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Special Topics and Review

Human mirror neuron system and its plasticity ****

Wei Chen [1,2], Tifei Yuan [3], Yin Wang [4], Jun Ding [1,2]

1Institute of Cognition and Behavioral Neuroscience, Hangzhou Normal University, Hangzhou 310018, Zhejiang Province,China
2Department of Psychology, Hangzhou Normal University, Hangzhou 310018, Zhejiang Province, China
3Department of Anatomy, Li Kai Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
4School of Life Sciences, Shanghai University, Shanghai 200436, China

Abstract
The mirror neuron system (MNS) was first discovered in non-human primates; these neurons fire when a monkey performs an action or observes another monkey (or even some people) performing that same action. Recent findings have suggested that neural rehabilitation might be achieved through the activation of the MNS in patients after stroke. We propose two major mechanisms (one involving adult neurogenesis and another involving brain-derived neurotrophic factor) that may underlie the activation, modulation and experience-dependent plasticity in the MNS, for further study on promoting central nerve functional reconstruction and rehabilitation of patients with central nervous system injury.
Key Words: mirror neuron system; adult neurogenesis; neural plasticity; rehabilitation; spinal cord injury

Wei Chen ★, Studying for master's degree, Institute of Cognition and Behavioral Neuroscience, Hangzhou Normal University, Hangzhou 310018, Zhejiang Province,China; Department of Psychology, Hangzhou Normal University, Hangzhou 310018, Zhejiang Province, China

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INTRODUCTION

A recent neurophysiological discovery has sparked interest in a new class of motor neurons; these neurons discharge not only when non-human primates perform hand or mouth actions, but also when simply observing another individual (or even some people) performing the same actions. These neurons, called mirror neurons,[1] are located in the lateral part of area F5, and the superior temporal sulcus of the macaque monkey. No studies have directly recorded single neurons from putative mirror neuron areas in humans; however, a number of studies have indirectly demonstrated the existence of a mirror system in the human brain. The mirror neuron system (MNS) is found in broad areas in the brain, and it is recognized to participate in action understanding, imitation, gestural communication-language evolution, social interaction and auditory modulation. It was also found that action observation, as well as imitation, could be used as an approach for systematic training in the rehabilitation of patients with motor impairment of the upper limb after stroke[2]. Recently, a study by Catmur *et al* showed that the motor representations of mirror neurons could be altered by training, suggesting experience-dependent neural system plasticity in adults[3]. It will be exciting to see how we can manipulate the MNS to control personal development and cure some MNS disorders. Here, we discuss possible players in MNS plasticity.

OBJECTIVE

This study was designed to summarize the progress in research on the MNS and its plasticity in the context of recovery after central nervous system injury.

MATERIALS AND METHODS

Data retrieval

Retrieval staff: the first author.

Time range: January 1991 to January 2008.

Keywords: mirror neuron system; plasticity and rehabilitation.

Databases: PubMed (http://www.ncbi.nlm.nih.gov/PubMed) and Chinese Biomedical Literature Database(CBM) (http://cbmwww.imicams. ac.cn/).

Number of papers retrieved: 504.

Retrieval methods

Inclusion criteria: plasticity of the MNS; rehabilitation methods based on the MNS.

Exclusion criteria: repetitive studies or objective-unrelated literature.

Literature type and data analysis: a total of

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Corresponding author: Jun Ding, Researcher, Masters's tutor, Institute director, Institute of Cognition and Behavioral Neuroscience, Hangzhou Normal University, Hangzhou 310018, Zhejiang Province, China; Tifei Yuan, Ph.D., Department of Anatomy, Li Kai Shing Faculty of Medicine, The University of Hong Kong, Hong Kong **E-mail:** yuantf@hku.hk

504 Chinese and/or English research articles were retrieved. There were 27 manuscripts coinciding with the above-mentioned inclusion criteria, including 23 articles related to molecular neurobiological mechanisms of plasticity of MNS[1-23], and 4 articles related to the role of the MNS in neurorehabilitation[24-27].

COMPREHENSIVE EVALUATION

Two molecular neurobiological mechanisms of plasticity in the MNS

Neural plasticity results from two aspects: changes in neural connections via new synapse formation or elimination, and modulation of synaptic efficiency. In this manuscript, we focus on adult neurogenesis and some important molecular players in the MNS.

Evidence of neurogenesis in the adult primate brain has been found in prefrontal, posterior, parietal, and inferior temporal cortices, in which it is involved in behavioral plasticity [4]. Moreover neurogenesis in the neocortex could be induced via manipulation of endogenous neural precursors *in situ*[5]. However, there is also evidence that adult neurogenesis is restricted to the olfactory bulbs and hippocampus[6]. For example, a study by Bhardwaj *et al*[7] found that non-neuronal cells were generated postnatally, but cortical neurons, including premotor cortex neurons, were born at or just before the time of birth. This raises the question of whether gliogenesis, which occurs at high levels in childhood[8], could affect the plasticity of the brain, especially the MNS. Non-neuronal plasticity induced by environmental and experiential factors is a robust phenomenon, and sometimes appears to parallel neuronal remodeling in both time and place[9]. Past studies by Ullian and Allen show that glial cells can promote synaptogenesis between CNS neurons, regulate synaptic function, and participate in synaptogenesis, morphology modification and synapse pruning[10-11]. Astrocytes form an intimate association with synapses throughout the adult CNS, where they help to regulate ion and neurotransmitter concentrations, and glial cells also actively participate in synaptic plasticity via regulation of CNS synapse numbers[12]. Thus, although neurogenesis in the MNS is still controversial, we can partly attribute MNS plasticity to the regulation of glial cells, which points out possible therapeutic ways to repair MNS dysfunction.

At the molecular level, brain-derived neurotrophic factor (BDNF) is worthy of attention when trying to understand MNS plasticity. BDNF induces the differentiation of neural stem cells into neurons, promotes the survival of newly generated neurons, enhances and consolidates long-term potentiation (LTP), and is thought to participate in learning and memory[13-14]. Studies from Oliff and Kleim show that motor training and environmental enrichment (EE) can both increase the BDNF level inside the brain[15-16], which provides one explanation for how motor training and EE produce rehabilitative effects in injured brain. BDNF and its receptor trkB mediate activity-dependent plasticity in a local and synapse-specific manner by controlling local translation, receptor trafficking and downstream signaling pathways[17]. We expect that BDNF-controlled circuit modeling and activity-dependent modification is also critical and important in MNS plasticity induced by motor training and visual stimuli. Additionally, there is some evidence that MNS disorders, such as autism, are related to altered BDNF signaling pathways[18] and genetic defects[19]. There are also defects in the serotonin signaling pathway in patients with autism[19-21]. Both BDNF and serotonin are very important regulators in the development of emotion disorders as well as normal emotional circuits[22], and recent findings by Canli and Lesch suggest that serotonin plays an important role in social cognition and behavior[23]. It is highly possible that serotonin and BDNF exert their function together and regulate MNS system plasticity at the molecular level. Furthermore, it would be interesting to compare the roles of serotonin and BDNF in emotion disorders and empathy disorders, which may tell us more about the psychological nature of depression.

MNS: a new tool for neurorehabilitation

So far, we have described two potential molecular neurobiological mechanisms for plasticity in the MNS. We would now like to introduce the possible use of "Action, Observation and Imitation", which would activate the MNS, as a new tool for neurorehabilitation. There is growing evidence that many forms of experience, from everyday interactions to intensive practice, can lead existing neurons to change their synaptic connectivity, forming entirely new receptive field organizations. This has been observed in the somatosensory system, with peripheral nerve stimulation, and in the visual system after striate cortex infarction with normal visual experience. In an experimental stroke model in cat, thalamo-cortical and intracortical plasticity has been described with conditioning of a motor response to a sensory stimulus. For the purpose of developing treatment approaches, it has been demonstrated that the extent and direction of stroke recovery depends on the nature of both the environment and the particular training stimuli used.

Previous studies have shown that modulation of MNS activity provides a prospective therapy for rehabilitation after stroke[24] as well as children with autism[25]. The hypothesis is that the MNS directly projects to and is involved in the motor system; thus, activation of the MNS by observation may induce activity-dependent plasticity in the motor system, and thereby restore the quality of neural connections. Spinal cord injury is one of the common causes of loss of motility; however, even the most effective treatments, namely, high-dose methylprednisolone following acute injury, fail to protect patients with longer-term injuries or promote rehabilitation.

MNS and spinal cord recovery

A recent study suggested that spinal cord recovery in primates involves the bilateral primary motor cortex during the early recovery stage and more extensive regions of the contralesional primary motor cortex and bilateral premotor cortex during the late recovery stage. This suggests that the brain gradually enhances the original neural systems or recruits other systems by synaptic plasticity during the late recovery stage for more stable control, while, in the early stages, it follows a strategy of reducing inhibition[26].

Interestingly, in the spinal cord, there is also an inhibitory mechanism that prevents the execution of observed actions, thus reducing the risk of overt movement generation[27]. In consideration of these findings, we propose that modulation of activity in the MNS, whether by action observation or virtual reality, could be well suited to treatments for spinal cord injury. It is worth noting that some patients with spinal cord injury could walk just because they were told that they will recover (placebo), which might be the result of action performances in minds.

CONCLUSION

It will be a long time before we can understand the plasticity of each functional part of the MNS. We also have to look for an integrated therapy combining modulation of the mirror neuron system and other brain areas, as well as multi-level treatments that take audio/emotional MNS into consideration, including those involved in sensory perceptions and emotion for instance. Insufficient social interactions and consequently inadequate sensory experiences might affect the development of the MNS, resulting in autism, and maybe some other emotion disorders; understanding the critical period in MNS development will be important in developmental psychology and clinical treatments. Last but not least, we have to identify possible genes that result in MNS disorders and integrate their functions into our current knowledge of MNS plasticity.

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What is already known on this topic: A new neurophysiological mechanism of the mirror neuron system (MNS) that appears to play a fundamental role in understanding, imitation, action observation, and motor learning, which might be beneficial for the recovery of motor functions following stroke; however, there are no data showing the use of MNS plasticity in rehabilitation from spinal cord injury.

What this study adds: MNS activities provide a new strategy to promote post-injury brain recovery. Two molecular neurobiological mechanisms of plasticity in the MNS involve adult neurogenesis and brain-derived neurotrophic factor. MNS may be a new tool for inducing spinal cord recovery.

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