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Neuroimaging in Stroke Recovery: A Position Paper from the First International Workshop on Neuroimaging and Stroke Recovery

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Introduction

The First International Workshop on Neuroimaging and Stroke Recovery was convened in February, 2004 in New York City. The purpose of the workshop was to describe the state of the field with regard to technical and analytical methods, to discuss the use of complementary imaging modalities, and to assess the current potential to apply functional neuroimaging to the development of rational treatment strategies for enhanced stroke recovery.

Presented herein is a summary statement of topics discussed at the workshop. These included (i) the clinical relevance of functional imaging changes after stroke for the motor and language systems; (ii) the technical challenges faced in moving towards establishing functional neuroimaging as a clinically useful tool; (iii) the contributions of neurophysiological probes such as transcranial magnetic stimulation (TMS) to improved understanding of the mechanisms underlying brain reorganization after stroke; and (iv) the potential role of neuroimaging in the assessment and development of rational pharmacological and behavioral therapies.

Clinical Relevance

Functional recovery commonly occurs in surviving stroke patients in the weeks and months following the injury. There is evidence from animal models that cerebral reorganization underlies at least some of this recovery and it is hoped that an understanding of the neurophysiological processes underlying this reorganization in the human brain will lead to a rational approach to the treatment of impairment. In animal models, focal brain damage triggers a number of changes at the molecular, cellular, and systems level, some of which alter the potential for cerebral reorganization and consequent functional recovery. Although the same techniques are not available to study the working human brain, functional brain imaging has provided insights into how the human brain responds to focal injury.

Most functional imaging studies in stroke survivors have focused on the motor or language system. Several exhaustive reviews of these studies can be found elsewhere [1-4], The

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following section will concentrate on the clinical relevance of these studies, and whether there are common themes to be derived from seemingly conflicting data.

Motor Recovery Studies

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) consistently demonstrate relative overactivations in motor-related brain regions during movement of the stroke-affected upper extremity compared to control subjects. In particular, additional task-related recruitment in the unaffected hemisphere has often been reported, rendering the activation pattern more bilateral. These increases are largely restricted to known motor-related regions, in particular the primary sensorimotor cortex, dorsolateral premotor cortex (PMd), ventrolateral premotor cortex (PMv), supplementary motor area (SMA), cingulate motor areas (CMA), parietal cortex, insula cortex and cerebellum [see, e.g., 5-10] There are also differences in brain activation patterns between individual stroke patients. Among chronic stroke patients, those with no residual impairment tend to have relatively normal activation maps compared to controls, while patients with more marked impairment exhibit greater recruitment in ipsilesional primary motor cortex (M1) [see, e.g., 11, 12] as well as in secondary motor areas bilaterally [12]. Other studies have demonstrated that a more bilateral pattern of activation in M1 as assessed by a laterality index is seen in those patients with poorer outcome [11, 13].

Other consistent findings relate to the topography of ipsilesional M1 activation, with extension of activation cluster towards the face area and posterior displacement of peak activation being consistently reported [7, 10, 14, 15]. However, the clinical significance of these findings remains elusive.

A key issue is how recovery or outcome is defined. In several studies patients were considered well recovered if they had made substantial functional gains to the point of being able to perform the motor task, e.g. finger tapping. Average group activation maps for stroke patients in these studies demonstrate increases in activation compared to controls, but it is likely that some patients in these groups had at least mild impairment. For instance, in a study where outcome was assessed using several different measures, a negative linear correlation between motor outcome and task-related brain activation was seen in a number of primary and secondary motor areas [12], such that even patients with mild impairment will recruit these regions over and above controls. Patients with more marked impairment, however, seem to recruit them to a greater degree. Thus if one considers outcome as an explanatory variable there appears to be some consistency in the findings from different studies, at least those involving patients with subcortical infarcts.

The importance of distinguishing individual motor regions and perhaps subregions when interpreting brain mapping studies after stroke merits emphasis. Although M1 plays a pivotal role in the generation of fractionated movements, the cortical motor system is thought to consist of a number of independent parallel motor loops that also includes PMd, SMA, CMA, and deep gray matter structures interconnected at the cortical level and with projections to spinal cord motor neurons [16]. These projections to spinal cord may play a role in the return of motor function after stroke, i.e., they may be recruited in response to damage to fast direct projections from M1 to spinal cord motor neurons. However, they are unlikely ever to completely substitute for those from M1 [17], explaining why patients reliant on secondary motor areas are left with some residual impairment.

Secondary motor areas can be further subdivided on the basis of function and cytoarchitecture. These subdivisions may be functionally important not least because some may influence motor behaviour through intact non-corticospinal pathways such as the

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reticulospinal tract, which receives bilateral inputs and projects to spinal interneurons that innervate distal motor neurons.

Cross-sectional studies of motor recovery cannot tell us about the evolution of the observed changes, which has obvious relevance to the process of reorganization. Longitudinal studies are considerably more difficult to implement, so few only are available. Those utilizing active motor tasks in patients with non-M1 infarcts tend to show early overactivations in many primary and secondary motor regions followed by a focusing towards a normal activation pattern [18-20], although one study demonstrated only increases in task-related activation in contralesional cerebellum with recovery [21]. In a study that used a composite measure of motor outcomes as an explanatory variable, early overactivations followed by reductions in a number of primary and secondary motor regions correlated negatively with recovery scores [22]. Such changes are reminiscent of those observed in the normal brain during motor skill learning [23].

Longitudinal studies employing passive rather than active movement are better suited to study patients with no residual movement in the early stages after stroke. In such studies there appears to be greater task-related activation at later compared to early stages post stroke in regions such as ipsilesional sensorimotor cortex and bilateral inferior parietal cortex [24, 25]. The pattern of activation varied significantly as a function of outcome, with the magnitude of activation being lower than that of controls except for well-recovered patients [25]. This once again underlines the importance of acquiring behavioral measures as explanatory variables. The differences in results from active or passive movement paradigms are as yet unexplained, but illustrate the importance of task and patient selection in experimental design.

Language Recovery Studies

As in studies of motor recovery, the relative importance of the contralesional and ipsilesional hemispheres for recovery from aphasia has been intensively investigated. One line of evidence from longitudinal studies suggests that return of left hemisphere language areas activation correlates with better behavioral outcome, whereas retention of right hemisphere activation correlates with poorer behavioral outcome [26]. Importantly, these authors suggested that it is destruction of primary cortical language areas by stroke that results in absence of left hemisphere language area activation, and thus poorer behavioral outcome. Nonetheless, some studies have shown correlation of good language recovery with emergence of homologous right hemisphere regions [27, 28]. Larger studies of language recovery will be needed to elucidate the role of contralesional activity early and late after stroke.

The details of network functional connectivity may be important to interpreting functional imaging studies after focal brain injury. In the above language studies, even when the left temporal lobe remained intact after stroke, activation may not be present during a language task if the patient is still aphasic, whereas that region’s structural and functional integrity may be demonstrated by producing activation in that location in response to a non-language task, for example sound identification [29]. This task-dependent dissociation for activation in a given region demonstrates that brain regions may be involved in multiple networks related to different brain functions, and that it is functional connectivity rather than anatomical location per se that determines the resulting pattern of regional activity following neurological dysfunction and recovery after stroke. Conceivably, behavior of different neuronal populations measured simultaneously within a single region could account for part of this effect [30].

One approach to assessing the functional significance of changes in brain activation after stroke is to parametrically modulate behavioral demands and then examine changes in activation. Blasi et al. [31], using a word-retrieval learning task, provided support for a functional contribution by right hemisphere activation in a relatively homogeneous group of patients improved after aphasia by demonstrating a task-related modulation of activity in the right dorsal inferior frontal gyrus (IFG) that healthy control patients displayed in the left dorsal IFG.

In a recent longitudinal study [32], there was positive correlation between increased performance over time and flow activations in superior temporal regions bilaterally, stressing the importance of a bihemispheric network. Also, negative correlation between performance and flow in non-temporal regions – such as the right superior frontal cortex – were reported, i.e., recovery was associated with a gradual 'normalisation' of the pattern. Interestingly, similar negative correlation with increased performance was seen in normal subjects longitudinally, suggestive of (re)learning being part of the recovery process in the aphasics.

Technical Challenges and Issues in Experimental Design and Analysis

The results of functional imaging experiments are only as reliable as the care with which the experiment is constructed and executed. The choice of experimental task, patient monitoring, patient selection, and approaches to analysis require careful consideration if a study is to successfully address its stated hypothesis.

The choice of experimental task is dependent on the experimental question under consideration. For example, a study of the relationship between brain activation and outcome should involve stroke patients with different performance abilities. Similarly it is to be hoped that a longitudinal study or one involving a therapeutic intervention will involve patients with improving performance abilities. This approach requires two considerations. Firstly, the clinical status must be characterized in a detailed and relevant manner. Secondly, each patient must perform the *same task* during the acquisition of fMRI data so that a meaningful comparison can be made across subjects or scanning sessions.

A change in the features of an experimental task can have substantial effect upon the pattern of brain activation. Regarding motor tasks, for example, changes in task complexity [33], as well as force [34], frequency [35], or range [36] of movement all have an effect on the pattern of normal brain activation. Maintaining a consistent task is therefore of great importance, but in stroke recovery studies equality of task may be interpreted in a number of ways. In particular a task may be consistent across patients with different abilities in terms of *absolute* or *relative* parameters.

Considering a simple motor experiment, absolute task parameters can be fixed (by setting the same target force and rate for every scanning session) but performing a task may be experienced as more or less effortful depending on the level of recovery. Thus differences in results across subjects/sessions might be attributed to differences in 'effort' exerted. Alternatively, the level of task difficulty can be fixed across subjects/sessions (but patients will perform the task at different absolute forces and rates). Thus differences in results across subjects/sessions might be attributed to differences in the absolute task parameters. Results must always be interpreted with these confounds in mind.

These considerations can lead to difficulties in data interpretation. Increased effort is a potentially useful strategy for a patient with motor, language, or cognitive impairment, and patients may find a task less effortful as their performance improves. Is the focus of interest the underlying substrate of functional improvement or its consequence? Of course both may

be of interest, but the choice of experimental design has an impact on which process is being studied. One approach is to build both approaches into the same study, e.g. [22], but this lengthens the experimental paradigm and time of scanning. Other approaches avoid the problem of performance confounds, e.g. passive limb movement, passive listening, but these are complementary approaches to active tasks, not substitutes for them.

One might also consider whether to use a task that is more likely to be relevant to each patient's disability, i.e. an *ecologically valid* task. However, patients with significant impairment are more likely to adopt new operational strategies towards such experimental tasks in an attempt to adapt to their impairment. Although of clinical interest, differences in strategy across a group represent a potential experimental confound if they are unexpected and not measured. One approach is therefore to use a simple task that minimizes difference in strategic approach to the task so that valid comparisons can then be made across subjects/sessions [37].

Once a paradigm has been selected it is important that task performance is monitored during the experiment. Normal intersubject variability can increase after stroke in light of changes in attention, mood, and other cognitive issues. Furthermore, new sources of variability can arise after stroke, such as a tendency towards mirror, or associated, movements. A number of solutions are available to address this concern. Some investigators record behavior during a pre-scan rehearsal [38]. Others incorporate the increasingly available instrumentation that is compatible with the MRI setting. This approach allows collected data to be incorporated into image analysis, thereby potentially improving statistical power by accounting for correlated variance in the measured scan signal.

Which patients should be scanned? Stroke patients are a heterogeneous group differing in age, site and size of infarct, patency of the arterial system, co-morbidities and concurrent medication. Patient selection will again depend on the experimental question. Results from highly selected patient subgroups may not generalize. Unselected groups however are susceptible to a number of uncontrolled variables, although it is possible to explore the effects of single factors (e.g. final outcome) or combinations of factors (e.g. final outcome, age, site of lesion) that best explain the variance in an imaging data set.

Collating data from different studies is hampered by the use of different experimental designs. Although two studies cannot be directly compared, data from both can contribute to the formation of a new testable hypothesis. Thus, in general, a single study should try to negate a single hypothesis generated from previous studies. For most questions this approach is entirely appropriate and standardization of experimental paradigms, patient selection and method of analysis across experiments is not required. In the case of an experimental question that requires a multi-centre approach, a technically feasible approach, standardization of such factors is required.

Several technical issues related to fMRI studies of stroke patients require further study. There is evidence that in patients with impaired cerebrovascular reserve or advanced narrowing of the cerebral arteries, the blood oxygen level-dependent (BOLD) fMRI signal may be reduced, or even become negative [39-41]. However, the chemical species most important to neuronal-vascular coupling of BOLD fMRI remains to be established, and so such data are of somewhat uncertain significance in the study of cerebrovascular disease. There is no evidence that the BOLD signal is erroneously detected in these patients, i.e. this is largely a problem of false negative results. It is not clear how the generation of the BOLD signal is affected by a number of parameters including time after stroke, large vessel disease and small vessel disease. A multimodal approach using different imaging techniques (BOLD, perfusion, hypercapnic challenge) and concurrent neurophysiological methods

(EEG, MEG) may be useful when addressing the influence of multiple physiological variables. These issues will require further empirical study.

The Clinical Relevance of Brain Activation Patterns after Stroke: A Role for Transcranial Magnetic Stimulation?

The behavioral significance of many of the changes in task-related brain activation following stroke remains unclear. Does an early shift of activity to the contralesional hemisphere, for example, mean compensatory networks are being recruited and the prognosis is good, or does it mean that the normal networks are dysfunctional and therefore the prognosis is poor? One simple explanation is that new regional activity seen with functional imaging represents recruitment and establishment of networks that have assumed a role in behavioral performance. In motor studies the significance of contralesional recruitment may be different for M1 compared to motor areas with more bilateral motor representation, such as PMd and SMA. Alternative explanations for changes after stroke are that new regional activity appears incidentally, as a consequence of the brain injury, for example as a result of infarction-induced disinhibition across the corpus callosum [42, 43], or that such activity reflects a non-specific increase in effort or attention because the given task is more difficult for the post-stroke patient. Imaging cannot sort out this problem alone, and studies employing TMS to explore the functional utility of such activations have been helpful in this regard.

While the limitations of TMS must be kept in mind – a patch of cortex within a single brain area is subjected to a powerful stimulation, and a single output describes the effects of this stimulation upon numerous types of neurons – this approach is proving to be invaluable.

Disruption of ipsilesional PMd [44] and contralesional PMd [11] by TMS increases motor reaction times in chronic stroke patients but not controls, suggesting PMd in both hemispheres is important for recovery. By taking account of the effects of TMS in patients with different outcomes, a possible dissociation in their roles may be discerned. TMS to ipsilesional PMd was most disruptive in patients with least impairment [44] suggesting it may be capable of supporting good recovery. TMS to contralesional PMd however was most disruptive in patients with greater motor impairment [11] suggesting functionally relevant recruitment of contralesional PMd in those with greatest need.

Similar studies have been performed to examine the role of contralesional M1. Previously TMS studies have found that stimulation of contralesional M1 produces motor evoked responses in the ipsilateral affected hand most often in those patients with a poorer outcome [45, 46]. This is in keeping with the finding of increased recruitment of contralesional M1 in patients with poorer outcome [11, 12] but does not resolve the issue of whether it is functionally relevant. TMS-induced disruption of function in contralesional M1 does not affect movements of the affected limb [11, 47], suggesting that recruitment of the contralesional M1 does not simply correspond to a new activity to replace the function of the damaged area. Motor areas of the unaffected hemisphere do not take over the functions lost with stroke in any simple and direct way.

What then might be the significance of the task related overactivations that are consistently seen in unaffected motor cortex? A number of hypotheses have been suggested, including changes in interhemispheric inhibition, changes in the actual behavioral phenotype generated by patients, an expression of relative complexity, and substitution of an overactivating area for the function of an injured area.

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Changes in inter-hemispheric interactions after stroke have been documented by TMS, made possible by the method's temporal resolution and its ability to study both excitation and inhibition. In terms of inhibition from the stroke hemisphere onto the non-stroke hemisphere, Shimizu et al. [48] described reduced inhibition within the contralesional M1 in patients with cortical stroke. In terms of inhibition from the contralesional M1 onto the ipsilesional M1, Murase et al. [43], found an abnormally high interhemispheric inhibitory drive over ipsilesional M1 during movement of the affected upper extremity. This abnormally high inhibitory influence upon stroke hemisphere motor areas could contribute to impairment. Future studi/es might assess the therapeutic potential arising from modifying either of these inhibitory drives using for example repetitive TMS to increase activity in the affected motor cortex or to decrease activity in the unaffected motor cortex. Other approaches might focus on directing bottom-up messages into the system, such as temporary deafferentation, forced use paradigms, passive movement, or somatosensory stimulation.

The Development of Pharmacological and Behavioral Interventions

Ultimately, this research aims to provide a basis for the development of rationale therapeutic strategies designed to restore function by minimizing impairment. Data derived from human brain mapping after stroke have the potential to provide useful information not available from other approaches such as behavioral exam or anatomical imaging. Functional imaging is unlikely to be useful purely as a marker of clinical improvement, something that is measurable with simple outcome scores. Functional imaging may be a useful marker of the potential for change in damaged brain. It is to be hoped that the potential of different therapeutic interventions can be assessed, both in groups and individuals. Serial studies over the course of a rehabilitation intervention have the potential to reveal patterns of brain reorganization that will guide decisions regarding optimal treatment intensity or duration. Brain mapping data might provide insights into the biological mechanisms underlying treatment-related gains during rehabilitation and offer the possibility of more directly comparing effects in human stroke with those observed in animal models. To achieve such goals will require researchers to develop or adopt well-defined rehabilitation and adjunct approaches, identify outcome measures that are relevant to the interventions, create functional activation paradigms that reveal the cerebral networks engaged by the therapeutic strategies, and apply this overall strategy to patients who have a range of lesions, impairments, and disabilities.

Functional imaging methods have adequate sensitivity in many cases to demonstrate drug [49] and rehabilitation effects [50-57] upon patients with stroke and in healthy subjects [58-62]. For example, a single dose of SSRI has been demonstrated to enhance motor network activation in a way that correlated with an improvement in motor performance in patients studied in the first month after stroke [49]. A current challenge is to determine capability and optimal methods to identify recovery-related therapeutic targets and prognostic factors. Neuroimaging techniques have the potential to assess the effects of pharmacologic agents upon excitation, inhibition, and synaptic efficacy [63]. Some of the promise and confounds in deploying functional neuroimaging in the context of rehabilitation are anticipated by studies of activity-dependent plasticity and learning in normal subjects.

Physical and language interventions enjoy broad acceptance in clinical practice. However, an active area of investigation seeks to identify details of optimal modalities and approaches. What, when, and how are such interventions best applied? For example, should a patient have his paretic limb stimulated very early after stroke or would a better outcome result from delayed introduction of physical therapy? Which is the most efficacious approach across therapies? What duration, frequency, and scheduling will maximize outcome? It is hoped that functional imaging will help resolve these issues.

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A number of pharmacologic interventions have been proposed for improving outcome after stroke. Based on experimental data such as that showing a depletion of mono-amines after stroke, and on encouraging results in preclinical studies, mono-amine enhancers such as amphetamine and SSRIs may be promising approaches for improving motor and language deficits after stroke. The data from animal studies has unambiguously demonstrated that pharmacological manipulations are only effective in promoting recovery when paired with behavioral re-enforcement. That this is also the case in human studies requires empirical support. Again, functional imaging might afford better understanding into these complex questions.

Brain mapping studies using TMS provide insights into the effects of specific drugs on cortical plasticity. Such studies have demonstrated, for example, that alpha and beta blockers, anticholinergics, NMDA antagonists and gabaergic drugs can exert deleterious effects on human use-dependent plasticity [64-67] while others such as D-amphetamine or levodopa enhance use-dependent plasticity [65, 68] or even elicit plasticity in individuals unresponsive to motor training alone [69]. All these studies assessed effects of single dose of drugs and chronic treatments, as those which will be given in patients, must now be tested. In this regard, chronic treatment in healthy subjects may have effects on brain function that are opposite to those of a single dose possibly due to processes such as down-regulation of stimulated receptors [63, 70]. Such assessments, based on neurophysiology and chemistry, might permit treatment decisions that are more precise than those made on clinical history or exam.

In some respects, the results of human brain mapping are only as good as the clinical/behavioral measures to which they are compared. The psychometric requirements of good clinical scales and behavioral outcome measures are many, for example, they must have the sensitivity to demonstrate therapeutic improvement. Tasks unrelated to the deficit of interest might also be tested, such as attention, to assess the extent to which a drug might achieve effect via modified cognitive function.

Further studies are needed to define the potential for human brain mapping to serve as a surrogate marker of restorative events, or as an alternative to clinical end-points in clinical rehabilitation studies after stroke. From the description of currently available studies given in previous sections there is clearly some way to go before achieving this goal. Experiments need to become more hypothesis-driven and a clearer understanding of the issues surrounding experimental design is required.

Conclusions

There is burgeoning evidence that the human brain responds to ischemic injury with mechanisms to promote recovery of function both earlier and later than had been previously suspected. Imaging techniques such as fMRI and PET as well as related neurophysiological techniques like TMS have demonstrated that the human brain has not only the capacity to activate alternative regions during recovery, but that the system is a dynamic one, subject to behavioral and pharmacological interventions that could potentiate recovery. Although there are many questions still to answer, clinicians and scientists now have a responsibility to come together to ask appropriate questions in a rigorous manner. We can be reasonably optimistic that future studies will translate into true benefits for patients with stroke.

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