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Biomarkers and predictors of restorative therapy effects after stroke

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Abstract

Many restorative therapies that promote brain repair are under development. Stroke is very heterogeneous, highlighting the need to identify target populations and to understand inter-subject differences in treatment response. Several neuroimaging measures have shown promise as biomarkers and predictors, including measures of structure and function, in gray matter and white matter. Choice of biomarker and predictor can vary with the content of therapy and with the population under study, for example, contralesional hemisphere measures may be of particular importance in patients with more severe injury. Studies of training effects in healthy subjects provide insights useful to brain repair. Limitations of published studies include a focus on chronic stroke, however the brain is most galvanized to respond to restorative therapies in the early days post-stroke. Multimodal approaches might be the most robust approach for stratifying patients and so for optimizing prescription of restorative therapies after stroke.

Keywords

stroke; neuroimaging; plasticity; biomarker

Introduction

Approximately 795,000 strokes occurring each year in the United States [1], with the rate of survival increasing in recent years. Thrombolytic therapy has been approved for the treatment of acute stroke, but only 5.2% of Americans receive intravenous tPA after stroke [2] and approximately half of those who are treated and survive nonetheless show long-term disability [3]. The need exists for additional therapeutic approaches to reduce disability after stroke.

While many patients show some degree of spontaneous recovery during the months after a stroke, this is generally incomplete. Restorative therapies aim to improve outcome not by salvaging threatened brain, as with reperfusion or neuroprotection drugs, but by promoting plasticity within surviving neural tissue [4, 5]. Restorative therapies typically have a therapeutic time window measured in days-weeks and so have the potential to be accessed by a large fraction of patients with a new stroke. Examples of such brain repair therapies include growth factors, cell-based therapies, and devices. Positive clinical trials have been reported in human studies for several classes of restorative therapy after stroke. These

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include robotics [6], constraint-induced movement therapy (CIMT) [7], and pharmacological therapy such as levodopa [8, 9] and selective serotonin reuptake inhibitors [10**]. In addition, several forms of non-invasive cortical stimulation such as rapid transcranial magnetic stimulation (rTMS) [11, 12, 13], transcranial direct current stimulation (tDCS) [14], and theta-burst stimulation (TBS) [15] have shown promise in early phase studies.

One hurdle to implementation of restorative therapies is the heterogeneity of stroke, as injury location and size vary widely from one patient to the next. The ability to assign the right patients to the right therapies would maximize treatment effects, for example, by confirming the presence of a therapy's biological target. Because cellular and molecular measurements are generally inaccessible in human subjects, a number of neuroimaging methods have been examined to better understand, predict, and guide post-stroke restorative therapies. This review will discuss recent studies of therapy-induced neuroplasticity, predictors of treatment effect, and biomarkers of behavioral improvement.

Neuroimaging provides insight into neuroplasticity after stroke in humans

An increasing number of studies have examined the mechanisms of spontaneous recovery after stroke. Animal studies have elucidated many of the cellular and molecular events [16], both near and remote from the lesion, that underlie spontaneous post-stroke improvements. These results are concordant with many of the findings form noninvasive neuroimaging methods in human subjects.

A wide number of neuroimaging methods exist for evaluating the state of central nervous system (CNS) function and structure after stroke. Brain function can be measured using functional magnetic resonance imaging (fMRI), positron emission tomography (PET), electroencephalography (EEG), magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), and near infrared spectroscopy. In many cases, these techniques measure the volume of regional brain activation, the magnitude of this activation, and the balance of activation across hemispheres, often reported as a laterality index, during a task or at rest. Each technique has its merits and limits, for example, MRI involves no isotopes and can also measure cerebral blood flow (CBF) and angiography; PET can be used to measure CBF, metabolism, neurochemistry, and receptor kinetics; and TMS and MEG have temporal resolution at the millisecond level. Techniques such as fMRI, EEG, and MEG provide estimates of functional connectivity (FC), which assesses lesion effects on neural networks near the infarct and remotely [17]. Effective connectivity evaluates not only changes in the temporal correlation of activation between regions after stroke, as with FC, but also the strength and directional influence of one brain region on another. Diffusion tensor imaging (DTI) is an MRI method for examining white matter integrity via measures such as fractional anisotropy (FA). Physiological measures such as TMS yield information such as the size of a cortical representation map, or the conduction of a motor evoked potential (MEP).

As no single method is sufficient to examine all aspects of neuroplasticity, a multimodal approach can be used in order to achieve the most robust understanding [18]. Imaging not only provides insight into the mechanisms of stroke recovery but also helps with development of therapeutic protocols that target these mechanisms [19].

Mechanisms of spontaneous recovery after stroke in humans

Neuroimaging studies have provided insights into human neuroplasticity and, in general, have been concordant with animal findings. After stroke in humans, focal injury reduces local tissue function and has distant effects on activity in a number of brain areas connected within a network. For example, after a stroke on one side of the brain, increased activation is

often seen in homologous regions within the contralesional hemisphere [20]. In general, the contribution of the contralesional hemisphere to spontaneous behavioral recovery after stroke is largest in patients with the greatest injury and deficits [21, 22]. Attention has therefore been paid to laterality of brain activation as a measure of altered brain function [23]. Changes in fMRI laterality have been related to altered interhemispheric interactions, suggesting that improved function of ipsilesional brain regions might be facilitated by normalizing the pathological interhemispheric interactions that arise post-stroke [24, 25]. However, changes in interhemispheric connectivity might facilitate behavioral improvement in some cases [26, 27]. Reductions in corticospinal tract (CST) integrity and interhemispheric white matter integrity are associated with poorer motor outcome after stroke [28, 29*, 30, 31] and might underlie observed changes in laterality of fMRI activation [32, 33] and in fMRI connectivity [34*]. Such studies suggest that multimodal imaging may be key to achieving the most precise understanding of the complex relationships between injury, function, and spontaneous changes in behavior after stroke, but it remains unclear how complex an approach is needed to answer basic questions about prediction and biomarkers in a therapeutic setting.

Many of the neuroimaging metrics described in the study of spontaneous recovery correlate with behavioral status and are therefore of interest to therapy-based studies. In addition, many of the principles of neuroplasticity described in relation to spontaneous recovery pertain to therapeutic studies after stroke.

Biomarkers of treatment-induced recovery

A biomarker is an indicator of disease state that is often useful clinically as a substitute measure, reflecting underlying molecular/cellular events that are difficult to measure directly. A good biomarker for stroke recovery might be one that reflects a brain event related to recovery and that correlates with behavioral state. A biomarker might be useful in a restorative therapeutic context by providing a measure related to the treatment's mechanism; such data might improve decision-making in the timing, duration, frequency, or intensity with which a treatment is prescribed. Both structural and functional neuroimaging measures have been examined as biomarkers, as have a range of blood tests.

Early neuroimaging studies examined correlates of treatment effects and reported enlargement of the ipsilesional motor map via TMS [35, 36], increased fMRI activation within ipsilesional secondary motor areas [37, 38, 39], and decreased activation of contralesional hemisphere areas associated with increased laterality of activation towards the ipsilesional hemisphere [40, 41]. Other studies described a treatment-associated bilateral increase in activation [42, 43] as well as a decrease in ipsilesional activation [44, 45]. Divergent results were considered a reflection of differences among the patient populations studied, such as differences in time post-stroke or in severity of deficits [46]. For example, Johansen-Berg et al [37] found that CIMT was associated with increased *ipsilesional* activation by fMRI, while Schaechter et al [47], in a study of patients with more severe impairments, found CIMT to be associated mainly with *contralesional* activation increases. Newer studies indicate that activation of brain areas beyond the normal pattern reflects the operations of an injured nervous system and is associated with presence of behavioral deficits, but this supranormal recruitment can support recovery, particularly in more severely impaired patients.

Functional: activation

Cortical plasticity during stroke recovery occurs within perilesional areas as well as across distributed networks and can be measured with techniques such as fMRI. A common type of biomarker study has been longitudinal investigation of treatment-induced changes in cortical

function in relation to a therapy targeting motor system function. In this context, research has provided clear evidence for the role of primary (M1) and secondary motor areas in supporting treatment-induced recovery, but new work has described a functional contribution of primary somatosensory cortex (S1). To evaluate changes in S1 with CIMT, paretic hands of seven chronic stroke patients with normal sensory function were passively moved during fMRI [48*]. Increased activation within ipsilesional S1 was found in association with treatment-induced gains in hand function. In some patients with chronic stroke, a shift of activation into the postcentral gyrus can support motor recovery which may be due, in part, to increased responsiveness to sensory input [49].

Recent studies examining effects of CIMT have begun to extend prior findings on patient-specific factors that differentially affect changes in brain function associated with behavioral gains. For example, Kononen et al [50*] found that patients with poorer baseline behavior showing the largest improvement on the Wolf Motor Function Test have the largest increases in activation within the ipsilesional sensorimotor cortex during finger flexion/extension. These findings vary with degree of CST injury. In the study by Kononen et al [50*], the three subjects lacking an MEP at baseline, indicating greater injury to the corticospinal system, had the greatest treatment-associated increases in ipsilesional somatosensory motor cortex (SMC) activation. Similarly, patients with CST injury from stroke showed increased SMC activation by TMS across a course of CIMT, while patients with an intact CST showed decreased SMC activation [51]. These findings are in contrast to the direction of the gradient in untreated stroke patients, where injury to the ipsilesional CST injury is associated with greater *contralesional* motor cortex activation [32]. The best outcomes after stroke are associated with return of activation to more normal patterns; similarly, restorative therapies, when effective, can normalize the direction of laterality of brain activity.

Functional changes in activation with explicit motor tasks, such as with CIMT, have been more extensively studied as compared to the mechanisms of implicit motor learning after stroke. Preliminary results found that implicit motor learning is accompanied by decreased dorsal premotor cortex (PMd) activation and greater superior frontal cortex fMRI activation, findings not seen with such learning in healthy controls [52*]. For patients with chronic stroke to learn an implicit motor task, a compensatory recruitment of brain areas associated with working memory and visuomotor processing may be needed. These findings emphasize that the mechanisms of behavioral improvement will likely differ according to the nature of a restorative therapy.

Increased movement of the paretic upper extremity and decreased reliance on the non-paretic upper extremity are core features of CIMT, however bilateral arm training has also been found to improve motor function in patients with chronic stroke. Whitall et al [53*] examined the functional mechanisms underlying improvement with bilateral arm training with rhythmic auditory cueing (BATRAC) training and, furthermore, contrasted results with dose-matched unilateral arm training. The two treatments exerted their beneficial effect through different mechanisms: motor function improvement was comparable among the two treatments but BATRAC resulted in significantly greater activation within ipsilesional primary and secondary motor cortex as well as contralesional superior frontal gyrus. Another comparative study found that mirror therapy, in which patients perceive their own unaffected hand movements as occurring in the affected hand, was associated with increased ipsilesional M1 activation relative to a control exercise lacking the mirror feature, but note that these fMRI findings were not accompanied by differences in arm improvement as measured by the Fugl-Meyer score [54]. Other potential mechanisms of mirror therapy effects include increased excitability within contralateral M1 [55*].

Non-invasive brain stimulation techniques have also been found to increase ipsilesional fMRI activation in association with behavioral improvement. Anodal (facilitatory) tDCS stimulation of the ipsilesional hemisphere was associated with greater behavioral gains (better response time) as compared to cathodal (inhibitory) tDCS of the contralesional hemisphere and was associated with increased activation within ipsilesional M1 and PMd [56]. Therefore, facilitatory stimulation of the ipsilesional hemisphere may lead to gains in motor function by increasing activation within ipsilesional motor areas. However, as has been suggested [53*] suggested, and as was described above with CIMT, certain principles exist in common across therapeutic categories. Thus in patients with more severe injury from stroke, reliance on the contralesional hemisphere may be greater, and so contralesional brain regions might be a key consideration for brain stimulation therapies [57].

Functional: connectivity

Serial imaging of fMRI connectivity has the potential to unlock how stroke treatments alter functional connections between brain areas and how those changes are related to behavioral gains. Resting-state FC, reflective of neural coupling in the absence of active task performance, is an attractive means to evaluate motor network changes in a clinical population such as stroke since it minimizes the effect of task-related motion artifact sometimes seen when scanning paretic subjects during a motor task. In a moderate-severely impaired chronic stroke population, Varkuti et al [58] evaluated the effects of robotic motor training and brain computer interface motor imagery training on resting-state FC. Increases in resting-state FC among several networks positively correlated with gains from both robotic and motor imagery training, although correlations were only found when both groups were combined.

Transcranial magnetic stimulation can also be used to interrogate changes in intra- and interhemispheric connectivity. Improved reaching with training increases ipsilesional M1 corticospinal excitability, decreases interhemispheric inhibition from the contralesional to the ipsilesional M1, and decreases intracortical inhibition of the affected triceps [59]. In terms of specificity of findings, note that these changes were not observed for the biceps, a muscle that was not the target of the reaching training. Before short-term reach training, patients with chronic stroke with larger interhemispheric inhibition from the contralesional to ipsilesional M1 had greater motor impairment; these patients also experienced the largest behavioral gains improvements with training. Restorative therapies can modulate both intrahemispheric and interhemispheric inhibition.

Connectivity is altered not only by motor training but also pharmacologically. A small group of subacute/chronic stroke patients with mild deficits showed reduced connectivity between ipsilesional M1 and supplementary motor area (SMA) at baseline. Subjects received a single dose of the noradrenergic drug reboxetine that was associated with small improvements in grip strength and finger-tapping speed [60]. Compared to placebo, noradrenergic therapy significantly increased connectivity between ipsilesional M1 and SMA, i.e., a partial restoration of the normal pattern, in proportion to behavioral improvements.

Multimodal imaging can provide insights into the anatomical underpinnings of changes in FC. In a study of motor skill learning in healthy subjects, there was a significant increase in gray matter volume within contralateral ventral striatum after 3 days of training and within secondary motor areas after 5 days [61*]. Task-related FC between the ventral striatum and the secondary motor areas was evident at day 3 and increased by day 5, suggesting a functional link between the anatomical changes in striatum and motor cortices. Moreover, structural changes were found within white matter weeks after these structural and functional gray matter changes. This study also emphasizes the potential importance of both white matter and gray matter to behavioral improvement with training.

Structural

White matter structure can change with therapy. Abundant preclinical research indicates that white matter structure and integrity are important to achieving behavioral gains with restorative therapies after stroke. However, this issue has been much less examined in human subjects. Several examples of changes in white matter integrity in parallel with training-induced behavioral gains have been described in healthy subjects [62, 63, 64, 65]. Changes in white matter integrity, measured as changes in FA via DTI, have also been described after intermittent theta burst stimulation applied to the affected left hemisphere in chronic aphasia [13], a therapy thought to induce plasticity via an LTP-like mechanism. Synaptic facilitation might increase cortical plasticity and so lead to changes in white matter integrity and thus altered interactions across broad cerebral networks. Such multimodal approaches, here combining noninvasive brain stimulation with neuroimaging investigations, are a strong approach to understanding the mechanisms by which treatments affect behavior [66].

Gray matter can also change with treatment, and such changes are structural as well as functional. Relatively few studies have examined changes in gray matter structure in relation to restorative therapies after stroke. Gauthier et al [67] administered CIMT to 16 chronic stroke patients for 10 days and found increased gray matter volume in bilateral sensorimotor cortices and hippocampi with MRI, a finding not observed in a control group, with degree of gray matter volume increase correlating with extent of increased use of the affected arm.

Assessment of structural changes in both gray matter and white matter can provide a broader picture than either measurement alone. In healthy subjects, training on a balancing task was associated with increased gray matter volume in frontal and parietal regions, with degree of volume increase correlated with degree of behavioral improvement [68**]. Interestingly, the integrity of white matter subjacent to some of these gray matter regions decreased, a finding attributed by the authors to learning-related increases in cell density and axonal/dendritic arborization, reducing water diffusion. White matter and gray matter changes with juggling training in healthy subjects also were found to colocalize [62]. Studies are needed to determine if these principles derived from studying learning in healthy subjects extend to neuroplasticity from restorative therapies after stroke.

Neuroimaging biomarkers also have the potential to serve as surrogate markers, although there are few studies examining this application. A surrogate marker can be used as a substitute for a biological measure of interest as long as certain assumptions are true, such as the need for the surrogate marker to lie in the pathway of the therapeutic intervention [69]. Surrogate markers can guide therapeutic decisions and serve as a unique source of biological insights. A surrogate marker is generally easy to obtain, which is not always the case for neuroimaging measures, but surrogate markers can be very cost effective for Phase II clinical trials. Common examples include blood pressure as a surrogate marker for vascular death, HIV RNA levels as a surrogate marker of progression to AIDS, or tumor size as a surrogate marker of survival.

Other

Other candidate biomarkers, of potential value alone or in combination with neuroimaging biomarkers, include direct measures of molecules related to inflammation, CNS injury, and angiogenesis obtained from blood samples [70, 71].

Summary Points

Functional imaging studies have measured neuroplasticity in relation to a number of restorative therapies, particularly motor training and brain stimulation. Neuroimaging

findings in relation to training and treatment are thought to reflect specific cellular and molecular mechanisms [72**], but some interpretations should be made with caution until the biological bases for MRI phenomena are better understood [73]. Fewer studies have examined changes in brain structure as a biomarker. In many cases, an increase in function within ipsilesional cortices is associated with treatment-induced gains in motor behavior; however, the choice of biomarker might vary with features of the patient population, such as time post-stroke or degree of impairment. Studies of training effects in healthy subjects provide insights that extend to studies of neuroplasticity after stroke. Across a number of neuroimaging methods and categories of restorative therapy, the best outcomes after stroke are associated with restoration of normal patterns of brain function. In patients with extensive unilateral injury, this may not be possible, and changes in the contralesional hemisphere may be a more important source of biomarker data. Choice of biomarker therefore varies with features of the patient population under study. The choice of biomarker for restorative therapies after stroke might also differ in relation to the content of treatment. Multimodal approaches are a powerful approach to understanding treatment mechanisms and treatment effects on behavior, showing that both white matter and gray matter are important for behavioral improvement.

Predictors of treatment-induced recovery

The heterogeneity of stroke makes prediction of treatment responders from non-responders a great challenge. The ability to predict response to therapy and prospectively separate subgroups could be useful for stratifying patients [74] to appropriate therapies in order to maximize behavioral gains, efficiently utilize rehabilitation and financial resources, and reduce variance to increase power in clinical trials.

Behavioral measures of motor impairment and function have been the most often used to predict outcome after stroke [75] but pre-treatment behavior alone is unlikely to sufficiently predict behavioral gains from restorative therapies. The final behavioral phenotype after stroke can arise from a number of different biological states. Therefore, patients might achieve an identical pre-treatment exam through very different neural processes, and such differences might be associated with important differences in response to a restorative therapy--a patient exploiting all possible compensatory brain mechanisms might be expected to have little room to improve while a patient with a similar exam who uses no compensatory mechanisms might be expected to derive greater treatment benefits.

Measurement of the structure or function of the biological target of interest, such as with neuroimaging techniques, is likely to provide an improved picture of the biological target and its capacity for reorganization as compared to what can be inferred from bedside behavioral assessments alone [76]. While this is not yet performed routinely in stroke patients, biological measures of the target tissue are routinely acquired in other areas of medicine to inform treatment decisions, such as an exercise treadmill test to evaluate cardiac function.

Functional: activation

Assessments of pre-treatment cortical activation have shown potential to predict treatment gains but study results vary. In a study of motor cortex stimulation combined with rehabilitation therapy, a measure of motor cortex function derived from fMRI improved the predictive value of baseline Fugl-Meyer score [77]. Subjects with a smaller degree of motor cortex activation during hand movements at baseline subsequently had larger gains in arm motor function as measured by serial Fugl-Meyer scores. These subjects also exhibited the greatest changes in motor cortex activation with treatment. Together, these results suggest

that a subset of patients had underused motor cortex resource that was recruited in support of behavioral gains from this form of therapeutic intervention.

The extent to which these results generalize across patients with different baseline function, or in response to a different form of restorative therapy, requires further study. One study that reached different conclusions found that greater baseline activation in a different cortical region, S1, predicts higher behavioral gains with therapy. Laible et al [48*] found that higher signal intensity within ipsilesional S1 at baseline was predictive of greater improvement in hand function with CIMT. The model here is that when S1 contributes to motor recovery from therapy, it needs to operate maximally. It is unknown whether the greater baseline activation in S1 is due to conservation of a healthy somatosensory system or due to post-stroke reorganization.

Although contralesional activation is often regarded as a less effective compensatory strategy for executing movement or speech, such a strategy may be useful to benefit from therapy. Among 16 patients with aphasia in the chronic phase, greater baseline activation in right-hemisphere regions including inferior frontal gyrus was associated with greater behavioral gains from constraint-induced aphasia therapy [78]. This might reflect greater use of cognitive reserve strategies.

Functional: connectivity

Using connectivity measures to predict gains from restorative therapies is relatively uncharted territory. Studies of recovery in the absence of therapy suggest predictive value of connectivity measures, albeit the relationships may differ with when studied in the context of a restorative therapy. Greater behavioral recovery from stroke is predicted by MEG- and fMRI-derived measures of resting FC within several ipsilesional and contralesional brain regions [79, 80]. Evaluating effective connectivity during a motor task, Rehme et al [26] found that reduced connectivity from secondary ipsilesional areas onto ipsilesional M1 correlated with recovery. These findings encourage exploring these metrics as predictors of response to a restorative therapy.

Structural

Injury to the CST is a very good correlate of motor function in chronic stroke but its value as a predictor of motor gains from treatment is mixed. One of the first predictive chronic studies found that CST FA asymmetry at baseline predicted behavioral improvement from a 30-day course of motor practice, and did so better than age, side of stroke, or baseline clinical assessment [81]. Also, the extent of overlap between an infarct and the normal tracts descending from M1 and PMd is a stronger predictor of motor gains from a course of robotic therapy than is infarct volume or baseline behavior [82]. Similar results were also reported by Lindenberg et al [83]. However, Globas et al [84] found that injury to the CST was not predictive of gains with bilateral or unilateral arm exercise training. It is unclear whether this divergence in findings is due to differences in the intervention, in the method by which CST injury was measured, or other factors.

In addition to descending CST integrity, interhemispheric connections could be predictive of treatment gains. A study of tDCS plus physical therapy found that the integrity of transcallosal fibers connecting bilateral M1 regions, measured as higher FA and lower diffusivity, predicted extent of behavioral improvement with therapy [85*].

The structural integrity of gray matter is also predictive of behavioral gains. In healthy subjects, bilateral cerebellar gray matter volume positively predicted motor skill learning as well as the volumetric changes in ipsilateral M1, as well as contralateral PMv and DLPFC [86]. This finding directly extends to results in patients receiving restorative therapies after

stroke. For example, poorer improvement after CIMT is predicted by reduced gray matter density in several areas remote from the infarct: bilateral cerebral peduncles, pons, cerebellum, ipsilesional SMA, premotor cortex, and contralesional temporal-occipital region [87**], suggesting that gray matter substrate within a distributed motor network is important for response to treatment in chronic stroke. A study in patients receiving epidural cortical stimulation reached similar findings, and furthermore found that greater behavioral gains from treatment were predicted by the presence of supranormal gray matter volume within several brain areas as determined prior to treatment [88].

In many areas of medicine, the response to a dynamic challenge is more informative than a single cross-sectional measure; the change in serum cortisol before vs. after introduction of IV ACTH is far more informative about adrenal function than is a single check of serum cortisol. Some studies suggest that this principle extends to stroke recovery. In two studies, early neurologic response to therapy significantly predicted long-term behavioral gains [40, 89].

Other

Initial studies suggest that variations in genotype might be useful for predicting stroke recovery, with the focus to date on predicting spontaneous recovery [90, 91].

Summary Points

Neuroimaging measures of function and structure improve the ability to predict behavioral gains after stroke. Studies suggest that the best predictive models will consider multiple forms of predictor variables, such as behavior and neuroimaging measures [81, 92].

Conclusions

The current review outlined a number of principles for biomarkers and predictors of restorative therapy effects after stroke. A number of key limitations exist. Most of the studies reviewed above have examined patients in the chronic phase, but the brain is most galvanized to respond to restorative therapies in the early days after a stroke [93, 94, 95]. Further studies of predictors and biomarkers in the early days following stroke onset are critically needed. Also, many studies have enrolled patients with relatively mild impairments and those with subcortical infarct [96] [97*]. A multimodal approach can provide the richest perspective on these issues. Greater insight into biomarkers and predictors of restorative therapy effects may be key to maximizing the impact of this emerging class of therapies for patients with stroke.

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