Chapter

Clinical Usefulness of Real-time Sensory Compensation Feedback Training on Sensorimotor Dysfunction After Stroke

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Abstract

The sensory dysfunction after the stroke also greatly affects motor function. In particular, it is known that the presence of sensory dysfunction in the fingers causes loss of somatosensory muscle reflex control and excessive muscle output when grasping objects. These are called sensorimotor dysfunction and have been shown to have a significant impact on prognosis. One element to improve this dysfunction is to reconstruct the "Sense of Agency (SOA) subject feeling" and it has become clear that SOA is enhanced by matching the collation information related to motor intention and sensory feedback in time. In order to reconstruct the SOA associated with the movement of the fingers of patients with sensorimotor dysfunction, it is important to match motor intentions while using visual information as compensation for tactile sensory information. Furthermore, considering the functional characteristics of the fingers, it is also important to adjust the fine muscle output from feedback information synchronously discriminating and recognizing somatosensory information generated by resistance, friction, etc., when an object is actively touched. This chapter outlines the importance of rehabilitation of sensory feedback for poststroke sensorimotor dysfunction and investigates the usefulness of intervention with a real-time sensory compensation feedback system that can input tactile sensory information via vibratory stimulation (deep sensation) to other body parts where sensory function is preserved.

Keywords: stroke, rehabilitation, sensorimotor dysfunction, neurofeedback, sensory feedback, sense of agency, EEG

1. Introduction

Stroke is one of the main diseases that cause sequelae disorders [1], typically including chronic sensory and motor dysfunction in the body [2]. These disorders are often not isolated but occur in combination with poststroke sensorimotor impairment (PSI). PSI in the hand, in particular, has a significant impact on functional disability, behavior, lifestyle [3], and quality of life (QOL) [4]. PSI limits the scope of the exercises and activities an individual can perform and is a factor in the degree of reliance on caregivers. One approach to this is neurorehabilitation. Neurorehabilitation is a concept or intervention approach that seeks to improve disability through interdisciplinary interventions that include physiotherapy. For successful rehabilitation of patients with different symptoms, it is important to identify the causative mechanisms of the disability and implement an individually optimized approach [5]. For this reason, it is important to input sensory feedback information properly in relation to motor images and intentions, without any time lag [6]. As a result, the sense of agency (SOA), which is one of the elements of body awareness, —'it is you yourself who moves your hand,'—increases and motor learning advances [7]. Since the primary motor cortex (M1) and coordinated activities in the parietal cortex area are involved in the SOA [8], enhancing the SOA may improve hand function by activating the nervous system for motor control centered in the corticospinal tract. However, there are no established treatments for PSI of the hand based on these perspectives, and improving hand dexterity remains a difficult task. This paper summarizes the impact of hand PSI on the body and mind and the approaches taken to date; further, the effectiveness of an intervention using a real-time feedback system for tactile perception discrimination as a new approach is discussed.

2. Concept of sensory disturbance as a sequela of stroke

Stroke is a general term for a disease in which the function of the brain is impaired due to abnormalities in the blood vessels in the brain. Blood clots form in the brain, blocking blood flow, clogging arteries, breaking blood vessels, and causing bleeding. If the myriad arteries in the brain rupture, the lack of oxygen leads to the sudden death of brain cells. Most strokes (87%) are ischemic infarctions [9]. Stroke is the second leading cause of death worldwide and the third leading cause of residual disability due to its severe impact on the brain and a large number of cases. The incidence of stroke increases with age, doubling after 55 years of age. However, in an alarming trend, between 1990 and 2016, strokes among people aged 20–54 years increased from 12.9% to 18.6% of all cases worldwide. Nevertheless, age-standardized cause mortality decreased by 36.2% in the same period [10]. All this means that while the rates of lives saved are increasing due to developments in medical care, the number of people with poststroke sequelae are also increasing. Additionally, it means that the socioeconomic burden of stroke patients with sequelae is increasing over time [11]. Therefore, despite advances in stroke management, poststroke care has a significant impact on families, the health system, and the economy. Thus, improvements in preclinical and clinical care may support not only the primary treatment of stroke but also successful recovery, rehabilitation, and prevention of sequelae. Therefore, stroke management systems need to include physiotherapy approaches in addition to existing primary care, as well as postdischarge occupational therapy and follow-up at poststroke care facilities.

One of the most serious sequelae after a stroke is hemiplegia, which consists of motor and sensory paralysis. Hemiplegia is a typical neurologically altered condition that can lead to physical and mental disability and affect daily living and quality of life. Therefore, 25–50% of stroke survivors require some form of assistance after discharge from the hospital. It is estimated that only 14% can recover sufficiently to perform activities of daily living [12]. While it is well known that motor paralysis affects motor function, sensory dysfunction of the upper extremities is also impaired in approximately 50–80% of adults after stroke, significantly limiting their ability to use the upper extremities [13–15]. This is poststroke sensorimotor impairment (PSI). Since these impairments not only interfere with sensory input but also diminish the use of the paralyzed upper extremity, PSI patients receive less sensorimotor information in daily life and are also more susceptible to factors such as vision, attention, and active awareness of working with objects [16]. Since they are constantly in this state, their attribution strategy can change, possibly resulting in misattribution even in the performance of the unparalyzed upper limb [17]. These factors make an approach to PSI, especially of the upper extremities, an important factor in constructing rehabilitation programs that improve the physical function and living ability of stroke patients.

3. Post-stroke sensorimotor impairment (PSI)

To date, most studies on upper limb motor function and recovery after stroke have been discussed in terms of brain plasticity. With normal brain function, upper limb movements the brain functional areas that govern them have a contralateral relationship, but after stroke this contralateral dominance pattern changes within a few weeks and the left-right difference decreases [18]. The poststroke period is characterized by activity in both hemispheres, and increased neural activity in the entire motor-related area has been reported [19]. In patients with right hemiplegia, brain activity associated with movement of the right upper extremity showed increased mobilization of the left dorsal premotor cortex (PM) and bilateral supplementary motor areas (SMA), in addition to shifting to the right hemisphere motor-related region (**Figure 1**). Moreover, the probability of mobilization of bilateral neural activity in many motor-related areas increases with the severity of paralysis [20], and the grip strength of the paralyzed hand is associated with the size of the motor-related cortical map being mobilized.

Accurate movement execution requires preparation, execution, and monitoring mechanisms based on network neural activity centered in the frontal lobe, parietal lobe, basal ganglia, and cerebellum, as well as motor-related areas [21]. Preparation and execution are performed by activation of the motor-related area systems, such as SMA and PM, to generate the preparatory potentials and preactivation of peripheral muscles necessary for purposeful exercise. The monitoring mechanism is the detection of sensory errors by the cerebellum and basal ganglia from the actual sensory input (feedback model) and the sensory information (forward model) predicted in advance. That error information is transmitted to the primary sensory cortex (S1), SMA, and PM. M1 receives the motor plans from the SMA and PM and generates the efference copy information, which is the basis of the forward model, and it constantly transmits to the parietal association area for comparison with the sensory feedback information. The sensorimotor integrative loop for enaction is the series of steps that must work properly to enable synaptic movement (**Figure 2**) [21]. This enables purposeful movements. The breakdown of these loops provokes unintentional involuntary movements. Therefore, while motor-related areas are strongly involved in muscle exertion in gross motor activities, such as grip strength, somatosensory areas are more active in the performance of skillful fine motor movements with the hands. In fact, by inputting the somatosensory information of the hand, the somatosensory area accurately represents the shape of the hand in the brain, integrates the necessary motor commands, and performs the selective activation of the muscles necessary for activities such as manipulating objects [22].

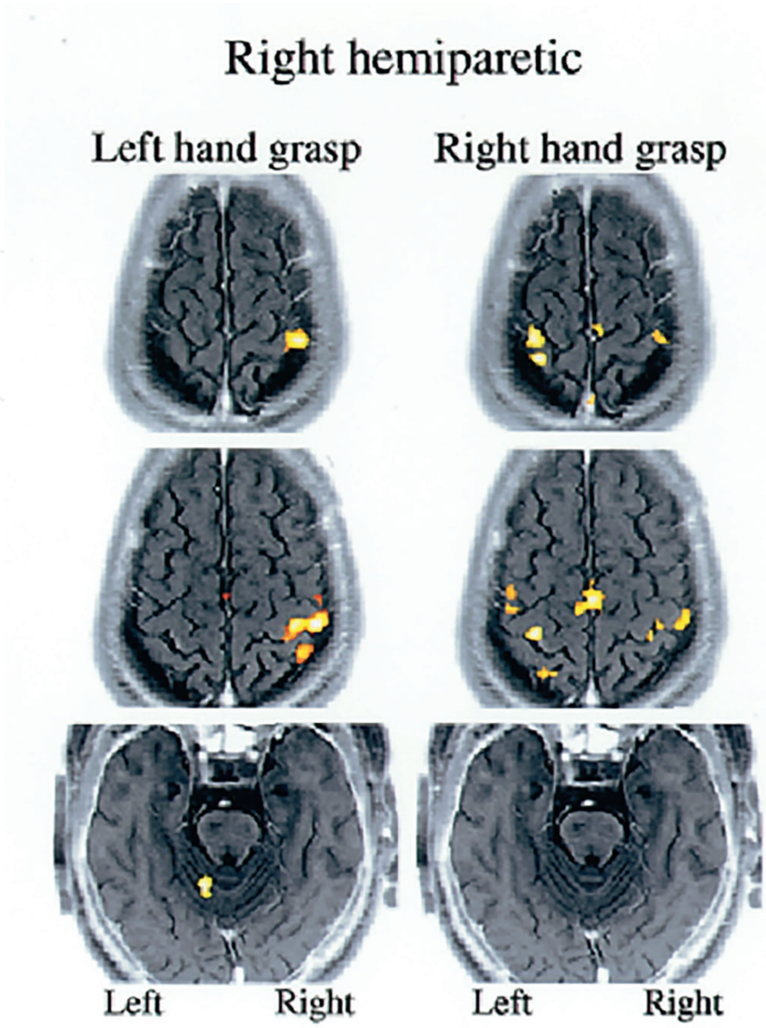

Figure 1.
In patients with post-stroke right hemiparesis, grasping movements of the paralyzed hand (right hand) showed a lateral shift of the motor cortex to the right hemisphere and increased neuromobilization of the left dorsal premotor cortex and bilateral supplementary motor cortex [19].

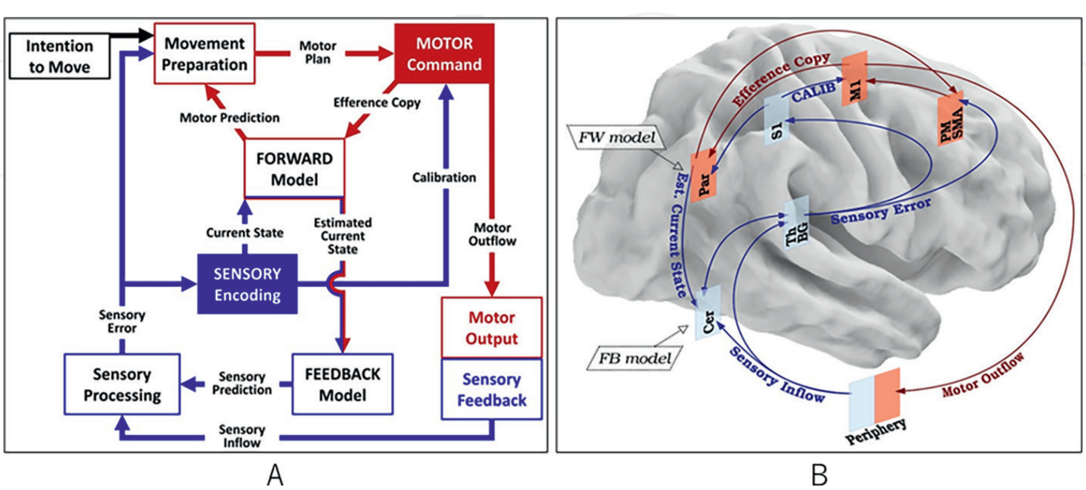

Figure 2.
Schematic diagram of the sensorimotor integrative loop for enacting (A) and the biological brain basis (B) [21]. The blue arrows indicate the flow of sensory feedback information, and the red arrows indicate the flow of forward information such as motor command, motor plan, and efference copy. In particular, the efference copy is an important element for comparing and predicting the kinaesthetic (forward model) and somatosensory (feedback model) consequences.

This suggests that if sensory information from the hands is not inputted into the brain, the selective activation of muscles needed for skillful movements may not occur, thereby causing problems in using the hands for movements such as using tools or buttoning a shirt. PSI of the hand caused by this sensory dysfunction has been reported to result from damage to the central nervous system's afferent pathways, such as the somatosensory area [23]. When these symptoms appear, the ability to perform the activities of daily living is greatly reduced and daily life becomes difficult [24]. Doyle et al. [13] reviewed 13 reports of various treatment interventions for upper extremity sensory impairment in 467 participants. They found that only two studies examined each specific intervention. and in many cases, there was insufficient evidence to support or refute their effectiveness in improving participants' functional status and participation. Therefore, they indicated the need for more appropriately designed and better-reported sensory rehabilitation studies. To solve these problems, it is necessary to grasp the sequence of the information processing mechanisms between the hand and the brain for somatosensory information to be connected to movement, from a neurological perspective, and put the elements required for that into the conditions of the intervention technique.

4. Effects of sensorimotor disorders on the hand

4.1 Neurological functioning of the hand

When manipulating an object, humans have a variety of inputs from tactile afferents in the hand to the brain, including the time course, magnitude, direction, and spatial distribution of contact forces, the shape of the contact surface (texture, roughness, softness, etc.), and friction between the contact surface and the fingers [25, 26]. To skillfully capture such tactile information, Meissner bodies, Merkel cells, Ruffini endings, and Pacinian corpuscles are located in the finger pads. These tactile afferents classify mechanical stimuli from the viewpoints of adaptation and receptive fields (**Figure 3A**); however, FA-II (40–400 Hz), which is predominantly Pacinian corpuscles, is sensitive to dynamic skin deformations at relatively high frequencies, and SA-II, which is mainly Ruffini corpuscles, is most readily excited by low-frequency skin deformation and can respond to sustained deformations [27]. FA-II and SA-II afferent nerves innervate the hand with a low and almost uniform density, ending deeper in the dermis and subcutaneous fibrous tissue. Hundreds of FA-II afferent nerves, distributed throughout the hand, increase neural excitation when the hand contacts or breaks contact with an object. SA-II afferent nerves, in contrast, respond to remotely applied lateral stretching of the skin and are sensitive to tangential shear strain to the skin that occurs during object manipulation [28, 29]. These sensory receptors are capable of discriminating differences in roughness and friction in detail (**Figure 3B**).

Therefore, it is possible to input information in response to various friction coefficients generated between the hand and the object due to the difference in spatial frequency characteristic information that can be captured. When humans manipulate an object, they need to hold the object statically and react and control the sharp friction generated in the finger pad. In particular, the function of the Pacinian corpuscle, which corresponds to the spatial frequency range from the micro to macro levels, plays an important role in hand control. It is a vibration that creates these spatial frequencies. Vibrations caused by friction are transmitted to

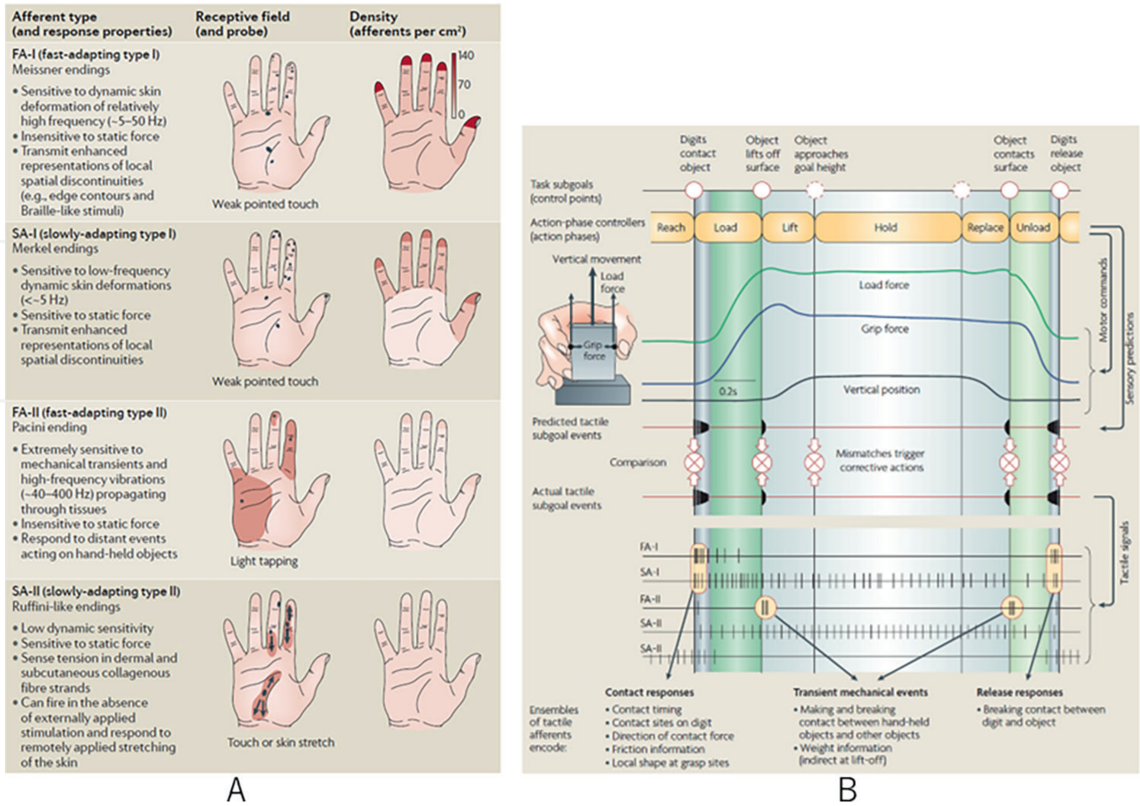

Figure 3.
Tactile innervation of the fingers (A) and sensorimotor control points in an object manipulation task (B) [26]. A: The inside of the human hand is equipped with four functionally district types of tactile afferents. B: Finger-object contact corresponds to a discrete sensory event characterized by the involvement of specific afferent nerves.

tactile receptors in the finger pad, and signals from the tactile receptors i.e., feedback information corresponding to hand movements, are inputs to the brain [30]. By detecting friction information generated when the hand touches the object through this process, the brain controls the force of the fingertip to avoid slipping, and this brain control system makes it possible to manipulate the object without dropping it [31]. Therefore, when considering rehabilitation for PSI after a stroke, it is necessary to compensate for the inputting of the frictional information sensed by the hand as somatosensory information, which is controlled in the brain and converted into execution of movement. This is thought to be important for the reorganization of sensorimotor functioning.

4.2 Problems caused by PSI in the hand

It is known that a decreased sense of belonging for one's own hand due to PSI induces a symptom called learned nonuse, in which the affected hand does not participate in the activities of daily living, independent of the degree of motor dysfunction [32]. This greatly reduces the abilities involved in the activities of daily living [33]. Despite good movement ability, survivors of sensory loss learn not to use their hands to perform tasks [34]. Thus, Carey et al. [35] reported that the somatosensory impairment status poststroke while hospitalized was associated with more loss of participation in activities in the absence of concomitant paralysis, compared with survivors without somatosensory loss. This predictive association was confirmed in a longitudinal cohort (N = 268) study of stroke survivors with mild disabilities. Additionally, PSI has a significant impact on quality of life [36]. All of this suggests that in patients with neurological disease who lose one or more senses the impact on their motor function may be serious, even if their muscle strength is not affected. After a stroke recovery of movement depends on the degree of sensory impairment [37]. Against this background, rehabilitation aimed at restructuring motor function may decrease the outcome of functional recovery in stroke patients unless it encompasses intervention for sensory impairment. Historically, however, clinicians and researchers have prioritized the motor sequelae of stroke and ignored somatosensory impairment [38]. This may be because symptoms arising from sensory disorders are more varied and often rely on the patient's subjective information, in contrast to motor dysfunctions, which can be objectively measured.

If sensory feedback information continues to be properly inputted through the body, top-down control that allows for quick and continuous movement can be achieved. When humans perform exercises and movements, the brain extracts and integrates sensory information on the body position that accompanies them. Concurrently, the body's future sensory state is estimated from motor commands based on higher-order top-down forward information such as memories, intentions, and intentions regarding previous experience and skills. These brain processing systems enable the activation of a predictive mechanism, called the internal forward model, that suppresses predicted sensory feedback [37, 39]. This top-down control, based on motor imagery and SOA, is largely the function of M1, an output mechanism to the corticospinal tract [40]. By utilizing this top-down control, humans can continually minimize the displacement of slip, when the hand contacts an object, without relying on sensory feedback information. Additionally, top-down control is constructed by continuous synchronous and sensitive feedback of friction information, e.g., vibration stimulus information inputs from the sensory receptors of the fingers to the brain, which is generated when the hand touches an object. Therefore, in rehabilitation, it is important to have an approach that enables continuous feedback of hand-touch friction information in a synchronous and precise manner. However, since it is difficult for PSI patients to precisely grasp sensory information from their hands, it is crucial to construct an approach theory that provides them with compensatory input stimuli and enhances their learning efficiency.

4.3 PSI of the hand and transformation of body awareness

Body awareness is self-body recognition and is the brain's systemic basis for motor development. This ability enables humans to recognize differences between themselves and others, as well as between themselves and the outside world, and to adapt their bodies to their environment. It has been reported that body awareness causes schizophrenic-like symptoms, such as hands that feel alien, like someone else's hands, or that someone is inserting such thoughts [41]. Gallagher et al. [41] have shown that it is important to have a "minimal self" to activate body awareness. The minimal self is the "immediate awareness of oneself as a body" through daily exercise and life experience. There is no need for oneself to be aware of that here. This allows for the identification of two separate modalities: the sense of ownership (SOO), which states that one's body is oneself, and the SOA, which states that one is the one running one's body.

SOO is explained by a phenomenon called the rubber hand illusion [42]. This phenomenon is an illusion in which an inanimate rubber hand feels like one's own hand. The illusion is induced by blocking the visual information of the rubber hand and the patient's actual hand and stimulating tactile information to the skin synchronously (misalignment is within a few hundred milliseconds). This suggests that human body recognition can be altered by a specific stimulus presentation, which is a vital discovery for the study of human body awareness. The sensation of possessing a rubber hand is accompanied by a change in hand position sense (proprioception), therefore, when patients are asked to indicate the location of their (invisible) hand, they indicate that it is near the rubber hand. This is known as intrinsic receptive drift and is the most widely used objective measure of the rubber hand illusion, suggesting a close relationship between intrinsic receptivity and a sense of body ownership [43]. This sense of physical ownership is generated by the integrated processing of somatosensory and visual information within the parietal lobe [44], and it has been reported that alterations in the sense of body ownership, for example, tend to produce illusions and phantom limb pain in limb amputees [45].

In contrast, an SOA is a basis for the creation of cooperative neural network activity in the prefrontal cortex [46] and, in addition to M1 [8], the insular cortex (especially the anterior regions), lower parietal lobe regions (supramarginal and angular gyri), anterior cingulate gyrus of the cortical midline structure, supplementary motor cortex, posterior cingulate gyrus, and precuneus of the cortical midline structure are involved in the formation and the establishment [47]. The comparative matching of motor intention and sensory feedback information is generated by synchronous processing in the brain [7], and the sense of subjectivity diminishes with a temporal lag (**Figure 4**) [48]. Previous studies have also shown that an SOA is created if the misalignment is within 500 ms [49].

The following four explanatory models and concepts can be used to explain the SOA:

1. Time axis of the predictive and postdictive processes.

2. Axis of awareness of the explicit and implicit levels.

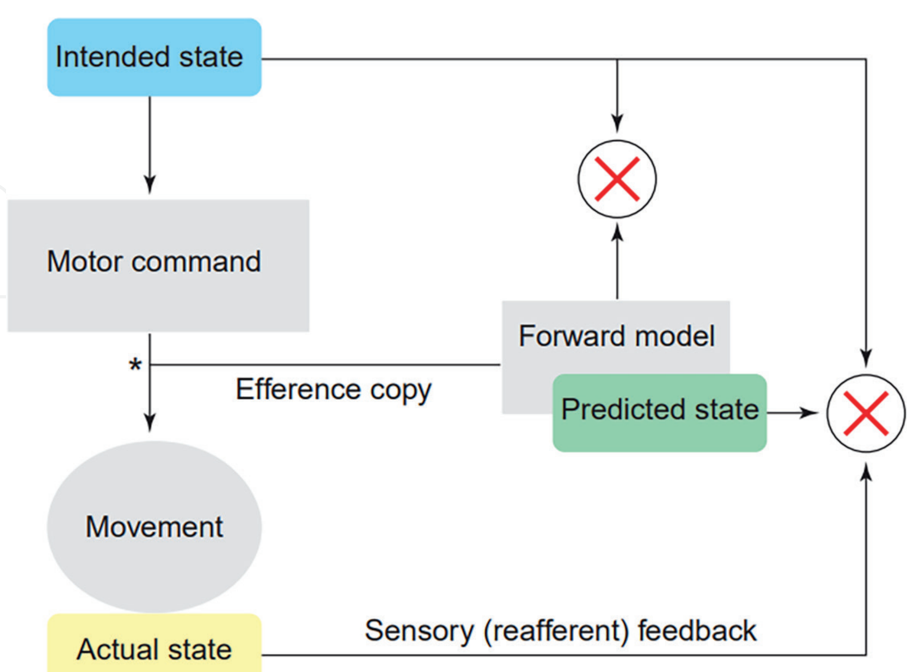

Figure 4.
The forward and feedback comparators [43]. Agreement in the forward comparator provides motor subjectivity to the movement.

3. Directed axes called internal cue and external cue.

4. A learning perspective that the sense of subjectivity is continually being renewed.

Point (1) is a perspective that includes a forecasting model. In general, an SOA is only a part of the self-consciousness associated with the act and is a feeling that can only be experienced after the act, but it can be modified by the postprocess, such as rewards obtained as a result of the act. Point (2) is a view of the hierarchy of conscious (conscious) and subconscious (unconscious) processes. Point (3) is that the SOA is supposed to be established based on various internal and external cues. Internal cues include intentions, objectives, plans, goals, predictive signals, priming, beliefs, knowledge, effort, and expectations of reward, while external cues include the effects of the action, contextual information, and rewards. The optimal SOA is based on the availability and reliability of each. The last point (4) is taken in terms of larger dynamics but is meant to be taken from the perspective of learning, where mechanisms such as these are not innate and fixed, but constantly updating as humans survive and adapt to their environment.

Furthermore, Synofzik et al. [50] state that an SOA exists hierarchically, with sensory and cognitive levels. An SOA generated by the temporal matching of information on movement intention and sensory feedback, as described above, is the feeling of agency (FOA) at the sensory level. Meanwhile, judgment of agency (JOA) is generated at the cognitive level when conceptual reasoning about discrimination of action types is processed and the status of SOA is made conscious in a form that can be verbalized. Therefore, it has been reported that even if the one executing a movement is the person himself or herself and if the actual sensory outcome deviates from the prediction, it may induce a decreased sense of body ownership and abnormal perceptions, such as numbness [51, 52].

Regarding alterations in body awareness in patients with PSI, it has been reported that SOA reduction is likely to induce involuntary movements [53], impair motor conversion [54], and reduce motivation and performance [55] during congruent movements. In PSI, the inputted sensory information is attenuated, resulting in, for example, inattention or indifference to the affected hand. Working to reorganize body awareness through neurorehabilitation may lead to active use of the affected hand and build a foundation for conscious and active movement in daily life.

5. Rehabilitation for PSI

5.1 Standard rehabilitation approach to PSI

Goal-oriented sensory input training after stroke hemiplegia [56] includes real-time feedback approaches to electrical, visual, and auditory stimulation, and more recently, robot-aided rehabilitation.

It has long been reported that real-time electrical stimulation of finger extensor muscles in response to voluntary movements produces excitation in the contralateral M1 and S1 regions and that electrical stimulation has the potential to improve hand motor function [57]. This approach is still being utilized today, with a 2019 study [58] describing the case of a 76-year-old male patient with hemiplegia for 8 years who underwent integrated volitional control electrical stimulator (IVES) treatment of the right flexor pollicis brevis, abductor pollicis brevis, and ulnar carpal extensor muscles. Upper limb function improved in a short period. This means that even those who have reached a plateau after a stroke may experience functional recovery of the upper extremity. Such functional improvements enhance active muscle control, suggesting that hand function is unlikely to improve if passive muscle contraction stimulation does not reach the electrical threshold for muscle contraction trigger stimulation [59]. Furthermore, it has been reported that electrical stimulation is effective in patients with mild to moderate paralysis who can actively move their hands, but less effective in patients with severe paralysis who cannot move their hands [60]. Electrical stimulation also allows patients with severe sensory dysfunction of the hand to perform movements, such as grasping cylinders and holding objects, but is less effective for skillful movements such as those performed while constantly moving the fingertips [61].

For visual stimuli, there is an approach to feedback visual information called mirror therapy [62]. Mirror therapy is an approach in which a mirror image of the healthy hand is presented in a mirror to create the illusion that the affected hand is moving as desired and to create the neural basis in the brain for the expression of motor execution. Mirror therapy has been reported to improve motor function in chronic stroke patients with mild sensory impairment and mild to moderate motor impairment [63]. Neural activity activated by this approach occurs in the primary motor cortex, precuneus, and posterior cingulate cortex, and these regions form a potential neural correlative network [64]. This means that for those who have developed discrepancies between different senses, such as visual and proprioceptive, mirror therapy may contribute to output coordination between motor output and sensory input. However, it has been noted that mirror therapy is effective only when the patient believes that "the hand in the mirror (the healthy limb) is his or her actual hand (the affected limb)" [65]. One possible reason for this is that in mirror therapy, the movement of the affected limb is not the result of movement due to active motor intention for the affected limb. It has been reported that a discrepancy between active motor imagery or intention and passive sensory information can induce abnormal perceptions, such as numbness [52], which may further degrade body awareness.

For auditory stimuli, auditory feedback is real-time phonological feedback on congruent movements, which promotes plastic changes in M1 and auditory-sensorimotor circuits and facilitates motor learning. Auditory feedback also involves M1 and auditory and integrative auditory-sensorimotor circuits [66]. However, the effects of auditory feedback on the motor learning process and the combination with other modalities, such as visual and tactile feedback, have not yet been studied in detail, so intensive experimental work will be required in the future [67].

Regarding robot-aided rehabilitation, robotic devices could help automate repetitive poststroke training in a controlled manner and increase treatment compliance by introducing them to patients [68]. The use of robotic devices allows patients to actively engage and thus perform advanced repetitive motor training, which may facilitate the reorganization of cranial nerve function and improve poststroke recovery [69]. Additionally, changes in patients can be assessed in terms of kinematic parameters, e.g., position and velocity, to capture the quantitative changes in intervention effectiveness [70]. At this point, however, the actual effectiveness of robotic training after stroke is still under debate. A review of randomized controlled trials reported that patients who received robot-assisted arm training after stroke had improved arm motor function but were not more likely to have improved activities of daily living compared to patients who received standard rehabilitation therapy [71].

5.2 Proposed new rehabilitation technique for PSI

Early intervention, task-oriented training, and intensity of repetition have been identified as determinants of motor function recovery [72]. Many rehabilitation approaches have been developed for PSI of the hand, and some effectiveness has been reported in restoring gross motor control of the hand (see 5.1. Standard Rehabilitation Approaches for PSI). However, since the hand is a part where tactile information inputs are due to minute friction from the finger pad, fine muscle adjustments are made to make it possible to manipulate an object without dropping it. It is often not possible to obtain fine adjustment strength using the muscles of the hands by simply providing strong or weak electrical or auditory feedback in response to hand movements. Additionally, an object can be grasped and controlled by synchronously matching visual information with hand movements, but visual information is used initially to define the kinematic plan of the reaching movement in the external coordinate system, and then the sensory receptors are used to coordinate the hand's motor output [73]. Therefore, the reliance on visual information lacks sensory information to monitor information inside the body, resulting in excessive hand motor output and uncontrolled dynamic friction.

What is important in rehabilitation for the functional reorganization of PSI is to restructure the body's awareness, to sense body ownership without being conscious of it, and, in other words, to be able to actively work on the paralyzed limb. So how do we develop a strategy for transformative body awareness restructuring?

As we have discussed, top-down control is responsible for predictive motor control and enables skillful movements with the hands. Since this control is built by the establishment of motor learning, it is important to establish motor learning to restore hand-motor function. Motor learning is the process of constructing and memorizing a new motor program and mastering that program and it enables behavior to adapt to the environment [74]. This neural basis is formed against a background of neuroplasticity in the brain's sensorimotor system centered on M1 and S1 [75]. The establishment of this motor learning is also closely related to the establishment of FOA and JOA in SOA. Improvement of SOA has the potential to increase neural excitation in PM, M1, and the corticospinal tracts and improve hand dexterity movements.

A necessary part of motor learning to enhance SOA is to work in situations where motor intention and sensory feedback are as temporally congruent as possible [76, 77]. Furthermore, regarding the stimulation of feedback in actual training, not only is the quantity an important factor in motor learning [37] but also the quality of feedback optimized for the body's condition and the envisaged movements [6, 78, 79]; it is important to take a comprehensive view and approach to these issues. The result is top-down control without sensory feedback stimulation [80, 81].

Based on these theories, to reconstruct body awareness associated with hand movements, in addition to synchronous matching of visual information at the expense of sensory information, a compensatory function that detects the dynamic friction that occurs when the hand touches an object in real-time is needed. Therefore, Kitai et al. [82] devised and verified an approach for sensory compensation by vibrational stimuli for vibration information (deep sensations). The deep senses are excellent at detecting pressure changes and mechanical forces associated with joint movement and transmitting them to the brain. This allows for motion control [83]. We will present a study that examined whether these concepts play a role in PSI and the impact they have on the neurological function of stroke patients.

6. Sensory compensatory training with tactile discrimination feedback training

6.1 Experiment

When the brain controls the body's movement, intrinsic receptors in muscles contribute greatly to its realization. The significant contribution of proprioceptive sensation to motor control is evidenced by a study [84] that reported that patients with proprioceptive disorders are unable to move their fingers well. In particular, PSI of the hand causes loss of reflexive control of muscles using somatosensory cues, resulting in variable muscle output when grasping an object with the hand [85]. Therefore, improving this dysfunction requires an increase in the SOA generated by temporally matching the information on motor intention and sensory feedback. This enables the hand to actively touch an object based on its functional characteristics, and real-time feedback information, based on recognition and discrimination of precise changes in sensory information caused by resistance and friction at the time of touch, enables fine adjustment of muscle output. In this study, we used the Yubi-Recorder (Tech Giken Co., Ltd., Kyoto, Japan), a real-time feedback system that enables compensatory input of tactile sensory information by vibrational stimulation (deep sensation) to other body parts with preserved sensory function, and verified the effectiveness of this approach.

6.1.1 Method

6.1.1.1 Participant

The participant was a 52-year-old right-handed man who had a right putaminal hemorrhage approximately 4 years ago and a right corona radiata infarct approximately 1 year later. The left hand was numb on a level of 11 on the Numerical Rating Scale (NRS) (0: not at all, 10: extremely strongly), with 10 indicating extremely strong numbness. There was also a loss of somatosensory and warm/pain sensation in the left upper and lower extremities. Motor paralysis was Brunnstrom stage III in the left upper extremity and IV in the left fingers. In the left-handed dexterity task, the patient needed the ability to carry small objects but had difficulty controlling object manipulation due to hand ataxia. The SOA of the left hand was decreased to 2/10, and sensorimotor dysfunction of the left hand was suspected due to the patient's complaint of "not being able to feel my hand."

6.1.1.2 Experimental procedures

To evaluate the immediate effects of training with the Yubi-Recorder on PSI in the left hand, we first performed a peg task with and without the Yubi-Recorder and then analyzed neural activity by EEG immediately after the task in both conditions. Next, to evaluate the intervention effect of training with the Yubi-Recorder, exercise tasks using the Yubi-Recorder were performed five times a week for 30 minutes/session for 6 weeks, and EEG activity were compared and analyzed after the first and last training sessions. The Yubi-Recorder is a device that can measure vibration information by detecting the vibrations that occur in the skin when the hand touches an object. **Figure 5** shows an example of a person wearing the Yubi-Recorder and performing an exercise task. The Yubi-Recorder system is capable of sensing information on the

Figure 5
shows an example of a person wearing the Yubi-Recorder and performing an exercise task. A sensor attached to the left index finger senses friction information on the object, which is transmitted to a small speaker-like oscillator on the face (the mapping of the finger and face in the brain are adjacent) and fed back as compensatory deep sensory information.

unevenness, flatness, curvature, and roughness of an object and can capture tactile stimuli from any shape, thus accommodating the multidirectional motion that is characteristic of fingers. The sensor is wound around the distal interphalangeal joint of the index finger, and the output from the sensor is modulated to a frequency that is perceived by humans, enabling the presentation of vibration information via a transducer. In this study, the device was attached to the distal interphalangeal joint of the index finger, tactile information on the ventral skin of the index finger was detected as vibration by a tactile sensor, and the tactile stimulus was synchronously presented to the user's own body, through a transducer, as a vibratory stimulus. The site of attachment of the transducer was the left acromion or the left temporal bone used in the vibratory sensory examination. The method used to select the vibrator attachment was to apply five different types of sandpaper to the left acromion or left temporal bone, and the area where the roughness of the sandpaper could be identified was determined to be the area where sensory compensation could be performed. The motor tasks were to insert a steel pin with the left hand (hereafter referred to as the peg task) to stack square blocks with a base length of 3 cm used in the course cube test with the left hand and to discriminate five sandpaper pieces using the ventral part of the left index finger; each task for 10 minutes (30 minutes total).

6.1.1.3 EEG analysis

EEG measurements were derived from 15 sites in accordance with the International 10–20 method. The measured data were spatially analyzed using exact low-resolution brain electromagnetic tomography (eLORETA) analysis, a three-dimensional method of imaging neural activity in the brain. The EEG data was then calculated as brain activity values (μV/mm^2) for each task condition on each voxel in a brain region divided into 6239 voxels and expressed as Brodmann area (BA) or Montreal Neurological Institute (MNI) coordinates [86]. An eLORETA-based SnPM analysis was used to compare the Yubi-Recorder results before and after the intervention [87].

6.1.2 Results

The immediate effect was high neural activity in the non-Yubi-Recorder condition, mainly in the left orbitofrontal cortex, left dorsal anterior cingulate cortex, left dorsolateral prefrontal cortex, and left supplementary motor cortex (**Figure 6A**). In the Yubi-Recorder condition, high neural activity was observed, mainly in the bilateral primary somatosensory cortices and the bilateral superior parietal and inferior parietal lobes (angular and supramarginal gyri) (**Figure 6B**).

Regarding the effect of a 6-week intervention with the Yubi-Recorder, higher neural activity was observed in the final session compared to the first session, mainly in the areas of both primary somatosensory cortices, both superior parietal lobes, both inferior parietal lobes (angular and superior marginal gyri), and the primary motor areas (**Figure 7**). The peg test showed an improvement in the left mean from 1.5 ± 0.5 to 3.0 ± 1.0, and the learnability assessment showed an improvement in the NRS of the SOA of the left hand from 2/10 to 5/10. A motor activity log, consisting of quality of movement items, also showed improvement.

6.1.3 Discussion

In this study, in addition to synchronous matching of visual information with hand skillful movement tasks, an approach using a system device, the Yubi-Recorder, which feeds vibration information back in real time, was used to improve hand PSI. The effects of this approach were investigated.

EEG verification of immediate effects showed increased neural activity in regions of the left frontal lobe responsible for cognitive and motor functions in the Yubi-Recorder nonwearing condition. It has been shown that a compensatory increase in neural activity in the healthy motor cortex area inhibits the recovery of function in

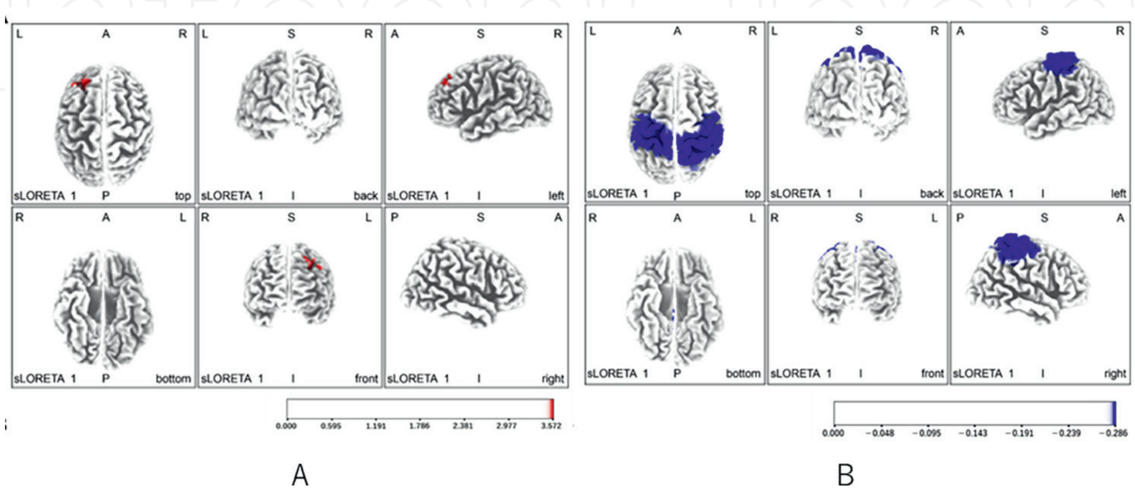

Figure 6.
Brain regions with immediate increased neural activity in the Yubi-Recorder non-attached condition (A) and attached condition (B) [85].

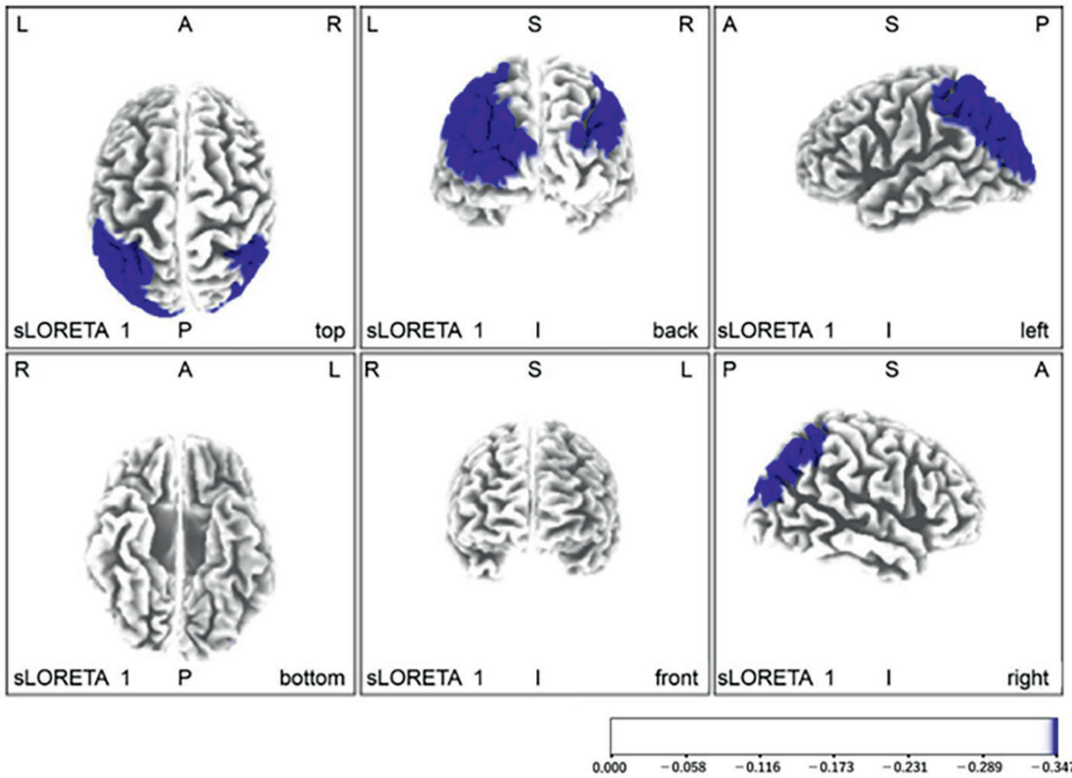

Figure 7.
Brain regions with increased neural activity after 6 weeks of Yubi-Recorder training [85].

the affected hand (interhemispheric inhibition [88]. Conversely, learned nonuse is said to progress if the patient fails to perform the intended movement even when using the affected limb [32]. The decreased SOA in this case also suggests that information collation on motor intent and sensory feedback did not match temporally and that the patient may have learned that the intended movement failed, suggesting that the left hand was not used. In contrast, the Yubi-Recorder resulted in increased neural activity in both sensorimotor cortices. Information flowing from the primary somatosensory cortex is integrated with auditory and visual information in the superior and inferior parietal lobes and stored as comprehensive cognitive information [89, 90]. The information needed for movement is then sent to the primary motor cortex, and hand-motor control is performed in the same region [91]. Thus, compensatory sensory input by the Yubi-Recorder may have immediately activated the sensorimotor areas and enhanced motor control of the left hand by making full use of these areas.

The results of the 6-week intervention were increased neural activity in the bilateral sensory and parietal association cortices and the primary motor cortex. Based on these findings, we hypothesized that 6 weeks of training with the Yubi-Recorder in this study improved peg-test performance by enabling top-down control using the sensorimotor domain during skillful movements. The motor activity log results also showed an improvement in the frequency of left-hand use and quality of movement in daily life. Motor learning is believed to produce behavioral change [92], and it is thought that the improvement in SOA in the present case also improved the frequency of left-hand use and the quality of movement in daily life.

These results indicate that training with the Yubi-Recorder can help reorganize top-down control and body awareness by cooperatively engaging the frontal lobe, where motor-related areas reside, and the parietal lobe, which is responsible for perceiving and integrating sensory information. This may serve as a rehabilitation tool for sensorimotor dysfunctions, such as PSI. This has shown the possibility of rehabilitation for sensorimotor dysfunctions, such as PSI.

7. Conclusion

Hands are an indispensable part of human daily life. In particular, to restore the most important function of the hand, "touch," it is necessary to understand that tactile perception between the hand and the object is produced by a very different principle, whether the tactile perception between the hand and the object is active or passive. In other words, we should always keep in mind that in active tactile perception, exploration takes place in the process of sensory reception, and that as stimuli, the motion command information for exploration is as important for the establishment of active tactile perception as the sensory reception information.

In the rehabilitation of hand PSI, which is the theme of this article, it is also outlined that it is of utmost importance to identify the causative mechanism of disability and implement an individually optimized approach. As an example, we showed the possibility of activating the sensorimotor domain and reorganizing body awareness by utilizing a device that provides real-time feedback on the vibrations that occur in the skin when an object is touched by a hand. We believe that the ideas described herein will be useful for therapists seeking to improve sensorimotor disorders worldwide.

This article presents several theories of brain function reorganization and motor learning in poststroke PSI patients based on neuroscientific evidence and presents an overview of effectiveness of sensory compensatory training with tactile discrimination feedback training. For this reason, it is important to understand the symptoms of PSI and the current gold-standard treatment. The development of a standardized approach is also essential to reduce treatment disparities among therapists. To extend the effectiveness of the standard approach to the fullest, it is necessary to consider appropriate feedback tailored to the patient's symptoms, such as those presented in this article.

Acknowledgements

This study was part of a research program funded by the JSPS (Grants-in-Aid for Scientific Research 22H03445). The funding source had no role in the study design/concept, data collection/analysis/interpretation, and manuscript preparation/submission.

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References

[1] Ikebe T, Ozawa H, Lida M, Shimamoto T, Handa K, Komachi Y. Long-term prognosis after stroke: A community-based study in Japan. Journal of Epidemiology. 2001;**11**(1):8-15. DOI: 10.2188/jea.11.8

[2] Kanzler CM, Schwarz A, Held JPO, Luft AR, Gassert R, Lambercy O. Technology-aided assessment of functionally relevant sensorimotor impairments in arm and hand of post-stroke individuals. Journal of Neuroengineering and Rehabilitation. 2020;**17**(1):128. DOI: 10.1186/s12984-020-00748-5

[3] Meyer S, De Bruyn N, Krumlinde-Sundholm L, Peeters A, Feys H, Thijs V, et al. Associations between sensorimotor impairments in the upper limb at 1 week and 6 months after stroke. Journal of Neurologic Physical Therapy. 2016;**40**(3):186-195. DOI: 10.1097/NPT.0000000000000138

[4] Meyer S, Karttunen AH, Thijs V, Feys H, Verheyden G. How do somatosensory deficits in the arm and hand relate to upper limb impairment, activity, and participation problems after stroke? A systematic review. Physical Therapy. 2014;**94**(9):1220-1231. DOI: 10.2522/ptj.20130271

[5] Coscia M, Wessel MJ, Chaudary U, Millán JDR, Micera S, Guggisberg A, et al. Neurotechnology-aided interventions for upper limb motor rehabilitation in severe chronic stroke. Brain. 2019;**142**(8):2182-2197. DOI: 10.1093/brain/awz181

[6] Kodama T, Katayama O, Nakano H, Ueda T, Murata S. Treatment of medial medullary infarction using a novel inems training: A case report and literature review. Clinical EEG and Neuroscience. 2019;**50**(6):429-435. DOI: 10.1177/1550059419840246

[7] David N, Newen A, Vogeley K. The "sense of agency" and its underlying cognitive and neural mechanisms. Consciousness and Cognition. 2008;**17**(2):523-534. DOI: 10.1016/j.concog.2008.03.004

[8] Buchholz VN, David N, Sengelmann M, Engel AK. Belief of agency changes dynamics in sensorimotor networks. Scientific Reports. 2019;**9**(1):1995. DOI: 10.1038/s41598-018-37912-w

[9] Kuriakose D, Xiao Z. Pathophysiology and treatment of stroke: Present status and future perspectives. International Journal of Molecular Sciences. 2020;**21**(20):7609. DOI: 10.3390/ijms21207609

[10] Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. Circulation Research. 2017;**120**(3):472-495. DOI: 10.1161/CIRCRESAHA.116.308398

[11] GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;**18**(5):439-458. DOI: 10.1016/S1474-4422(19)30034-1

[12] Zancan A, Rodigari A, Gigli Berzolari F, Borrelli P. Risk factors for long-term care after hemiplegia from cancer-related brain surgery: A pilot study for new prediction model. European Journal of Physical and Rehabilitation Medicine.

2019;**55**(6):735-742. DOI: 10.23736/S1973-9087.19.05840-4

[13] Doyle S, Bennett S, Fasoli SE, McKenna KT. Interventions for sensory impairment in the upper limb after stroke. Cochrane Database of Systematic Reviews. 2010;**2010**(6):CD006331. DOI: 10.1002/14651858.CD006331.pub2

[14] Villepinte C, Catella E, Martin M, Hidalgo S, Téchené S, Lebely C, et al. Validation of French upper limb Erasmus modified Nottingham Sensory Assessment in stroke. Annals of Physical and Rehabilitation Medicine. 2019;**62**(1):35-42. DOI: 10.1016/j.rehab.2018.03.004

[15] Hossain D, Scott SH, Cluff T, Dukelow SP. The use of machine learning and deep learning techniques to assess proprioceptive impairments of the upper limb after stroke. Journal of Neuroengineering and Rehabilitation. 2023;**20**(1):15. DOI: 10.1186/s12984-023-01140-9

[16] van Stralen HE, van Zandvoort MJ, Dijkerman HC. The role of self-touch in somatosensory and body representation disorders after stroke. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2011;**366**(1581):3142-3152. DOI: 10.1098/rstb.2011.0163

[17] Miyawaki Y, Otani T, Morioka S. Dynamic relationship between sense of agency and post-stroke sensorimotor deficits: A longitudinal case study. Brain Sciences. 2020;**10**(5):294. DOI: 10.3390/brainsci10050294

[18] Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, et al. Harnessing neuroplasticity for clinical applications. Brain. 2011;**134**(6):1591-1609. DOI: 10.1093/brain/awr039

[19] Fujii Y, Nakada T. Cortical reorganization in patients with subcortical hemiparesis: Neural mechanisms of functional recovery and prognostic implication. Journal of Neurosurgery. 2003;**98**(1):64-73. DOI: 10.3171/jns.2003.98.1.0064

[20] Ward NS, Brown MM, Thompson AJ, Frackowiak RS. Neural correlates of outcome after stroke: A cross-sectional fMRI study. Brain. 2003;**126**(Pt6):1430-1448. DOI: 10.1093/brain/awg145

[21] Perruchoud D, Murray MM, Lefebvre J, Ionta S. Focal dystonia and the sensory-motor integrative loop for enacting (SMILE). Frontiers in Human Neuroscience. 2014;**8**:458. DOI: 10.3389/fnhum.2014.00458

[22] Winges SA. Somatosensory feedback refines the perception of hand shape with respect to external constraints. Neuroscience. 2015;**293**:1-11. DOI: 10.1016/j.neuroscience.2015.02.047

[23] Borich MR, Brodie SM, Gray WA, Ionta S, Boyd LA. Understanding the role of the primary somatosensory cortex: Opportunities for rehabilitation. Neuropsychologia. 2015;**79**(Pt B):246-255. DOI: 10.1016/j.neuropsychologia.2015.07.007

[24] Suda M, Kawakami M, Okuyama K, Ishii R, Oshima O, Hijikata N, et al. Validity and reliability of the semmes-weinstein monofilament test and the thumb localizing test in patients with stroke. Frontiers in Neurology. 2021;**11**:625917. DOI: 10.3389/fneur.2020.625917

[25] Johansson RS, Flanagan JR. Coding and use of tactile signals from the fingertips in object manipulation tasks. Nature Reviews. Neuroscience. 2009;**10**(5):345-359. DOI: 10.1038/nrn2621

[26] Ryan CP, Bettelani GC, Ciotti S, Parise C, Moscatelli A, Bianchi M. The interaction between motion and texture in the sense of touch. Journal of Neurophysiology. 2021;**126**(4):1375-1390. DOI: 10.1152/jn.00583.2020

[27] Johansson RS, Landström U, Lundström R. Responses of mechanoreceptive afferent units in the glabrous skin of the human hand to sinusoidal skin displacements. Brain Research. 1982;**244**(1):17-25. DOI: 10.1016/0006-8993(82)90899-x

[28] Westling G, Johansson RS. Responses in glabrous skin mechanoreceptors during precision grip in humans. Experimental Brain Research. 1987;**66**(1):128-140. DOI: 10.1007/BF00236209

[29] Knibestöl M. Stimulus-response functions of slowly adapting mechanoreceptors in the human glabrous skin area. The Journal of Physiology. 1975;**245**(1):63-80. DOI: 10.1113/jphysiol.1975.sp010835

[30] Yoshioka T, Craig JC, Beck GC, Hsiao SS. Perceptual constancy of texture roughness in the tactile system. The Journal of Neuroscience. 2011;**31**(48):17603-17611. DOI: 10.1523/JNEUROSCI.3907-11.2011

[31] Maeno T, Kawai T, Kobayashi K. Analysis and design of a tactile sensor detecting strain distribution inside an elastic finger. In: Proceedings. 1998 IEEE/RSJ International Conference on Intelligent Robots and Systems. Innovations in Theory, Practice and Applications (Cat. No.98CH36190). Vol. 3. Victoria, BC, Canada: IEEE; 1998. pp. 1658-1663. DOI: 10.1109/IROS.1998.724836

[32] Taub E, Uswatte G, Mark VW, Morris DM. The learned nonuse phenomenon: Implications for rehabilitation. Europa Medicophysica. 2006;**42**(3):241-256

[33] de Azevedo JA, Barbosa FDS, Seixas VM, da Silva Scipioni KRD, Sampaio PYS, da Cruz DMC, et al. Effects of constraint-induced movement therapy on activity and participation after a stroke: Systematic review and meta-analysis. Frontiers in Human Neuroscience. 2022;**16**:987061. DOI: 10.3389/fnhum.2022.987061

[34] Connell LA, McMahon NE, Adams N. Stroke survivors' experiences of somatosensory impairment after stroke: An interpretative phenomenological analysis. Physiotherapy. 2014;**100**(2):150-155. DOI: 10.1016/j.physio.2013.09.003

[35] Carey LM, Matyas TA, Baum C. Effects of somatosensory impairment on participation after stroke. The American Journal of Occupational Therapy. 2018;**72**(3):7203205100p1-7203205100p10. DOI: 10.5014/ajot.2018.025114

[36] Wu X, Wang R, Wu Q, Liao C, Zhang J, Jiao H, et al. The effects of combined high-frequency repetitive transcranial magnetic stimulation and cervical nerve root magnetic stimulation on upper extremity motor recovery following stroke. Frontiers in Neuroscience. 2023;**17**:1100464. DOI: 10.3389/fnins.2023.1100464

[37] Bolognini N, Russo C, Edwards DJ. The sensory side of post-stroke motor rehabilitation. Restorative Neurology and Neuroscience. 2016;**34**(4):571-586. DOI: 10.3233/RNN-150606

[38] Kalra L. Stroke rehabilitation 2009: Old chestnuts and new insights. Stroke. 2010;**41**(2):e88-e90. DOI: 10.1161/STROKEAHA.109.572297

[39] Fuehrer E, Voudouris D, Lezkan A, Drewing K, Fiehler K. Tactile suppression

stems from specific sensorimotor predictions. Proceedings of the National Academy of Sciences of the United States of America. 2022;**119**(20):e2118445119. DOI: 10.1073/pnas.2118445119

[40] Kodama T, Nakano H, Katayama O, Murata S. The association between brain activity and motor imagery during motor illusion induction by vibratory stimulation. Restorative Neurology and Neuroscience. 2017;**35**(6):683-692. DOI: 10.3233/RNN-170771

[41] Gallagher II. Philosophical conceptions of the self: implications for cognitive science. Trends in Cognitive Sciences. 2000;**4**(1):14-21. DOI: 10.1016/s1364-6613(99)01417-5

[42] Botvinick M, Cohen J. Rubber hands 'feel' touch that eyes see. Nature. 1998;**391**(6669):756. DOI: 10.1038/35784

[43] Abdulkarim Z, Ehrsson HH. No causal link between changes in hand position sense and feeling of limb ownership in the rubber hand illusion. Attention, Perception, & Psychophysics. 2016;**78**(2):707-720. DOI: 10.3758/s13414-015-1016-0

[44] Matsumiya K. Separate multisensory integration processes for ownership and localization of body parts. Scientific Reports. 2019;**9**(1):652. DOI: 10.1038/s41598-018-37375-z

[45] Schmalzl L, Kalckert A, Ragnö C, Ehrsson HH. Neural correlates of the rubber hand illusion in amputees: A report of two cases. Neurocase. 2014 Aug;**20**(4):407-420. DOI: 10.1080/13554794.2013.791861

[46] Kang SY, Im CH, Shim M, Nahab FB, Park J, Kim DW, et al. Brain networks responsible for sense of agency: An EEG study. PLoS One. 2015;**10**(8):e0135261. DOI: 10.1371/journal.pone.0135261

[47] Fukushima H, Goto Y, Maeda T, Kato M, Umeda S. Neural substrates for judgment of self-agency in ambiguous situations. PLoS One. 2013;**8**(8):e72267. DOI: 10.1371/journal.pone.0072267

[48] Sato A, Yasuda A. Illusion of sense of self-agency: Discrepancy between the predicted and actual sensory consequences of actions modulates the sense of self-agency, but not the sense of self-ownership. Cognition. 2005;**94**(3):241-255. DOI: 10.1016/j.cognition.2004.04.003

[49] Maeda T, Takahata K, Muramatsu T, Okimura T, Koreki A, Iwashita S, et al. Reduced sense of agency in chronic schizophrenia with predominant negative symptoms. Psychiatry Research. 2013;**209**(3):386-392. DOI: 10.1016/j.psychres.2013.04.017

[50] Synofzik M, Vosgerau G, Newen A. Beyond the comparator model: A multifactorial two-step account of agency. Consciousness and Cognition. 2008;**17**(1):219-239. DOI: 10.1016/j.concog.2007.03.010

[51] Miyawaki Y, Otani T, Morioka S. Impaired relationship between sense of agency and prediction error due to post-stroke sensorimotor deficits. Journal of Clinical Medicine. 2022;**11**(12):3307. DOI: 10.3390/jcm11123307

[52] Katayama O, Osumi M, Kodama T, Morioka S. Dysesthesia symptoms produced by sensorimotor incongruence in healthy volunteers: An electroencephalogram study. Journal of Pain Research. 2016;**9**:1197-1204. DOI: 10.2147/JPR.S122564

[53] Nahab FB, Kundu P, Maurer C, Shen Q, Hallett M. Impaired sense of agency in functional movement disorders: An fMRI study. PLoS One. 2017;**12**(4):e0172502. DOI: 10.1371/journal.pone.0172502

[54] Kranick SM, Moore JW, Yusuf N, Martinez VT, LaFaver K, Edwards MJ, et al. Action-effect binding is decreased in motor conversion disorder: implications for sense of agency. Movement Disorders. 2013;**28**(8):1110-1116. DOI: 10.1002/mds.25408

[55] Ziadeh H, Gulyas D, Nielsen LD, Lehmann S, Nielsen TB, Kjeldsen TKK, et al. "Mine Works Better": Examining the influence of embodiment in virtual reality on the sense of agency during a binary motor imagery task with a brain-computer interface. Frontiers in Psychology. 2021;**12**:806424. DOI: 10.3389/fpsyg.2021.806424

[56] Mazzoleni S, Duret C, Grosmaire AG, Battini E. Combining upper limb robotic rehabilitation with other therapeutic approaches after stroke: Current status, rationale, and challenges. BioMed Research International. 2017;**2017**:8905637. DOI: 10.1155/2017/8905637

[57] Han BS, Jang SH, Chang Y, Byun WM, Lim SK, Kang DS. Functional magnetic resonance image finding of cortical activation by neuromuscular electrical stimulation on wrist extensor muscles. American Journal of Physical Medicine & Rehabilitation. 2003;**82**(1):17-20. DOI: 10.1097/00002060-200301000-00003

[58] Suzuki R, Muraoka Y, Yamada S, Asano S. Integrated volitional control electrical stimulation for the paretic hand: A case report. Journal of Physical Therapy Science. 2019;**31**(10):844-849. DOI: 10.1589/jpts.31.844

[59] de Kroon JR, Ijzerman MJ, Chae J, Lankhorst GJ, Zilvold G. Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. Journal of Rehabilitation Medicine. 2005;**37**(2):65-74. DOI: 10.1080/16501970410024190

[60] Mangold S, Schuster C, Keller T, Zimmermann-Schlatter A, Ettlin T. Motor training of upper extremity with functional electrical stimulation in early stroke rehabilitation. Neurorehabilitation and Neural Repair. 2009;**23**(2):184-190. DOI: 10.1177/1545968308324548

[61] Kita K, Otaka Y, Takeda K, Sakata S, Ushiba J, Kondo K, et al. A pilot study of sensory feedback by transcutaneous electrical nerve stimulation to improve manipulation deficit caused by severe sensory loss after stroke. Journal of Neuroengineering and Rehabilitation. 2013;**13**(10):55. DOI: 10.1186/1743-0003-10-55

[62] Ramachandran VS, Altschuler EL. The use of visual feedback, in particular mirror visual feedback, in restoring brain function. Brain. 2009;**132**(Pt 7):1693-1710. DOI: 10.1093/brain/awp135

[63] Colomer C, Noé E, Llorens R. Mirror therapy in chronic stroke survivors with severely impaired upper limb function: A randomized controlled trial. European Journal of Physical and Rehabilitation Medicine. 2016;**52**(3):271-278

[64] Nogueira NGHM, Parma JO, Leão SESA, Sales IS, Macedo LC, Galvão ACDR, et al. Mirror therapy in upper limb motor recovery and activities of daily living, and its neural correlates in stroke individuals: A systematic review and meta-analysis. Brain Research Bulletin. 2021;**177**:217-238. DOI: 10.1016/j.brainresbull.2021.10.003

[65] Franz EA, Fu Y, Moore M, Winter T, Mayne T, Debnath R, et al. Fooling the brain by mirroring the hand: Brain

correlates of the perceptual capture of limb ownership. Restorative Neurology and Neuroscience. 2016;**34**(5):721-732. DOI: 10.3233/RNN-150622

[66] Bangert M, Peschel T, Schlaug G, Rotte M, Drescher D, Hinrichs H, et al. Shared networks for auditory and motor processing in professional pianists: evidence from fMRI conjunction. NeuroImage. 2006;**30**(3):917-926. DOI: 10.1016/j.neuroimage.2005.10.044

[67] Rosati G, Rodà A, Avanzini F, Masiero S. On the role of auditory feedback in robot-assisted movement training after stroke: Review of the literature. Computational Intelligence and Neuroscience. 2013;**2013**:586138. DOI: 10.1155/2013/586138

[68] Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: A systematic review. Neurorehabilitation and Neural Repair. 2008;**22**(2):111-121. DOI: 10.1177/1545968307305457

[69] Liepert J, Bauder H, Wolfgang HR, Miltner WH, Taub E, Weiller C. Treatment-induced cortical reorganization after stroke in humans. Stroke. 2000;**31**(6):1210-1216. DOI: 10.1161/01.str.31.6.1210

[70] Colombo R, Pisano F, Micera S, Mazzone A, Delconte C, Carrozza MC, et al. Assessing mechanisms of recovery during robot-aided neurorehabilitation of the upper limb. Neurorehabilitation and Neural Repair. 2008;**22**(1):50-63. DOI: 10.1177/1545968307303401

[71] Mehrholz J, Platz T, Kugler J, Pohl M. Electromechanical and robot-assisted arm training for improving arm function and activities of daily living after stroke. Cochrane Database of Systematic Reviews. 2008;**4**:CD006876. DOI: 10.1002/14651858.CD006876.pub2

[72] Malouin F, Richards CL, McFadyen B, Doyon J. Nouvelles perspectives en réadaptation motrice après un accident vasculaire cérébral [New perspectives of locomotor rehabilitation after stroke]. Medical Science (Paris). 2003;**19**(10):994-998. DOI: 10.1051/medsci/20031910994

[73] Sarlegna FR, Sainburg RL. The roles of vision and proprioception in the planning of reaching movements. Advances in Experimental Medicine and Biology. 2009;**629**:317-335. DOI: 10.1007/978-0-387-77064-2_16

[74] Spampinato D, Celnik P. Multiple motor learning processes in humans: Defining their neurophysiological bases. The Neuroscientist. 2021;**27**(3):246-267. DOI: 10.1177/1073858420939552

[75] Macías M, Lopez-Virgen V, Olivares-Moreno R, Rojas-Piloni G. Corticospinal neurons from motor and somatosensory cortices exhibit different temporal activity dynamics during motor learning. Frontiers in Human Neuroscience. 2022;**16**:1043501. DOI: 10.3389/fnhum.2022.1043501

[76] Max L, Maffett DG. Feedback delays eliminate auditory-motor learning in speech production. Neuroscience Letters. 2015;**591**:25-29. DOI: 10.1016/j.neulet.2015.02.012

[77] Fourneret P, Jeannerod M. Limited conscious monitoring of motor performance in normal subjects. Neuropsychologia. 1998;**36**(11):1133-1140. DOI: 10.1016/s0028-3932(98)00006-2

[78] Koseki K, Mutsuzaki H, Yoshikawa K, Endo Y, Kanazawa A, Nakazawa R, et al. Gait training using a hip-wearable

robotic exoskeleton after total knee arthroplasty: A case report. Geriatric Orthopaedic Surgery & Rehabilitation. 2020;**11**:2151459320966483. DOI: 10.1177/2151459320966483

[79] Liu M, Ushiba J. Brain-machine Interface (BMI)-based Neurorehabilitation for Post-stroke Upper Limb Paralysis. The Keio Journal of Medicine. 2022;**71**(4):82-92. DOI: 10.2302/kjm.2022-0002-OA

[80] Patel N, Jankovic J, Hallett M. Sensory aspects of movement disorders. Lancet Neurology. 2014;**13**(1):100-112. DOI: 10.1016/S1474-4422(13)70213-8

[81] Manita S, Suzuki T, Homma C, Matsumoto T, Odagawa M, Yamada K, et al. A top-down cortical circuit for accurate sensory perception. Neuron. 2015;**86**(5):1304-1316. DOI: 10.1016/j.neuron.2015.05.006

[82] Kitai K, Odagiri M, Yamauchi R, Kodama T. Evaluation of intervention effectiveness of sensory compensatory training with tactile discrimination feedback on sensorimotor dysfunction of the hand after stroke. Brain Sciences. 2021;**11**(10):1314. DOI: 10.3390/brainsci11101314

[83] Chesler AT, Szczot M, Bharucha-Goebel D, Čeko M, Donkervoort S, Laubacher C, et al. The role of PIEZO2 in human mechanosensation. The New England Journal of Medicine. 2016;**375**(14):1355-1364. DOI: 10.1056/NEJMoa1602812

[84] Ghez C, Gordon J, Ghilardi MF: Impairments of reaching movements in patients without proprioception. II. Effects of visual information on accuracy. Journal of Neurophysiology 1995;73(1):361-372. 1 doi:10.1152/jn.1995.73.1.361

[85] Ingemanson ML, Rowe JR, Chan V, Wolbrecht ET, Reinkensmeyer DJ, Cramer SC. Somatosensory system integrity explains differences in treatment response after stroke. Neurology. 2019;**92**(10):e1098-e1108. DOI: 10.1212/WNL.0000000000007041

[86] Collins DL, Holmes CJ, Peters TK, Evans C. Automatic 3-D model-based neuroanatomical segmentation. Human Brain Mapping. 1995;**3**:190-208. DOI: doi.org/10.1002/hbm.460030304

[87] Pascual-Marqui RD. Instantaneous and lagged measurements of linear and nonlinear dependence between groups of multivariate time series: Frequency decomposition. arXiv. 2007;**0711**:1455. DOI: 10.48550/arXiv.0711.1455

[88] Takeuchi N, Izumi S. Maladaptive plasticity for motor recovery after stroke: Mechanisms and approaches. Neural Plasticity. 2012;**2012**:359728. DOI: 10.1155/2012/359728

[89] Wasaka T, Kida T, Kakigi R. Facilitation of information processing in the primary somatosensory area in the ball rotation task. Scientific Reports. 2017;**7**(1):15507. DOI: 10.1038/s41598-017-15775-x

[90] Impieri D, Zilles K, Niu M, Rapan L, Schubert N, Galletti C, et al. Receptor density pattern confirms and enhances the anatomic-functional features of the macaque superior parietal lobule areas. Brain Structure & Function. 2019;**224**(8):2733-2756. DOI: 10.1007/s00429-019-01930-9

[91] Kaneko F, Shibata E, Okawada M, Nagamine T. Region-dependent bidirectional plasticity in M1 following quadripulse transcranial magnetic stimulation in the inferior parietal cortex. Brain Stimulation.

2020;**13**(2):310-317. DOI: 10.1016/j.brs.2019.10.016

[92] Ostry DJ, Darainy M, Mattar AA, Wong J, Gribble PL. Somatosensory plasticity and motor learning. The Journal of Neuroscience. 2010;**30**(15):5384-5393. DOI: 10.1523/JNEUROSCI.4571-09.2010