Mirror neuron therapy for hemispatial neglect patients

Wei Wang1,*, Xin Zhang2,*, Xiangtong Ji1, Qian Ye1, Wenli Chen1, Jun Ni3, Guangyu Shen3, Bing Zhang3, Ti-Fei Yuan* & Chunlei Shan1,5

1Department of Rehabilitation Medicine, First Affiliated Hospital of Nanjing Medical University, Nanjing, 210029, China, 2Department of Radiology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, 321 Zhongshan Road, Nanjing, China, 3The affiliated hospital of Nantong University, Nantong, China, 4School of Psychology, Nanjing Normal University, Nanjing, 210097, China, 5Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, China.

Mirror neuron system (MNS) based therapy has been employed to treat stroke induced movement disorders. However, its potential effects on patients with hemispatial neglect were uninvestigated. The present study set out to test the therapeutic efficiency of video watching of series of hand actions/movements (protocol A) in two patients with left hemispatial neglect, due to the right hemisphere stroke. The video containing dynamic landscape of natural scene or cities but not human/animals was used as the protocol B. The “ABA” training procedure for 3 weeks therefore allows us to internally control the individual differences. Before and after each week of training, the Chinese behavioral inattention test- Hongkong version (CBIT-HK) was implemented to evaluate the hemispatial neglect severity. Functional magnetic resonance imaging (fMRI) experiment was implemented in two health subjects to reveal the difference of brain activation between protocol A and B. The results showed that protocol A rather than protocol B significantly improved the CBIT-HK scores at first and third weeks, respectively. Protocol A induced more bilateral activations including right inferior parietal lobe (supramarginal gyrus), which belongs to MNS and is also critical region resulting to hemineglect. Conclusion: MNS activation can provide a novel therapy for hemispatial neglect patients.

The unilateral neglect (hemineglect) is also defined as unilateral spatial neglect or hemispatial neglect, which includes the loss of visual perception to objects within the visual area opposite to lesion hemisphere (commonly right lesion and left hemineglect). Hemispatial neglect is common as complications of patients following brain injuries1, and the incidence ranged 10%–82% for right hemisphere stroke patients2, mainly as 40%–44%. Right inferior parietal lobule is considered as the main brain region responsible for left hemispatial neglect2–7. The presence of hemispatial neglect leads to adverse effects on motor activities, and the life of quality in patients4.

Mirror neuron is one of the most important discoveries in neuropsychology field. Mirror neuron will fire both when executing the movement (e.g. hand movement) and observing the same movement2. Mirror neuron is therefore considered as important neural substrate for action understanding, imitation, language learning and empathy. Mirror neuron system (MNS) mainly includes inferior frontal gyrus (BA44), premotor cortex (BA6), and inferior parietal lobule (BA39,40) in the brain2. It has been found that mirror neuron system activation could lead to improvements in motor functions in stroke patients6,11, as well as language functions of stroke patients with aphasia (unpublished data). Given the fact that hemispatial neglect is due to the dysfunction of inferior parietal lobule (critical MNS areas), we wonder if the activation of MNS by hand action observation could result in improvements of hemispatial neglect symptoms.

Methods

Behavioral experiment. Clinical data. The study has been performed according to the guidelines of clinical medical research in Nanjing Medical University and has been approved by the ethic committee of medical research on human subjects in Nanjing Medical University. Informed written consents were obtained from both cases. Case 1: Male, 64 years old, right handed, middle school education. The patient was admitted to the hospital on Jan 2014 due to the sudden headache, vomiting and left side body paralysis. The head CT revealed hemorrhage at the right occipital and parietal lobe (see Fig. 1A). The patient was treated to lower the intracranial pressure, nervous system nutrition, improve the micro-circulation. The patient was then diagnosed as left hemispatial neglect. On Feb 2014, the Brunnstrom stages: Left upper limb III, left hand IV, and left lower limb IV. The mini-mental state examination (MMSE) scored 29. The patient also received muscle stretch training, balance training, standing training, and other routine activities of daily rehabilitation.
Flip Angle were acquired using EPI with the following parameters: TR = 2000 ms, TE = 30 ms, Flip Angle = 90°, FOV = 192*192*140 mm³, Acquisition Matrix = 64*64, number of slices = 35, slice thickness = 4 mm and number of repetitions = 180. A 3D T1-weighted, high-resolution anatomical image set was also acquired from each subject for functional map overlay with the following parameters: TR = 9.8 ms, TE = 4.6 ms, Flip Angle = 8°, FOV = 200*200*192 mm³, Acquisition Matrix = 200*180, number of slices = 192, slice thickness = 1 mm.

Results

Behavior performance on BIT. We found that in compared to pre-test, the protocol A training at the first and third weeks significantly improved conventional test score, behavioral test score and the total CBT-HK scores (P < 0.05), while the protocol B training did not (except for total score in case 2).

In compared to the second week training with protocol B, the protocol A training at the third week exhibited benefits in all aspects (P < 0.05) (Table 1).

fMRI Results and Comparison of fMRI activations between Protocol A and B. Common activations induced by Protocol A and B include bilateral occipital, ventral occipitotemporal, premotor cortex and left superior parietal cortex. The difference of activation areas or stronger activations in Protocol A rather than Protocol B are showed in Fig. 2B.

The Fig. 2B and 2C indicated that for JXT (upper), Protocol A induced more activations in left ventral primary motor and sensory area (BA4, BA1–3), left inferior parietal lobule(supramarginal gyrus, BA 40), left Wernicke area(superior temporal gyrus, BA22), right superior parietal lobule (BA5), right inferior parietal lobule(supramarginal gyrus, BA 40) and right ventral occiptotemporal cortex (BA37).

The Fig. 2B and 2C also illustrated that for ZSC (lower), Protocol A induced more activations in left superior lobule (BA 5), left inferior parietal lobule (including supramarginal gyrus, BA 40), left Wernicke area(superior temporal gyrus, BA22), left ventral occipitotemporal cortex (BA37), right superior parietal lobule (BA5), right inferior parietal lobule (including upper part of supramarginal gyrus, BA 40) and right ventral occiptotemporal cortex (BA37).

The cluster volume, MNI coordinates of activations in the Right Inferior Parietal Lobule or Right Supramarginal Gyrus (BA 40) of JXT and ZSC were showed in Table 2 (Table 2).

Discussion

In recent years, the mirror neuron system (MNS) activation has been employed in brain rehabilitation from stroke, especially for motor function and language functions. However, to our knowledge, the present study is the first to explore the potential benefits of MNS therapy on hemispatial neglect. We found that the protocol A resulted in clear and better rehabilitation effects on all cases presented, in compared to the protocol B. Not only from literature but also from fMRI experiment results in this study, we can believe that hand action observation (Protocol A) could induce or induce more (than Protocol B) activations in MNS especially in inferior parietal lobule(including supramarginal gyrus BA40), which is the most critical lesion site for hemineglect. This proved that MNS activation therapy could potentially treat hemispatial neglect.

The neural mechanisms underlying MNS activation therapy are unknown. It is proposed that the activation of MNS led to brain plasticity, potentially mediated by glutamatergic and neurotrophic mechanisms – which were found to be important in activity dependent brain plasticity. In addition, right inferior parietal lobule belongs to the MNS, the activation of which might facilitate the functioning of this brain region, and therefore improve the relative spatial perception or attention function. Whether the MNS therapy contributes to facilitated brain reorganization is yet to be understood in future studies.

We found that one week training with protocol A was sufficient to improve the visual spatial perception in the patients. In fact, it is
shown that the hemispatial neglect could be partly treated with short-period training (e.g. 2 days or 4 days prism training); on the other hand, this is in accordance with the fact that MNS activation therapy was able to improve the motor function and language function in very short period (1–2 weeks)\textsuperscript{15,16}.

The present study adopted “ABA” sequence for video training. ABA is highly suitable for studies in department of rehabilitation, given the same hospitalization period for most patients; in addition, ABA is used to judge for the effects of self-recovery, tiring effect on training. Therefore the score decrease at the

**Figure 2 | fMRI experiment.** (2A): Demo of the run of video blocks (This is Run 1, i.e. Protocol ABBA. In Run2, is Protocol BAAB). The images were taken by the authors, and the hand picture is from Xiangtong Ji. (2B): Illumination of distinct activations by Protocol A (stronger than Protocol B); upper is JXT and lower is ZSC. Blue solid arrow is corresponding to the Supramarginal Gyrus (BA 40) and blue hollow arrow is corresponding to the right Inferior Parietal Lobule. (2C): 2D illumination of distinct activations by Protocol A (stronger than Protocol B), upper is JXT and lower is ZSC. Yellow solid arrow is corresponding to the Supramarginal Gyrus(BA 40) and yellow hollow arrow is corresponding to the Right Inferior Parietal Lobule.
second week excluded the possibility of self-recovery in the patients.

The present study however requires more cases with longer-training period and longitudinal fMRI experiments for hemineglect patients in future experiments.

1. Parton, A., Malhotra, P. & Husain, M. Hemispatial neglect. J Neurol Neurosurg Psychiatry 75, 13–21 (2004).
2. Stone, S. P., Halligan, P. W. & Greenwood, R. J. The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. Age Ageing 22, 46–52 (1993).
3. Pedersen, P. M., Jorgensen, H. S., Nakayama, H., Raaschou, H. O. & Olsen, T. S. Hemineglect in acute stroke—incidence and prognostic implications. The Copenhagen Stroke Study. Am J Phys Med Rehabil 76, 122–127 (1997).
4. Ringman, J. M., Saver, J. L., Woolson, R. F., Clarke, W. R. & Adams, H. P. Frequency, risk factors, anatomy, and course of unilateral neglect in an acute stroke cohort. Neurology 63, 468–474 (2004).
5. Vallar, G. Extrapersonal visual unilateral spatial neglect and its neuroanatomy. NeuroImage 14, 552–58, doi:10.1006/nimg.2001.0822 (2001).
6. Halligan, P. W., Fink, G. R., Marshall, J. C. & Vallar, G. Spatial cognition: evidence from visual neglect. Trends Cog Sci 7, 125–133 (2003).
7. Mort, D. J. et al. The anatomy of visual neglect. Brain 126, 1986–1997, doi:10.1093/brain/awg200 (2003).
8. Di Monaco, M. et al. Severity of unilateral spatial neglect is an independent predictor of functional outcome after acute inpatient rehabilitation in individuals with right hemispheric stroke. Arch Phys Med Rehabil 92, 1250–1256, doi:10.1016/j.apmr.2011.03.018 (2011).
9. Rizzolatti, G. & Craighero, L. The mirror-neuron system. Annu Rev Neurosci 27, 169–192, doi:10.1146/annurev.neuro.27.070203.144230 (2004).
10. Small, S. L., Buccino, G. & Solodkin, A. The mirror neuron system and treatment of stroke. Dev Psychobiol 54, 293–310, doi:10.1002/dev.20504 (2012).
11. Sale, P. & Franceschini, M. Action observation and mirror neuron network: a tool for motor stroke rehabilitation. Eur J Phys Rehabil Med 48, 313–318 (2012).
12. Small, S. L., Buccino, G. & Solodkin, A. Brain repair after stroke—a novel neurological model. Nat Rev Neuro 9, 698–707, doi:10.1038/nrneurol.2013.222 (2013).
13. de Vries, S. & Mulder, T. Motor imagery and stroke rehabilitation: a critical discussion. J Rehabil Med 39, 5–13, doi:10.2340/16501977-0820 (2007).
14. Iacoboni, M. & Mazzotti, J. C. Mirror neuron system: basic findings and clinical applications. Ann Neurol 62, 213–218, doi:10.1002/ana.21198 (2007).
15. Marangolo, P., Cipolliari, S., Fiori, V., Razzano, C. & Caltagirone, C. Walking but not barking improves verb recovery: implications for action observation treatment in aphasia rehabilitation. PLoS One 7, e38610, doi:10.1371/journal.pone.0038610 (2012).
16. Marangolo, P. et al. Improving language without words: first evidence fromaphasia. Neuropsychologia 48, 3824–3833, doi:10.1016/j.neuropsychologia.2010.09.025 (2010).

Acknowledgments
The study was supported by National Natural Science Foundation of China (No. 81171853, No. 81472163), Jiangsu Provincial Natural Science Foundation (No. BK201150), Six Talents Peak Project of Jiangsu Province (No. N2011-WS-100), Fund of Jiangsu Province Health Development Project with Science and Education, Jiangsu Provincial Special Program of Medical Science (BL2011029), and the Priority Academic Program Development of Jiangsu Higher Education Institutions. The study is also supported by "Hundred Talents program", "Qing Lan Project" of Nanjing Normal University and Jiangsu Provincial Natural Science Foundation (No. BK20140917) (TY).

Author contributions
W.W., X.J., Q.Y., W.C., B.Z., T.Y. and C.S. designed the study; W.W., X.J., Q.Y., W.C., J.N., G.S., T.Y. and C.S. performed the study; W.W., J.N., G.S., T.Y. and C.S. analyzed the data; W.W., T.Y. and C.S. wrote the manuscript; all authors have read the approved the final version of the manuscript.

Additional information
Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Wang, W. et al. Mirror neuron therapy for hemispatial neglect patients. Sci. Rep. 5, 8664; DOI:10.1038/srep08664 (2015).

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder in order to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/

| Table 1 | The conventional and behavioral test scores |
|---------|------------------------------------------|
|         | Conventional test | Behavioral test | CBIT-HK total score |
|         | Case 1 | Case 2 | Case 1 | Case 2 | Case 1 | Case 2 |
| Pre-test | 40    | 45    | 8     | 15    | 48    | 60    |
| 1 week   | 61a   | 75a   | 19a   | 31a   | 80a   | 106ab |
| 2 weeks  | 48    | 61    | 15    | 23    | 63    | 84a   |
| 3 weeks  | 70ab  | 82ab  | 31ab  | 44ab  | 101ab | 126ab |

Note: *P < 0.05 in compared to pre-test; *P < 0.05 in compared to 2 weeks.

| Table 2 | Activations in the Right Inferior Parietal Lobule or Right Supramarginal Gyrus (BA 40) |
|---------|-----------------------------------------------|
| Subject | Brain Area                     | Cluster Volume(mm3) | MNI Coordinates(x, y, z) | T   | Z  |
| JXT     | R Supramarginal Gyrus            | 4887               | 61,−24,24                | 5.13| 5.03|
| ZSC     | R Supramarginal Gyrus            | 1782               | 36,−35,44                | 4.91| 4.82|
|         | R Inferior Parietal Lobule       | 3078               | 45,−35,54                | 3.94| 3.89|
Erratum: Mirror neuron therapy for hemispatial neglect patients

Wei Wang, Xin Zhang, Xiangtong Ji, Qian Ye, Wenli Chen, Jun Ni, Guangyu Shen, Bing Zhang, Ti-Fei Yuan & Chunlei Shan

*Scientific Reports* 5:8664; doi: 10.1038/srep08664; published online 02 March 2015; updated on 26 August 2015

In the original version of this Article, Wei Wang and Xin Zhang were incorrectly listed as being affiliated with 'Shanghai University of Traditional Chinese Medicine, Shanghai. 201203, China' (affiliation 5) and Chunlei Shan was listed as not being affiliated with 'Shanghai University of Traditional Chinese Medicine, Shanghai. 201203, China.' These errors have been corrected in the PDF and HTML versions of the Article.