



## Role of beta-band resting-state functional connectivity as a predictor of motor learning ability



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### ABSTRACT

It has been suggested that resting-state functional connectivity (rs-FC) between the primary motor area (M1) region of the brain and other brain regions may be a predictor of motor learning, although this suggestion is still controversial. In the work reported here, we investigated the relationship between M1 seed-based rs-FC and motor learning. Fifty-three healthy volunteers undertook random button-press and sequential motor learning tasks. Five-minute resting-state data acquisition was performed between the two tasks. Oscillatory neural activities during the random task and the rest period were measured using magnetoencephalography. M1 seed-based rs-FC was calculated for the alpha and beta bands using amplitude envelope correlation, in which the seed location was defined as an M1 position with peak event-related desynchronization value. The relationship between rs-FC and the performance of motor learning was examined using whole brain correlation analysis. The results showed that beta-band resting-state cross-network connectivity between the sensorimotor network and the core network, particularly the theory of mind network, affected the performance of subsequent motor learning tasks. Good learners could be distinguished from poor learners by the strength of rs-FC between the M1 and the left superior temporal gyrus, a part of the theory of mind network. These results suggest that cross-network connectivity between the sensorimotor network and the theory of mind network can be used as a predictor of motor learning performance.

### 1. Introduction

The primary motor area (M1) is the one of the most important regions of the brain for motor function and motor learning (Baker, 2007; Cheyne et al., 2008; Crone et al., 1998; Mawase et al., 2017; Muthukumaraswamy, 2010; Uehara et al., 2017). Low-frequency components of brain activity, such as alpha and beta bands, have been reported to be important neurophysiological factors in motor functions (Cheyne, 2013; Miller et al., 2010; Muthukumaraswamy, 2010; Sugata et al., 2014). Recent studies have reported that oscillatory neural activities in the beta-band

over the M1 are associated with motor learning (Krause et al., 2016; Pollok et al., 2014). Oscillatory neural activities in the alpha and beta bands have been observed to be modulated following motor learning (Gentili et al., 2015; Mehrkanoon et al., 2016). In addition, alpha and beta oscillations in the sensorimotor cortex are observed in relation to motor execution (Leocani et al., 2001; Salmelin and Hari, 1994), motor preparation (Pfurtscheller et al., 1997), motor imagery (Pfurtscheller et al., 2006), and motor learning (Pollok et al., 2014) and is considered as a mechanism to improve information processing during these tasks (Basar et al., 2001; Palva and Palva, 2007; Sabate et al., 2012).

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Furthermore, functional connectivity within the range of alpha and beta band activities are suggested to be related to physical and mental fitness (Douw et al., 2014). Such neurophysiological aspects have been proposed as useful predictors of motor learning performance (Manuel et al., 2018; Mary et al., 2016, 2017; Wu et al., 2014). However, some studies have reported that capacity for motor learning shows significant variability between individuals (Golenia et al., 2014; King et al., 2012). In addition, improvement in the prediction accuracy of motor learning ability may be valuable for evaluating prognoses with respect to the therapeutic effects of rehabilitation for patients with stroke, trauma, and other neural conditions (Burke and Cramer, 2013).

Motor learning refers to improvement in the performance of sensory-guided motor behavior through practice (Krakauer and Mazzoni, 2011). The acquisition of new skills through motor practice is essential for the interaction with the environment and to make adjustments in which multiple elements of movement are integrated. To quantitatively evaluate the acquisition of a new skill, the serial reaction time task (SRTT), which involves implicit and explicit learning of a finger movement sequence, was used (Nojima et al., 2018; Sugata et al., 2018). Implicit motor learning refers to improvement in the performance of a sequence without knowledge of the sequence (Robertson, 2009), whereas explicit motor learning involves conscious recollection with knowledge of the sequence. There are multiple different memory systems in the neural substrates. For example, the contralateral primary motor cortex (M1) has been identified as an important region for implicit motor learning (Muellbacher et al., 2002; Robertson et al., 2005).

Functional connectivity is manifested as a temporal synchronization of neural activity between anatomically separated brain regions (Aertsen et al., 1989; Friston, 2001). Spontaneous fluctuations of brain activity at rest, termed resting-state functional connectivity (rs-FC), are highly organized phenomena (Fox et al., 2005). Such inter-regional interactions reflect signal transduction between brain regions and are associated with behavioral performance (Guggisberg et al., 2015; Hipp et al., 2011). Several studies have attempted to predict motor learning ability using temporal synchronization by neural oscillations or functional MRI (fMRI) blood oxygenation level-dependent changes in distinct brain regions (Bonzano et al., 2015; Mary et al., 2017; Mehrkanoon et al., 2016; Stillman et al., 2013). A recent study reported that beta-band rs-FC between M1 and the parietal area is positively associated with motor learning (Wu et al., 2014), whereas another study showed a negative correlation between rs-FC in the M1-parietal area and motor learning (Mary et al., 2016). Alpha band rs-FC has also been reported to be associated with motor learning (Manuel et al., 2018). Considering that the M1 forms functional networks with several motor association areas, such as the premotor cortex, supplementary motor area, and the parietal area during movement (Herz et al., 2012), functional connectivity involving M1 as the seed region may be a strong predictor of motor learning. However, as described above, the relationship between M1 seed-based rs-FC and motor learning has not yet been clarified, and the relationship is still controversial.

In the present study, we hypothesized that M1 seed-based rs-FC is a strong predictor of motor learning. To investigate this hypothesis, we examined the relationship between M1 seed-based rs-FC and motor learning ability. Magnetoencephalography (MEG) was used because it has advantages for the analysis of neurophysiological signals over electroencephalograms (EEG) and fMRIs. MEG has higher spatial resolution than EEG and can record direct correlates of neural activity with higher temporal resolution than fMRI (Baillet, 2017; Palva and Palva, 2012; Singh, 2012). In the present study, participants performed a sequential motor learning task after recording 5-min resting-state MEG data. The M1 seed-based rs-FC was calculated in the alpha and beta bands using amplitude envelope correlation (AEC). The relationship between rs-FC and performance of motor learning was then examined using whole brain correlation analysis.

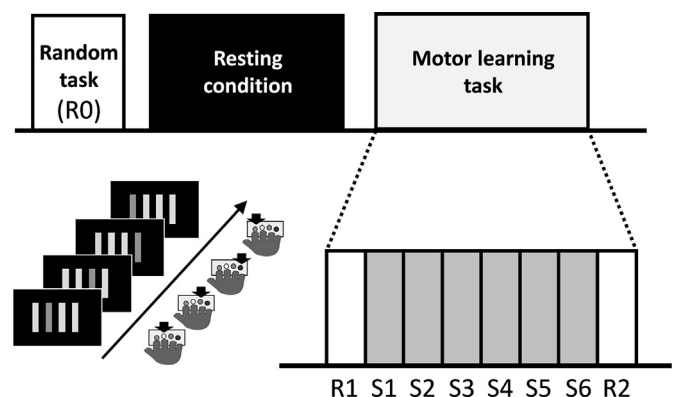
## 2. Materials and methods

### 2.1. Participants

Fifty-three healthy volunteers ( $32.9 \pm 6.7$  years; 22 females) participated in this study. All participants were right-handed, as determined by the Edinburgh Handedness Inventory Test (Oldfield, 1971). No participant had a history of neurological or psychiatric disease, and all had a normal or corrected-to-normal vision. In accordance with the Declaration of Helsinki, we explained the purpose and possible consequences of this study to all participants and obtained their informed consent before the study commenced. The Ethical Review Boards of Oita University Faculty of Medicine and Junwakai Memorial Hospital approved the protocols of this study (No.982 and No.0524-2).

### 2.2. Experimental design and procedure

All participants were naive to the present study. The participants performed a 12-digit motor sequence learning task, i.e., SRTT, in which participants were required to react with their four right-hand fingers (index, middle, ring, and little fingers; Fig. 1) (Nissen and Bullemer, 1987). Four horizontal bars were displayed on the screen. When the color of a bar changed from gray to blue, participants were instructed to press the corresponding button as quickly and accurately as possible. If a participant pressed the correct button, the next stimulation was presented after 1 s. If a participant pressed an incorrect button, the stimulation was unchanged until the participant pressed the correct button. This motor learning task consisted of six sequence blocks ( $S_1$ – $S_6$ ) and two random blocks ( $R_1$ ,  $R_2$ ). Random blocks were set before ( $R_1$ ) and after the six sequence blocks ( $R_2$ ). Prior to the motor learning task, all participants underwent a random button-press task, which consisted of two random blocks (192 button presses) to define the M1 seed region for subsequent seed-based functional connectivity analysis. The sequence blocks comprised eight repeats of twelve stimuli in the same sequence. Thus, a total of 576 button presses were performed in a sequence block, whereas 192 button presses were performed in a random block. Five-minute resting-state data were acquired between the random task and the motor learning task. A previous study has shown that the eyes-closed resting condition is better identified as a convenient arousal baseline, with the eyes-open resting condition serving as a convenient activation baseline, particularly for tasks that involve visual processing (Barry et al., 2007). Therefore, we applied the eyes-closed condition to the resting-state MEG recordings in the present study. All participants were instructed to stay awake and still with their eyes closed during



**Fig. 1.** Experimental procedure. Before the motor learning task, participants undertook a random button-press task (R0) to define the M1 seed region for subsequent seed-based functional connectivity analysis. Then, 5-min resting-state data were acquired. Participants then performed a 12-digit motor sequence learning task consisting of six sequence blocks ( $S_1$ – $S_6$ ) and two random blocks ( $R_1$ ,  $R_2$ ).

resting-state MEG recordings.

In the random button-press task and motor learning tasks, the visual stimuli were displayed using a visual presentation system (Presentation, Neurobehavioral Systems, Albany, CA, USA) and a DLP projector (TAXAN KG-PH1005, Kaga Micro Solution Co., Ltd, Tokyo, JPN) on a rear projection screen (ELEKTA, Helsinki, FIN) located 1.5 m from the participants' eyes. Response times were collected using a completely non-magnetic and non-electronic response device (PKG-932, Current Designs, Philadelphia, USA).

### 2.3. MEG measurements

MEG measurements were made using a 306-channel whole-head MEG system (Vector-view, ELEKTA Neuromag, Helsinki, FIN) during the random button-press task and under resting conditions in a magnetically-shielded room. During MEG measurement, the participant was seated in a comfortable chair. MEG signals were digitally recorded using an online 500 Hz low-pass filter at a sampling rate of 1020 Hz. To remove eye movement artifacts after offline analysis, electrooculogram (EOG) was simultaneously recorded.

We acquired structural MRIs using a 3.0 T MRI system (Achieva 3T, Philips Inc., Amsterdam, NLD). At least 50 head- and face-surface points were determined by a 3D digitizer (FastSCAN Corba, Polhemus, Colchester, VT, USA), and three head localization coils attached to the participant's head were used to align the MEG data with the individual brain MRI results. The data from the 3D digitizer were superimposed on each individual's MRI data with an anatomical accuracy of a few millimeters.

### 2.4. MEG data preprocessing

In order to eliminate environmental noise, we applied signal space separation to the MEG data in the random button-press task and resting condition (Taulu et al., 2005). MEG data were analyzed using Brainstorm software (Tadel et al., 2011). Data were resampled to 1000 Hz, and an offline band-pass filter between 0.1 and 100 Hz and a band-elimination filter between 58 and 62 Hz were applied to eliminate the environmental noise. Eye-blink artifacts in the MEG data were separated using EOG and rejected by signal-space projection, a method for removing external disturbances (Tadel et al., 2011). In the random button-press task, we defined the onset time of the button-press as 0 ms. The time window of an epoch was defined as  $-1000$  to  $1000$  ms. Among the 192 button presses, unsuitable epochs were excluded from the analysis. These epochs were defined as those that included error responses, anticipatory responses, responses outside the mean value  $\pm 2$  SD for each block, and contamination by excessive muscle activity. In the resting task, MEG data were segmented into 30 non-overlapping 10-s epochs. Artifact-contaminated epochs were manually detected and excluded from the analysis.

### 2.5. MEG source estimation

In order to estimate the source model, a source-level analysis was performed using 204 planar-type gradiometers, which are powerful enough to detect the largest signal just over local cerebral sources (Otsuru et al., 2014). Reconstruction and segmentation of the cortical surfaces were performed using Freesurfer software (<https://surfer.nmr.mgh.harvard.edu/>) for each participant's anatomical MRI. Vertices of the cortical surface were set as 15,000 points. Tomographic reconstruction of the data was created by generating an overlapping-sphere head model based on the shape of the head obtained from the structural MRI of each participant. A noise covariance matrix was computed from 3-min empty-room recordings taken before each session. The inverse imaging model estimated the distribution of brain currents that accounted for data recorded at the sensors. In order to compute the source distribution, the minimum norm estimate was applied to MEG data in the random

button-press task and resting condition using the Brainstorm default parameters.

Then, source data were divided into the following two frequency bands: alpha (8–13 Hz); beta (13–25 Hz), using a finite impulse response filter. A Hilbert transformation was performed on the filtered signals to obtain complex-valued analytic signals. To avoid filtering edge effects, source data from  $-700$  ms to  $700$  ms were set as the analysis time window. The source power spectral density of each frequency band was calculated from the square of the absolute value of the complex-valued signals. The resulting oscillatory powers were normalized by the baseline time window ( $-700$  to  $-500$  ms, in dB). Considering that a previous study showed that the patterns of functional connectivity in MEG show high variability when using a common seed for all subjects (Wens et al., 2014), individual peak event-related desynchronization (ERD) (Engel and Fries, 2010; Pfurtscheller and Aranibar, 1979; Salmelin and Hari, 1994) value was detected in M1, which was defined by the Desikan-Killiany Atlas (Desikan et al., 2006), between  $-500$  and  $500$  ms and set as a seed region.

### 2.6. rs-FC

The rs-FC analysis was carried out with a seed-based design using the Brainstorm default parameters. To estimate the AEC, orthogonalization was performed to eliminate the pairwise effect of linear signal mixing on the long-range temporal correlations and to allow the assessment of the relationship between local cortical scaling exponents without the artificial coupling of these regions (Blythe et al., 2014; Zhigalov et al., 2017). Seed location was individually defined for each participant, based on the peak ERD around the M1 in the random button-press task. Then, M1 seed-based rs-FC was estimated using AEC analysis. AEC is calculated by correlating the amplitude envelopes of two oscillatory brain activities, which are defined as the absolute value of the Hilbert transform of a cortical oscillation. High AEC values indicate synchronous amplitude envelope fluctuations between oscillations. Thus, AEC can detect synchronization between functional brain networks within frequency bands (Bruns et al., 2000; Doron et al., 2012; Hipp et al., 2012; Zamm et al., 2018). In the present study, the Hilbert transformation was applied to the filtered signals, i.e., alpha (8–13 Hz) and beta (13–25 Hz) bands, to obtain complex-valued analytic signals. Thereafter, Pearson's correlation coefficients were calculated using AEC in each frequency band. The rs-FC maps were projected on the default anatomy (ICBM152) in order to share the same rs-FC maps between individuals.

### 2.7. Motor learning index

In order to examine motor performance in the sequential motor learning task, response time was calculated as the time from the stimulus onset to that of a correct button-press and was averaged for each block. Anticipatory responses and responses outside the mean value  $\pm 2$  SD for each block were excluded from all analyses. To examine the extent of improvement in sequential motor learning, differences in response time among eight blocks were computed using two-way analysis of variance in SPSS (version 25). Referring to the previous studies using SRTT (Pollak et al., 2014; Sugata et al., 2018), motor learning index was defined by calculating the difference in response time between the R1 block and the last block (S6) in the sequence learning. Thus, motor learning index in this work has higher values indicating greater decreases in response time.

### 2.8. Correlation analysis between motor learning index and rs-FC

To examine whether rs-FC is associated with motor learning, we calculated the correlation coefficient between the M1 seed-based rs-FC and the motor learning index among the 53 participants using Pearson's correlation coefficient over the whole brain. To control for multiple comparisons, the statistical  $p$ -value was corrected for false discovery rate (FDR) over the whole brain. Although a previous study used FDR

correction with  $q$ -thresholds as high as 0.2 (Genovese et al., 2002), we employed statistical testing with FDR correction at a  $q$ -value of 0.001, to strictly control the  $p$ -value. The statistically significant level of  $p$  was therefore  $9.36e-05$ . Voxels with significant values were considered to be statistically significant and were superimposed on the template anatomy. In order to examine oscillatory neural activity and the motor learning index, the relationship between individual peak ERD values in the alpha and beta bands during the random button-press task and the motor learning index was also examined using Pearson's correlation.

### 2.9. Prediction of motor learning ability

We performed decoding analysis to examine whether good learners can be distinguished from poor learners based on the brain areas with a significant correlation between M1 seed-based rs-FC and the motor learning index. In the present study, good learners and poor learners could be separated by the median value of motor learning index. Participants with a motor learning index above the median value were defined as good learners and those with a median value of motor learning index or below the median value were defined as poor learners.

To classify good and poor learners, a linear support vector machine (SVM) (Kamitani and Tong, 2005) was applied in each brain region with significant correlation between the motor learning index and rs-FC. The peak strength of rs-FC between M1 and brain regions with significant correlations between rs-FC and motor learning index was used as a decoding feature, respectively. Prediction accuracy was evaluated using 10-fold cross-validation. Each dataset was divided into 10 parts, and the classifiers were constructed based on 90% of the dataset—the training set—and tested on the remaining 10% so that the testing dataset was independent of the training dataset for each iteration (Sugata et al., 2012). This procedure was repeated ten times. The averaged percentage of correct results over all runs was used as a measure of decoder performance.

Furthermore, we performed multiple regression analysis to predict good learners and poor learners using the strength of peak rs-FC value in the brain regions with significant correlations between rs-FC and the motor learning index. The motor learning index was set as a dependent variable, and the strength of the peak rs-FC value between the M1 region and brain regions with significant correlations between rs-FC and the motor learning index was defined as the explanatory variable.

## 3. Results

### 3.1. Motor learning task

We examined motor performance during the motor learning task. The results showed significant differences between blocks ( $F_{(7,416)} = 3.516$ ,  $p = 0.001$ ,  $\eta^2 p = 0.056$ ). In order to further investigate the differences between R1 and other blocks, *post hoc* analysis was performed. The results showed significant differences between R1 and S6 ( $p = 0.027$ ) (Fig. 2). Thus, the delta response time between R1 and S6 was defined as the motor learning index in this work.

### 3.2. Correlation between motor learning index and rs-FC

In order to define the seed region for M1 seed-based functional connectivity analysis, the M1 location with the peak ERD value was detected between  $-500$  ms and  $500$  ms in individual participants. Fig. 3A shows the averaged oscillatory neural activities and seed locations (white circles) defined by peak ERD values in the alpha and beta bands. Seed-based rs-FC analyses were performed for the relationship between M1 seed locations and the whole brain. The results showed clear sensorimotor networks (Brookes et al., 2011; Mantini et al., 2007) in both alpha and beta bands (Fig. 3 B).

After calculating the M1 seed-based rs-FC in individuals, the correlation coefficient between the strength of rs-FC in the alpha and beta

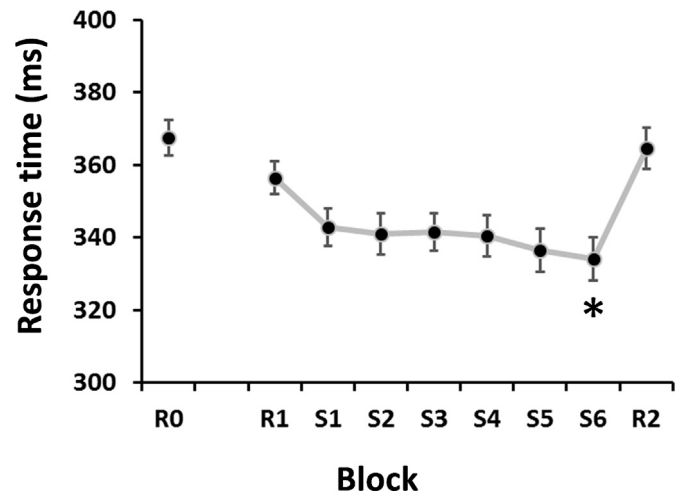


Fig. 2. Mean response time during the random button-press task and sequence motor learning task. Response times were significantly different among the blocks ( $p = 0.001$ ), and multiple comparison showed significant differences between R1 and S6 ( $*p = 0.027$ ). Error bars indicate the standard error.

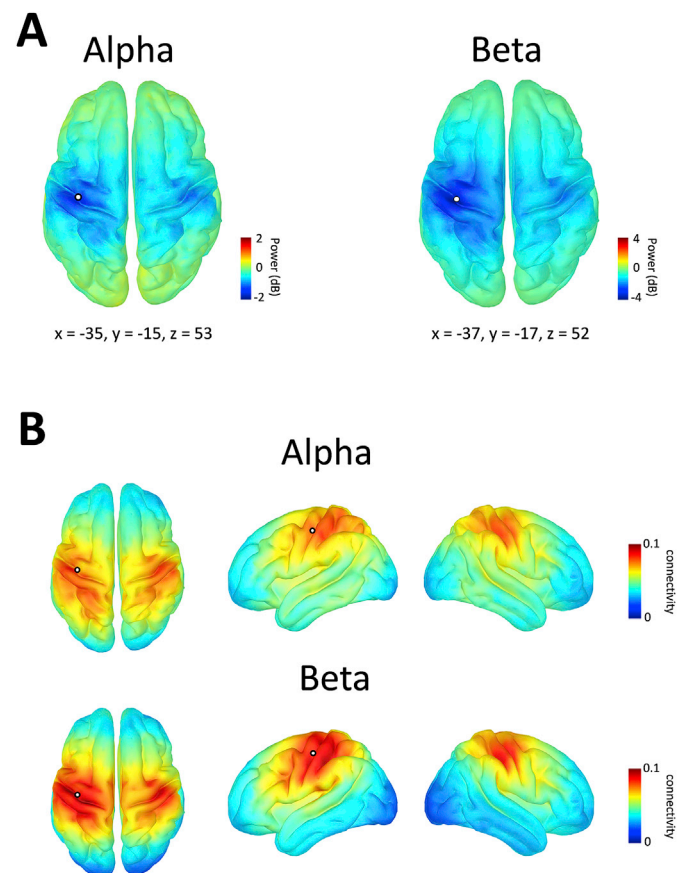
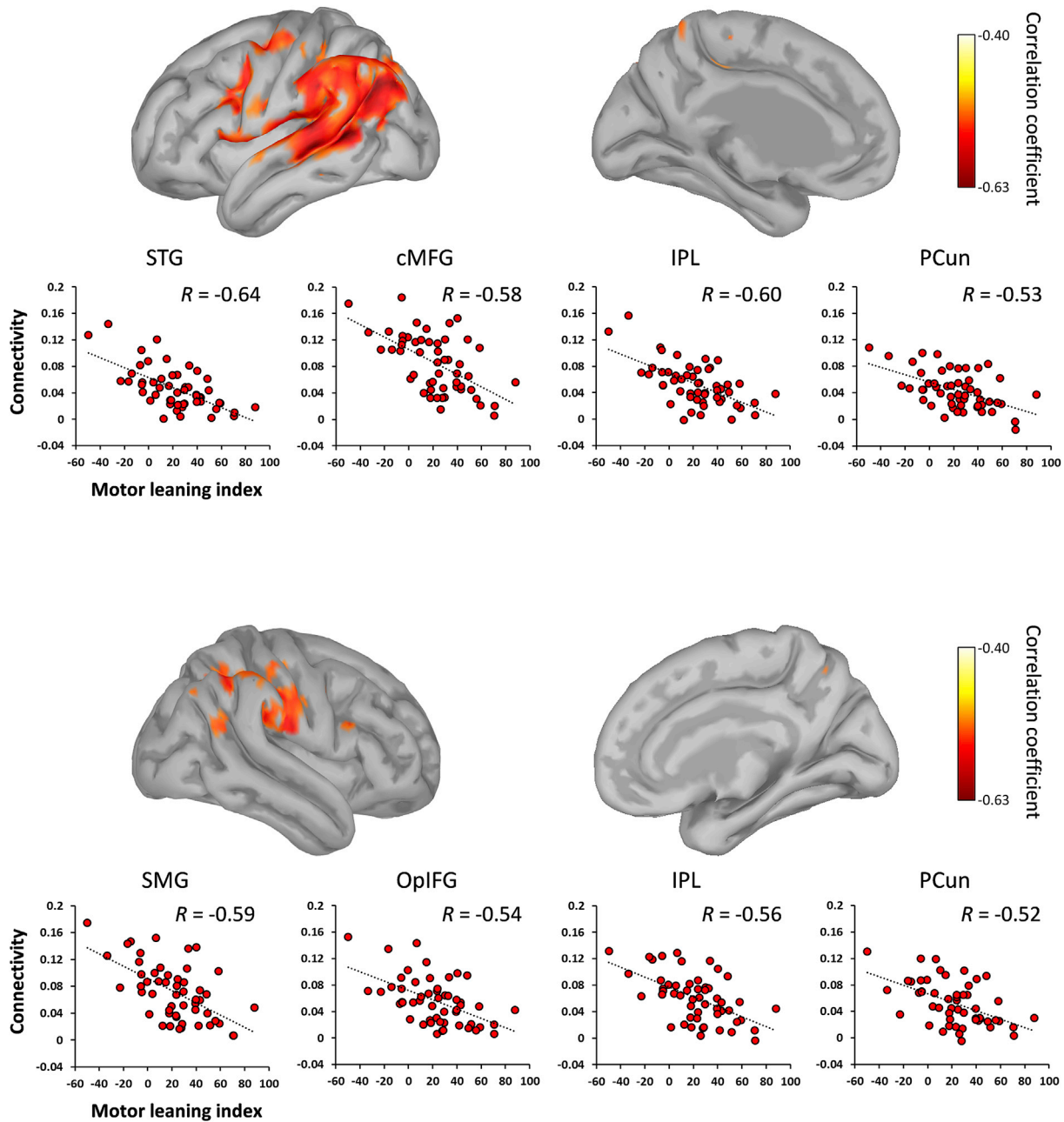


Fig. 3. (A) Grand averaged oscillatory neural activity in the alpha and beta bands during the random button-press task (R0). Robust ERDs in the alpha and beta bands were observed over the left sensorimotor areas. White circles indicate averaged localization of the M1 seed regions. (B) Seed-based rs-FC between left M1 (white circles) and the whole brain. The sensorimotor network was observed in both alpha and beta bands.

bands and the motor learning index was computed for all participants. Fig. 4 shows the correlation map between beta-band rs-FC and motor learning index over the whole brain ( $p < 0.001$ , FDR-corrected). Significant negative correlations were localized mainly to the left temporal





**Fig. 4.** Spatial distribution of significant correlations between M1 seed-based rs-FC and motor learning index. Significant negative correlations were observed in the left temporal gyri, bilateral sensorimotor areas, opercular inferior frontal gyri, and parietal areas. The strongest correlation was obtained from the left superior temporal gyrus, indicating that subjects with strong rs-FC between left M1 and the left superior temporal gyrus had low performance in the subsequent motor learning task. STG; superior temporal gyrus, cMFG; caudal middle frontal gyrus, IPL; inferior parietal lobule, PCun; precuneus, SMG; supramarginal gyrus, OpIFG; opercularis inferior frontal gyrus.

gyri, bilateral sensorimotor areas, opercular inferior frontal gyri, and parietal areas (Fig. 4, Table 1). The strongest correlation was observed in the left superior temporal gyrus, indicating that subjects with strong rs-FC between the left M1 and the left superior temporal gyrus had low performance in the subsequent motor learning task. No significant correlations were observed in the alpha band between rs-FC and motor learning index.

To further examine the relationship between the motor learning index and neurophysiological aspects, we examined the magnitude of ERD values in the individual seed locations and motor learning index using Pearson's correlation coefficients. However, there was no significant relationship between ERD values and motor learning index in either alpha or beta bands (Fig. 5). In addition, we performed correlation

analyses between the peak magnitudes of ERD and the motor learning index in the brain regions with significant correlations between rs-FC and the motor learning index. However, no significant relationships were observed between the ERD value and motor learning index in either the alpha or beta bands of each brain region (Supplementary Fig. 1).

### 3.3. Prediction of good learners and poor learners

To examine whether good learners can be distinguished from poor learners based on the rs-FC, we carried out classification analysis using SVM. Classification analysis was performed on the data from the beta-band rs-FC because significant correlations between rs-FC and motor learning were obtained only in the beta-band rs-FC. The strength of rs-FC

**Table 1**

Coordinates of significant correlation coefficients between M1 seed-based rs-FC and motor learning index.

Brain region	Hemisphere	MNI coordinates			Correlation coefficient
		X	y	z	
Superior Temporal Gyrus	Left	-53.2	-51.0	17.9	-0.64
Middle Temporal Gyrus	Left	-60.8	-517	11.5	-0.61
Inferior Parietal Lobule	Left	-42.2	-63.7	28.5	-0.61
Supramarginal Gyrus	Left	-46.8	-44.5	43.2	-0.60
Supramarginal Gyrus	Right	41.6	-41.9	43.4	-0.59
Caudal Middle Frontal Gyrus	Left	-26.0	-8.3	48.0	-0.58
Superior Parietal Lobule	Left	-40.8	-45.2	37.3	-0.58
Opercularis Inferior Frontal Gyrus	Left	-44.2	7.1	22.6	-0.57
Postcentral Gyrus	Left	-61.9	-14.9	11.9	-0.57
Postcentral Gyrus	Right	68.4	-16.2	24.5	-0.57
Precentral Gyrus	Left	-45.1	1.3	34.4	-0.57
Inferior Parietal Lobule	Right	37.4	-58.5	45.2	-0.56
Superior Parietal Lobule	Right	33.6	-55.9	44.8	-0.55
Transverse Temporal Gyrus	Left	-51.7	-21.4	11.8	-0.55
Opercularis Inferior Frontal Gyrus	Right	47.9	17.8	29.2	-0.54
Precentral Gyrus	Right	49.6	4.1	37.3	-0.54
Precuneus	Left	-9.6	-77.9	47.4	-0.53
Lateral Occipital Gyrus	Left	-41.0	-64.4	10.9	-0.52
Precuneus	Right	10.1	-59.5	51.3	-0.52

in the 19 locations with significant correlations between motor learning index and rs-FC (Table 1) was used as a decoding feature to classify good and poor learners. The boundary of the motor learning index between good learners and poor learners was set to 23.7, based upon the median value of the motor learning index. Participants with a motor learning index above the boundary were defined as good learners ( $n = 26$ ; age  $33.4 \pm 7.2$  years), and participants with scores below the boundary were defined as poor learners ( $n = 27$ ; age  $32.0 \pm 6.1$  years).

The classification analysis showed that good and poor learners could be clearly distinguished by the strength of the rs-FC between the M1 and the left superior temporal gyrus (75.7%), right post central gyrus (76.0%), right superior parietal lobule (74.2%), and right opercular inferior frontal gyrus (70.1%; Fig. 6).

We also performed multiple regression analysis to determine whether good and poor learners could be predicted using the peak strength of the rs-FC in the brain regions with significant correlations between rs-FC and the motor learning index. However, good and poor learners could not be predicted (Supplementary Table 1).

#### 4. Discussion

The present study examined the relationship between M1 seed-based rs-FC and motor learning ability. In addition, alpha and beta oscillations in the sensorimotor cortex are observed in relation to motor performance variables, motor execution (Leocani et al., 2001; Salmelin and Hari, 1994), motor preparation (Pfurtscheller et al., 1997), and motor learning (Krause et al., 2016; Pollok et al., 2014). We focused the rs-FC on the alpha and beta bands. The results showed significant correlations between beta-band M1 seed-based rs-FC and motor learning index. Good learners could be clearly distinguished from poor learners using the strength of the rs-FC between the M1 and the left superior temporal gyrus as a classification feature. These results suggest that M1 seed-based rs-FC in the beta-band can be a strong predictor of motor learning.

Previous resting-state fMRI studies have shown that hemodynamic

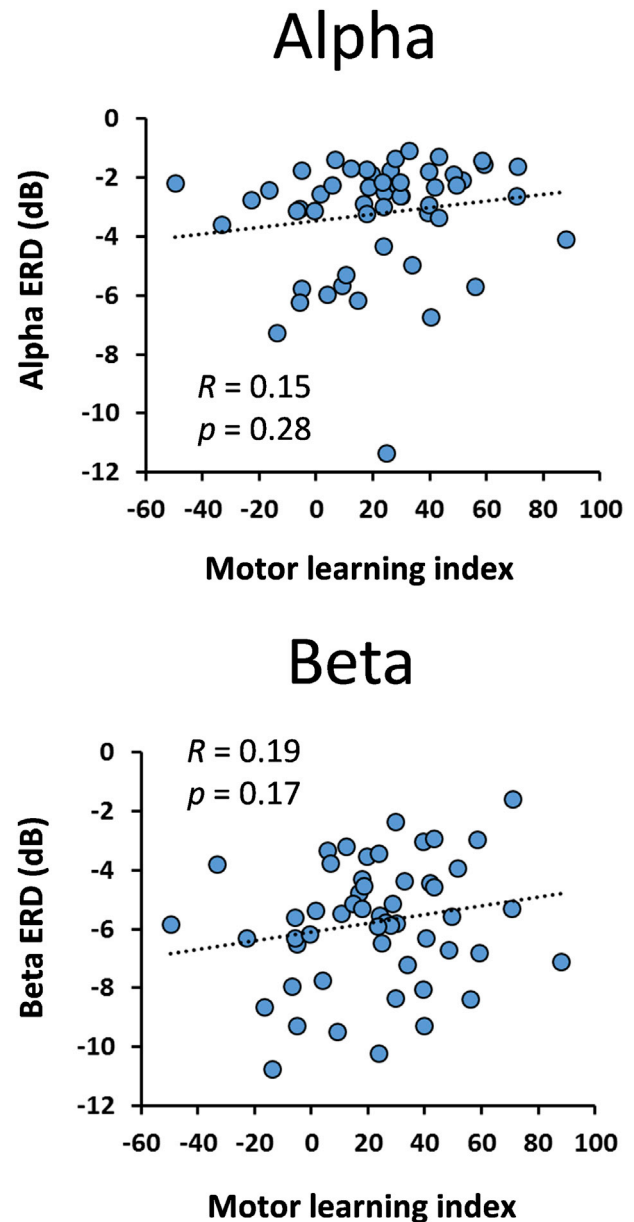
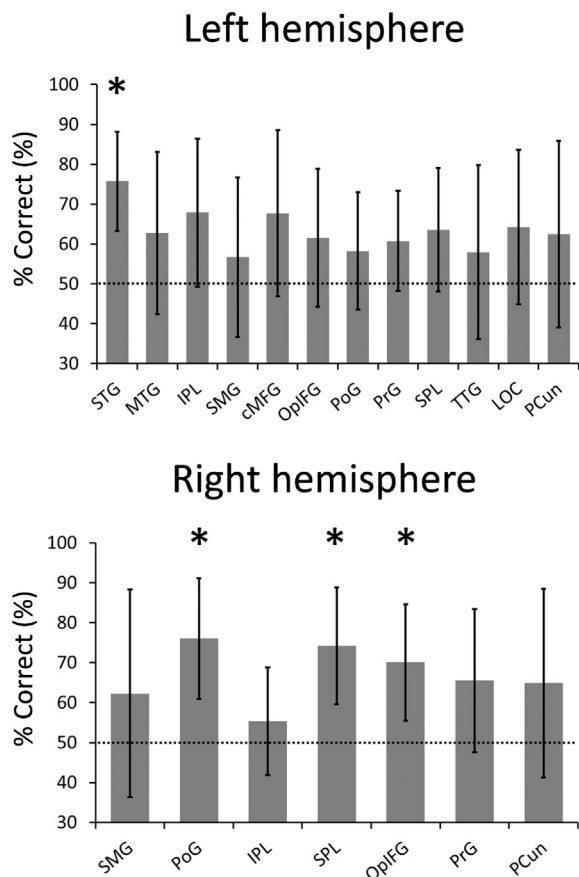


Fig. 5. Scatter diagrams showing the motor learning index and ERD values in the individual M1 seed locations. There was no significant relationship between motor learning index and ERD values in either alpha or beta bands.

activity during rest is spatially organized in highly structured networks of brain regions (Beckmann et al., 2005; Damoiseaux et al., 2006). The rs-FC has been reported to involve several brain regions, termed sensorimotor (Biswal et al., 1995; Fox et al., 2006), default-mode (Damoiseaux et al., 2006; Mantini et al., 2007), core (Buckner and Carroll, 2007; Buckner et al., 2013; Spreng et al., 2009), visual, and auditory networks (Damoiseaux et al., 2006; Mantini et al., 2007), which interact with each other (Baker et al., 2014; de Pasquale et al., 2012).

Recently, the relationship between neural and hemodynamic resting-state networks has been demonstrated using AEC of oscillatory alpha and beta activities and topography from fMRI (Brookes et al., 2011; de Pasquale et al., 2012). Hipp et al. (2012) reported that AEC across cortical regions is strongest in the alpha to the beta range. Another study reported that alpha and beta fluctuations correlate with default-mode networks, whereas beta and gamma fluctuations are related to sensorimotor networks (Mantini et al., 2007). These results indicate that alpha and beta AECs reflect long-range neuronal interactions within large-scale cortical



**Fig. 6.** Classification accuracy of motor learning index between good learners and poor learners. Good and poor learners were clearly distinguished by the strength of the rs-FC between the M1 and the left superior temporal gyrus, right post central gyrus, right superior parietal lobule, and right opercular inferior frontal gyrus ( $*p < 0.05$ ). The highest value was obtained in the left superior temporal gyrus. Error bars indicate 95% confidence intervals of classification accuracy. Horizontal dotted line donates chance level. STG; superior temporal gyrus, MTG; middle temporal gyrus, IPL; inferior parietal lobule, SMG; supra-marginal gyrus, cMFG; caudal middle frontal gyrus, OpIFG; opercularis inferior frontal gyrus, PoG; postcentral gyrus, PrG; precentral gyrus, SPL; superior parietal lobule, TTG; transverse temporal gyrus, LOC; lateral occipital gyrus, PCun; precuneus.

networks. A recent study using MEG reported that the strength of AEC cross-network interaction between sensorimotor networks and default-mode networks is related to motor learning ability (Mary et al., 2016). While this work provides the first evidence demonstrating a relationship between the strength of the AEC cross-network interaction and motor learning ability, these researchers could not rule out the possibility that other cross-network interaction effects on motor learning ability were overlooked due to the small sample size.

In the present study, we observed strong negative correlations between beta-band seed-based rs-FC and motor learning index in the left temporal gyri, bilateral sensorimotor areas, opercular inferior frontal gyri, and parietal areas. These brain regions overlapped significantly with parts of the core network, particularly the “theory of mind” network (Buckner et al., 2008; Carrington and Bailey, 2009; Patel et al., 2019; ; Spreng et al., 2009). The theory of mind is the ability to think about mental states, such as thoughts and beliefs in oneself and others, and underlies social interactions (Koster-Hale and Saxe, 2013). Its network is thought to overlap significantly with the default-mode network (Christoff et al., 2016; Raichle et al., 2001; Yang et al., 2015). Buckner et al. (2013) have recently suggested that rest is an internal task state with potential performance differences. Considering that resting-state may be just

another arbitrary task state (Deco and Corbetta, 2011), it is not surprising if cross-network interactions between sensorimotor networks and theory of mind networks are induced during the resting condition. A recent study has suggested that mentalizing networks, including the theory of mind networks, may be grounded in sensorimotor networks (Paracampo et al., 2017). From the viewpoint of motor learning, Mary et al. (2016) reported that lower cross-network connectivity between resting-state sensorimotor networks and parts of the default-mode network facilitate motor learning. However, as described above, these researchers could not rule out the possibility that other cross-network interactions related to motor learning were overlooked due to the small sample size. In the present study, we recruited 53 participants, and showed a strong negative correlation between M1 seed-based resting-state beta AEC and motor learning index. Spectrally, beta oscillations are thought to be informative regarding the performance of motor learning (Ozdenizci et al., 2017) and the mechanisms related to motor maintenance (Brovelli et al., 2004; Engel and Fries, 2010). In addition, stronger beta oscillations have been observed if maintenance of the current motor status is intended or predicted (Engel and Fries, 2010). Furthermore, default-mode network in the beta band has relation with self-related and internal processes (Mary et al., 2016; Raichle, 2015), suggesting that higher beta-band cross-network interactions between the sensorimotor network and parts of the theory of mind network during resting state may inhibit implicit sequential motor learning and lower beta-band cross-network interactions between them conversely facilitate it. Indeed, default-mode network is affected by motor training such as motor imagery (Ge et al., 2015; Zhang et al., 2014).

Good learners and poor learners were well distinguished by the strength of rs-FC between the M1 and the left superior temporal gyrus, right postcentral gyrus, superior parietal lobule, and opercular inferior frontal gyrus. Among these brain regions, the superior temporal gyrus and opercular inferior frontal gyrus are involved in the core network, particularly the theory of mind network (Carrington and Bailey, 2009; Spreng et al., 2009). In addition, the superior parietal lobule is associated with dorsal-attention network, which also belongs to core network (Spreng et al., 2009) and relates on voluntary or goal-directed orientation of attention (Fox et al., 2006), suggesting that specific cross-network connectivity between the sensorimotor network and the core network may contain important information, which can be used to predict good and poor learners in the sequential motor learning task. The right post-central gyrus belongs not to the core network but the sensorimotor network (Brookes et al., 2011; Mantini et al., 2007), suggesting that parts of the sensorimotor network may also contain important information for the prediction of motor learning ability. In the present study, we also performed multiple regression analysis to determine whether good and poor learners can be predicted using the peak strength of rs-FC in the brain regions with significant correlations between rs-FC and motor learning index. However, we could not predict good and poor learners using regression analysis, suggesting that rs-FC is not likely to become a predictor for motor learning level.

The present study also examined whether the magnitude of ERDs in the alpha and beta bands during a random button-press task can be a predictor of performance of the subsequent motor learning task because of its strong relation to motor function (Engel and Fries, 2010; Pfurtscheller and Aranibar, 1979; Sugata et al., 2017). However, there was no significant correlation between the two variables. Previous studies have demonstrated the relationship between the magnitude of beta ERD during motor skill acquisition and motor learning (Boonstra et al., 2007; Houweling et al., 2008; Pollok et al., 2014), whereas the present study examined the relationship between ERD during the random button-press task and performance in a subsequent motor learning task, and no significant correlation was observed. This result suggests that ERDs recorded prior to the motor learning task cannot be used as predictors of subsequent motor learning ability.

In the present study, we examined the relationship between M1 seed-based rs-FC values and motor learning in the alpha and beta bands. Our



findings demonstrated that beta-band resting-state cross-network connectivity between the sensorimotor network and the core network affected the performance of subsequent motor learning tasks. On the other hand, a recent study reported the relationship between alpha/gamma phase amplitude coupling over the parietal and frontal cortex and sequential motor learning (Tzvi et al., 2016). Other studies have suggested a relationship between gamma oscillation and motor learning (Joundi et al., 2012; Miller et al., 2010; Pogosyan et al., 2009; Sugata et al., 2018), indicating that gamma oscillation may contain important information related to motor learning. Therefore, neural oscillations of the gamma frequency may provide neural profiles for predicting motor learning capacity and further studies are warranted.

In summary, the present study raises the possibility that beta-band resting-state cross-network connectivity between the sensorimotor network and the theory of mind network affects performance in a subsequent motor learning task. By using the strength of the rs-FC between the M1 and the left superior temporal gyrus as a classification feature, good learners could be distinguished from poor learners. These results suggest that specific cross-network connectivity between sensorimotor networks and the theory of mind networks may contain important information for predicting motor learning ability.

#### Declaration of competing interest

None of the authors declares any conflict of interest. This work was supported by a grant for KAKENHI (16K16429, 18H03132) grants funded by the Japan Society for the Promotion of Science (JSPS).

#### CRediT authorship contribution statement

**Hisato Sugata:** Conceptualization, Methodology, Investigation, Software, Validation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration, Funding acquisition. **Kazuhiro Yagi:** Methodology, Resources, Software. **Shogo Yazawa:** Methodology, Resources. **Yasunori Nagase:** Methodology, Resources. **Kazuhiro Tsuruta:** Methodology, Resources. **Takashi Ikeda:** Software. **Ipppei Nojima:** Methodology, Formal analysis. **Masayuki Hara:** Formal analysis. **Kojiro Matsushita:** Formal analysis. **Kenji Kawakami:** Investigation, Resources. **Keisuke Kawakami:** Investigation, Resources.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroimage.2020.116562>.

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