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·Review·

Recovery mechanisms of somatosensory function in stroke patients: implications of brain imaging studies

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Somatosensory dysfunction is associated with a high incidence of functional impairment and safety in patients with stroke. With developments in brain mapping techniques, many studies have addressed the recovery of various functions in such patients. However, relatively little is known about the mechanisms of recovery of somatosensory function. Based on the previous human studies, a review of 11 relevant studies on the mechanisms underlying the recovery of somatosensory function in stroke patients was conducted based on the following topics: (1) recovery of an injured somatosensory pathway, (2) peri-lesional reorganization, (3) contribution of the unaffected somatosensory cortex, (4) contribution of the secondary somatosensory cortex, and (5) mechanisms of recovery in patients with thalamic lesions. We believe that further studies in this field using combinations of diffusion tensor imaging, functional neuroimaging, and magnetoencephalography are needed. In addition, the clinical significance, critical period, and facilitatory strategies for each recovery mechanism should be clarified.

Keywords: stroke; somatosensory recovery; brain mapping; brain plasticity

Introduction

Somatosensory function has several important implications for stroke patients. First, somatosensory dysfunction is common in such patients, with a reported incidence of up to 65%[1,2]. Second, somatosensory feedback is necessary for the execution of precise movements; therefore, somatosensory dysfunction can lead to functional impairment[3-5]. Third, somatosensory dysfunction can accompany the complications of stroke, such as abnormal movements or central pain[1,6]. Finally, somatosensory function is needed to protect patients from harmful stimuli and dangerous situations.

The focus of stroke rehabilitation has shifted to the concept of brain plasticity[3]. Elucidating the mechanisms for the recovery of impaired function is important for stroke rehabilitation because it can provide a basis for the establishment of strategies using a scientific approach. With developments in brain mapping techniques, many studies have investigated the mechanisms of recovery in patients with stroke, with a particular focus on motor function[7-12]. However, relatively little is known about the mechanisms of recovery of somatosensory function[13-23].

In the current review, we used electronic databases (Pubmed and Medline) to identify relevant studies from 1966 to 2012 based on the following keywords: stroke, brain plasticity, rehabilitation, somatosensory recovery, brain mapping, positron emission tomography (PET), functional MRI (fMRI), diffusion tensor imaging (DTI), and magnetoencephalography (MEG). We focused on the mechanisms of injury-dependent spontaneous somatosensory recovery from human adult stroke and excluded intervention-dependent somatosensory recovery. Based on these criteria, 11 studies[13-23] were selected (Table 1).

Mechanisms of Recovery of Somatosensory Function in Patients with Stroke

Among the various functions of the brain, the mechanisms of recovery of motor function have been most comprehensively investigated. Several mechanisms have been proposed, including contributions from the unaffected motor cortex, perilesional reorganization, recovery of a damaged lateral corticospinal tract, and contributions from secondary motor areas or aberrant neural pathways[7,9,10,24]. By contrast, far fewer studies have investigated the mechanisms of recovery of somatosensory function. Here, we reviewed the findings on this topic, based on the 11 studies in humans, according to the following sub-topics: (1) recovery of an injured somatosensory pathway[15], (2) peri-lesional reorganization[13,17], (3) contribution of the unaffected somatosensory cortex[16,20,21,23], (4) contribution of the secondary somatosensory cortex (SII)[14], and (5) recovery mechanisms in patients with thalamic lesions[18,19,22]. The thalamus, a synaptic relay in the somatosensory pathways, may be involved independently in the plasticity of the somatosensory system; therefore, a review of this sub-topic was conducted separately.

Recovery of an Injured Somatosensory Pathway

Previously, regeneration in the human central nervous system was considered impossible. However, with the development of brain mapping techniques, the potential of the human brain to recover following brain injury has been widely accepted[7,9,10,25,26]. However, few studies have investigated the recovery of an injured somatosensory

Table 1. Previous studies on the mechanisms of somatosensory recovery in patients with stroke

Authors	Publication year	No. of patients	Etiology	Location of lesion	Evaluation tool
Recovery of injured somatosensory pathway					
Hong and Jang[15]	2010	1	Hemorrhage	Subcortical	fMRI, DTI (integrity)
Peri-lesional reorganization					
Cramer *et al.*[13]	2000	1	Infarct	Postcentral gyrus, superior parietal lobule	fMRI
Jang *et al.*[17]	2010	1	Infarct	Primary sensori-motor cortex	fMRI
Contribution of unaffected somatosensory cortex					
Weder *et al.*[23]	1994	5	Infarct	Basal ganglia or thalamus	PET ([^{15}O] butanol)
Rossini *et al.*[21]	1998	19	Infarct (15)	Cortical or subcortical	MEG
			Hemorrhage (4)		
Rossini *et al.*[20]	2001	17	Infarct	Middle cerebral	MEG
			Hemorrhage	artery territory	
Jang[16]	2011	2	Infarct	Infarct: middle cerebral artery territory	fMRI
			Hemorrhage	Hemorrhage: frontoparietal lobe	
Contribution of secondary somatosensory cortex					
Forss *et al.*[14]	1999	6	Infarct	Middle cerebral	MEG
				artery territory	
Recovery mechanism in patients with thalamic lesions					
Ohara and Lenz[19]	2001	1	Infarct	Thalamus	Microelectrode
					stimulation study
Staines *et al.*[22]	2002	4	Infarct (2)	Thalamus	fMRI
			Hemorrhage (2)		
Lee *et al.*[18]	2011	11	Hemorrhage	Thalamus	fMRI

PET, positron emission tomography; fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging; MEG, magnetoencephalography.

pathway in patients with stroke[15]. In 2010, Hong and Jang demonstrated the mechanism of recovery of somatosensory function in a patient with subcortical intracerebral hemorrhage[15]. The patient presented with severe somatosensory dysfunction on the left side at onset, and the function of the affected side showed recovery to the normal state at seven weeks after onset. Longitudinal fMRIs for touch and passive movements, and DTIs for the medial lemniscus performed at 3 and 7 weeks after onset indicated good recovery of the injured pathways.

Peri-lesional Reorganization

Among the mechanisms of recovery of somatosensory function, peri-lesional reorganization has been actively studied in animal models[27-29]. However, to the best of our knowledge, only two cases involving stroke patients have been reported[13,17]. Cramer *et al.* (2000), using fMRI, reported in a patient with a cortical infarct in the postcentral gyrus and anterior aspect of the superior parietal lobule that only the precentral gyrus was activated during finger stimulation at 6 months after onset[13]. Therefore, the author proposed that reorganization of the somatosensory function of the infarcted area occurred in the precentral gyrus during recovery in this patient. In a more recent study using fMRI[17], Jang *et al.* (2010) found that, in a patient with severe sensorimotor dysfunction of the left hand, which first occurred at the onset of an infarct in the right primary sensorimotor cortex centered on the precentral knob, sensorimotor function of the hand appeared to be reorganized in the lateral area[17]. At 6 months from onset, when the sensorimotor function of the affected hand had recovered to normal, fMRI showed activation of the contralateral primary sensorimotor cortex, centered on the precentral knob, during active and passive movements, and touching of the unaffected hand, but activation of the lateral area of the infarcted primary sensorimotor cortex of the right hemisphere occurred during the three types of stimulation of the affected hand.

Cortical reorganization can depend on the activation of existing – but normally ineffective – neural connections, and/or on the growth of new connections[30]. Mechanistically, reorganization into the adjacent intact cortex after the occurrence of a primary motor cortex infarct may indicate the recruitment of alternative motor representation sites. This is possible because the corticospinal tract has several areas of origin other than the primary motor cortex[31,32], including the premotor cortex, the parietal cortex, and the mediolateral representation of the primary motor cortex. In a similar manner, with regard to somatosensory function, several studies have reported an overlap of somatotopy in the primary somatosensory cortex (SI) and SII[33-35]. In addition, there is general agreement that the primary motor cortex and SI overlap, and that the primary motor cortex receives somatosensory input directly from the thalamus[36-39]. This phenomenon may be the basis for the peri-lesional reorganization of somatosensory function.

Contribution of the Unaffected Somatosensory Cortex

Considerable evidence of the contribution of the ipsilateral somatosensory cortex to somatosensory function in the normal human brain has been reported[40-42]. In addition, findings from a recent study (2009) demonstrated that the degree of contribution from the ipsilateral S1 was greater than that for motor function[43]. Findings from several studies have demonstrated the contribution of the unaffected somatosensory cortex to somatosensory recovery after stroke[16,20,21,23]. Using PET, Weder *et al.* (1994) reported in five patients with chronic thalamic or basal ganglia infarcts, activation of the bilateral sensorimotor cortex by the performance of a somatosensory discrimination task using the affected hand[23]. In two studies using MEG, Rossini *et al.* (1998, 2001)[20,21] demonstrated the contribution of the unaffected hemisphere to somatosensory recovery in 19 and 17 stroke patients. Recently, two stroke patients (patient 1: intracerebral hemorrhage in the frontoparietal lobe, patient 2: middle cerebral artery infarct) whose proprioception appeared to be recovered by the unaffected somatosensory cortex have been reported[16]. The subscale for kinesthetic sensation (full score: 24) of the Nottingham Sensory Assessment showed improvement from 2 at stroke onset to 8 (patient 1) and 12 (patient 2) at 6 months after onset[44]. fMRI conducted 6 months after onset showed that activation of the unaffected SI and posterior parietal cortex occurred without activation in the affected cortex during passive movements of either hand.

Several researchers have suggested that the putative mechanism of the contribution of the unaffected cortex may be explained by the disinhibition hypothesis, as described for the mechanism of motor recovery of the ipsilateral motor

pathway[45,46]. The balance between normal cortices is maintained through transcallosal inhibition. However, upon the occurrence of stroke, interhemispheric transcallosal inhibition shifts from the affected side toward the unaffected side. As a result, the excitability of the unaffected cortex can increase and contribute to somatosensory recovery.

Contribution of the Secondary Somatosensory Cortex

SII, located in the parietal operculum adjacent to the dorsal insula, has been shown to connect directly with the thalamus through thalamocortical pathways without a relay in SI[47-53]. In addition, bilateral receptive fields of SII respond to both contra- and ipsilateral stimuli[35,53] and to callosal connections from the SII area of the opposite hemisphere[54]. This rich connectivity characteristic of SII indicates that this cortex could be an alternative location for brain plasticity.

Some studies have demonstrated a possible contribution of SII to the recovery of somatosensory function[14,55]. In adult monkeys, cortical reorganization of 0.5–2 mm occurs in SI after deafferentation[56-60]. In contrast, after removal of the entire post-central hand representation, reorganization of SII extends up to 5 mm, leaving no detectable zones of unresponsiveness[55]. These results suggest the possibility that SII has greater plasticity after injury. In comparison, a study of human subjects described a potential role for the SII in somatosensory recovery[14], demonstrating that six patients with right middle cerebral artery infarct showed unaffected (left) SII activation by stimulation of the affected (left) median nerve, compared to activation of the left SI and SII by stimulation of the unaffected (right) median nerve.

Recovery Mechanisms in Patients with Thalamic Lesions

The thalamus, a synaptic relay in the ascending somatosensory pathway, transfers somatosensory input to the cerebral cortex, playing an important role in somatosensory function. Therefore, the thalamus may be involved independently in the plasticity of the somatosensory system[22,61-64].

A few studies have reported on mechanisms of somatosensory recovery in stroke patients with thalamic lesions[18,19,22]. In 2001, Ohara and Lenz in a case of thalamic stroke detected the reorganization of the somatosensory nucleus of the thalamus in a stereotactically-guided microelectrode exploration during surgery for the control of tremor[19]. The reorganization was also found to occur in other thalamic nuclei located anterior to the infarct[19]. Subsequently, Staines *et al.* (2002) attempted to demonstrate the mechanism of somatosensory recovery in four stroke patients with thalamic lesions (two patients with infarct and two with hemorrhage). They performed serial fMRI during somatosensory stimulation from the early to the chronic stage of stroke, and found an association of somatosensory recovery with the enhancement of SI activation in the affected hemisphere[22]. Recently, Lee *et al.* (2011)[18] reported fMRI findings in patients with chronic thalamic hemorrhage. They recruited 11 consecutive patients who had ventroposterolateral lesions resulting from thalamic hemorrhage and severe proprioceptive dysfunction of the affected side at onset[18]. fMRI in response to proprioceptive input three months after onset revealed a positive association of proprioception with relative activity in the SI ipsilateral rather than contralateral to the affected hand. Therefore, they concluded that the recovery of proprioceptive function of the affected hand occurred through the normal medial lemniscus and its thalamocortical pathway.

Conclusions

Since somatosensory function does not require the active execution of tasks and high levels of cognition to the same extent as motor function, the evaluation of somatosensory function may be easier. However, far fewer studies have reported on the mechanisms of recovery of somatosensory function in patients with stroke, compared to those of motor function. Therefore, further research on the mechanisms of recovery of somatosensory function in patients with stroke is necessary. In particular, recent developments in DTI allow three-dimensional identification and estimation of the medial lemniscus and spinothalamic tract[65-67]. However, to the best of our knowledge, only one DTI study has reported on the mechanisms of recovery of somatosensory function[15]. Therefore, combined studies using DTI, functional neuroimaging, and MEG to elucidate the mechanisms of recovery of somatosensory function in patients with stroke should be encouraged. In addition,

to provide a detailed understanding of such mechanisms, including their clinical significance, critical period, and facilitation strategies, comprehensive investigations should be conducted.

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