Activity-Dependent Neurorehabilitation Beyond Physical Trainings: "Mental Exercise" Through Mirror Neuron Activation

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Abstract

The activity dependent brain repair mechanism has been widely adopted in many types of neurorehabilitation. The activity leads to target specific and non-specific beneficial effects in different brain regions, such as the releasing of neurotrophic factors, modulation of the cytokines and generation of new neurons in adult hood. However physical exercise program clinically are limited to some of the patients with preserved motor functions; while many patients suffered from paralysis cannot make such efforts. Here the authors proposed the employment of mirror neurons system in promoting brain rehabilitation by "observation based stimulation". Mirror neuron system has been considered as an important basis for action understanding and learning by mimicking others. During the action observation, mirror neuron system mediated the direct activation of the same group of motor neurons that are responsible for the observed action. The effect is clear, direct, specific and evolutionarily conserved. Moreover, recent evidences hinted for the beneficial effects on stroke patients after mirror neuron system activation therapy. Finally some music-relevant therapies were proposed to be related with mirror neuron system.

Keywords

Mirror neuron system; brain stimulation; neurorehabilitation; stroke.

INTRODUCTION

Physical activity changes muscle mass and tone, cardiovascular functioning, as well as the brain. For instance, the gray matter in relevant brain regions areas expanded following sport training (such as juggle or Ballet Dance) within very short time [1, 2]. Correspondingly, participation in physical activity has been demonstrated to be helpful for reduction of physical diseases, metal disorders and brain rehabilitation [3]. The underlying mechanisms have been partly understood. For instance, running could upregulate endogenous neurogenesis [4] or prevent the aging-related reduction of that [5]; it could also influence the central dopaminergic, noradrenergic and serotonergic systems, induce expression of neurotrophins and neuropeptides [6], and mentally be rewarding as well as antidepressive [7]. There are growing evidences on the positive effects of physical exercises from brain function and cognitive-affective performance to rehabilitation, as well as various clinical reports including immune modulation and neurotrophic hypothesis [8]. However, physical excises-based rehabilitation strategies are not well-suited to all cases, especially those patients with motor deficiencies after stroke or spinal cord injury, for instance. Direct activation of the motor cortex/spinal cord has been proposed for such rehabilitations, based on the theory of activity-dependent plasticity [9]. The difficulty is that the deep brain stimulation or intracranial electrical stimulation requires invasive procedures to implant the electrode into the brain; while the repetitive transcranial magnetic stimulation (rTMS) instrument is costly for general applications [10]. Here we discuss the feasibility of a non-physical activity-dependent rehabilitation approach, with proved clinical efficacy. That is, the brain stimulation approach based on mirror neuron system activations.

THE MIRROR NEURON SYSTEM

“Ago Ergo Cogito”: "I act, therefore I think". The mirror neuron system reflects the link between motion and understanding [11, 12]. Mirror neuron was discovered in the premotor area in monkey, which would fire during both execution and observation of similar actions [13, 14]. Thus, mirror neurons were considered a possible neurobiological substrate to certify the theoretical existence of a common code or pair-work between the visual and the motor representations of the similar actions [11, 15]. As the active intermodal mapping model explained visual images of an action and motor commands are both mapped to a multimodal representation, while proprioception offers a critical feedback system. In the direct mapping model, mirror neurons allow for a mapping between visual and motor systems [11, 36]. Following studies revealed the existence of the whole mirror neurons system (MNS), with diverse functions such as action understanding, imitation-based learning and empathy [13, 16-18]. Anatomically, in monkey the MNS was located to the inferior frontal gyrus (area F5), and the inferior parietal lobule (superior temporal sulcus as well in some studies), while in human functional magnetic resonance imaging (fMRI) evidences suggested for inferior frontal cortex and superior parietal lobe [13]. Further, intracranial depth electrode recording of the single neuron activity confirmed the existence of human MNS [19]. The deficiency of MNS could lead to social deficiency such as the autism in children-“seeing is not understanding” [20, 21]. These data indicate that motor action mirroring mediated by parieto-frontal mirror network is impaired in autism [22]. On the other hand, this opened the possibility to develop MNS as a therapeutic target for social behavior disorders (Fig. 1). The vision therapy has been defined as a program to develop, improve, remediate, and enhance visual performance. The designed vision program has been adopted to improve the cognitive ability of autism children. Different approaches to stimulation MNS for autism have been proposed in past decade [23, 24]. Whether the repairing of the “broken mirror” could fully restore social behavior is yet to be examined in more patients [25-27]. The other possibility is the treatment of aphasia as brain areas for language shared some regions with MNS. The Broca’s aphasia patients also showed deficits in action understanding and recognition [28]. It has been realized that brain stimulation could act as a treatment for aphasia [29- 32]. On the other hand, it has been shown that action observation and execution helps the use of verbs in language [33], and gesture treatment could improve the noun as well as verb retrieval in aphasia patients [34], arguing for the feasibility to treat aphasia with MNS activation. On the other hand, a recent study proved that mirror neuron therapy could restore the hemineglect caused by stroke [35].

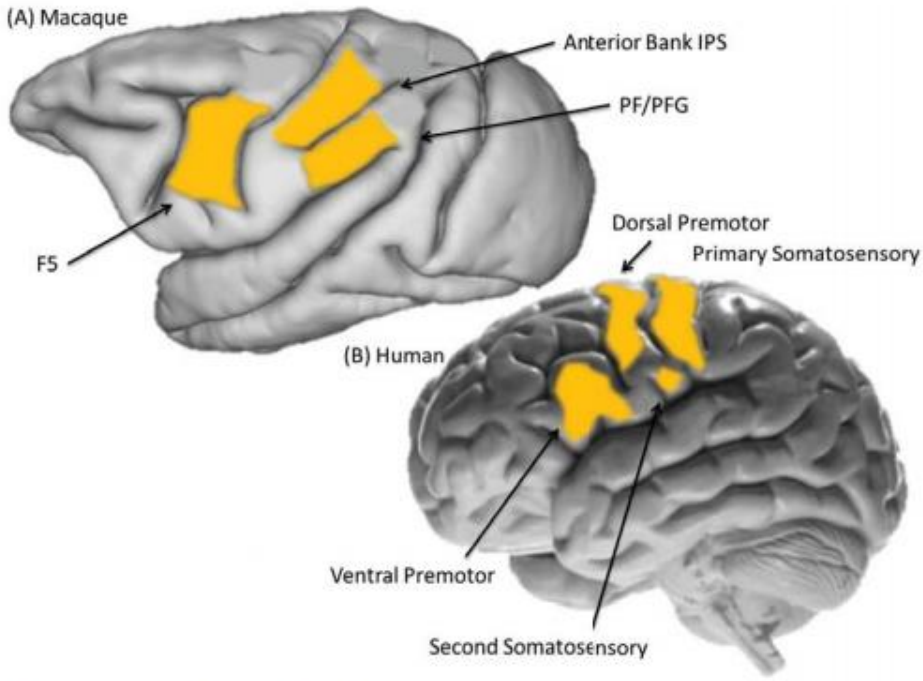

Fig. (1). Brief scheme of human and monkey mirror neuron system.

WATCH SOMEONE WALKING, AND ABLE TO WALK AGAIN?

Interestingly, MNS is still plastic and could be changed in adult brain [36, 37], indicating that the adult MNS could be activated for other types of therapies. There are several advantages to activate MNS in practice. Firstly, MNS is intact in most patients except those with autism. Secondly, MNS has widespread neuroanatomical connections to different brain regions, even with the major effect in motor system. Thirdly, the activation of MNS is direct, with high temporal resolution, allowing for patterned stimulation. Fourthly, MNS activation therapy does not rely on surgical implantation or special instruments. Fifthly, MNS could be activated both visually and audially. Sixthly, the MNS activation leads to activity that was encoded in physiological signals. All these characteristics suggested that MNS activation therapy could be ideal as a mild brain stimulation approach, with conceivably beneficial effects [38]. The direct hypothesis underlying premotor area activation is the activation of motor pathways, leading to the potential restoration of motor function in deficit patients after repetitive stimulation. Excitingly, clinical evidences proved that action observation could improve the motor recovery in post-stroke patients [39-46]. It is possible that MNS activation leads to the “training” of spared motor cortex neurons and promote the reorganization or even axonal sprouting in the injured brain [47]. Moreover, the motor cortex activation by MNS leads to spinal cord inhibition, which prevents the execution of observed actions during watching [48]. This has been found to be the similar during spinal cord injury recovery in primates, with graded cortical recruitment in extended period [49], showing the upregulated inhibition during the recovery to promote the system stability. Therefore MNS activation approach could be fit into the spinal cord injury rehabilitation scheme.

MNS AND MUSIC THERAPY

Mirror neurons also respond to action-specific auditory stimuli, which were named as “audio-visual” mirror neurons [50]. Overwhelming evidence shows that mirror neuron system as a

highly specialized cortical network in the skilled musician's brain that codes the relationship between gestures (both their visual and sensorimotor representation) and the corresponding sounds that are produced. Moreover, this effect can be regarded as a result of musical learning [51]. This opened more possibility to activate mirror neuron system in promoting rehabilitation, which could be, possibly, achieved by online virtual pets [52] or designed multi-media techniques. On the other hand, this suggested that auditory function impairment might be restored with specifically designed MNS training procedures. This idea is yet to be clinically tested. As a unique and multi-modal stimulus, music transfers visual, auditory, somatosensory and proprioceptive information simultaneously. Interestingly, music can lead to brain activities related to imitation/synchronization [53, 54]. Additionally, the inferior frontal gyrus and the ventral premotor cortex (including Broca's area) that belong to MNS participated in music execution and listening [55]. For instance, music perception activates Broca's area, just as singing or "mind imagination" of playing instruments [56]. These evidences strongly argued for the potential function of MNS during music-relevant behaviors. It should be noted that in autism patients, both normal and superior abilities for music processing (pitch memory and absolute pitch, etc.) could be found as well.

The music based activation of MNS therefore provided alternative option of brain activity manipulation beyond visual training therapy, as well as the possibility of mutlisensory stimulation. For instance, Melodic intonation therapy is one of music-based therapeutic interventions for aphasia [57, 58]. However, speculation surrounds why and how it might improve outcomes in aphasia. Based mirror neuron hypotheses, it can be considered as a category of putative mechanisms to integration/association functions of the brain and possibly the human mirror neuron system. Therefore, synchronized singing in MIT could promote activation of an "auditory-vocal interface" to improve articulatory motor function [59]. These available approaches are ready to be modified from a MNS based perspective for further studies. Music therapy has already been employed to treat some disorders discussed above, such as aphasia [60], stroke [61, 62]. It is acknowledged that the psychosomatic effects of music also contributed to the beneficial aspects of music therapy [63]; whether MNS activation also mediates such effects are to be examined.

CONCLUSION

Traumatic brain injury significantly affect the life quality of patients, leading to behavioral disturbances [64]. Mirror neuron system has clinically been demonstrated for a long time in brain post-injury rehabilitation. On the other hand, the disturbance of mirror neuron system might correlates with emotion disorder besides the social cognition defects [20], which could be deleterious for brain plasticity and recovery-"Nocebo effect" (Latin for "I will harm"). However the proportion of the role by MNS is still to be determined. To conclude, given the wide interactions of mirror neuron system in brain functions, especially the motor system, manipulation of MNS activities provides a new strategy to promote post-injury brain recovery without necessary physical movements. It is hoped that future investigations could prove the clinical efficiency of MNS-based brain stimulation therapies to not only the post-trauma/stroke rehabilitation, but also for neurodegenerative diseases in the motor system, such as Parkinson's disease. Finally, all of assumption for MNS-based neurorehabilitation are obeyed as warning as follow: "Reliable information about the function of mirror neurons can be obtained only by research based on developmental history, system-level theory, and careful experimentation" [14].

LIST OF ABBREVIATIONS

fMRI = Functional Magnetic Resonance Imaging

MNS = Mirror Neurons System

rTMS = Repetitive Transcranial Magnetic Stimulation

REFERENCES

[1] Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Neuroplasticity: changes in grey matter induced by training. Nature 2004; 427(6972): 311-2.

[2] Hanggi J, Koeneke S, Bezzola L, Jancke L. Structural neuroplasticity in the sensorimotor network of professional female ballet dancers. Hum Brain Mapping 2010; 31(8): 1196-206.

[3] Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 2008; 9(1): 58-65.

[4] Pereira AC, Huddleston DE, Brickman AM, et al. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci USA 2007; 104(13): 5638-43.

[5] Kronenberg G, Bick-Sander A, Bunk E, Wolf C, Ehninger D, Kempermann G. Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. Neurobiol Aging 2006; 27(10): 1505-13.

[6] Thakker-Varia S, Krol JJ, Nettleton J, et al. The neuropeptide VGF produces antidepressant-like behavioral effects and enhances proliferation in the hippocampus. J Neurosci 2007; 27(45): 12156- 67.

[7] Brene S, Bjornebekk A, Aberg E, Mathe AA, Olson L, Werme M. Running is rewarding and antidepressive. Physiol Behav 2007; 92(1-2): 136-40.

[8] Stein DJ, Collins M, Daniels W, Noakes TD, Zigmond M. Mind and muscle: the cognitive-affective neuroscience of exercise. CNS Spectr 2007; 12(1): 19-22.

[9] Claflin ES, Krishnan C, Khot SP. Emerging treatments for motor rehabilitation after stroke. Neurohospitalist 2015; 5(2): 77-88.

[10] Dimyan MA, Cohen LG. Contribution of transcranial magnetic stimulation to the understanding of functional recovery mechanisms after stroke. Neurorehabil Neural Repair 2010; 24(2): 125-35.

[11] Rizzolatti G, Fogassi L. The mirror mechanism: recent findings and perspectives. Phil Trans Royal Soc Lond Ser B Biol Sci 2014; 369(1644): 20130420.

[12] Oztop E, Kawato M, Arbib MA. Mirror neurons: functions, mechanisms and models. Neurosci Lett 2013; 540: 43-55.

[13] Rizzolatti G, Craighero L. The mirror-neuron system. Annu Rev Neurosci 2004; 27: 169-92.

[14] Cook R, Bird G, Catmur C, Press C, Heyes C. Mirror neurons: from origin to function. Behav Brain Sci 2014; 37(2): 177-92.

[15] D'Ausilio A, Bartoli E, Maffongelli L. Grasping synergies: a motor-control approach to the mirror neuron mechanism. Phys Life Rev 2015; 12: 91-103.

[16] Casile A, Caggiano V, Ferrari PF. The mirror neuron system: a fresh view. Neuroscientist 2011; 17(5): 524-38.

[17] Cattaneo L, Rizzolatti G. The mirror neuron system. Arch Neurol 2009; 66(5): 557-60.

[18] Zult T, Howatson G, Kadar EE, Farthing JP, Hortobagyi T. Role of the mirror-neuron system in cross-education. Sports Med 2014; 44(2): 159-78.

[19] Mukamel R, Ekstrom AD, Kaplan J, Iacoboni M, Fried I. Singleneuron responses in humans during execution and observation of actions. Curr Biol 2010; 20(8): 750-6.

[20] Iacoboni M, Dapretto M. The mirror neuron system and the consequences of its dysfunction. Nat Rev Neurosci 2006; 7(12): 942-51.

[21] Fecteau S, Lepage JF, Theoret H. Autism spectrum disorder: seeing is not understanding. Curr Biol 2006; 16(4): R131-3.

[22] Casartelli L, Molteni M. Where there is a goal, there is a way: What, why and how the parieto-frontal mirror network can mediate imitative behaviours. Neurosci Biobehav Rev 2014; 47: 177-93.

[23] Ramachandran VS, Seckel EL. Synchronized dance therapy to stimulate mirror neurons in autism. Med Hypoth 2011; 76(1): 150- 1.

[24] Zhu H, Sun Y, Zeng J, Sun H. Mirror neural training induced by virtual reality in brain-computer interfaces may provide a promising approach for the autism therapy. Med Hypoth 2011; 76(5): 646-7.

[25] Perkins TJ, Bittar RG, McGillivray JA, Cox, II, Stokes MA. Increased premotor cortex activation in high functioning autism during action observation. J Clin Neurosci 2015; 22(4): 664-9.

[26] Pokorny JJ, Hatt NV, Colombi C, Vivanti G, Rogers SJ, Rivera SM. The Action Observation System when Observing Hand Actions in Autism and Typical Development. Autism Res 2015; 8(3): 284-96.

[27] Fishman I, Keown CL, Lincoln AJ, Pineda JA, Muller RA. Atypical cross talk between mentalizing and mirror neuron networks in autism spectrum disorder. JAMA Psychiatry 2014; 71(7): 751-60.

[28] Fazio P, Cantagallo A, Craighero L, et al. Encoding of human action in Broca's area. Brain 2009; 132(Pt 7): 1980-8.

[29] Naeser MA, Martin PI, Treglia E, et al. Research with rTMS in the treatment of aphasia. Restor Neurol Neurosci 2010; 28(4): 511-29.

[30] Martin PI, Naeser MA, Ho M, et al. Research with transcranial magnetic stimulation in the treatment of aphasia. Curr Neurol Neurosci Rep 2009; 9(6): 451-8.

[31] Ahlsen E. Embodiment in communication--aphasia, apraxia and the possible role of mirroring and imitation. Clin Linguist Phonetics. 2008; 22(4-5): 311-5.

[32] Lee J, Fowler R, Rodney D, Cherney L, Small SL. IMITATE: An intensive computer-based treatment for aphasia based on action observation and imitation. Aphasiology 2010; 24(4): 449-65.

[33] Marangolo P, Bonifazi S, Tomaiuolo F, et al. Improving language without words: first evidence from aphasia. Neuropsychologia 2010; 48(13): 3824-33.

[34] Raymer AM, Singletary F, Rodriguez A, Ciampitti M, Heilman KM, Rothi LJ. Effects of gesture+verbal treatment for noun and verb retrieval in aphasia. J Int Neuropsychol Soc 2006; 12(6): 867- 82.

[35] Wang W, Zhang X, Ji X, et al. Mirror neuron therapy for hemispatial neglect patients. Sci Rep 2015; 5: 8664.

[36] Catmur C, Walsh V, Heyes C. Sensorimotor learning configures the human mirror system. Curr Biol 2007; 17(17): 1527-31.

[37] Schunke O, Schottle D, Vettorazzi E, et al. Mirror me: Imitative responses in adults with autism. Autism 2015; [Epub ahead of print]. [38] Buccino G. Action observation treatment: a novel tool in neurorehabilitation. Phil Trans Royal Soc Lond Ser B Biol Sci 2014; 369(1644): 20130185.

[39] Ertelt D, Small S, Solodkin A, et al. Action observation has a positive impact on rehabilitation of motor deficits after stroke. Neuroimage 2007; 36(Suppl 2): T164-73.

[40] Small SL, Buccino G, Solodkin A. The mirror neuron system and treatment of stroke. Dev Psychobiol 2012; 54(3): 293-310.

[41] Franceschini M, Agosti M, Cantagallo A, Sale P, Mancuso M, Buccino G. Mirror neurons: action observation treatment as a tool in stroke rehabilitation. European journal of physical and rehabilitation medicine 2010; 46(4): 517-23.

[42] Dohle C, Pullen J, Nakaten A, Kust J, Rietz C, Karbe H. Mirror therapy promotes recovery from severe hemiparesis: a randomized controlled trial. Neurorehabilitation and neural repair. 2009; 23(3): 209-17.

[43] Altschuler EL, Wisdom SB, Stone L, et al. Rehabilitation of hemiparesis after stroke with a mirror. Lancet 1999; 353(9169): 2035-6.

[44] Brunner IC, Skouen JS, Ersland L, Gruner R. Plasticity and response to action observation: a longitudinal FMRI study of potential mirror neurons in patients with subacute stroke. Neurorehabil Neural Repair 2014; 28(9): 874-84.

[45] Frenkel-Toledo S, Bentin S, Perry A, Liebermann DG, Soroker N. Mirror-neuron system recruitment by action observation: effects of focal brain damage on mu suppression. NeuroImage 2014; 87: 127- 37.

[46] Small SL, Buccino G, Solodkin A. The mirror neuron system and treatment of stroke. Devel Psychobiol 2012; 54(3): 293-310.

[47] Numata K, Murayama T, Takasugi J, Monma M, Oga M. Mirror observation of finger action enhances activity in anterior intraparietal sulcus: a functional magnetic resonance imaging study. J Jpn Phys Ther Assoc 2013; 16(1): 1-6.

[48] Baldissera F, Cavallari P, Craighero L, Fadiga L. Modulation of spinal excitability during observation of hand actions in humans. Eur J Neurosci 2001; 13(1): 190-4.

[49] Nishimura Y, Onoe H, Morichika Y, Perfiliev S, Tsukada H, Isa T. Time-dependent central compensatory mechanisms of finger dexterity after spinal cord injury. Science 2007; 318(5853): 1150-5

[50] Kohler E, Keysers C, Umilta MA, Fogassi L, Gallese V, Rizzolatti G. Hearing sounds, understanding actions: action representation in mirror neurons. Science 2002; 297(5582): 846-8.

[51] Proverbio AM, Calbi M, Manfredi M, Zani A. Audio-visuomotor processing in the Musician's brain: an ERP study on professional violinists and clarinetists. Sci Rep 2014; 4: 5866.

[52] Altschuler EL. Play with online virtual pets as a method to improve mirror neuron and real world functioning in autistic children. Med Hypotheses 2008; 70(4): 748-9.

[53] D'Ausilio A. Mirror-like mechanisms and music. ScientificWorldJournal 2009; 9: 1415-22.

[54] Molnar-Szakacs I, Overy K. Music and mirror neurons: from motion to 'e'motion. Soc Cogn Affect Neurosci 2006; 1(3): 235-41.

[55] Fadiga L, Craighero L, D'Ausilio A. Broca's area in language, action, and music. Ann NY Acad Sci 2009; 1169: 448-58.

[56] Tillmann B, Janata P, Bharucha JJ. Activation of the inferior frontal cortex in musical priming. Brain Res Cogn Brain Res 2003; 16(2): 145-61.

[57] Sparks R, Helm N, Albert M. Aphasia rehabilitation resulting from melodic intonation therapy. Cortex 1974; 10(4): 303-16.

[58] Norton A, Zipse L, Marchina S, Schlaug G. Melodic intonation therapy: shared insights on how it is done and why it might help. Ann NY Acad Sci 2009; 1169: 431-6.

[59] Merrett DL, Peretz I, Wilson SJ. Neurobiological, cognitive, and emotional mechanisms in Melodic Intonation Therapy. Front Hum Neurosci 2014; 8: 401.

[60] Tomaino CM. Effective music therapy techniques in the treatment of nonfluent aphasia. Ann NY Acad Sci 2012; 1252(1): 312-7.

[61] van Wijck F, Knox D, Dodds C, Cassidy G, Alexander G, Macdonald R. Making music after stroke: using musical activities to enhance arm function. Ann NY Acad Sci 2012; 1252(1): 305-11.

[62] Forsblom A, Laitinen S, Sarkamo T, Tervaniemi M. Therapeutic role of music listening in stroke rehabilitation. Ann NY Acad Sci 2009; 1169: 426-30.

[63] Sarkamo T, Tervaniemi M, Laitinen S, et al. Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. Brain 2008; 131(Pt 3): 866-76.

[64] Jorge RE. Neuropsychiatric consequences of traumatic brain injury: a review of recent findings. Curr Opin Psychiatry 2005; 18(3): 289- 99.