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Brain repair after stroke—a novel neurological model

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Abstract

Following stroke, patients are commonly left with debilitating motor and speech impairments. This article reviews the state of the art in neurological repair for stroke and proposes a new model for the future. We suggest that stroke treatment—from the time of the ictus itself to living with the consequences—must be fundamentally neurological, from limiting the extent of injury at the outset, to repairing the consequent damage. Our model links brain and behaviour by targeting brain circuits, and we illustrate the model though action observation treatment, which aims to enhance brain network connectivity. The model is based on the assumptions that the mechanisms of neural repair inherently involve cellular and circuit plasticity, that brain plasticity is a synaptic phenomenon that is largely stimulus-dependent, and that brain repair required both physical and behavioural interventions that are tailored to reorganize specific brain circuits. We review current approaches to brain repair after stroke and present our new model, and discuss the biological foundations, rationales, and data to support our novel approach to upper-extremity and language rehabilitation. We believe that by enhancing plasticity at the level of brain network interactions, this neurological model for brain repair could ultimately lead to a cure for stroke.

Introduction

Following a large stroke that produces considerable impairments, patients can recover a degree of function, and many can walk, drive, communicate, and interact sufficiently for good quality of life.[1,2] The vast majority of patients, however, can no longer work,[3,4] and many cannot maintain independence.[5,6] Furthermore, a substantial number of stroke

survivors do not retain enough function to maintain social connectedness, leading to isolation and loneliness. Finally, depression and anxiety are common after stroke,[7] which exacerbates an already difficult situation.

The ultimate goal of stroke treatment—after treatment of the initial insult to limit its extent and severity— should be the repair and reorganization of the injured brain to bring about a cure. Although such a statement might seem obvious, this perspective differs fundamentally from current poststroke therapeutic strategies. The emphasis of both motor therapy and speech and language therapy after stroke is on education, and therapists work intensively with patients to ameliorate motor or language impairments and to improve function. The most effective types of such 'reeducation' involve focused instruction and practice that are based on theories about how therapeutic behaviours affect specific impairments. The more common approach, however, is to use *ad hoc*, individually tailored instruction and practice. Whereas researchers tend to favour the former approach, practitioners tend to use the latter.

Current practice in rehabilitation focuses on ways to circumvent deficits (compensation) rather than to cure them (remediation), as this strategy is the most efficient way to achieve good functional outcome.[8,9] In compensatory recovery, behaviour is changed to meet environmental needs, and neurological restoration is bypassed. Existing tools for outcome assessment generally do not distinguish compensation from remediation[9,10] and, as compensation is a more rapid and cost-effective approach, it tends to be the preferred option for insurers, therapists and—in many cases—patients. Moreover, medical reimbursement is geared towards the most rapid achievement of functional goals, assessed via the functional independence measure (FIM).[11] Patients and families are typically given low expectations of rehabilitation, as such relearning can be quite meagre and can take tremendous effort over a long time.

In this context, a number of theoretical approaches to re-education have been proposed for treatment of both motor impairments and speech and language deficits. Some of these strategies have emphasized parallels between stroke recovery and learning,[12–16] such as occurs in child development,[17–20] whereas others have built complex multicomponent functional models to enable targeting of fractionated portions of impaired movements[21–24] or linguistic skill.[25] In addition, some models have aimed at development of compensatory behaviours that bypass known functional deficits.[19,21,22,26,27]

The above examples of theory-driven approaches to re-education emphasize how both the theory and the therapy address the repair process at a behavioural level. For active clinicians, practical common sense plays a more prominent part than theory, frequently leading therapists to work on rote learning of impaired skills and elimination of perceived obstacles, such as the effects of altered upper motor neuron influences on the arm or mouth. Despite the clear rationality of these educational endeavours, no strong medical evidence exists to support a given intervention over another for any specific patient or set of deficits. Granted, different types of behavioural interventions can lead to different short-term gains, but whether the type of therapy affects long-term outcomes remains unclear.[28–30] Furthermore, treatment by a highly trained expert might not have advantages over treatment by a trained

volunteer or by a robotic device.[31] The result is essentially a stalemate in long-term stroke outcomes for over half a century.

In this article, we argue for a paradigm shift in poststroke therapy towards physiological repair of the underlying damage. We discuss findings from basic neuroscience, especially those concerning organization of the motor system, that can serve as a theoretical framework for treatment of poststroke aphasia and upper-limb motor dysfunction. We review studies that have tested this model in translational research to treat poststroke deficits as well as impairments in other motor syndromes. Promising biological interventions in development are beyond the scope of this article, and have been reviewed elsewhere.[32–34] Two approaches in particular— constraint-induced therapy for upper-limb function[35–37] and language,[38,39] and therapy using mirrors[40–42]—have been motivated by biological rationales and lead to consistent changes in the brain.

A new model

In light of increasing understanding of the physiological underpinnings of poststroke deficits, and limited efficacy of current approaches to rehabilitation, the time is right to start on a completely different therapeutic track, to rethink basic assumptions of poststroke therapy, and to effect a paradigm shift[43] in the way we view stroke and its consequences. Towards this goal, we advocate a biomedical model in which both motor therapy and speech therapy are understood in terms of physical repair (remediation) of the neural circuits that underlie the impaired functions. This perspective assumes that damage to the brain produces the impairment, and that repair or reorganization of the affected neural circuits can lead to a cure for the disease. Remediation and repair can be achieved via two basic routes: direct restoration, in which the original circuits are reinstated; and/or indirect restoration, in which related neural circuits are recruited to perform the original functions.[44] For example, therapy for gait, hand motor function, speech and language, memory, attention and affect could be devised for direct or indirect rebuilding of damaged neural circuits that mediate those functions.

If the goal of motor or language therapy is to stimulate cerebral plasticity as a means of improving function, precise definition of 'plasticity' is essential to enable measurement of this parameter. In this Review, we use the notion developed by Donald Hebb,[45] as articulated by Johansson,[46] that neuronal cortical connections can be remodelled by experience,[45,47] owing to changes in chemistry and anatomy[48–50] Plasticity in adult animals is defined at the cellular and molecular level by increases in dendritic branching, the number of synapses per neuron, and expression of genes encoding trophic factors; and at the systems level by changes in cortical representation areas, and in cortical maps that develop in response to sensory input, experience and brain lesions.[46]

Rebuilding brain circuits to recover speech and motor functions does not depend solely on endogenous biological factors, but also on exogenous input, as brain plasticity is inherently stimulus-dependent.[51,52] Developmentally, neural networks are shaped by intensive experience inherent in years of practice, and some evidence suggests that brain remodelling after injury might require similar levels of experience.[53–57] For example, in all studies of

pharmacological intervention for stroke rehabilitation, drug efficacy is dependent on accompanying behavioural practice.[58] This finding is consistent with the well-established notion in synaptic physiology that plasticity depends on stimulus-driven patterns of neural activity[59] Furthermore, when computational neural network models are experimentally 'damaged', functional restoration is not possible solely through replacement of lost 'tissue', but requires additional training.[60,61] Moreover, the nature of the triggering stimulus probably affects the degree of neural circuit modification.

Despite the dependence of drug effectiveness on concomitant behavioural interventions, little work has been undertaken to address the interaction between brain physiology and clinical phenotype. The very few approaches from the pre-imaging era that were based on biological rationales have not been validated, or at least not completely, with modern biological tools. For example, the biological rationale of Melodic Intonation Therapy,[62,63] the only aphasia therapy approved by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology,[64] was not supported by subsequent imaging studies.[65]

Physiology of therapy

Since the now classic studies of Lawrence and Kuypers in macaques,[66,67] a large body of literature has focused on the effects of lesions in the corticospinal tract (CST) on motor deficits and extent of recovery. Reports tend to agree on the existence of a correlation between ipsilateral or contralesional CST damage and degree of motor deficits,[68–71] whereas the association between CST integrity and degree of motor recovery is less clear.[72]

A complicating issue is the nature of the CST itself, which is not one tract but multiple tracts. In addition to efferent fibres originating in cortical area M1 (which are sometimes equated with the CST), dorsal and ventral premotor regions, the supplementary motor area, the motor cingulate cortex and parietal regions (superior parietal cortex and S1) communicate directly with the spinal cord,[73,74] terminating onto both spinal motor neurons and interneurons.[75,76] Direct corticofugal connections are thought to underpin the ability to perform skilled hand movements, whereas corticofugal fibres from association motor regions target inter-neurons,[77–79] providing modulatory effects on motor neuronal activity.[80]

The consequences of the organization of the CST fibres are twofold. The first consequence is the magnitude of the effects of different pathways on the physiology of spinal motor neurons. For example, activation of a single corticomotor neuron in the primary motor cortex can produce direct responses in single motor units or multi-units on electromyography.[81] Lesions in these direct M1 efferents in stroke, therefore, produce permanent impairment of individualized finger movements, but not other movements that can recover.[66,67,82–84] The second consequence of CST organization relates to motor repair. The organization of different cortical regions and their spinal projections, as determined by imaging studies, have suggested potential mechanisms of recovery through recruitment of association motor regions.[85–88] A more direct physiological assessment of this hypothesis through use of transcranial magnetic stimulation (TMS) in patients with stroke has confirmed these imaging findings.[89]

The mirror neuron system

We posit that successful treatment of aphasia or upper-limb motor dysfunction after stroke requires neural repair and reorganization that theoretically includes neural rewiring through stimulus-dependent plasticity. This approach requires a carefully tailored stimulus or behavioural intervention that can modulate relevant circuits to produce desired neural connectivity. The behavioural intervention must be developed according to findings from basic neuroscience that link brain circuitry with behaviour.

Among the most remarkable neurophysiological findings of the past several decades is the discovery of mirror neurons in various regions of the macaque cerebral cortex. Mirror neurons are notable because they discharge both during the execution of goal-directed actions performed with different biological effectors (for example, the mouth or hand), and during observation of another individual performing the same or a similar action .[90,91] Increasing evidence suggests that a similar mirror neuron system is present in the human brain, and that it could have a role in action recognition, coding of motor intentions, and motor learning.[92–95] The anatomy and physiology of the mirror neuron circuit, and its possible role in several cognitive functions[96–98] and rehabilitation[99,100] have been previously reviewed.

Motor imitation

Motor imitation is sometimes incorrectly regarded as a relatively unimportant cognitive task. However, it is particularly developed in humans, and intrinsically linked to language and culture.[101–103] Imitation of actions involves motor observation, motor imagery, and action execution. Imitation of speech requires these steps as well as other highly complex processes at additional levels (for example, phoneme identification and word recognition).

Involvement of the mirror neuron system in motor imitation, especially imitation of hand actions, has been suggested by brain imaging studies[104–106] and basic neurophysiology investigations that highlighted the importance of a network between premotor frontal regions and association regions in the parietal and temporal lobes.[98,107]

Behaviourally, observation of the lips, tongue and mouth of a speaker improves speech perception, particularly under noisy conditions[108] or when the auditory signal is degraded.[109,110] This effect arises from shared neural substrates for action observation and action execution,[111–113] particularly of the mouth and lips during speech.[114–118] The neural mechanism that links the behaviour with the brain network is observation–execution matching,[119,120] whereby a perceiver matches observed actions to a repertoire of previously executed actions via a circuit that includes posterior inferior frontal and ventral premotor cortices, the inferior parietal lobule, and the posterior superior temporal sulcus.[116,121,122]

To investigate the putative human mirror neuron network for observation and production (execution) of speech, we analysed functional MRI brain imaging data for effective connectivity among active brain regions in healthy adults.[123] Participants performed a simple task that involved observation and imitation of an audiovisual clip of an individual saying a simple consonant– vowel syllable. We focused on six brain regions: ventral

premotor cortex and inferior frontal gyrus (combined region); inferior parietal lobule (including intraparietal sulcus); primary motor and sensory cortices; dorsal premotor cortex; posterior superior temporal gyrus and sulcus; and anterior superior temporal gyrus and sulcus.

We used our results to generate a model (Figure 1) in which connections from posterior superior temporal to inferior parietal cortex, from inferior parietal to ventral premotor cortex, and from ventral pre motor to primary sensory–motor cortex were among the strongest in both hemispheres during execution and observation. In addition to the results illustrated here in the left hemisphere, there were interesting and subtle differences in connections within the right hemisphere and between hemispheres.[123]

Action observation treatment

Basic neuroscience research on mirror neurons and their connections has suggested a new approach to poststroke treatment that is based on principles of motor physiology. Although this new direction does not yet constitute a fully developed rehabilitation model, it could provide the means by which such a goal can be achieved.

A rehabilitative approach that is based on findings in physiology enables direct assessment of changes through application of imaging and/or electrophysiology, and direct measures of CST excitability via TMS. Development of functional biomarkers could enable customization of therapy on the basis of an individual's neurophysiological measures. By monitoring the long-term neuroanatomical and neurophysiological consequences of therapy, functions with the largest burden of impairment can be specifically targeted at the individual level. We suggest that systematic observation of meaningful actions followed by their execution (action observation treatment [AOT]) could be a viable rehabilitative strategy for patients with motor impairment and aphasia after stroke.

AOT for motor dysfunction

In AOT, patients with motor impairment carefully and systematically observe a series of videos that display everyday actions such as drinking coffee, reading the newspaper, or walking. Actions are chosen on the basis of their ecological value. Every action is divided into three or four motor segments with increasing degrees of difficulty. For example, in hand therapy, the action of having a cup of coffee can be decomposed into motion segments of reaching for the cup, turning the spoon, and bringing the coffee to the mouth. Each motion segment is presented for 3 min in the observation phase. At the end of the segment, patients perform the observed action (execution phase). The total time for the session— including instructions—takes about 90 min, and sessions are repeated daily for 4 weeks (Figure 2).

Results in patients—AOT has been used for rehabilitation of patients with chronic ischaemic stroke (>6 months after the acute event), cerebral palsy, or Parkinson disease (PD), and in patients with non-neurological disorders, such as those undergoing orthopaedic surgery of the hip or knee.

In a pivotal randomized controlled study in patients with chronic ischaemic stroke in the territory of the middle cerebral artery,[124] AOT was applied to treat upper-limb motor functions. Patients in the control group observed video clips that were related to historical, scientific or geographical issues and had no specific motor content. In this study, the Stroke Impact Scale, the Wolf Motor Function Test, and the Frenchay Arm Test were the functional scales used to quantify changes in motor abilities. The results showed significant improvement of motor functions over a 4-week treatment compared with the stable pretreatment baseline and the control group. Similar results have since been reported by another group.[125] The improvement lasted for at least 8 weeks after the end of the intervention. Functional MRI during object manipulation before and after therapy showed a significant increase in activity in the bilateral ventral premotor cortex, bilateral superior temporal gyrus, the supplementary motor area and the contralateral supramarginal gyrus. On the basis of these data, we concluded that action observation promotes recovery of motor functions after stroke by reactivation of motor areas that contain the putative human correlate of the macaque mirror neuron system.

In a randomized controlled study,[126] we investigated the efficacy of AOT in complementing pharmacology for PD. For this trial, participants in the active group observed videos depicting everyday life actions, including postural actions and walking, whereas those in the control group observed movies devoid of specific motor content. The active group improved more from baseline relative to the control group as measured on two functional scales: the Unified Parkinson Disease Rating Scale and the FIM.

AOT has also been used to reduce freezing of gait in patients with PD.[127] Given that the mirror neuron system is heavily interconnected with the basal ganglia and has a role in motor planning and motor learning,[128] it is possible that AOT promotes reorganization and maintenance of cortical loops and cortical connections with the striatum and thalamus.[129] This notion is also supported by the fact that action observation in PD is accompanied by increases in beta oscillatory activity of the subthalamic nucleus in association with the alpha and beta desynchronization on EEG that is seen over the motor cortex.[130]

In an additional randomized controlled study, AOT was used for treatment of upper-limb motor dysfunction in children with cerebral palsy aged 6–11 years.[131] One group of children observed daily actions appropriate for their age, whereas another group observed documentaries with no specific motor content. Functional evaluation using the Melbourne Assessment Scale of upper-limb motor functions showed that children undergoing AOT performed significantly better than controls after treatment. These results potentially provide insight into the ontogenesis of the mirror neuron system: the apparent targeting of central motor representations of actions in these children by AOT suggests that the mirror neuron system is fully functional at this age. Furthermore, these findings raise the question of whether this treatment affected an already developed motor representation in these children, or rather contributed to development of new motor representations of the presented actions.

Interestingly, in patients with non-neurological disorders, AOT might also improve motor recovery. In a randomized controlled trial in postsurgical orthopaedic patients, all of whom received conventional physiotherapy, those who observed video clips showing daily actions

and subsequently imitated them scored better on functional scales than did patients who observed video clips with no motor content and then executed the same actions as patients in the AOT group.[132] These findings are particularly interesting because they suggest that a treatment that affects brain representations of the lower limb can affect performance even when motor impairment has a non-neurological cause.

Underlying physiology—The clinical phenotype of patients with stroke after AOT is encouraging, and preliminary studies in humans suggest cortical reorganization results from this intervention.[124] Direct measures of repair, however, must be identified before the precise physiological effects of this therapy can be determined.[133–135] In this context, numerous reports are available on lesion analysis regarding the association between specific brain lesions and concomitant motor deficits and recovery.[72,136]

On the basis of motor physiology and knowledge of the many cortical sources of spinal projections, as well as mechanisms of recovery involving association motor regions, we can discuss the possible mechanisms of the effect of AOT on physiological recovery. In a small study involving four patients after stroke, TMS of the ipsilesional dorsal premotor cortex (PMd) increased the amplitude and reduced the latency of motor evoked potentials in the affected hand, representing a facilitatory effect on hand motor function.[89] The investigators concluded that plastic changes in PMd after stroke might enable reorganization of motor circuits, perhaps with establishment of direct connections of the PMd with the spinal cord. Changes in the PMd may be reinforced via the ventral premotor cortex (PMv), which expands (in macaques) in proportion to M1 lesion size.[137] Extending these notions to AOT, in which both PMd and PMv are clearly involved, a potential mechanism for repair could involve reorganization of the corticofugal system, whereby the function of the PMd shifts at the level of the spinal cord from a modulatory role to a role similar to that of the primary motor cortex. At the same time, the PMv would reinforce not only motor output via the PMd but also any residual outflow from M1.[138]

AOT for aphasia

We believe that the action observation–execution matching system could be of considerable benefit in aphasia therapy after stroke, particularly for speech production. The role of this system in predicting the consequences of motor activity,[139,140] and in comprehension of sentences that describe actions,[141] gives this approach great potential in aiding language recovery more generally.

Results in patients—AOT for aphasia is currently at an earlier stage on the translational path than motor rehabilitation, and randomized controlled trials are lacking for this indication. Preliminary data[142,143] show that observation and execution of action might favour retrieval of action-related words in aphasic patients with a selective deficit for verb retrieval, which supports the notion that the motor system interacts with the language system.

We have recently developed a therapeutic approach, called IMITATE, which is based on matching observation and execution in speech, and is currently being tested in a clinical trial in patients with aphasia following stroke.[144,145] IMITATE therapy involves silent

observation of audiovisually presented words and phrases that are spoken aloud by six talkers, followed by a period during which the participant orally repeats the stimuli. The clinical trial is a randomized single-blind controlled trial (the researcher, but not the participant, knows whether the participant is receiving IMITATE or a control therapy). Treatment is provided intensively (90 min per day) for 6 weeks, with weekly incremental increases in difficulty from monosyllabic words to disyllabic words, disyllabic sentences, and finally longer utterances, combined with progressively increasing rate of speech. Functional MRI scans are obtained before, during and after therapy.

Recent work in neural network computer models suggests that gradual incremental learning has theoretical advantages.[146] We are currently analysing data from 19 patients with aphasia following left middle cerebral artery stroke, and have preliminary results showing significant improvement on an overall language score from pretreatment to post-treatment in the IMITATE group, but not in the control group.[147]

Underlying physiology—In an effort to understand the physiological mechanism of AOT for aphasia therapy, we have recently completed a polysomnography study that assessed brain plasticity related to a single (extended) session of IMITATE therapy. [148,149] Increasing evidence in healthy humans and animals suggests that slow-wave activity (SWA) during sleep plays an important part in regulating synaptic plasticity and reorganization.[150–152] The theory posits that strengthening of synaptic efficacy in a specific cortical area during the day should be followed by increases in SWA in that cortical area compared with the rest of the cortex during sleep.[150] This effect relies on the notion that stronger synapses lead to stronger cortico-cortical connections and, in turn, in increased synchronization among populations of neurons.[153] Increased synchronization is then reflected in slow waves of larger amplitude on the EEG.[154]

We found that a single exposure to IMITATE resulted in increases in local SWA on EEG during subsequent sleep over the predicted target regions of AOT, particularly over the right parietal cortex (unaffected by the lesion). Furthermore, changes in SWA over the left precentral areas predicted behavioural changes, supporting the role of perilesional areas in predicting positive functional responses.[155] These data suggest the value of AOT in affecting specific neural systems that are related to observation and imitation of speech as described above,[156] and are consistent with existing models of language recovery that implicate both ipsilesional and contralateral circuits.[157,158] The specific contributions of the two hemispheres to recovery following unilateral stroke differs depending on the size, type and location of the infarct,[159,160] and differs in very early (neonatal and early childhood) stroke compared with adult stroke.[161] One emerging notion is that functional connectivity between the two superior temporal gyri is a marker of receptive language outcome after aphasic stroke, both in adults[162] and neonates.[163]

Conclusions

In this Review, we have outlined a new model for neural repair and rehabilitation in which we suggest that stroke treatment—from the ambulance to the return home— must be fundamentally neurological. This approach is quite different from current practice standards

for post-stroke therapeutics, in which physical therapy and speech and language therapy emphasize education, compensation for deficits that are expected to exist permanently, or making limited gains in function through training of unspecified brain circuits.

Our neurological model is based on three critical assumptions: that the mechanisms of neural repair inherently involve cellular and circuit plasticity; that brain plasticity is fundamentally a synaptic phenomenon that is largely stimulus-dependent; and that brain repair must incorporate biological interventions— ultimately to replace or augment some lost brain tissue—via behavioural interventions that are carefully tailored for re organization of specific brain circuits. Notably, recovery can be viewed as part of a continuum in which certain types of large brain lesions require augmentation of the anatomical substrate in addition to alteration of network connectivity in the existing (and new) neural substrate.

We have proposed a novel approach to rehabilitation of motor impairment and speech that aims at remediation of functions and promotion of plasticity in networks that were previously associated with prelesion behaviours. AOT is a good example of an approach that harnesses the putative mirror neuron system, which is involved in both execution and understanding of everyday life actions. Development of AOT not only depends on knowledge of the underlying biology, but therapeutic efficacy relates closely to the nature of the biological changes that it produces.

What are the features of action–observation— followed by imitation of the action—that could promote plasticity in the appropriate networks for motor skill and speech? First, this network can be triggered by multiple sensory inputs (visual, auditory and proprioceptive), and/or through additive effects if such inputs are weakened by disease. Furthermore, the widely distributed nature of the network suggests many anatomical and physiological routes to network activation. Second, activation of the network during motor observation increases the excitability of cortical motor outputs via the corticospinal path associated with execution of those movements, even in the absence of overt movements. Third, the network is strongly associated with goal-oriented, ecologically valid actions that were previously present in the repertoire of the patient. Consequently, observation followed by imitation of an observed action avoids the fragmentation of the actions into smaller components, as is typically done in current rehabilitative practice, instead emphasizing execution of the action as a whole. Fourth, its effects can be applied to numerous neurological and non-neurological conditions.

Future clinical trials should assess how this treatment affects neuronal circuits that are involved in motor control and speech, and how this approach could be integrated with other biological approaches to neurorehabilitation.

Acknowledgments

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Key points

- The ultimate goal of stroke treatment—after the initial insult has been appropriately limited in extent and severity—should be to repair the injured brain to effect a cure

- Current practice focuses on compensation, which is cheaper and quicker than brain repair and remediation, but involves low outcome expectations

- Rebuilding brain circuits to recover motor functions and speech depends on endogenous biological factors and exogenous input, as brain plasticity is inherently stimulus-dependent

- Several stroke treatment programmes based on physiological rationales aimed at repairing brain circuits are currently undergoing testing

- Action observation treatment for hand motor dysfunction is based on macaque research in action understanding, and has shown some preliminary success for treatment of stroke and other neurological injuries

- Action observation treatment for speech and language dysfunction seems to affect brain plasticity and have some benefit

Review criteria

The articles in this Review were found through a search of PubMed, focusing on search terms "brain repair", "stroke" , "treatment", "plasticity", "hand movement", and "language". We focused on articles that studied animal or human physiology for the construction and application of treatments for post-stroke therapy.
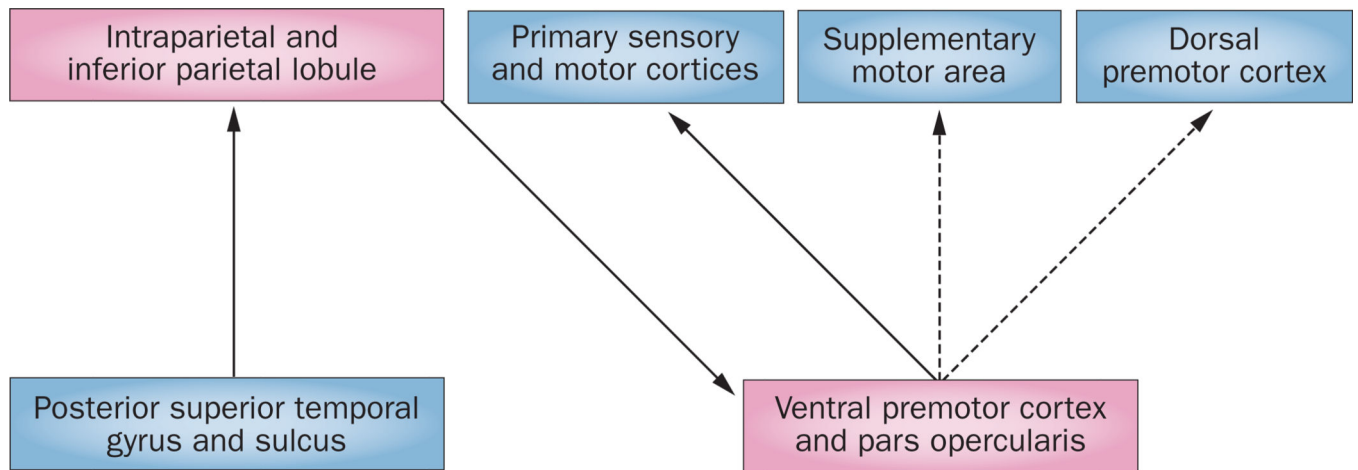
Figure 1.
Possible mirror neuron network for syllable observation and imitation. A model of shared brain networks activated by observation and execution of speech, as determined by functional MRI in humans.[123] Solid lines show connections that are common to observation and imitation, whereas dashed lines show connections that are more important in imitation than in observation. Pink rectangles represent core nodes in the putative 'mirror neuron' network. These networks suggest that a flow of information during imitation—starting at the posterior superior temporal cortex and ending in the motor cortex—enhances input to the motor cortex in the service of speech execution.

Figure 2.
Visual stimuli for action observation treatment. During action observation treatment, patients watch video sequences containing daily life hand and arm actions[124] (top panels) or leg and foot actions[132] (bottom panels) for 6 min, and then perform the action for 6 min, using the same movement and objects shown in the video clip. On each day of treatment, a 'unit' of three limb movements of increasing complexity is presented. In each video, the presented action is shown from three perspectives. A complete session consists of three or four such videos. Patients typically undergo 20 rehabilitation sessions over 20 consecutive weekdays. During both observation and execution, patients are instructed to focus on the goal of the action rather than on the movement *per se*.