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Biomarkers of Recovery after Stroke

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Abstract

Purpose of review—A better understanding of the molecular events underlying stroke recovery might be useful to optimize restorative therapies. Measurement of these events, however, is generally inaccessible in humans, at least at the molecular level. Substitute measures, or biomarkers, that are accessible and that provide useful insights might provide deeper insights into spontaneous recovery in humans. This review considers advances in insights into using biomarkers to understand recovery from stroke, and to serve as a surrogate measure of stroke recovery, including in a clinical trial context.

Recent findings—Among the key recent findings is that measures of brain function and injury are the strongest predictors of treatment effect, moreso than behavioral measures are despite the reliance on behavioral measures as study entry criteria. Functional neuroimaging studies have provided insights into therapeutic mechanism of action. In addition, measures of CNS function have been used to estimate individual therapy needs, findings that suggest the potential to tailor restorative therapies to the specific needs of individual patients.

Summary—Many therapies are emerging as potentially useful to promote improved recovery after stroke. Continued advances in biomarkers are providing new insights into the neurobiology of both spontaneous and therapy-induced brain repair after stroke.

Keywords

stroke; plasticity; recovery; therapy

Introduction

Stroke is a major source of disability. Most patients do not reach the hospital in time to receive acute therapies. The majority of those who do receive such therapies nevertheless still have significant disability, as spontaneous stroke recovery is generally incomplete[1]. One area of therapeutics that has the potential to further reduce disability revolves around restorative therapeutics. A restorative therapy can be defined as one that aims to improve outcome by promoting repair and restoration rather than by salvaging acutely threatened tissue. Restorative interventions under study have included growth factors, cells, small molecules, intensive and activity-based therapy, robotics, neuroprosthetics, electromagnetic brain stimulation, and cognitive strategies such as motor imagery[2]. Restorative therapies for stroke span the spectrum in terms of readiness for patient application, including publication of positive phase 3 trial results[3,4]. Whether the focus is on spontaneous recovery or on therapy-induced repair,

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a better understanding of the underlying cellular and molecular events might be useful to improve patient outcomes.

Measurement of the events underlying recovery, however, is generally inaccessible in humans, at least at the molecular level. Substitute measures, or biomarkers, that are accessible and that provide useful insights might provide deeper insights into spontaneous recovery in humans, and might also serve as surrogate markers in clinical trials of restorative therapies.

Biomarkers: general considerations

In the simplest case, a biomarker of stroke recovery would be a measure that correlates with clinical status or with clinical evolution. Such a marker might be useful in constructing or testing a biological model of recovery. A well-designed functional neuroimaging study can also provide biomarker data around a specific subset of neural events, for example, providing insights into specific neurochemical components of plasticity[5,6].

Biomarkers in a clinical trial might serve as a surrogate marker, which has been defined as “a laboratory measurement…used as a substitute for a clinically meaningful endpoint.…”[7] One of the earliest examples in stroke recovery was from Carey et al[8], who hypothesized that affected limb training would be associated with increased reliance on the ipsilesional motor system, that is, that measures of ipsilesional motor system function were a biomarker for treatment effects. These authors found that, in subjects with chronic stroke prior to training, affected hand finger tracking movements activated contralesional brain areas. However, after training at this task, the normal pattern of laterality of brain activation was restored, with activation shifting to ipsilesional brain regions.

In general, surrogate markers are particularly useful in phase 2 trials, for example, to probe biological activity of a proposed therapy, to inform the decision whether or not to proceed to phase 3[9,10], or by helping define a target population[11].” Examples include blood pressure as a surrogate marker for vascular death, HIV RNA levels as a marker of progression to AIDS, or tumor size as a marker of survival. Biomarker data might also be used to guide features of therapy in ways that behavioral or demographic data can not. This perspective has received increased attention in the acute stroke setting, where some studies have suggested that diffusion-perfusion mismatch might be a useful surrogate marker of salvable penumbra [12-14].

A number of caveats exist when considering the utility of a biomarker in this context. Surrogate endpoints are generally easier to measure than behavioral endpoints are, easier to standardize, and save time and money[9,15]--but these features are not always applicable for many of the imaging or physiological measures proposed as recovery-related surrogate endpoints. A measure has reduced potential to serve as a valid surrogate endpoint when it is not in the causal pathway of the disease process, when the therapeutic intervention selectively affects physiology of the surrogate, or when the surrogate measure does not fully capture the net effect of treatment on the clinical outcome[9,16]. The usual clinometrics considered for any outcome measure, such as validity, reliability, sensitivity, and specificity (see Figure 1), are pertinent to any discussion of biomarkers but in general have been incompletely assessed in the setting of stroke recovery[17-20]. Numerous influences and other covariates relevant to other aspects of stroke[21] are likely important to biomarkers of recovery and vastly complicate assessment of these markers.

Recovery after stroke

Animal studies have provided insights into the cellular and molecular events underlying spontaneous and treatment-induced stroke recovery for which human biomarkers might be

useful. As reviewed elsewhere[22-24], these include structural changes in axons, dendrites, and synapses; increased activation and migration of endogenous neural stems; plus changes in extracellular matrix, growth factor levels, glia, angiogenesis, and excitability. In some cases, these changes arise bilaterally after a unilateral stroke. Cortical representational maps can shift and expand in relation to injury, behavioral recovery, and training.

Human studies of stroke recovery also provide information useful for selecting biomarkers of recovery. Overall, the best spontaneous return of behavior is associated with the greatest return of activity in primary cortex. Useful compensatory brain responses include increased activation in secondary areas that are normally connected to the injured zones through a distributed network, a shift in interhemispheric lateralization towards the contralesional hemisphere, and shifts in representational maps surrounding the infarcted zone. In general, the best behavioral outcomes after stroke are associated with the greatest return of brain function towards the normal state of organization[25]. Some authors have suggested that those events that support spontaneous recovery are likely to be the same events that are measured as biomarkers[26].

A biomarker might be selected on any of several bases. For example, a biomarker might be selected as it correlates with a cross-sectional estimate of behavioral status, with change in behavioral status over time, with response to a therapeutic intervention, or in relation to a key covariate of interest. The choice of test used might vary across these situations, but as described below, likely substantial overlap exists. Choice of biomarker might also emphasize pragmatic issues: most patients with stroke are often infirm with reduced capacity for extended testing; many have a range of stroke-related deficits, such as inattention, aphasia, or depression, that reduce capacity to undergo testing; and have relevant concomitant medical and demographic issues, such as median age in the eight decade.

Biomarkers of potential value to recovery after stroke

A number of measures of potential interest are available to serve as a biomarker of recovery. The most elementary examples are simple behavioral measures, such as short-distance measures of gait as a marker of overall vascular or social status[27], index finger extension as a predictor of arm recovery[28], or a blood test as a marker of subsequent clinical outcome [29]. Simple brain imaging measures also have potential value, for example, with total infarct volume correlating with, and predicting, overall neurological status[30,31].

More complex anatomical imaging measures are also of potential value as biomarkers of recovery. Imaging of region pertinent to specific neurotransmitters might have value for specific hypotheses such as those related to memory[32]. High resolution MRI can detect changes in cortical thickness[33], sometimes increased with treatment[34]. Diffusion tensor imaging (DTI) measures the tendency of water movement to be directional, and so reflects injury when stroke reduces the linearity of water movement, or fractional anisotropy, within a directional tract such as the corticospinal. DTI data provide a measure of white matter tract status that not only describes injury[35], but also can provide insights into repair[36]. DTI, like fMRI[37], is of particular value to translational science in brain repair because the same measurements obtained in animal models can be used in human subjects. Multimodality approaches provide rich insights in this context[38,39].

Measures of CNS function might also be useful biomarkers. Physiological measures such as motor system transcranial magnetic stimulation (TMS) can yield information on the size of a cortical representational map, or on the speed/magnitude of the motor evoked potential (MEP), reflections of CNS injury[40]. Brain function can be measured with functional MRI (fMRI) or positron emission tomography (PET), as well as with electroencephalography or magnetoencephalography. Use of such methods can measure the volume of regional activation, such as the volume of Broca's area activated during a speech output task; the magnitude of

activation, such as the height of parietal activation during a spatial attention task; or the balance of activation across hemispheres, sometimes reported as the laterality index (LI). PET can provide a direct measure of many processes including regional blood flow, metabolism, and receptor ligand occupation. Other tissue function measures include measures of cortical excitability or inhibition, or assessments of the connectivity between various cortical regions [41].

Measurement of tissue function introduces complexities that do not arise with measurement of tissue anatomy. To activate the brain with fMRI or PET, the subject must engage in a specific behavioral paradigm, correctly, according to instructions, on cue--at times a challenge after stroke. The behavioral paradigm must be carefully selected to probe the brain functional circuit of interest. These issues influence the utility of such a biomarker, and do so in a manner that might vary across sites.

There are many types of relationship that a biomarker might have with the process or behavior of interest. A biomarker might simply be a direct correlation with the level of activity in a specific brain area. For example, better outcome has been found to correlate with larger activation maps within ipsilesional motor cortex using a range of techniques[42,43]. In such cases, a TMS, fMRI, or PET measure might be used to determine which patients have more of a useful recovery-related process ongoing. A useful biomarker might also have an inverse correlation, for example, with reduced blood flow[44], activation[25], or evoked potentials [45] in specific brain areas at times corresponding to better behavioral outcome. A biomarker might involve excitatory or inhibitory[46] measures.

Although a preponderance of evidence suggests that the most critical processes for behavioral recovery take place in the ipsilesional hemisphere, a number of observations suggest that events useful to recovery can also be measured in the contralesional hemisphere[47-51]. In studies of brain activation, the LI[52] has been a useful metric for defining the activation balance between hemispheres, with recent studies providing refined methods for its determination[53].

Potential applications of stroke recovery biomarkers

A biomarker for recovery that is found to be valid and reliable might be employed in several different ways to improve patient outcomes. Functional neuroimaging measures might be used to guide dose of therapy, much as serum TSH is used to guide treatment of hypothyroidism or exercise treadmill testing is used to guide treatment of chest pain. Repeated measurement of fMRI laterality measurements[54] or motor evoked potential by TMS[55] have been found useful in this regard, with change over time in these measures suggesting potential modifications of a restorative therapy dose. Given that individual patient responses to a restorative therapy are highly variable, great promise exists in the use of biomarkers to guide qualitative or quantitative treatment choices in order to derive maximum patient gains.

A biomarker that can substantially improve prediction of spontaneous outcome[56], or of response to treatment, might be of enormous value to clinicians and clinical trialists. One candidate measure is fMRI-based. In patients with chronic stroke, smaller ipsilesional primary motor cortex activation during fMRI predicted gains from motor related therapy, and did so more strongly than many other clinical or imaging metrics did[57] (Figure 2). Stinear et al [35] achieved good success at predicting arm motor gains from therapy using DTI-based measures of white matter integrity, TMS-based measures of motor system function, demographics, and behavioral status.

Much work remains to bring biomarkers of stroke recovery to the point of utility. The degree of variance in behavioral outcome after therapy explained by biomarkers remains limited. For example, a measure of CNS injury based on DTI accounted for only 38% of the variance in

clinical gains in one study[35]; an fMRI-based measure of CNS function, only 20%[57]. Also, a recent meta-analysis[58] examined functional neuroimaging as a biological marker of treatment effects. Concerns highlighted included that published data are skewed given that most studies using biomarkers in this context have preferentially enrolled patients with good baseline behavioral status, and so the value of recovery biomarkers in most patients remained less explored. Also, many studies using recovery biomarkers have focused on patients in the chronic phase of stroke, but data on patients in the initial weeks post-stroke are needed given that such biomarkers might also prove important, and vary from chronic phase findings[59, 60], during this acute time period. The optimal technique to use for deriving biomarker data remains unclear, with few publications directly comparing measurements across modalities.

Nevertheless, recent studies investigating biomarkers of recovery following stroke have provided useful insights into treatment mechanism, patient selection, and prognosis. These findings are facilitating emergence of restorative therapies in patients with stroke, and thus deliver on the promise to reduce disability after stroke.

Conclusion

Biomarkers that measure CNS injury and function have the potential to provide insights into recovery, serve as surrogate markers in clinical trials, and possibly guide therapeutic decision making in a manner than can improve outcomes for individual patients. Recent findings are exciting and heuristic, but further studies are needed for such biomarkers to reach the point of widespread utility.

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* of special interest

** of outstanding interest

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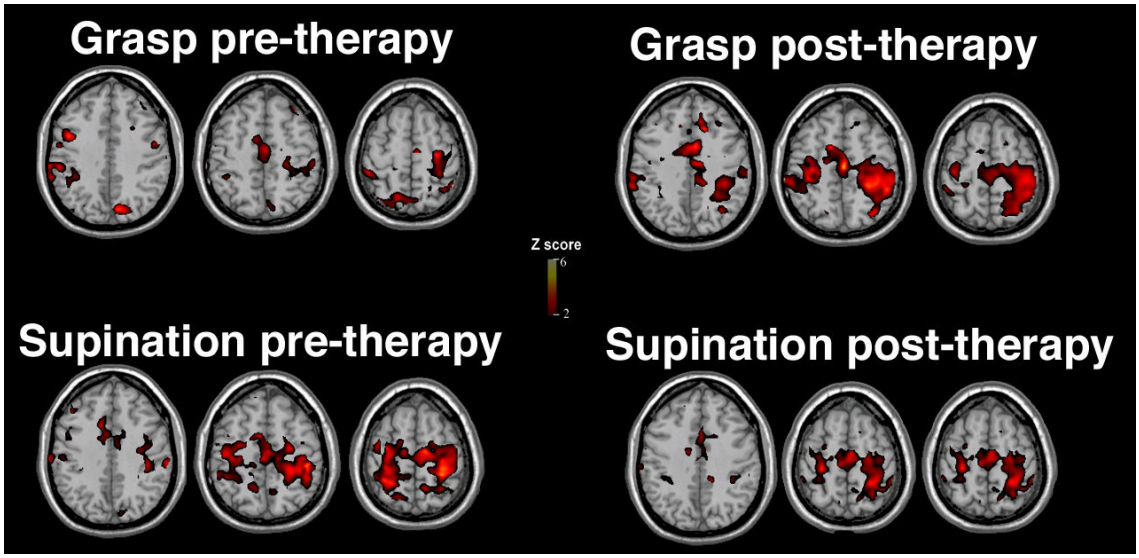

Figure 1.

Specificity of fMRI measures in relation to post-stroke therapy. Ten patients with chronic left brain hemiparetic stroke underwent fMRI scanning during two tasks, received three weeks of robotic therapy, then underwent repeat fMRI scanning. The content of the robotic therapy emphasized grasp/release movements. Group fMRI maps are displayed for 9 (bottom row) to 10 (top row) patients in whom such data were available. The top row shows evolution of fMRI activation for the task that was extensively practiced as part of therapy, with a significant 20-fold increase in left primary sensorimotor cortex activation. The bottom row shows that this increase was absent for a control task, pronation-supination, that relied on similar muscles but that was not rehearsed as part of therapy. The results suggest specificity of therapy effects on an fMRI biomarker[17].

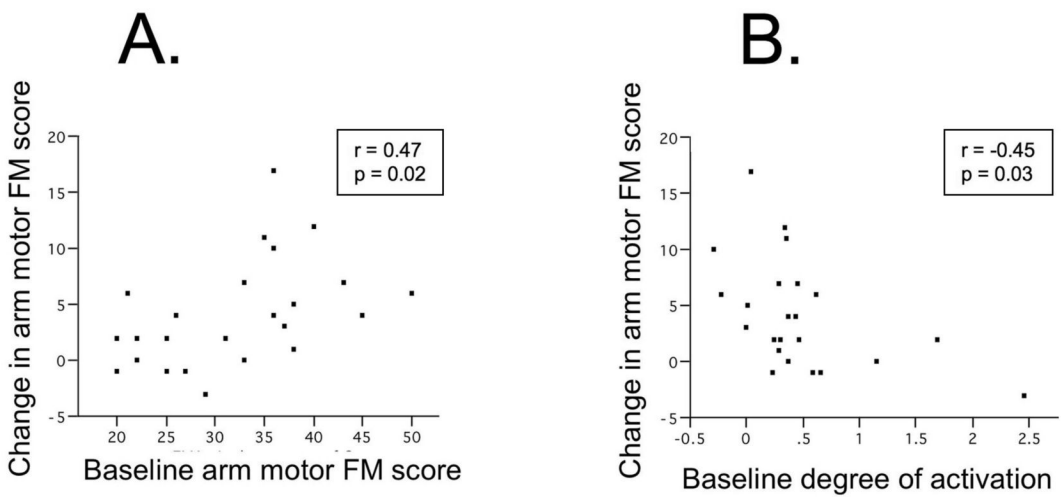

Figure 2.

Potential of fMRI to provide an independent measure for predicting response to therapy in chronic stroke. Twenty four patients underwent baseline behavioral and fMRI testing received six weeks of therapy, and had repeat behavioral testing. Measures of (A) baseline motor status, the arm motor Fugl-Meyer (FM) score and of (B) baseline brain function, the degree of activation in ipsilesional primary motor cortex as measured from fMRI brain mapping each predicted behavioral gains from subsequent therapy, and survived as the only such predictors in a multivariate model. Note that variables not surviving in the model included the classic stroke outcome predictors of age, time post-stroke, and infarct volume. In this population, better baseline motor status predicted greater gains from therapy. Also, lesser baseline motor cortex function during distal upper extremity movements predicted greater gains, suggesting underuse of available motor cortex resource at baseline. The two variable model, while exciting in its emphasis that behavioral and fMRI measures can have independent and complementary value, nevertheless only explained 40% of the variance in response to therapy[57].