EDITORIAL

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Neuroimaging: a new challenge in neurorehabilitation of stroke patients

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Technological progress in neuroimaging over the last twenty years has introduced a big challenge to explore anatomy and physiopathology. Technological evolution involves a closer dialogue between neuroradiologists who investigate imaging potential and physicians who orient its applications.

Nowadays an effort should be made to bring the technological world of imaging closer to the clinical world, starting a necessary teamwork.

However due to speedy advances in this field, performance quality in neuroimaging is often improved within the space a few moths, meaning that neuroradiologists are, as of yet, unable to explore the full potential of this equipment.

Technological evolution is mainly based on the equipment's ability to gather an increasing amount of information in a shorter time.

The ability to acquire an ever increasing amount of information produces smaller spatial resolution, resoluting in something near to a histology. Acquisition of this information improves the temporal resolution, allowing to discriminate the structural differences produced in few milliseconds, enabling us to explore the produced changes.

Therefore radiology seems ready to face both morphological and functional studies.

Better spatial resolution, meaning the ability to distinguish the details, giving the present ability to visualise nervous roots, the more and more smaller vessels by angioMRI, bringing the target near the histological field.

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High evolution MRI using microscopy surface coils is a promising method to realize extraordinary images like that in the Figure 1, produced in our Radiology Institute, where we are close to identifying the nervous fastide from the adipose tissue of the perinevrium in a tibial nerve section at the popliteous.[1]

Studies using micro coil surface are beginning but the first promising clinical applications are still unavailable yet. Utilizing powerful and safer magnetic fields [2] will warrant exploring enormous potentialities like the "MRI microscopy" showed in biology, pathology and genetic experimental studies with animals.[3]

Among the functional methods, fMRI holds a great importance. As the following studies are showing, it enables the recognition of the cerebral areas in metabolic activity during a task, by means of the ability to recognize the signal difference between oxy and desoxyhaemoglobin, and the rapidity of acquisition which permits to quick check rapidly these cerebral areas, in order to distinguish different oxygen consumptions, meaning more active and less active neuronal populations.

It is well known, nowadays, that fMRI enables the localization an enormous number of cerebral functions, both sensory, motor and cognitive functions, by executing selective tasks: by means of this non invasive method we look at the brain to know the human behaviour.[4]

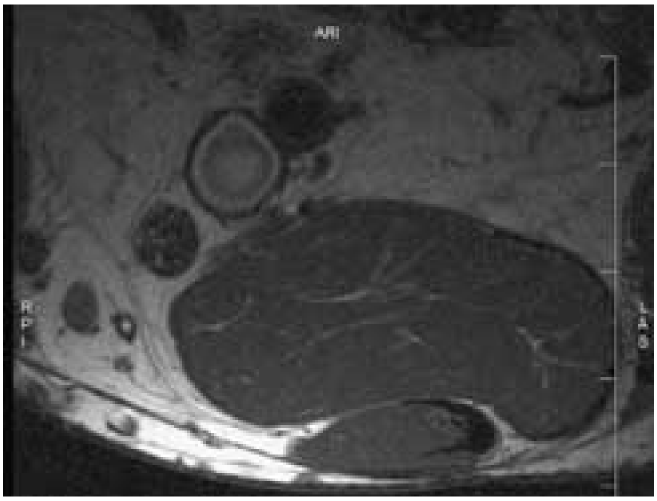

Figure 1.—HR-MRI: T1W section to the popliteous; axial section of tibial nerve (diameter 0.6 mm).

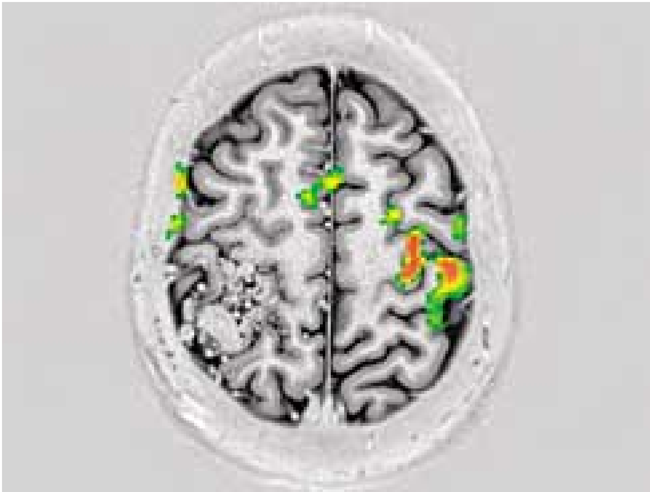

Figure 2.—fMRI: activation of controlateral motor cortex in right fronto-parietal arteriovenous malformation.

This functional imaging promises further potential possibilities, as some studies recorded in describing cerebral plasticity in physiological and pathological conditions [5] (Figure 2), helping in the fascinating research on the intrinsic mechanisms of cerebral functioning, showing mirror function,[6] and contributing to study therapeutic and rehabilitative strategies.[7, 8]

Diffusion weighted imaging (DWI), as discussed in this paper, permits identification of the intrinsic and extrinsic molecular movements in brain cells, allowing us to understand where these movements are reduced, as in cerebral areas in the start of ischemia because of the loss of ionic membrane exchanges in swollen cells, or increased, as in cystic tumoral necrosis where molecules are more fluid based as opposed to the exudates in an abscess.

Diffusion tensor imaging (DTI) allows direct examination *in vivo* of some aspects of brain microstructure, quantitative measures reflecting integrity of white matter fiber tracts, neuroanatomy, fiber connectivity and brain development, in normal and in pathological subjects and during functional recovery. DTI has been found to be superior to conventional MRI in differentiate pathology.[9]

The exciting outlook of these techniques, both structural and functional, is linked not only to the evocative images that they produce but, above all, to the ability to measure the signal and explore axons' integrity and their eventual changes in relation to pathological situations or after therapy.[10]

How do neuroimaging techniques help us to best understand the impairment suffered by patients after stroke?

The studies published in this journal show the promising role of neuroimaging in a patient's neurorehabilitation: by recording the cervical and subcortical performance during cognitive, behavioural, motor and sensory tasks, these studies could lead to the stratification of patients, based on the likely response to a rehabilitative intervention; it could help us in the future to understand the recovery prognosis and to program specific, more effective therapeutic strategies.

The challenge is to learn enough about the mechanisms of plasticity enabling to guide them, suppressing changes that may lead to undesirable behaviours whilst accelerating or enhancing those that result in a behavioural benefit for the subject or patient.[11]

The following are the main patterns of changes mechanisms that occur after practising motor, perceptual and cognitive tasks.

Patterns of activation changes:

— activation decreases, recorded in the majority of areas activated during a training, that results as an increased neural efficiency in a task so that fewer neurons fire strongly in response to a specific task or stimulus.[12] Studies on changes in functional activation are managed after practice on higher cognitive tasks [13] such as a computer game Tetris, a complex visuospatial motor task. The studies observed a widespread decrease in the glucose metabolic rate after several weeks of moderate training correlated with improvements in task performance. These findings are understood as reflecting an increase in neural efficiency;

— activation increases referred to both practice related expansions in increases in the strength or amplitude of activations in a cerebral region and the spatial extent of cortical representations as a result of recruitment of additional cortical units with practice. While activation decrease is observed after cognitive training, activation increase is observed mostly after extensive practice on sensory or motor tasks.[14]

Patterns of reorganization of activation, the most commonly observed pattern after practice:

— redistribution of functional activation (increased and decreased) in the same areas at the beginning of practice with a change to activation levels. This is observed in studies involving visuomotor tasks [15] and motor tasks.[16] This is the case of the study on activation changes after training on a robotic arm to reach for a target:[17] a redistribution of activation was observed from frontal posterior areas using PET. It reflects a decreased demand on control or attentional areas during the training, showed as a decreased activation, and an increased activation in task specific areas mainly involved in the task;

— functional reorganization of activations (“Process switching”), of different undamaged loci, in a compensatory activation pattern to perform tasks that usually engage the injured region. This activation pattern may later diminish after recovery.

In cognitive task training in an injured brain a reactivation of additional functional brain areas can occur which relate to a compensatory effect, but with further training the compensatory mechanism may decrease, showing a restored normal function.

In aphasic stroke patients, after language training, there is an increased activation of the right hemisphere cognitive control areas in the subacute phase of language recovery, then an increased activation of the left hemisphere specific language areas and a reduction in activation of the right hemisphere cognitive control areas.[18]

Data suggests that extensive practice on a verbal working memory task can lead to improvement related processes which may generalize to improve performances on other unpractised working memory tasks [19] and significant transfer of practice related improvement to similar cognitive tasks can occur.[20] On the contrary, after sensory and motor tasks the extensive practice results in increased connectivity within primary cortex which leads to a highly specific improvement in the trained task only, not generalizing to different task sequences or stimuli.[21]

Patients with chronic stroke functional imaging studies demonstrated a linear negative correlation between outcome and task-related brain activation in a number of secondary motor areas such the dorsolateral premotor cortex (PMd), the supplementary motor area and cingulated motor areas.[22] While patients with residual impairment have relatively normal activation maps, patients with more marked impairment recruit larger portions of secondary motor areas.

Using transcranial magnetic stimulation (TMS), Fridman *et al.*[23] showed that stimulation to ispilesional PMd was disruptive in patients with little impairment and more disruptive when contralesional on PMd in patients with greater motor impairment.[24] These results suggest a functional relevant recruitment of contralesional PMd in patients with greater needs and the rule of the ipsilateral PMd as an “executive” motor region similar to the primary motor cortex.

How can these results help us to best treat our patients?

We know that the changes that take place in the human brain after a focal injury need an environment that drives or modulates them. It means that the environment, the behavioural and pharmacological contexts can influence cerebral reorganization, and the process of recovery and function.

Ward in this journal emphasizes that treatments which can be considered as inputs are those that interact with the system, the damaged brain, to optimise the functional organization of the damaged system leading to recovery.

It is worth noting that an input is only able to successfully drive a change when the brain regions and networks with which it interacts are intact and are able to influence motor output pathways. An other way is if the technique is designed to influence the brain to facilitate activity-driven change. This is the case of repetitive TMS, which increases excitability in targeted brain areas. The action mechanism of these interventions is not well understood, but the results of the studies are promising.

The techniques in neuroimaging should facilitate an understanding of the interventions mechanisms designed to reduce impairments, mainly drugs and rehabilitative techniques and to manage a patient's tailored rehabilitation program.

Ward,[25] reviewing some interesting studies, proposes some hypothesis helping driving the changes in neurorehabilitation in a paretic hand:

1) Reduction of somatosensory input from the intact hand. In patients with chronic stroke, cutaneous anaesthesia of the intact hand results in temporary functional gains in the paretic hand.[26] This is the rational on the basis of the proposed immobilization of the unaffected hand in chronic stroke with the constraint induced movement therapy.

2) Increase in somatosensory input from the paretic hand may improve motor function:[27] this is always the stimulation administered during rehabilitative therapy.

3) Anaesthesia of a body part proximal to the paretic hand, *e.g.* upper arm, may result in some benefit of hand motor function.[28]

4) Plasticity of the peri-infarct and non primary motor regions of the affected motor cortex may be enhanced by neurorehabilitative interventions: TMS synchronously applied to a human motor cortex engaged in a motor training task improves function in the controlateral hand.[29]

5) Activity in the intact motor cortex may be downregulated: TMS applied to one motor cortex results in activation in the opposite motor cortex down regulating motor cortical excitability in the opposite hemisphere. It is consistent with the concepts of a physiological balance and reciprocal inhibitory projections between both hemispheres. In stroke patients it seems that this balance is disturbed, specifically, they show an abnormally high interhemisperic inhibitory drive from the primary motor cortex in the unaffected hemisphere to Mi in the lesioned primary motor area hemisphere;[30] a finding more prominent in more impaired patients. Some studies show that TMS applied to one motor cortex in healthy subjects results in improvement in motor performance in the ipsilateral hand.[31]

An interesting example of using neuroimaging techiniques to deeper understand the patient behaviour is the study of Amedi *et al.* [32] Amedi emphasizes the overlap between the neural substrates of visual perception and visual imagery. The Authors demonstrate that deactivation of the auditory cortex (and to some extent of somatosensory and subcortical visual structures) as measured by MRI, unequivocally differentiates visual imagery from visual perception. Results suggest that pure visual imagery corresponds to the isolated activation of visual cortical areas with concurrent deactivation of "irrelevant" sensory processing that could disrupt the image created by our "mind's eye".

Lacourse *et al.* [33] demonstrated congruent activation of the cortical and subcortical motor system during both novel and skilled learning phases of a right hand self paced bottom press sequence executed and imaged, supporting the effectiveness of motor imagery-based mental practice techniques.

Neurostimulation, including noninvasive brain stimulation techniques, provide an opportunity to modulate brain plasticity in a controlled and specific manner.

Dynamic shifts in the strength of pre-existing connections across distributed neural networks, changes in task-related cortico-cortical and cortico-subcortical coherence and modifications of the mapping between behaviour and neural activity take place in response to changes in afferent input or efferent demand. Such rapid, ongoing changes may be followed by the establishment of new connections through dendritic growth and arborisation. However, they harbour the danger that the evolving pattern of neural activation may in itself lead to abnormal behaviour: in fact plasticity, being the mechanism for development and learning, could also be a cause of pathology. The challenge we face is to learn enough about the mechanisms of plasticity to modulate them in order achieve the best behavioural outcome for a given subject.[11]

In fact there are also many negative results of the brain's capacity for plasticity and reorganization. At is the case of phantom limb pain, which is the consequence of cortical reorganization in the absence of sensory motor stimulation [34] or focal hand dystonia in a musician after long term overuse involving repetitive specific movements.[35] The potential use of neuroimaging techniques in localizing both the effects of injury and the effects of training could lead us to modulate neural plasticity for optimal behavioural gain.

The discovery that experience-driven changes in the human brain can occur from a neural to a cortical level throughout the lifespan has stimulated a proliferation of research into how neural function changes in response to experience, enabled by innovative neuroimaging methods. They need for careful attention to practice-related changes occurring on the behavioural, cognitive and neural levels of analysis.[36] We suggest that functional and effective connectivity analyses may make important contributions to our understanding of changes in functional anatomy occurring as a result of practice on tasks.

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