Colouring rehabilitation with functional neuroimaging

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Summary

Neuroimaging is becoming an increasingly important means of detecting changes in biochemical, microstructural and functional patterns occurring during rehabilitation. In magnetic resonance imaging (MRI), “advanced techniques”, such as functional MRI, relaxometry, diffusion tensor imaging and spectroscopy, are making it possible to investigate these changes in vivo, together with brain function. This review highlights how advances in the field of MRI can shed light on the relationship between cerebral reorganisation after focal damage and functional recovery, providing insights that might be translated into clinical benefits for patients.

KEY WORDS: advanced techniques, magnetic resonance imaging, recovery, rehabilitation.

Introduction

Scientific research in the field of rehabilitation is based on the measurement and evaluation of function before and after therapy. Neuroimaging is becoming an increasingly important means of detecting changes in biochemical, microstructural and functional patterns occurring during rehabilitation. Scientific studies in this field should consider three main issues: the mechanism and timing of brain injury and recovery, the methods best able to assess rehabilitation therapies, and the role of neuroimaging techniques. These three aspects are interrelated, making this a particularly challenging research field.

The mechanism and timing of brain injury and recovery

It is crucial when planning rehabilitation and neuroimaging strategies for a patient with brain injury to know the mechanism underlying the injury, as the mechanism of injury affects the recovery; it is known, after all, that different outcomes can be observed in patients with stroke, traumatic brain injury, or multiple sclerosis. Acute injuries do not give the brain enough time to adapt its functional circuits, whereas in chronic diseases, in which the damage is progressive and cumulative, the brain is able to generate functional rearrangements (e.g. the recruitment of vicarious circuits); this kind of functional reorganisation could explain the “functional reserve” phenomenon (1,2).

Several changes occur during recovery following a brain injury (3,4): biochemical changes precede functional rearrangements, which may include recruitment and modulation of different functional areas, and synaptogenesis. All these changes vary in duration, spatial extent and degree of complexity, depending on the underlying disease mechanism. Thus, the mechanism and timing of the injury affect the modality, duration and aspects of the neurological recovery.

Methods for assessing rehabilitation therapies

There are a number of aspects to bear in mind when planning studies of rehabilitation, particularly ones involving neuroimaging techniques. A main consideration is the choice of appropriate inclusion criteria to ensure the recruitment of a homogeneous study group. Furthermore, given that, as we have said, the mechanisms and timing of recovery processes can vary according to the type of injury and the patients involved, it is crucial to ensure that the specific changes are assessed after the appropriate interval of time, namely that in which these specific changes occur. In short, a study should seek to include “similar” patients in a “similar” recovery phase. In this regard, it is important to consider that clinical and functional scales may not be powerful enough to detect the type of changes occurring during the recovery and recruitment may be inaccurate if based only on clinical criteria; in other words, these scales may not reflect changes occurring in the neuroanatomy of specific functional pathways, but rather represent a global assessment of a general brain function. For this reason, they may not be an adequate tool for guaranteeing the recruitment of patients in similar recovery phases.

Moreover, cognitive functions may affect responses in functional magnetic resonance imaging (fMRI) tasks. A neuropsychological assessment should thus be performed before and after the rehabilitation therapy in order to assess how changes in cognitive functions might have affected the recovery. Patients with similar neurological deficits may have le-
sions located anywhere along the functional pathways of the brain and neuroimaging is useful for localising these lesions (the depiction of spinal lesions may be more challenging). Care should be taken to select the most suitable MRI technique. Summarising, recruitment may be inaccurate if based only on clinical criteria, and biased if based only on neuroimaging techniques. In the latter case the imaging technique, which should be assessed, is used to classify patients: this ex-post classification of patients may generate a bias with potential circular analysis of the results. When an adequate sample cannot be recruited, a larger sample of patients is needed.

The role of neuroimaging in rehabilitation

Neuroimaging is a powerful tool for assessing functional changes occurring during recovery. Magnetic resonance imaging, followed by positron emission tomography (PET), is the most practical and accurate technique for assessing brain anatomy and function. In MRI scanners the signal, spatial resolution and/or scan time improve proportionally with the magnetic field strength, thus increasing both the image quality and the amount of information available for “advanced” quantitative imaging techniques. These techniques are termed “advanced” because they allow quantitative assessment of microstructural and biochemical features of the brain; studies using these techniques are usually performed by dedicated personnel at scientific research centres. By using these advanced techniques it is possible to investigate, in vivo, the function of the brain, the changes occurring during rehabilitation and to detect awareness in disorders of consciousness (5,6). Advanced techniques give neuroimaging a fifth dimension. This fifth dimension (after the 3D spatial dimension and changes over time) is functional information (7). Indeed, these techniques, providing the colour maps that have been so prominent in the literature over the past two decades, are able to depict brain function. One particularly interesting approach is the integration of morphological and fMRI data with electrophysiological measurements, which further enhances the combination of MRI assessment (structural and follow-up) with functional information.

Structural MRI

Structural volume analysis of the brain using voxel-based morphometry is a technique for measuring the volume of the brain components (grey and white matter, CSF spaces) by brain region. Voxel-based morphometry on structural MRI scans showed changes in cortical volume after constraint-induced therapy (8).

Relaxometry

Relaxometry methods, i.e. T1, T2, T2* and magnetisation transfer (MT), provide quantitative microstructural information, reflecting molecules and protein content, and could be useful for assessing and quantifying deafferentation and tissue damage, particularly in diffuse axonal injury. Relaxometry methods are based on the compartmentalisation of a molecule, with its magnetic features (haemosiderine or blood flow for instance), or on the modulation, by contrast material or by the natural exchange with free unbound water, of the electronic cloud surrounding the nucleus. These methods can increase sensitivity in the detection of lesions and help to quantify the injury for recruitment and classification purposes.

Functional MRI

Functional MRI (fMRI) maps the brain areas that are “activated” during a task and the technique depends very much on the tasks, scan paradigms, and analysis methods used; however, fMRI cannot discriminate the type of activation (excitation or inhibition) nor exclude the involvement of other areas during the task. A number of studies have assessed changes in fMRI activation patterns before and after therapy and some of them have found outcomes to be correlated with rehabilitation and fMRI data. Their results are summarised briefly as follows (3,9):

i) fMRI activation patterns change with functional reorganisation and recovery (2,10-12). Spared neighbouring functional areas may acquire the functions of the damaged region (13,14). The more extensive the accessory activation area, the poorer the results of rehabilitation will be. The extent of residual fMRI activation is correlated with recovery (15-17). Increased activation in secondary motor areas was observed during force production in persons with more severe strokes (18).

ii) An effective recovery is based on enhanced utilisation of both ipsi- and contralateral resources (19,20). There is an increased contralateral activity, which probably facilitates control of recovered functions (20,21). A laterality index to quantify the interhemispheric balance between the affected and unaffected activated cortices could be used to assess functional motor outcome (22). In one study of patients with a motor deficit due to a lacunar infarct in the pyramidal tract, early activation in the ipsilesional M1, S1 and insula was found to be related to recovery: the greater the activation the better the recovery (19). In stroke patients in the subacute stage, increased activity of motor areas in the contralateral hemisphere during simple movement of the affected hand has been shown to correlate with motor outcome (23). In well recovered patients, the hemispheric balance of BA4p activation was found to be significantly less lateralised than in control subjects; and ipsilesional BA4p activation showed a positive correlation with motor performance (24). An increase of the laterality index in the sensorimotor cortex has been observed during follow up (12). The symmetrical activation of contralateral brain regions is probably due to absence of hemispheric inhibition, by transcallosal fibres, and is inversely correlated with recovery (25). In bilingual patients with chronic aphasia, fMRI results indicated that the same cerebral regions were recruited for both languages before and after training (26,27).

iii) Rehabilitation therapies cause fMRI changes (28,29). Passive proprioceptive training applied for four weeks is able to modify brain sensorimotor activity after a stroke (30), while constraint-induced movement therapy is associated with increased contralateral cortical activity on fMRI (31). The extent of improvement following constraint-induced therapy does not depend on the location of the
neurological damage, despite the existence of a pre-
treatment relationship between infarct location and in-lab-
atory motor ability. This dissociation could be explained
by brain plasticity induced by constraint-induced therapy
(32). Functional MRI studies have also shown that motor
rehabilitation, visual biofeedback and constraint-induced
movement therapy affect the activation pattern and could
be useful to improve recovery (15, 33-35).

Traumatic brain injury patients submitted to cognitive
training showed improved performance of attention
tasks accompanied by fMRI-documented changes in at-
tentional network activation (36). The results of fMRI
studies investigating consciousness in coma and the
vegetative state are, instead, difficult to interpret (37).

Functional MRI changes have been documented in pa-
tients with visual neglect submitted to optokinetic train-
ing; these patients showed activation of areas normally
involved in spatial attention plus a compensatory recruit-
ment of left hemisphere areas (38).

Repetitive transcranial magnetic stimulation has also
been shown, on fMRI studies, to induce changes in the
sensorimotor networks associated with sensory percep-
tion and motor performance (39,40).

In chronic aphasia patients, it has been shown that re-
modelling of cortical functions is possible even years af-
after a stroke, the behavioural gain obtained possibly be-
ing mediated by brain regions that had been partially de-
prived of input after the initial stroke (41).

iv) fMRI changes are recorded in spinal cord injury (42,
43). As motor ability improves postinjury, there is a pro-
gressive increase in the volume of M1 activation during
movement of the affected limb (40). In addition, there is
a shift of the activation occurring during the movement
of healthy muscular groups into the representation ar-
eas of deafferented muscular groups (44).

Diffusion-based methods

Diffusion-based methods include diffusion-weighted im-
aging (DWI), diffusion tensor imaging (DTI), and MR
tractography. Diffusion-weighted imaging is based on a
signal reduction in the echo-planar sequences provoked
by a migration of water molecules from one point to an-
other (45,46). Water diffusion is altered in many dis-
eases, in particular in cytotoxic and vasogenic oedema
(29,47); its changes reflect variations in cellularity or in
the width of the interstitial spaces in the brain (48,49).

Diffusion tensor imaging measures the anisotropy of wa-
ter molecule diffusion and the preferential direction of
water diffusion. The preferential direction of water is
along the same direction as fibre bundles, whereas its
diffusion is low perpendicular to them. The technique
is able to quantify tissue damage severity (50,51) and to
detect changes occurring during disease and rehabilita-
ton (52-58). Tractography, by virtually "connecting" ad-
Jacent voxels in which water diffusion shows similar
prevalemt direction, makes it possible to infer the path-
ways of the nerve fibres from the diffusion tensor image.
In addition, probabilistic tractography can be used to es-
timate the probability of a connection between two cere-
bbral areas. It is possible to combine tractographic meth-
ods and fMRI to show changes after recovery (59).

Functional MR activated areas could be used as seed
point to generate a connectivity map, which may not de-
pict the actual functional pathways, but rather represent
the effect of the overexpression of areas that are no
longer inhibited (60).

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy measures the small
fraction of signals not derived from water or fat, but co-
ming instead from specific molecules generally termed
"metabolites", e.g. neurotransmitters, amino acids, and
energy metabolism molecules. Each metabolite may
be interpreted as a marker of a biochemical pathway or
a structure: N-acetyl aspartate is a marker of the pre-
se of neurons, choline (Cho) an indirect marker of mem-
brane turnover, and creatine (Cr) a marker of ener-
gy metabolism. Magnetic resonance spectroscopy data
have shed light on brain injury, showing that bio-
chemical changes are inversely correlated with out-
come. It has been observed that 1.5 months after tra-
umatic brain injury MR spectra, especially NAA levels
of normal-appearing grey matter, have a prognostic pre-
dictive significance for recovery of cognitive functions
(61,62). Severely injured patients not responding to
treatment have clear reduction of relative NAA levels;
in patients with moderate damage and partially re-
ponding to treatment the NAA decrease is less
marked and associated with an increased Cho level;
MR spectra are often normal in patients showing a
good treatment response (63).

One limitation of neuroimaging is that advanced MR
techniques are difficult to perform in the spine, where
functional rearrangement also occurs during rehabilita-
tion (44). The latest high-field MRI scanners do allow the
application of advanced MR techniques in the spine, al-
though their spatial resolution is limited. Further studies
are needed to assess the capability of these methods to
depict subtle changes occurring during recovery.

It should be pointed out that several of these fMRI
studies are often performed with few patients. The re-
results should be interpreted carefully; they may be due
to the recruitment criteria or to the fact that fMRI is cor-
related with a global scale, assessing several complex
functions.

Other important aspects to consider before conducting
neuroimaging studies are the absence of contraindica-
tions to MR examinations (ferromagnetic elements and
medical devices) and patient compliance with the tech-
nique. These techniques are currently performed by trai-
ened personnel in specialist centres (research hospitals).

Concluding remarks

In conclusion, knowledge of the mechanism and timing
of brain injury and recovery is crucial for deciding re-
cruitment criteria and imaging techniques. Neuroim-
gaging is a powerful tool for investigating biochemical,
microstructural and functional changes occurring during
rehabilitation and may help to increase understanding of
the mechanisms underlying functional rearrangement
and recovery. More studies of large populations are
needed to further assess mechanisms and future strate-
gies of rehabilitation.

High-field MRI scanners improve advanced quantitative
techniques and allow study of the spine, but these mag-
nets are available only in research hospitals. We can speculate that in the future rehabilitation therapies will be planned by combining clinical examination with a fifth dimension of information: functional neuroimaging colour maps.

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