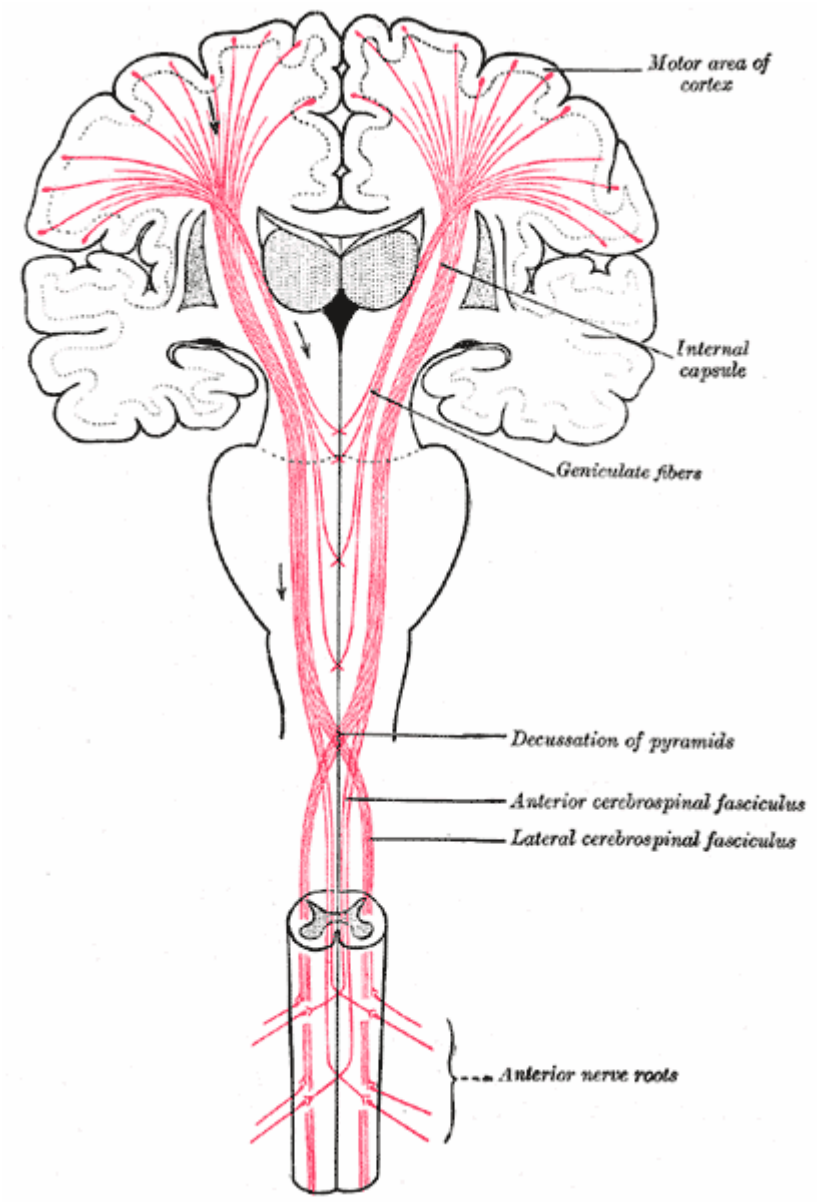
UPPER MOTOR NEURON

Upper motor neurons are motor neurons that originate in the motor region of the cerebral cortex or the brain stem and carry motor information down to the final common pathway, that is, any motor neurons that are not directly responsible for stimulating the target muscle. The main effector neurons for voluntary movement lie within layer V of the primary motor cortex and are called Betz cells. The cell bodies of these neurons are some of the largest in the brain, approaching nearly 100μm in diameter. 5

These neurons connect the brain to the appropriate level in the spinal cord, from which point nerve signals continue to the muscles by means of the lower motor neurons. The neurotransmitter glutamate transmits the nerve impulses from upper to lower motor neurons where it is detected by glutamatergic receptors.

Lesions

Upper motor neuron lesions are indicated by spasticity, muscle weakness, exaggerated reflexes, clonus, and an out toeing (flaring) of toes and extensor plantar response known as the Babinski sign.


Motor area of cortex
Internal capsule
Geniculate fibers
Decussation of pyramids
Anterior cerebrospinal fasciculus
Lateral cerebrospinal fasciculus
Anterior nerve roots

Pathways

Upper motor neurons travel in several pathways through the CNS:

Tract	Pathway	Function
Corticospinal tract	From the motor cortex to lower motor neurons in the ventral horn of the spinal cord	The major function of this pathway is fine voluntary motor control of the limbs. The pathway also controls voluntary body posture adjustments.
Corticobulbar tract	From the motor cortex to several nuclei in the pons and medulla oblongata	Involved in control of facial and jaw musculature, swallowing and tongue movements.
Tectospinal tract / Colliculospinal tract	From the superior colliculus to lower motor neurons	Involved in involuntary adjustment of head position in response to visual information.
Rubrospinal tract	From red nucleus to lower motor neurons	Involved in involuntary adjustment of arm position in response to balance information; support of the body.
Vestibulospinal tract	From vestibular nuclei, which processes stimuli from semicircular canals	It is responsible for adjusting posture to maintain balance.
Reticulospinal tract	From reticular formation	Regulates various involuntary motor activities and assists in balance.

THE DESCENDING MOTOR PATHWAYS: INTRODUCTION

Sherrington called the motor neuron the final common pathway. All the subtle signals converging from several descending tracts as well as afferent input from the periphery are somehow integrated on the motor neuron, which subsequently conducts the appropriate signal out to the muscle. Because so many different pathways converge on the motor neuron, the contribution of any single tract to the final motor act is extremely difficult to determine. 4

Several descending pathways have been shown to effect changes in the activity of motor neurons. The anatomical courses of these pathways have been extensively studied from their origins in various areas of the brain to their synaptic contacts with the motor neurons. The precise physiological roles of these pathways have been studied but the information is limited because of several factors. Principal among them is the fact that most of the work has concerned the motor neurons innervating hind limbs of the cat. Studies on primates have been continuing, but a big problem is the somewhat suspect attempt to wed the neurophysiology of the cat's movement performance to the neuroanatomy of the human's.

Another problem lies in the fact that a common tool for studying the function of nerve pathways is electrical stimulation. While there seems to be little alternative to this procedure, the meaningfulness of artificially induced volleys of impulses is questionable when one considers that tile natural influences on motor neurons are spatially and temporally varied and probably achieve their effects by virtue of a pattern of impulses rather than a repetitive volley. Recent attempts have been made to study the neurophysiology of movement by recording neuromuscular potentials accompanying spontaneous movement. This is certainly a desirable approach but is also limited by the fact that even simple body movements are neurally very complex. Thus attempts to relate the anatomical and physiological events associated with these movements are difficult and hard to interpret.

Nevertheless, much has been learned concerning the role of the nervous system in such activities as walking, running, and the regulation of postural movements. It now appears that there are "pattern generators" or "prewired" groups of neurons within the central nervous system producing a wide variety of basic motor programs. "Command" neurons activate these pattern generators when a particular movement is called for. Here, we will examine some of these pattern generators as well as the role of the brain and its descending pathways in initiating and regulating movement.

UPPER AND LOWER MOTOR NEURONS

Electrophysiological studies have shown that the motor cortex resembles a map showing a distorted image of the body turned upside down and reversed left to right. Some motor pathways to the skeletal musculature of the body arise directly from cells within the cerebral motor cortex, while others arise from subcortical areas of the brain and brainstem.

Neurons that originate in the cerebral motor cortex. the cerebellum, or various brainstem nuclei that send axon, into the brain stem and spinal cord to activate cranial or spinal motor neurons are called upper motor neurons, Those cranial and spinal motor neurons which actually

innervate muscles are the lower motor neurons. The latter include the alpha and gamma motor neurons of spinal nerves. Upper motor neurons are found entirely within the CNS, while the fibers of lower motor neurons are part of the PNS.

Upper motor neurons are clustered together to form descending tracts in the brain and spinal cord. Such tracts are commonly named according to their site of origin and the region of their distribution. An example is the corticospinal tract, which originates in the cerebral cortex and is distributed to the spinal cord. Another is the rubrospinal tract. which originates in the red nucleus (nucleus ruber) of the midbrain and is distributed to the spinal cord. The lower motor neurons of spinal nerves are somatotopically organized in the anterior horn of the spinal cord gray matter. In general, those innervating the distal limb musculature are located in the lateral aspects of the anterior horn, while those innervating proximal limb muscles are found in the intermediate region, The most medial group of motor neurons innervates the musculature of the appendicular and pelvic girdles.

PATTERN GENERATORS AND THE CENTRAL PROGRAM FOR MOVEMENT

Upper motor neurons don't simply stimulate lower motor neurons and produce movement. The highly skilled and coordinated movements of which humans are capable would seem to require a more complex and involved system. While little is known of the highly involved and integrated activity which occurs in the brain's neural circuits during even a simple body movement, it now appears that highly coordinated and very complex systems of interneurons regulate the precise timing and sequencing of muscle activity which is observed in such movements. There is also increasing evidence that groups of interneurons cause specific patterns of impulses to fire in the lower motor neurons associated with a given coordinated movement. The central theory is that these interneurons form pattern generators within the CNS which produce the basic motor program. At the spinal cord level the pattern generator is composed of a set of local control centers located in the gray matter. There are neurons within these centers which coordinate muscular synergies and generate timing signals. Command neurons activate these pattern generators when a particular coordinated movement is required. The result of such activation is that the lower motor neurons fire in a properly sequenced and timed pattern to produce a coordinated movement.

Identification of specific command neurons for a particular human movement is a difficult process and a speculative one at best. It may be that upper motor neurons from the brain and brainstem function in this respect for voluntary movements and reflex postural adjustments. In some invertebrates, however, the activation of a single interneuron is sufficient to excite an entire coordinated muscle behavior. For example, stimulation of the giant axon of the crayfish produces a coordinated tail flip which propels it away from the stimulus. Similarly, stimulation of

the Maunther cells of teleost fishes produces a tail flip propelling the fish away from the stimulus. These cells are part of the reticulospinal tract neurons in the fish and apparently serve as command neurons that activate the pattern generator which carries the motor program for tail flip.

It is presumptuous to assume that all movements proceed in accordance with pattern generators and prewired motor programs. Nevertheless, it may be that certain basic coordinated movements of the limbs and trunk may proceed in a very general way under the influence of such programs, while the initiation and fine tuning of the movement requires input from descending and sensory pathways. The upper motor neurons of some descending motor pathways no doubt serve as command neurons for certain movement patterns. Variations in the discharge patterns of these neurons determine the variability of the programmed response. There is evidence that a change in the firing frequency of certain command neurons leads to a change in the intensity of the response. If the coordinated movement involves a postural system, altering the firing rate alters the magnitude of postural adjustment. If a locomotor system is involved, the frequency of the movement cycle will vary with changes in the frequency of command neuron firing. Other command neurons produce the same motor pattern regardless of their firing rates. Their role seems to be simply turning the program on and off. Still others may regulate the magnitude of the programmed response. Most of the vertebrate work involving motor programs has dealt with locomotor activity in the cat. Perhaps we can get a feel for the intricate features of such programs by an examination of this work.

DESCENDING MOTOR PATHWAYS: ANATOMOPHYSIOLOGY

Descending motor pathways are defined as those which initiate or modify performance and which originate in the brain. While several tracts have been anatomically identified and physiologically studied, it is still speculative to assume that we fully understand what contribution any given tract makes to a spontaneous movement. To electrically stimulate a descending tract, observe a movement response, and then assume that the observed response represents the function of the tract is surely dangerous. The tract may have other, perhaps more important, functions to perform which are not observed in the movement. Or possibly the participation of the tract in a spontaneous movement of the same kind may be of considerably different magnitude. Nevertheless, stimulation of descending motor pathways does produce activity in groups of flexor and extensor muscles. Examination of these effects may give us valuable clues as to the role of these pathways in normal spontaneous movement.

The Corticospinal Tracts

The corticospinal tracts are often called the pyramidal tracts because they form pyramid-shaped enlargements on the anterior surface of the medulla. They are primarily concerned with controlling skilled movements of the distal extremities and, in particular, facilitation of those alpha and gamma motor neurons which innervate the distal flexor muscles (Fig-3). There is also evidence that they inhibit distal extensor muscles. The upper motor neurons of these tracts originate in the precentral gyrus of the cerebral cortex. From here their fibers pass without synapsing all the way to their terminal destinations in the spinal cord gray matter. After leaving the cortex, the fibers descend through the posterior limb of the internal capsule, through the middle portion of the cerebral peduncles to the basilar portion of the pons, and on into the medulla oblongata where they form the medullary pyramids. Most of the fibers (85 percent) cross over (decussate) to the opposite side in the pyramidal decussation, where they continue to descend in the lateral funiculus of the spinal cord as the lateral corticospinal tract (LCST). The tract descends all the way to sacral levels with fibers continually leaving it in order to synapse on interneurons in laminae IV, V, VI, VII, and VIII. Some even synapse directly on alpha and gamma motor neurons in lamina IX (Fig-3). Those corticospinal fibers which do not decussate in the medulla continue descending on the same (ipsilateral) side of the cord and become the anterior corticospinal tract (ACST). This tract does not extend below the midthoracic level. Fibers leave the tract at various levels to cross over in the anterior white commissure to synapse on interneurons in lamina VIII.

Corticospinal Stimulation of Motor Neurons

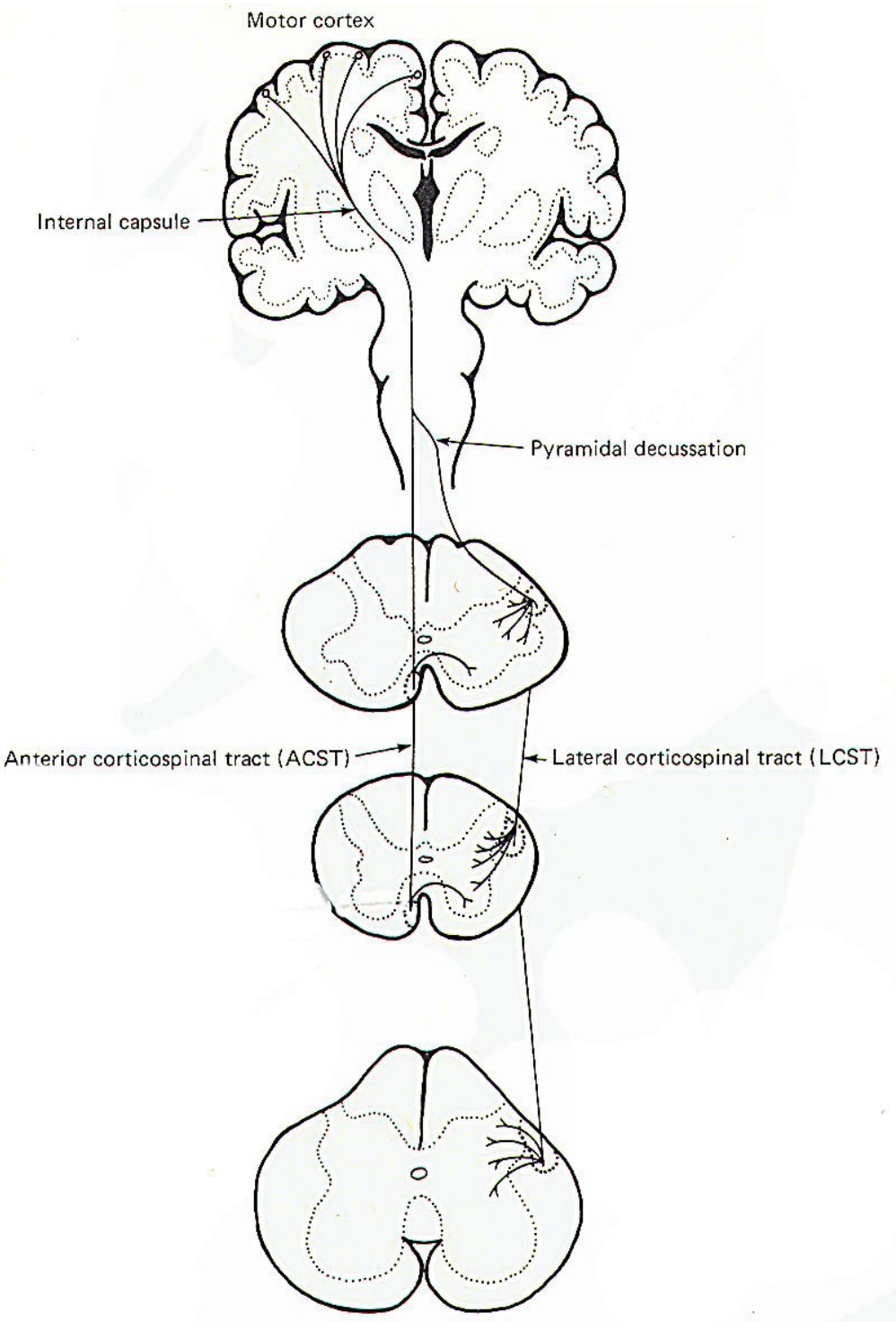
Electrical stimulation of the cortical areas from which the corticospinal tracts arise excites many more motor neurons to distal forelimb muscles in the baboon than it does motor neurons to proximal muscles. In fact, proximal limb muscles are frequently not activated at all by cortical stimulation. The more dextrous the distal muscles are, the greater effect the corticospinal tracts seem to have on their activity. Following cortical stimulation, larger EPSPs are seen in the motor neurons to skilled distal flexors than are observed in proximal muscle motor neurons.

Destruction of the Corticospinal Tracts

Studies have shown that following complete bilateral pyramidal tract section in monkeys, they are still able to perform a wide range of activities using the body and limbs and are able to walk and climb in a normal manner. Their principal and most dramatic shortcoming is in their ability to perform skillful manipulative tasks with the fingers and hands. In similar tests of manipulative skills in monkeys with unilateral pyramidal tract sections, it was found that skilled movements in

the affected hand were dramatically reduced relative to the normal hand. However, the animals were still able to move the whole limb around the joints of the pectoral and pelvic girdles with no trouble and they showed no difficulty in performing combined movements of the limbs and the body. Thus it seems probable that the corticospinal system is directed effectively to facilitating movements requiring skill and dexterity of the distal musculature.

Fig-3



The Corticobulbar Tract

This tract is composed of fibers originating in the precentral gyrus of the lower quarter of the motor cortex. The descending fibers leave the motor cortex and pass through the posterior limb of the internal capsule just anterior and medial to the corticospinal tract fibers. From here they continue on through the cerebral peduncles just medial to the corticospinal tract fibers to terminate in the motor nuclei of cranial nerves III and IV in the midbrain; V, VI. and VII in the pons; and IX, X, XI, and XII in the medulla. The corticobulbar fibers from one side of the brain project to the motor nuclei on both sides of the brainstem (Fig-4).

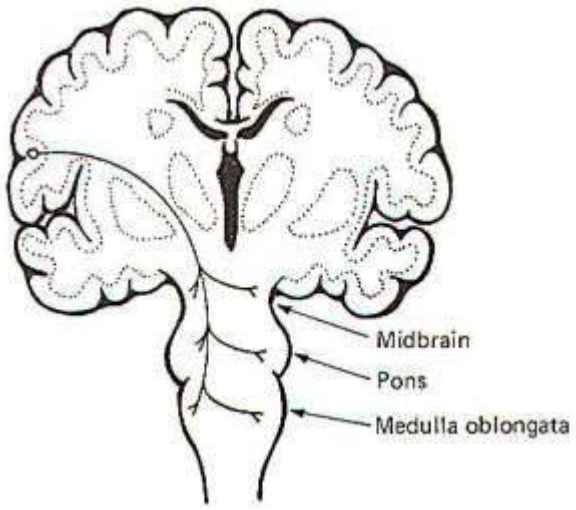


Fig-4

The Rubrospinal Tract

The fibers of this tract originate in the red nucleus (nucleus ruber) of the midbrain. They cross over near their point of origin and descend contralaterally in the lateral funiculus of the cord adjacent to the lateral corticospinal tract (Fig-5). Before leaving the brainstem, some fibers of the tract enter the reticular formation. As the tract descends through the spinal cord, fibers leave it and synapse on interneurons in laminae V. VI. and VII. Cells in the posterior portion of the red nucleus give rise to axons influencing motor neurons of the neck and upper limbs. while fibers from the anterior portion descend to lumbar levels where they influence lower limb muscles.

Ablation studies in which the tracts are experimentally cut have shown that the corticospinal and rubrospinal tracts have somewhat similar effects on the motor neurons. When the rubrospinal tracts of monkeys were damaged on top of earlier pyramidal tract sections. the loss of skilled control of the distal musculature became even more severe and yet there was little or no loss of control in the proximal muscles. Lawrence and Kuypers concluded that a laterally placed group of descending fibers, which they called the lateral system (corticospinal, rubrospinal, and possibly other tracts), is primarily concerned with delivering cortical control to the distal limb

musculature. Independent electrical stimulation of the intact rubrospinal tract facilitates flexor and inhibits extensor alpha and gamma motor neurons to the distal muscles.

Considering that the red nucleus receives input from the same area of the cerebral cortex as the corticospinal tracts, the similarity of their actions may not be too surprising. The red nucleus also receives input from the deep cerebellar nuclei and possibly the basal nuclei as well. Nevertheless, as previously pointed out, the reader should bear in mind that ablation and electrical stimulation studies give us an incomplete picture of the function of a descending, or for that matter any, tract in the central nervous system. Further, whatever information is obtained relates to the unnatural experimental situation and not necessarily to normal function in the intact spontaneous animal.

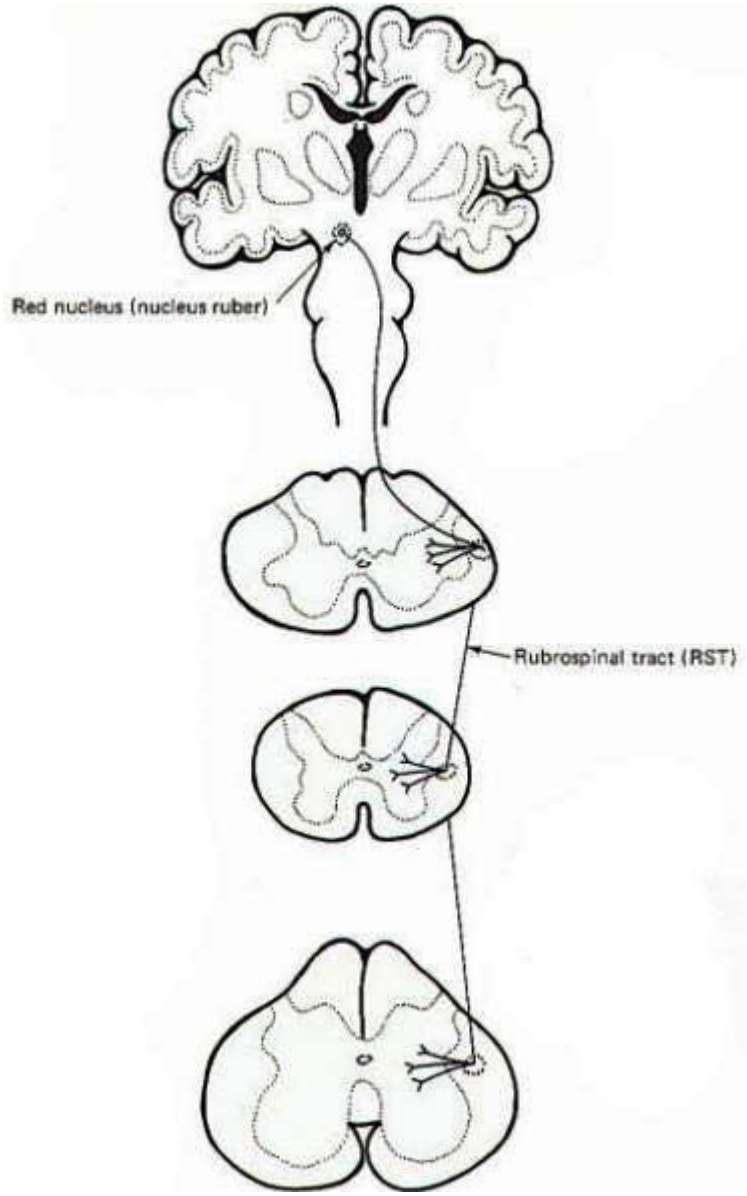


Fig-5

The Reticulospinal Tracts

The reticular formation is an indistinct group of cell bodies clustered in the core of the brainstem. They don't form distinct nuclear groups like those found elsewhere in the CNS. The reticulospinal tracts represent groups of fibers which originate in the reticular formation and descend into the spinal cord (Fig-6). Those fibers which originate in the medullary reticular formation show both a crossed and an uncrossed component which descend in the lateral funiculus of the spinal cord as the lateral reticulospinal tract (LRST). The descending fibers in this tract periodically leave and synapse principally on interneurons in lamina VII. Those fibers arising chiefly in the pontine reticular formation represent the medial reticulospinal tract (MRST). Fibers in this tract descend ipsilaterally in the anterior funiculus to all levels of the cord, periodically leaving to synapse in laminae VII and VIII.

The reticulospinal tracts exert both somatic and autonomic control. The somatic control involves both facilitation and inhibition of alpha and gamma motor neurons at all cord levels. Some cells in the medulla and medullary reticular formation (the inhibitory center of Magoun and Rhines) exert a strong inhibitory effect through the reticulospinal tracts on all types of alpha and gamma motor neurons. On the other hand, cells in the upper medullary and pontine reticular formation exert a strong facilitatory effect on alpha and gamma motor neurons. Accordingly, the idea of an "inhibitory" and "excitatory" center in the brain stem has been postulated. It may be that many of the modulating effects of the cerebral cortex and the cerebellum are mediated through these "centers" since both feed into the reticular formation.

The reticulospinal tracts influence autonomic effects through their influence on preganglionic neurons in the intermediolateral horn of the spinal cord gray matter. Most of these fibers are derived from the lateral reticulospinal tract with a smaller number coming from the medial reticulospinal tract. It is undoubtedly simplistic to assume that the reticulospinal tracts are the only descending tracts regulating autonomic control. Some fibers of the corticospinal and vestibulospinal tracts have also been implicated.

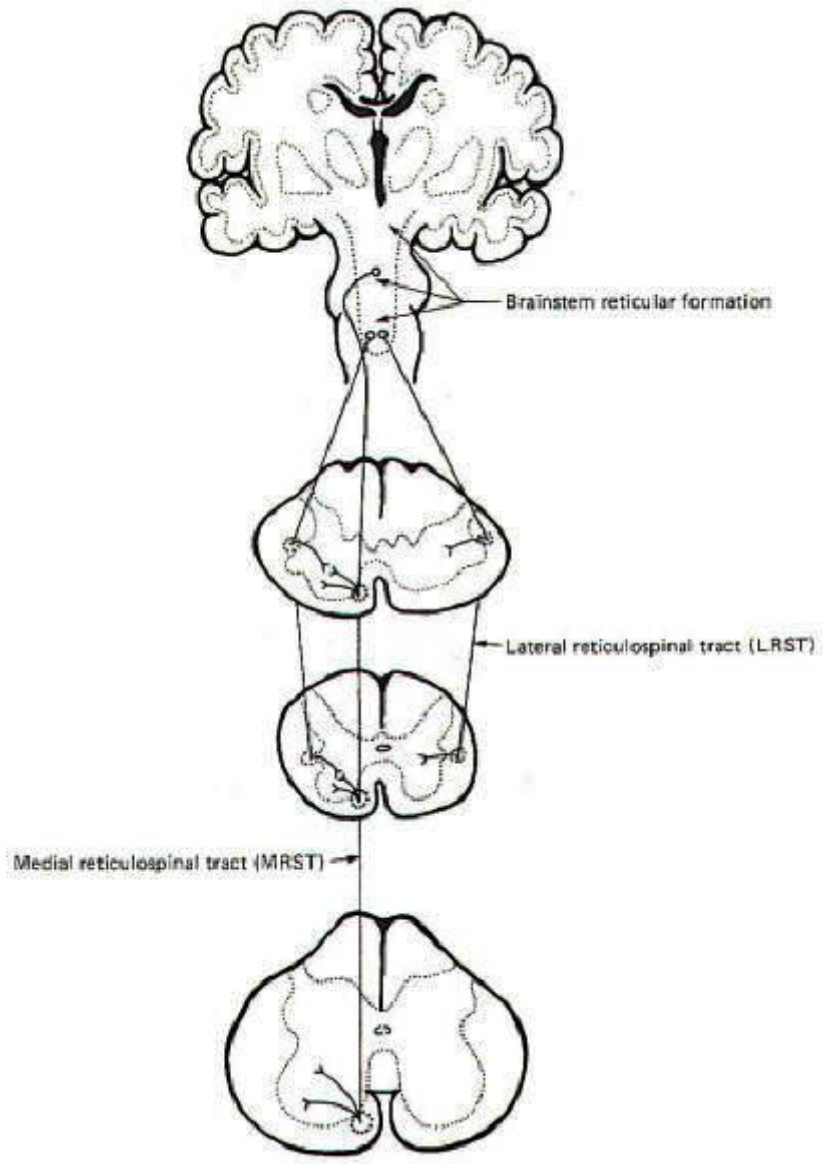


Fig-6

The Vestibulospinal Tracts

The vestibulospinal tracts originate in the vestibular nuclei of the brainstem. Those fibers originating in the lateral vestibular (Deiter's) nucleus descend ipsilaterally in the anterior funiculus and form the lateral vestibulospinal tract (LVST) (Fig-7). The fibers of this tract terminate in laminae VII, VIII, and IX at all levels of the cord. The vestibulospinal tracts facilitate extensor and inhibit flexor alpha and gamma motor neurons. Input from the vestibular apparatus to the vestibular nuclei via cranial nerve VIII presupposes an antigravity or postural role for the lateral vestibulospinal tract. Activity in this tract is also influenced by input to the vestibular nuclei from the cerebellum. Arising from the medial vestibular nucleus are the fibers of the medial vestibulospinal tract (MVST). While there is a small crossed component, most of its

fibers descend ipsilaterally only as far as the midthoracic cord, where they too synapse in laminae VII, VIII, and IX. The function of this tract may be similar to that of the lateral vestibulospinal tract, but its precise role is largely unknown.

Interstitiospinal Tract

The descending fibers of this tract arise in the interstitial nucleus of Cajal (an accessory nucleus of III) in the tegmentum of the midbrain. They descend ipsilaterally only to the cervical level of the cord, where they synapse in laminae VI, VII, and VIII. The tract may play a role in reflex movements of the head and neck in response to visual stimuli, but its function is largely unknown and probably more complex.

Tectospinal Tract

The descending fibers of this tract arise chiefly in the tectum of the superior colliculus. Some of them decussate and others don't. In either case they only descend to cervical levels where they synapse in laminae VI, VII, and VIII. The tract has been implicated in mediating visual reflexes but, again, its function is largely unknown.

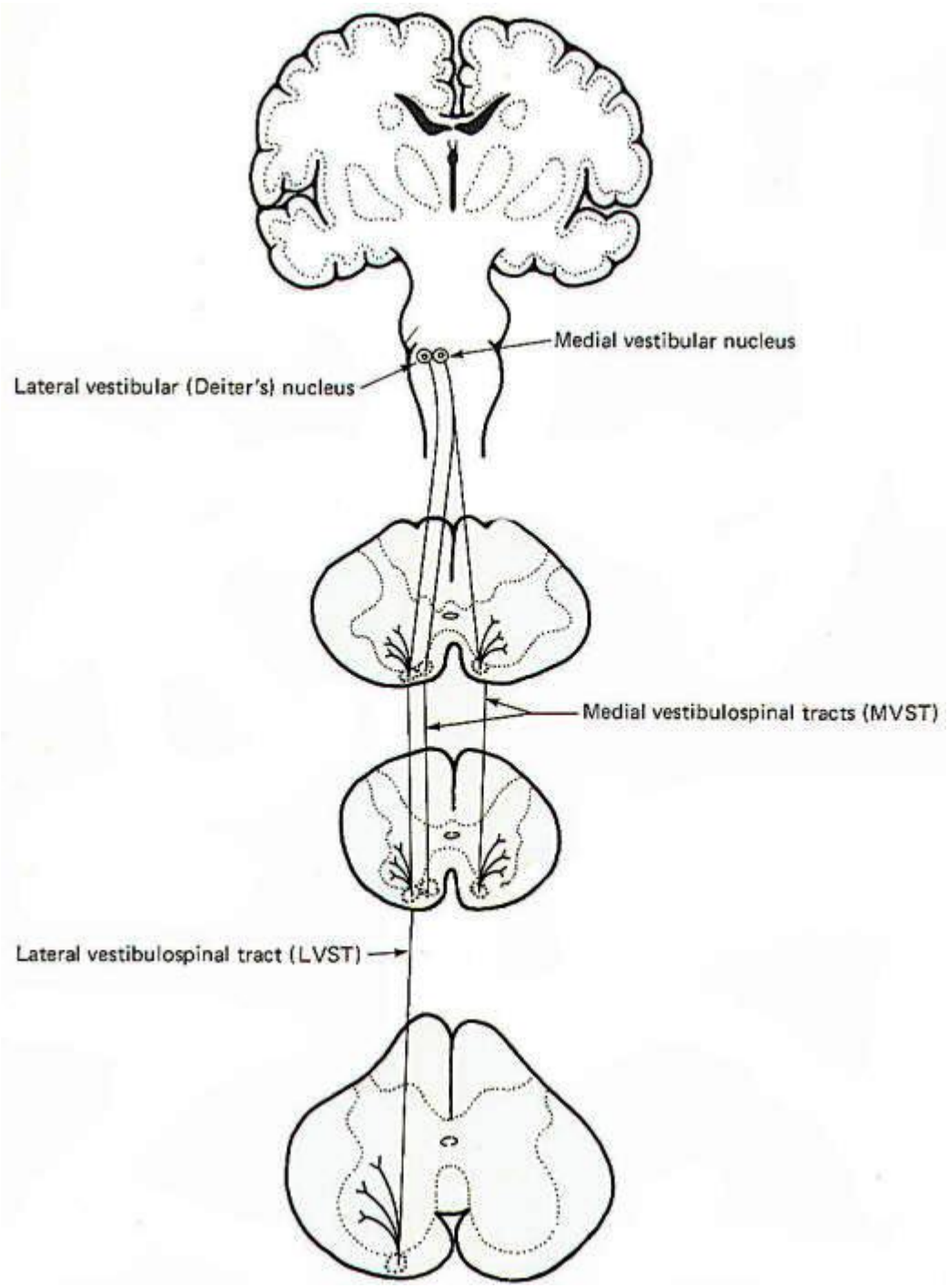


Fig-7

Our brain is considered a mystery and to understand it, one would need to be a neurosurgeon, neuroanatomist and neurophysiologist. 4

A concrete approach: APB muscle (Abductor Pollicis Brevis)

As in the upcoming sections we are going to focus in APB region, a concrete point of the Primary Motor Cortex (M1), hereby is exposed its peripheral correlate:

- APB innervation is via the median nerve, medial cord, lower trunk, and roots C8, T1.
- Origin: The muscle originates in the palmar retinaculum and the tubercle of the scaphoid and trapezium.
- Insertion: The muscle is inserted at the base of the proximal phalanx of the thumb.
- Activation Maneuver: Abduction of the thumb (movement of the thumb out of the plane of the palm) activates the muscle.

Median Nerve

The Median Nerve arises from the lateral and medial cords of the brachial plexus as a mixed nerve derived from the C6 and T1 roots. 19 It supplies most forearm flexors and the muscles of the thenar eminence. It also subserves sensation to the skin over the lateral aspect of the palm and the dorsal surfaces of the terminal phalanges, along with the volar surfaces of the thumb, the index and middle fingers, and half of the ring finger. The sensory fibers of the index and middle fingers enter the C7 root through the lateral cord and middle trunk, whereas the skin of the thumb receives fibers mainly from C6, with some contribution from the C7 root, through the lateral cord and upper or middle trunk. The median nerve innervates no muscles in the upper arm. It enters the forearm between the two heads of the pronator teres, which it supplies along with the flexor carpi radialis, palmaris longus, and flexor digitorum superficialis. A pure muscle branch, called the anteriior interosseous nerve, innervates the flexor pollicis longus, pronator quadratus, and flexor digitorum profundus I and II. The main median nerve descends the forearm and, after giving off the palmar sensory branch, which innervate the skin over the thenar eminence, passes through the carpal tunnel between the wrist and palm. It supplies lumbricals I and II after giving rise to the recurrent thenar nerve at the distal edge of the carpal ligaments. This muscle branch to the thenar eminence innervates the abductor pollicids brevis, the lateral half of the flexor pollicis brevis, and the opponens pollicis. 19

2.2. SPASTICITY

2.2.1. PHYSIOPATHOLOGY OF SPASTICITY

Spasticity, flexion and extension spasms occur after lesions of motor descending pathways. Three different mechanisms can explain these disorders of tone: pure muscular alterations, segmental synaptic sprouting and liberation of spinal reflex activity.
This last mechanism, which is also the most classically described has been studied long ago. Spasticity is therefore described as a motor disturbance characterised by an increment of the tonic stretching reflexes –muscular tone-, depending on velocity, with exageration of the tendinous reflexes, which obbey to a hyperexcitability of the stretching reflex and may accompany cerebral and medullary lesions.

Among the most frequent aetiologies stand out the cerebral lesions produced by anoxya, toxics, metabolic encephalopaties, tumours, abscesses, stroke, arteriovenous malformations and traumatisms; or also medullary lesions, as inflammatory or demyelinizant diseases, tumours, traumatisms and degenerative diseases.

Amongst all pathophysiological hypotheses which can explain spasticity we find:

- Hyperexcitability of

    a) Alpha motoneuron –increment of the dynamic excitability of motor fuse-,

    b) Gamma motoneuron, or

- Reduction of presynaptic inhibition. -the diminishment of the descending inhibitory influences (reticulospinal)

The **reduction of presynaptic inhibition** is the only one to have been clearly demonstrated.
20-22

2.2.1. SPASTICITY PATTERNS IN UPPER EXTREMITIES

The most habitual acquired lesion in adults uses to be of vascular cause/etiology (VCA) or traumatic (CET).

The most commont pattern of the patient who has suffered a VCA/stroke and presents an important increase or the tone is the one of « Decortication-Triple Flexion » (indicates damage to the corticospinal tract), which consists in :

- Adduction of the upper extremity at shoulder level with the extremity attached to the body.
- Elbow flexion in severe degree, more than 90º.
- Pronation of forearm and wrist, although some cases may present supination attitude.
- Palmar flexion at the wrist ≥90º.
- Flexion of metacarpofalageal articulation (MCF) of approximately 90º.
- Flexion of the interfalangical (IF) proximal and distal articulations ≥45º, which determines « claw hand ».
- Flexion of the MCF and IF articulations with the thumb included in the palm.

In sum up, the most common pattern is the shoulder's adduction, with elbow flexion, wrist flexion and claw hand. Some cases present, furthermore, shoulder retropulsion.

Patients with acquired brain damage of traumatic origin can present also decortication pattern (flexion pattern) or descerebration (extension pattern with important component of internal rotation). In both cases is produced, also, palmar flexion, wrist pronation and flexion of the MCF articulation.

Pattern repercussion

The triple-flexor pattern of the upper limb interpheres in its useful active movility, and can provoke pain and articular limitation. Its main characteristics are :

a) It interpheres fundamentally in manipulation and prension, sujection of objects with the upper limb.

b) It difficults getting dressed in the superior part of the body.

c) It difficults hygiene, fundamentally of upper limb (palm and axilla).

d) It can even repercute in the trunk equilibrium in sitting posture.

e) The flexor pattern, associated or not to the upper limb's retropulsion, difficults the troncular equilibrium both while sitting and walking.

Exploration and functional assessment

The evaluation of the upper limb must be done in a global way, as the brain lesion influences the whole upper limb overall, not only in each articulation or muscle group. It will be considered :

- Postural pattern
- Motor control : Brunnstrom's scale.
- Muscle tone assessment : Ashworth's modified scale.
- Articular balance' assessment : shoulder, elbow, wrist and fingers.
- Assessment of claw and pinch force: use as evaluation instruments a cubes' or coins' tower.
- Presence or not of pain.
- Assessment of the daily life activities.

2.3. TRANSCRANIAL MAGNETIC STIMULATION: BACKGROUND AND PHYSICAL BASIS [6-8]

Transcranial magnetic stimulation (TMS) is a noninvasive method to excite the elementary unit of the nervous system; neurons in the brain: weak electric currents are induced in the tissue by rapidly changing magnetic fields (electromagnetic induction). This way, brain activity can be triggered with minimal discomfort, and the functionality of the circuitry and connectivity of the brain can be studied.

Repetitive transcranial magnetic stimulation is known as rTMS and can produce longer lasting changes. Numerous small-scale pilot studies have shown it could be a treatment tool for various neurological conditions (e.g. migraine, stroke, Parkinson's disease, dystonia, tinnitus) and psychiatric conditions (e.g. major depression, auditory hallucinations).

Background

The principle of inductive brain stimulation with eddy currents has been noted since the 19th century. The first successful TMS study was performed in 1985 by Anthony Barker et al. in Sheffield, England. Its earliest application was in the demonstration of conduction of nerve impulses from the motor cortex to the spinal cord. This had been done with transcranial electrical stimulation a few years earlier, but use of this technique was limited by severe discomfort. By stimulating different points of the cerebral cortex and recording responses, e.g., from muscles, one may obtain maps of functional brain areas. By measuring functional imaging (e.g. MRI) or EEG, information may be obtained about the cortex (its reaction to TMS) and about area-to-area connections.

First publications about TMS

Pioneers in the use of TMS in neuroscience research include Anthony Barker, Vahe Amassian, John Rothwell of the Institute of Neurology, Queen Square, London, Mark S. George, MD of the Medical University of South Carolina, David H. Avery, MD of the University of Washington at Seattle, Charles M. Epstein of Emory University, Drs. Mark Hallett, Leonardo G. Cohen, and Eric Wassermann of the National Institutes of Health, and Alvaro Pascual-Leone of Harvard Medical School. Currently, thousands of TMS stimulators are in use. More than 3000 scientific publications have been published describing scientific, diagnostic, and therapeutic trials.

Effects on the brain

The exact details of how TMS functions are still being explored. The effects of TMS can be divided into two types depending on the mode of stimulation:

a) Single or paired pulse TMS

The pulse(s) causes neurons in the neocortex under the site of stimulation to depolarise and discharge an action potential. If used in the primary motor cortex, it produces muscle activity referred to as a motor-evoked potential (MEP) which can be recorded on electromyography (EMG). If used on the occipital cortex, 'phosphenes' (flashes of light) might be detected by the subject. In most other areas of the cortex, the participant does not consciously experience any effect, but his or her behaviour may be slightly altered (e.g. slower reaction time on a cognitive task), or changes in brain activity may be detected using Positron Emission Tomography or fMRI. Effects resulting from single or paired pulses do not outlast the period of stimulation. A wider review of TMS can be found in The Oxford Handbook of Transcranial Magnetic Stimulation. 23

b) Repetitive TMS (rTMS)

Repetitive TMS produces effects which last longer than the period of stimulation. rTMS can increase or decrease the excitability of corticospinal or corticocortical pathways depending on the intensity of stimulation, coil orientation and frequency of stimulation. The mechanism of these effects is not clear although it is widely believed to reflect changes in synaptic efficacy akin to long-term potentiation (LTP) and long-term depression (LTD). 24

As such, it is important to distinguish TMS from repetitive TMS (rTMS) as they are used in different ways for different purposes.

TMS in Research

One reason TMS is important in cognitive psychology/neuroscience is that it can help demonstrate causality. A non-invasive mapping technique such as fMRI allows researchers to see what regions of the brain are activated when a subject performs a certain task, but this is not proof that those regions are actually used for the task; it merely shows that a region is associated with a task. If activity in the associated region is suppressed (i.e. 'knocked out') with

TMS stimulation and a subject then performs worse on a task, this is much stronger evidence that the region is used in performing the task.

For example: subjects asked to memorize and repeat a stream of numbers would be likely to show activation in the prefrontal cortex (PFC) via fMRI, indicating the association of this brain region in short-term memory. If the researcher then interfered with the PFC via TMS, the subjects' ability to remember numbers might decline, and the researcher would have evidence that the PFC is used for short-term memory, because reducing subjects' PFC capability led to reduced short-term memory.

This **'knock-out' technique** (also known as virtual lesioning) can be done in two ways:

a) Online TMS: where subjects perform the task and at a specific time in the task (usually after less than 200ms), a TMS pulse is given to a particular part of the brain. If this affects task performance it may be deduced that this part of the brain was involved with the task at that particular time point.

b) Offline repetitive TMS: where performance at a task is measured initially and then repetitive TMS is given over a few minutes, and the performance is measured again. This technique has the advantage of not requiring a time line of how the brain processes the task. A variant of this technique is the 'enhancement' technique, where repetitive TMS is delivered to enhance performance. But the latter is even harder to achieve than the 'knock-out' technique.

Transcranial magnetic stimulation is used in research to dissect the physiological mechanisms underlying motor deficits, spontaneous motor recovery, and the beneficial effects of therapeutic interventions. In this field, a lot of parameters related with both corticospinal and corticocortical excitability are studied in order to evaluate the diagnosis and prognosis of stroke patients.

Risks of TMS

Single pulse TMS is regarded as safe although seizures following single pulse TMS stimulation have have been reported in some patients with stroke or other disorders involving the central nervous system. 25 Seizures from single or paired pulse TMS are rare, especially in patients without pre-existing conditions that affect the central nervous system such as epilepsy. rTMS has been reported to cause seizures in normal individuals at certain combinations of stimulation frequency and intensity. Guidelines have since been instituted regarding the maximum safe frequency and intensity combinations of rTMS. 26

Common adverse effects of TMS are:

- Discomfort or pain related to the stimulation of the scalp and associated nerves and muscles on the overlying skin. Discomfort is rarely a problem for single pulse TMS but some people may find rTMS quite uncomfortable.

- Rapid deformation of the TMS coil produces a loud clicking sound which scales with stimulator intensity. The sound has been characterized as deceptively mild sounding and has the potential to affect hearing, given sufficient exposure (particularly relevant for rTMS). Hearing protection may be offered to prevent this.

- rTMS in the presence of EEG electrodes can result in electrode heating and, in severe cases, skin burns. 27

Clinical uses of TMS

The uses of TMS and rTMS can be divided into diagnostic and therapeutic uses.

Diagnosis

TMS is used currently clinically to measure activity and function of specific brain circuits in humans. The most robust and widely-accepted use is in measuring the connection between the primary motor cortex and a muscle (i.e. MEP amplitude, MEP latency, central motor conduction time). This is most useful in stroke, spinal cord injury, multiple sclerosis and motor neuron disease. There are numerous other measures which have been shown to be abnormal in various diseases but few are validated or reproduced and more importantly, no one knows the significance of these measures. The most famous is short-interval intracortical inhibition (SICI) which measures the internal circuitry (intracortical circuits) of the motor cortex described by Kujirai et al. in 1993. 28

Plasticity of the human brain can also be measured now with repetitive TMS (and variants of the technique, e.g. theta-burst stimulation, paired associative stimulation) and it has been suggested that this abnormality of plasticity is the primary abnormality in a number of conditions.

Therapy

A large number of studies with TMS and rTMS have been conducted for a variety of neurological and psychiatric conditions but few have been confirmed and most show very modest effects, if any. Multiple controlled studies support the use of this method in treatment-resistant depression; it has been approved for this indication in Europe, Canada, Australia, and the US.

Some conditions which have been reported to be responsive to TMS-based therapy are:

- Amblyopia
- Amyotrophic lateral sclerosis
- Auditory Hallucinations associated with Schizoaffective Disorders
- Chronic pain
- Dysphasia
- Dystonia
- Epilepsy
- Fibromyalgia
- Hemispatial neglect
- Major depression
- Migraine
- Obsessive-compulsive disorder
- Parkinson’s Disease
- Phantom limb
- Stroke
- Nonfluent aphasia
- Tinnitus

Technical information

TMS is simply the application of the principle of induction to get electrical current across the insulating tissues of the scalp and skull without discomfort. A coil of wire, encased in plastic, is held to the head. When the coil is energized by the rapid discharge of a large capacitor, a rapidly changing current flows in its windings. This produces a magnetic field oriented orthogonally to the plane of the coil. The magnetic field passes unimpeded through the skin and skull, inducing an oppositely directed current in the brain that flows tangentially with respect to skull. The current induced in the structure of the brain activates nearby nerve cells in much the same way as currents applied directly to the cortical surface. The path of this current is complex to model because the brain is a non-uniform conductor with an irregular shape. These magnetic fields do not directly affect the whole brain; they only reach about 2-3 centimeters into the brain directly beneath the treatment coil. With stereotactic MRI-based control, the precision of targeting TMS can be approximated to a few millimeters 11.

Precision error

Standard error is conditioned by the precision in the register of the physical characteristics of cranium, which is provided by the equipment after introducing the anatomical landmarks of the head into the equipment. An standard error of 2 mm^2 is accepted.

Typical data:

- **Magnetic field:** often about 2 Tesla on the coil surface and 0.5 T in the cortex.
- **Current rise time:** zero to peak, often around 70-100 microseconds.
- **Wave form:** monophasic or biphasic.
- **Repetition rate for rTMS:** below 1 Hz (slow TMS), above 1 Hz (rapid-rate TMS).

TMS-Coils' types

The design of transcranial magnetic stimulation coils used in either treatment or diagnostic/experimental studies may differ in a variety of ways. These differences should be considered in the interpretation of any study result, and the type of coil used should be specified in the study methods for any published reports.

The most important considerations include:

- The type of material used to construct the core of the coil
- The geometry of the coil configuration
- The biophysical characteristics of the pulse produced by the coil.

With regard to coil composition, the core material may be either a magnetically inert substrate (i.e., the so-called 'air-core' coil design), or possess a solid, ferromagnetically active material (i.e., the so-called 'solid-core' design). Solid core coil design result in a more efficient transfer of electrical energy into a magnetic field, with a substantially reduced amount of energy dissipated as heat, and so can be operated under more aggressive duty cycles often mandated in therapeutic protocols, without treatment interruption due to heat accumulation, or the use of an accessory method of cooling the coil during operation. Varying the geometric shape of the coil itself may also result in variations in the focality, shape, and depth of cortical penetration of the magnetic field. Differences in the coil substance as well as the electronic operation of the power supply to the coil may also result in variations in the biophysical characteristics of the resulting magnetic pulse (e.g., width or duration of the magnetic field pulse). All of these features should be considered when comparing results obtained from different studies, with respect to both safety and efficacy. 29, 30

A number of different types of coils exist, each of which produce different magnetic field patterns. Some examples:

- Round coil: the original type of TMS coil.
- Figure-eight coil (i.e. butterfly coil): results in a more focal pattern of activation.
- Double-cone coil: conforms to shape of head, useful for deeper stimulation.
- Deep TMS (or H-coil): currently being used in a clinical trial for the treatment of patients suffering from clinical depression.
- Four-leaf coil: for focal stimulation of peripheral nerves. 31

Shape/function comparison between TMS stimulation coils:
Figure-8 TMS coils vs. Circular TMS coils

If two round coils are placed side by side, so that the current flow in the same direction at the junction point, the induced electric fields will add together and be maximum below the junction. This design, known as a “figure-8” or “butterfly” coil, allows focal stimulation at a limited and clearly definable location. Because of this greater focality, figure-8 coils are used more often than round coils in research and clinical applications.

The figure-8 coil junction can be extended along a line, producing a “double-D” configuration and possibly augmentation of the central field. A flat figure-8 coil is a good compromise between efficiency and focality. However, penetration of the induced electric field tends to be more limited than with a circular coil, because the two side loops are usually smaller. In most TMS applications the electric field induced by the side loops can be safely ignored. But with a double-cone figure-8 coil the side fields may approach 50% of the maximum field below the coil center. If stimulator output is increased above 150% of the subject’s motor threshold, the field below the side loops will be in a range known to produce CNS effects.

With figure-8 coils, the isopotential lines of the induced electric field form an oval or rounded rectangle, whose long axis is parallel to the direction of current flow at the coil junction.

The “size” of the cortical area stimulated depends on the specific intensity needed to produce a particular effect. In most situations this intensity is not exactly known, so that the area of stimulation in a given application cannot be precisely determined. An exception is the production of TMS motor maps: if the cortical representation of the muscle studied is a single point, then ideally the resulting map will be an oval whose shape reflects the electric field contour lines. The oval will become larger as stimulus intensity is increased, and its edges will be determined by the locations at which the induced field falls to threshold for the intended neurophysiological effect. 23

2.4. MOTOR EVOKED POTENTIALS (MEPs)

Evoked Potentials: general approach

An evoked potential (or "evoked response") is an electrical potential recorded from the nervous system of a human or other animal following presentation of a stimulus, as distinct from spontaneous potentials as detected by electroencephalography (EEG) or electromyography (EMG).

Evoked potential amplitudes tend to be low, ranging from less than a microvolt to several microvolts, compared to tens of microvolts for EEG, millivolts for EMG, and often close to a volt for ECG. To resolve these low-amplitude potentials against the background of ongoing EEG, ECG, EMG and other biological signals and ambient noise, signal averaging is usually required. The signal is time-locked to the stimulus and most of the noise occurs randomly, allowing the noise to be averaged out with averaging of repeated responses.

Signals can be recorded from cerebral cortex, brain stem, spinal cord and peripheral nerves. Usually the term "evoked potential" is reserved for responses involving either recording from, or stimulation of, central nervous system structures. Thus evoked compound motor action potentials (CMAP) or sensory nerve action potentials (SNAP) as used in nerve conduction studies (NCS) are generally not thought of as evoked potentials, though they do meet the above definition. 32

Motor Evoked Potentials (MEP)

Motor evoked potentials (MEP) are recorded from muscles following direct stimulation of exposed motor cortex, or transcranial stimulation of motor cortex, either magnetic or electrical. Transcranial magnetic MEP (TCmMEP) potentially offer clinical diagnostic applications. Transcranial electrical MEP (TCeMEP) has been in widespread use for several years for intraoperative monitoring of pyramidal tract functional integrity.

During the 1990s there were attempts to monitor "motor evoked potentials", including "neurogenic motor evoked potentials" recorded from peripheral nerves, following direct electrical stimulation of the spinal cord. It has become clear that these "motor" potentials were almost entirely elicited by antidromic stimulation of sensory tracts—even when the recording was from muscles (antidromic sensory tract stimulation triggers myogenic responses through synapses at the root entry level -apart from the threshold-dependent stimulation of motor fibers). TCMEP,

whether electrical or magnetic, is the most practical way to ensure pure motor responses, since stimulation of sensory cortex cannot result in descending impulses beyond the first synapse (synapses cannot be backfired). 8 , 33

Facilitation

Motor Evoked Potentials can be enhanced in TMS by certain maneuvers. This phenomenon is called “facilitation”. For example, mild voluntary contraction of the target muscle would reduce the threshold stimulus intensity, increase the amplitude, and decrease the latency of the Compound Muscle Action Potential (CMAP). A voluntary contraction between 2% and 6% of maximal surface electromyography (EMG) activity or 10% to 20% root mean square maximal integrated electrical muscle activity would be sufficient to produce the optimal effects. No significant gain occurs when contraction increases beyond this level. In addition, there have been observations of facilitation by contracting a nearby ipsilateral muscle and/or a contralateral homologous muscle. A lesser facilitating effect also can be induced by nonspecific maneuvers such as sticking out the tongue or counting aloud. However, these spreads of facilitation needs further investigation. Facilitation produced by voluntary contraction can be explained in part by the recruitment of the faster conducting neurons at the cortical level and in part by the lowerng of the motoneuron threshold at the spinal level. MS of peripheral nerves usually does not require facilitation.

Motor evoked potentials also can be influenced (facilitated) by the posture of the patient. For example, in TMS of the lower limb muscles, the amplitude of the CMAP is increased significantly with the patient standing upright rather than lying supine. However, the mechanism of postural facilitation probably is different from that of voluntary contraction because it does not shorten the onset latency of the CMAP. More interestingly, facilitation also can be induced by percutaneous electric stimulation of the peripheral nerve or the dermatome. This method of electrical facilitation potentially may provide an easy, reproducible, and quantitative way to standardize facilitation in the future. 19

2.5. NAVIGATED TMS: THE FUNCTIONAL MAPS OF THE MOTOR CORTEX 9-12

Transcranial magnetic stimulation (TMS) can be used for non-invasive assessment of cortical physiology and descending motor pathways. However, the focus or exact site of cortical activation is considerably widespread in traditional TMS. When combined with MRI-based navigation, it allows specific anatomical areas of the cortex to be stimulated. The peripheral muscle responses to TMS are commonly measured as motor evoked potentials (MEPs).

A Navigated Transcranial Magnetic Stimulation (nTMS) system was cleared in the end of 2009 by the FDA for mapping of the motor cortex. Clinical use of this system includes a variety of cases, from the functional and topographic evaluation prior to neurorehabilitation' proceedings to the presurgical assessment of patients with brain tumors.
One advantage is that nTMS and computed electric field strength reduce stimulator-dependent differences in the motor threshold.
The motor threshold (MT) is a fundamental parameter for evaluating cortical excitability in transcranial magnetic stimulation (TMS) despite remarkable variation, both within, and between subjects. 34

Some authors 9, 35 intended to test whether the variation could be reduced by targeting the stimulation on-line and modelling the TMS-induced electric field on individual MR images. Navigated TMS was used to map the primary motor cortex for the representation area of the thenar muscles (abductor pollicis brevis, APB) and to determine the MT. They concluded that on-line navigation can be used to reduce the variation caused by different stimulator types and individual subject anatomy.

Other study groups compared the accuracy of cortical mapping, as well as the congruity of the motor thresholds (MT) and MEPs between navigated and non-navigated TMS procedures. 35 The MTs were similar from session-to-session with no inter-hemispheric differences, and with and without navigation. The stimulus location was more spatially discrete in navigated TMS producing more stable MEPs with significantly higher amplitudes and shorter latencies. In summary, MEPs exhibit significant differences depending on whether navigation is used. However, the MTs are not significantly dependent on the discrete stimulation site.

2.5.1. The normal map of primary motor area.

2.5.1.1. The primary motor cortex

Motor cortex is a term that describes regions of the cerebral cortex involved in the planning, control, and execution of voluntary motor functions.

Anatomy of the motor cortex
The motor cortex can be divided into six main parts:

- The neocortex, composed of six layers: molecular, external granule, external pyramidal, internal granule, internal pyramidal, and multiform.

- The primary motor cortex (or M1), responsible for generating the neural impulses controlling execution of movement.

- And the secondary motor cortices, including:
    - The posterior parietal cortex, responsible for transforming visual information into motor commands,
    - The premotor cortex, responsible for motor guidance of movement and control of proximal and trunk muscles of the body,
    - And the supplementary motor area (or SMA), responsible for planning and coordination of complex movements such as those requiring two hands.
- Other brain regions outside the cortex are also of great importance to motor function, most notably the cerebellum and subcortical motor nuclei.

Early work on motor cortex function

In the 1950s Canadian neurosurgeon Wilder Penfield developed a surgical procedure to relieve epilepsy. His initial procedure was to electrically probe the surface of the patient's cortex to find the problem area. During such investigations, he discovered that stimulation of Brodmann's area 4 readily elicited localised muscle twitches. Furthermore, there appeared to be a “motor map” of the body surface along the gyrus that comprises area 4. Area 4 is therefore now known as the primary motor cortex. Following this discovery, he discovered that stimulation of regions which are in front of the M1 caused more complicated movements; however, more electrical current was required to initiate movements from these areas. These 'premotor' cortical areas are located in Brodmann's area 6.

The motor cortical areas are now typically divided into three regions which have 2 different functional roles:

1. Primary motor cortex (M1)
2. Pre-motor area (PMA)
3. Supplementary motor area (SMA)

Penfield's experiments have made everything seem pretty straightforward: the purpose of M1 is to connect the brain to the lower motor neurons via the spinal cord in order to tell them which particular muscles need to contract. These upper motor neurons are found in layer 5 of the motor cortex and contain some of the largest cells in the brain (Betz cells whose cell bodies can be up to 100 micrometres in diameter. For comparison, rod photoreceptors are about 3 micrometres across). The descending axons of these layer 5 cells form the cortico-spinal or pyramidal tract. However, a single layer 5 forms synapses with many lower motor neurons which innervate different muscles. Furthermore, the same muscle is often represented over quite large regions of the brain's surface, and there is an overlap in the representation of different regions of the body. These facts mean that M1 neurons do not form simple connections with lower motor neurons. The activity of a single M1 neuron could cause contraction of more than one muscle; this suggests that M1 may not simply be coding the degree of contraction of individual muscles.

2.5.1.2. Functional mapping of the motor cortex

Non-activity responses in the motor cortex

Functional magnetic resonance imaging (fMRI) scans of persons reading words have shown that the act of reading a verb that refers to a face, arm, or leg action causes increased blood flow and activity in the motor cortex. The areas of the motor cortex that are active correspond to sites of the motor cortex that are associated with that activity. For example, reading the word lick would increase blood flow in sites corresponding to tongue and mouth movements. While reading the verbs, blood flow also increases in premotor regions, Broca's area and Wernicke's area. Based on this information, it has been proposed that word understanding hinges on activation of interconnected brain areas that assimilate information about a particular word and its associated actions and sensations.

TMS-based motor cortex mapping

Cortical representation maps derived by transcranial magnetic stimulation (TMS) are often used, *inter alia*, in studying the plasticity of the brain. Parameters such as map area, map volume, optimal stimulation site and centre of gravity are commonly used to quantify changes in the topography of the motor cortex. However, reports on the stability of these parameters over time has not been always conclusive. In an Australian study 36, the areas of the scalp from which responses were evoked from corticospinal cells projecting to three intrinsic hand muscles were systematically mapped with TMS at intervals of 24 hours, one week and two weeks from eight normal subjects. The area, "volume" and centre of gravity of these maps did not change significantly over this period. It was concluded that mapping with TMS was suitable for studies which aim to study the effect of various interventions on the cortical representation of individual muscles in human subjects.

MOTOR MAP CHARACTERISTICS

- **Area (cm2).** Area is calculated from the number of excitable grid loci stimulated, expressed in cm2.
- **Volume.** Volume of the map refers to the sum of the relative motor-evoked potential (MEP) amplitudes across all excitable locations.
- **Maximal amplitude (mV)**. Maximal amplitude refers to to the highest peak-to-peak amplitude MEP elicited.
- **Resting MT.** The resting motor threshold (MT) is expressed as percentage of magnetic stimulator output.
- **Distance between amplitude-weighted center of gravity (mm).** The x, y, and z coordinates of the center of gravity were calculated by multiplying the coordinate at each position by its amplitude weight and summing over all positions.
- **Distance between optimal loci (mm).** The reported distance between optimal loci is the calculated distance between the loci where maximal amplitude MEP is elicited in the two mapping sessions. 23 (Chapt.20)

TMS and pre-interventions' planning

TMS is safe, non-invasive, and allows for assessment of various brain functions. It has been increasingly used over the past decade, especially to obtain functional maps of the motor cortex. When TMS is applied to restricted areas of the scalp, it elicits MEPs in contralateral muscles, which may be used to map the location and extent of motor cortical outputs for several muscles. Several studies have proven the value of TMS to assess normal motor cortical

function as well as brain plasticity as a result of skill acquisition or pathological lesions. There are several others instances when the use of TMS for motor cortical mapping may provide substantial contributions to the medical field. These include measuring brain responses to injury (as in stroke recovery), providing a tool to evaluate interventions for enhancing recovery, evaluating cortical excitability in different diseases affecting the nervous system, and assessing patients with lesions near eloquent cortex (e.g. speech and primary motor cortices) prior to surgical interventions (i.e. presurgical planning).

The importance of mapping motor cortex, as well as other functional cortical areas, with regard to presurgical planning includes the well-known variability of functional patterns of the cortical surface. A cortical mapping technique, which relates cortical surface anatomy, pathology, and function, is invaluable for aiding the surgeon's decision regarding the feasibility of a surgical procedure. It also adds important insight as to the optimum approach for surgical therapy. Finally, the technique to be described has added appeal because of the fact that it best mimics the intraoperative cortical surface electrical stimulation technique used in neurosurgical centers for locating eloquent cortical areas.

The utility of a mapping technique for presurgical planning will depend on two essential considerations:

i) The precision of a mapping technique for targeting specific functional brain regions;

ii) Given a stable pathological lesion, the mapping results should remain accurate over the short term because the mapping technique will typically be carried out several days prior to a surgical procedure. These two considerations have recently been addressed experimentally.

Precision of TMS for brain mapping

Traditionally TMS has been delivered using skull or scalp landmarks in a "blind fashion", holding the TMS coil in place while stimulation is delivered. Some have used head frames to immobilize the person's head; others mark the coil contour on a swimming cap worn by the individual being stimulated. However, displacement of the coil may occur, resulting in stimulation of different brain regions from those intended, and potentially affecting the results of the intervention. 23

Other groups have described a TMS mapping technique using stereotactic optic guidance. The purpose of this technique is to facilitate visualization of the cortical surface, and to guide placement of the TMS coil relative to the cortical surface of an individual. Thus, specific brain regions can be stimulated, while controlling for coil movements relative to the individual's brain. The system is described below.

First, a 3D model of the brain and head of the person undergoing TMS is obtained. An anatomical magnetic resonance imaging scan of the brain is acquired using a 1.5 T scanner (TR 35ms, TE 5ms, slice thickness of 1.5 mm, FOV 24cm, acquisition matrix of 256x256 voxels) resulting in 124 contiguous double-echo slices. Using the multi-step algorithms developed in each institution, the 3D reconstructions of head and brain are obtained. The 3D model displays the skin surface of the scalp and face as well as the underlying cortical surface of the brain. The center of the 3D reconstructed model is used as the origin of a Cartesian system that serves to locate any coordinate in the scalp or cortical surface.

Second, a co-registration procedure is performed in order to align the subject's head with the virtual 3D model. This step involves using a stereotactic optical tracking system. Using three cameras mounted on a mobile arm, the system detects and tracks infrared light-emitting diodes (LEDs) when placed under their view. The LEDs are used to track a subject's head and TMS coil under the cameras' view, which is done by securely taping LEDs to both the subject and the coil. Then, with a probe that has two LEDs and is a component of the tracking system, we record the position of the LEDs in the subject, and several landmarks easily identified in the subject's head. Next, several points are traced over the skin surface and a matching procedure is carried out to evaluate the accuracy of the co-registration procedure. This is followed by calibration of the coil, so that the focal point of a figure-8 coil (i.e. the center point of the bottom surface) can be tracked. The focal point of a figure-8 coil is selected for tracking purposes because this is where the peak magnetic field and induced electric field occurs. Using the above-described probe, the location of the LEDs attached to the coil is recorded as well as several predetermined points on the coil's surface, including the focal point. The result is that the optical tracking system can track the subject's head and the TMS coil under the cameras' view, and relative to each other. The system has an accuracy of about 1 mm when the coil and subject are within 1 m distance from the cameras. Detailed description of the co-registration algorithm can be found elsewhere. The system detects head and coil movements in three dimensions, relative to each other, including detection of coil tilt and rotation (referred to as 3D angle). Details on the geometry premise used to calculate the 3D angle are available elsewhere. Coil placement is guided in real time: the image is available instantaneously and is updated at a rate of five times per second. In a previous study, the precision attained using this optical tracking system was evaluated. In this study, single-pulse TMS was delivered over the optimal location to obtain first dorsal interosseus muscle responses in normal volunteers. A blind technique, using markings of the figure-8 contour on a swimming cap worn by the volunteer to guide coil placement over the scalp, was compared to a guided technique, using the optical tracking system described. The authors also compared the effects of three levels of stimulation intensity.

They attempted to reproduce the coil position at the optimal location using a blind vs guided approach. It was found that using the guided technique resulted in a smaller number of cortical

regions stimulated. In addition, the distances between the cortical optimal locus and loci stimulated during subsequent stimulation trials were significantly shorter using the guided technique (<2mm compared to 10-14 mm using a blinded technique). The differences of 3D angle achieved during the initial stimulation at the optimal location and subsequent trials attempting to reproduce it were also significantly smaller using the guided technique. These findings were more evident at lower stimulation intensities, as expected, since higher stimulation intensity is associated with current spread and responses may be elicited by stimulating a location further from the intended target cortical locus. This study also showed that guided stimulation resulted in higher probability of eliciting MEPs, and that the MEPs obtained were of higher amplitudes and areas. The coefficients of variation did not decrease significantly. In addition, a significant improvement in the precision to deliver TMS targeted cortical regions was noted and illustrated some of the physiological consequences.

Other authors have also found improvement in precision for scalp placement of a coil by using other methods such as a 3D digitizer or a chin rest and clamping the coil. However, the system developed by our group allows quantification of error in coil placement and real time optical guidance for stimulation, and is frameless, allowing for greater subject comfort. The conclusion reached was that optical guidance to assist TMS studies improves the precision for coil placement. 23 (Chapter 20)

2.5.2. CHANGES OF FUNCTIONAL MAPS: THE NEUROPLASTICITY.

Transcranial magnetic stimulation is under active study in the treatment of a range of psychiatric and neurological disorders. The mechanisms by which intermittent focal brain stimulation with TMS could exert lasting effects in illnesses subserved by distributed neuronal networks are at present largely unknown. To be of lasting benefit beyond the period of stimulation, enduring changes in the functioning of the target pathways would need to be invoked. One proposed mechanism by which such lasting changes might come about is synaptic plasticity. As a non-invasive, relatively safe technique for fairly selective stimulation of cortical structures, TMS is a uniquely suitable research tool for the study of neural plasticity in humans.

The objective of this section is twofold. First, we discuss synaptic plasticity as a potential mechanism of enduring changes in function observed after relatively brief periods of repetitive, rTMS. Second, we explore how principles of synaptic plasticity may be exploited in the rational design of future rTMS paradigms in psychiatric disorders, taking into account interactions between rTMS and pharmacological manipulations. (…)

Definition of plasticity

Plasticity may be broadly defined as a use-dependent enduring change in neural structure and function. This definition would encompass such phenomena as acute amphetamine-induced dendritic sprouting of neurons in the nucleus accumbens and prefrontal cortex, activity-dependent neurogenesis in the hippocampus, and behavioural sensitization to psychostimulants. These examples illustrate a variety of neural plasticity effects with different induction protocols (e.g. drug administration, electrical stimulation) and outcome measures (e.g. locomotor activity, dopamine release, neurogenesis).

A more narrow definition of plasticity would be activity dependent-change in synaptic efficacy. Long-term potentiation (LTP) is the most widely studied version of synaptic plasticity and refers to enduring strengthening of synapses. LTP's counterpart is long-term depression (LTD), the enduring weakening of synaptic strength. Typically, "synaptic" strength is measured as excitatory postsynaptic potentials (EPSPs) in response to electrical stimulation.

Characteristics of plasticity

Synaptic plasticity has several characteristics that can be described.

- ***Associativity*** refers to the concurrent stimulation of input neurons converging on the same output neuron, a condition that favours the induction of LTP.

- ***Coincidence*** refers to the simultaneous firing of pre- and postsynaptic neurons, a condition favouring LTP induction.

- ***Input specificity*** refers to the selective strengthening of active synapses, but not other synapses without input activity. Changes in synaptic efficacy are long-lasting and may occur in two directions. **Synaptic strength** can increase **or potentiate** up to a certain maximum at which "saturation" occurs. The decrease in synaptic strength is known as **depotentiation or depression**.

Although LTP has predominantly been studied in the hippocampus, it has been demonstrated in other brain areas, including the prefrontal cortex (PFC). (…)

Neuroanatomical and neurochemical considerations

One possible mechanism of associativity is the cooperative action of postsynaptic receptors. For example, the excitatory neurotransmitter glutamate binds to multiple receptors. The ionotropic group of glutamate receptors includes alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors, which are cation channels activated by glutamate. During weak glutamate stimulation, only AMPA receptors permeable to sodium are active. During stronger glutamate stimulation, AMPA receptor activity will become sufficient to activate NMDA receptors. NMDA channels in their resting state are blocked by Mg2+. After sufficient depolarization by sodium influx through AMPA channels the NMDA channels become unblocked and permeable to Ca2+ ions. Thus, the NMDA and AMPA receptors are able to integrate glutamate neurotransmission from convergent glutamatergic afferents.

The PFC receives convergent glutamate inputs from the VSUB, amygdale, and thalamus. In addition, there is convergence of glutamate- and dopamine-containing afferents on PFC neurons as mentioned above.

Similar convergence of glutamate and dopamine inputs is present in the nucleus accumbens (NAC). This neuro-anatomical convergence sets up the possibility of associativity. Not surprisingly, then, LTP has been observed in the NAC and PFC.

Coincidence-induced LTP could occur between inputs from amygdale or VSUB and outputs from PFC or NAC. The convergence in the NAC may be relevant for PFC rTMS-induced plasticity, since PFC rTMS induces dopamine release in the basal ganglia and since dysfunction of the basal ganglia (of which the NAC is part) is involved in several neuropsychiatric disorders.

Clinical significance of Long-Term Potentiation (LTP)

The hippocampus is critically involved in learning and memory. LTP in the hippocampus is therefore an attractive cellular model of memory storage in the hippocampus. Indeed, LTP induction in the hippocampus accompanies the learning of new tasks.

The PFC is more involved in working memory, rather than the storage of permanent memories. This raises the question of what clinical significance LTP in the PFC might have. One possibility is that LTP could selectively strengthen specific inputs into the PFC, thereby filtering access of some inputs over other ones and thus representing a cellular mechanism of attention. Alternatively, LTP could strengthen specific neural circuits within the PFC or boost PFC metabolism and function overall, including executive, planning, and motor functions. Whereas LTP's possible role in PFC cognitive functions is of special interest with respect to psychiatric disorders, LTP in the PFC has been best studied in the motor cortex.

Repetitive TMS studies of LTP in the motor cortex

23 (Chapt.38)

Repetitive TMS

TMS is a non-invasive, relatively safe technique for fairly selective stimulation of cortical structures in human and nonhuman subjects. TMS allows remote stimulation of superficial cortical structures up to 2 cm below the surfaced of the human skull. TMS directly produces a large simultaneous activation of both excitatory and inhibitory neurons at the site of stimulation, resulting in inhibitory activity silencing local neural firing. More distant areas are activated through excitatory long-range pathways.

Motor cortex plasticity shares some features with LTP

It is no surprise that PFC LTP has been best characterized in the motor cortex because of several features that make it appealing for LTP experiments. Electrophysiological outcome measures, e.g. motor-evoked potentials (MEPs), are objective, well defined, and can be correlated with behavioural measures, e.g. acceleration or strength of movements.

The coincidence of pre- and postsynaptic neuron firing induces LTP in the motor cortex of primates. Through an electronic chip implanted in the motor cortex, presynaptic inputs were triggered by neural firing recorded in postsynaptic outputs. Moreover, motor learning accompanied the LTP.

Convergent inputs from motor cortex and medial longitudinal nerve (MLN) address the associativity feature of LTP. Paired Associative Stimulation (PAS) of MLN and motor cortex results in LTP or LTD of MEPs, depending on the PAS interval. Fast repetitive thumb movements resulted in learning, as measured by an increase in the peak acceleration of practiced thumb movements. Movement practice prevented subsequent LTP induction, but fostered subsequent LTD, consistent with saturation of MEPs during motor learning. Thus motor cortex plasticity possesses several characteristics of LTP.

LTP in humans

To date, plasticity studies in humans have been limited, since reported effects on synaptic plasticity are often weak, highly variable between individuals, and rarely last longer than 30 min. In comparison with the frequencies and train durations that have typically been used to induce LTP with direct electrical stimulation, parameters of stimulation for TMS protocols are relatively weak and limited by the risk of TMS side-effects, such as the risk of seizure. Recently investigators applied TMS in theta-burst fashion (50 Hz bursts, repeated at a 5 Hz frequency) to the motor cortex in humans. The protocol appeared safe and seems to hold promise as a powerful LTP inducer. Indeed, the authors observed long-lasting changes of up to 1 h in motor cortex electrophysiological measures. They observed accompanying behavioural potentiation as measured by the reaction time of the hand. Subsequent work has tested the clinical potential of theta burst stimulation (TBS) to the motor cortex to improve motor recovery following stroke, with some encouraging initial results in six chronic stroke patients. Likewise, it would be of great interest to determine whether modulation of LTP via TBS could have clinical significance in psychiatric disorders, specifically when applied to the dorsolateral prefrontal cortex (dlPFC). TBS has indeed been applied to brain regions outside of the primary motor cortex, with evidence of lasting inhibition demonstrated in the frontal eye fields and the occipital cortex. This

work has suggested that the parameters of stimulation to effectively induce excitatory effects with intermittent TBS may differ for non-motor cortical areas.

While the evidence of lasting changes in the amplitude of corticospinal responses is consistent with LTP, it does not constitute proof that these changes come about via LTP. A direct measure of LTP in humans would be extremely useful to explain the mechanism of action of these lasting changes in function. A recent report describes one proposed measure which appears to offer supportive evidence of cortical LTP in humans. Cortical responses to single TMS pulses were measured through high density electroencephalography (hdEEG) before and after applying rTMS (5 Hz, 1500 pulses) to the motor cortex. The authors observed significant potentiation of EEG responses bilaterally over the premotor cortex at latencies of 15-55 ms; magnetic artifacts prevented the measurement of earlier peaks. In addition, they observed potentiation of motor responses to TMS as measured by motor-evoked potentials (MEPs).

This study had several limitations. It is unclear how long the potentiation of EEG responses to TMS lasted, since responses were measured for only 10 min in quiet wakefulness. Hence, it is unclear if the study satisfied the longevity requirement of LTP. It is also unclear how MEPs could be potentiated while cortical activity was not. The behavioural significance of the MEPs (e.g. increased force or accelerated muscle contraction) was not assessed. Nevertheless, the hdEEG outcome measure is appealing, since it mimics EPSPs, the prototypical outcome measure in LTP experiments. It will be of note to see if this experiment can be replicated in other brain areas of psychiatric interest, e.g. the dlPFC, providing an intermediate outcome measure for the selection of TMS or TBS dosing parameters to maximize LTP- or LTD-like effects.

Pharmacological manipulation of motor cortex plasticity

Since many psychotropic medications affect neurotransmitter function, pharmacological studies of human motor cortex plasticity are relevant to consider. In general, while the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) suppresses LTP, other neurotransmitter systems studied so far enhance LTP; they include glutamate, dopamine, norepinephrine, and acetylcholine. So far, serotonergic agents have failed to affect LTP induction. Of note, the dopamine receptor agonists cabergoline and methylphenidate enhance cortical LTP, in agreement with enhanced induction of PFC LTP in the rat. It will be of interest to examine how norepinephrine, acetylcholine, serotonin, and other neurotransmitters affect PFC LTP in the rat. Another testable possibility is whether dopamine receptor agonists can potentiate the pharmacological effects of small doses of glutamate receptor agonists in humans, as the rat study suggests. The potential and need for translational neurobiological research is clear.

Conclusions: human motor cortex plasticity

Overall it has thus far been difficult, if not impossible, to link LTP, the cellular model of learning and memory, to behaviour. The difficulty is that studies attempting to establish such a link have essentially been correlative, so that a causal role of LTP in learning and memory cannot be definitively established. TMS experiments of plasticity in the human motor cortex have been limited by the intensity and frequency of TMS protocols. Effects on MEPs have been inconsistent and short-lasting. It remains to be demonstrated whether the observed potentiation of motor cortical output has to do with changes at the synaptic level. Nevertheless, the observation of robust (>= 50%) and enduring (>=20 min) increases of MEPs by theta-burst stimulation is promising. It will be interesting to see if similar plasticity will apply to other brain areas of psychiatric interest, e.g. the dlPFC. Motor cortex plasticity is of particular clinical interest to neurorehabilitation of motor function, e.g. after stroke. The TMS experience with motor cortex plasticity should guide future studies of plasticity in other brain areas of psychiatric interest, e.g. the dlPFC. 23 (Chapt.38)

2.6. TRACTOGRAPHY (DIFFUSION TENSOR IMAGING): CORTICO-SUBCORTICAL CONNECTIVITY: THE DISCONNECTION SYNDROMES.

13-16

DTI Tractography Provides White Matter 'Roadmap'

Some scientists are using innovative signal processing algorithms to map white matter tracts, providing neuroscientists and neurosurgeons with valuable information about the brain.

This is a very new technique, and a lot of what neuroradiologists and researchers are doing is basic science, but neurosurgeons are already using their images to plan surgeries.

Modern imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) can distinguish between gray matter and white matter in the brain, and functional MRI (fMRI) can be used to create maps of brain function in the cortex. Such images are used to guide surgeons' preoperative planning as they try to decide how to resect a tumor, arteriovenous malformation or epileptogenic area without disrupting vital cognitive centers.

White matter, on the other hand, is not well defined by these imaging technologies, and its important role in cognition has necessarily been neglected. fMRI tends to show the brain as a collection of distinct processing areas, but the truth is that the brain is a network and it's important to understand the connections. Cutting the connection between important processing areas in the cortex, or between the cortex and subcortical centers such as the spinal cord, can be just as damaging as disrupting those areas themselves.

Diffusion tensor imaging (DTI) data allow neuroradiologists to perform tractography to map those connections by following the bundles of axonal tracts that make up white matter. DTI is done by means of the same large magnets that produce MRIs, but the mathematical algorithms used look at the movement of water in the brain.

DTI tractography relies on the fact that it is easier for water to diffuse along the axon of a neuron than it is to diffuse across the axonal membrane. By defining the greatest movement of water molecules in those neural cells, we can define the direction that axons are running in any given part of the brain. Linking up that information from many points across the whole brain provides direct axonal pathways from one part of the brain to others.

Neurological surgeons continue to electrically map brain function around a lesion once the surgery begins, but DTI provides vital information that other imaging technology can't. Preoperative imaging still includes CT scans, MRI, magnetoencephalography (MEG) and EEGs,

but only DTI tractography will show white matter connections between cortical and subcortical processing areas.

DTI BACKGROUND

DTI exploits the anisotropic nature of water diffusion in highly structured media like white matter to estimate the principal orientation of fibers within each voxel. Water molecules diffuse most readily parallel to the fibers; axon membranes and their surrounding myelin sheaths act as barriers to diffusion across the fibers. Therefore, the direction of greatest water mobility may be identified with the principal fiber orientation. At each voxel throughout the brain, the anisotropy is characterized by a diffusion tensor, and the direction of greatest diffusibility is determined by its principal eigenvector. DTI yields a discrete sampling of the diffusion tensor field throughout the brain. Mapping of the principal fiber orientations involves a reduction of the tensor field to a vector field consisting of the principal eigenvector at each voxel. The fiber tracts coursing through the white matter are modeled by streamlines of this vector field. The process of generating white matter fiber paths from DTI data is tractography. Many functional white matter tracts have been anatomically defined. Several relatively large and surgically important functional tracts can be modeled by DTI tractography, including the corticospinal and corticobulbar tracts (motor pathways), arcuate fasciculus (language pathways), optic radiations (visual pathways), and callosal projections (interhemispheric pathways).

A study group in Boston generate DTI fiber tracks on a Siemens Leonardo workstation using a DTI task card. Seed points are defined within regions of interest, guided by known anatomy. Tracks are generated bidirectionally from each seed point by a numerical integration procedure subject to constraints that filter out divergent paths related to noise, finite spatial resolution, and fiber crossings. The tractography procedure yields a set of coregistered fiber tracks, each in the form of a linear curve specified by 3D coordinates. These curves are subsequently passed to the visualization tool, which visualizes the curves in the same manner as a diffusion tensor field. 37

DTI vs fMRI

fMRI BACKGROUND

Functional MRI detects alterations in cerebral blood flow and oxygen metabolism that co-localize with neural activation. fMRI images are acquired while the patient performs specified cognitive or behavioral tasks in the MRI scanner. Our fMRI presurgical planning studies activate and localize sensorimotor and language regions. Prior to visualization, the fMRI and structural datasets are co-registered. fMRI processing is performed on a Linux workstation using MEDx. For each task paradigm, the fMRI analysis yields a volume of activated voxels that is subsequently passed to the visualization tool.

VISUALIZATION APPLICATION

The visualization tool integrates the volume data and tractography geometry data. The voxel imaging data is rendered with a high quality and high performance volume rendering engine. The track geometry is rendered as 3D streamlines. This uses the optimal technique for each representation as they are equally important to the task.
The application is capable of rendering multiple color-encoded functional activation volumes and fiber tract bundles. The user interface allows individual volumes and tracts to be switched on or off, allowing various comparisons and degrees of visual complexity.

A voxel clipping plane allows flexible visualization of select brain regions. The clipping plane may be rotated and translated arbitrarily and the entire visualization volume may be rotated and scaled arbitrarily. Ease of use for rotating and zooming the object, changing transparency, and rotating and pushing the clipping planes are critical to the UI.

The clipping plane can be applied to the geometry in an adjustable manner, or not at all. Changing the offset between the voxel clip plane and the geometry clip plane allows the user to follow the tracts from the voxel clipping plane into the surrounding white matter. The visualization tool facilitates interactive exploration by the neuroradiologist and neurosurgeon, clarifying important functional and structural anatomic relationships within the brain for optimal planning of the surgical approach.

The visualization application runs on a Linux workstation equipped with a TeraRecon VolumePro 1000 3D volume rendering engine. The 3D streamlines are based on 3d paths from the DTI Task Card saved as .trk files and read by the TrackIO utility. The GLE Extrusion Library and OpenGL are used to create the 3D streamline geometry. The VolumePro 1000 uses the

depth buffer created while rendering the geometry to stop rays as they are being cast. This allows for precise generation and compositing of the voxel and geometry data.

Comparison between fMRI and Tractography

The most outstanding difference between these two systems is that fMRI shows the neuronal bodies, and Tractography is showing the tracts, the axons, the pathways and connections followed by defined groups of neurons.

fMRI shows the regions which activate in relationship with some brain functions, but Tractography localizes the exact points where the “responsible” nervous cells are located, and allows physiologically objectivable actions at the peripheral and central levels to demonstrate it.

Because of this localization feature, this accuracy and specificity, we consider Tractography as a superior technique than fMRI, specially when planning therapeutic procedures.

2.6.1. Cortico-subcortical Connectivity: The disconnection Syndromes. 13-16

In a brain composed of localized but connected specialized areas, disconnection leads to dysfunction. This simple formulation underlay a range of 19th century neurological disorders, referred to collectively as disconnection syndromes. Although disconnectionism fell out of favour with the move against localized brain theories in the early 20th century, in 1965, an American neurologist brought disconnection to the fore once more in a paper entitled, 'Disconnexion syndromes in animals and man'. In what was to become the manifesto of behavioural neurology, Norman Geschwind outlined a pure disconnectionist framework which revolutionized both clinical neurology and the neurosciences in general. For him, disconnection syndromes were higher function deficits that resulted from white matter lesions or lesions of the association cortices, the latter acting as relay stations between primary motor, sensory and limbic areas. From a clinical perspective, the work reawakened interest in single case studies by providing a useful framework for correlating lesion locations with clinical deficits. In the neurosciences, it helped develop contemporary distributed network and connectionist theories of brain function. Geschwind's general disconnectionist paradigm ruled clinical neurology for 20 years but in the late 1980s, with the re-emergence of specialized functional roles for association cortex, the orbit of its remit began to diminish and it became incorporated into more general models of higher dysfunction. By the 1990s, textbooks of neurology were devoting only a few pages to classical disconnection theory. Today, new techniques to study connections in the living human brain allow us, for the first time, to test the classical formulation directly and broaden it beyond disconnections to include disorders of hyperconnectivity. In a review 15 (Catani et al., 2005) on

the 40th anniversary of Geschwind's publication, are described the changing fortunes of disconnection theory and adapt the general framework that evolved from it to encompass the entire spectrum of higher function disorders in neurology and psychiatry.

Connectivity 23 (Chapt.34)

Typically, region A is said to be connected with region B only if neurons A possess synaptic connections with neurons B. But current techniques for studying neural connectivity in the human brain do not provide such a level of spatial neuron-to-neuron specificity. With the exception of post-mortem studies of short-range cortical connectivity with the carbocyanine tracer CiI, most current research focuses on in vivo studies of structural and functional connectivity at the macroscopic level. This work is carried out with a variety of brain-mapping techniques, including structural and functional MRI, PET, TMS, EEG and Magnetoencephalography. In this context, the term “connectivity” refers either to the structural properties of white matter and major fiber tracts, namely structural connectivity, or to the statistical relationship in neural activity recorded simultaneously in a number of spatially distinct regions, namely functional connectivity. Under certain circumstances, we can also evaluate how one region influences anogher, that is effective connectivity.

Studies of structural connectivity in the healthy human brain focus on assessing the volume and structural properties of major white matter pathways. The former can be measured with a computational analysis of regular (e.g. T1- and/or T2-weighted) anatomical images whereas the latter is most often captured with diffusion tensor imaging (DTI) or magnetization transfer imaging (MTI). The main advantage of the “anatomical” approach is the ease of data acquisition: 15-30 min of scanning thime provides a wealth of data covering the entire brain and, hence, all major pathways. The main drawback is the lack of information about the point-to-point neural connectivity (but see recent successes of certain versions of fiber tractography) and, by definition, absence of information about the functional state of a given pathway.

Functional connectivity can be defined operationally as the extent of correlation in brain activity measured across a number of spatially distinct brain regions. When discussing various approaches to the study of functional connectivity in the human brain, Horwitz (2003) /// pointed out that conclusions reached by different investigators regarding the presence or absence of functional connectivity between a set of brain regions depend on the type of measurement (e.g. functional MRI, EEG, MEG), type of analysis (e.g. correlation, structural equation modelling), and, most importantly, the state of the subject during the recording of brain activity (rest, type of stimulation/task). The main advantage of this statistical approach to the assessment of connectivity is the fact that it can be readily applied to almost any dataset acquired with the current brain-mapping tools. The main disadvantage is the complexity of its interpretation.

Perhaps, functional connectivity should be viewed as yet another way to represent functional neuroimaging data rather than to indicate neural connectivity per se.

Effective connectivity attempts to describe causal effects exerted by one brain region onto another. Effective connectivity can be inferred through a perturbation or through the observation of temporal order of neural events (Granger causality). At least theoretically, the latter approach is possible in the case of electrophysiological signals. It is still unclear, however, whether relatively short (a few milliseconds) delays in monosynaptic pathways can be discerned using EEG or MEG measures, which are based on a spatially integrated response of a large population of neurons. For this reason, we would argue that the perturbation approach ("perturb-and-record") seems to be the only technique available today to assess truly effective connectivity. This can be achieved by combining brain imaging with brain stimulation.

2.7. **THE CONCEPT OF NEUROMODULATION** 17 , 38

Physiological Neuromodulation

Neuromodulation is the process in which several classes of neurotransmitters in the nervous system regulate diverse populations of neurons (one neuron uses different neurotransmitters to connect to several neurons). As opposed to direct synaptic transmission, in which one presynaptic neuron directly influences a postsynaptic partner (one neuron reaching one other neuron), neuromodulatory transmitters secreted by a small group of neurons diffuse through large areas of the nervous system, having an effect on multiple neurons. Examples of neuromodulators include dopamine, serotonin, acetylcholine, histamine and others.

A neuromodulator is a relatively new concept in the field, and it can be conceptualized as a neurotransmitter that is not reabsorbed by the pre-synaptic neuron or broken down into a metabolite. Such neuromodulators end up spending a significant amount of time in the CSF (cerebrospinal fluid), influencing (or modulating) the overall activity level of the brain. For this reason, some neurotransmitters are also considered as neuromodulators. Examples of neuromodulators in this category are serotonin and acetylcholine. More specifically, neuromodulation is often contrasted with classical fast synaptic transmission. In both cases the transmitter acts on local postsynaptic receptors, but in the former case the receptors are typically 7-membrane spanning G-protein coupled receptors while in the latter case they are ligand-gated ion channels. The former type of synaptic transmission often involves effects on voltage-gated ion channels, and is quite slow. The latter type is much faster. A related distinction is also sometimes drawn between modulator and driver synaptic inputs to a neuron, but here the emphasis is on modulating ongoing neuronal spiking versus causing that spiking.

Neuromuscular systems

Neuromodulators may alter the output of a physiological system by acting on the associated inputs (for instance, central pattern generators). However, modeling work suggests that this alone is insufficient, because the neuromuscular transformation from neural input to muscular output may be tuned for particular ranges of input. Stern et al. (2007) suggest that neuromodulators must act not only on the input system but must change the transformation itself to produce the proper contractions of muscles as output.

Diffuse modulatory neurotransmitter systems

Neurotransmitter systems are systems of neurons in the brain expressing certain types of neurotransmitters, and thus form distinct systems. Activation of the system causes effects in large volumes of the brain, called volume transmission.

The major neurotransmitter systems are the noradrenaline (norepinephrine) system, the dopamine system, the serotonin system and the cholinergic system. Drugs targeting the neurotransmitter of such systems affects the whole system, and explain the mode of action of many drugs.

Most other neurotransmitters, on the other hand, e.g. glutamate, GABA and glycine, are used very generally throughout the central nervous system.

Comparison

System	Origins	Targets	Effects
Noradrenaline system	Locus coeruleus	Adrenergic receptors in: • Spinal cord • Thalamus • Hypothalamus • Striatum • Neocortex • Cingulate gyrus • Cingulum • Hippocampus • Amygdala	• Arousal • Reward system
	Lateral tegmental field	• Hypothalamus	
Dopamine system	Dopamine pathways: Mesocortical pathway Mesolimbic pathway Nigrostriatal pathway Tuberoinfundibular pathway	Dopamine receptors at pathway terminations.	Motor system, reward system, cognition, endocrine, nausea
Serotonin system	Caudal dorsal raphe nucleus	Serotonin receptors in: • Deep cerebellar nuclei • Cerebellar cortex • Spinal cord	Increase (introversion), mood, satiety, body temperature and sleep, while decreasing nociception.
	Rostral dorsal raphe nucleus	Serotonin receptors in: • Thalamus • Striatum • Hypothalamus • Nucleus accumbens • Neocortex • Cingulate gyrus • Cingulum • Hippocampus • Amygdala	
Cholinergic system	Pedunculopontine nucleus and dorsolateral tegmental nuclei (pontomesencephalotegmental complex)	(mainly) M1 receptors in: • Brainstem • Deep cerebellar nuclei • Pontine nuclei • Locus ceruleus • Raphe nucleus • Lateral reticular nucleus • Inferior olive • Thalamus • Tectum • Basal ganglia • Basal forebrain	• Learning • Short-term memory • Arousal • Reward
	Basal optic nucleus of Meynert	(mainly) M1 receptors in: • Neocortex	
	Medial septal nucleus	(mainly) M1 receptors in: • Hippocampus • Neocortex	

Noradrenaline system

The noradrenaline system consists of just 1500 neurons on each side of the brain, which is diminutive compared to the total amount of more than 100 billion neurons in the brain. Nevertheless, when activated, the system plays major roles in the brain, as seen in table above. Noradrenaline is released from the neurons, and acts on adrenergic receptors.

Dopamine system

The dopamine system consists of several pathways, originating from the ventral tegmentum or substantia nigra as examples. It acts on dopamine receptors.
Parkinson's disease is at least in part related to failure of dopaminergic cells in deep-brain nuclei, namely the substantia nigra. Treatments potentiating the effect of dopamine precursors have been proposed and effected, with moderate success.

Dopamine Pharmacology

Cocaine, for example, blocks the reuptake of dopamine, leaving these neurotransmitters in the synaptic gap longer.
AMPT prevents the conversion of tyrosine to L-DOPA, the precursor to dopamine; reserpine prevents dopamine storage within vesicles; and deprenyl inhibits monoamine oxidase (MAO)-B and thus increases dopamine levels.

Serotonin system

The serotonin system in the CNS contains only 1% of total body serotonin, the rest being found as transmitters in the peripheral nervous system[citation needed]. It travels around the brain along the medial forebrain bundle and acts on serotonin receptors. In the peripheral nervous system (such as in the gut wall) serotonin regulates vascular tone.
Serotonin Pharmacology
Prozac is a selective serotonin reuptake inhibitor (SSRI), hence potentiating the effect of naturally released serotonin.

Cholinergic system

Acetylcholine has functions both in the peripheral nervous system (PNS) and in the central nervous system (CNS) as a neuromodulator.

In the peripheral nervous system, acetylcholine activates muscles, and is a major neurotransmitter in the autonomic nervous system.
In the central nervous system, acetylcholine and the associated neurons form a neurotransmitter system, the cholinergic system, which tends to cause anti-excitatory actions.
In the autonomic nervous system (ANS) Acetylcholine is one of many neurotransmitters and the only neurotransmitter used in the motor division of the somatic nervous system. (Sensory neurons use glutamate and various peptides at their synapses.) Acetylcholine is also the principal neurotransmitter in all autonomic ganglia.

In Peripheral Nervous System

In the peripheral nervous system, acetylcholine activates muscles and, as commented, is a major neurotransmitter in the autonomic nervous system. When acetylcholine binds to acetylcholine receptors on skeletal muscle fibers, it opens ligand-gated sodium channels in the cell membrane. Sodium ions then enter the muscle cell, initiating a sequence of steps that finally produce muscle contraction. Although acetylcholine induces contraction of skeletal muscle, it acts via a different type of receptor (muscarinic) to inhibit contraction of cardiac muscle fibers.

In the Autonomic Nervous System

In the ANS, acetylcholine is released in the following sites:

- All pre- and post-ganglionic parasympathetic neurons
- All preganglionic sympathetic neurons
- Preganglionic sympathetic fibers to suprarenal medulla, the modified sympathetic ganglion; on stimulation by acetylcholine, the suprarenal medulla releases epinephrine and norepinephrine
- Some postganglionic sympathetic fibers
- Pseudomotor neurons to sweat glands.

In Central Nervous System

In the central nervous system, ACh has a variety of effects as a neuromodulator upon plasticity, arousal and reward. ACh has an important role in the enhancement of sensory perceptions when we wake up and in sustaining attention.

Damage to the cholinergic (acetylcholine-producing) system in the brain has been shown to be plausibly associated with the memory deficits associated with Alzheimer's disease. ACh has also been shown to be the most important inducer of REM sleep.

Pathways
There are three ACh pathways in the CNS:

- Pons to thalamus and cortex
- Magnocellular forebrain nucleus to cortex
- Septohippocampal

Other neurotransmitters

The gamma-aminobutyric acid (GABA) system is more generally distributed throughout the brain. Nevertheless, it has an overall inhibitory effect.

Opioid peptides - these substances block nerve impulse generation in the secondary afferent pain neurons. These peptides are called opioid peptides because they have opium-like activity. The types of opioid peptides are:

- Endorphins
- Enkephalins
- Dynorphins
- Substance P
- Octopamine

Other uses

Neuromodulation also refers to the medical procedure used to alter nervous system function, mostly known about the relief of pain. This use consists primarily of electrical stimulation, lesioning of specific regions of the nervous system, or infusion of substances into the cerebrospinal fluid. Electrical stimulation are devices such as Spinal Cord Stimulators (SCS) (surgically implanted) or transcutaneous electrical nerve stimulation devices (externally placed).

2.7.1. Therapeutic neuromodulation: defining a new treatment platform 23 (Chapt.39)

It has been proposed that TMS, along with other device-based therapies emerging in neurorehabilitation, may define a potential new treatment platform, since they share some common features, and because of the strikingly different approach to treatment that they present in comparison with existing therapeutics for stroke. It therefore becomes important to consider the potential impact of these novel treatments on changing the clinical process of treatment of stroke for the patient and the clinician, and implications for clinical trial design.

Device-based therapies (e.g. TMS, vagus nerve stimulation, direct current depolarization) share a common process of delivering an electrical current to the CNS. The method and localization of the current delivery differs markedly with the different interventions. These approaches exploit the fact that neuronal tissue is an electrochemically active substrate, and also build on the emerging knowledge that the pathophysiology of neurological and psychiatric diseases manifest themselves as functional disturbances in distributed neuronal networks in the brain.

As advantage, the TMS method is applied in an outpatient setting with no surgical intervention or anesthetic procedure. Moreover, the regional anatomic and spatial localization of therapeutic intervention is much greater with TMS than it is with other devices.

Another important way in which non-pharmacological somatic interventions differ from the pharmacotherapies is that they are applied episodically rather than continuously. Medications can be thought of as exerting a tonic sustained action on the brain, moving it from one neurochemical state to another. By comparison, therapeutic neuromodulation is more temporallyh and spatially localized, and therefore represents a dynamic interplay of the specific intervention with the adaptive response of the brain during the extended periods of absence of the therapeutic intervention itself. While the neurobiologic significance of this difference is not completely understood, the clinical implications of this difference could be considerable. For example, it is possibly that the episodic nature of their application may contribute to their tolerability. Tolerability can have a substantial impact on the risk-benefit outcome.

Data derived from transcranial magnetic stimulation (TMS) studies suggest that transcallosal inhibition mechanisms between the primary motor cortex of both hemispheres may contribute to the reduced motor performance of stroke patients. Grefkes et al. 38 investigated the potential of modulating pathological interactions between cortical motor areas by means of repetitive TMS using functional magnetic resonance imaging (fMRI) and dynamic causal modeling (DCM). Eleven subacute stroke patients were scanned 1-3 months after symptom onset while performing whole hand fist closure movements. After a baseline scan, patients were stimulated with inhibitory 1-Hz rTMS applied over two different locations: (i) vertex (control stimulation) and

(ii) primary motor cortex (M1) of the unaffected (contralesional) hemisphere. Changes in the endogenous and task-dependent effective connectivity were assessed by DCM of a bilateral network comprising M1, lateral premotor cortex, and the supplementary motor area (SMA). The results showed that rTMS applied over contralesional M1 significantly improved the motor performance of the paretic hand. The connectivity analysis revealed that the behavioral improvements were significantly correlated with a reduction of the negative influences originating from contralesional M1 during paretic hand movements. Concurrently, endogenous coupling between ipsilesional SMA and M1 was significantly enhanced only after rTMS applied over contralesional M1. Therefore, rTMS applied over contralesional M1 may be used to transiently remodel the disturbed functional network architecture of the motor system. The connectivity analyses suggest that both a reduction of pathological transcallosal influences (originating from contralesional M1) and a restitution of ipsilesional effective connectivity between SMA and M1 underlie improved motor performance.

3. OBJECTIVES

3.1. To **assess normal primary motor areas (M1)** in five **normal** subjects and their **connectivity** by means of three techniques:

- Magnetic Resonance (**MR)** for 3D imaging,
- Neuronavigated Transcranial Magnetic Stimulation (**nTMS)**, for cortical mapping, and
- Diffusion Tensor Imaging (**DTI)**, for subcortical anatomy –tractography, connectivity analysis.

3.2. To find the **excitability threshold** and the **stimulation's coordinates** for the APB point.

Assessment of a concrete cortex-muscle pathway involves in this case the location of the Abductor Pollicis Brevis (**APB**) point in the primary motor area (M1). This is performed by means of: brain mapping by nTMS, measurement of its physiology through Motor Evoked Response and evaluation of its connectivity –Tractography- with DTI. Then, the normal group's assessment would supply the average values respect to which subsequent patients' groups could be compared -and considered or not as potential subsidiary of neuromodulator treatment.

3.3. To establish in this way the first steps of a helpful and feasible **"functional assessment prior to neuromodulatory treatment" protocol** oriented to the neuro-rehabilitation of patients with **spastic hand after stroke**, and looking for the progressive changes in their neuronal networks.

4. MATERIAL

4.1. Five normal subjects to perform the cortical mapping of Primary Motor Area (M1) and its connectivity studies, performed by means of fMRI, Navigated TMS and DTI.

TMS stimuli were delivered by means of a MagPro30 magnetic stimulator from Medtronic®, and muscle responses were collected through surface electrodes from Abductor Pollicis Brevis (APB), using an EMG equipment KeyPoint®.Net from Medtronic. Continuous EMG recording was held, also while performing stimulation, to ensure that the stimulation was delivered in complete muscle relaxation. Navigated TMS maps were obtained by means of a NBS (Navigated Brain Stimulation) Nexstim from eXimia ®, and maps were exported with DICOM export software and loaded into a Dextroscope ® equipment to perform DTI studies of the fibers underlying the motor points mapped by means of the navigated TMS.

4.2. Technical equipment: Electrophysiological Devices and Specifications:

4.2.1. Magnetic Resonance (MRI) following specific requirements to be compatible with the Neuronavigator's software (NBS).

4.2.2. Neuronavigated Magnetic Transcranial Stimulation (nTMS).

4.2.2.1. Magpro30 Magnetic Stimulator from Medtronic®.

4.2.2.2. NBS System Nexstim from eXimia® for obtaining nTMS maps.

4.2.3. EMG equipment KeyPoint®.Net from Medtronic. For "physiological check-out" by means of Evoked Potentials.

4.2.4. DICOM export software: Exporting maps from NBS to DTI.

4.2.5. Diffusion Tensor Imaging (DTI): Performance of the normal motor maps' Hot Spots' Tractography. Dextroscope®. The vectorial calculation mathematical algorithm was deterministic, with an angle of tolerance of 30º.

4.2.1. Magnetic Resonance (MRI) following specific requirements to be compatible with the Neuronavigator's software.

MRI Requirements. Loading anatomical images (MRI) into eXimia NBS.

Before using eXimia NBS, there is need to acquire and set up the MR images of the patient.

- Acquire good quality MR images comprising of the whole head so that ears, nose, and the head surface are clearly visible.

- It is very important that there are no wrinkles or skin folds on the patient's scalp (due to a headrest, for example) during the MR imaging or during stimulation. If there is a discrepancy in the patient's head surface between the MR imaging and NBS head registration, there will be inaccuracies in TMS stimulation.

- Do not use visible hearing protection inside the MRI.

How to load MR images into eXimia NBS

a. Copy the MRI stack into the MRI_DATA folder on the NBS computer system.

b. Store the MRI stacks so that one set of images of one subject is in one folder.

c. You can structure the folders inside the MRI_DATA folder according to your own needs.

The following table describes more accurately how to prepare MR images for eXimia NBS and how to load MR images in eXimia NBS.

Field of view (FOV)	• Neither the scanning table or headrest should be included in the FOV. • MRI markers and landmarks must be included in the scan (if used). • The forehead, eyes, ears and entire nose (the tip of the nose must not be cropped) must be included in the scan. • There must be no markers over the face, or ears of the patient (if needed, a marker may be used on the chin of the patient).
Scan attributes	• T1-weighted images required. • 3D MR scans may be used. • Voxel size approximately 1x1x1 mm. • Sagittal images are recommended, axial and coronal images are supported. • Sequential scans of 1 mm thickness and 0 mm slice gap required. • Pixel size, matrix size and table position must not be altered during the scan.
Suggested 3D T1 sequences (scanner specific)	• Siemens: • MPRAGE • GE: • SPGR • Philips: • T1-FFE or TFE • Acquire anatomical images without using sensitivity encoding (SENSE) technique because the scanner reconstruction algorithm removes noise and modifies the image gray scale histogram used by the NBS system.
Angulation	• Positive and negative values may be used, but must not be altered during the scan. • Angulation should be less than +/- 10 degrees.
Patient orientation	• Head first, supine. Make sure that the patient scalp is as smooth as possible (no wrinkles in the skin caused by a headrest, for example).
Image compression	• Save the MRI data on a CD-ROM in uncompressed format.
Format	• DICOM format is recommended. Analyze format is supported.

Table: MR image requirements

4.2.2. Neuronavigated Magnetic Transcranial Stimulation (nTMS).

4.2.2.1. MagPro30 Magnetic Stimulator from Medtronic® 39

MagPro comprehends a line of non-invasive magnetic stimulation systems including both dedicated and general-purpose stimulators, all of which can be connected to an EMG system. This represents a variety of systems for use in neurophysiology, neurology, rehabilitation, as well as therapeutic research.

The MagPro 30 is an advanced, high performance magnetic stimulator designed primarily for clinical use. Its applications are:

- Physiology examination of the motor pathways in the peripheral nervous system
- Improving muscle function in a therapeutic manner

4.2.2.2. NBS System from EXimia® for obtaining nTMS maps: Navigated Brain Stimulation for non-invasive mapping of the cortex 34

The Nexstim Navigated Brain Stimulation (NBS) System from EXimia® creates an accurate and detailed map of the critical functions of the cortex using a standard MRI brain scan.

NBS uses stereotactic infrared guided system, that positions the transcranial magnetic stimulation (TMS) coil, into the MRI, previously loaded into the computer. This allows to non-invasively stimulation of precise areas of the cortex (estimated surface area of cortex stimulation is about 10 mm).

Sophisticated, real-time data processing and modeling enables unsurpassed accuracy and control of the electric filed (E-field) inside the brain. Integrated EMG monitoring instantly shows the responses to stimuli in the central nervous system (CNS) and the peripheral nerves. NBS results are presented as detailed color maps of the critical eloquent areas visualized in a 3-D rendering of the brain.

NBS allows confident interpretation of measurement results since it is a direct method, like electrocortical stimulation. Avoiding the uncertainty of indirect methods, like fMRI for example, is a crucial advantage in neurosurgical decision making. NBS also performs cortical mapping faster and more cost-effectively than alternative functional imaging modalities.

4.2.3. EMG equipment KeyPoint®.Net from Medtronic. For "physiological check-out" by means of Evoked Potentials.

Keypoint ®.NET EMG/EP Systems 40
A conventional EMG equipment used in the Neurophysiology Department.
It is used here to record most of responses after cortical motor area stimulation.

4.2.4. DICOM export/import software: Exporting maps from NBS to DTI.

DICOM is a global Information-Technology **standard** that is used in virtually all hospitals worldwide. Its current structure, which was developed in 1993, is designed to ensure the interoperability of systems used to: Produce, Store, Display, Process, Send, Retrieve, Query or Print medical images and derived structured documents as well as to manage related workflow. DICOM is known as NEMA Standard PS3, and as ISO Standard 12052. 41

4.2.5. Dextroscope® (Volume Interactions, Ltd.) with stereoscopic vision.

Diffusion Tensor Imaging (DTI): Performance of the normal motor maps' Hot Spots' Tractography. 42

We used a virtual reality workstation (Dextroscope®) to develop a simulation of primary motor cortex M1.

Providing a three-dimensional interactive environment, it constitutes a great help to plan and properly simulate a wide variety of procedures –from the most conservative neurorehabilitation techniques to wide neurosurgical interventions.

5. METHODS

5.1. Primary Motor Area (M1) maps by means of Navigated TMS

TMS stimuli were delivered by means of a magnetic stimulator, and muscle responses were collected through surface electrodes from Abductor Pollicis Brevis (APB), using an EMG/EP device. Continuous EMG recording was held, also while performing stimulation, to ensure that the stimulation was delivered in complete muscle relaxation. Navigated TMS maps were obtained by means of a NBS system, and maps were exported with DICOM export software and loaded into a Dextroscope ® equipment to perform DTI studies of the fibers underlying the motor points mapped by means of the navigated TMS.

5.1.1. Motor threshold at rest (MTR) of the APB muscle.

Using biphasic single pulses the intensity threshold stimuli for the APB was obtained. Threshold intensity was defined as the intensity needed to obtain the 50% of responses bigger than 50 microV of amplitude response from the APB.
Then, the intensity of the stimulus was increased until reach the 110% of threshold intensity for the APB. Responses of the APB obtained at this intensity, were measured in latency and amplitude. Muscle responses were collected by means of bipolar surface electrodes (20Hz-10KHz band pass filter, gain of 100 microV, sweep duration of 100 miliseg. in the EMG equipment).

(*)"Threshold": The level at which a clear and abrupt transition occurs from one state to another. In this context, the term refers to the voltage level at which an action potential is initiated in a single axon or a group of axons.

5.1.2. Hot Spots (at 110% of motor threshold) of the APB muscle in five healthy, future "control", patients.

Once APB response was obtained, the TMS coil was moved in different orientations until the better response was obtained. This maneuver is repeated moving the coil along the primary motor area, to obtain the better response of each muscle and determining thus the hot spot position. These muscle Hot Spots points were located on the cortex and plotted in the NBS table maps. Control over the maneuver is assessed by means of the muscular responses obtained.

SUBJECT	SEX	AGE	THRESHOLD (%)	M1 APB					
				Hot Spot	Latency (ms)	Amplitude (mV)	Intensity (%TMR)	Dose (V/m)	Single stim. (Y/N)

Parameters:

- **Hot Spot:** coordinates given by the software, corresponding to each precise 3D area where each of the considered stimuli elicits its expected peripheral activity.
- **Latency (ms)**
- **Amplitude (mV)**
- **Intensity (%MTR):** Percentage of the Motor Threshold at Rest, (% of stimulation respect to the total charge). Such charge intensity of the capacitor/condenser corresponds to the number of volts/m^2 which the cortex would receive.

  (*)Capacitor or condenser: An electric circuit element used to store charge temporarily, consisting in general of two metallic plates separated and insulated from each other by a dielectric.
- **Dose (V/m)**
- **Single stim. (Y/N)**: Single Vs. Repetitive stimulus. In this case, it is given single stimulus always.

5.2. To export the Hot Spot points' Map and load into the Dextroscope to perform the DTI. DTI uses a deterministic mathematical algorithm method with a 30º angle tolerance threshold.

5.3. This methodology would be adapted to at least five stroke patients with spastic sequelae, outlining a feasible protocol by adding the next procedures:

5.3.1. To determine the spasticity level by means of clinical quantitative tests, such as the measurements of hand angles position (hand, elbow and shoulder -at rest and when stretching). (See *"Spasticity Patterns"* at the Introduction section).

5.3.2. To determine the improvement of the patients by means of manuality tests (for example, scrolling in holes in wood task).

5.4. Development of a project, a diagnostic-therapeutic protocol based on neuronavigated rehabilitation of post-stroke patients (see "Results" and "Discussion" sections).

5.5. Statistical analysis: Average and two-Standard Deviations of the five healthy subjects' obtained data would be performed (see "Results" section).

6. RESULTS

6.1. Cortical mapping performed in 5 normal subjects.

6.2. Accuracy –Cortical anatomy of M1 Area

6.3. Physiological Evaluation –Response to evoked potentials

6.4. Cortico Sub-cortical connectivity

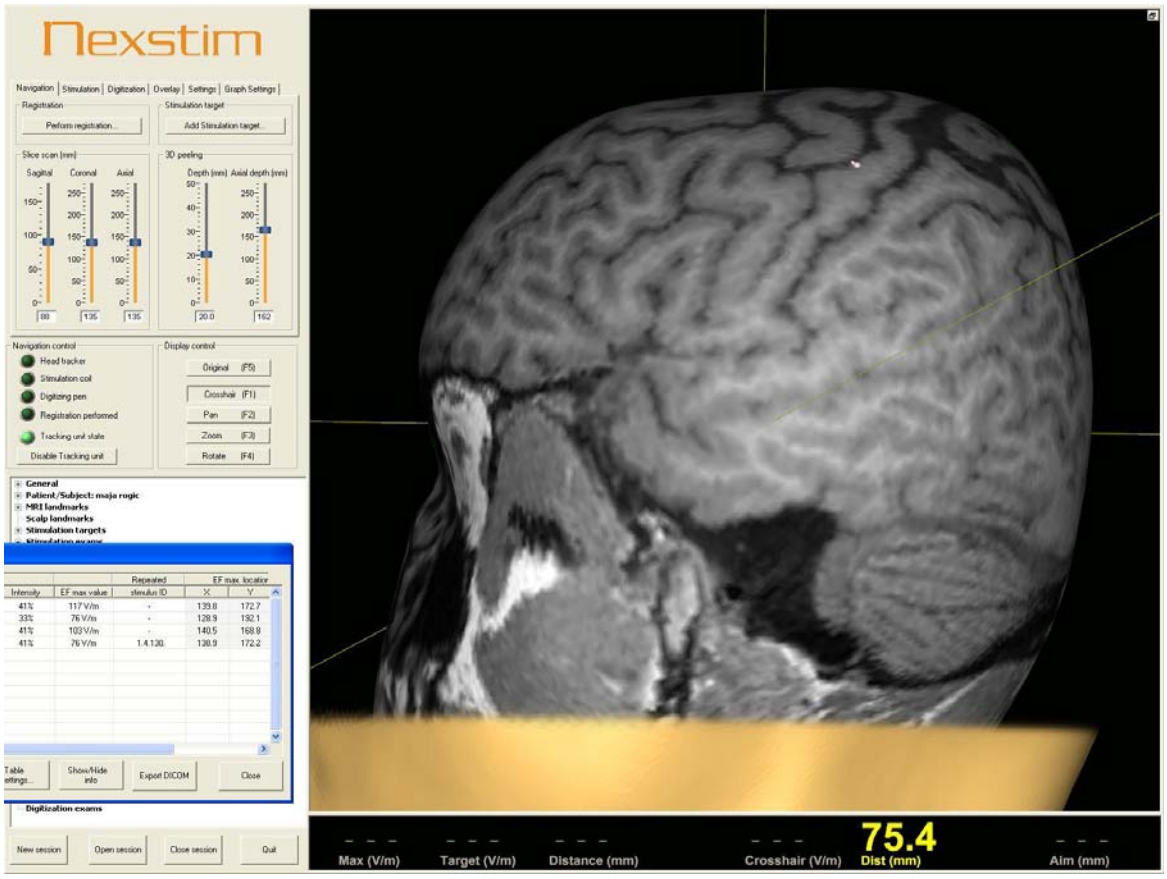
6.5. Statistical analysis

6.6. Development of a diagnostic-therapeutic protocol based on neuronavigated rehabilitation of post-stroke patients.

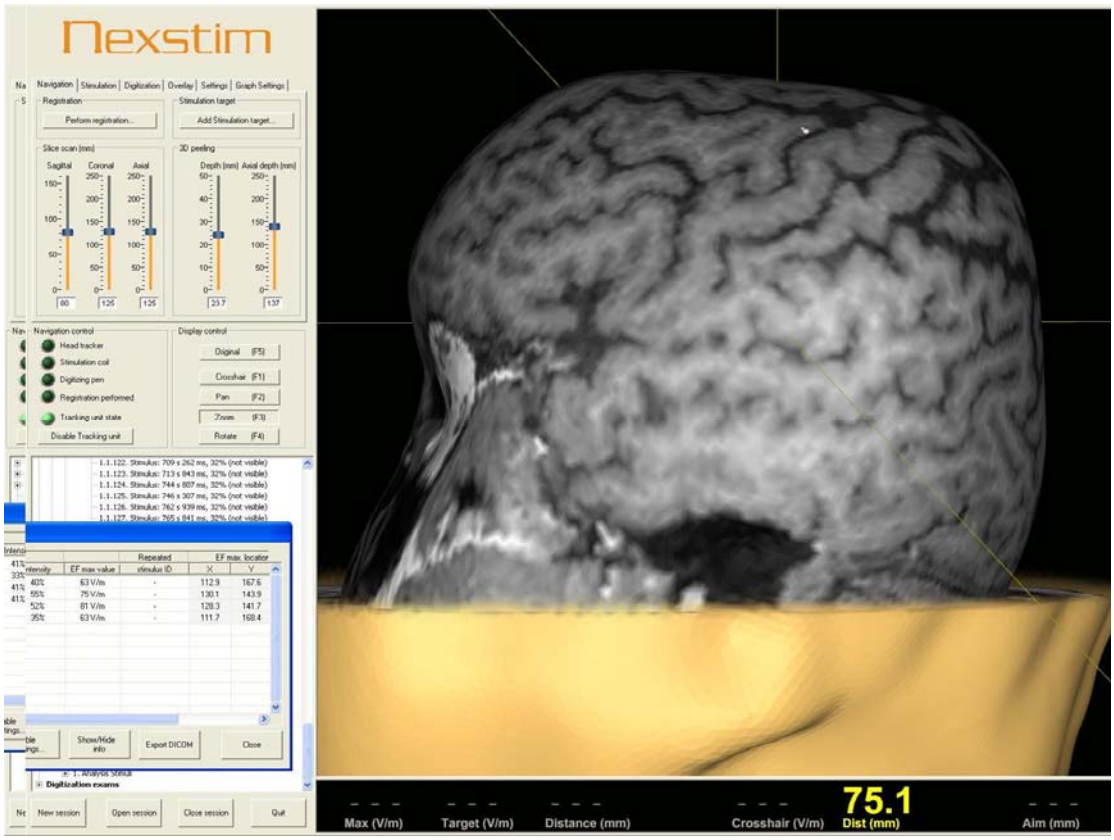
A structural and functional map of the five healthy patients was performed, showing the location of their APB's hot spots, their cortico-subcortical projections, and the latency, amplitude and threshold of their motor evoked potentials. Consequently, their mean values could serve as control data for further comparisons with stroke patients.

6.1. Cortical mapping –without surgical checking/test- was performed in 5 patients.

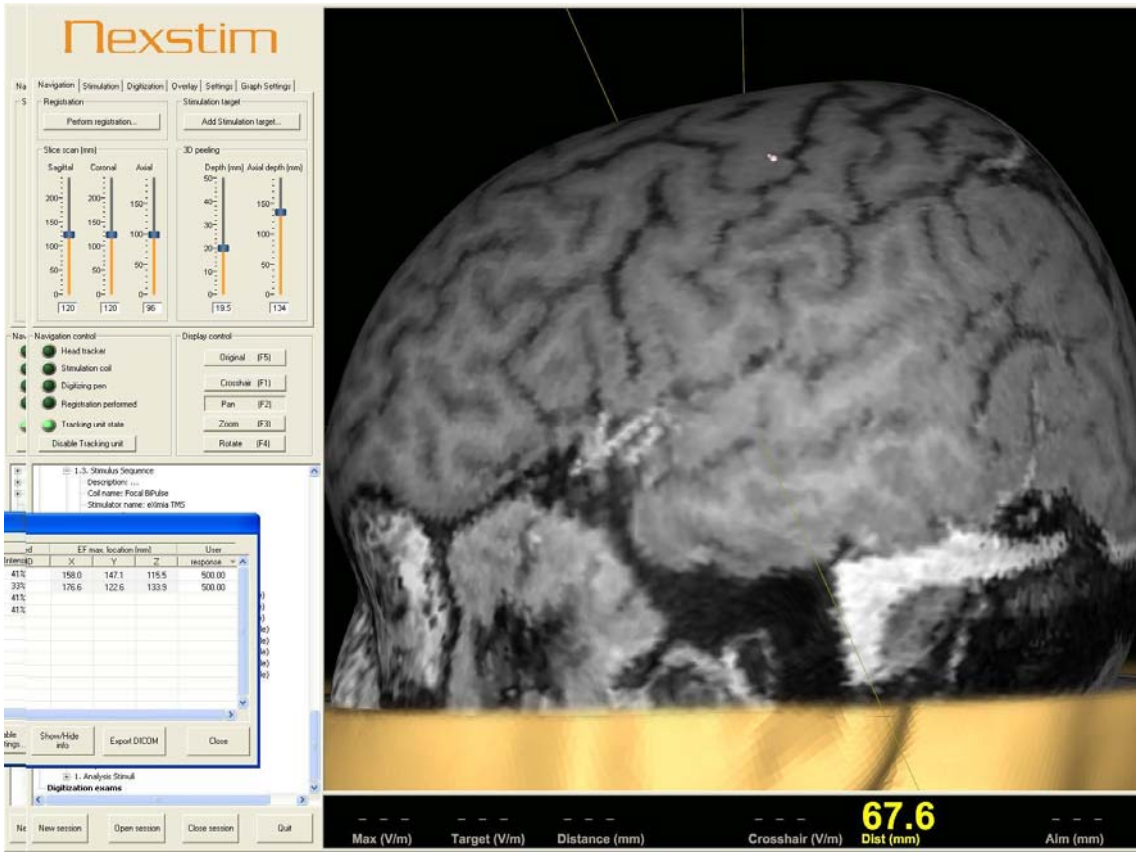
RESULTS:



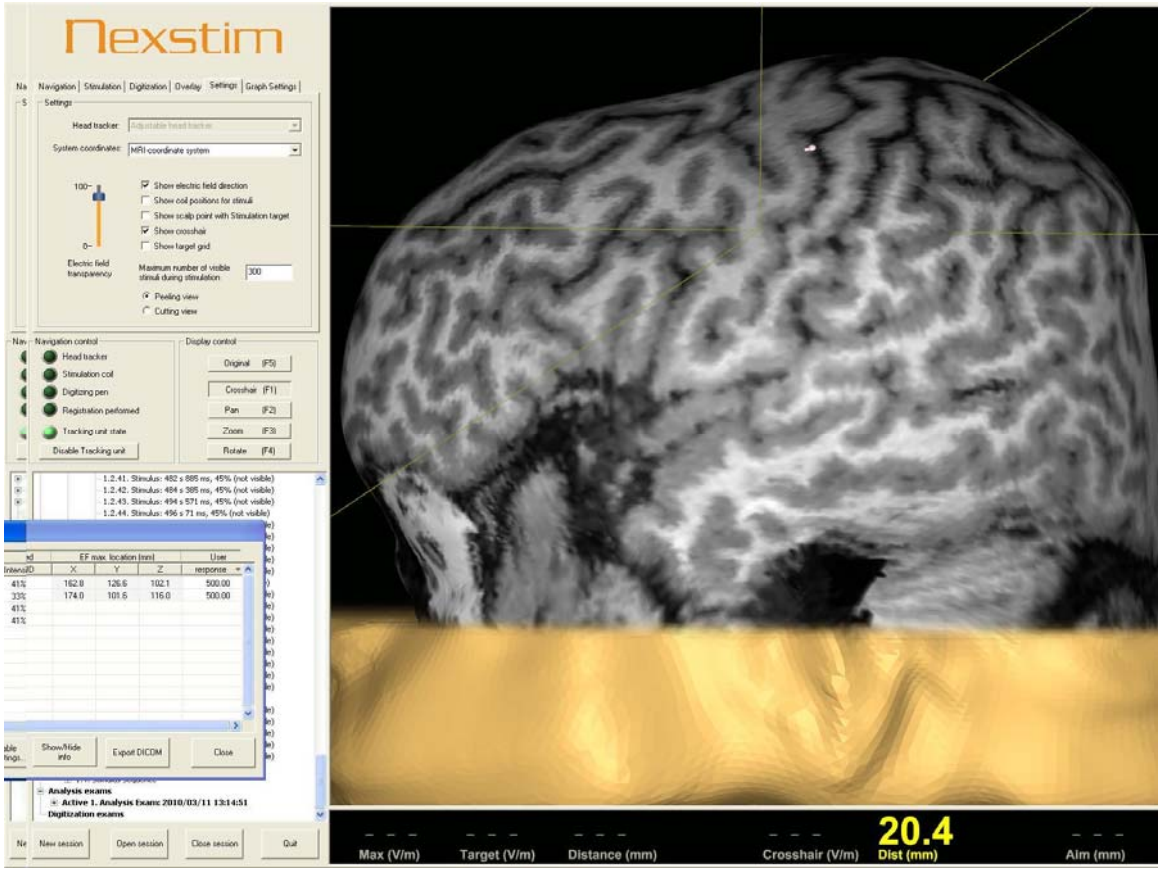
APB Mapping 1 (Patient "M")



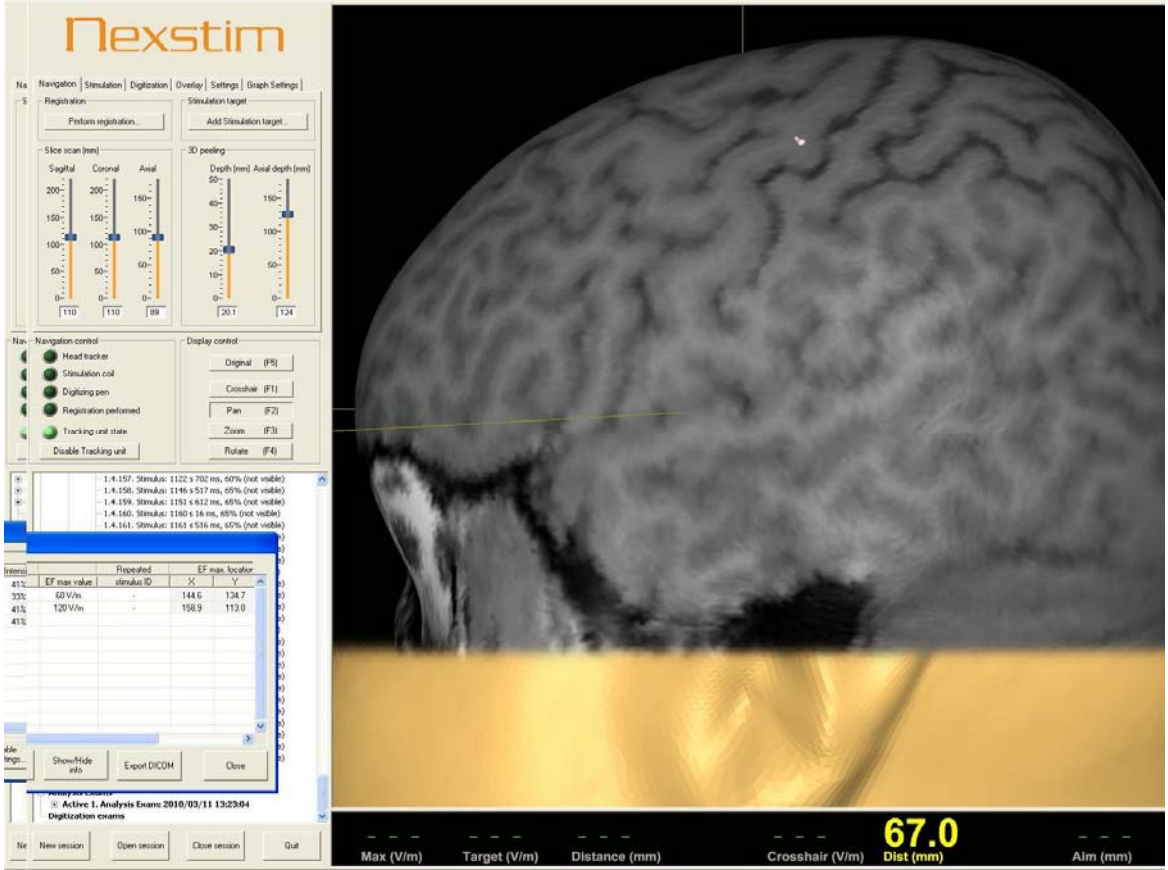
APB Mapping 2 (Patient “V”)



APB Mapping 3 (Patient “G”)



APB Mapping 4 (Patient “J”)



APB Mapping 5 (Patient “A”)

6.2. Accuracy –Cortical anatomy of M1 Area

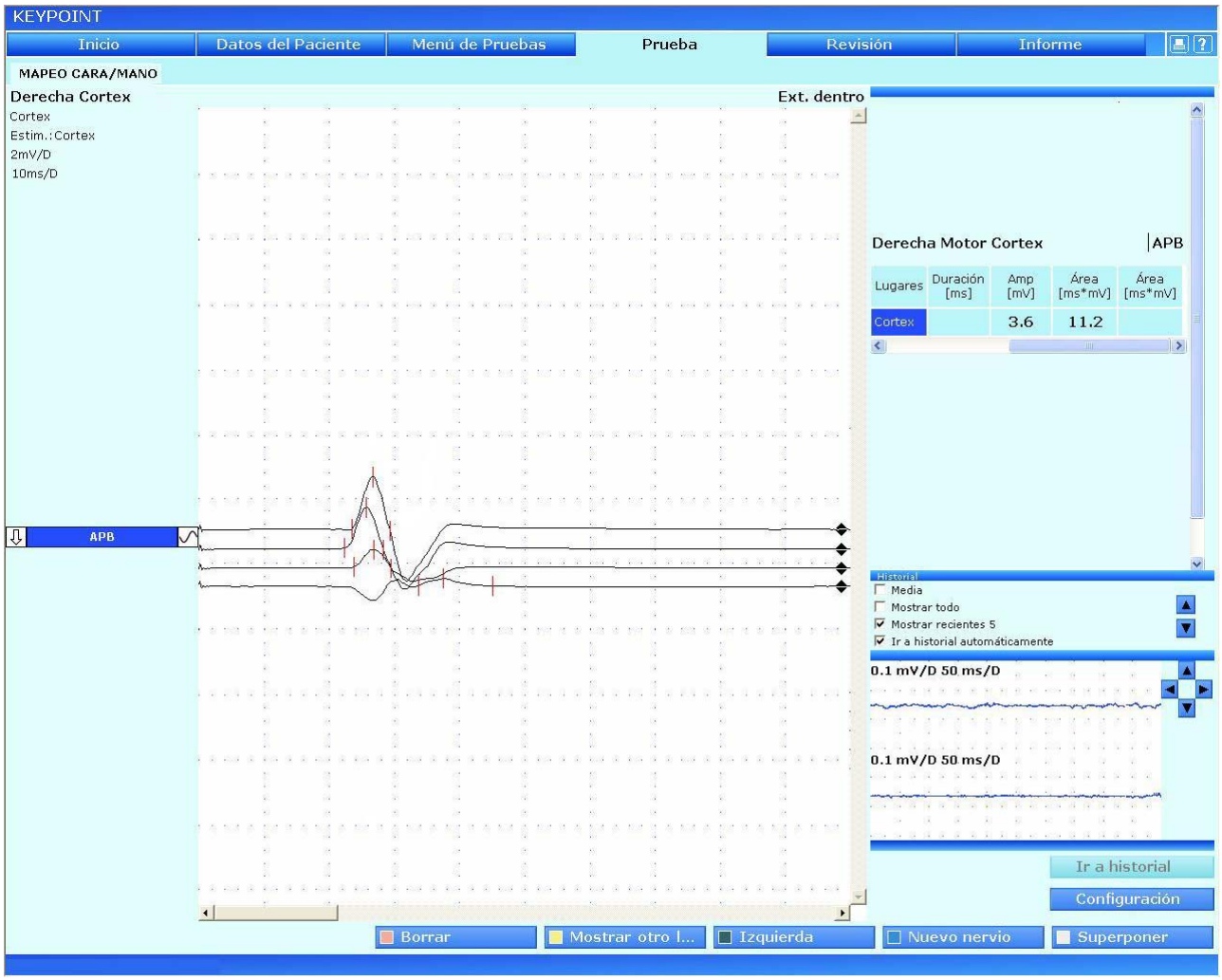
Anatomic comparison measurements of nTMS and DCS maps results are shown in the table. Considering the APB point from all the patients, overlapping is about 75% of surface, and the distance difference is about 5mm of average.

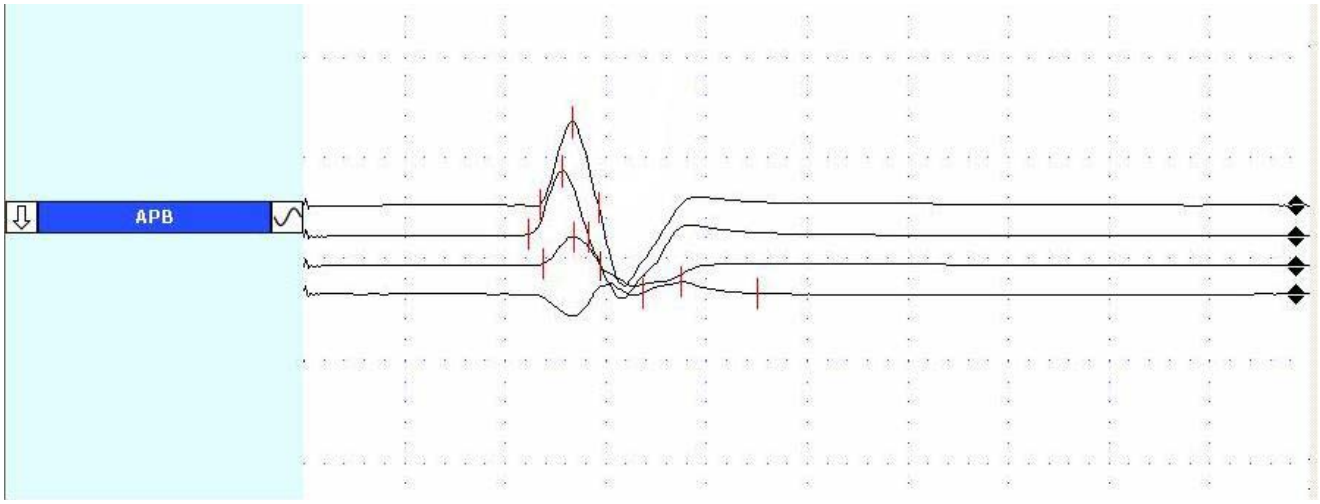
SUBJECT	SEX	AGE	THRESHOLD (%)	M1 APB					
				Hot Spot	Latency (ms)	Amplitude (mV)	Intensity (110% of TMR)	Dose (V/m)	Single stim. (Y/N)
M	F	27	33	1.1.42	22.7	0.44	37	74	Y
V	M	65	38	3.2.41	22.6	0.3	40	74	Y
G	M	50	39	1.1.22	25	0.72	39	85	Y
J	M	32	33	1.1.84	20.8	0.054	33	71	Y
A	F	31	28	1.2.6	22.4	0.36	31	60	Y

6.3. Physiological Evaluation –Response to evoked potentials-

When looking at the arm and hand muscles, all positive response to TMS were positive to Direct Cortical Stimulation (DCS) while all negative points to DCS were also negative to TMS, when these areas were stimulated.

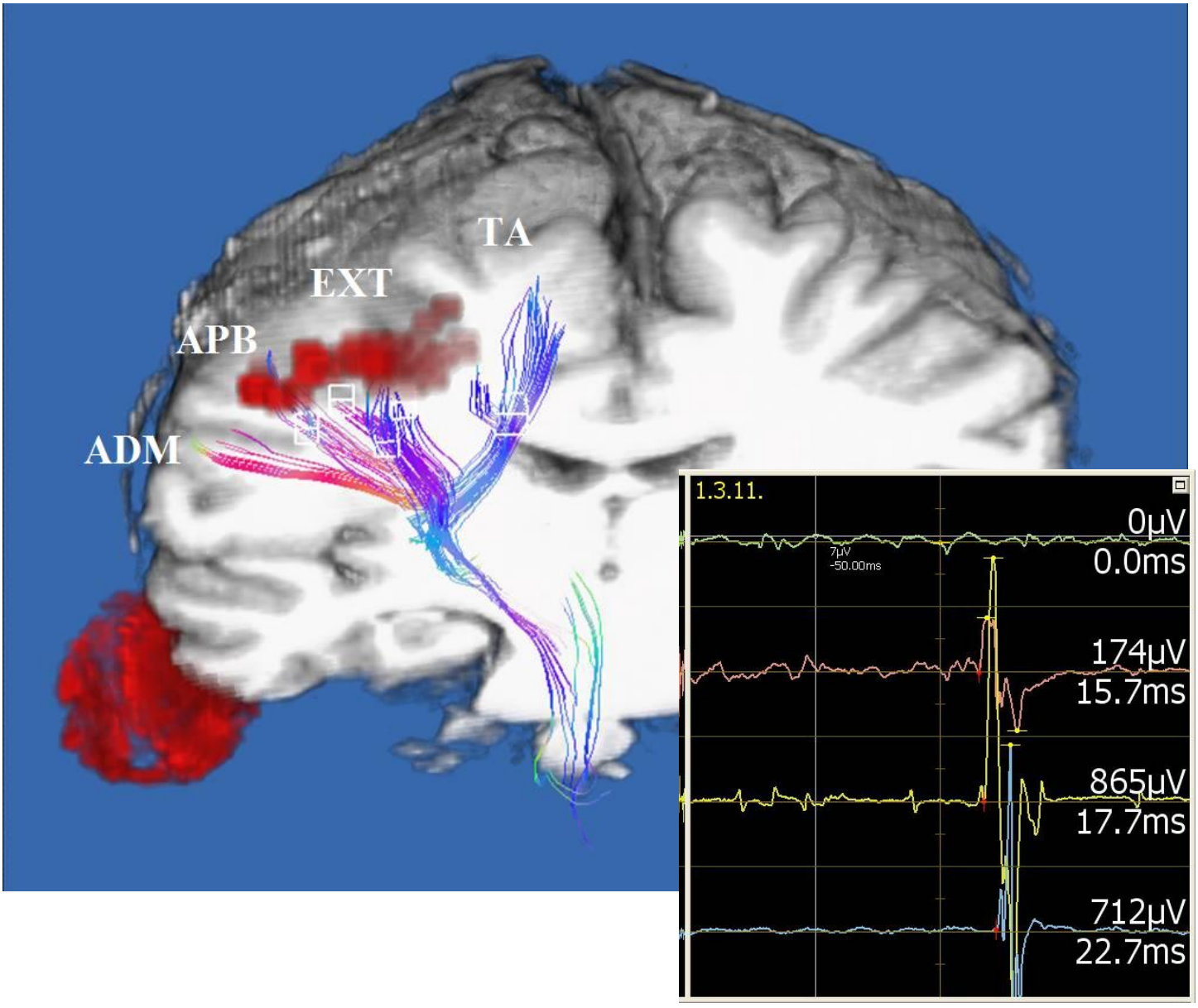
Among other muscles, Abductor Pollicis Brevis (APB) was the most accessible when checking its response evaluation.

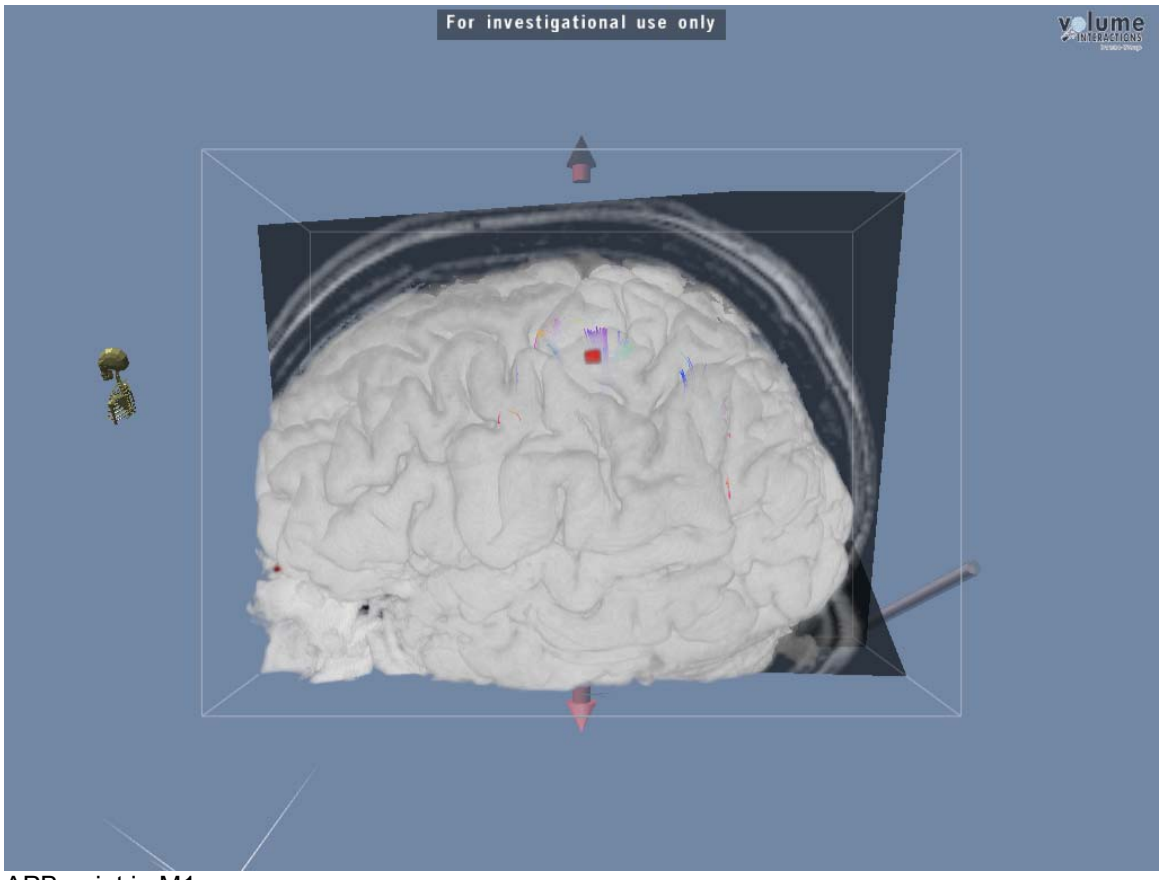

KEYPOINT
Inicio
Datos del Paciente
Menú de Pruebas
Prueba
Revisión
Informe
MAPEO CARA/MANO
Derecha Cortex
Ext. dentro
Cortex
Estim.: Cortex
2mV/D
10ms/D
Derecha Motor Cortex
APB
Lugares
Duración [ms]
Amp [mV]
Área [ms*mV]
Área [ms*mV]
Cortex
3.6
11.2
APB
Historial
Media
Mostrar todo
Mostrar recientes 5
Ir a historial automáticamente
0.1 mV/D 50 ms/D
0.1 mV/D 50 ms/D
Ir a historial
Configuración
Borrar
Mostrar otro l...
Izquierda
Nuevo nervio
Superponer


APB

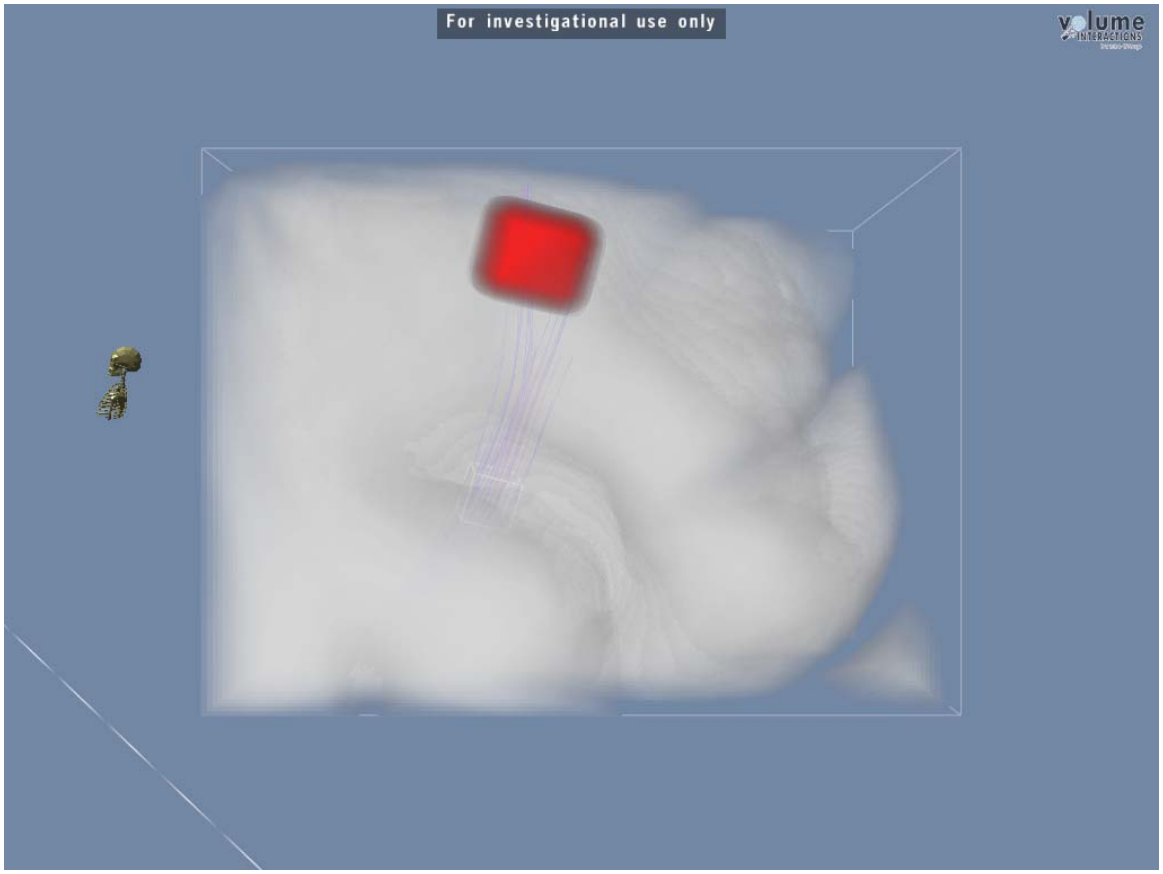
6.4. Cortico Sub-cortical connectivity

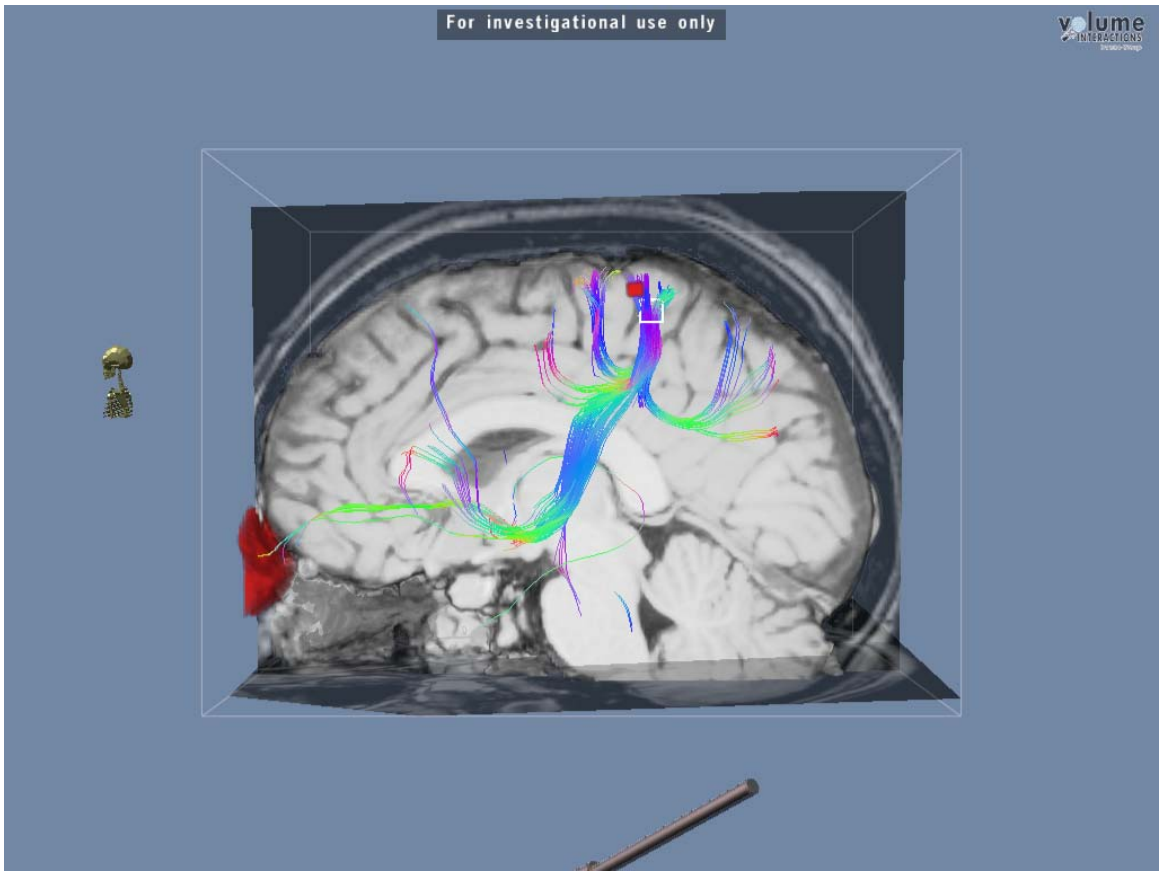
ROI emplacement at the nTMS points of the motor area display the fiber tracts in an easily recognized pyramidal tract and the whole sub-cortical pathway is shown until midbrain is reached. This anatomical tract can be related to the cortical hot spot motor point to each identified muscle by means of the EMG response, and fiber populations of the fiber tract can also be related with the amplitude of the EMG response (Compound Motor Action Potential, CMAP).





APB point in M1 area





Cortico-subcortical connectivity. Origin: APB's "Hot spot"

6.5. Statistical analysis

SUBJECT	SEX	AGE	THRESHOLD (%)	M1 APB					
				Hot Spot	Latency (ms)	Amplitude (mV)	Intensity (110% of MTR)	Dose (V/m)	Single stim. (Y/N)
M	F	27	33	1.1.42	22.7	0.44	37	74	Y
V	M	65	38	3.2.41	22.6	0.3	40	74	Y
G	M	50	39	1.1.22	25	0.72	39	85	Y
J	M	32	33	1.1.84	20.8	0.054	33	71	Y
A	F	31	28	1.2.6	22.4	0.36	31	60	Y
AVERAGE	-	41	34.2	-	22.7	0.3748	36	72.8	-
±SD	-	± 16,078	± 4,438	-	± 1,5	± 0,241	± 3,873	± 8,927	-
±2SD	-	± 32,156	± 8,876	-	± 3	± 0,482	± 7,746	±17,854	-
RANGE (AV±SD)	-	(24.922, 57.078)	(29.762, 38.638)	-	(21.2, 24.2)	(0.1338, 0.6158)	(32.127, 39.873)	(63.873, 81.727)	-
RANGE (AV±2SD)	-	(8.844, 73.156)	(25,324 , 43.076)	-	(19.7, 25.7)	(-0.1072(e), 0,8568)	(28,254 , 43,746)	(54.946, 90.654)	-

Of the five healthy subjects studied,

- 60% were male (3 out of 5) and 40% were female.
- They were aged 41±16,078 years old
- Average Motor Threshold at Rest (MTR): 34,2 ± 4,438 %
- The Hot Spots are codes given by the NBS software, meaning coordinates at cortex.
- Average latency: 22,7 ± 1,5 ms
- Average amplitude: 0,3748 ± 0,241 mV
- Average intensity (110% of MTR): 26 ± 3,873
- Average dose: 72,8 ± 8,927 V/m
- The given stimuli were all of them single.

6.6. Development of a diagnostic-therapeutic protocol based on neuronavigated rehabilitation of post-stroke patients, which would meet the next material requirements (see “Discussion” section for the Funtional outcome’ parameters):

6.6.1. Post-stroke patients to perform the cortical mapping in the M1 Area.

6.6.2. Tractography (DTI) in the post-stroke patients.

6.6.3. To apply Neuromodulatory therapy by means of nTMS.

6.6.4. In patients with improvement, perform a second map of M1 and connectivity studies to study/assess the changes –if there are measurable changes. (Neuronavigation, Cortical mapping, Tractography by DTI).

6.6.5. Analysis of the benefits of the therapy: The functional outcome measurements for spasticity would include active and passive thumb abductions, thumb oppositions and pinch-force where measured ½-1h before, 1/2h and 2 days after each rTMS session and 2 months after the last rTMS (see table at the “Discussion” section).

7. DISCUSSION

This is a preliminary step to define a motor map with precision, in order to establish with accuracy the characteristics of the Penfield homunculus in each subject, with the objective of further therapeutic applications.

7.1. Cortical Anatomy of the M1 Area

To perform a motor cortex map in patient by Navigated TMS takes about 40 minutes, including MRI loading, measuring the threshold of thenar muscles at rest, and the mapping of the whole primary motor area. During the study, any of the patients referred any complain after stimulation, nor any undesired effect of complication, like seizures etc., have being occurred. 43, 44

7.2. Physiological evaluation (response to evoked potentials)

When looking at the arm and hand muscles, all positive response to TMS were positive to Direct Cortical Stimulation (DCS) while all negative points to DCS were also negative to TMS, when these areas were stimulated.
Among other muscles, Abductor Pollicis Brevis (APB) was the most accessible when checking its response evaluation, in part because of the wider representation and easier approach of the fine hand muscles over the cortex –helpful for establishing the first references of the brain mapping.

7.3. Study of the Cortico-Subcortical Connectivity

The aim of the study was to perform de DTI by exporting cortical NTMS maps into Dextroscope and to show the fiber tracts involved in the cortical area stimulated, in association of muscle amplitude response, for each muscle in each point, in order to have the sub-cortical anatomy but the DTI not only functionally identified, but also functionally evaluated.

Accuracy in anatomic localization of the NTMS has been previously demonstrated by other research groups, more related to neurosurgery 38 45-47 and their data are similar of ours, with a variation from nine to five millimeters. This variation may be due to the brain shift after craniotomy, to measurement difficulties in a three dimension measurement or to intrinsically variation due to the technical accuracy of the equipments. However this difference from 9 to 5 millimeters can be assumed surgically and lets into a reference point that is enough for surgeon

orientation and in consequence, less number of stimulations needs to be delivered to perform a complete functional map, diminishing the time of cortical examination needed and the risk of post-stimulation seizures. Of course border of resection will always need to be mapped.

DTI methodology uses two mathematical algorithms. The **Deterministic** method has more specificity but less sensibility. The **Probabilistic** method has less specificity, but more sensibility. For pyramidal motor fiber tract studies we chose the Deterministic (more specific) tract, however in non primary areas the Probabilistic method can be more reliable in order to show more connections, thanks to the major sensibility of this method. This lower specificity maybe compensated by the knowledge of the stimulation point, and its functional study and recording.

Deterministic DTI has an anatomical **accuracy of 5 millimeters**, as it has been measured by other research groups 48-50 –in the case of neurosurgical approaches, by means of per-operatory subcortical stimulation.

Despite the anatomic accuracy estimated from 5 to 9 mm for the nTMS, and about 5 mm for the DTI, it provides a clear and orientative information, adding a functional localization of motor cortical points location and of the fiber tracts going down through the pyramidal tract. Also, as we know the amplitude and latency of the motor responses of each point, this physiological information can be transferred also to the fiber tracts by means of color scale, which can be illustrative for the relevance of each fiber tracts independently.

However, the conversion of the area or the point of stimulation, which is a representative idea of functional location, into the anatomical representation of the fiber tracts needs a more detailed discussion. Even considering the sensibility and specificity of the mathematical algorithm used for the DTI, the ROI is placed on a mere representative point were cortex has been stimulated. On an ideal way, the stimulation point must be converted on a volume, as the ROI it is, and probably this volume must have the dimensions of the magnetic field, which is also a volume, with the size or dimension of the intensity of the stimulus. Once the cortex map is made with the volume of the magnetic field that reach an area of cortical neurons population, the ROI volume adjusted to the magnetic field volume, may display a more precise and real population of fiber tracts.

Using the hot spot, that is the maximal amplitude response for each muscle, we get a cortical somatotopic map, but also we have the physiological information of the amplitude and latency response. If these points are transferred to the MRI to perform the DTI from these points, we can also add by means of color scale, the functional information of the response.
Ideally, to be more precise the volume of the point must contain, and be a representation of, the volume of the magnetic field delivered, then the DTI has to be adjusted to that volume and

plot the fibers included in that volume. DTI from that point of course does not represent the whole populations of fibers of the pyramidal tract, but only the fibers contained in the volume of the ROI adjusted for that point, that will carry the fibers from the hot spot muscle point.

Neurosciences' achievement of knowledge's process is based on the paradigm of disconnection produced by injuries, ischemia or tumours, its functional impairment related to the injured anatomic structures. Here we delivered stimulation, observed the physiological response to the stimuli, located the function and studied its connections.

This methodology is, finally, a fusion between physiology and anatomy of both, cortical and sub-cortical anatomy and functional localization. And here has been employed only in the most well known area of the human cortex and its sub-cortical connections.

Moreover, its is a very suggestive method to be used in other more complex areas, using the paradigm of disconnection by the use of the magnetic stimuli, and locating the disconnected function by the navigation system, the additional DTI studies of the area stimulated can give us more information of the connectivity of this functional localized areas.

In case of the absence of response at 110% of the threshold intensity, we increase stimuli at 120%, if any response is obtained at this intensity we ask to the patient for a small contraction and we measure the cortical muscle localization when the muscle response is seen.

7.4. Design of a Neurorehabilitation Project

This study has established the preliminary phases of a Neurorehabilitation project which would consist of neuromodulatory interventions (like contralesional 1-Hz rTMS, or direct proceedings) on motor function of spastic hand in stroke patients with ipsilateral motor corticospinal tracts.

The functional outcome measurements would involve:

- Active and passive thumb abductions (both radial and palmar),
- Thumb oppositions against each of the other fingers, and
- Pinch-force.

These would be measured:

- ½-1h before each rTMS session,
- 1/2 h and 2 days after each rTMS session, and
- 2 months after the last rTMS.

-	Pre 1st rTMS	Post 1st rTMS	2 days post 1st rTMS	Pre 2nd rTMS	Post 2nd rTMS	2 days post2nd rTMS	Pre 3rd rTMS	Post 3rd rTMS	2 days post3rd rTMS	2 months post 3rd rTMS
Radial abduction of thumb (activeº/passiveº)										
Palmar abduction of thumb (activeº/passiveº)										
Thumb oppositions:										
To 2nd finger (+/-)										
To 3rd finger (+/-)										
To 4th finger (+/-)										
To 5th finger (+/-)										
Pitch-Force (kg)										

Each patient would provide about 70 data, both quantitative and qualitative, which could be analyzed to verify the positive outcomes during their follow-up.

7.4.1. Background: Historical context, physical and scientific basis of the Transcranial Magnetic Stimulation 6-8

Therapies for motor recovery after stroke or traumatic brain injury are still not satisfactory. The intensive physical therapy shows still limited results about functional gains. The goal of motor training is to minimize functional disability and optimize functional motor recovery. This is thought to be achieved by modulation of plastic changes in the brain. Therefore, adjunct interventions that can augment the response of the motor system to the behavioural training might be useful to enhance the therapy-induced recovery in neurological populations. In this context, non-invasive brain stimulation appears to be an interesting option as an add-on intervention to standard physical therapies. Two non-invasive methods of inducing electrical currents into the brain have proved to be promising for inducing long-lasting plastic changes in motor systems: transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). These techniques represent powerful methods for priming cortical excitability for a subsequent motor task, demand, or stimulation. Thus, their mutual use can optimize the plastic changes induced by motor practice, leading to more remarkable and outlasting clinical gains in rehabilitation. In this project we would discuss how these techniques can enhance the effects of a behavioural intervention and the clinical evidence to date.

The application of transcranial magnetic stimulation involves non-invasive stimulation of the cerebral cortex using externally applied magnetic fields. The treatment of illnesses with magnetized iron-containing stones was practiced in ancient Egyptian and Greek medicine. In 18th century Europe, Franz Mesmer claimed to heal the sick with magnetism, believing that magnetic forces held a special power over human behaviour. Magnetic fields were then applied in the treatment of neurological disorders. Various reports in 20th century European medical literature indicate the use of electromagnetism in the treatment of peripheral neuropathies and neuromuscular disorders. In the 1990s, considerable publicity was given to claims that magnets promoted the healing of various disorders of the body. Rarely were these claims supported by controlled studies. It was in this atmosphere, one of popular interest in magnetic therapy, that transcranial magnetic stimulation evolved as a scientific tool and gained acceptance in neuropsychiatry.

The first scientific attempts to use magnetic energy to alter brain activity were conducted by D'Arsonval in 1898 and Thompson in 1910 33. They built magnetic stimulators powerful enough to stimulate retinal cells and evoke perception of light flashes in human subjects. However, they were not powerful enough to activate the cerebral cortex. Merton and Morton showed in 1980 that it was possible to stimulate the motor area of the cortex through the intact scalp 8. They used a brief, high-voltage, electric shock to produce a motor evoked potential. A suitable instrument with sufficient power to activate cortical neurons was not designed until 1985 51, 52. It was shown that transcranial magnetic stimulation achieved the same effect as electrical stimulation of the cortex. Yet, contrary to the conditions of electrical stimulation, transcranial magnetic stimulation achieved its ends by using painless means. This device was adopted by the neurologists for measuring nerve conduction time. Single-pulse transcranial magnetic stimulation has moved into routine clinical neurophysiology laboratory.

Scientific basis

The interdependent relationship between electricity and magnetism is well recognized. Passage of an electric current through a coil of wire generates a magnetic field perpendicular to the current flow in the coil. If a conducting medium, such as the brain, is adjacent to the magnetic field, the current will be induced in the conducting medium. The flow of the induced current will be parallel but opposite in direction to the current in the coil. Thus, transcranial magnetic stimulation has been referred to as “electrodeless” electrical stimulation to emphasize that the magnetic field acts as the medium between electricity in the coil and induced electrical currents in the brain.

The effects of magnetic energy on the nervous system have been investigated extensively and the physiological effects of transcranial magnetic stimulation have been well documented. Transcranial magnetic stimulation may be applied as single-pulse transcranial magnetic

stimulation or paired-pulse transcranial magnetic stimulation. Single pulses affect brain function for just a few milliseconds. Repeated rhythmic application of transcranial magnetic stimulation is called repetitive transcranial magnetic stimulation. If the stimulation occurs faster than once per second (1 Hz), it is referred to as fast-repetitive transcranial magnetic stimulation.

Changes may be induced in the electrochemical properties of the neurons by repetitive transcranial magnetic stimulation, and these persist for some time after the termination of the stimulation. A rapid method of conditioning the human motor cortex using low intensity rTMS at 50 Hz produces a long-lasting effect on motor cortex in healthy people after an application period of only 20 to 190 seconds (Huang et al 2005). This is a version of the classic theta burst stimulation protocol and has implications for the development of clinical applications of rTMS. Cortical excitability increases with higher frequency pulses and decreases with lower frequency pulses. With the ability to increase or decrease cerebral activity, repetitive transcranial magnetic stimulation can partially correct overactivity or underactivity and has the potential to “tune” the cortex.

Mechanisms of action of transcranial magnetic stimulation. Studies with intracranial electrodes in rhesus monkeys have provided information about the nature and spatial extent of the repetitive transcranial magnetic stimulation-induced electric field. Corticospinal tract development, aspects of motor control, and medication effects on corticospinal excitability have been studied fairly extensively in nonhuman primates using single-pulse transcranial magnetic stimulation. Experimental studies reveal that transcranial magnetic stimulation-evoked motor responses result from direct excitation of corticospinal neurons at or close to the axon hillock. Repetitive transcranial magnetic stimulation can induce the following changes that can be exploited for therapeutic purposes:

• Changes in brain monoamines.

• Reduction of the detrimental effects of oxidative stress in neurons that may have a neuroprotective effect.

• Changes in beta-adrenergic receptor binding.

• Gene induction.

• Changes in cerebral blood flow.

Furthermore:

- Transcranial magnetic stimulation preferentially activates different structures than transcranial electrical stimulation. These differences occur because different structures in the motor cortex have a differential threshold to the different techniques of stimulation (Di Lazzaro et al 2004).

- Transcranial magnetic stimulation-evoked slow waves lead to a deepening of sleep and an increase in EEG slow-wave activity (Massimini et al 2007).

- TMS acts by generating magnetic fields in the brain which simulate neuro-chemical changes and stimulate neuronal activity translating into increased secretion of growth factors such as brain derived neurotrophic factor (BDNF). This is followed by positive effects of these growth and survival factors on neuronal sprouting, re-organization and also potentially on neurogenesis. Hence it is postulated that TMS will have a positive effect on the recovery rate and extent of recovery after stroke. Deep TMS produces directed electromagnetic fields that can induce excitation or inhibition of neurons deep inside the brain. The treatment is non-invasive, with no significant side effects, and no need of hospitalization or anesthesia.

- TMS was yet found to be effective and safe in the set up of depression: using brain stimulation deep TMS of the prefrontal cortex was found to exert potent antidepressant effects on patients not previously responsive to antidepressant drugs in two different studies. Therefore, it is expected that TMS will also be safe in patients with stroke.

8. CONCLUSIONS

In this work, we have focused into the assessment of normal primary motor areas (M1) in five normal subjects and their connectivity by means of three techniques: MR, nTMS and DTI. A physiological evaluation of the mapped areas was performed through the Motor Evoked Response. Then, we focused in finding the excitability threshold and the stimulation's coordinates for the APB point.

Here are provided the first steps for a feasible neurorehabilitation project, based on the accurate brain mapping prior to the transcranial magnetic stimulation of the precise recoverable and/or coadjuvant areas involved in a stroke. Thus, the natural phenomena of neuromodulation and neuroplasticity would be enhanced, conducting to an improvement of motor outcome.

Such project would aim for establishing the basis of a "functional assessment prior to neuromodulatory treatment" protocol, concretely oriented towards the neurorehabilitation of patients with spastic hand after stroke, and performed in parallel with the periodical functional assessment of the progressive changes in their neuronal networks.

From this approach, it would be desirable to meet these objectives in the near future, so that many potentially treatable stroke patients can get the benefits of the newest neuromodulatory therapies and recover with the best results.

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