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The sensory side of post-stroke motor rehabilitation

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Abstract

Contemporary strategies to promote motor recovery following stroke focus on repetitive voluntary movements. Although successful movement relies on efficient sensorimotor integration, functional outcomes often bias motor therapy toward motor-related impairments such as weakness, spasticity and synergies; sensory therapy and reintegration is implied, but seldom targeted. However, the planning and execution of voluntary movement requires that the brain extracts sensory information regarding body position and predicts future positions, by integrating a variety of sensory inputs with ongoing and planned motor activity. Neurological patients who have lost one or more of their senses may show profoundly affected motor functions, even if muscle strength remains unaffected. Following stroke, motor recovery can be dictated by the degree of sensory disruption. Consequently, a thorough account of sensory function might be both prognostic and prescriptive in neurorehabilitation. This review outlines the key sensory components of human voluntary movement, describes how sensory disruption can influence prognosis and expected outcomes in stroke patients, reports on current sensory-based approaches in post-stroke motor rehabilitation, and makes recommendations for optimizing rehabilitation programs based on sensory stimulation.

Keywords

Stroke; motor recovery; sensory stimulation; motor rehabilitation; sensorimotor integration; non-invasive brain stimulation

1. Introduction

The integration of bodily and environmental information brought about by the different senses is fundamental for optimal motor performance. The importance of sensory information for motor function can be appreciated considering that many pathological disturbances of sensorimotor processing dramatically alter normal motor control. As well, internal and external sensory signals are beneficial to motor rehabilitation (Patel, Jankovic, & Hallett, 2014). Sensory input also plays a fundamental role in motor recovery after stroke.

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In fact, there is no motor training that can be considered purely motor, as any type of motor stimulation implies, to varying degrees, integration of sensory information. We generally talk about physical rehabilitation from a strictly '*motor*' perspective, commonly neglecting the adjuvant role of sensory inputs. The current review addresses this issue, starting with an overview of evidence, which documents the importance of sensory processing for motor function, the cortical networks and mechanisms underlying sensorimotor integration, and how sensory impairments affect post-stroke motor recovery. Additionally, we offer a panorama of the rationale and efficacy of sensory approaches for post-stroke motor rehabilitation, primarily focusing on those based on somatosensory, visual, auditory or multisensory stimulation, and targeting hemiparesis and goal-directed movements. Finally, the potential of novel protocols of non-invasive brain stimulation for promoting and guiding sensorimotor plasticity is outlined.

2. Sensory influence on motor performance

Somesthesia is one of the most relevant sources of sensory information for the motor system. The somatosensory system processes information about, and represents, several modalities of somatic sensation (i.e., touch, pain, temperature, proprioception). However, substantial processing occurs even in the motor system. Neurophysiologic mapping studies in several mammalian species have demonstrated that stimulation of cutaneous, muscle and joint afferents can drive neurons in the primary motor cortex (MI) (Strick & Preston, 1982a, b; Tanji & Wise, 1981), and cortical motor representations can be rapidly altered by peripheral nerve lesions in both developing and adult rats (Donoghue & Sanes, 1987; Sanes, Suner, & Donoghue, 1990). This evidence indicates that MI cannot be considered solely as a motor structure; rather, it is involved in the processing of somatosensation via its anatomical and functional connections with primary (SI) and secondary (SII) somatosensory cortices, and also with the sensory thalamus (Nudo, Milliken, Jenkins, & Merzenich, 1996). Secondary motor areas, i.e. Supplemental Motor Area (SMA) and Premotor Cortex (PM), also respond to sensory inputs (Romo, Ruiz, Crespo, Zainos, & Merchant, 1993).

The gating of sensory input for motor control is a good example of the functional interplay between somatosensory and motor systems. Sensory gating is exerted by integrating afferent somatosensory inputs from peripheral receptors with the motor output at several levels in the ascending sensory pathway and in the cerebral cortex, consistent with serial transmission of afferent sensory activity from spinal cord to SI, and then to MI (Ghez & Pisa, 1972; Hantman & Jessell, 2010; Jiang, Lamarre, & Chapman, 1990; Seki & Fetz, 2012; Tsumoto, Nakamura, & Iwama, 1975). Gating of somatic sensation is evident in the reduction of somatosensory-evoked responses in SI, MI, and PM during preparation and execution of voluntary limb movement (Angel & Malenka, 1982; Bays, Flanagan, & Wolpert, 2006; Blakemore, Wolpert, & Frith, 1998), along with the increased psychophysical threshold for detecting tactile stimuli during movement (Milne, Aniss, Kay, & Gandevia, 1988). This mechanism is for attenuating irrelevant sensory input to motor cortices and helps motor neurons achieve a better motor-set for the upcoming movements (Seki & Fetz, 2012).

In humans, different forms of somatosensory stimulation have been shown to facilitate motor behavior: peripheral nerve stimulation, muscle tendon vibration, paired associative

stimulation and tactile learning can improve motor performance by increasing corticospinal excitability and enlarging the representation of the stimulated body part in MI (Edwards et al., 2014; Ridding, Brouwer, Miles, Pitcher, & Thompson, 2000; Wu, van Gelderen, Hanakawa, Yaseen, & Cohen, 2005). Moreover, chronic nociception may hinder central movement control and motor retraining, by reducing activity of the corresponding muscle, and altering motor and proprioceptive processing. Indeed, various tonic nociceptive stimuli (i.e., heat, chemical, and mechanical) applied to human muscle tissue result in long-lasting inhibition of the motor system, which is mediated by cortical and spinal motor circuits (Nijs et al., 2012).

Lesion studies further support the importance of somatosensation for motor behavior. In monkeys, devastating impairments in motor control emerge after focal lesions in SI (Xerri, Merzenich, Peterson, & Jenkins, 1998). Instead, lesions in the posterior MI hand area result in behavioral deficits akin to tactile agnosia, which is typically seen after SI lesions. In this condition, the animal reaches for food items, but does not appear to know whether the item is actually in the hand. Moreover, damage to the anterior MI hand area also disrupts proprioception, as demonstrated by the emergence of deficits in the metrics of reach (Friel et al., 2005; Nudo, 2006; Nudo, Friel, & Delia, 2000).

Another sensory modality relevant for motor control and skill acquisition is vision. Among others, a key source of visual information for the motor system is the Mirror Neuron System (MNS). Mirror neurons are visuomotor cells identified in the monkey's ventral PM and rostral inferior parietal lobule (IPL) that fire at the sight of object-oriented actions performed by other individuals. A fronto-parietal MNS active during both action observation and execution also exists in the human brain (Rizzolatti & Craighero, 2004). Since their discovery, it has been hypothesized that mirror neurons play an important role in action recognition and motor learning. Action observation may promote motor execution through the stimulation of an internal model, which helps to consolidate sensorimotor representation, and is used when individuals need to learn or re-learn motor functions (Rizzolatti & Craighero, 2004; Avenanti, Candidi, & Urgesi, 2013). Of interest, the MNS also comprises audio-visual mirror neurons that respond to the auditory representation of actions (Rizzolatti & Craighero, 2004).

With respect to audition, sounds can arouse and raise excitability of spinal motor neurons mediated by auditory-motor circuitry at the reticulo-spinal level, while rhythmically structured sound patterns are helpful for entraining the timing of muscle activation, ultimately facilitating movement during rhythmic actions (Thaut, Kenyon, Schauer, & McIntosh, 1999). Auditory influences on the motor system are well exemplified by musical performance. Playing a musical instrument involves an intense experience that promotes the acquisition of specialized sensorimotor skills (Wan & Schlaug, 2010). Musicians learn and repeatedly practice the association of motor acts with specific sounds and visual patterns while receiving continuous multisensory (visual-auditory) feedback (Wan & Schlaug, 2010). This associative learning can strengthen functional connections between auditory and motor regions (e.g., arcuate fasciculus), while activating parietal regions. Trained musicians also show anatomical differences in MI, PM, and the cerebellum, as compared to non-musicians

(Herholz & Zatorre, 2012). Such use-dependent plasticity suggests the potential for music as an adjuvant treatment for motor disorders.

Finally, the vestibular system provides the subjective sense of self-motion and orientation, and integrates information from different sensory modalities to generate accurate complex motor behaviors, such as navigation and reaching, gaze stabilization and the control of balance and posture (Angelaki & Cullen, 2008). Vestibular function is crucial in motor rehabilitation, being associated with gait speed, balance, independence, wheel-chair mobility and reaching in stroke patients.

Producing movement in response to sensory stimuli also involves complex sensorimotor computational processes. From the sensory side, various sensory modalities are coded in differing reference frames (i.e., vision in retinal or eye-centered coordinates, sound in head-centered coordinates, and touch in body-centered coordinates). From the motor side, the locations of the sensory stimuli must ultimately be transformed into the natural coordinates of the muscles in order to make appropriate movements (Andersen & Buneo, 2002). These processes do not occur in specific areas, rather they are supported by parallel circuits connecting the posterior parietal cortex (PPC) to frontal motor areas (Rizzolatti, Luppino, & Matelli, 1998). Having subregions dedicated to the planning of eye, reaching, and grasping movements, PPC provides different submechanisms for integrating visual, proprioceptive and tactile inputs (Andersen & Buneo, 2002). These parallel fronto-parietal pathways allow sensorimotor representations to be flexibly combined to drive downstream motor activity: information from parietal areas flows into premotor regions in the frontal lobe where information about stimulus and body position is combined with goal representations. The parietal cortex is also critical for adjusting these estimates based on incoming information during movement (i.e., motor-to-sensory transformations) (Andersen & Buneo, 2002; Andersen & Cui, 2009).

Predicting the consequences of one's own actions is another key feature of sensorimotor control. Theories of motor control (e.g., Wolpert, Ghahramani, & Jordan, 1995) suggest that internal models generate motor commands that are sent to the periphery to produce the desired movement; these internal models combine sensory inputs (*feedback* control), prior knowledge and volitional intention (*feedforward* control) to produce motor commands and control motor output. Through feedback control, information concerning the discrepancies (errors) between the desired movement and the actual sensory consequences associated with its execution are used to generate subsequent motor commands. In feed-forward control, motor commands are generated directly from the goal of the action and other internal signals. To achieve a high level of accuracy, this function requires learning from experience (Frey et al., 2011). Therefore, optimal motor behavior is based on both feed-forward and feedback control. By using an efferent copy of the motor command, together with an internal model of the action goal, a prediction of the consequences of one's actions can be generated (Wolpert et al., 1995). Such predictions can be used to maintain perceptual stability and to control actions in the presence of feedback delays (Cullen, 2004), and they constitute the signal upon which motor awareness is constructed (Blakemore, Wolpert, & Frith, 2002).

Together, the above examples highlight that parietal and frontal areas are both endowed with motor and sensory properties that need to be integrated for optimal motor behavior (Frey et al., 2011).

3. The role of sensory function in motor recovery

When the motor cortex is injured, the brain attempts to maintain motor control by remapping sensorimotor interactions, through the recruitment of secondary motor areas, primary sensory cortices and higher-order association areas involved in sensorimotor transformations (Ward & Cohen, 2004). For example, in adult squirrel monkeys, an ischemic infarct to MI results in a new direct projection pathway from PM to the SI, with SI showing a cluster of terminals and cell bodies after MI lesion, which did not exist in animals with intact MI. The emergence of this new pathway may represent a repair strategy to reconnect the motor areas with somatosensory input, by-passing the lesioned MI (Frost, Barbay, Friel, Plautz, & Nudo, 2003; Dancause et al., 2005).

Many lines of evidence support that the restoration of effective sensorimotor interactions within the damaged motor system is crucial for motor recovery. First, in the early post-stroke phase, the cortical activity in response to somatosensory input predicts late motor outcomes (Zeman & Yiannikas, 1989). Absence of cortical activation by sensory stimulation is associated with poorer outcome in stroke patients (Gallien et al., 2003), while the increased activation of MI and SI by somatosensory stimulation correlates with improvements in neurological scores between the acute and chronic stages of illness (Huang et al., 2004); moreover, the degree of improvement in hand function correlates with the activation peak changes within the ipsilesional SI (Laible et al., 2012). On the other hand, in patients with poorer recovery, movements of the paretic limb are associated with a compensatory recruitment of parallel sensorimotor networks, including the bilateral dorsolateral PM, SMA, cingulate motor areas, and parietal cortices (Ward & Cohen, 2004).

Somatosensory or visual field loss negatively impacts the functional outcome of patients with hemiplegia (Han, Law-Gibson, & Reding, 2002). Permanent tactile and proprioceptive loss reduces motor control of the affected limb, disrupts balance in upright stance and ambulation, and decreases awareness of limb position and movement (Twitchell, 1954). A recent single case has described a patient with a cerebral infarction localized to the postcentral gyrus, showing severe loss of motor control (in particular, impaired fine manual skills, with a partial improvement only under visual support) as a direct consequence of proprioceptive loss. The affected hand movements were associated with depressed activation of the sensorimotor network in the damaged hemisphere, featured by reduced activity of MI and the absence of activation in SI and other motor areas (such as PM, SMA) normally recruited during unilateral voluntary movements (Kato & Izumiyama, 2015).

The formation of abnormal internal models from irregular, unreliable sensory feedback also impacts higher-order motor function, leading to erroneous feedforward and feedback computations (Frey et al., 2011). Additionally, the loss of awareness or inattention to sensory events, even when not accompanied by primary sensory deficits, may worsen muscle synergistic patterns and strength of the upper paretic limb, hampering motor recovery and

functional outcome. Indeed, perceptual-attentional disorders, such as hemispatial neglect, represent a well-known negative prognostic factor in motor functional recovery (Farne et al., 2004; Nijboer, Kollen, & Kwakkel, 2014).

Based on these findings, it is not surprising that motor recovery can be enhanced by sensory stimulation. Intra- and inter-hemispheric changes in sensorimotor coupling constitute an important pathophysiological aspect of motor impairment after stroke. In patients suffering from severe motor deficits, all stages of sensorimotor integration, from primary sensory areas to associative multisensory regions (e.g., PM, PPC) may show changes in effective connectivity after stroke (Grefkes & Fink, 2011). Lesions to multisensory ‘*connector hubs*’ (such as parietal areas), produce larger and more widespread disturbances in cortico-cortical interactions than lesions to ‘*provincial hubs*’, such as SII (Grefkes & Fink, 2011; Honey & Sporns, 2008). Multisensory connector hubs represent modules of the cortex essential for integrating information derived from sensory and motor systems, which are supported by dense connections to many nodes, even anatomically distant. Damage at this level most likely disrupts the system-wide sensorimotor integrative processes essential for optimal motor behavior. Alternately, provincial hubs represent intra-modular centers predominantly linked to closely neighboring areas, which may cause, when damaged, more selective, modality-specific sensory impairments, or may result in pure motor dysfunction. Such disorders can be more easily compensated for through the activity of intact connector hubs.

It is also important to consider that lesions extending beyond MI into the sensorimotor parietal and premotor areas may impair the ability to make use of sensory feedback during movements, as in the case of optic ataxia or visuo-spatial hemineglect, or may disrupt cognitive functions related to action, ultimately worsening the motor deficit. For example, limb apraxia, whose hallmark is the inability or difficulty to plan purposeful limb movements (i.e., gestures), has an adverse influence on functional abilities and on patients’ responsiveness during physical therapies (Dovern, Fink, & Weiss, 2012). The inability to detect the mismatch between the motor predictions and the sensory feedback may cause anosognosia for hemiplegia, which represents another considerable burden for motor rehabilitation, since it leads to suboptimal benefits and a significantly poorer prognosis (Jenkinson, Preston, & Ellis, 2011). These examples emphasize the unfavorable outcomes of injuries to primary sensory cortices and higher-order association regions, respectively resulting in sensory loss and impaired higher-level sensorimotor processes, which further exacerbate the motor difficulties of stroke patients and reduce the efficacy of physical therapies, hence worsening the motor prognosis.

4. Sensory-based strategies to enhance post-stroke motor recovery

Re-establishing sensory processing and sensorimotor interactions in the stroke-damaged motor system appears to be essential for improving motor function. Accordingly, re-learning and compensation for lost motor function may benefit from sensory therapies (Schabrun & Hillier, 2009). Although further controlled studies are needed in this field, in the following we offer an overview of some promising sensory-based approaches to post-stroke motor rehabilitation (see Fig. 1); the examples are meant to be illustrative, rather than exhaustive.

4.1. Somatosensory approaches

Different methods are used to stimulate and strengthen somatosensory processing in motor rehabilitation. Early methods were very simple and coarse, including strategies such as skin stroking, quick muscle stretch, use of ice or heat, overall based on the concept of proprioceptive neuromuscular facilitation (Voss, 1967). Such methods have been then substituted by more sophisticated approaches such as Therapeutic Electrical Stimulation (TES) and Functional Electrical Stimulation (FES) (Schuhfried, Crevenna, Fialka-Moser, & Paternostro-Sluga, 2012). TES comprises simple electrical muscle stimulation inducing repetitive muscle contraction and electromyography- or position-triggered neuromuscular electrical stimulation, in which muscle contraction is induced by voluntary movement and sensory electrical stimulation. TES was shown to improve voluntary motor control by strengthening muscles, increasing motor control and range of motion, reducing spasticity, and decreasing pain (Schuhfried et al., 2012). Recent systematic reviews (De Kroon, Van der Lee, I Jzerman, & Lankhorst, 2002; Stein, Fritsch, Robinson, Sbruzzi, & Plentz, 2015) of randomized controlled trials (RCTs) assessing the effect of different TES methods (namely, neuromuscular electrical stimulation, electromyography-triggered electrical stimulation, positional feedback stimulation training and transcutaneous electrical nerve stimulation) on post-stroke upper limb hemiparesis further confirm the greater efficacy of TES, as compared to traditional physical therapies, for restoring motor control. In these reviews, motor control was indexed by various clinical outcomes such as active range of motion, isometric and grip strength, spasticity and sensorimotor functions (including amplitude of movement, coordination, reflex activity, pain and sensitivity). Although the impact on functional abilities was rarely assessed, the benefit was apparent (Powell, Pandyan, Granat, Cameron, & Stott, 1999; Cauraugh, Light, Kim, Thigpen, & Behrman, 2000).

FES consists of a functional substitute, as the patient uses the stimulation to execute a function. Since the defining feature of FES is to provoke muscle contraction and to produce a functionally useful movement during stimulation (Schuhfried et al., 2012), this technique can be easily integrated into task-oriented rehabilitation programs, rendering them more feasible and easier for patients. For instance, the combined use of FES (which was controlled by an iterative learning of goal-oriented activities) with practice of functional abilities (e.g., activities with real objects) ameliorates shoulder flexion, and elbow, wrist and index finger extension (Hughes, Hallewell, Kutlu, Freeman, & Meadmore, 2014). Moreover, FES seems useful in both acute and chronic stages of stroke (Knutson et al., 2012). When combined with walking training, it also improves hemiplegic gait (Laufer, Ring, Sprecher, & Hausdorff, 2009). Finally, FES is also useful for improving motor functions in everyday life (Howlett, Lannin, Ada, & McKinsty, 2015), as indexed by higher scores obtained by patients in activity performance domains of the International Classification of Function (ICF). The therapeutic effects of FES on motor performance are postulated to arise through sensory facilitation of neural plasticity, by increasing the strength of afferent inputs to promote motor learning (Schuhfried et al., 2012). A recent near-infrared spectroscopy (NIRS) study showed the occurrence of a shift in the cortical brain perfusion from the contralesional to ipsilesional sensorimotor cortex after a FES treatment, which was associated with the clinical improvement in motor function in chronic stroke patients with moderate residual hemiparesis (Hara, Obayashi, Tsujiuchi, & Muraoka, 2013). A

contemporary approach targeting brain plasticity is Peripheral Nerve Stimulation (PNS). PNS is applied via surface electrodes to the skin overlying peripheral nerves or via a mesh-glove for whole-hand electrical stimulation. Depending on the stimulation frequency, PNS may enhance or reduce cortical excitability. The length of stimulation influences the duration of the PNS-induced effects. Multiple sessions of PNS lead to long-term improvements in functional motor outcomes in chronic and subacute stroke patients (Celnik, Hummel, Harris-Love, Wolk, & Cohen, 2007; Conforto et al., 2010; Ng & Hui-Chan, 2007). When combined with motor training, PNS has additional positive effects on cerebral plasticity (Celnik et al., 2007) and leads to greater outcomes on various dexterity indexes (McDonnell & Ridding, 2006). Preliminary evidence suggests that repetitive peripheral magnetic stimulation might also be useful to promote motor or sensory recovery (Beaulieu & Schneider, 2013; Krewer, Hartl, Müller, & Koenig, 2014).

Various manual therapeutic protocols are also used to enhance somatosensory awareness, including techniques such as sensory re-education or tactile kinesthetic guiding. Anatomically specific sensory and positional awareness can occur with passive or active-assisted movement, as well as with manual techniques such as stroking and tapping. Recently, a novel rehabilitation treatment combining intensive somatosensory and motor stimulation of the upper limb has been developed for stroke patients with chronic hemiparesis and severe disability (de Diego, Puig, & Navarro, 2013). This technique aims at improving the sensation of the hand by means of training either stereognosis (the patient holds different objects, previously seen and felt, and places them in order accordingly to their size, consistency, weight or shape) or touch (the patient identifies different textures with the eyes closed, previously haptically explored with eyes open) (see also, Smania, Montagnana, Faccioli, Fiaschi, & Aglioti, 2003). This technique is accompanied by active functional retraining of the affected upper limb. Importantly, during the treatment, the motion of the unaffected upper limb is restricted. When compared to a control group, where the sensory and motor re-training was not prioritized, the experimental group showed a higher tendency for improved motor function (assessed with the Fugl Meyer Assessment scale), along with enhanced tactile and proprioceptive abilities (i.e., tactile discrimination, direction of passive motion, weight discrimination of objects).

Decreasing the somatosensory input from the intact hand is another strategy to enhance sensorimotor function in the paretic hand. This can be obtained with an ischemic nerve block, focal anesthesia, or a pharmacological block of specific nerve trunks by injection. In chronic stroke, this sensory strategy was shown to improve performance in the paretic hand in motor and somatosensory tasks (Floel et al., 2004; Voller et al., 2006; Sens et al., 2013), with the behavioral gains briefly outlasting the duration of anesthesia (Floel et al., 2004). The induced motor improvements may be ascribed to a somatosensory-induced re-balancing of interhemispheric interactions, similar to that proposed for Constraint-Induced Movement Therapy. Transient anesthesia of body parts adjacent to the paretic hand, as in the upper arm, also results in training-dependent improvements in motor function, presumably by allowing the weaker hand representation to expand over the stronger proximal representations in the motor cortex (Muellbacher et al., 2002). It is noteworthy that in clinical practice, these last strategies have limited applications, but they hold great theoretical value for understanding

mechanisms through which sensory deafferentation can drive post-stroke motor plasticity in the cerebral cortex.

Finally, dynamic and static postural devices are typically included in the definition of technology for sensory afferent modulation. Their relevance in postural rehabilitation has increasingly been validated (Laffont et al., 2014).

4.2. Visual approaches

The power of visual feedback for the treatment of post-stroke hemiparesis was demonstrated by Ramachandran and colleagues (Ramachandran & Altschuler, 2009), using the Mirror Box Illusion (MBI). Here, the patient sits in front of a mirror that is oriented perpendicular to his/her midline, blocking the view of the (affected) limb, positioned behind the mirror. When looking into the mirror, the patient sees the reflection of the unaffected limb positioned as the affected limb. This arrangement creates a visual illusion whereby movement of the intact limb may be perceived as affecting the paretic limb. MBI can improve functional recovery of the invisible paretic arm, through improvements in the range of motion, speed and accuracy, especially in cases of severe hemiparesis. Further evidence supports the efficacy of MBI for upper-limb and lower-limb motor recovery in subacute and chronic stroke patients (Altschuler et al., 1999; Radajewska et al., 2013; Sütbeyaz, Yavuzer, Sezer, & Koseoglu, 2007; Yavuzer et al., 2008). Of interest, MBI also has positive effects on motor planning, spatial efficiency in movement execution as well as multi-joint coordination, surface and temperature sensitivity, and spatial hemi-neglect (Dohle et al., 2009; Wu, Huang, Chen, Lin, & Yang, 2013). Viewing the mirror reflection of the paretic hand increases the excitability of MI and the functional interaction between somatosensory and motor areas in the affected hemisphere (Saleh, Adamovich, & Tunik, 2014). MBI also shifts the activation balance within MI toward the affected hemisphere (Michielsen et al., 2011a). The precise mechanisms whereby MBI contributes to post-stroke motor recovery are still unclear. Originally, it was hypothesized that paralysis following stroke might have a *learned* component, which could possibly be ‘unlearned’ by means of the mirror illusion through the sensory feedback (vision and proprioception) (Ramachandran & Altschuler, 2009). Other authors have proposed that MBI might be a form of visually-guided motor imagery (Stevens & Stoykov, 2003) based on the activation of the MNS (Yavuzer et al., 2008). Recent evidence from neuroimaging and transcranial magnetic stimulation studies emphasizes the role of the sensory-motor mismatch (Michielsen et al., 2011b; Senna, Russo, Parise, Ferrario, & Bolognini, 2015). Watching the reflection of self-generated movements in a mirror increases attentional demands for the integration of vision and proprioception and neural activity in multisensory areas associated with self-awareness and spatial attention. These effects may translate into an increased awareness of the affected limb, which is also helpful for counteracting learned non-use (Bolognini, Russo, Vallar, 2015).

By representing observed actions in the motor cortex, the MNS may serve as an alternative means to access the motor system after stroke (Buccino, Solodkin, & Small, 2006). From this perspective, Action Observation Therapy (AOT) was developed with the aim of activating the motor system through vision by generating an internal representation of the observed action that can be targeted for motor learning. Observation with intent to imitate

the observed action is fundamental for priming the motor system for execution (Brass, Bekkering, Wohlschläger, & Prinz, 2000). In chronic and acute stroke, AOT coupled with physical practice may enhance use-dependent plasticity by activating spared areas of the MNS and, improving upper- and lower-limb motor function (e.g., walking) (Franceschini et al., 2012; Park, Kim, Lee, & Oh, 2014).

4.3. Auditory approaches

Auditory rhythmic stimulation facilitates gait training, enhancing the improvement of gait velocity and stride length in patients with lower-limb hemiparesis (Thaut et al., 2007). When combined with bilateral arm training, auditory rhythm improves measures of sensorimotor impairment, isometric strength and range of motion in the paretic upper extremities, as well as functional motor performance (Whitall, Waller, Silver, & Macko, 2000). Incorporating real-time auditory feedback of performance errors is also a useful strategy for enhancing the clinical outcomes of robotic therapies (Secoli, Milot, Rosati, & Reinkensmeyer, 2011). An original auditory-based approach to motor rehabilitation is Music-Supported Therapy (MST). MST involves repetitive exercises using musical instruments in order to train fine and gross motor functions in patients suffering from mild to moderate upper limb paresis. In acute and chronic stroke patients, MST was shown to improve motor performance at various levels (speed, accuracy and movement smoothness), generalizing to untrained movements (Altenmüller, Marco-Pallares, Münte, & Schneider, 2009; Schneider, Schönle, Altenmüller, & Münte, 2007). Superior motor control in daily activities is achieved with MST, as compared to conventional physical therapy (Schneider et al., 2007). Gains in motor skills by MST are related to increased ipsilesional MI excitability (Amengual et al., 2013; Grau-Sanchez et al., 2013), and the reinforcement of functional connectivity between auditory and premotor regions (Rodriguez-Fornells et al., 2012). Although mechanisms rendering the motor system sensitive to auditory priming and timing of stimulation still need to be elucidated, there is evidence suggesting that the time structure of music, namely the rhythm, is the essential element relating music specifically to motor behavior. Auditory rhythm can improve motor control in various ways, offering internal reference intervals that can guide the timing of motor responses. The motor system is physiologically sensitive to arousal by the auditory system; furthermore, the neural activity from the auditory rhythm stimulates neural motor activity, which tends to become entrained to the auditory signal frequency (Thaut et al., 1999).

4.4. Combined use of different sensory stimulations

Through different parallel cortical and subcortical mechanisms, the human brain integrates the information derived from various sensory modalities into a coherent representation of the surrounding events, a function known as *multisensory integration*. By facilitating the processing of sensory inputs and increasing their salience, multisensory integration can improve motor responses to sensory events. It is also important to consider that many multisensory processes appear to be largely preserved in stroke patients, especially in those affected by focal brain damage, likely because multiple, parallel, cortical and subcortical pathways are available for the synthesis of multisensory information (Bolognini Convento, Rossetti, & Merabet, 2013; Bolognini et al., 2015a). So far, the benefit of multisensory versus unisensory, *modality-specific* stimulation on the recovery of motor functions has not

been established. Similarly, it is not known to what extent multisensory functions spared by the brain injury may be advantageous for post-stroke motor recovery, as shown in the case of sensory deficits, which can be compensated, at least partially, by multisensory processing.

Some motor rehabilitation approaches actually offer multisensory environments. For example, the rehabilitation context that can resemble real-time feedback from different senses (e.g., visual, auditory, and tactile) and simulates real-world interactions is offered by Virtual Reality (VR). VR may involve non-immersive to fully immersive applications, depending on the degree to which the user is isolated from real surroundings when interacting with the virtual environment (Fluet & Deutsch, 2013). The advantage of VR is to provide patients with on-line sensory feedback of their motor performance. Such sensory feedback can be modified, given in isolation or coupled with real sensory information; in this way, conflicting or congruent sensorimotor information can be used to guide online motor performance (Fluet & Deutsch, 2013). By combining different sensory feedback, VR can enhance the multisensory drive onto the motor system, facilitating recovery. Moreover, the multisensory environment, coupled with real-life simulations, induces appropriate motivation and arousal, which are crucial components of learning in stroke patients. For upper-limb rehabilitation, reaching tasks have been used, requiring retrieval or transport of virtual objects to shelves or table tops in virtual environments that progress from simple (a shelf) to complex (a supermarket). The games involve intercepting moving objects, piloting an avatar, or sport simulations. For walking recovery, simulations are delivered in a variety of environments requiring walking tasks and navigation. In upper-limb treatment, VR was shown to induce improvements at the motor function level and/or activity level, with the largest improvements occurring in the acute stage of recovery (Laver, George, Thomas, Deutsch, & Crotty, 2012). VR also enhances velocity and walking distance in robot-based gate training (Mirelman, Bonato, & Deutsch, 2009). When combined with treadmill training, balance is improved (Yang et al., 2011). Importantly, motor gains successfully transfer from the virtual to the real world, generalizing to untrained activities (Fluet & Deutsch, 2013). The neural underpinnings of motor recovery by VR include enhanced cortical reorganization of the ipsilesional sensorimotor system and a reduction of the interhemispheric imbalance (Jang et al., 2005). The unsolved issue is to what extent VR is efficacious for activation of multisensory integration mechanisms, and whether multisensory feedback is really superior to unisensory feedback.

Brain-computer interface systems (BCIs) are used to promote integration between motor learning and multisensory feedback. BCIs record, decode, and translate measurable neurophysiological signals to drive external devices without participation of the spinal and peripheral motor system (Daly & Wolpaw, 2008). In this way, this technology permits action through brain signals, acquired and decoded by means of electroencephalogram oscillations, event-related brain potentials, real-time functional magnetic resonance, and near-infrared spectroscopy. The output of the BCIs provides multisensory feedback to users, allowing them to modulate brain activity. Feedback consists of differing sensory information (visual, auditory, tactile and kinaesthetic stimuli) by robotic devices or FES (Daly & Wolpaw, 2008). By establishing a close contingent connection between the neural correlate of an intention to move (i.e., neuroelectric or metabolic brain activity associated with the intended movement) and the consequent sensory feedback of the movement, BCIs may facilitate associative

learning. For example, BCI training can involve positive *proprioceptive* feedback (feeling and seeing hand movements, or passive or active mobilization of the limb through an external device) and reward that is time-contingent upon control of ipsilesional sensorimotor brain oscillation, which increases the beneficial effects of physiotherapy in chronic stroke patients without residual finger movements (Ramos-Murguialday et al., 2013). *Visual* feedback of cortical activity during motor imagery-based training can also augment motor recovery in patients with severe hemiparesis (Mihara et al., 2013).

Virtual reality rehabilitation robotics is another technique proposing multisensory -visual, auditory and haptic- stimulation, with tightly controlled dose and important performance feedback that can be manipulated, as for example by increasing errors. The devices vary broadly in operation and effect, but for the upper extremity, evidence exists for efficacy and cost benefit; hence they are becoming progressively adopted to supplement labor-intensive current practices (Volpe et al., 2009). How each component of the multisensory experience contributes to the final clinical improvement has not been systematically evaluated, although the physical assistance provided by the robot (according to movement initiation rules), the real-time visual position feedback, and the auditory feedback about successful target completion, are all considered important elements for voluntary controlled improvement with practice (Molier, Van Asseldonk, Hermens, & Jannink, 2010).

Multisensory stimulation can also be provided through the combination of different sensory therapies. For example, 4 weeks of MBI combined with FES, as an adjuvant to conventional therapy, induces a larger improvement of upper limb hemiparesis, as compared to conventional therapy with FES without the MBI (Kim, Lee, & Song, 2014). MBI coupled with somatosensory stimulation, the last administered through a mesh glove, is more effective than the MBI alone in improving hand motor functions, such as gross manual dexterity, grasping abilities, with benefits translated to functional independence measures (Lin et al., 2014). Furthermore, the combined use of MBI and FES promotes a greater amelioration of gait disabilities (i.e., velocity, step and stride length, assessed by gait analysis) in stroke patients with lower limb hemiparesis, as compared to either MBI alone or sham MBI therapy (Ji, Cha, Kim, & Lee, 2014).

Future studies should establish whether a combination of sensory stimulation techniques (auditory plus tactile plus visual) is more effective than unisensory protocols (e.g., solely visual feedback). Multisensory stimulation may prove more beneficial considering the facilitatory effects of multisensory integration, shown both at a behavioral and a physiological level, documented in healthy individuals and in stroke patients with sensory (visual, auditory, or tactile) deficits (Bolognini et al., 2013, 2015a).

4.5. Driving sensorimotor plasticity with non-invasive brain stimulation

Non-invasive brain stimulation techniques (i.e., Transcranial Magnetic and Direct Current Stimulation, respectively TMS and tDCS) are currently considered a promising approach for post-stroke motor rehabilitation (Brunoni et al., 2012; Cortes, Black-Schaffer, & Edwards, 2012). So far, MI has been the targeted area for driving motor recovery with TMS and tDCS. However, purposeful manipulation of cortical plasticity and excitability in primary sensory and associative sensorimotor regions may have a therapeutic potential, given the role of

these areas in the process of post-stroke motor recovery. This strategy may be even superior in the case of extensive damage to motor pathways. In healthy individuals, repetitive TMS and tDCS of PM and of SI can indeed increase the excitability of the ipsilateral MI (Boros, Poreisz, Münchau, Paulus, & Nitsche, 2008; Jacobs et al., 2014; Rizzo et al., 2004). Cortico-cortical paired TMS stimuli to PPC and MI potentiate ipsilateral corticospinal excitability (Koch et al., 2007), facilitate neuroplasticity in MI and modulate PPC-MI connectivity (Chao et al., 2015), as compared with unconditioned MI stimulation. At a behavioral level, premotor stimulation facilitates the consolidation of learned motor behaviors (Nitsche et al., 2010), while parietal stimulation improves skilled hand motor functions by facilitating action planning and gesture recognition (Bolognini, et al., 2015b; Convento, Bolognini, Fusaro, Lollo, & Vallar, 2014). This evidence is relevant for developing novel therapeutic approaches for modifying motor excitability and sensorimotor interaction of injured motor areas.

TMS pulses can also be paired with sensory stimulation, as in paired associative stimulation protocols (PAS). PAS protocols offer a strategy to concurrently reinforce sensorimotor integration, and drive motor plasticity in stroke patients putatively through the potentiation of the transmission of sensory inputs to the motor system. In the prototypical form of PAS, a suprathreshold magnetic stimulation of the human hand MI is paired with a preceding electrical stimulation of the median nerve to induce a temporally dependent, rapidly forming and persistent modulation of hand muscle cortical excitability (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000). PAS-induced aftereffects are due to associative plasticity in MI that would normally be driven by sensorimotor integration processes. In stroke patients, PAS was shown to facilitate excitability of corticospinal projections to the muscles on the paretic side, improving functional outcome (Castel-Lacanal et al., 2009; Jayaram & Stinear, 2008). Recently, a new PAS protocol has been developed that couples primary visual cortex activation, elicited by hemifield pattern-reversal visual evoked potentials (VEPs), with TMS to the ipsilateral MI (Suppa, Voti, Rocchi, Papazachariadis, & Berardelli, 2013).

Furthermore, recent findings from our own group indicate that more naturally generated afference (from the repetitive passively moving limb) can be synchronized with repetitive TMS to modulate corticospinal pathway excitability, providing a more potent effect than rTMS alone (Edwards et al., 2014).

5. Summary and recommendations

Twenty-five years after the publication of Reding and Potes's paper (Reding & Potes, 1988), showing that recovery of motor function following stroke is worsened by somatosensory and visual impairments, there is still no consensus on if and how sensory function should be targeted in post-stroke motor rehabilitation. We reviewed different lines of evidence showing that successful motor control and learning are critically dependent on effective sensory processing and integration. To date, there is some promising, proof-of-principle, evidence supporting the clinical value of sensory-based approaches to motor therapies, especially for upper limb hemiparesis. However, current evidence is still insufficient to delineate the optimal type and dose of sensory therapies and the need of using them as substitution of, or in conjunction with, motor rehabilitation. Additionally, it is still unknown whether and how

the clinical characteristics of the patients (e.g., stage of illness, severity of motor disorders, lesion location, hemorrhagic vs. ischemic stroke, and the presence of sensory or cognitive deficits) can predict the efficacy of sensory therapy for motor recovery. This knowledge has implications for the optimization of sensory-based training, including the choice of the sensory modality to be targeted, as well as the selection of patients that may benefit. It is surprising that the majority of studies did not systematically assess or report, beyond the primary motor disorders, the presence of concurrent sensory deficits (visual, proprioceptive, tactile, auditory), as assessed with clinical tests, or through neurophysiological indexes of intact cortical processing in sensory areas (e.g., visual and somatosensory evoked potentials). Nor has the presence of neuropsychological cognitive dysfunction been systematically assessed in patients engaged in sensory-based rehabilitation, notwithstanding the negative impact of visuo-spatial neglect, anosognosia for hemiplegia, ataxia and apraxia on both spontaneous and training-induced motor recovery. Spatial and temporal impairments in the auditory modality may also compromise response to auditory feedback or musical training. The goal of the sensory stimulation may also vary. For example, in the case of a major motor dysfunction with spared sensory function, sensory-based treatments could be used with the aim of ‘priming’ the motor system, as to prepare it for practice, or of ‘augmenting/facilitating’ sensorimotor interactions during the motor practice (Pomeroy et al., 2011). Conversely, in the presence of a sensory deficit, specific intervention to train or reactivate the impaired sensory system would be advisable; these could be provided in parallel to the motor exercises for paresis. Finally, the neural underpinning of sensory-driven motor recovery could be tracked for a better understanding of which mechanism should be targeted with the sensory stimulation.

These reflections prompt fresh working principles on how to develop and optimize the sensory side of post-stroke motor rehabilitation, which has been for a long time largely neglected, and has been obscured by major emphasis traditionally given to the motor side of rehabilitation.

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References

- Altenmüller E, Marco-Pallares J, Münte TF, Schneider S. Neural reorganization underlies improvement in stroke-induced motor dysfunction by music-supported therapy. *Annals of the New York Academy of Sciences*. 2009; 1169(1):395–405. [PubMed: 19673814]
- Altschuler EL, Wisdom SB, Stone L, Foster C, Galasko D, Llewellyn DM, Ramachandran VS. Rehabilitation of hemiparesis after stroke with a mirror. *The Lancet*. 1999; 353(9169):2035–2036.
- Amengual JL, Rojo N, Veciana de Las Heras M, Marco-Pallarés J, Grau-Sánchez J, Schneider S, Vaquero L, Juncadella M, Montero J, Mohammadi B, Rubio F, Rueda N, Duarte E, Grau C, Altenmüller E, Münte TF, Rodríguez-Fornells A. Sensorimotor plasticity after music-supported therapy in chronic stroke patients revealed by transcranial magnetic stimulation. *PLoS One*. 2013; 8(4):e61883. [PubMed: 23613966]
- Andersen RA, Buneo CA. Intentional maps in posterior parietal cortex. *Annual Review of Neuroscience*. 2002; 25(1):189–220.

- Andersen RA, Cui H. Intention, action planning, and decision making in parietal-frontal circuits. *Neuron*. 2009; 63(5):568–583. [PubMed: 19755101]
- Angel RW, Malenka RC. Velocity-dependent suppression of cutaneous sensitivity during movement. *Experimental Neurology*. 1982; 77(2):266–274. [PubMed: 7095061]
- Angelaki DE, Cullen KE. Vestibular system: The many facets of a multimodal sense. *Annual Review of Neuroscience*. 2008; 31:125–150.
- Avenanti A, Candidi M, Urgesi C. Vicarious motor activation during action perception: Beyond correlational evidence. *Frontiers in Human Neuroscience*. 2013; 7:185. [PubMed: 23675338]
- Bays PM, Flanagan JR, Wolpert DM. Attenuation of self-generated tactile sensations is predictive, not postdictive. *PLoS Biology*. 2006; 4(2):e28. [PubMed: 16402860]
- Beaulieu LD, Schneider C. Effects of repetitive peripheral magnetic stimulation on normal or impaired motor control. A review. *Neurophysiologie Clinique/Clinical Neurophysiology*. 2013; 43(4):251–260. [PubMed: 24094911]
- Blakemore SJ, Wolpert DM, Frith CD. Central cancellation of self-produced tickle sensation. *Nature Neuroscience*. 1998; 1(7):635–640. [PubMed: 10196573]
- Blakemore SJ, Wolpert DM, Frith CD. Abnormalities in the awareness of action. *Trends in Cognitive Sciences*. 2002; 6(6):237–242. [PubMed: 12039604]
- Bolognini N, Convento S, Rossetti A, Merabet LB. Multisensory processing after a brain damage: Clues on post-injury crossmodal plasticity from neuropsychology. *Neuroscience and Biobehavioral Reviews*. 2013; 37(3):269–278. [PubMed: 23253947]
- Bolognini N, Convento S, Banco E, Mattioli F, Tesio L, Vallar G. Improving ideomotor limb apraxia by electrical stimulation of the left posterior parietal cortex. *Brain*. 2015b; 138(Pt 2):428–39. [PubMed: 25481002]
- Bolognini N, Russo C, Vallar G. Crossmodal illusions in neurorehabilitation. *Frontiers in Behavioral Neuroscience*. 2015a; 9:212. [PubMed: 26321933]
- Boros K, Poreisz C, Münchau A, Paulus W, Nitsche MA. Premotor transcranial direct current stimulation (tDCS) affects primary motor excitability in humans. *European Journal of Neuroscience*. 2008; 27(5):1292–1300. [PubMed: 18312584]
- Brass M, Bekkering H, Wohlschläger A, Prinz W. Compatibility between observed and executed finger movements: Comparing symbolic, spatial, and imitative cues. *Brain and Cognition*. 2000; 44(2):124–143. [PubMed: 11041986]
- Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, Edwards DJ, Valero-Cabre A, Rotenberg A, Pascual-Leone A, Ferrucci R, Priori A, Boggio PS, Fregni F. Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. *Brain Stimulation*. 2012; 5(3):175–195. [PubMed: 22037126]
- Buccino G, Solodkin A, Small SL. Functions of the mirror neuron system: Implications for neurorehabilitation. *Cognitive and Behavioral Neurology*. 2006; 19(1):55–63. [PubMed: 16633020]
- Castel-Lacanal E, Marque P, Tardy J, de Boissezon X, Guiraud V, Chollet F, Loubinoux I, Moreau MS. Induction of cortical plastic changes in wrist muscles by paired associative stimulation in the recovery phase of stroke patients. *Neurorehabilitation and Neural Repair*. 2009; 23(4):366–372. [PubMed: 19060132]
- Cauraugh J, Light K, Kim S, Thigpen M, Behrman A. Chronic motor dysfunction after stroke recovering wrist and finger extension by electromyography-triggered neuromuscular stimulation. *Stroke*. 2000; 31(6):1360–1364. [PubMed: 10835457]
- Celnik P, Hummel F, Harris-Love M, Wolk R, Cohen LG. Somatosensory stimulation enhances the effects of training functional hand tasks in patients with chronic stroke. *Archives of Physical Medicine and Rehabilitation*. 2007; 88(11):1369–1376. [PubMed: 17964875]
- Chao CC, Karabanov AN, Paine R, Carolina de Campos A, Kukke SN, Wu T, Wang H, Hallett M. Induction of Motor Associative Plasticity in the Posterior Parietal Cortex–Primary Motor Network. *Cerebral Cortex*. 2015; 25(2):365–373. [PubMed: 23968834]
- Conforto AB, Ferreiro KN, Tomasi C, dos Santos RL, Moreira VL, Marie SK, Baltieri SC, Scaff M, Cohen LG. Effects of somatosensory stimulation on motor function after subacute stroke. *Neurorehabilitation and Neural Repair*. 2010; 24(3):263–272. [PubMed: 19884642]

- Convento S, Bolognini N, Fusaro M, Lollo F, Vallar G. Neuromodulation of parietal and motor activity affects motor planning and execution. *Cortex*. 2014; 57:51–59. [PubMed: 24769545]
- Cortes M, Black-Schaffer RM, Edwards DJ. Transcranial magnetic stimulation as an investigative tool for motor dysfunction and recovery in stroke: An overview for neurorehabilitation clinicians. *Neuromodulation*. 2012; 15(4):316–325. [PubMed: 22624621]
- Cullen KE. Sensory signals during active versus passive movement. *Current Opinion in Neurobiology*. 2004; 14(6):698–706. [PubMed: 15582371]
- Daly JJ, Wolpaw JR. Brain–computer interfaces in neurological rehabilitation. *The Lancet Neurology*. 2008; 7(11):1032–1043. [PubMed: 18835541]
- Dancause N, Barbay S, Frost SB, Plautz EJ, Chen D, Zoubina EV, Stowe AM, Nudo RJ. Extensive cortical rewiring after brain injury. *The Journal of Neuroscience*. 2005; 25(44):10167–10179. [PubMed: 16267224]
- de Diego C, Puig S, Navarro X. A sensorimotor stimulation program for rehabilitation of chronic stroke patients. *Restorative Neurology and Neuroscience*. 2013; 31(4):361–371. [PubMed: 23524843]
- De Kroon JR, Van der Lee JH, IJzerman MJ, Lankhorst GJ. Therapeutic electrical stimulation to improve motor control and functional abilities of the upper extremity after stroke: A systematic review. *Clinical Rehabilitation*. 2002; 16(4):350–360. [PubMed: 12061468]
- Dohle C, Püllen J, Nakaten A, Küst J, Rietz C, Karbe H. Mirror therapy promotes recovery from severe hemiparesis: A randomized controlled trial. *Neurorehabilitation and Neural Repair*. 2009; 23(3):209–217. [PubMed: 19074686]
- Donoghue JP, Sanes JN. Peripheral nerve injury in developing rats reorganizes representation pattern in motor cortex. *Proceedings of the National Academy of Sciences*. 1987; 84(4):1123–1126.
- Dovern A, Fink GR, Weiss PH. Diagnosis and treatment of upper limb apraxia. *Journal of Neurology*. 2012; 259(7):1269–1283. [PubMed: 22215235]
- Edwards DJ, Dipietro L, Demirtas-Tatlidede A, Medeiros AH, Thickbroom GW, Mastaglia FL, Krebs HI, Pascual-Leone A. Movement-generated afference paired with transcranial magnetic stimulation: An associative stimulation paradigm. *Journal of Neuroengineering and Rehabilitation*. 2014; 11(1):31. [PubMed: 24597619]
- Farnè A, Buxbaum LJ, Ferraro M, Frassinetti F, Whyte J, Veramonti T, Angeli V, Coslett HB, Ladavas E. Patterns of spontaneous recovery of neglect and associated disorders in acute right brain-damaged patients. *Journal of Neurology, Neurosurgery and Psychiatry*. 2004; 75(10):1401–1410.
- Floel A, Nagorsen U, Werhahn KJ, Ravindran S, Birbaumer N, Knecht S, Cohen LG. Influence of somatosensory input on motor function in patients with chronic stroke. *Annals of Neurology*. 2004; 56(2):206–212. [PubMed: 15293272]
- Fluet GG, Deutsch JE. Virtual reality for sensorimotor rehabilitation post-stroke: The promise and current state of the field. *Current Physical Medicine and Rehabilitation Reports*. 2013; 1(1):9–20. [PubMed: 24579058]
- Franceschini M, Ceravolo MG, Agosti M, Cavallini P, Bonassi S, Dall’Armi V, Massucci M, Schifini F, Sale P. Clinical relevance of action observation in upper-limb stroke rehabilitation: A possible role in recovery of functional dexterity. A randomized clinical trial. *Neurorehabilitation and Neural Repair*. 2012; 26(5):456–462. [PubMed: 22235059]
- Frey SH, Fogassi L, Grafton S, Picard N, Rothwell JC, Schweighofer N, Corbetta M, Fitzpatrick SM. Neurological principles and rehabilitation of action disorders computation, anatomy, and physiology (CAP) model. *Neurorehabilitation and Neural Repair*. 2011; 25(5):6S–20S. [PubMed: 21613534]
- Friel KM, Barbay S, Frost SB, Plautz EJ, Hutchinson DM, Stowe AM, Dancause N, Zoubina EV, Quaney BM, Nudo RJ. Dissociation of sensorimotor deficits after rostral versus caudal lesions in the primary motor cortex hand representation. *Journal of Neurophysiology*. 2005; 94(2):1312–1324. [PubMed: 15872062]
- Frost SB, Barbay S, Friel KM, Plautz EJ, Nudo RJ. Reorganization of remote cortical regions after ischemic brain injury: A potential substrate for stroke recovery. *Journal of Neurophysiology*. 2003; 89(6):3205–3214. [PubMed: 12783955]

- Gallien P, Aghulon C, Durufle A, Petrilli S, De Crouy AC, Carsin M, Toulouse P. Magnetoencephalography in stroke: A 1-year follow-up study. *European Journal of Neurology*. 2003; 10(4):373–382. [PubMed: 12823488]
- Ghez C, Pisa M. Inhibition of afferent transmission in cuneate nucleus during voluntary movement in the cat. *Brain Research*. 1972; 40(1):145–151. [PubMed: 4338259]
- Grau-Sánchez J, Amengual JL, Rojo N, Veciana de las Heras M, Montero J, Rubio F, Altenmüller E, Münte TF, Rodríguez Fornells A. Plasticity in the sensorimotor cortex induced by Music-supported therapy in stroke patients: A TMS study. *Frontiers in Human Neuroscience*. 2013; 7:494. [PubMed: 24027507]
- Grefkes C, Fink GR. Reorganization of cerebral networks after stroke: New insights from neuroimaging with connectivity approaches. *Brain*. 2011; 134(Pt 5):1264–76. [PubMed: 21414995]
- Han L, Law-Gibson D, Reding M. Key neurological impairments influence function-related group outcomes after stroke. *Stroke*. 2002; 33(7):1920–1924. [PubMed: 12105376]
- Hantman AW, Jessell TM. Clarke's column neurons as the focus of a corticospinal corollary circuit. *Nature Neuroscience*. 2010; 13(10):1233–1239. [PubMed: 20835249]
- Hara Y, Obayashi S, Tsujiuchi K, Muraoka Y. The effects of electromyography-controlled functional electrical stimulation on upper extremity function and cortical perfusion in stroke patients. *Clinical Neurophysiology*. 2013; 124(10):2008–2015. [PubMed: 23706813]
- Herholz SC, Zatorre RJ. Musical training as a framework for brain plasticity: Behavior, function, and structure. *Neuron*. 2012; 76(3):486–502. [PubMed: 23141061]
- Honey CJ, Sporns O. Dynamical consequences of lesions in cortical networks. *Human Brain Mapping*. 2008; 29(7):802–809. [PubMed: 18438885]
- Howlett OA, Lannin NA, Ada L, McKinstry C. Functional electrical stimulation improves activity after stroke: A systematic review with meta-analysis. *Archives of Physical Medicine and Rehabilitation*. 2015; 96(5):934–943. [PubMed: 25634620]
- Huang M, Davis LE, Aine C, Weisend M, Harrington D, Christner R, Stephen J, Edgar JC, Herman M, Meyer J, Paulson K, Martin K, Lee RR. MEG response to median nerve stimulation correlates with recovery of sensory and motor function after stroke. *Clinical Neurophysiology*. 2004; 115(4):820–833. [PubMed: 15003762]
- Hughes AM, Hallewell E, Kutlu M, Freeman C, Meadmore K. Combining electrical stimulation mediated by iterative learning control with movement practice using real objects and simulated tasks for post-stroke upper extremity rehabilitation. *Neurosonology and Cerebral Hemodynamics*. 2014; 10(2):117–122.
- Jacobs MF, Tsang P, Lee KG, Asmussen MJ, Zapallow CM, Nelson AJ. 30Hz Theta-burst stimulation over primary somatosensory cortex modulates corticospinal output to the hand. *Brain Stimulation*. 2014; 7(2):269–274. [PubMed: 24486137]
- Jang SH, You SH, Hallett M, Cho YW, Park CM, Cho SH, Lee HY, Kim TH. Cortical reorganization and associated functional motor recovery after virtual reality in patients with chronic stroke: An experimenter-blind preliminary study. *Archives of Physical Medicine and Rehabilitation*. 2005; 86(11):2218–2223. [PubMed: 16271575]
- Jayaram G, Stinear JW. Contralesional paired associative stimulation increases paretic lower limb motor excitability post-stroke. *Experimental Brain Research*. 2008; 185(4):563–570. [PubMed: 17973101]
- Jenkinson PM, Preston C, Ellis SJ. Unawareness after stroke: A review and practical guide to understanding, assessing, and managing anosognosia for hemiplegia. *Journal of Clinical and Experimental Neuropsychology*. 2011; 33(10):1079–1093. [PubMed: 21936643]
- Ji SG, Cha HG, Kim MK, Lee CR. The effect of mirror therapy integrating functional electrical stimulation on the gait of stroke patients. *Journal of Physical Therapy Science*. 2014; 26(4):497. [PubMed: 24764619]
- Jiang W, Lamarre Y, Chapman CE. Modulation of cutaneous cortical evoked potentials during isometric and isotonic contractions in the monkey. *Brain Research*. 1990; 536(1):69–78. [PubMed: 2085763]

- Kato H, Izumiyama M. Impaired motor control due to proprioceptive sensory loss in a patient with cerebral infarction localized to the postcentral gyrus. *Journal of Rehabilitation Medicine*. 2015; 47(2):187–190. [PubMed: 25268114]
- Kim H, Lee G, Song C. Effect of functional electrical stimulation with mirror therapy on upper extremity motor function in poststroke patients. *Journal of Stroke and Cerebrovascular Diseases*. 2014; 23(4):655–661. [PubMed: 23867040]
- Knutson JS, Harley MY, Hisel TZ, Makowski NS, Fu MJ, Chae J. Contralaterally controlled functional electrical stimulation for stroke rehabilitation. *Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society*. 2012; 2012:314–317.
- Koch G, Fernandez Del Olmo M, Cheeran B, Ruge D, Schippling S, Caltagirone C, Rothwell JC. Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. *The Journal of Neuroscience*. 2007; 27(25):6815–6822. [PubMed: 17581969]
- Krewer C, Hartl S, Müller F, Koenig E. Effects of repetitive peripheral magnetic stimulation on upper-limb spasticity and impairment in patients with spastic hemiparesis: A randomized, double-blind, sham-controlled study. *Archives of Physical Medicine and Rehabilitation*. 2014; 95(6):1039–1047. [PubMed: 24561057]
- Laffont I, Bakhti K, Coroian F, van Dokkum L, Mottet D, Schweighofer N, Froger J. Innovative technologies applied to sensorimotor rehabilitation after stroke. *Annals of Physical and Rehabilitation Medicine*. 2014; 57(8):543–551. [PubMed: 25261273]
- Laible M, Grieshammer S, Seidel G, Rijntjes M, Weiller C, Hamzei F. Association of activity changes in the primary sensory cortex with successful motor rehabilitation of the hand following stroke. *Neurorehabilitation and Neural Repair*. 2012; 26(7):881–888. [PubMed: 22396499]
- Laufer Y, Ring H, Sprecher E, Hausdorff JM. Gait in individuals with chronic hemiparesis: One-year follow up of the effects of a neuroprosthesis that ameliorates foot drop. *Journal of Neurologic Physical Therapy*. 2009; 33(2):104–110. [PubMed: 19556919]
- Laver K, George S, Thomas S, Deutsch JE, Crotty M. Cochrane review: Virtual reality for stroke rehabilitation. *European Journal of Physical and Rehabilitation Medicine*. 2012; 48(3):523–530. [PubMed: 22713539]
- Lin KC, Chen YT, Huang PC, Wu CY, Huang WL, Yang HW, Lai HT, Lu HJ. Effect of mirror therapy combined with somatosensory stimulation on motor recovery and daily function in stroke patients: A pilot study. *Journal of the Formosan Medical Association*. 2014; 113(7):422–428. [PubMed: 24961183]
- McDonnell MN, Ridding MC. Afferent stimulation facilitates performance on a novel motor task. *Experimental Brain Research*. 2006; 170(1):109–115. [PubMed: 16328288]
- Michielsen ME, Selles RW, van der Geest JN, Eckhardt M, Yavuzer G, Stam HJ, Smits M, Ribbers GM, Bussmann JB. Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: A phase II randomized controlled trial. *Neurorehabilitation and Neural Repair*. 2011a; 25(3):223–233. [PubMed: 21051765]
- Michielsen ME, Smits M, Ribbers GM, Stam HJ, van der Geest JN, Bussmann JB, Selles RW. The neuronal correlates of mirror therapy: An fMRI study on mirror induced visual illusions in patients with stroke. *Journal of Neurology, Neurosurgery and Psychiatry*. 2011b; 82(4):393–8.
- Mihara M, Hattori N, Hatakenaka M, Yagura H, Kawano T, Hino T, Miyai I. Near-infrared spectroscopy-mediated neurofeedback enhances efficacy of motor imagery-based training in poststroke victims a pilot study. *Stroke*. 2013; 44(4):1091–1098. [PubMed: 23404723]
- Milne RJ, Aniss AM, Kay NE, Gandevia SC. Reduction in perceived intensity of cutaneous stimuli during movement: A quantitative study. *Experimental Brain Research*. 1988; 70(3):569–576. [PubMed: 3384055]
- Mirelman A, Bonato P, Deutsch JE. Effects of training with a robot-virtual reality system compared with a robot alone on the gait of individuals after stroke. *Stroke*. 2009; 40(1):169–174. [PubMed: 18988916]
- Molier BI, Van Asseldonk EH, Hermens HJ, Jannink MJ. Nature, timing, frequency and type of augmented feedback; does it influence motor relearning of the hemiparetic arm after stroke? A systematic review. *Disability and Rehabilitation*. 2010; 32(22):1799–1809. [PubMed: 20345249]

- Muellbacher W, Richards C, Ziemann U, Wittenberg G, Weltz D, Boroojerdi B, Cohen L, Hallett M. Improving hand function in chronic stroke. *Archives of neurology*. 2002; 59(8):1278–1282. [PubMed: 12164724]
- Ng SS, Hui-Chan CW. Transcutaneous electrical nerve stimulation combined with task-related training improves lower limb functions in subjects with chronic stroke. *Stroke*. 2007; 38(11):2953–2959. [PubMed: 17901383]
- Nijboer TC, Kollen BJ, Kwakkel G. The impact of recovery of visuo-spatial neglect on motor recovery of the upper paretic limb after stroke. *PLoS One*. 2014; 9(6):e100584. [PubMed: 24950224]
- Nijs J, Daenen L, Cras P, Struyf F, Roussel N, Oostendorp RA. Nociception affects motor output: A review on sensory-motor interaction with focus on clinical implications. *The Clinical Journal of Pain*. 2012; 28(2):175–181. [PubMed: 21712714]
- Nitsche MA, Jakoubkova M, Thirugnanasambandam N, Schmalfuss L, Hulleman S, Sonka K, Paulus W, Trenkwalder C, Happe S. Contribution of the premotor cortex to consolidation of motor sequence learning in humans during sleep. *Journal of Neurophysiology*. 2010; 104(5):2603–2614. [PubMed: 20844115]
- Nudo RJ. Plasticity. *NeuroRx*. 2006; 3(4):420–427. [PubMed: 17012055]
- Nudo RJ, Friel KM, Delia SW. Role of sensory deficits in motor impairments after injury to primary motor cortex. *Neuropharmacology*. 2000; 39(5):733–742. [PubMed: 10699440]
- Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *Journal of Neuroscience*. 1996; 16(2):785–807. [PubMed: 8551360]
- Park HR, Kim JM, Lee MK, Oh DW. Clinical feasibility of action observation training for walking function of patients with post-stroke hemiparesis: A randomized controlled trial. *Clinical Rehabilitation*. 2014; 28(8):794–803. [PubMed: 24569652]
- Patel N, Jankovic J, Hallett M. Sensory aspects of movement disorders. *The Lancet Neurology*. 2014; 13(1):100–112. [PubMed: 24331796]
- Pomeroy V, Aglioti SM, Mark VW, McFarland D, Stinear C, Wolf SL, Corbetta M, Fitzpatrick SM. Neurological principles and rehabilitation of action disorders rehabilitation interventions. *Neurorehabilitation and Neural Repair*. 2011; 25(5 Suppl):33S–43S. [PubMed: 21613536]
- Powell J, Pandyan AD, Granat M, Cameron M, Stott DJ. Electrical stimulation of wrist extensors in poststroke hemiplegia. *Stroke*. 1999; 30(7):1384–1389. [PubMed: 10390311]
- Radajewska A, Opara JA, Kucio C, Blaszczyzyn M, Mehlich K, Szczygiel J. The effects of mirror therapy on arm and hand function in subacute stroke in patients. *International Journal of Rehabilitation Research*. 2013; 36(3):268–274. [PubMed: 23528388]
- Ramachandran VS, Altschuler EL. The use of visual feedback, in particular mirror visual feedback, in restoring brain function. *Brain*. 2009; 132(Pt 7):1693–710. [PubMed: 19506071]
- Ramos-Murguialday A, Broetz D, Rea M, Läer L, Yilmaz Ö, Brasil FL, Liberati G, Curado MR, Garcia-Cossio E, Vyziotis A, Cho W, Agostini M, Soares E, Soekadar S, Caria A, Cohen LG, Birbaumer N. Brain-machine interface in chronic stroke rehabilitation: A controlled study. *Annals of Neurology*. 2013; 74(1):100–108. [PubMed: 23494615]
- Reding MJ, Potes E. Rehabilitation outcome following initial unilateral hemispheric stroke. Life table analysis approach. *Stroke*. 1988; 19(11):1354–1358. [PubMed: 3188120]
- Ridding MC, Brouwer B, Miles TS, Pitcher JB, Thompson PD. Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects. *Experimental Brain Research*. 2000; 131(1):135–143. [PubMed: 10759179]
- Rizzo V, Siebner HR, Modugno N, Pesenti A, Münchau A, Gerschlagel W, Webb RM, Rothwell JC. Shaping the excitability of human motor cortex with premotor rTMS. *The Journal of Physiology*. 2004; 554(2):483–495. [PubMed: 14555728]
- Rizzolatti G, Luppino G, Matelli M. The organization of the cortical motor system: New concepts. *Electroencephalography and Clinical Neurophysiology*. 1998; 106(4):283–296. [PubMed: 9741757]
- Rizzolatti G, Craighero L. The mirror-neuron system. *Annual Review of Neuroscience*. 2004; 27:169–192.

- Rodriguez-Fornells A, Rojo N, Amengual JL, Ripollés P, Altenmüller E, Münte TF. The involvement of audio–motor coupling in the music-supported therapy applied to stroke patients. *Annals of the New York Academy of Sciences*. 2012; 1252(1):282–293. [PubMed: 22524370]
- Romo R, Ruiz S, Crespo P, Zainos A, Merchant H. Representation of tactile signals in primate supplementary motor area. *Journal of Neurophysiology*. 1993; 70(6):2690–2694. [PubMed: 8120609]
- Saleh S, Adamovich SV, Tunik E. Mirrored feedback in chronic stroke recruitment and effective connectivity of ipsilesional sensorimotor networks. *Neurorehabilitation and Neural Repair*. 2014; 28(4):344–354. [PubMed: 24370569]
- Sanes JN, Suner S, Donoghue JP. Dynamic organization of primary motor cortex output to target muscles in adult rats I. Long-term patterns of reorganization following motor or mixed peripheral nerve lesions. *Experimental Brain Research*. 1990; 79(3):479–491. [PubMed: 2340868]
- Schabrun SM, Hillier S. Evidence for the retraining of sensation after stroke: A systematic review. *Clinical Rehabilitation*. 2009; 23(1):27–39. [PubMed: 19114435]
- Schneider S, Schönle PW, Altenmüller E, Münte TF. Using musical instruments to improve motor skill recovery following a stroke. *Journal of neurology*. 2007; 254(10):1339–1346. [PubMed: 17260171]
- Schuhfried O, Crevenna R, Fialka-Moser V, Paternostro-Sluga T. Non-invasive neuromuscular electrical stimulation in patients with central nervous system lesions: An educational review. *Journal of Rehabilitation Medicine*. 2012; 44(2):99–105. [PubMed: 22334346]
- Secoli R, Milot MH, Rosati G, Reinkensmeyer DJ. Effect of visual distraction and auditory feedback on patient effort during robot-assisted movement training after stroke. *Journal of NeuroEngineering and Rehabilitation*. 2011; 8(1):1–10. [PubMed: 21226898]
- Seki K, Fetz EE. Gating of sensory input at spinal and cortical levels during preparation and execution of voluntary movement. *The Journal of Neuroscience*. 2012; 32(3):890–902. [PubMed: 22262887]
- Senna I, Russo C, Parise CV, Ferrario I, Bolognini N. Altered visual feedback modulates cortical excitability in a mirror-box-like paradigm. *Experimental Brain Research*. 2015; 233(6):1921–1929. [PubMed: 25850405]
- Sens E, Knorr C, Preul C, Meissner W, Witte OW, Miltner WH, Weiss T. Differences in somatosensory and motor improvement during temporary functional deafferentation in stroke patients and healthy subjects. *Behavioural Brain Research*. 2013; 252:110–116. [PubMed: 23735321]
- Smania N, Montagnana B, Faccioli S, Fiaschi A, Aglioti SM. Rehabilitation of somatic sensation and related deficit of motor control in patients with pure sensory stroke. *Archives of Physical Medicine and Rehabilitation*. 2003; 84(11):1692–1702. [PubMed: 14639572]
- Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain*. 2000; 123(3):572–584. [PubMed: 10686179]
- Stein C, Fritsch CG, Robinson C, Sbruzzi G, Plentz RD. Effects of electrical stimulation in spastic muscles after stroke systematic review and metaanalysis of randomized controlled trials. *Stroke*. 2015; 46(8):2197–2205. [PubMed: 26173724]
- Stevens JA, Stoykov ME. Using motor imagery in the rehabilitation of hemiparesis. *Archives of Physical Medicine and Rehabilitation*. 2003; 84(7):1090–1092. [PubMed: 12881842]
- Strick PL, Preston JB. Two representations of the hand in area 4 of a primate. I. Motor output organization. *Journal of Neurophysiology*. 1982a; 48(1):139–149. [PubMed: 6288884]
- Strick PL, Preston JB. Two representations of the hand in area 4 of a primate. II. Somatosensory input organization. *Journal of Neurophysiology*. 1982b; 48(1):150–159. [PubMed: 7119842]
- Suppa A, Li Voti P, Rocchi L, Papazachariadis O, Berardelli A. Early visuomotor integration processes induce LTP/LTD-like plasticity in the human motor cortex. *Cerebral Cortex*. 2013; 25(3):703–12. [PubMed: 24057659]
- Sütbeyaz S, Yavuzer G, Sezer N, Koseoglu BF. Mirror therapy enhances lower-extremity motor recovery and motor functioning after stroke: A randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*. 2007; 88(5):555–559. [PubMed: 17466722]
- Tanji J, Wise SP. Submodality distribution in sensorimotor cortex of the unanesthetized monkey. *Journal of Neurophysiology*. 1981; 45(3):467–481. [PubMed: 7218010]

- Thaut MH, Kenyon GP, Schauer ML, McIntosh GC. The connection between rhythmicity and brain function. *Engineering in Medicine and Biology Magazine*. 1999; 18(2):101–108. [PubMed: 10101675]
- Thaut MH, Leins AK, Rice RR, Argstatter H, Kenyon GP, McIntosh GC, Bolay HV, Fetter M. Rhythmic auditory stimulation improves gait more than NDT/Bobath training in near-ambulatory patients early poststroke: A single-blind, randomized trial. *Neurorehabilitation and Neural Repair*. 2007; 21(5):455–459. [PubMed: 17426347]
- Tsumoto T, Nakamura S, Iwama K. Pyramidal tract control over cutaneous and kinesthetic sensory transmission in the cat thalamus. *Experimental Brain Research*. 1975; 22(3):281–294. [PubMed: 1052680]
- Twitchell TE. Sensory factors in purposive movement. *Journal of Neurophysiology*. 1954; 17(3):239–252. [PubMed: 13163711]
- Voller B, Flöel A, Werhahn KJ, Ravindran S, Wu CW, Cohen LG. Contralateral hand anesthesia transiently improves poststroke sensory deficits. *Annals of Neurology*. 2006; 59(2):385–388. [PubMed: 16358329]
- Volpe BT, Huerta PT, Zipse JL, Rykman A, Edwards D, Dipietro L, Hogan N, Krebs HI. Robotic devices as therapeutic and diagnostic tools for stroke recovery. *Archives of Neurology*. 2009; 66(9):1086–1090. [PubMed: 19752297]
- Voss DE. Proprioceptive neuromuscular facilitation. *American Journal of Physical Medicine & Rehabilitation*. 1967; 46(1):838–898.
- Wan CY, Schlaug G. Music making as a tool for promoting brain plasticity across the life span. *The Neuroscientist*. 2010; 16(5):566–577. [PubMed: 20889966]
- Ward NS, Cohen LG. Mechanisms underlying recovery of motor function after stroke. *Archives of Neurology*. 2004; 61(12):1844–1848. [PubMed: 15596603]
- Whitall J, McCombe Waller S, Silver KH, Macko RF. Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. *Stroke*. 2000; 31(10):2390–2395. [PubMed: 11022069]
- Wolpert DM, Ghahramani Z, Jordan MI. An internal model for sensorimotor integration. *Science*. 1995; 269(5232):1880–1882. [PubMed: 7569931]
- Wu CW, van Gelderen P, Hanakawa T, Yaseen Z, Cohen LG. Enduring representational plasticity after somatosensory stimulation. *Neuroimage*. 2005; 27(4):872–884. [PubMed: 16084740]
- Wu CY, Huang PC, Chen YT, Lin KC, Yang HW. Effects of mirror therapy on motor and sensory recovery in chronic stroke: A randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*. 2013; 94(6):1023–1030. [PubMed: 23419791]
- Xerri C, Merzenich MM, Peterson BE, Jenkins W. Plasticity of primary somatosensory cortex paralleling sensorimotor skill recovery from stroke in adult monkeys. *Journal of Neurophysiology*. 1998; 79(4):2119–2148. [PubMed: 9535973]
- Yang S, Hwang WH, Tsai YC, Liu FK, Hsieh LF, Chern JS. Improving balance skills in patients who had stroke through virtual reality treadmill training. *American Journal of Physical Medicine and Rehabilitation*. 2011; 90(12):969–978. [PubMed: 22019971]
- Yavuzer G, Selles R, Sezer N, Sütbeyaz S, Bussmann JB, Köseo lu F, Atay MB, Stam HJ. Mirror therapy improves hand function in subacute stroke: A randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*. 2008; 89(3):393–398. [PubMed: 18295613]
- Zeman BD, Yiannikas C. Functional prognosis in stroke: Use of somatosensory evoked potentials. *Journal of Neurology, Neurosurgery & Psychiatry*. 1989; 52(2):242–247.

Fig. 1. Schematic representation of the major sensory influences on the (cortical) motor system, and the related sensory-based approaches to post-stroke motor rehabilitation.