Neuroscience Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience Research

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

Action observation facilitates motor cortical activity in patients with stroke and hemiplegia

Marina Tani [a], Yumie Ono [b,*], Miku Matsubara [b], Satoko Ohmatsu [a], Yoshihiro Yukawa [a], Masashi Kohno [a], Takanori Tominaga [a]

[a] Murata Hospital, 4-2-1, Tajima, Ikuno-ku, Osaka 544-0011, Japan
[b] Health Science and Medical Engineering Laboratory, Department of Electronics and Bioinformatics, School of Science and Technology, Meiji University, 1-1-1 Higashi-mita, Tama-ku, Kawasaki, Kanagawa 213-8571, Japan

ARTICLE INFO

Article history:
Received 9 May 2017
Received in revised form
28 September 2017
Accepted 10 October 2017
Available online xxx

Keywords:
Event-related desynchronization
Electroencephalogram
Motor imagery
Stroke
Rehabilitation
Action observation

ABSTRACT

Motor imagery (MI) is a mental practice that reproduces the visual- and/or kinesthetic-modality brain activations accompanying movement. It is a useful rehabilitation technique as the affected motor cortex can be stimulated in patients with stroke and hemiplegia. However, most patients with stroke have difficulty with MI owing to advanced age and/or higher-cognitive dysfunction, thus impairing their ability to internally simulate the action. We therefore investigated whether action observation (AO), an alternative form of motor stimulation that works via the mirror-neuron system, could facilitate motor cortical activity in such patients. Combined AO and physical training of the observed actions has been reported to have a positive impact on motor deficits after stroke. Eleven patients with stroke and hemiplegia affecting the hand performed MI and AO with verbal and video instructions under 19 channels of electroencephalogram (EEG) recording. The event-related desynchronization (ERD) was measured as an electroencephalographic marker of motor cortical activity. The ERD power in the AO condition ($30.0 \pm 5.0\%$) was significantly higher than that in the MI condition ($12.2 \pm 3.9\%$). These results suggest that AO could be a good option for patients with stroke who have difficulty using MI to effectively stimulate and reestablish cortical-peripheral motor pathways.

1. Introduction

Upper-limb motor impairment after stroke is reported to often result in poor functional recovery compared with lower-limb motor impairment (Duncan et al., 1992) and remains a serious dysfunction (Van der Lee et al., 2001). Providing efficient and effective training for restoring upper-limb function is therefore considered important for rehabilitating stroke survivors to the point of regaining the activities of daily life and social participation (Wade et al., 1983).

Motor imagery (MI) is one of the potential techniques for enhancing motor recovery in patients with stroke when used concurrently with physical practice (Zimmermann-Schlatter et al., 2008; Eaves et al., 2016). MI is currently defined as a dynamic neuronal state wherein one internally rehearses the movement in working memory regardless of the existence of actual movement output (Decety and Grezes, 1999). Since the brain regions involved in movement execution and MI mostly overlap (Solodkin et al., 2004), mental training through MI may help patients retrain and reconstruct the formerly lost motor pathways.

Event-related desynchronization (ERD) is an event-related decrease in the mu-band (8–13 Hz) oscillatory activity recorded over the brain. When recorded over the sensorimotor cortex, it finds use as a measure of the excitation representing a central motor command, in MI as well as in movement execution (Pfurtscheller and Neuper, 1997). The mu rhythm is thought to represent the spontaneous firing (or idling state) of the thalamocortical motor circuit. ERD may result from the arrival of a depolarizing input from the thalamus that suppresses neuron activity in cortical layer IV (Lopes da Silva, 1991; Pfurtscheller et al., 1997). In healthy participants, the strength of an MI-induced ERD correlates well with corticospinal excitability (Takemi et al., 2013) and, in patients with stroke, with functional impairment (Kaiser et al., 2012).

Despite its demonstrated usefulness in sports science, combining MI with conventional therapy for stroke rehabilitation remains to be validated. Evidence of usefulness in this application remains modest due to the inconsistent outcomes of past studies (Zimmermann-Schlatter et al., 2008). Significantly, many patients with stroke have difficulty in generating MI in clinical settings in

* Corresponding author.
E-mail address: yumie@meiji.ac.jp (Y. Ono).

https://doi.org/10.1016/j.neures.2017.10.002
0168-0102/

Table 1
Patient profiles.

Case	Age	Sex	Type of stroke	Damaged lesion	Hemiplegic side	Time since Stroke, Days	fin/ BRS	SIAS	Higher brain function disorder	Frequency range for ERD detection	MMSE
1	67	F	I	R IC	L	541	V	2	NS	7–11	28
2	43	F	I	R F, P, T, BG, CR, Ins	L	162	III	1	USN Frontal lobe dysfunction,	9–13	29
3	73	M	I	R IC	L	1260	IV	2	NS	6–10	–
4	76	F	H	R Th	L	33	III	1	USN, Frontal lobe dysfunction	8–12	25
5	75	M	I	R F,IC	L	54	IV	2	USN, Frontal lobe dysfunction	6–10	21
6	47	M	H	R PU	L	320	III	1	USN, Frontal lobe dysfunction	6–10	27
7	55	F	I	R F, P, BG, CR, Ins	L	537	III	1	NS	8–12	–
8	75	M	I	L P	R	22	V	2	NS	8–12	21
9	72	M	I	L GP	R	18	V	2	NS	8–12	27
10	59	M	I	L BG,CR	R	69	V	2	Aphasia, Apraxia, Frontal lobe dysfunction	6–9	24
11	37	F	H	L PU	R	1919	III	1	Aphasia	8–12	–

Abbreviations;: M, Male; F, Female; I, Infarction; H, Hemorrhagic; PU, Putamen; BG, Basal ganglia; CR, Corona radiata; GP, Globus pallidus; P, Parietal lobe; Th, Thalamus; F, Frontal lobe; Ins, Insula; IC, Internal capsule; T, Temporal lobe; BRS, Brunnstrom stage; SIAS, Stroke Impairment Assessment Set; ERD, Event-Related Desynchronization; USN, Unilateral spatial neglect; MMSE, Mini–Mental State Examination; NS, No obvious symptom; R, Right; L, Left. MMSE was not performed on participants 3, 7, and 11 as the clinicians confirmed their cognitive ability as normal.

response to conventional verbal instructions. Moreover, Gregg et al. (2010) reported an interindividual difference in ability to generate MI, and De Beni et al. (2007) reported that the age of the participant affects their ability to generate MI. These findings raise the possibility that patients with stroke have difficulty in performing MI due to advanced age and/or an impaired ability to internally simulate an action without execution. The dependence of MI on the diverse abilities of patients may be limiting the use of MI-based mental practice for neurorehabilitation (Teo and Chew, 2014). A more reliable method for stimulating the affected motor cortex may be required to reach the next level of therapeutic outcomes.

Action observation (AO) is another promising methodology for promoting motor cortical activation even in the stroke brain. Acting via the brain's mirror neuron system (MNS), AO can subconsciously and directly activate the same group of motor neurons as those responsible for producing the observed action in the observer (Rizzolatti et al., 2001, 2014). Indeed, AO facilitates corticomotor excitability, improves motor function (Nojima et al., 2015), and appears to be a reliable technique for improving upper limb function after stroke (Buccino, 2014; Kim, 2015). These findings suggest that the involvement of the MNS plays a key role in inducing robust motor cortical activity and facilitating functional recovery of the stroke brain. However, most studies investigating the effect of AO in patients with stroke rely on a corticomuscular functional examination, such as motor evoked potential, and little attention has been paid to the effect of AO on ERD (Kim et al., 2011, 2014; Frenkel-Toledo et al., 2014, 2016; Behmer and Fournier, 2016). Previous studies in patients with stroke show that the AO-induced ERD is reduced in the affected hemisphere relative to the unaffected hemisphere (Frenkel-Toledo et al., 2014) and the extent of this impairment of the ERD correlates with the severity of ideomotor apraxia (Frenkel-Toledo et al., 2016). However, the contribution of the MNS to inducing ERD has not been clearly demonstrated due to the lack of any direct comparison between AO and MI in the same patients. Using sequential trunk exercises, Kim et al. (2014) reported AO to be superior to MI because it evoked stronger ERD in patients with stroke. However, all patients were in a chronic stage in that study and those with apraxia or cognitive impairment had been excluded. Since rehabilitation is maximally beneficial during the acute and recovery stages of stroke rather than the chronic stage, and since a non-negligible ratio of patients with stroke present with accompanying cognitive dysfunction, the beneficial effect of AO should be investigated in such patient populations.

The purpose of this study is, therefore, to examine the difference in ERD between MI and AO in a patient population ranging from acute to chronic stage and including those who suffer from cognitive dysfunction. We test the hypothesis that AO induces a larger ERD than does MI. If AO can help patients with stroke to produce robust ERDs despite having difficulty with MI, they might benefit from the ability of AO to activate the affected motor cortex and thus facilitate recovery.

2. Methods

2.1. Participants

Eleven patients with stroke participated in this study. All participants gave their written informed consent. The study was approved by the local ethics committee of Murata Hospital. Patients who had a bilateral lesion, mental disorder, or other neurologic disorder were excluded. The average time interval between stroke onset and the experiment was 466 days (range, 18–1,919 days). The age of the participants ranged from 37 to 76 years (mean ± standard deviation: 64.1 ± 7.8 years). The detailed patient profile is summarized in Table 1. On the day of the experiment, we evaluated the degree of paralysis by Brunnstrom recovery stage of the hand. We evaluated the degree of sensory disturbance based on the superficial touch and position senses of the upper extremity using the stroke impairment assessment set. Frontal lobe dysfunction of the cognitive and executive functions, including inhibitory control, problem solving, planning, and attentional switching was assessed by the trail making test, the frontal assessment battery, and the behavioral assessment of the dysexecutive syndrome. The scores of the participants who diagnosed with frontal lobe dysfunction are summarized in Table 2.

2.2. Experimental procedures

All participants performed the experimental task under two conditions, using MI and using AO (Fig. 1). Both conditions consisted of 50 trials, each trial consisting of a "Rest" and a "Task" period, shown alternately on a 20.1-in. LCD monitor placed 50 cm from the participant. To maximize MNS activity, participants were instructed to gaze at the center of the screen, avoid eye movement throughout the experiment (Maranesi et al., 2013), and minimize body motion. The experimenter carefully observed the

Please cite this article in press as: Tani, M., et al., Action observation facilitates motor cortical activity in patients with stroke and hemiplegia. Neurosci. Res. (2017), https://doi.org/10.1016/j.neures.2017.10.002

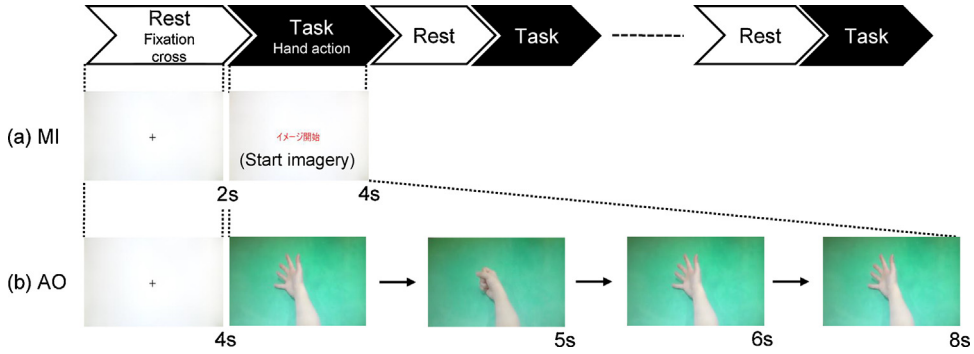

Fig. 1. Block design of the video stimuli in (a) MI and (b) AO sessions. (a) In the MI condition, each session consisted of 2 s of Rest and 2 s of Task, repeated 25 times. Participants imagined the hand action of 'grasp' during the Task phase. (b) In the AO condition, each session consisted of 4 s of Rest and 4 s of Task, repeated 25 times. Participants watched the hand action of 'grasp' during the first half of the Task phase. Participants performed two sessions in each condition with a rest between. MI, motor imagery; AO, action observation.

Table 2
Detailed assessment scores for frontal lobe dysfunction in selected participants. Bold font indicates that the score was below the cutoff value for the age of the participant and indicative of frontal lobe dysfunction. A dash means that the participant could not complete the test.

Case	TMT(A)	TMT(B)	FAB	BADS
2	**287**	**188**	**13**/18	17/24
4	**199**	**304**	**9**/18	**11**/24
5	**420**	–	**5**/18	–
6	**135**	**139**	16/18	**13**/24
10	**378**	–	**12**/18	**11**/24

Abbreviations: TMT, trail making test (parts A and B); FAB, frontal assessment battery; BADS, behavioral assessment of the dysexecutive syndrome.

participant to confirm head and body stability during the experiment.

During the Rest period, participants were instructed to look at a black fixation cross on a white background while maintaining a relaxed state. In the MI condition, after 2 s of Rest, verbal instructions were presented on the screen for a further 2 s (Task, Fig. 1a). The instructions encouraged participants to imagine opening and grasping with their paralyzed hand. The required timing of the hand movement to be imagined was fully explained to the participants before electroencephalogram (EEG) recording. In the AO condition, after 4 s of Rest, a 4-s video clip of a hand on the participant's paralyzed side opening and grasping was presented on the screen (Task) instead of verbal instructions. Since only the first 2 s of the video clip contained the moving hand (Fig. 1b), the durations of motor imagery in MI and motor observation in AO were consistent. The 50 trials were divided into two sessions of 25 trials, and the participants performed both sessions with a short break between.

2.3. EEG recording

Participants were seated in a comfortable armchair while wearing an EEG head cap (Miyuki Giken, Tokyo, Japan) connected to the EEG recording system (Neurofax EEG-1200; Nihon Koden, Tokyo, Japan). EEG data were recorded at a sampling rate of 500 Hz from 19 tin electrodes at Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2 of the International 10–20 System of electrode placement, with two additional reference electrodes attached to the left and right auricles. Each electrode was filled with Electrode Gel (Tokibo, Tokyo, Japan) to ensure good electrical contact between the electrodes and the skin. Electrode impedance was maintained below 10 kΩ. During the experiment, participants were instructed to keep their arms and hands relaxed. Actual execution of hand movement was prohibited throughout the experiment due to the presence of great interindividual variability in the participants' level of motor control. The surface electromyogram (EMG) of the first dorsal interosseous muscles on the paralyzed side was simultaneously monitored to confirm absence of muscular activity during MI or AO.

2.4. EEG analysis

Fig. 2 illustrates our method of ERD detection, which used time-frequency analysis of the EEG by wavelet transform. We determined ERD over the sensorimotor cortex on the affected hemisphere of the patient. Thus, in a patient with right hemiplegia, we analyzed the EEG at the C3 electrode with right-hand MI or AO, and in a patient with left hemiplegia, at the C4 electrode with left-hand MI or AO. We also determined the ERD by the same method at the counterpart electrode to enable comparison of ERD powers between the affected and unaffected hemispheres. ERD power was calculated as a percent difference of mu-band activities between Rest and Task periods using the following equation:

$$\text{ERD power } (\%) = 100 \times \frac{Baseline - \max ERD}{Baseline},$$

where *Baseline* refers to the mean power of the baseline mu-band activity during the last 1-s of the Rest period, and max*ERD* indicates the minimum mean power of mu-band activity during any 1-s interval within the first 2 s of the Task period (Fig. 2). Trials contaminated with artifacts defined as large (outside the amplitude range −100 to +100 μV) were excluded from the analysis. Preliminary analysis confirmed a wide interindividual frequency range for mu-band activity, ranging from 6 to 13 Hz in patients with stroke, which is consistent with a previous report from another group (Buch et al., 2008). Therefore, we determined for each participant the optimal frequency range for mu-band activity by selecting the frequency range that showed the largest average ERD power. The selected frequency ranges are shown in Table 1. To determine these individual best frequency ranges of mu-band activity, three experienced technicians blind to the experimental conditions and patient information evaluated time-frequency representations of the EEG signal averaged over trials and conditions. The three estimates of the participant-specific mu-band frequency ranges were averaged and rounded up, and then defined as the optimal frequency range for that participant on which to base further analysis.

The coefficient of variation (CV) of the mu-band power, a ratio of the standard deviation to the mean, was calculated during Rest and Task periods under both conditions to investigate whether the mean ERD power was affected by unstable mu-band activity, especially in participants with lower mean ERD power. Scalp distribution of ERD power was calculated using the topoplot function of EEGLAB (Delorme and Makeig, 2004). The images from all patients were averaged to obtain the grand-mean topographic

Please cite this article in press as: Tani, M., et al., Action observation facilitates motor cortical activity in patients with stroke and hemiplegia. Neurosci. Res. (2017), https://doi.org/10.1016/j.neures.2017.10.002

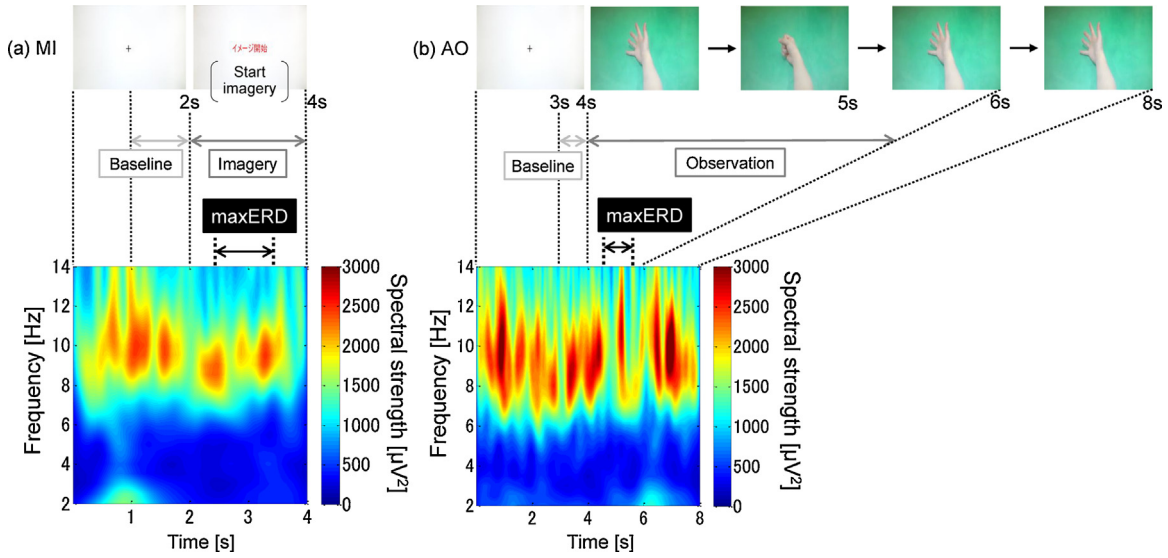

Fig. 2. Analysis time windows in (a) MI and (b) AO sessions and representative results of wavelet transform-based time-frequency analysis (Shown are data from electrode C3, participant 8, right hemiplegia, right-hand imagery.) ERD power was calculated by dividing the maximum suppression of mu-band activity (maxERD) during the first 2 s of the Task period (Imagery) by the baseline mu-band activity during the last 1 s of the Rest period (Baseline). MI, motor imagery; AO, action observation; ERD, event-related desynchronization.

images of ERD power under AO and MI conditions. (The topographic images of the patients with right hemiplegia were mirror-imaged about the midline before this averaging to ensure comparability with the left-hemiplegia cases.) We also investigated the correlation between individual cognitive ability and ERD power under MI and AO. Cognitive ability was represented by score on the mini-mental state examination (MMSE, Table 1). Since the absolute ERD power showed large interindividual variation under both MI and AO, due to differences in damaged brain regions and the severity of sensory-motor dysfunction, we focused on the relationship between individual MMSE scores and within-subject differences in ERD power between AO and MI.

2.5. Statistics

Normality of the data was confirmed using the Shapiro-Wilk test. The strength of the ERD power was compared between the two conditions using the paired *t*-test. The Pearson correlation coefficient (r) between ERD power differences and MMSE scores was also calculated for a subgroup of participants ($n = 8$) whose MMSE scores were available. We used statistical package for the social sciences v.20 for Windows (IBM Corporation, Armonk, NY, USA) for the statistical calculations, and p values less than 0.05 were considered statistically significant.

3. Results

Fig. 3 shows individual and grand-mean ERD powers under MI and AO, determined at the corresponding electrodes above the affected motor area (at C4 for participants 1–7 and at C3 for participants 8–11). The mean ERD powers under MI and AO in patients post-stroke were $12.2 \pm 3.9\%$ and $30.0 \pm 5.0\%$, respectively, showing a statistically significant increase in ERD power under AO compared with MI. Furthermore, in all participants, AO showed a larger ERD power compared with MI. Participants 4, 5, 6, 7, 8, and 10 showed a more than 10% increase in the ERD power under AO compared with MI. The increase of ERD power under AO was statistically larger than that under MI with participants 7 and 10. Furthermore, although participant 7 showed no ERD under MI, a strong and robust ERD was obtained with AO. Participant 9 showed negative ERD under both

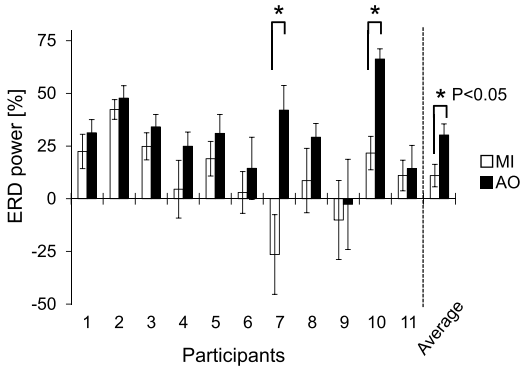

Fig. 3. Individual and grand-averaged ERD power in MI and AO conditions. The numbers 1–7 correspond to participants 1–7, all with left hemiplegia. Shown is the mean ERD power at electrode C4 during left-hand imagery. The numbers 8–11 correspond to participants 8–11, all with right hemiplegia. Shown is mean ERD power at electrode C3 during right-hand imagery. Asterisks show statistically significant differences between MI and AO conditions. Confidence limits on bars show standard error calculated across trials. ERD, event-related desynchronization; MI, motor imagery; AO, action observation.

conditions; however, the increase in mu-band activity was minor under AO compared with MI. Fig. 4 shows the CV of mu-band power during Rest and Task under the two conditions. In participant 9, whose mean ERD was negative, a tendency of mu-band power to fluctuate over trials was observed under both conditions of Rest and Task and under both MI and AO.

The topographic images of ERD power under MI and AO also support the conclusion of increased ERD power under AO compared with MI (Fig. 5). The increase in ERD power was small and localized in the affected cortical area under MI, while under AO, we observed a more distributed suppression of mu-band activity expanding to the prefrontal and parietal areas. All participants showed activity in prefrontal and/or parietal areas during AO in addition to the sensorimotor cortex. We calculated the ERD power of both the affected and unaffected hemispheres of all participants (Fig. 6). Most participants showed a tendency to larger ERD power in the unaffected hemisphere. However, statistically significant differences were seen in participants 3 and 10, showing enhanced ERD power on the affected side. Although not statistically significant,

Please cite this article in press as: Tani, M., et al., Action observation facilitates motor cortical activity in patients with stroke and hemiplegia. Neurosci. Res. (2017), https://doi.org/10.1016/j.neures.2017.10.002

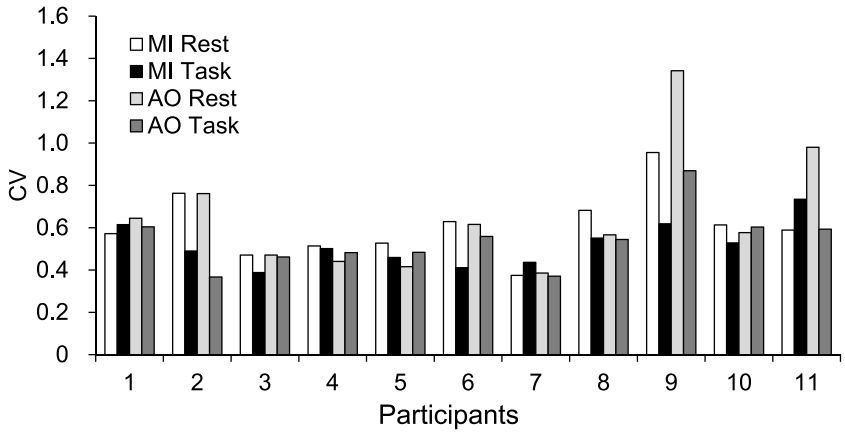

Fig. 4. Individual CVs (dimensionless) during Rest and Task from the affected motor area under MI and AO conditions. CV, coefficient of variation; MI, motor imagery; AO, action observation.

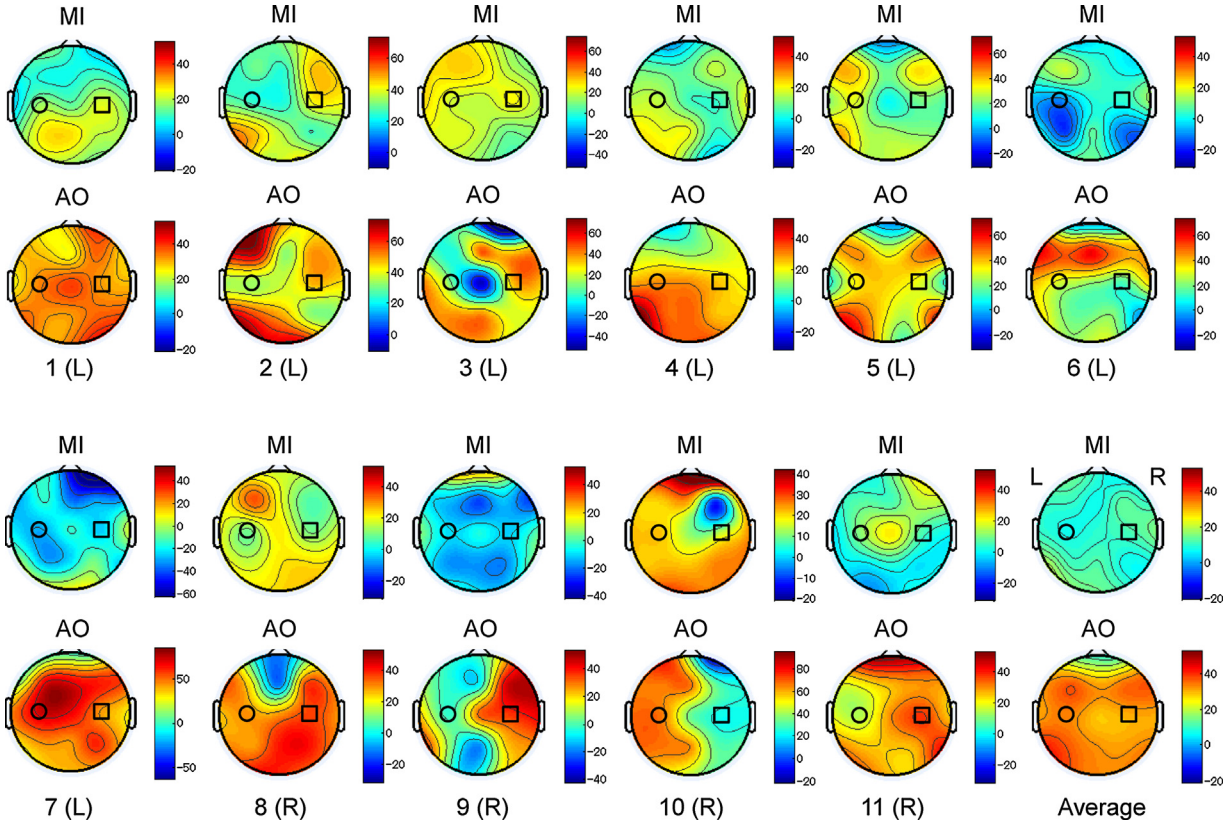

Fig. 5. Topographical representation of mean ERD power during MI and AO in patients with stroke. Electrode positions for C3 and C4 are indicated as open circle and square, respectively. The affected hemisphere is shown in parentheses next to the case number. The topographical maps of all patients were averaged to show the grand-averaged topographical representation (Average). Before averaging, the topographical maps of the right-hemiplegia patients were mirror-imaged through the midline for compatibility with the data from the left-hemiplegia cases. Color bar shows the strength of ERD as a percentage. (L), left hemiplegia; (R), right hemiplegia; ERD, event-related desynchronization; MI, motor imagery; AO, action observation.

participants 9 and 11 showed more than twice the ERD power on the unaffected hemisphere compared with the affected hemisphere during AO.

The logarithm of ERD power increase under AO relative to MI tended to show a negative correlation with the MMSE score ($r = -0.610$, $p = 0.108$; Fig. 7).

4. Discussion

We investigated the ERD power under conditions of MI and AO in patients with stroke and showed that AO could induce stronger ERD in the motor cortex compared with MI. Under the AO condition, more than half of our participants showed an increase in ERD power by greater than 10% compared with MI. Our finding of augmented ERD power under AO versus MI confirmed previous reports of results obtained in healthy participants (Kim et al., 2011) and in chronic patients with stroke but without higher-brain dysfunction (Kim et al., 2014). Our results further revealed the robustness of AO for increasing ERD power in patients with stroke in the acute and recovery stages regardless of the existence of higher-brain dysfunction.

Please cite this article in press as: Tani, M., et al., Action observation facilitates motor cortical activity in patients with stroke and hemiplegia. Neurosci. Res. (2017), https://doi.org/10.1016/j.neures.2017.10.002

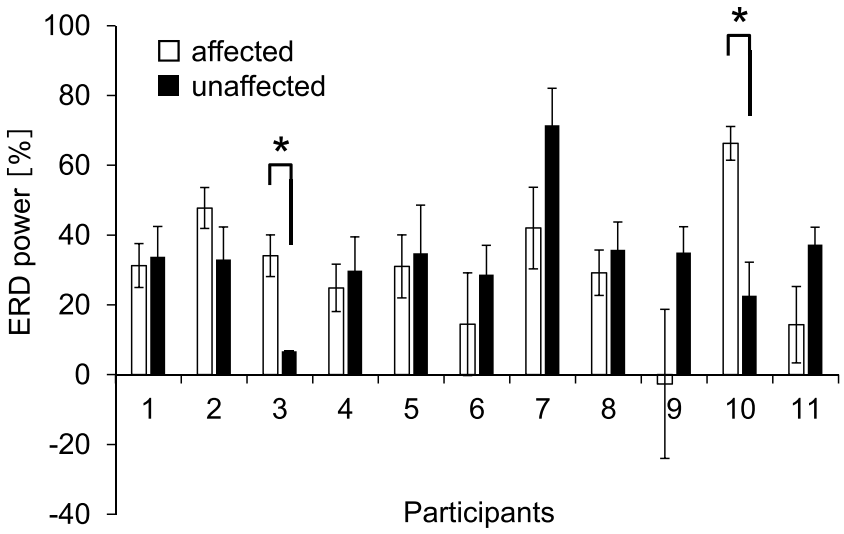

Fig. 6. Mean ERD power from the affected and unaffected hemispheres during AO. Asterisks show statistically significant differences between affected and unaffected hemispheres. Confidence limits on bars show standard error calculated across trials. ERD, event-related desynchronization; AO, action observation.

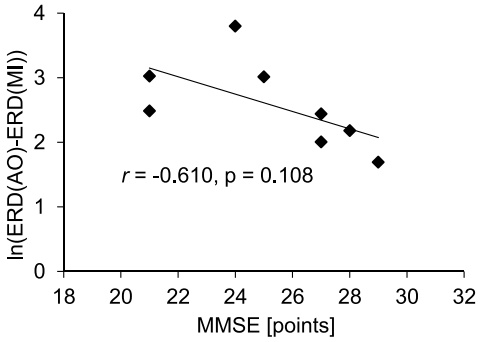

Fig. 7. Relationship between MMSE scores and the increase in ERD power seen under AO relative to MI. ERD, event-related desynchronization; MI, motor imagery; AO, action observation; MMSE, mini-mental state examination.

Our results demonstrated that AO of fine hand movement is effective in enhancing transmission of cortical motor commands from the stroke-affected brain. Of clinical importance is that the enhancement of ERD by AO over that by MI was observed in patients with higher-brain dysfunction, severe movement disorder, and/or sensory disturbance (Table 1). One possible explanation for the augmented ERD in AO is the nature of AO, in which visual stimulation showing body movement automatically and subconsciously stimulates the motor-related cortical areas that correspond to the observed movement through the MNS (Tipper, 2010). Moreover, we observed an additional AO-related oscillatory activity change in the prefrontal and parietal areas as well as in the motor area, confirming a strong association of AO with the MNS. This is different from the neuronal mechanism of MI, which requires an intrinsic voluntary process of the motor cortices (Mulder et al., 2004; Holmes and Calmels, 2008; Cattaneo et al., 2009). Achieving such process might require higher cognitive load and be more difficult for patients with stroke hemiplegia compared to passively receiving an extrinsic stimulation in the case of AO. The augmented differences in ERD power between AO and MI along with the lower MMSE scores well support this hypothesis.

Our results also provide the electrophysiological proof-of-concept of action-observation therapy (AOT), which has been proposed as a method for recovering motor function during rehabilitation. Buccino et al. (2006) reported a significant improvement in upper limb function in an AOT group compared with the normal-treatment group. In that study, post-intervention analysis by functional magnetic resonance imaging (fMRI) showed reactivation of the motor systems, such as the premotor area, superior temporal gyrus, supplementary motor area, and the contralateral supramarginal gyrus in patients with stroke. Our findings of a significant increase in ERD power under AO versus MI even after a single session support the favorable outcomes found in repetitive AOT training in terms of motor rehabilitation and cortical plasticity (Buccino et al., 2006).

Most participants, especially participants 9 and 11, showed greater activation in the unaffected hemisphere than in the affected hemisphere. This observation is consistent with a previous study of AO in patients post-stroke (Frenkel-Toledo et al., 2014). Participant 9 in this study was tested 18 days after stroke developed. Grefkes and Fink (2014) report a phenomenon of post-stroke reorganization of the cerebral networks in which motor cortical activity of the unaffected hemisphere supports activation of the affected motor area in the other hemisphere. This agrees with a previous observation by Jaillard et al. (2005), who reported that finger tapping on the paralyzed side evoked motor-related cortical activity in both the affected and unaffected hemispheres within 20 days after stroke; however, the activity was localized to the affected hemisphere 4 months later. We infer that in participant 9, the unaffected hemisphere demonstrated this early compensatory activity during AO. Moreover, Taub et al. (2002) pointed out a potential interference with functional recovery of the affected hemisphere post-stroke due to excessive, learned transfer of use to the unaffected side in daily life. Disuse of the affected hemisphere may have influenced the enhanced ERD power seen on the unaffected side in participant 11, for whom more than 5 years had elapsed since development of severe motor paralysis. Participants 2, 3, and 10 showed a tendency to larger ERD strength, or a significantly larger ERD strength, in the affected hemisphere as opposed to the unaffected hemisphere. Since these participants suffered from subcortical damage that included the motor pathway (corona radiata or internal capsule), the augmented ERD seen on the affected side might reflect a state of enhanced workload of the ipsilesional motor cortex to "compensate for the corticospinal output damage" (Rossini et al., 2007). However, a larger number of participants and direct observation of the remaining corticospinal tracts are required to confirm this hypothesis.

Participant 9 failed to show positive mean ERD power under both conditions. The larger fluctuation in the mu-band power seen

Please cite this article in press as: Tani, M., et al., Action observation facilitates motor cortical activity in patients with stroke and hemiplegia. Neurosci. Res. (2017), https://doi.org/10.1016/j.neures.2017.10.002

in this participant compared with the others might signal the presence of some interference with mean ERD power. Itil et al. (1970) reported that tension and uneasiness could decrease alpha wave activity. Since our experiment was the first EEG measurement participant 9 had undergone since cerebral infarction, a tense state due to an unaccustomed procedure might have affected mu-band activity during the experiment.

Participants 4, 6, and 7 showed severe sensory and motor deficits. Patients with severe sensory and motor deficits often have a poor prognosis. Our results confirmed the low ERD power in these patients under the MI condition. However, AO induced positive and larger ERD power than did MI even in these patients, suggesting that visual presentation of motion remained advantageous for stimulating the affected motor area. The tendency to larger ERD power under AO compared with MI in participants with lower MMSE scores also indicates the usefulness of motor-visual stimulation for inducing motor cortical activity, since it is effective even in patients with low cognitive function.

Similarly, we observed enhanced ERD power under AO versus MI in participant 10 who had severe apraxia. Buxbaum et al. (2000) reported that apraxia is not only a disorder of the parietal lobe's function of cross-modal integration but is also an impairment of the fronto-parietal network's function of generating a body schema (Naito et al., 2016) through the motor imagery of actions. Therefore, due to apraxia, participant 10 might have had difficulty with the voluntary planning of simulation of action needed by MI. However, dysfunction of the frontal-parietal network might also impair AO effectiveness, since this network is shared by the AO-related activation of the MNS. The contradictory increase in ERD power seen in this participant during AO relative to MI may reflect impaired function of the MNS, but arise in this case from deteriorated suppression of actual execution of the observed action during AO. Brass et al. (2009) suggested a potential role of combined activation of the anterior fronto-median cortex and the temporo-parietal junction in inhibiting the imitative behavior that is often seen in patients with prefrontal dysfunction. This participant suffered from clear frontal lobe dysfunction with limited paralysis, often showing difficulty in inhibiting action imitation in the clinical setting. Therefore, the visually driven, assive extrinsic stimulation of AO might have overactivated the motor cortex and resulted in larger ERD power compared with MI.

Limitations of this study are the small number of patients and the diverse patient status, such as differences in higher-brain functional status. However, the overall result showed AO to be advantageous over MI for inducing a robust ERD response. Although care should be taken with the point that the motor neurons involved in AO, MI, and the actual execution of action may not be completely identical (Mukamel et al., 2010), these results suggest an advantage of AO for inducing robust motor commands for effective cortico-motor reorganization in patients with stroke with hand-paralysis, regardless of the severity of motor paralysis, the presence of sensory disturbance, or the presence of higher-brain dysfunction. To further utilize AO in neurorehabilitation, investigating the combined effect of AO and MI on ERD power (Nedelko et al., 2012; Eaves et al., 2016) in patients with stroke is necessary to validate a rehabilitation strategy for guiding these patients beyond passive stimulation by AO, in which MI serves as a stepping-stone to voluntary generation of functional motor cortical activity. It would also be of further interest to determine the differences between the neuronal representations of imagined and executed motor processes in patients with stroke. Further research on ERD changes and any corresponding functional recovery from hand hemiplegia through repetitive training in AO will be of interest to determine the most appropriate facilitation of cortico-motor circuits in these patients.

Funding

This work was supported by JSPS KAKENHI Grant Number JP16K01520.

References

Behmer Jr., L.P., Fournier, L.R., 2016. Mirror neuron activation as a function of explicit learning: changes in mu-event-related power after learning novel responses to ideomotor compatible, partially compatible, and non-compatible stimuli. Eur. J. Neurosci. 44 (10), 2774–2785.
Brass, M., Ruby, P., Spengler, S., 2009. Inhibition of imitative behaviour and social cognition. Philos. Trans R. Soc. Lond. B Biol. Sci. 364 (1528), 2359–2367.
Buccino, G., Solodkin, A., Small, S.L., 2006. Functions of the mirror neuron system:implications for neurorehabilitation. Cogn. Behav. Neurol. 19 (1), 55–63.
Buccino, G., 2014. Action observation treatment: a novel tool in neurorehabilitation. Philos. Trans. R. Soc. Lond. Ser. B 369 (1644), 20130185.
Buch, E., Weber, C., Cohen, L.G., Braun, C., Dimyan, M.A., Ard, T., Mellinger, J., Caria, A., Soekadar, S., Fourkas, A., Birbaumer, N., 2008. Think to move: a neuromagnetic brain-computer interface (BCI) system for chronic stroke. Stroke 39 (3), 910–917.
Buxbaum, J., Giovannetti, T., Libon, D., 2000. The role of the dynamic body schema in praxis: evidence from primary progressive apraxia. Brain Cogn. 44 (2), 166–191.
Cattaneo, L., Caruana, F., Jezzini, A., Rizzolatti, G., 2009. Representation of goal and movements without overt motor behavior in the human motor cortex: a transcranial magnetic stimulation study. J. Neurosci. 29 (36), 11134–11138.
De Beni, R., Pazzaglia, F., Gardini, S., 2007. The generation and maintenance of visual mental images: evidence from image type and aging. Brain Cogn. 63 (3), 271–278.
Decety, J., Grezes, J., 1999. Neural mechanisms subserving the perception of human actions. Trends Cogn. Sci. 3, 172–178.
Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J. Neurosci. Methods 134 (1), 9–21.
Duncan, P.W., Goldstein, L.B., Matchar, D., Divine, G.W., Feussner, J., 1992. Measurement of motor recovery after stroke: outcome assessment and sample size requirements. Stroke 23 (8), 1084–1089.
Eaves, D.L., Riach, M., Holmes, P.S., Wright, D.J., 2016. Motor imagery during action observation: a brief review of evidence, theory and future research opportunities. Front. Neurosci. 10 (514), 1–10.
Frenkel-Toledo, S., Bentin, S., Perry, A., Liebermann, D.G., Soroker, N., 2014. Mirror-neuron system recruitment by action observation: effects of focal brain damage on mu suppression. Neuroimage 87, 127–137.
Frenkel-Toledo, S., Liebermann, D.G., Bentin, S., Soroker, N., 2016. Dysfunction of the human mirror neuron system in ideomotor apraxia: evidence from mu suppression. J. Cogn. Neurosci. 28 (6), 775–791.
Grefkes, C., Fink, G.R., 2014. Connectivity-based approaches in stroke and recovery of function. Lancet Neurol. 3 (2), 206–216.
Gregg, M., Hall, C., Butler, A., 2010. The MIQ-RS: A suitable option for examining movement imagery ability. Evid. Based Complement. Altern. Med. 7 (10), 249–257.
Holmes, P., Calmels, C., 2008. A neuroscientific review of imagery and observation use in sport. J. Mot. Behav. 40 (5), 433–445.
Itil, T.M., Gannon, P., Hsu, W., Klingenberg, H., 1970. Digital computer analyzed sleep and resting EEG during haloperidol treatment. Am. J. Psychiatry 127 (4), 462–471.
Jaillard, A., Martin, D.M., Garambois, K., Lebas, J.F., 2005. Vicarious function within the human primary motor cortex? A longitudinal fMRI stroke study. Brain 128, 1122–1138.
Kaiser, V., Daly, I., Pichiorri, F., Mattia, D., Müller-Putz, G.R., Neuper, C., 2012. Relationship between electrical brain responses to motor imagery and motor impairment in stroke. Stroke 43 (10), 2735–2740.
Kim, T.H., Cruz, A., Ha, J.H., 2011. Differences in learning facilitatory effect of motor imagery and action observation of golf putting. J. Appl. Sci. 11 (1), 151–156.
Kim, J., Lee, B., Lee, H.S., Shin, K.H., Kim, M.J., 2014. Differences in brain waves of normal persons and stroke patients during action observation and motor imagery. J. Phys. Ther. Sci. 26 (2), 215–218.
Kim, K., 2015. Action observation for upper limb function after stroke: evidence-based review of randomized controlled trials. J. Phys. Ther. Sci. 27 (10), 3315–3317.
Lopes da Silva, F.H., 1991. Neural mechanisms underlying brain waves: from neural membranes to networks. Electroencephalogr. Clin. Neurophysiol. 79 (2), 81–93.
Maranesi, M., Ugolotti Serventi, F., Bruni, S., Bimbi, M., Fogassi, L., Bonini, L., 2013. Monkey gaze behaviour during action observation and its relationship to mirror neuron activity. Eur. J. Neurosci. 38 (12), 3721–3730.
Mukamel, R., Ekstrom, A.D., Kaplan, J., Iacoboni, M., Fried, I., 2010. Single-neuron responses in humans during execution and observation of actions. Curr. Biol. 20 (8), 750–756.
Mulder, T., Zijlstra, S., Zijlstra, W., Hochstenbach, J., 2004. The role of motor imagery in learning a totally novel movement. Exp. Brain Res. 154 (2), 211–217.
Naito, E., Morita, T., Amemiya, K., 2016. Body representations in the human brain revealed by kinesthetic illusions and their essential contributions to motor control and corporeal awareness. Neurosci. Res. 104, 16–30.

Please cite this article in press as: Tani, M., et al., Action observation facilitates motor cortical activity in patients with stroke and hemiplegia. Neurosci. Res. (2017), https://doi.org/10.1016/j.neures.2017.10.002

Nedelko, V., Hassa, T., Hamzei, F., Schoenfeld, M.A., Dettmers, C., 2012. Action imagery combined with action observation activates more corticomotor regions than action observation alone. J. Neurol. Phys. Ther. 36 (4), 182–188.
Nojima, I., Koganemaru, S., Kawamata, T., Mima, T., 2015. Action observation with kinesthetic illusion can produce human motor plasticity. Eur. J. Neurosci. 41 (12), 1614–1623.
Pfurtscheller, G., Neuper, C., 1997. Motor imagery activates primary sensorimotor area in humans. Neurosci. Lett. 239, 65–68.
Pfurtscheller, G., Neuper, C., Andrew, C., Edlinger, G., 1997. Foot and hand area mu rhythms. Int. J. Psychophysiol. 26, 121–135.
Rizzolatti, G., Fogassi, L., Gallese, V., 2001. Neurophysiological mechanisms underlying the understanding and imitation of action. Nat. Rev. Neurosci. 2 (9), 661–670.
Rizzolatti, G., Cattaneo, L., Fabbri-Destro, M., Rozzi, S., 2014. Cortical mechanisms underlying the organization of goal-directed actions and mirror neuron-based action understanding. Physiol. Rev. 94, 655–706.
Rossini, P.M., Altamura, C., Ferreri, F., Melgari, J.M., Tecchio, F., Tombini, M., Pasqualetti, P., Vernieri, F., 2007. Neuroimaging experimental studies on brain plasticity in recovery from stroke. Eura Medicophys. 43 (2), 241–254.
Solodkin, A., Hlustik, P., Chen, E.E., Small, S.L., 2004. Fine modulation in network activation during motor execution and motor imagery. Cereb. Cortex 14 (11), 1246–1255.
Takemi, M., Masakado, Y., Liu, M., Ushiba, J., 2013. Event-related desynchronization reflects downregulation of intracortical inhibition in human primary motor cortex. J. Neurophysiol. 110, 1158–1166.
Taub, E., Uswatte, G., Elbert, T., 2002. New treatments in neurorehabilitation founded on basic research. Nat. Rev. Neurosci. 3, 122–131.
Teo, W.P., Chew, E., 2014. Is motor-imagery Brain-computer interface feasible in stroke rehabilitation? PM&R 6, 723–728.
Tipper, S.P., 2010. From observation to action simulation: the role of attention, eye-emotion, and body state. Q. J. Exp. Psychol. 63 (11), 2081–2105.
Van der Lee, J.H., Snels, I.A., Beckerman, H., Lankhorst, G.J., Wagenaar, R.C., Bouter, L.M., 2001. Exercise therapy for arm function in stroke patients: a systematic review of randomized controlled trials. Clin. Rehabil. 15 (1), 20–31.
Wade, D.T., Langton-Hewer, R., Wood, V.A., Skilbeck, C.E., Ismail, H.M., 1983. The hemiplegic arm after stroke: measurement and recovery. J. Neurol. Neurosurg. Psychiatry 46 (6), 521–524.
Zimmermann-Schlatter, A., Schuster, C., Puhan, M.A., Siekierka, E., Steurer, J., 2008. Efficacy of motor imagery in post-stroke rehabilitation: a systematic review. J. Neuroeng. Rehabil. 5, 8.

Please cite this article in press as: Tani, M., et al., Action observation facilitates motor cortical activity in patients with stroke and hemiplegia. Neurosci. Res. (2017), https://doi.org/10.1016/j.neures.2017.10.002