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Authors
Cassidy, Jessica M
Cramer, Steven C

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Spontaneous & Therapeutic-Induced Mechanisms of Functional Recovery After Stroke

Jessica M. Cassidy, DPT, PhD[1] and **Steven C. Cramer, MD**[1,2,3,4]

[1]Departments of Neurology, University of California, Irvine

[2]Anatomy & Neurobiology, University of California, Irvine

[3]Physical Medicine & Rehabilitation, and the University of California, Irvine

[4]Sue & Bill Gross Stem Cell Research Center, University of California, Irvine

Abstract

With increasing rates of survival throughout the past several years, stroke remains one of the leading causes of adult disability. Following the onset of stroke, spontaneous mechanisms of recovery at the cellular, molecular, and systems levels ensue. The degree of spontaneous recovery is generally incomplete and variable amongst individuals. Typically, the best recovery outcomes entail the restitution of function in injured but surviving neural matter. An assortment of restorative therapies exists or is under development with the goal of potentiating restitution of function in damaged areas or in nearby ipsilesional regions by fostering neuroplastic changes, which often rely on mechanisms similar to those observed during spontaneous recovery. Advancements in stroke rehabilitation depend on the elucidation of both spontaneous and therapeutic-driven mechanisms of recovery. Further, the implementation of neural biomarkers in research and clinical settings will enable a multimodal approach to probing brain state and predicting the extent of post-stroke functional recovery. This review will discuss spontaneous and therapeutic-induced mechanisms driving post-stroke functional recovery while underscoring several potential restorative therapies and biomarkers.

Keywords

stroke; neuroimaging; plasticity; biomarker; rehabilitation; repair

Introduction

Stroke alters the landscape of the brain, compromising the function of various systems and structures. In conjunction with increasing survival rates over the past several years, stroke remains one of the leading causes of long-term disability in the United States and other developed countries [1]. The financial repercussions associated with stroke and subsequent

Corresponding Author: Steven C. Cramer, MD, University of California, Irvine Medical Center, 200 S. Manchester Ave, Suite 206, Orange, CA 92868-4280, Phone: (714) 456-6876, Fax: (714) 456-8805, scramer@uci.edu.

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disability are substantial, totaling over 30 billion dollars annually [2]. Behavioral deficits following stroke span domains of cognition, sensation, vision, and language with motor-related impairments most abundant [3]. Most patients experience some degree of spontaneous recovery, defined by Kwakkel et al. [4] as the amount of improvement in body function and activity determined solely by time.

Spontaneous recovery, however, is often incomplete and the recovery rates of neurological function vary. Impairments of the motor system are most frequently diagnosed and, consequently, most studied in the literature [3]. The majority of motor function gains occur within the first three months post-stroke [4–7]. Whereas, recovery of visuospatial neglect and orientation follow 5–6 months after stroke [8–10], and gains in cognition [11], memory [12], and language function [13, 14] may extend over a period of months to years post-stroke. Individual factors such as genetics [15–17], previous medical comorbidities, initial severity of deficits, and age [18], stroke mechanism, neuroanatomical details such as lesion size and location, and areas spared injury [19–22] impact recovery.

To address the underlying complexity of recovery and stroke heterogeneity, a wide spectrum of restorative treatments encompassing drugs, stem cells, behavioral therapies, robotics, and non-invasive brain stimulation exists [23]. Accompanying this vast array of restorative therapies is a growing list of potential therapeutic targets. One viable therapeutic target rich in recovery potential is the *penumbra*, or the peri-infarct region. In astronomy, the penumbra is a region of half light and shadow [24]. In acute stroke, it has been defined as a region of electrical failure but preserved energy metabolism that holds recovery potential [25]. The conceptualization of the penumbra, in the context of stroke rehabilitation, is a region that survived the initial insult and is galvanized for reorganization in support of recovery. Other therapeutic targets include both local and remote non-injured areas. The aim of the above treatment approaches is to boost restitution of function in the penumbra and in functionally-related targets by fostering neuroplastic change [26]. Often, the underlying mechanisms of these therapies rely on similar mechanisms observed during spontaneous recovery. Both spontaneous and therapeutic-induced mechanisms of plasticity that promote the resumption of activity and function in stroke-damaged areas can positively impact post-stroke recovery. However, as discussed below, not all plasticity mechanisms support restitution of function in stroke-damaged areas and structures.

The proceeding discussion will review both spontaneous and therapeutically- induced mechanisms of post-stroke recovery while highlighting the growing assortment of restorative therapies and promising biomarkers of functional recovery in stroke.

Spontaneous Mechanisms of Functional Recovery

Stroke triggers a cascade of cellular and molecular events that facilitates neural protection and spontaneous recovery [27]. Animal studies have enhanced our understanding of these mechanisms and in-depth reviews are provided elsewhere [28, 29]. In short, experimental stroke models depict subsequent growth of synapses and dendrites [30–32], axonal remodeling and angiogenesis [33–35], increased expression of growth-related genes and proteins [36], and enhanced brain excitability mediated by alterations in *N*-methyl-D-

aspartate (NMDA) and gamma-aminobutyric acid (GABA) receptor subtypes [37] and upregulation of NMDA receptors [38]. These events are not confined exclusively to the peri-lesioned region. Stroke-induced modulations in synaptic efficacy arise in homologous regions in the contralesional hemisphere [30], in ipsilesional areas functionally and/or structurally connected to the lesioned area [39], and even downstream in the spinal cord [40].

These brain changes, driven by discrete physiological and pathological events, can be organized into three recovery epochs. The first epoch occurs during the initial hours after stroke onset and represents an opportunity to salvage threatened tissue, e.g., via reperfusion or neuroprotection. The second epoch commences days to weeks following stroke and corresponds to an initiation of brain repair. Mechanisms of spontaneous recovery are most robust during this time. The third epoch denotes a chronic phase of brain repair when the brain is relatively stable with regards to endogenous repair-related events but modifications in brain structure and function are still possible. Because these epochs delineate periods of neuroprotection and repair, they pose important clinical implication related to the delivery of restorative therapies.

The application of restorative therapies (discussed below) in humans further elucidates the above-described cellular and molecular underpinnings of post-stroke functional recovery, but obtaining precise molecular measurements similar to those in animals proves difficult. Neuroimaging and brain mapping approaches comprising functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), electroencephalography (EEG), magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), and near infrared spectroscopy (NIRS), for example, provide a systems-level perspective of brain repair. This primary focus of this review entails fMRI, TMS, and EEG application to examine spontaneous and treatment-induced mechanisms of post-stroke functional recovery.

Studies employing fMRI, TMS, and EEG have shown modulations in local and distant cortical and subcortical activity, changes in interactions between hemispheres, shifts in cortical representational maps, and alterations in functional and effective brain connectivity. Many of these events contributing to spontaneous recovery are compensatory. In other words, areas and/or structures distinct from the injured area assume function of the injured area. These compensatory events may provide some benefit to individuals with considerable stroke-related injury and severe functional deficits [41–43]. However, compensatory events may also have the opposite effect on individuals with less severe post-stroke injury and deficits similar to how a crutch may simultaneously improve gait function for more impaired individuals and hinder gait function in less impaired individuals. Typically, mechanisms of stroke recovery that promote restitution of function to injured areas typically yield better rehabilitation outcomes [44].

One particular event that has received limited attention to date but may be important in stroke recovery is diaschisis. As one of several theories of functional recovery originally postulated by Von Monakow in the early 20th century, diaschisis entails a decline in function in brain areas spatially discrete but functionally connected to the site of injury [45]. Both

animals [37, 46, 47] and humans [48] demonstrate diaschisis with changes in cerebral blood flow, metabolism, and neurotransmitter activity in areas distant from the lesion. A reversal of diaschisis is suggestive of recovery, but additional work is needed to better understand the timing of diaschisis and the process of diaschisis reversal relative to time post-stroke.

Modulation of Local Cortical Structure & Function

Stroke injury to cortex and underlying white matter results in reduced cortical activity and cortical thickness [49, 50]. Over time, a resurgence of activity occurs in conjunction with functional motor recovery [44, 42, 51, 52, 49]. Similar time-dependent shifts in cortical activity for language [53, 54] and spatial attention [55] also arise and correlate with positive functional recovery in these domains. Schaechter et al. [49] compared functional activation and cortical thickness between individuals with chronic stroke and healthy controls following a unilateral tactile stimulation activity during fMRI. Compared to control subjects, individuals with stroke demonstrated significantly greater activation in areas along the ventral postcentral gyrus and significantly greater cortical thickness within these same areas. These results depict area-specific functional and structural plasticity following stroke.

TMS is another modality used to examine local cortical function. TMS involves non-invasive brain stimulation, operating through electromagnetic induction [56], and enables individuals the ability to probe motor pathway physiology and cortical network excitability [57]. When a TMS pulse of sufficient intensity is delivered to the motor cortex region, a downstream muscle response, referred to as a motor-evoked potential (MEP), occurs. Examination of various properties of the MEP such as size, area, and latency provide valuable information about cortical and corticospinal tract excitation. Studies utilizing TMS in stroke demonstrate an initial downregulation in ipsilesional hemisphere excitability often with an absent MEP, elevated motor thresholds [58–61], diminished MEP size [62, 63], and/or prolonged MEP conduction time [64]. In instances of profound corticospinal tract damage, stimulation of the contralesional hemisphere elicits MEPs in the ipsilateral (i.e. stroke affected) hand [65], suggestive of uncrossed contralesional corticospinal tract fibers contributing to stroke-affected (i.e. ipsilateral) extremity movement.

Shifts in motor threshold and MEP properties over time, consistent with increased cortical excitability in the ipsilesional hemisphere, are associated with positive recovery [66, 67]. Mangonotti et al. [66] observed a significant decrease in ipsilesional motor threshold during a timeframe spanning 5–7 days to 30 days post-stroke in individuals that exhibited improvements across several activities of daily living (i.e. feeding, grooming, dressing, etc.).

Modulation of Brain Regions Distant From Injury

In addition to diminished activity in the ipsilesional hemisphere, increased activation in sites distant from the infarct occurs resulting in the formation of distributed motor, language, and attention networks, sometimes bilaterally [68–74]. The utility of these distributed networks in post-stroke recovery is dependent on the amount of clinical impairment, the extent of injury, and the complexity of the functional task. The contralesional hemisphere is a particularly controversial area under study [75] especially in the context of upper-extremity motor recovery (detailed review by Buetefisch, 2015) [76]. Numerous studies support the

role of the contralesional hemisphere in recovery of the stroke-affected upper-extremity [43, 41, 77–80]. However, other studies view the contralesional hemisphere as a hindrance [81–83]. For example, in an exploratory study that examined cortical activity during an fMRI hand squeezing task in individuals with chronic, subcortical stroke, investigators found increased activation in contralesional primary motor and premotor cortices that negatively correlated to use of the stroke-affected arm [84]. As another example that recruitment of contralesional sensorimotor areas is not always a favorable event in the context of motor performance after stroke, significant correlations have been reported between increased contralesional primary sensorimotor cortex activation and poorer performance on a fine motor task [85]. The role of the contralesional hemisphere in functional recovery is complex and requires further investigation.

Changes in Ipsilesional and Contralesional Hemisphere Interaction

Stroke affects the interactions between hemispheres as evidenced by changes in the distribution of the blood-oxygen-level-dependent (BOLD) signal activation (i.e. laterality index) and by changes in the amount cortical inhibition imparted by one hemisphere onto the other (i.e. interhemispheric inhibition, IHI). The BOLD signal is an *indirect* measure of neural activity based on changes in blood flow and deoxyhemoglobin concentration [86]. IHI is a type of GABAergic-driven cortical inhibition [87–89] measured by applying a single TMS pulse to one hemisphere and a second TMS pulse to the homologous region on the other hemisphere several milliseconds later.[90] A decrease in MEP amplitude and/or area following the delivery of two TMS pulses (paired-pulse TMS) compared to the delivery of a single TMS pulse is indicative of IHI.

Individuals with stroke often exhibit a negative laterality index [68], a measure that reflects increased recruitment of the contralesional hemisphere, relative to the ipsilesional hemisphere, when performing various motor tasks using their stroke-affected extremity. Indeed, brain mapping studies show increased recruitment of contralesional motor, supplementary, and premotor cortical areas with voluntary movement from the stroke-affected extremity [91, 92, 70, 74, 85, 93–96]. The extent of contralesional hemisphere activation is typically predicated on the integrity of the corticospinal tract, with greater contralesional hemisphere activation associated with greater ipsilesional corticospinal tract injury [97–99]. Better motor outcomes are generally associated with progressive reductions in contralesional hemisphere recruitment and/or increased recruitment in the ipsilesional hemisphere, comparable to a pre-stroke contralateral motor organization scheme [44, 51, 52, 68, 85, 93, 100–103], although the extent to which this finding generalizes likely varies according to severity of impairment.

Imbalances in transcallosal–mediated [104, 90, 105] IHI also emerge after stroke. Compared to healthy controls, individuals with stroke typically demonstrate greater inhibition in the contralesional to ipsilesional primary motor cortex direction [105–108] and/or less inhibition in the ipsilesional to contralesional primary motor cortex direction [105, 109]. Murase et al. [106] measured the amount of IHI during a simple reaction time paradigm using paired-pulse TMS. Subjects with stroke did not demonstrate significant differences in IHI at rest compared to controls. However, just prior to movement initiation of the stroke-affected hand,

individuals demonstrated an increase in IHI in the contralesional to ipsilesional primary motor cortex direction that correlated to reduced finger-tapping speed and overall motor performance. In contrast, control subjects demonstrated a decrease in IHI, indicative of facilitation, prior to movement onset. Future research is required to better understand the relationship between cortical vs. subcortical lesion involvement and IHI as current work is inconclusive [104, 105, 109, 110].

Shifting of Cortical Representational Maps

Another compensatory response to stroke is reorganization or re-mapping of somatotopic representation. Somatotopic ordering, or maps, exist in cortex, white matter, and subcortical structures such as basal ganglia [111–113]. These maps are found in numerous neural systems including auditory and vision, with much of the map reorganization literature focused on sensorimotor cortex. The most striking illustrations of cortical re-mapping following ischemic injury are in non-human primates that depict changes in map size and location occurring in conjunction with underlying axonal sprouting and the formation of new neuronal connections [39, 114, 115]. Lesion size influences the extent of cortical re-mapping [116], and subsequent rehabilitation/behavioral training alters map size and location [114, 115, 117].

In humans, studies employing fMRI [100, 101, 118, 119] and TMS [119–121, 64] depict stroke-driven alterations in map representation. Several studies have reported shifts in motor cortex hand representation in dorsal [122], ventral [100, 101, 120, 123–125], and posterior [101, 119, 126, 127, 102] directions that may represent the extent of corticospinal tract injury [128–131]. Previous work has also shown that the side and extent of injury and degree of behavioral impairment likely influence the reorganizational pattern [100, 101]. Available data suggests that while the relative position of certain map fine features shift when stroke injures these maps, key features of map organization, such as the arm motor map being dorsal to the face motor map, do not [101]. More positive motor outcomes are significantly associated with the preservation of ipsilesional motor map area [118].

Alterations in Functional & Effective Connectivity

An emerging area of study in post-stroke recovery centers on brain network connectivity (reviewed by Friston, 2011)[132]. Resting-state fMRI and EEG are attractive tools to measure functional connectivity, defined as low-frequency temporal correlations in the BOLD signal or synchronization of electrical oscillations, respectively, between distinct brain regions [133, 132, 134, 135]. In contrast to task-oriented fMRI that requires subjects to complete a physical task during scanning, during resting-state fMRI the subject maintains a relaxed but awake state. One important advantage of resting-state fMRI is that subjects' physical impairments do not confound BOLD signal interpretation as they may in task-oriented fMRI. However, as with task-oriented fMRI, interpretation of functional connectivity is complicated whenever the stroke injures the very areas under study, as one must then disentangle injury effects from plasticity effects within the same zone. One strategy to address this issue is to exclude damaged regions of interest [137] or exclude subjects with a pre-specified percentage of damage to those region(s) of interest under study from analyses [138].

Research has demonstrated disruptions in resting-state functional connectivity involving regions of motor [139, 137, 140], sensory, attention, and language [141] early after stroke. These disruptions often relate to the extent of white matter damage [142, 143]. Akin to previous animal work [144], functional recovery positively correlates to resting-state connectivity between interhemispheric networks. Indeed, our laboratory found that resting-state connectivity between contra- and ipsilesional primary motor cortex correlated with treatment-induced gains in motor function ($r = 0.45$, $p = 0.01$) [138].

EEG measures of coherence or phase and amplitude consistency of neural oscillations between two brain regions may function as additional probes of those processes evaluated with resting-state fMRI functional connectivity analyses as above [145, 146]. Dubovik et al. [147] found greater disruption of functional connectivity in the alpha frequency band in individuals with stroke relative to healthy controls. Further, diminished coherence in the alpha frequency band related to the severity of motor and cognitive deficits. Similar to post-stroke imbalances in interhemispheric inhibition favoring the contralesional hemisphere [105–108], Gerloff and colleagues [148] discovered greater cortico-cortical coherence in the contralesional hemisphere and reduced coherence in the ipsilesional hemisphere in individuals with chronic stroke. These results further demonstrate a compensatory functional shift in the contralesional hemisphere direction.

Effective connectivity studies extend functional connectivity studies by utilizing sophisticated modeling techniques on task-based and resting-state fMRI and EEG to explain the direction and causal relationship between two remote brain regions [134, 149, 150]. Rehme et al. [151] applied dynamic causal modeling to task-based fMRI data to examine effective connectivity between ipsilesional primary and secondary motor regions. The group found reduced positive couplings between supplementary motor area and ventral premotor cortices with ipsilesional M1 immediately after stroke that eventually increased (i.e. strengthened) over time and related to positive functional recovery. Collectively, functional and effective connectivity provides insight to the intricate brain circuitry that comprises brain networks. This information may prove especially valuable when considering post-stroke therapies and corresponding therapeutic targets.

Treatment-Driven Functional Recovery Mechanisms

There are many types of restorative therapies and combinations of restorative therapies currently under study (Table 1): activity and cognitive-based training [93, 98, 152–156], robotics and brain computer interface systems [157–159], non-invasive brain stimulation [160–162], pharmacological compounds [163–166], stem cells [167, 168], and growth factors [169]. Several meta-analyses provide treatment effect sizes for arm motor impairment following therapy: 0.34 (constraint-induced movement therapy, CIMT) [170], 0.55 (repetitive TMS) [162], 0.65 (robotic arm training) [171], and 0.92 (selective serotonin reuptake inhibitors) [172]. The implementation of these therapies to clinical practice may be hindered in part by the overall quality of evidence available. Many studies are underpowered and issues of heterogeneity between studies and inconsistent data reporting exist.

Comprehensive reviews of restorative therapies and their purported mechanisms are available [173, 174]. Briefly, several of the above therapies manipulate the peripheral nervous system while others directly stimulate brain matter. The mechanisms of action of various pharmacological-based restorative therapies may also elucidate those mechanisms asserting neuroplastic change post-stroke. For instance, the Fluoxetine for Motor Recovery After Acute Ischemic Stroke (FLAME) study investigated motor recovery in non-depressed patients randomly assigned to oral fluoxetine (20 mg/day) or placebo pill for three months [165]. Patients receiving fluoxetine displayed significantly greater gains in arm/leg Fugl-Meyer motor score at day 90 than the placebo group (a 9.7 point difference between groups on a 100-point scale, $p = 0.003$). In this study, the underlying interaction of fluoxetine and neurotransmitters resulted in enhanced motor recovery outcomes. In general, treatment-driven and spontaneous mechanisms of recovery overlap.

Carey et al. [93] observed activation of contralesional brain regions when subjects with chronic stroke performed a finger tracking exercise using their stroke-affected hand. Following a series of training sessions, subjects demonstrated significant changes in brain laterality consistent with increased utilization of the ipsilesional hemisphere. Importantly, improvement in finger tracking accuracy and shifts in brain activation translated to gains in functional activity with significant increases in Box and Block scores. Results from this seminal study demonstrated a resumption of ipsilesional hemisphere activity and an improvement in stroke-affected hand function resulting from task-specific training. Other work has shown similar shifts in cortical activation and an enlargement of ipsilesional motor map representation following various motor rehabilitation programs including CIMT that involves forced-use of the hemiparetic arm [103, 155, 156, 175, 176]. Recent work employing robotic upper-extremity training exhibited changes in EEG coherence between ipsilesional primary motor, premotor [177], and bilateral primary sensory areas [157]. Specifically, heightened coherence in the high frequency beta band (defined as 20–30 Hz by Wu et al. [177] and 24–33 Hz by Pellegrino et al. [157]) correlated with upper-extremity motor function improvement. Together, these results reinforce previous work showing associations between motor system function and the beta frequency band [135, 178]. Additionally, enhanced resting-state fMRI network connectivity involving supplementary and bilateral motor cortices and visuospatial areas with the cerebellum and association areas also correlated with gains in upper-extremity function following robotic and brain-computer interface-led upper-extremity training [159].

Due to the high frequency of motor-related impairments after stroke and their impact on overall post-stroke disability, a large portion of rehabilitation literature focuses on treatment of motor deficit. Nonetheless, repetitive TMS [179] and behavioral training [180] in individuals with post-stroke hemineglect resulted in improvements in spatial attention and neglect tasks. Accompanying these behavioral improvements were increases in bilateral white-matter integrity and cortical activation in structures and areas associated with visual attention. Pilot work in patients with aphasia also demonstrated comparable increases in cortical activity in language-specific areas following a two-week language rehabilitation program [154]. Collectively, these findings illustrate domain-specific structural and functional changes following targeted interventions. The ability of restorative therapies to

exert both behavioral and neuroplastic change strengthens the potential to translate these therapies to clinical practice.

Brain Repair & Treatment Considerations

Timing of Treatment Delivery

Many studies examining therapeutic-induced mechanisms of recovery occur during the chronic phase. In a rodent stroke model, Clarkson and colleagues [181] found that administration of AMPA receptor agonists several days after stroke enhanced stroke-affected forelimb use, whereas earlier administration adversely affected recovery. These findings provide evidence that neural targets relevant to repair at one timepoint may not be relevant at a later timepoint.

A similar message was provided by the study by Biernaskie et al [184], who found that introducing enriched rehabilitation 5 days after experimental stroke in rodents improved behavioral outcomes, possibly on the basis of enhanced dendritic growth within undamaged motor cortex. However, the same intervention introduced 30 days after stroke had no effect; introduction 14 days after stroke had an intermediate effect.

Because treatment effects vary based on their timeframe of delivery, one cannot simply extrapolate intervention findings from a chronic stroke population to an acute stroke population. Relatedly, great debate surrounds the timing of therapy initiation. Early commencement of CIMT in a rodent stroke model led to an exacerbation of neural injury [182]. However, others have found enhanced expression of growth-related proteins and dendritic growth in the ipsilesional hemisphere and improved behavioral outcomes following early vs. late CIMT [183] and reaching training [184] in rodents.

Similar CIMT investigation in humans also demonstrates variable findings. The Extremity Constraint Induced Therapy Evaluation (EXCITE) trial was a prospective, single-blind, randomized, multisite clinical trial that compared a two-week CIMT program to customary care in 222 enrolled individuals with moderate motor arm impairment resulting from stroke 3–9 months earlier [185]. Subjects receiving CIMT demonstrated a significant improvement in both primary outcome measures: a 52% reduction in time to complete tasks (Wolf Motor Function Test) and a 76–77% increase in quantity and quality of stroke-affected arm movement (Motor Activity Log). These improvements were significantly greater than those observed for the control group receiving customary care and persisted for one year. A related study from the EXCITE trial followed and involved the comparison of two delivery timeframes of the same two-week CIMT program [186]. Subjects receiving early (3–9 months post-stroke) and delayed (15–21 months post-stroke) CIMT demonstrated improvements in the Wolf Motor Function Test and Motor Activity Log from pretest to 12 months following CIMT administration. However, the early CIMT group exhibited a significantly greater amount of improvement than the delayed CIMT group. These group differences were not significant at long-term follow-up (24 months after study enrollment). In a smaller-scale comparison of early vs. late CIMT, individuals receiving early (< 9 months post-stroke) CIMT demonstrated greater behavioral improvement of the stroke-affected upper-extremity compared to those receiving late (> 12 months post-stroke) CIMT.

Yet, those receiving late CIMT showed greater changes in cortical reorganization as assessed by positional shifts in TMS motor maps [187]. The consensus from these studies is that early rehabilitation is safe and preferable to late onset therapy.

Treatment Dosage

Treatment dosage (i.e. frequency, duration, and intensity) also influences functional recovery. The relationship between treatment dosage and functional improvement is not straightforward. Restated, more does not always equate to better, and research in post-stroke motor [188] and language [189] function confirm this assertion. The VECTORS study randomized subjects with acute stroke to traditional upper-extremity therapy, dose-matched CIMT, or high-intensity CIMT [188]. All groups demonstrated positive recovery and, importantly, no anatomical MRI evidence of lesion enlargement. However, participants randomized to the high-intensity CIMT demonstrated *less* motor improvement at three months post-stroke compared to the other groups. In a related study examining treatment dosage, participants receiving aphasia rehabilitation in a distributed (6 hours per week for 8 weeks) vs. intensive (16 hours per week for 3 weeks) schedule demonstrated significantly greater improvements immediately after therapy and at one-month follow-up. Additional work is necessary to examine associated structural and functional brain changes with varying therapeutic dosages.

Severity of Baseline Impairment

Differences in baseline functional status amongst subjects can impact the informative value of brain mapping in discerning underlying, therapeutic-induced recovery mechanisms. Könönen et al. [156] observed greater increases in sensorimotor cortex activation following CIMT amongst subjects possessing poorer hand motor behavior at baseline. These findings parallel previous work [98] illustrating greater supplementary motor cortex activation following CIMT in participants with diminished corticospinal tract integrity. Differences in baseline functional status may therefore influence subsequent patterns of therapeutic-driven neurological reorganization and may account for discrepancies in the literature regarding the efficacy of certain therapies and/or drugs. An overwhelming amount of post-stroke intervention studies include fairly well-recovered individuals. However, as the above studies indicate, expanding interventional studies to include participants with severe impairment or poor functional recovery is necessary towards our understanding of therapy-induced mechanisms of recovery.

The Role of Biomarkers

Biomarkers are measurements that demonstrate strong associations to disease state and progression [190]. For example, HIV RNA levels serve as a marker for AIDS and thyroid stimulating hormone concentration acts a marker for hyper/hypothyroidism. A biomarker might also be conceptualized as providing correlative behavior in a cross-sectional manner, as predicting future behavioral course, or as being measured serially in parallel with behavioral observations. A stroke biomarker, therefore, signifies an underlying brain state event linked to behavioral status or to recovery and behavioral change [191]. Examples of stroke biomarkers include measures of structure and function and genetic measures (Table

2). Past work has shown corticospinal tract injury to be predictive of spontaneous motor recovery [192] and treatment-induced motor recovery [22]. The implementation of biomarkers in stroke rehabilitation would address several existing challenges in the field of stroke. One challenge is to understand and control the amount of heterogeneity between patients with regards to functional recovery and its response to therapeutic intervention. A second challenge is that behavioral-based stroke measures commonly used in the hospital and clinic settings likely do not fully capture post-stroke neurological change and functional improvement [138]. Biomarkers combined with well-established behavioral measurements provide a more complete account of post-stroke brain change.

Though there are no established biomarkers in stroke recovery, there are several potential examples in domains of language and motor function. For instance, Marchina and colleagues [193] found that the volume of stroke-related damage (i.e. lesion load) to the left arcuate fasciculus predicted speech impairment. Additional work has also shown right arcuate fasciculus volume predictive of language recovery following left hemisphere stroke [194]. Blicher et al. [152] found significant correlations between behavioral improvement of the stroke-affected hand and changes in the GABA:Creatine ratio in primary motor cortex of individuals 3–12 months post-stroke participating in a CIMT program. Decreases in the GABA:Creatine ratio were associated with greater gains in motor function. Additional work is warranted to substantiate these findings. Other examples of potential stroke biomarkers include total infarct volume [195], white matter tract injury [20–22, 138, 196], cortical activation [42, 52, 91, 175, 138, 197, 198] and connectivity [139, 137, 145, 147, 177, 138, 199], and genetic polymorphisms derived from simple blood tests [15, 16, 200]. These measures may serve an important role in guiding treatment, stratifying subjects in intervention studies, and ultimately predicting functional outcome and response to therapy. Future research is necessary to confirm the reliability and validity of potential stroke biomarkers.

Difficulty associated with distinguishing cellular and molecular mechanisms of spontaneous stroke recovery in humans is an additional challenge that may limit the identification and accessibility of stroke biomarkers in humans. Brain mapping and blood analysis will continue to guide the development of human stroke biomarkers; however, future advancements in the capability of probing the human brain will likely uncover additional potential biomarkers.

Summary & Conclusions

Destruction of the neural environment following stroke propels a series of spontaneous recovery mechanisms at the cellular, molecular, and systems levels. These mechanisms are often compensatory and incomplete since many individuals continue to endure persistent disability years following their stroke. The heterogeneity of stroke has spurred the development of numerous restorative therapies that harness neuroplasticity [26] to reinstate activity in injured but surviving areas to ultimately improve motor, sensory, language, and cognitive impairments. Often, the mechanisms underlying these therapies rely on similar mechanisms as observed in spontaneous recovery. Several factors such as time of delivery, dosage, and severity of baseline impairment likely influence the effects of restorative

therapies. Finally, identifying human stroke biomarkers will enhance clinical and research practices and result in greater insight into functional recovery mechanisms.

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Table 1

Examples of Restorative Therapies Under Study

Activity-Based Therapies
occupational Therapy
physical Therapy
speech Therapy
constraint-induced movement therapy (CIMT)
gait training
Cognitive-Based Therapies
motor imagery
mirror therapy
virtual reality
augmented reality
mental rehearsal
Device-Based Therapies
robotics *
telerehabilitation *
brain-computer interface
vagal nerve stimulation
Sensory Stimulation
passive limb movement
electrical stimulation
Brain Stimulation
repetitive transcranial magnetic stimulation
transcranial direct current stimulation
epidural cortical stimulation
Pharmacologic Therapies
amphetamine
methylphenidate
amantidine
memantine
carbidopa/levodopa
fluoxetine, escitalopram, and other selective serotonin reuptake inhibitors
escitalopram
inosine
ropinirole
sildenafil
niacin
atorvastatin
donepezil
Biologicals
basic fibroblastic growth factor

brain derivied neurotophic factor
vascular endothelial growth factor
erythropoietin
granulocyte-colony stimulating factor
monoclonal antibodies
Stem Cells
endogenous stem cells
exogenous stem cells
xenografts
transformed tumor cells
umbilical cord cells
embryonic and fetal stem cells
induced pluripotent stem cells
adult stem cells such as mesenchymal stromal cells

* These device-based therapies might also be classified as activity-based.

Table 2

Potential Stroke Biomarkers Under Study

Structural
infarct volume
extent of cortical injury
extent of white matter injury
extent of injury to specific sites of gray or white matter
white matter integrity
percent corticospinal tract injury *(tract-specific lesion load)*
Functional
activation within ipsilesional hemisphere sites *(intensity or volume; peri-lesional or remote)*
activation within contralesional hemisphere sites *(intensity or volume)*
laterality index, expressing hemispheric balance in activation between homologous sites
resting state functional connectivity
event-related synchronization and desynchronization
cortical excitability, facilitation, and inhibition
motor evoked potentials (*presence, threshold, latency, and magnitude*)
Genetic
BDNF val^{66}met polymorphism
ApoE4 allele
Dopamine polygene score

ApoE = apolipoprotein E; BDNF = brain-derived neurotrophic factor. Note that numerous techniques are available for functional assessments, depending on biomarker, such as fMRI, PET, SPECT, EEG, MEG, and TMS.