Impact of the Upper Limb Physiotherapy on Behavioral and Brain Adaptations in Post-Stroke Patients

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Review:

Many stroke patients suffer from motor impairments due to paralysis, and consequently, motor paralysis of upper limbs seems to be particularly prone to residual impairment compared to that of lower limbs. Although ‘learned non-use’ that by managing reasonably well using only the unaffected upper limb in their actions, the patients can achieve their desired behavior, and these success experiences strengthen this pattern of behavior can be interpreted as a post-stroke adaptation, physiotherapy may lead to poor recovery of motor impairment. This review article discusses the impact of upper limb physiotherapy after stroke on behavioral/brain adaptations. Our previous studies demonstrated that patients with severe post-stroke sensorimotor impairments in a chronic phase might have abnormal functional connectivity. To prevent such adaptation after stroke, upper limb physiotherapy is important. In rehabilitation practices, hyper-adaptation has been often observed in not only behavioral but also brain changes. Although several studies are reporting clinical efficacy in patients with moderate to mild paralysis, there might be no effective treatment for patients with severe motor paralysis. To overcome these serious problems, we have developed a novel approach, kinesthetic illusion induced by visual stimulation (KINVIS) therapy. We showed that the effects of KINVIS therapy with therapeutic exercise on upper limb motor functions were mediated by spasticity, and functional connectivity in the brain was also changed with the improvement of motor function after KINVIS therapy. Brain changes underlying behavioral changes need to be more examined, and the adaptation of stroke patients needs to be clarified in detail.

Keywords: stroke, rehabilitation, kinesthetic illusion, virtual reality, resting-state brain functional connectivity

1. Introduction

Motor impairments of post-stroke patients can often result in negative adaptation. Many patients with stroke suffer from these impairments due to paralysis. It was reported that about 290,000 individuals per year experienced a stroke each year in Japan [1]. Annually, 13.7 million people worldwide suffer a stroke [2], and the social and economic impact of the disease is extremely high. Impairments after stroke can result in a variety of sensory, motor, cognitive, and psychological symptoms. The most common and widely recognized impairments after stroke are motor impairments, in most cases affecting the control of the movement of the face, arm, and leg on one side of the body known as hemiparesis. Upper limb motor paralysis after stroke seems to be particularly prone to residual impairment. In 80% of stroke cases, upper limb motor function is not restored to a practical level [3]. It has also been reported that 85% of patients with stroke had sensorimotor paralysis of the upper limb, and 55%–75% had residual upper limb dysfunction at 3–6 months after the onset of stroke, which was associated with decreased health-related quality of life [4]. For humans, the upper limbs, especially the hands and fingers, are the interface between the environment and themselves, and using the hands as intended in life is an essential requirement for improving the quality of life.

Changes in the affected upper limb are often more pronounced than those in the affected lower limb [5]. Specifically, many post-stroke patients cannot control grasping, finger-tip force, and timing during the manipulation of an object [6]. Patients with such disability can often experience failures (e.g., spilling food/drinks and/or dropping objects on the floor) in their daily actions, which require upper limb control, because of their upper limb paralysis. These failure experiences can result in suppression of the use of the affected limb. Moreover, by managing reasonably well using only the unaffected upper limb in their actions, the patients can achieve their desired behavior (i.e., compensatory behavioral pattern). Consequently, these successful experiences lead to strengthening this
pattern of behavior. These processes are called ‘learned non-use’ [7, 8]. The learned non-use can disturb recovery of motor impairment in post-stroke patients through abnormal interhemispheric inhibition or hyper muscle tone resulting from the compensatory behavioral patterns (i.e., excessive uses of an unaffected limb) [9, 10]. In an animal study, this disturbance is also supported by no substantial functional reorganization in the infarcted zone in the absence of post-stroke training [11]. Although these processes can be interpreted as post-stroke negative adaptations, they may lead to poor recovery of motor impairment and therefore result in severe residual paralysis of the upper limb in a chronic phase after stroke.

In general, spontaneous recovery from stroke-induced motor impairments typically occurs during the first 30 days up to 3 months after symptom onset in patients with stroke [12, 13]. For this early post-stroke period, results from longitudinal functional magnetic resonance imaging (fMRI) studies in humans and rats showed that blood oxygenation level-dependent (BOLD) activity increased in ipsilesional sensorimotor cortex and decreased in the contra-lesional one concomitant to behavioral improvements [14–19]. These results indicated a typical change in the brain activities after a stroke that the contralesional hemisphere activity increased in the early post-stroke period and then its excessive activity decreased with behavioral recovery. Physiotherapy may contribute to enhance behavioral recovery through such a typical change. Except for in the hyperacute stage, physiotherapy for paralysis after stroke recommend in various guidelines [20, 21]. The present review article discusses the impact of upper limb physiotherapy after stroke on these behavioral/brain adaptations. In addition, novel approaches to the challenge of solving the problems of chronic severe stroke patients have will be presented.

2. Behavioral/Brain Adaptations in Post-Stroke Patients

As mentioned above, when the human central nervous system is damaged, motor function is severely impaired. It is known that the course of behavioral and brain recovery differs among patients. Rehme et al. [22] investigated the temporal evolution of intra- and interhemispheric (dys-)connectivity from the acute to the early chronic phase post-stroke using fMRI. While healthy subjects had positive connectivity of the ipsilesional supplementary motor area and premotor cortex with the ipsilesional primary motor cortex (M1), this positive connectivity was reduced in patients with stroke in the acute stage. Importantly, this connectivity among these areas increased with recovery and predicted a better outcome. In other words, motor function favorably improved in patients whose connectivity was increased, whereas motor function was poorly improved in patients whose connectivity was not increased in the early chronic phase. These findings suggest that such patients who poorly improved motor function may suffer from severe paralysis with abnormal brain connectivity. Indeed, our previous study confirmed this abnormal brain connectivity of post-stroke patients with severe paralysis in the chronic phase.

Our previous study investigated the relationship between resting-state functional connectivity (rs-FC) and motor functions in patients with severe post-stroke sensorimotor impairments in a chronic phase [23]. The results suggest that rs-FC of inferior parietal sulcus in the affected hemisphere (aIPS)-inferior parietal sulcus in the unaffected hemisphere (uIPS) is associated with the skilled motor functions of the hands and fingers, and that rs-FC of inferior parietal lobe in the unaffected hemisphere (uIPL)-dorsal premotor cortex in the unaffected hemisphere (uPMd) is involved in the gross motor functions of the shoulders and elbows. Regarding the former (aIPS-uIPS), some studies have suggested that activities in the parietal areas are associated with motor preparations before performing finger movements [24, 25]. Because motor preparations, such as motor imagery, play an important role in performing hand and finger movements, the activities in the parietal areas including the IPS can contribute to motor performances. Interestingly, our previous result, however, indicated that the stronger the rs-FC of aIPS-uIPS, the weaker the finger motor functions (i.e., negative correlation). Parietal regions have been known to interact with ipsilateral occipital or frontal regions; however, the connectivity in our previous study did not do so (connectivity between contralateral IPSs). This result, therefore, suggests that patients with severe post-stroke sensorimotor impairments in a chronic phase can have specific functional connectivity in their brain. In other words, their rs-FC may represent a deviation from a normal one, although it remains unclear how their functional connectivity changed after stroke. This deviation can result from brain damages and/or sensorimotor impairments due to stroke and be associated with hand/finger motor performances.

Regarding the latter (uIPL-uPMd), the previous result showed a negative correlation between the uIPL-uPMd rs-FC and shoulder/elbow gross motor functions. This correlation manner is similar to that regarding rs-FC of aIPS-uIPS, i.e., the stronger their rs-FC, the weaker their motor functions. Projections from the inferior parietal to premotor cortices through the superior longitudinal fasciculus II and III may be involved in producing the gross limb movements, such as reaching [26, 27]. Moreover, the premotor region can have bilateral projections to the reticular formation (i.e., cortico-reticular pathway) [28–30] which then bilaterally projects to proximal or trunk muscles. It has been considered that these pathways can be driven to realize posture control required before gross limb movements [28, 29]. Given these findings, the negative correlation observed in the previous study [23] might reflect adaptive brain activities, which are because of severe motor impairments, to compensate for motor functions on paretic limbs through the bilateral projections related to proximal or trunk control. Taken together, patients with severe post-stroke sensorimotor impairments in a chronic phase might have abnormal functional con-
nectivity, possibly formed depending on a stroke-onset time course. Such connectivity may represent one of the post-stroke adaptations in the brain.

3. Physiotherapy of Post-Stroke Patients for Hyper-Adaptation

We have demonstrated that patients with severe post-stroke sensorimotor impairments in a chronic phase can have adaptive functional connectivity in their brains. This abnormal connectivity might be associated with hand/finger motor performances. To prevent such adaptation, as mentioned above, upper limb physiotherapy is important. It is considered that a typical example of hyper-adaptation is the recovery process by physiotherapy after central nervous system disease such as stroke [31]. In rehabilitation practices, such hyper-adaptation has been often observed in not only behavioral but also brain changes. For example, constraint-induced movement therapy (CIMT) involves ipsilesional limb restraint with the training of the paretic arm [32]. CIMT is widely used in rehabilitation field to overcome the learned non-use of the affected limb [33]. There is moderate evidence of the therapeutic effects of CIMT. In addition, mirror therapy [34], mental practice [35], and virtual therapy [36] are shown to have beneficial effects with moderate-quality evidence [37]. Additionally, clinical trials using the brain-machine interface have been demonstrated [38,39]. These training for upper limb motor paralysis of post-stroke can alter brain function and structure. Animal studies providing initial evidence that both functional and structural brain reorganization occurs after localized infarctions have highlighted the importance of postinjury training [40]. In particular, task-specific training postinfarction induces synaptogenesis [41], dendritic branching and growth [42], and the formation of new long-range connections [43], all of which may be conducive for postinjury plasticity to occur. Brain plasticity induced by physiotherapy might prevent suffering from severe paralysis in a chronic phase.

However, these therapies have been implemented in patients with dexterity [34–36], that is, there might be no effective treatment for patients with severe motor paralysis. For example, since CIMT requires the ability to manipulate objects to a certain extent using only the paretic upper limb, CIMT is applicable for patients with less than moderate paralysis but not for patients with severe paralysis. Furthermore, post-stroke patients with severe paralysis are unable to move their limbs enough or imagine moving their limbs even during mental practice [44]. Previously, several clinical trials for post-stroke patients with severe paralysis in a chronic phase were reported, but no intervention seems to be effective [45,46]. Since few influential results have been reported, other significant therapeutic approaches for post-stroke patients with severe motor paralysis in a chronic phase should be developed.

4. A Novel Approach for Post-Stroke Patients with Severe Upper Limb Motor Paralysis

To overcome these serious problems, we have developed a novel approach for patients with severe motor paralysis after stroke. We have applied a psychological phenomenon to approach such patients. Kinesthetic illusion induced by visual stimulation (KINVIS) is defined as the psychological phenomenon in which a person who is resting feels as if a part of his/her own body is moving or feels the desire to move a body part while watching a movie of the body part that is moving [47]. This phenomenon is implicit motor imagery that is carried as a result of cognitive augmentation of the paralyzed real body with a virtual body for patients with upper limb motor paralysis. An approach using KINVIS does not require voluntary movements and may apply to post-patients with severe paralysis. Other interventions do not also require voluntary movement on the affected side, such as mirror therapy and mental practice. However, because mirror therapy may increase interhemispheric inhibition and mental practice requires to imagine moving an affected limb with long-term non-use, these interventions may be inappropriate for post-stroke with severe paralysis. In addition, the application of cross reality (xR) technology such as virtual and augmented reality improves self-body perception by allowing patients with long-term paralysis, who have difficulty even in imagining movement, to experience kinesthetic perception. As KINVIS therapy, we applied neuromuscular electrical stimulation in combination with intervention with KINVIS.

We have reported several experimental physiological studies for healthy subjects applying KINVIS. We have reported that intervention using KINVIS has physiological effects on motor-associated areas in the brain [48–50]. A specific brain network is activated during KINVIS [50,51]. The first report of the physiological effects of visual stimulation indicated an enhancement of M1 excitability [48], which is sustained after KINVIS with peripheral nerve electrical stimulation for 60 minutes as long-term potentiation [52]. Furthermore, while cortical excitability after non-use of an upper limb in healthy subjects was decreased [53], intervention using KINVIS during non-use prevented this decrease [54]. Other studies have also shown the clinical effectiveness of intervention using KINVIS in clinical trials for post-stroke patients [55,56]. However, the application of KINVIS to the intervention required time-consuming preparation, such as acquiring videos in advance. To establish the therapeutic utility of KINVIS we have developed a clinically reasonable system, named Kinvis™ (Figs. 1(A) and (B)). Our systematized kinesthetic illusion’s system realizes the virtual augmentation of motor functions by cognitively replacing the paralyzed body with a virtual body.
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5. Clinical Trial Using KiNvis™ System for Patients with Severe Motor Paralysis After Stroke

We conducted a clinical trial of 11 patients with very severe motor paralysis after stroke in the chronic phase (time from stroke onset to be more than 4 months) using the KiNvis™ system [47]. The intervention in this clinical trial consisted of 10 days of intervention on weekdays (Fig. 1(C)). The intervention included KINVIS therapy and conventional therapeutic exercise (TherEx). The participants have applied visual stimulation for 20 minutes using the KiNvis™ system.

5.1. Behavioral Effect of KINVIS Therapy with TherEx (Fig. 2) [47]

KINVIS therapy with TherEx resulted in significant improvements in upper limb motor function, and the effect size was moderate. It was surprising to observe such improvements in post-stroke patients with severe upper limb motor paralysis in the chronic phase of altered brain functional connectivity (see Section 2). The clinical efficacy of this novel approach had been demonstrated. We found four studies that were conducted in the past with similar inclusion criteria [38, 39, 46, 57]. Among those, the effect size was more than medium in only two articles. The effect size in our study was comparable to that of the previous four articles, indicating that the KINVIS therapy may be a powerful, effective approach for chronic, severe paralysis after stroke. Importantly, the duration of intervention in our study was much shorter than that in the previous four studies. The duration of the intervention was at least 2 weeks in one study and more than 3 weeks in the other three studies. The intervention duration in our study was only 10 days, which is an advantage of KINVIS therapy with TherEx.

In addition, the modified Ashworth scale (MAS) of the wrist flexor muscles improved above the minimum clinically important difference [58]. As no previous study has indicated an effect on spasticity except for medication studies [58, 59], this result is of great clinical importance. Moreover, the decrement in spasticity in the wrist joint flexor muscles would now allow patients to proceed to TherEx, particularly in the case of patients with severely paralyzed upper extremities, who are in a sustained clenching state, making it impossible to apply any TherEx without KINVIS therapy. Since patients were released from the sustained clenching state by KINVIS therapy, decreased muscle tone led to ease of exercise. This result suggests that KINVIS therapy is better applied before TherEx. There is currently no study reporting similar results, thus this new approach may be useful in improving paralysis therapy.

5.2. Effects of KINVIS Therapy with TherEx Mediated by Spasticity (Fig. 3) [23]

In the above section, we described the effects of KINVIS therapy with TherEx on motor function and spasticity, respectively. Additionally, we used a path analysis (mediation model) in structural equation modeling and investigated whether improvements in upper limb motor functions after KINVIS therapy with TherEx were induced through spasticity improved by therapy. Interest-
highlights the necessity to explore its mechanism.

Effects of KINVIS. This clinical effect is noteworthy and unclear; however, these may characterize the clinical effects of TherEx after KINVIS therapy. First, the rs-FC of uIPS-uIPs became positively correlated with motor function. This relationship changed significantly between before and after the intervention. Furthermore, the rs-FC of uPL-uPMD became to no longer showed a significant correlation with motor function. These changes in relationships were induced within only 10 days in patients in the chronic phase after stroke and occurred in parallel with the behavioral improvement. That is, KINVIS therapy with TherEx might have induced hyper-adaptation in patients with severe motor paralysis that had led to negative adaptation caused by sustained abnormal motor function and brain activity. The functional role of the high correlation in these brain region combinations is a subject of future research. Thus, this is a very important study that revealed that the intervention using kinesthetic illusion caused changes in the biological signals of fMRI, regardless of changes in behavioral data such as motor function and spasticity.

5.3. Changes in the Relationship Between Motor Function and Rs-FC After KINVIS Therapy (Fig. 4) [47]

As mentioned above (Section 2), there were negative correlations between motor function and alPS-uIPS and uPL-uPMD, and patients with severe post-stroke sensorimotor impairments in a chronic phase might have abnormal functional connectivity, possibly formed depending on a stroke-onset time course. Interestingly, this relationship changed dramatically after KINVIS therapy with TherEx. First, the rs-FC of uIPS-uIPS became positively correlated with motor function. This relationship changed significantly between before and after the intervention. Furthermore, the rs-FC of uPL-uPMD became to no longer showed a significant correlation with motor function. These changes in relationships were induced within only 10 days in patients in the chronic phase after stroke and occurred in parallel with the behavioral improvement. That is, KINVIS therapy with TherEx might have induced hyper-adaptation in patients with severe motor paralysis that had led to negative adaptation caused by sustained abnormal motor function and brain activity. The functional role of the high correlation in these brain region combinations is a subject of future research. Thus, this is a very important study that revealed that the intervention using kinesthetic illusion caused changes in the biological signals of fMRI, regardless of changes in behavioral data such as motor function and spasticity.

6. Conclusion

In this review article, we have discussed physiotherapy and adaptation in terms of post-stroke patients, especially those with severe upper limb motor paralysis, and then described that the behavioral/brain adaptations occurred due to physiotherapy. In addition, in post-stroke patients that had led to negative adaptation with severe paralysis in a chronic phase, intervention of repeated exercise (i.e., TherEx) after cognitive augmentation (i.e., KINVIS therapy) induced hyper-adaptation, that is, improvement of upper limb motor functions and alternation of relationship functional brain connectivity and motor functions. In the future, it is necessary to clarify the mechanism by which KINVIS therapy changes functional connectivity in the brain. Brain changes underlying behavioral changes also need to be more examined, and the adaptation of stroke patients needs to be clarified in detail.

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Fig. 4. Changes in relationship between Fugl-Meyer assessment score and resting-state functional connectivity [47]. aIPS, inferior parietal sulcus in the affected hemisphere; uIPS, inferior parietal sulcus in the unaffected hemisphere; uIPL, inferior parietal lobule in the unaffected hemisphere; uPMd, dorsal premotor cortex in the unaffected hemisphere; rs-FC, resting-state functional connectivity.

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