Session Title: Neuroimaging as a physiological marker to guide a strategy for rehabilitation

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Proposed Discussion Questions:

- Can a therapy for aphasia, paresis, neglect etc. be chosen based on how it alters a short-term TMS, fMRI or the response to other techniques, i.e., the intervention appears to engage or fails to alter the expected regions of interest?
- Can these techniques help define the optimal intensity and duration of a therapy using repeated measures over the time of treatment?
- What intervention, if any, should serve as the control condition for a training paradigm plus neuroimaging study executed over weeks or months?
- What set of longitudinal data are needed to make reliable brain-behavior correlations as training proceeds?

Additional Discussion:

The advantages of using uniform clinical outcome measures between studies.

Can functional neuroimaging offer information that is not clinically evident?

Summary of Discussion:

While there is increasing evidence that the neuroimaging techniques might be used in stroke studies, less is known about their relationship with functional outcome following stroke. More precisely, how do these new neuroimaging modalities compare with clinical testing) in assessing the potential of patients to respond to treatments. However, neuroimaging studies of stroke survivors are not every day clinical practice while the clinical scales are less expensive and more practical. Since the time since stroke and current clinical scores seem not to be good predictors of the potential for further recovery in late stroke, their combination with neuroimaging data may allow us to gain predictive power. In addition, neuroimaging biomarkers may increase test sensitivity by being less exposed to subjective interpretation compared to the clinical biomarkers. Furthermore, these biomarkers would be especially useful for the design of randomized clinical trials to estimate sample size and define inclusion criteria, i.e., including only those patients with potential for treatment response.

The facilitators suggested the goal of developing predictors of the capacity of patients to make further improvements in their sensorimotor and cognitive impairments, and consequently to identify the patients who are unlikely to make a clinically meaningful neurological recovery within the context of a specified strategy for acute stroke therapy, rehabilitation or neural repair.
This approach could justify withdrawal from a rehabilitation intervention and administration of other possible interventions to these patients. It is clear that an ideal prognostic biomarker should be readily available, easily reproducible, and associated with a high degree of specificity for poor outcome.

This session concentrated on the role of neuroimaging techniques, in particular fMRI, as a potential predictor of further functional improvement. For example, Dr. Cramer has shown that in 24 stroke patients who participated in 6 weeks of rehabilitation therapy with or without motor cortex stimulation, the best predictor for treatment gains was lower motor cortex BOLD activation [1]Another study mentioned during this section was that of Dong et al., 2006 about the role of serial fMRI as a physiological indicator for “dose-response” interactions during a task-specific intervention. More precisely, by using fMRI, the M1 activation in 8 moderately impaired stroke patients was measured midway through a 2-week arm-focused intervention in order to capture adaptations induced by the initial week of training. These midway M1 adaptations (ipsilateral hemisphere) were used to anticipate post-therapeutic behavioral changes in impaired hand function. Furthermore, this correlation between brain activation adaptations and behavioral improvement, called “brain-behavior correspondence” by the authors combined with initial impairment level might be used to guide the optimal duration for this task-specific therapy. Similar data were provided by Koski et al[2], whose data suggested that TMS measures of the corticomotor pathways across

one day of therapy might predict the treatment-induced plasticity and behavioral gains (for upper extremity) over subsequent weeks in patients with moderate to more impaired deficits after stroke.

However, when using fMRI to study neural response in patients with stroke, there are several issues to consider. Although detailed theoretical background to this technique was beyond the scope of this session, the facilitators pointed out the impact of impaired cerebrovascular reserve or advanced narrowing of the cerebral arteries on the BOLD signal (see Hamzei et al., 2003; Rossini et al., 2004)[3, 4]. Additionally, it still is not clear how the BOLD signal is affected by parameters such as time after stroke and large or small vessel disease. Consequently, a multimodality approach using different imaging techniques (BOLD, perfusion scanning) and concurrent neurophysiological methods (EEG, MEG, TMS) was proposed to address the influence of different physiologic variables. For example, Stinear et al (2007)[5] by using a multimodality approach (TMS, structural and functional MRI) characterized the state of the motor system in chronic stroke patients to predict the functional gains made in a subsequent motor practice intervention. The structural integrity of the CST was assessed by the presence or absence of MEPs (TMS) in the affected arm, and FA values of PLIC (DTI), while the lateralization of brain activation during a motor task was assessed by fMRI. The TMS measures suggested that in patients with MEPs, meaningful motor gains were still possible 3 years after stroke while in patients without MEPs, limited gains were reported. In contrast, the fMRI measures (i.e., brain activity lateralization) were not able to predict future functional gains through motor practice. However, that might be explained by the motor task evaluated during fMRI (self paced opening and closing of the hand that might induce variability in performance).

The next key question addressed in this session was the potential to study the brain's capacity to be changed by a perturbation such as TMS to temporally and briefly manipulate cortical physiology. Numerous examples exist in the literature whereby a virtual lesion created by TMS provided insight into how function of specific brain regions related to behavioral status. This approach may serve as a behaviorally independent assay of connectivity between cortical areas.

Another important question was whether these changes in motor system reorganization might help define the optimal intensity and duration of a therapy. Therapy can be considered as an input that interacts with a damaged system (in our case, stroke) and the aim of this input is to optimize the functional reorganization of this system. This input may succeed in driving functionally useful changes if it interacts with intact brain regions and networks that influence motor output pathways. Pharmacological and repetitive TMS therapies, may also drive activity-dependent spared pathways. Genetic factors could be a source of important interactions. For example, in the study of Kleim et al. (2006)[6], the presence of the BDNF polymorphism was found to modify experience-dependent plasticity in corticospinal output in healthy subjects.

Whether changes in fMRI patterns predict skill recovery was another important question. The answer may depend on patient criteria selection, including only well recovered patients who could perform a distal motor task at baseline and patients with a small lesion affecting only M1 or subcortical white matter. \Ward et al (2003, 2004)[7, 8] studied motor system changes by using fMRI in a such a group of patients, suggesting that during recovery from stroke, the nervous system may retain the ability to exploit the redundancy of the motor system by using intact and connected motor regions (i.e., secondary motor areas in the impaired and unimpaired hemispheres) to generate motor output. In other words, damage of a motor network could be partially compensated by activity in another region. However, the functional relevance of recruitment of these secondary motor regions is not fully understood. Based on the previous studies and following the Symposium discussion, two approaches were suggested to better understand neural substrates of functional reorganization: (i) use TMS to transitively disrupt these regions and measure differential behavioral effects in stroke patients vs. healthy, an approach that in a handful of studies does support that increased activity in secondary brain areas contributes to the final behavioral state (eg Lotze et al, J Neurosci, 2006)[9]; and (ii) measure how task-related activity covaries with modulation of task parameters (i.e., force modulation). Less is known about the functional changes underlying therapy-induced recovery in more severely impaired patients.

However, it is unlikely that the cerebral motor system response to injury involves a simple substitution of one motor region with another by taking new roles. Reorganization is often not successful in returning motor function

to normal and seems to be determined by the extent of anatomic damage (damage of cortical motor regions, white matter pathways, and even which hemisphere is affected).

Cross sectional versus longitudinal studies

There are fewer longitudinal fMRI studies compared to cross sectional studies in stroke patients. The longitudinal studies generally suggest that functional recovery is associated with a lateralization of the task-related brain activation patterns towards the ipsilesional hemisphere, ie contralateral to movement. However, it is impossible to know whether the brain activation patterns returned to pre-stroke levels given persistent structural damage. From cross-sectional studies, it is clear that brain activation patterns will not return to normal in most of the cases. Thus, the longitudinal changes of motor activation patterns may represents an increase in efficiency, synaptic efficacy, and learning within the spared motor networks (Dobkin, Neurorehabil Neural Repair, 2007). The focusing of task-related brain activation will tend toward the most efficient system available. It is clear that brain activation pattern of an individual patient at one time point represents the state of reorganization within the available system and depends on a number of factors: anatomical lesion, premorbid state of the brain, drug treatments, genetic status (see previous section). All these factors influence the potential activity-driven changes within the intact motor networks, the putative mechanism of motor therapy.

The advantage of uniform clinical outcome measures between studies.

The facilitators pointed out the variability of clinical outcome measures between studies using functional neuroimaging techniques, in particular fMRI for understanding treatment effects after stroke.

However, it is clear that stroke-related impairments (i.e., motor, sensory, cognitive, language, etc) recover to different extents at different rates after stroke and the stroke treatment may affect various stroke-related impairments. Most studies in stroke treatments rely on composite clinical rating scales as outcome measures (i.e., modified Rankin scale, NIHSS). By using these composite scales, an important gain in one domain might be over or under estimated as little or no gain in another, when the domains are unequally weighted (i.e., motor vs. cognitive). The facilitators suggested using specific scales as primary outcome measure that address only one domain that is relevant to the rehabilitation intervention (i.e., motor recovery). For example, Dr. Cramer suggested using the Fugl-Meyer scale to assess upper extremity impairment. In addition, by using these specific scales, a stroke recovery treatment might be described as a treatment to improve a specific neurological function, such as “recovery of arm motor function”. Furthermore, the best primary outcome measure seems to be the within-subject change scores (for example, a change in FM score of 4 may be clinically significant) rather than a single cross-sectional value. Consequently, by using within-subject change scores, the sample size requirements of clinical trial may be reduced. Use of uniform measures across studies has been widely adopted, with success in dementia, multiple sclerosis, and spinal cord injury, and is much needed in the field of stroke recovery.

Can functional neuroimaging offer information that is not clinically evident?

The overall opinion was yes. Functional neuroimaging provides insights into biological mechanisms underlying functional recovery and potential targets for different therapies when anatomic imaging or behavioral assessment do not (i.e. Yozbatiran et al., 2006)[10]. In other words, the value of functional neuroimaging is to predict treatment response over time of an intervention and possibly to triage patients according to their brain’s physiological status rather than only by the clinical examination.

During the Symposium, the focus of the discussion was on functional neuroimaging biomarkers at the level of neuronal systems, rather than cells or molecules. Both approaches (systems and cellular) have something to teach each other about brain plasticity following injury. Magnetic resonance spectroscopy (1H-MRS) provides an imaging probe of neuronal metabolism (cellular level) that measures brain metabolites including N-acetylaspartate (NAA), a compound localized exclusively in neurons and their dendritic and axonal processes. A decrease of NAA concentration has been described in the brain lesion’s core, indicating neuronal loss, and in remote brain regions that appear normal on conventional MRI, indicating decreased neuronal metabolism. However, there is currently no direct evidence that changes at the cellular (i.e., decreased NAA concentrations) level are related to changes at the systemic (i.e., increased/decreased motor-related activation) level. Furthermore, the relationship between these cellular changes and functional recovery is unknown.

Other points:

Should therapeutic resources be focused on patients with good prognosis or should increased resources be channeled to patients with poor prognosis?
Changes in motor performance over time poses a neuroimaging confounder. A task is needed that probes the changeability of the cerebral motor system in the context of motor practice but how the task is performed over time is understood in terms of changes in electromyographic, kinematic, and spatiotemporal measures that can be monitored during scanning to allow an accurate interpretation of neuroimaging data.
Multiple sites are needed to enter enough subjects into an fMRI-rehabilitation trial after stroke or TBI. Data collected across sites ought to be more generalizable than the usual single site trial that includes fewer than 10 subjects. However, issues in standardizing the imaging techniques across centers are not fully resolved.

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