Arm Function after Stroke: From Physiology to Recovery

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ABSTRACT

There are varying degrees of spontaneous improvement in arm paresis over the first 6 months after stroke. The degree of improvement at 6 months is best predicted by the motor deficit at 1 month despite standard rehabilitative interventions in the ensuing 5 months. Animal studies indicate that the loss of fine motor control, especially individuation of the digits, is due to interruption of monosynaptic corticomotoneuronal connections. Spasticity occurs because of loss of cortical modulatory control on descending brain stem pathways and spinal segmental circuits but is not a major cause of motor dysfunction. Quantitative studies of reaching movements in patients suggest that arm paresis consists of higher-order motor planning and sensorimotor integration deficits that cannot be attributed to weakness or presence of synergies. Cortical stimulation experiments in animals and functional imaging studies in humans indicate that motor learning and recovery after stroke share common brain reorganization mechanisms. Rehabilitation techniques enhance learning-related changes after stroke and contribute to recovery. Future research will benefit from using quantitative methods to characterize the motor impairment after stroke and by applying concepts in motor learning to devise more physiologically based rehabilitation techniques.

KEYWORDS: Stroke, hemiparesis, recovery, motor learning, reorganization

Objectives: On completion of this article, the reader will have acquired new knowledge on experimental motor physiology and functional imaging that will change how he thinks about recovery and rehabilitation of arm paresis after stroke.

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The purpose of this review is to acquaint neurologists with recent findings in experimental motor physiology and functional imaging that give reason for optimism and new thinking with regard to recovery and rehabilitation of arm paresis after stroke. Most neurologists involved in the care of patients after stroke focus on intervention and workup in the acute setting and management of risk factors to prevent recurrence in the outpatient setting. Involvement in rehabilitation does not go much beyond writing prescriptions for physical

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and occupational therapy. The relative noninvolvement of neurologists in rehabilitation is partly the result of long-standing nihilism about the prospects for recovery from brain injury in adults and the existence of three non-neurological specialties dedicated to rehabilitation. However, with recent advances in structural imaging, which allow clinicoanatomical correlations not previously possible, and accumulating evidence that the adult brain can reorganize after injury, neurologists are in the position to revisit stroke syndromes, revise notions of stroke natural history, and promote more scientific and patient-specific approaches to rehabilitation. Until recently, the scientific rigor of the rehabilitation literature has left a lot to be desired. For example, in a Clinical Practice Guideline published in 1995, only 7 of 32 recommendations concerning stroke rehabilitation practice were based upon experimental evidence.[1]

"Hemiparesis" is a collective term that lumps together the positive and negative motor symptoms that occur after stroke. It can be ventured that most neurologists, despite frequent use of the term "hemiparesis," have little interest in the physiological mechanisms of the paretic deficit. This is reflected in a preference for nominal and ordinal disability and quality-of-life scales in clinical trials rather than physiological measurements of impairment. It is clear, however, that more quantitative measures are needed to evaluate efficacy of therapeutic interventions. It has recently been stated that the failure of many recent clinical stroke trials may relate to the choice of outcome measures rather than to the lack of efficacy of the agent under investigation.[2]

The current review will be divided into five sections: (1) natural history of clinical recovery from arm paresis after stroke, (2) animal studies investigating the anatomy and physiology of the motor system as it pertains to upper limb paresis, (3) quantitative studies of motor control and motor learning in patients with hemiparesis, (4) functional imaging and transcranial magnetic stimulation (TMS) studies of brain reorganization after stroke, and (5) the relationship of motor learning to recovery.

NATURAL HISTORY OF ARM PARESIS AND PREDICTORS OF RECOVERY

Stroke is the leading cause of long-term disability among adults in the United States, and hemiparesis is the most common impairment after stroke. Longitudinal studies of recovery after stroke suggest that only $\sim$50% of patients with significant arm paresis recover useful function.[3,4] Initial severity of paresis remains the best predictor of recovery of arm function.[2,3,5] One study showed that the Fugl-Meyer[6] (FM) score at 30 days predicted 86% of the variance in recovery of motor function at 6 months.[2] This oft-cited study raises several important issues pertinent to the study of stroke recovery. First, the authors make a good case for using a measure of impairment, the FM score, rather than a measure of disability, the Barthel index, to assess recovery of function. The difference between impairment and disability highlights the critical distinction between true recovery or restoration of function, as opposed to compensation. For example, a patient with right arm paresis who learns to perform activities of daily living (ADLs) with her left arm has compensated but has not recovered. Measurements of impairment are more likely than measurements of ADLs or handicap to distinguish true recovery from compensation. Second, the FM score at 30 days was a better predictor of the FM score at 6 months than the FM score at day 5, which indicates that there is significant variability in the degree of spontaneous recovery occurring in the first month poststroke. Third, the finding that most of the variance in outcome at 6 months was determined by the first 30 days implies that whatever occurred in terms of rehabilitation in the ensuing 5 months made little impact. This suggests that patients with the worst prognosis at 6 months need to be the focus of novel and intensive rehabilitation strategies. Indeed, it will be easier to detect an effect of a novel treatment strategy in this group.

Attempts to use lesion location to predict arm recovery have so far only been able to show greater probability of recovery from hemiparesis for cortical than for subcortical lesions.[7,8] In particular, lesions in the most posterior part of the posterior limb of the internal capsule have the poorest outcome,[9] presumably due to convergence of a majority of axons from primary motor cortex (M1). One study followed 41 patients, with near plegia or plegia 2 weeks after stroke (Action Research Arm Test score $<$ 9/56), for 2 years.[5] Seventy-five percent of those patients with lesions restricted to cortex recovered isolated upper limb movements, whereas only 6% of patients with subcortical strokes did so. This marked difference may be because initial measurements were only 2 weeks poststroke. It is possible that patients with cortical lesions who remain plegic at 1 month would not show such a favorable outcome. Nevertheless, the results suggest that hemiparesis may come in distinct subtypes.

In summary, severity of arm paresis in the first month after stroke remains the strongest predictor of outcome and likely reflects the degree of damage done to cortical motor areas and the corticospinal tract. It is to be hoped that the impact of initial severity can be lessened with new rehabilitation techniques in the first 6 months poststroke. Cortical and subcortical strokes may require different rehabilitative approaches. Finally, it is now known that chronic stroke patients ($>$ 6 months) respond to rehabilitation, and so it is conceivable that the patients who do not show significant responses by 6 months may need more extended periods of rehabilitation.

PHYSIOLOGY OF HEMIPARESIS AND MOTOR RECOVERY IN NONHUMAN ANIMALS

Classic studies in the 1960s and 1970s examined the behavioral consequence of motor pathway lesions in monkeys and subprimates.[10–14] It was hoped that these studies would serve as a model for the motor effects of stroke in humans. Most commonly, pyramidotomies were performed. The pyramidal tract is made up of corticobulbar and corticospinal pathways. Projections from cortex to descending brain stem pathways are functionally separate and are sometimes referred to as "parapyramidal tracts." In two seminal papers, Lawrence and Kuypers[10,11] described the distinct behavioral effects of damage to the pyramidal tract as compared with damage to brain stem descending pathways. Bilateral pyramidotomy caused permanent loss of independent movements of the digits in macaques, as assessed by the loss of ability to retrieve pellets from small food wells. Independent finger movements only recovered if there was some degree of sparing of pyramidal tract fibers. It is notable that no other significant motor deficits were apparent in these monkeys 5 months after pyramidotomy. There was no obvious residual weakness, and spasticity did not occur. The monkeys were able to sit, run, and swing from bars. To grip a bar, all the digits flex together whereas retrieval of a food pellet requires a precision grip with isolated movements of individual digits. These results are congruent with the common bedside finding in patients with stroke of preserved grip strength but inability to independently move the fingers.

Lesions of brain stem descending pathways (i.e., the interstitiospinal, tectospinal, vestibulospinal, and reticulospinal tracts) produced a syndrome quite distinct from pyramidotomy, with primarily axial and postural abnormalities and relative preservation of distal limb control. Complementary studies in the cat[15] revealed the existence of parapyramidal fibers in the medial part of the internal capsule that project down to the medulla to inhibit reticulospinal projections. Interruption of these corticoreticular pathways leads to the unbalanced action of the reticulospinal tract on spinal cord circuits causing increased muscle tone. These findings in monkeys and cats help to explain spastic hemiparesis in humans. Pure pyramidal lesions are rare in humans but when they occur, there is hemiparesis without increased tone.[16] Ischemic strokes occur most commonly in motor cortical areas, in subcortical white matter, and in the pons, regions in which pyramidal fibers are intermixed with cortical projections to lateral and medial brain stem nuclei, which then project down to the spinal cord. Damage to these regions therefore can result in a combination of negative signs, paresis, and positive signs, spasticity. Paresis arises from loss of input to motoneurons in the ventral horn. Loss of finger individuation in particular is the result of damage to monosynaptic corticomotoneuronal connections. Spasticity arises, in part, from loss of cortical inhibitory control on brain stem motor nuclei and spinal reflex circuits and is comprised of increased resting tone, hyperreflexia, and the clasp knife phenomenon. Spastic signs are elicited at rest but the degree to which spasticity plays a role during actual movement remains uncertain. We shall return to this matter in the next section.

PHYSIOLOGY OF ARM PARESIS IN PATIENTS WITH STROKE

Quantitative Studies of Reaching Movements after Stroke

Although measures of motor performance and functional status are commonly used in clinical trials on stroke, these measures suffer from serious shortcomings: ceiling and floor effects, reliance upon subject effort, and observer ratings. The latter poses a great threat of bias, especially in trials in which a double-blind protocol is not possible. Quantitative tasks that assess the motor deficit objectively minimize these shortcomings and are sensitive to small changes in performance. A promising approach is suggested by motor control research on arm reaching movements in healthy subjects. This work, conducted over the past 2 decades, has established a framework for the computational stages that underlie visually guided reaching movements.[17] Motor control theorists make an important distinction between the geometry of a movement (kinematics) and the forces needed to generate the movement (dynamics). This distinction can be better understood by imagining tracing a circle in the air with your hand or with your foot. The circle may have the same radius and be traced at the same speed with the hand and the foot but completely different muscles and forces are needed to generate the circle in the two cases. Similarly, reaching trajectories involving more than one joint consistently have invariant kinematic characteristics: straight paths and bell-shaped velocity profiles,[18] which suggest reaching trajectories are planned in advance without initial need to take account of limb dynamics. Target location, initially encoded in visual coordinates, is transformed into an intended movement of the hand with an extent and direction.[19] In the execution phase, motor commands take the complex viscoelastic and inertial properties of multijointed limbs into account so that the appropriate force is applied to generate the desired motion. This is known as the "inverse dynamic problem" because it is necessary to compute joint torques from the desired limb trajectory given the inertial properties and configuration of the limb (Fig. 1). Two separate inertial properties of the arm produce characteristic errors if they are not controlled during reaching. The first property relates to direction-dependent changes in inertial resistance to

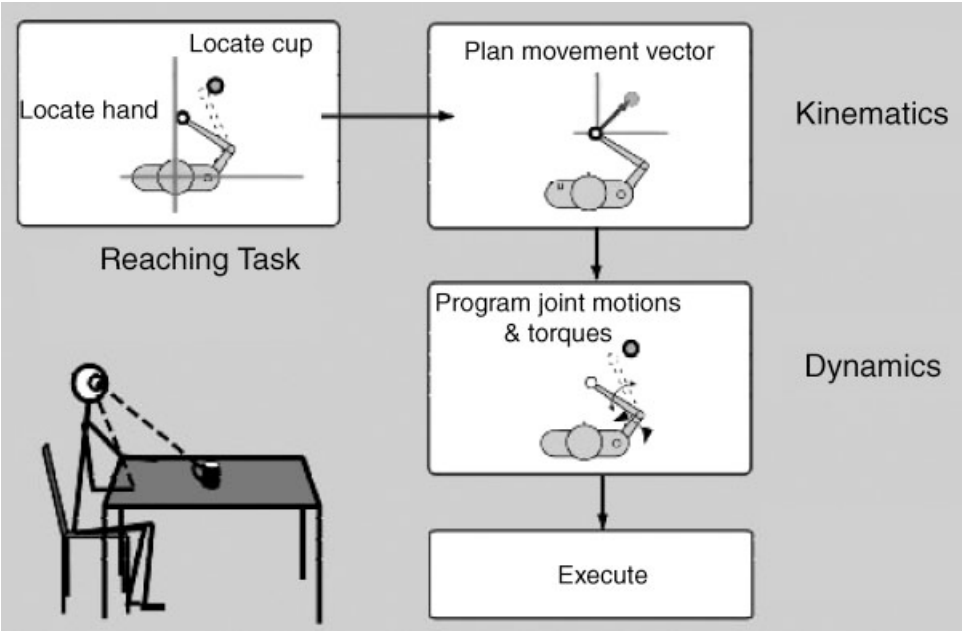

Figure 1 Computational stages for planning and execution of a visually guided reaching task.

motion of the forearm segment (inertial anisotropy).[20,21] The arm has greatest inertia in directions that require rotation of the elbow and shoulder joints and lowest inertia when only the elbow joint rotates. The second problem associated with the control of a multijoint mechanical system is the fact that movement at one joint produces torques that act at all other joints (interaction torques),[22] and therefore joints cannot be controlled independently from each other. Studies demonstrate that control of both inertial anisotropy and the effects of interaction torques can be compensated for by anticipatory (feed-forward) control acquired through learning and is critically dependent on proprioception.[23,24] Thus motor control is modular; even a simple reaching movement is made up of separate operations, each of which may or may not be affected by a lesion.[25]

The presence of unwanted motor synergies after stroke has been described in the literature for over 30 years.[26,27] Synergies are stereotypic patterns of muscle coactivation that limit independent control of single joints. For example, with the flexor synergy, there is supination of the forearm and flexion of the elbow when the shoulder flexes and abducts. Conversely, with the extensor synergy, there is pronation of the forearm and extension of the elbow when the shoulder extends and adducts. These terms were originally chosen because these synergies superficially resembled the enhanced extensor and flexor reflexes observed in spinalized cats and dogs.[28] Recently, a rigorous quantitative approach was used to characterize abnormal muscle coactivation patterns in the arm after stroke.[29–31] Subjects were required to use elbow and shoulder muscles to generate isometric forces at the wrist to move and then hold a screen cursor in one of eight radially arrayed targets displayed on a computer screen. Electromyograms (EMGs) were recorded from six elbow and six shoulder muscles. There were three main results for patients compared with age-matched controls. First, there were shifts in the resultant direction of a weighted measure of maximal EMG activation for each muscle. Second, each muscle showed activation over a broader range of directions (i.e., a loss of focus). Third, correlation analysis revealed flexor and extensor synergies not present in healthy subjects. Thus, this study was able to quantify a reduction in the number of possible muscle combinations available to generate aimed forces after stroke. The etiology of these unwanted synergies remains uncertain but a combination of the following three mechanisms is likely: interruption of monosynaptic corticomotoneuronal connections to proximal muscles, reversion to control by descending brain stem pathways, and changes in segmental reflex circuits.

Other kinematic and dynamic trajectory abnormalities after stroke, which cannot be explained by weakness, spasticity, or muscle synergies, have been described. One study examined reaching movements in the horizontal plane and found that patients with chronic hemiparesis have abnormalities in interjoint coordination, quantified by the degree of correlation between elbow and shoulder excursions, for movements both in and out of typical flexor and extensor synergies.[32] These abnormal movements suggest a deficit in transforming a planned trajectory into the appropriate corresponding joint angles. There has been only one published study examining the control of limb dynamics during reaching movements in stroke.[33] This study characterized spatial abnormalities in the kinematics

and dynamics of multijoint movements in six patients with mild to moderate arm paresis. Patients made systematic directional errors that, on the basis of inverse dynamic analysis and EMG analysis, seem to be caused by an inability to anticipate the effects of shoulder acceleration on acceleration at the elbow (i.e., a deficit in feed-forward compensation for interaction torques). A similar failure to compensate for interaction torques has been observed in deafferented patients,[24] thought to be due to decalibration of an internal model of limb dynamics. None of the patients with hemiparesis had a proprioceptive deficit, and so it can be conjectured the deficit is either caused by interruption of projections from areas that represent limb dynamics or due to decalibration from nonuse. The concept of a loss of skill from nonuse is one of the premises behind constraint-induced therapy. The complex issue of concomitant sensory loss along with hemiparesis is beyond the scope of this review and is actually a topic that has been neglected in the literature. It is clear, however, that demonstrable loss of proprioception or tactile sensation, in addition to hemiparesis, indicate a reduced probability of recovery. Control abnormalities of the arm after stroke are likely analogous to the loss of finger individuation in the hand, an idea consistent with the finding in humans that corticospinal projections to deltoid muscles are comparable in strength to those to the intrinsic muscles of the hand.[34]

Although this review emphasizes arm over finger control, recent work on the somatotopic organization of motor cortex argues against stark divisions of modules controlling hand, elbow, or shoulder.[35] Instead, cortical mechanisms that control the shoulder and elbow are integrated with those of the wrist and hand, as part of the system subserving reaching, prehension, and object manipulation.[36] So far it has not been possible to correlate specific kinematic and dynamic abnormalities with infarct location. However, it has been shown that hemiparesis can result from a wide variety of lesion locations including those outside the precentral gyrus and its projections.[37] It is possible that with more detailed quantitative analysis in the future, different types of hemiparesis will become discernible. This will have implications for rehabilitation as it would make it possible to direct therapy to a patient's specific deficits.

Spasticity

As discussed above, spasticity refers to a set of positive signs thought to be caused by adaptation of spinal segmental circuits to loss of modulatory cortical control.[38] These signs include velocity-dependent increase in muscle tone from increased excitability of the tonic stretch reflex, hyperreflexia from increased excitability of the phasic stretch reflex, and the clasp-knife phenomenon from loss of descending inhibition on flexor reflex afferents,[39] all of which can present together or separately. For example, in a study of the biceps brachii tendon jerk in patients with hemiparesis,[40] the increased tendon jerk response developed progressively over a year whereas increased tone reached a peak at 1 to 3 months and then decreased. The treatment of spasticity has been strongly emphasized in stroke rehabilitation. The influential Bobath approach is predicated on the idea that spasticity is the key factor that interferes with normal motor functioning.[41] However, spasticity only develops in $\sim$19 to 39% of patients with hemiparesis.[42,43] There is scant evidence that spasticity contributes to impairment of voluntary movement and significant evidence to the contrary. For example, a study using a torque motor[44] found that patients, compared with controls, had increased resistance to limb displacement at rest but not when the arm was actively moving, suggesting that spasticity does not contribute to motor control abnormalities in hemiparesis. In another study, both stretch-evoked muscle activity via EMG activity (hyperreflexia) and resistance to passive stretch (hypertonia) were measured in the arms of patients with hemiparesis.[44] There were two main findings. First, hypertonia was associated with muscle contracture rather than with reflex hyperexcitability. Second, no relationship was found between hypertonia and either weakness or loss of dexterity. In a recent study of 95 patients with first-time stroke,[43] severe functional disability occurred almost equally in patients with and without spasticity. The authors concluded that "the focus on spasticity in stroke rehabilitation is out of step with its clinical importance."

The Ipsilesional Arm

In 1973, Alf Brodal, a Norwegian professor of anatomy, published an article entitled: "Self-Observations and Neuroanatomical Considerations after a Stroke."[45] This article is filled with observations of great physiological interest. In particular, Brodal became aware that although he had suffered a right subcortical stroke, the quality of his writing with his right hand had deteriorated. Several studies have subsequently reported abnormalities in the "unaffected" arm after stroke, including control of distal movements.[46,47] Interestingly, the nature of these deficits can differ depending on whether the infarct is in the dominant or nondominant hemisphere.[48–52] Most recently, strikingly abnormal step-tracking movements have been described in the ipsilesional wrist of patients with hemiparesis.[53] The observed trajectory errors in amplitude and direction were due largely to inappropriate temporal sequencing of muscle activity. One possible explanation is that there is interruption of the uncrossed ipsilateral corticospinal projection to distal muscles. Support for this explanation comes from functional imaging studies, which show bilateral M1 activation during unilateral finger

movements.[54,55] An alternative explanation is that stroke in one hemisphere alters transcallosally mediated inhibitory effects on M1 in the opposite hemisphere.[56–58]

The involvement of the "unaffected arm" after stroke has several important implications. First, even distal control of the arm is under bilateral hemispheric control. Second, age-matched healthy subjects should be used as controls in future studies rather than patients' unaffected arm. Third, collapsing findings for left and right hemiparesis are questionable given the differences in some control abnormalities in the ipsilesional arm with dominant and nondominant hemisphere strokes. Finally, the involvement of the ipsilesional arm reinforces the importance of sensitive quantitative studies to detect differential abnormalities that would otherwise be missed on bedside examination or by outcome scales.

BRAIN REORGANIZATION AFTER STROKE

An online literature search on Pubmed under "brain reorganization after stroke" gives a rough indication of the increase in interest in the neural correlates of recovery from stroke. From 1981 to 1990 there were three publications; from 1991 to 2000, 48; and from 2001 to 2004, 72. These studies reveal that, in addition to recovery through reduction in edema and metabolic disturbances, restitution of the ischemic penumbra, and resolution of diaschisis, the adult brain is capable of reorganization to recover lost function. Reorganization can occur in cortical regions immediately adjacent to the infarct[59] or remote from the infarct, both in the same[60,61] and in the opposite hemisphere.[62,63] The mechanisms of both adjacent and remote reorganization are under active investigation and are thought to include unmasking of latent synapses, facilitation of alternative networks, synaptic remodeling, and axonal sprouting. Several reviews on the subject of brain reorganization have been published recently,[64–69] and so this section will be selective and focus on conceptual and methodological issues pertaining to inferring recruitment of brain areas remote from the infarct.

Functional Imaging

Over the past 15 years, functional brain imaging has been the primary tool to study brain reorganization after stroke in humans. Study designs have been both cross-sectional[70–74] and longitudinal.[75–77] Cross-sectional studies have usually recruited well-recovered patients whereas longitudinal studies have correlated patient improvement at multiple time points with changes in brain activation. Initial cross-sectional studies in well-recovered patients consistently showed additional regions of activation, both in the ipsi- and contralesional hemisphere, compared with age-matched controls performing the same motor task. These results suggested that these additional regions contribute to restoration of motor function. However, subsequent longitudinal studies show either a reduction in novel activation over the time course of recovery[75,76] or that additional activations correlate with poor motor outcome.[77] To begin to resolve this apparent contradiction, it is fruitful to conjecture what the results of an ideal cross-sectional study and an ideal longitudinal study should look like in order to infer recovery-related reorganization.

The ideal cross-sectional study should select patients who had significant hemiparesis at stroke onset but at the time of imaging have fully recovered to the point that no measurement can detect a difference between them and age-matched controls. If these conditions could be met, additional activation seen in the patients compared with controls, given identical motor performance, would be strong evidence for reorganization. This hypothetical scenario, however, raises a question: Does full motor recovery ever occur? Should it be defined as the ability to complete a task regardless of whether alternative muscle activations are required or should the term be reserved for the ability to complete the task in the same way as healthy controls? Either type of recovery could potentially lead to a novel pattern of brain activation. One version of takeover of function, call it the strong version, implies that there is redundancy in the motor system such that a similar pattern of muscle activations can be achieved using alternative neural circuits. The weak version of takeover is that an alternative motor strategy is adopted to approximate the goal of the lost behavior. The ideal cross-sectional study depends on the strong version of recovery, at least for the within-scanner task, even if a challenging and sensitive out-of-scanner task may always unmask performance deficits or subtle kinematic differences in patients.

Initial cross-sectional positron-emission tomography studies of stroke recovery approximated the ideal, with additional ipsi- and contralesional activations in patients compared with controls despite full recovery.[70,71] However, the within-scanner motor task, finger opposition, was not amenable to detailed kinematic analysis and performance may therefore not have been identical to controls. For example, there could have been more proximal movement and decreased finger individuation in the patients. In addition, patients made mirror movements, which casts doubt on the significance of the ipsilateral motor activations. However, similar ipsilateral activation was later reported in a functional magnetic resonance imaging (fMRI) experiment that controlled for mirror movements.[73]

It is safer to infer that novel activation is related to restoration of function if there is an initial deficit followed by recovery. This is especially true for studies of higher cognitive functions, such as language, where a novel pattern of activation may reflect an atypical premorbid pattern rather than reorganization.[78]

Nevertheless, with simple motor tasks, for which the functional anatomy is more consistent across subjects, it is of interest to ask whether the absence of symptoms in the presence of a lesion is because the brain has reorganized to maintain normal motor performance. This argument has had more traction with slow progressive diseases than in stroke. For example, patients with multiple sclerosis without motor or sensory impairment in the arms[79] or with only a single episode of optic neuritis[80] have been investigated with fMRI and found to have increased ipsilateral motor activation that correlates with lesion burden. It has been concluded that the novel activation maintains normal motor function despite the presence of lesions. Similar reasoning has recently been applied to patients with critical carotid or middle cerebral artery stenosis causing unilateral hemispheric hypoperfusion without infarction. Results showed increased contralesional motor activation despite a normal motor examination, again suggesting reorganization to maintain normal motor performance.[81]

More recent functional imaging studies of stroke recovery have shifted from cross-sectional studies to longitudinal studies, based on the premise that recovery is a dynamic process that cannot be captured at a single time point. The ideal longitudinal study should show improvement in motor behavior that is paralleled by increased activation in an area not activated in controls. Notably, no longitudinal study to date has been able to demonstrate this. Instead, they show the opposite, with either reduced additional activation as recovery proceeds[75,76] or a negative correlation between outcome and magnitude of additional activation.[77] However, these results were in patients with subcortical stroke, a group perhaps most likely to recover through a return to ipsilesional patterns of cortical activation. The situation may differ with cortical strokes, which have not yet been adequately investigated.[82] The contradiction between cross-sectional and longitudinal studies may arise because of differences in the degree of patient recovery. Full recovery seems to be mediated by a return to normal activation patterns but if this is not possible, additional areas are recruited that allow partial recovery.

Assessing the Role of Regions Remote from the Infarct with Real and Virtual Lesions

Functional imaging can only show that an area of activation correlates with motor behavior but not that it is necessary for recovery. If an area of novel activation mediates recovery then there should be reemergence of the original deficit when the area is inactivated. This test has been applied in animal models with ablation or muscimol infusion and in humans with TMS. A lesion of the hand representation in primary sensorimotor cortex in adult macaques resulted in complete loss of dexterity in the hand for 1 to 2 months. At around 3 to 4 months, there was a return to $\sim$30% of prelesion dexterity. This improvement was reversed with muscimol infusion into the ipsilesional dorsal and ventral premotor areas but not with muscimol infusion into perilesional cortex or contralesional M1.[60] More recently, it was shown that an ischemic lesion in the forelimb region of M1 in squirrel monkeys led to expansion of the hand representation in ipsilesional ventral premotor cortex (PMv).[61] Interestingly, the degree of map reorganization in PMv was proportional to the amount of hand representation destroyed in M1. This result in monkeys provides a clue as to why novel functional activation patterns are seen most in patients with the greatest deficit. Similar results have been obtained using TMS in patients after stroke. Four patients with capsular infarcts and good recovery from moderate to severe hemiparesis underwent single-pulse TMS to the ipsilesional dorsal premotor cortex (PMd), which caused a delay in reaction time for the contralateral hand in patients but not in controls.[63] In these well-recovered patients, TMS applied to contralesional M1 or PMd had no effect on reaction time. The same approach was used in a group of patients with more variable degrees of recovery.[83] TMS applied to contralesional PMd led to an increase in reaction time in the patients but not in controls. Importantly, the magnitude of the effect of TMS on contralesional PMd was correlated with the degree of hand impairment, consistent with the studies in monkeys described above. Thus reorganization can occur in cortex adjacent to the infarct, in premotor regions in the ipsilesional hemisphere, and in motor regions in the contralesional hemisphere. Recruitment of more remote regions may depend both on the extent and location of the infarct and on stroke severity. Further evidence that remote regions contribute to recovery comes from reports of reemergence of stroke deficits in patients who suffer a second stroke on the opposite side. Miller-Fisher[84] described two patients with substantial recovery from pure motor hemiparesis who presented with quadriparesis when they suffered subsequent mirror lesions (proven at autopsy) on the opposite side, the capsule in one patient and the medulla in the other patient. A similar case has been reported more recently.[85]

THE RELATIONSHIP OF MOTOR LEARNING TO RECOVERY

Several studies now indicate that motor learning, rather than just repeated use, is required for lasting brain reorganization. For example, repetitious thumb flexions lead to changes in the excitability of M1, as measured by TMS thresholds, that last only a few minutes,[86] whereas increase in finger sequencing skill leads to longer-lasting changes in M1.[87,88] Experiments in the squirrel monkey showed that the cortical map of the distal forelimb area only underwent reorganization when training required

an increase in skill and not just simple repetition of an overlearned task.[89] A similar result was demonstrated with TMS in healthy humans.[90] Thus learning, rather than just use, is needed for lasting changes in M1 and these changes are dependent on sensory input. In addition, motor learning tasks, like after injury, also lead to recruitment of additional cortical and subcortical regions, both contra- and ipsilateral to the moving limb.[91,92]

Rehabilitation is predicated on the assumption that practice or training leads to improvement. Given this assumption, it is surprising how few studies have tested for a motor learning impairment after stroke. So far, the presence of a motor learning deficit after stroke in humans has yet to be convincingly demonstrated.[93,94] No studies have compared functional imaging changes that occur with learning with those that occur with motor recovery, and only recently have principles from the motor learning or motor memory literature been applied to stroke rehabilitation.

Although there are aspects of reorganization that are probably unique to brain injury, there are large overlaps with development[62,95] and motor learning,[89,96] and it is becoming increasingly clear that learning-related plasticity, both at the network and synaptic levels, contributes to and can be enhanced to promote recovery after stroke. A recent study in a rat stroke model demonstrates the critical interaction between rehabilitation and spontaneous recovery processes early after stroke.[97] Rehabilitation initiated 5 days after focal ischemia was much more effective than waiting for 1 month before beginning rehabilitation. This difference correlated with the degree of increased dendritic complexity and arborization in undamaged motor cortex. A similar time window effect, albeit longer than in rats, has been shown in patients after stroke, with the greatest gains from rehabilitation occurring in the first 6 months.[98]

Experiments in monkeys also demonstrate the importance of motor learning after brain injury.[99] After ablation of the primary sensory hand area, known to have dense connections with M1, monkeys were able to execute previously learned tasks normally but they were unable to learn new skills. In another set of experiments, a subtotal lesion confined to a small portion of the motor representation of one hand resulted in further loss of hand territory in the adjacent, undamaged cortex if the hand was not used. Subsequent reaching relied on compensatory proximal movements of the elbow and shoulder. However, forced retraining of skilled hand use prevented loss of hand territory adjacent to the infarct. In some instances, the hand representations expanded into regions formerly occupied by representations of the elbow and shoulder. These results suggest that after local damage to the motor cortex, rehabilitative training can shape subsequent recovery-related reorganization in the adjacent intact cortex.

Regardless of whether recovery-related networks are the same or different from learning-related networks, the results above suggest that these networks are more likely to change with real-world practice (i.e., through a learning effect) than just with isolated repeated movements of the affected limb. These results also suggest that if execution-related impairments can be assisted, for example with a robot arm[100] or functional electrical stimulation,[101] then learning-related changes may be harnessed more effectively as both these techniques allow patients to experience movement-related feedback, time-locked to their motor commands.

The most fundamental principle in motor learning is that degree of performance improvement is dependent on the amount of practice. However, it has been known for some time that practice can be accomplished in several ways that are more effective than blocked repetition of a single task.[102] This literature has not had great impact on the rehabilitation field. Traditionally, therapists ask patients to perform the same movement or, more recently, the same task, repeatedly. For example, a component of constraint-induced therapy (CIT)[103] is extended (6 hours) daily task-oriented practice for 2 weeks. However, it is well known from the motor learning literature that variable practice is more effective than massed practice. Introducing task variability in any given session increases retention even though performance during acquisition is worse than if the task were constant.[104] A hypothetical example is reaching to pick up a cup on a table. The therapist can either have the patient reach and grasp the same cup at a fixed distance repeatedly or have the patient pick up the cup at varying speeds and distances. Although the patient may reach for the cup better during the constant session, the patient reaches for the cup better at retention after the variable session. Another benefit of variable practice is that it increases generalization of learning to new tasks. Another robust finding is that of contextual interference: random ordering of n trials of X tasks leads to better performance of each of the tasks after a retention interval.[102] So in the reaching example, the patient would reach randomly for a cup, then a spoon, then a telephone. The effect of practice schedule on retention of motor learning sorely needs to be applied to research on rehabilitation techniques and motor recovery after stroke. For example, the assumed motor recovery plateau 6 months after stroke[105] may well reflect asymptotic learning after massed practice rather than a true biological limit. This conclusion is supported by studies that show a benefit for CIT in patients with chronic stroke.[106–108]

CONCLUSIONS

"Hemiparesis" is a blanket term for a heterogeneous condition made up of weakness, motor control

abnormalities, and spasticity. Spasticity does not contribute greatly to motor dysfunction and its treatment is inordinately emphasized. Studies in humans and animal models strongly suggest that brain reorganization mechanisms associated with motor learning also operate during recovery and rehabilitation. In order for rehabilitation techniques to maximally co-opt and enhance mechanisms of spontaneous motor recovery after stroke, an evidence-based approach that applies the quantitative methods and concepts of motor control and motor learning is essential. The late gains that can be seen after 6 months, for example with CIT, are likely to be dependent on slow-learning mechanisms that are distinct from the fast-learning mechanisms that interact with spontaneous reorganization in the acute and subacute stroke periods.

Functional imaging and TMS will provide insight into the neural correlates of recovery and provide the basis for future attempts at augmentation, for example, through cortical stimulation.

Skill acquisition in healthy subjects can take years of practice, and yet we expect patients to reach maximal performance after short periods of rehabilitation. It can be predicted that patients will benefit from greatly extended periods of rehabilitation geared toward their specific deficits.

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