Journal of Clinical Neuroscience 60 (2019) 79–83

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical study

Activation of mirror neuron system during gait observation in sub-acute stroke patients and healthy persons

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ARTICLE INFO

Article history:
Received 31 August 2018
Accepted 27 September 2018

Keywords:
Gait observation
Mirror neuron system
Stroke
fMRI

ABSTRACT

The observation of walking improves gait ability in chronic stroke survivors. It has also been suggested that activation of the mirror neuron system contributes to this effect. However, activation of the mirror neuron system during gait observation has not yet been assessed in sub-acute stroke patients. The objective of this study was to clarify the activation of mirror neuron system during gait observation in sub-acute stroke patients and healthy persons. In this study, we sequentially enrolled five sub-acute stroke patients who had undergone gait training and nine healthy persons. We used fMRI to detect neuronal activation during gait observation. During the observation period in the stroke group, neural activity in the left inferior parietal lobule, right and left inferior frontal gyrus was significantly higher than during the rest period. In the healthy group, neural activity in the left inferior parietal lobule, left inferior frontal gyrus, left middle frontal gyrus, left superior temporal lobule and right and left middle temporal gyrus was significantly higher than during the rest period. The results indicate that the mirror neuron system was activated during gait observation in sub-acute stroke patients who had undergone gait training and also in healthy persons. Our findings suggest that gait observation treatment may provide a promising therapeutic strategy in sub-acute stroke patients who have experienced gait training.

1. Introduction

Reconstruction of gait is one of the main goals of stroke rehabilitation [1]. Recent studies have combined action observation with gait training as a treatment for reconstructing gait in chronic stroke survivors who were able to walk independently [2,3]. Observing the actions of a healthy person combined with gait training is thought to be helpful for promoting motor ability [4–6].

In 1996, it was reported that neural activity occurred in the ventral premotor cortex area of monkeys, both when the monkeys performed an action and when they observed a similar action made by another monkey or by the experimenter. The neurons activated in this way were named "mirror neurons" [7–9]. The premotor cortex in the monkey is similar to the inferior frontal gyrus (Brodmann areas 44 and 45) in humans [10]. A later study revealed that mirror neurons are activated in humans when observing hand and arm actions [11,12]. Further studies confirmed the activity of mirror neurons in the inferior parietal lobule and superior temporal sulcus [11,13,14]. The area comprising the inferior frontal gyrus, inferior parietal lobule and superior temporal sulcus has been called the "mirror neuron system" [10,15,16]. Functional magnetic resonance imaging (fMRI) studies have suggested that the mirror neuron system is also activated when observing other kinds of movement. Neural activity in the parietal lobe was reported when observing actions such as kicking a ball and grasping a cup, suggesting that the mirror neuron system is activated when observing movements of the feet, hands and mouth [17]. Furthermore, activation of the mirror neuron system during action observation has been shown to contribute to motor learning [18].

Ertelt et al. [6] reported that activation of the mirror neuron system when observing the upper limb movements of a healthy person was related to improvements in the paretic upper limb function in chronic stroke survivors. Many studies have also shown

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https://doi.org/10.1016/j.jocn.2018.09.035
0967-5868/

that action observation improves upper limb functioning in stroke survivors [19–23]. In addition, action observation treatment improves gait ability not only in chronic stroke survivors with independent gait ability [2,3,24,25], but also in the patients with orthopaedic disease and Parkinson's disease [26,27]. However, the relationship between the improvement in gait ability through gait observation and the activation of the mirror neuron system remains to be determined. Furthermore, activation of the mirror neuron system during gait observation treatment in sub-acute stroke patients and healthy persons has not been assessed to date. If the mirror neuron system is activated by gait observation in sub-acute stroke patients during gait training, then it could be helpful for patients undergoing rehabilitation in the sub-acute phase after stroke. We tested our hypothesis that gait observation activates the mirror neuron system in sub-acute stroke patients during gait training as well as in healthy persons.

Our results show, for the first time, that the mirror neuron system is activated during gait observation in sub-acute stroke patients during gait training and in healthy persons.

2. Methods

2.1. Participants

We recruited stroke patients who were admitted to the stroke care unit of the Tokushima University Hospital from January 2015 to June 2016. We also recruited healthy control participants using advertisements. The inclusion criteria for acute stroke patients were adults aged 40–70 years and National Institutes of Health Stroke Scale (NIHSS) score of 9 or less (i.e., mild stroke) [28]. The NIHSS evaluates the level of consciousness, visual fields, facial palsy, upper limb and lower limb motor drift, ataxia, sensation, language and dysarthria. Scores range from 0 to 42 points with lower scores representing milder impairment [29]. Exclusion criteria were stroke patients with a prior history of stroke, unilateral spatial neglect, visual impairment interfering with the study protocol, major cognitive problems and orthopaedic disease of the lower limbs. Stroke patients who had no experience of gait training were also excluded because previous studies have reported that the mirror neuron system is not activated if the observer has no experience of gait training [30,31]. Informed consent was received from all participants. The study was approved by the Ethics Committee of Tokushima University and was conducted in accordance with the Declaration of Helsinki of 1996.

2.2. Assessment of stroke patients

Depending on their clinical presentation and condition at admission, patients were examined with computed tomography and/or magnetic resonance imaging. Diagnoses were made by neurosurgeons and neurologists in all cases. A physiotherapist with 11–12 years' experience assessed patients using the NIHSS, modified Rankin Scale (mRS) [32], Brunnstrom Recovery Stage (BRS) [33] and Functional Ambulation Classification (FAC) [34]. The mRS is a measure of global disability that has been widely used to assess outcomes after stroke. The scale consists of six grades from 0 (no symptoms) to 5 (severe disability), while 6 indicates death [32]. The BRS evaluates the motor recovery process in six stages following stroke hemiplegia. Patients who display complete flaccidity and no voluntary movement are classified as stage one, and when spasticity disappears and near-normal joint movements return they are classified as stage six [33]. The FAC is a functional walking test that evaluates ambulation ability by determining how much human support the patient requires when walking, regardless of whether a personal assistive device is used. Scores range from 0 to 5 and lower scores represent more severe disability [34].

2.3. MRI data acquisition and functional imaging

Anatomical and functional images were recorded using a 3T GE MR 750 MRI scanner (GE Healthcare, Waukesha, WI, USA) with a 32-channel head coil. Anatomical T1-weighted images were acquired using the standard imaging parameters (repetition time (RT) = 8.1 ms, echo time (ET) = 3.6 ms, flip angle = 15°, slices = 90, slice thickness = 1.8 mm, field of view (FoV) = 240 × 240 mm, matrix = 320 × 256 × 1.8 mm, voxel size = 0.75 × 0.9375 × 1.8 mm^3). For functional imaging, a gradient-echo planar imaging (EPI) sequence with the following parameters was used: RT = 3000 ms, ET = 27 ms, flip angle = 90°, slices = 35, slice thickness = 4 mm, FoV = 240 × 240 mm, matrix = 128 × 128 × 4 mm, voxel size = 1.875 × 1.875 × 4 mm^3.

The present study used a block design. Fig. 1 shows the flow of the study. The fMRI block-design consisted of two tasks: six 30-s rest periods and six 30-s observation blocks. Rest periods and observation blocks were presented alternately and the total task time was 6 min. Each run consisted of 10 scan volumes, and thus the total number of volumes was 120 (6 rest periods × 10 scan volumes + 6 observation blocks × 10 scan volumes = 120 scan volumes). The participants were asked to look at a static cross on a white board during the rest period and to watch a healthy adult man (62 years old) walking during the observation block. With respect to using a photograph in an online open-access publication, we obtained written informed consent from a man. Participants were instructed to maintain their attention during both blocks to accurately capture their neuronal activities.

The first 5 of the 120 scan volumes were discarded to allow the magnet to stabilise, and the remaining 115 scan volumes per run were used in the analysis. Pre-processing was performed using Statistical Parametric Mapping (SPM12) and Matlab R2016b.

The images were realigned to correct for head motion and corrected for differences in slice timing within each image. T1-weighted anatomical images were co-registered with the main image of each subject. Each co-registered T1-weighted anatomical image was normalised to the Montreal Neurological Institute T1 image template [35]. Finally, the normalised images were smoothed using an isotropic Gaussian kernel of 8 mm full-width-at-half-maximum.

2.4. Lesion volumes

We constructed a lesion overlap image for stroke patients. We manually outlined the profiles on the individual T1-weighted images slice-by-slice using the MRIcron software package, thereby creating a lesion mask for each patient. After the spatial normalisation process, the combination of all individual lesion masks was used to construct a group lesion mask for the patients.

2.5. Statistical parametric mapping

Statistical parametric mapping was performed using SPM12 and Matlab R2016b. To perform a best fit of the measured fMRI time series using a general linear model, a boxcar function defining the timing of the paradigm was convolved with a canonical hemodynamic response function. The parameter estimates for each condition in each individual were compared using linear contrasts. We obtained the images of the observation blocks for individual analysis.

In the individual analysis, we obtained images that represented the normalised task-related increment of the MR signal of each subject for each predefined contrast. These contrast images were

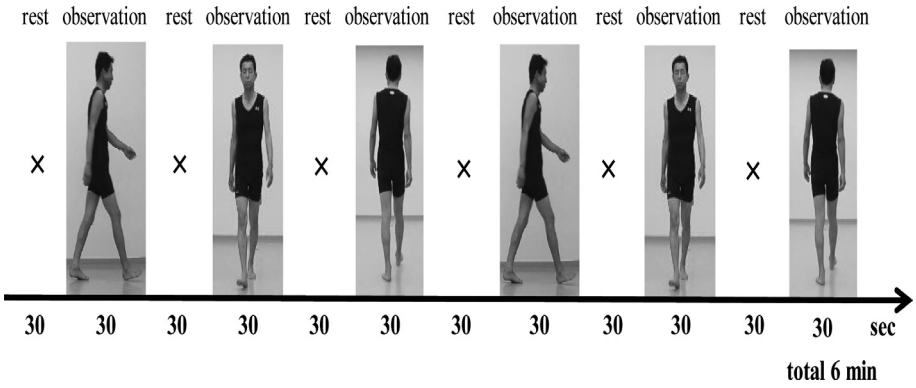

Fig. 1. fMRI block-design. The fMRI block design consisted of two tasks: six 30-s rest blocks and six 30-s observation blocks, which were presented alternately. The total task time was 6 min.

used for the group analysis. A single sample *t*-test was performed for every voxel in the brain to obtain population inferences. The statistical threshold for the spatial extent test on the clusters was set at $p < 0.05$ and corrected for multiple comparisons (family-wise error) over the whole brain [36].

Finally, a region of interest analysis was performed. Statistically significant voxel coordinates were transformed from the Montreal Neurological Institute to automated anatomical labelling and Brodmann areas by nonlinear transformation.

3. Results

3.1. Characteristics of subjects

During the recruitment period, 470 stroke patients were admitted to the stroke care unit of Tokushima University hospital, and 5 of these patients were recruited. Nine healthy persons were also enrolled. Table 1 reports the subjects' characteristics. The subjects in each group were of a similar age: 47–63 years in the stroke group and 50–59 in the healthy group. The proportion of men in the healthy group (33.3%) was lower than in the stroke group (80.0%). Four out of five stroke patients suffered a cerebral haemorrhage. Putamen haemorrhage was confirmed in four of the five stroke patients. Almost all patients received conservative treatment except one who was treated with intravenous thrombolysis. fMRI was evaluated on average 13.4 days after the onset stroke.

3.2. Neural activations were observed in stroke and healthy subjects during gait observation

Fig. 2 shows the fMRI patterns of neuronal activation in the stroke group and healthy group while watching a person walking. In the stroke group, significantly higher neural activation was observed during gait observation than during the rest period in the left inferior parietal lobule, right and left inferior frontal gyrus (triangularis), right postcentral, right and left precuneus, left inferior temporal lobule, left middle occipital gyrus, left lingual gyrus ($p < 0.01$) and right paracentral lobule ($p < 0.05$) (Table 2). The activated area included at least part of the mirror neuron system.

In the healthy group, neural activation in the left inferior parietal lobule, right and left middle temporal gyrus, right angular gyrus, left precentral gyrus ($p < 0.01$), left inferior frontal gyrus (orbital), left middle frontal gyrus, left superior temporal lobule (pole) and right superior parietal lobule ($p < 0.05$) was significantly higher during observation blocks than during the rest period (Table 2).

Table 1
Characteristics of subjects.

Stroke group		Sex	Diagnosis	Lesion	Hemiparetic side	Treatment	From time since stroke to scan (day)	mRS	NIHSS	BRS	FAC
No	Age (Yo)										
1	63	M	CH	Putamen	L	Conservative	16	4	6	4	0
2	62	M	CH	Putamen	L	Conservative	15	4	6	4	2
3	47	M	CH	Putamen	R	Conservative	12	4	6	4	0
4	57	F	CH	Putamen	R	Conservative	12	4	8	4	0
5	55	M	CI	Internal capsule	L	t-PA	12	4	7	4	1
Mean	56.8	4M	4 CH	4 Putamen	2 R	4 conservative	13.4	4.0	6.6	4.0	0.6
SD	6.4						1.9	0.0	0.9	0.0	0.9
Healthy group		Sex									
No	Age (Yo)										
1	59	M									
2	53	F									
3	52	F									
4	58	M									
5	55	F									
6	53	F									
7	54	F									
8	52	M									
9	50	F									
Mean	54.0	3M									
SD	2.9										

SD, standard deviation; M, male; F, female; CH, cerebral haemorrhage; CI, cerebral infarction; R, right; L, left; t-PA, tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; BRS, Brunnstrom Recovery Stage of lower limb; FAC, Functional Ambulation Classification.

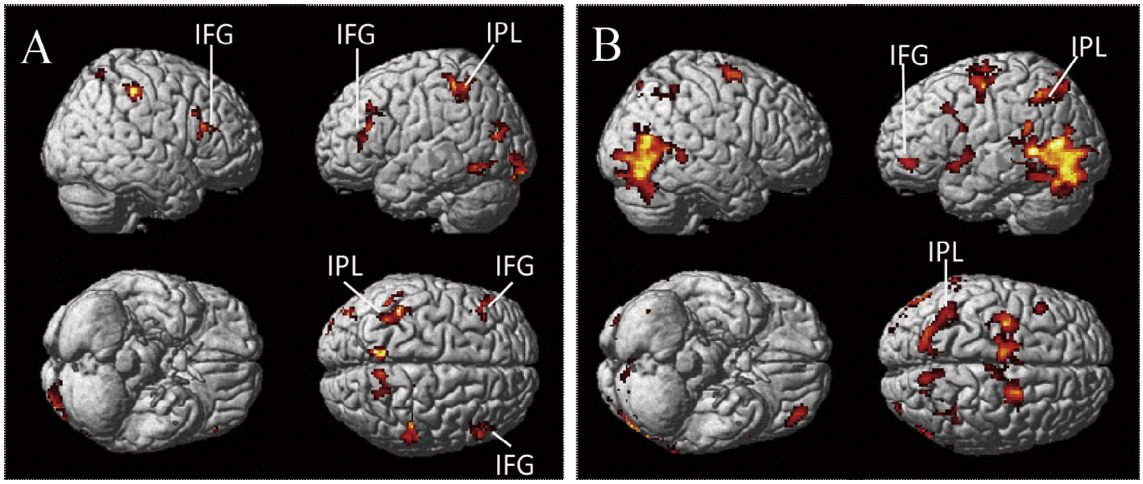

Fig. 2. Neural activity in the (A) stroke and (B) healthy groups. IPL, Inferior parietal lobule; IFG, Inferior frontal gyrus.

Table 2
Neural activities associated with gait observation in the stroke group and healthy group.

Stroke group (n = 5)						
Location side	Area	BA	MNI coordinates			$p_{(FWE)}$
			x	y	z	
L	Inferior parietal lobule	40	−34	−38	44	p < 0.01
L	Inferior parietal lobule	40	−56	−40	52	p < 0.05
L	Inferior frontal gyrus (triangularis)	45	−48	28	22	p < 0.01
R	Inferior frontal gyrus (triangularis)	45	54	26	20	p < 0.01
R	Postcentral	2	48	−30	50	p < 0.01
R	Paracentral lobule	–	14	−38	50	p < 0.05
R	Precuneus	5	6	−56	58	p < 0.01
L	Precuneus	5	−10	−60	60	p < 0.01
L	Inferior temporal lobule	37	−52	−58	−10	p < 0.01
L	Middle occipital gyrus	39	−40	−82	20	p < 0.01
L	Lingual gyrus	18	−22	−100	−14	p < 0.01
Healthy group (n = 9)						
Location side	Area	BA	MNI coordinates			$p_{(FWE)}$
			x	y	z	
L	Inferior parietal lobule	40	−32	−52	42	p < 0.01
L	Inferior frontal gyrus (orbital)	47	−38	48	−10	p < 0.05
L	Middle frontal gyrus	44	−44	18	40	p < 0.05
L	Superior temporal lobule (pole)	38	−52	10	−10	p < 0.05
L	Middle temporal gyrus	37	−52	−68	10	p < 0.01
R	Middle temporal gyrus	37	52	−64	0	p < 0.01
R	Superior parietal lobule	7	12	−72	54	p < 0.05
R	Angular gyrus	40	32	−54	42	p < 0.01
L	Precentral gyrus	-	−32	−6	62	p < 0.01

L, left; R, right; BA, Brodmann's area; MNI, Montreal Neurological Institute; $p_{(FWE)}$, family-wise error correction p value <0.05.

4. Discussion

This study is the first to demonstrate neural activation through gait observation in sub-acute stroke patients and healthy persons. Significant activation was found in the left inferior parietal lobule, right and left inferior frontal gyrus (triangularis), right postcentral, right paracentral lobule, right and left precuneus, left inferior temporal lobule, left middle occipital gyrus and left lingual gyrus during gait observation in the stroke group. As the inferior parietal lobule, superior temporal sulcus and the area comprising the inferior frontal gyrus has been called the "mirror neuron system" [10,15,16], our findings suggest the activation of mirror neuron system. Furthermore, the observed visual information is passed from the occipital lobe to the ventral side of the temporal association area and dorsal side of the parietal association area [37]. The ventral pathway processes morphological information in the inferior temporal lobule [37]. The dorsal pathway, which includes the superior parietal lobule, inferior parietal lobule and premotor cortex network, mainly processes spatial information and executes action [37]. Considering the ventral and dorsal pathways of visual information processes, our results suggest that the information obtained from gait observation was input as visual information to the occipital lobe of the lingual gyrus and middle occipital gyrus and processed as action by the inferior temporal lobule and inferior parietal lobule. It has been reported that neural activation in the inferior parietal lobule, inferior frontal gyrus and superior temporal sulcus indicates activation of the mirror neuron system [10,15]. Taken together, our findings indicate that the mirror neuron system is at least partly activated stimulated through visual input by the observation of gait in sub-stroke patients.

Interestingly, neural activity in the triangularis, which is part of the inferior frontal gyrus, was confirmed in the sub-stroke patients. The triangularis is known as Broca's area, which is related to language production, internal verbalisation, movement execution

and action recognition [17,38]. Considering our results, these functions of Broca's area may relate to the gait observation effects in sub-acute stroke patients.

In healthy subjects, previous studies reported neural activity while observing upper and lower extremity and mouth movements [39,40]. However, there was no report regarding neural activation during gait observation. We first demonstrated the neural activation of the superior parietal lobule, angular gyrus and precentral gyrus during gait observation in the healthy group. Our findings have no discrepancy with the previous studies indicating the relationship between the neural activation and the observation of movements in healthy subjects [39,40].

During gait observation in the healthy group, significant neural activation was observed in the left inferior parietal lobule, left inferior frontal gyrus (orbital), left middle frontal gyrus, left superior temporal lobule (pole), right and left middle temporal gyrus, right superior parietal lobule, right angular gyrus and left precentral gyrus. Activity in the left superior temporal lobule and left middle temporal lobule, which are adjacent to the superior temporal sulcus, was also confirmed. Our results therefore indicate that the mirror neuron system in healthy persons is activated by the observation of gait.

Our study has several limitations. First, although this study demonstrated the instantaneous neural activity during gait observation, it did not reveal the long-term influence of gait observation on neural activity in stroke patients. Second, our results do not provide information about the neural activity of independent ambulatory stroke patients, because the stroke patients in this study were still unable to walk independently. Third, the sample size of the stroke patients in this study was small. Finally, we used the gait of a healthy adult man as the walking model. Therefore, the influence of gender and aging on neural activity is unknown. We will address these issues in further studies.

We observed the activation of the mirror neuron system during gait observation in stroke patients and healthy persons. Notably, other regions apart from the mirror neuron system were activated during gait observation. These findings suggest that gait even observation in the early post-stroke phase is a potentially useful approach for stroke patients during gait training.

Conflict of interest

The authors have no conflict of interest.

Acknowledgment

We thank the participants and staff members who helped with this study.

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